International Journal of
Molecular Sciences

MDPI

Review

Joint Tissues: Convergence and Divergence of the Pathogenetic Mechanisms of Rheumatoid Arthritis and Osteoarthritis

Marina O. Korovina [1,2], Anna R. Valeeva [1,3], Ildar F. Akhtyamov [4], Wesley Brooks [5], Yves Renaudineau [6], Gayane Manukyan [7] and Marina I. Arleevskaya [1,2,*]

1 Central Research Laboratory, Kazan State Medical Academy, Kazan 420012, Russia; koporulina.mo@gmail.com (M.O.K.); anna-valeeva@mail.ru (A.R.V.)
2 Institute of Fundamental Medicine and Biology, Kazan (Volga Region) Federal University, Kazan 420008, Russia
3 Department of Applied Ecology, Institute of Environmental Sciences, Kazan (Volga Region) Federal University, Kazan 420008, Russia
4 Department of Traumatology, Orthopedics and Surgery of Extreme Conditions, Kazan State Medical University, Kazan 420012, Russia; yalta60@mail.ru
5 Department of Chemistry, University of South Florida, Tampa, FL 33620, USA; wesleybrooks@usf.edu
6 Department of Immunology, School of Medicine, CHU Toulouse, INSERM U1291, CNRS U5051, University Toulouse III, 31000 Toulouse, France; renaudineau.y@chu-toulouse.fr
7 Laboratory of Molecular and Cellular Immunology, Institute of Molecular Biology NAS RA, Yerevan 0014, Armenia; gaya.manukyan@gmail.com
* Correspondence: marleev@mail.ru

Abstract

Rheumatoid arthritis (RA) and osteoarthritis (OA) are frequently occurring multifactorial diseases affecting joints. OA and RA may share not only tissue locations but also some molecular mechanisms. We compared different pathologies: anti-cyclic citrullinated peptide antibody (ACCP)-positive RA—the classical 'antigen-driven' pathology, starting in synovia with no signs of inflammatory process; ACCP-negative RA, starting with synovial inflammation triggered by nonspecific factors, which becomes a chronic process due to inherited innate immune peculiarities; and OA, starting with inadequate chondrocyte functioning and cartilage degradation with inflammation as a driving force. Notable coincidences in RA and OA development were revealed: shared mutations of 29 genes encoding molecules involved in immune-inflammatory processes and in ECM production; unidirectional association of OA and ACCP-negative RA with non-genetic triggers; and overactivation of signaling pathways with the same consequences for RA and OA. Innate and adaptive immune responses were involved in OA development. Similar to that observed in RA, lymphoid nodular aggregates were revealed in 30% of OA synovia. Myeloid, and especially pauci-immune and fibroid synovial pathotypes, are possible in OA. Indistinguishable from that in RA, pannuses were found in OA articular tissues. Thus, these coincidences may be evidence of evolution of some OA variants in RA.

Keywords: osteoarthritis; rheumatoid arthritis; gene mutations; trigger factors; signaling pathways; joint tissues

Academic Editor: Antonella Fioravanti

Received: 28 July 2025
Revised: 5 September 2025
Accepted: 6 September 2025
Published: 8 September 2025

Citation: Korovina, M.O.; Valeeva, A.R.; Akhtyamov, I.F.; Brooks, W.; Renaudineau, Y.; Manukyan, G.; Arleevskaya, M.I. Joint Tissues: Convergence and Divergence of the Pathogenetic Mechanisms of Rheumatoid Arthritis and Osteoarthritis. *Int. J. Mol. Sci.* **2025**, *26*, 8742. https://doi.org/10.3390/ijms26178742

1. Introduction

Rheumatoid arthritis (RA) and osteoarthritis (OA) are two widespread multifactorial diseases that affect joints. In recent years, the perception of OA as a purely degenerative process has changed. The inflammatory process in the arthritic joint is recognized as

the more important component of the pathogenesis and even a trigger for OA [1]. The well-known players in RA pathogenesis and the targets for biological disease modifying antirheumatic drug, TNFα and IL-1β, were recognized as drivers of catabolic signaling in OA joints [2,3]. On the other hand, RA is one of the causes of secondary OA, and the RA inflammatory process can be the driving force of such OA development. In spite of the well documented dependence of secondary OA symptoms on RA duration [4], changed serum levels of various cartilage turnover markers (N-terminal propeptide of collagen IIA, cross-linked C-telopeptide of collagen II, oligomeric matrix protein) in correlation with radiographic/MRI joint damage signs, signifying possible OA initiation, were demonstrated to occur early in RA patients [5,6]. Curiously, as many as 20% of 247 persons at the 3rd (arthalgia) and 4th (undifferentiated arthritis) preclinical RA stages exhibited joint symptoms that were provoked by unusual excessive joint activity, while among 461 eRA patients, there were none in which such activity was identified as a trigger of the disease [7]. The question arises whether imbalance appears in the pre-RA stage and whether it is one of the triggers of RA.

The recognition of inflammation as an OA driver has brought about the idea to apply the groups of drugs used in RA to OA therapy—corticosteroids, methotrexate, biologics [8–13]. The results of primarily short-term therapy (4 weeks–6 months) presented in the references mentioned above and a number of other publications are contradictory. Therefore, there is a need for long-term trials.

An assumption can be made that contradictory results are due to differences in the patients included in the study. The difficulty is that OA as a multifactorial disease might have various phenotypes. The existence of different RA phenotypes is not in doubt. The two most well characterized phenotypes are the variants with or without antibodies against cyclic citrullinated peptides (ACCPs) with the obvious differences of the initial pathogenic mechanisms discussed in this review.

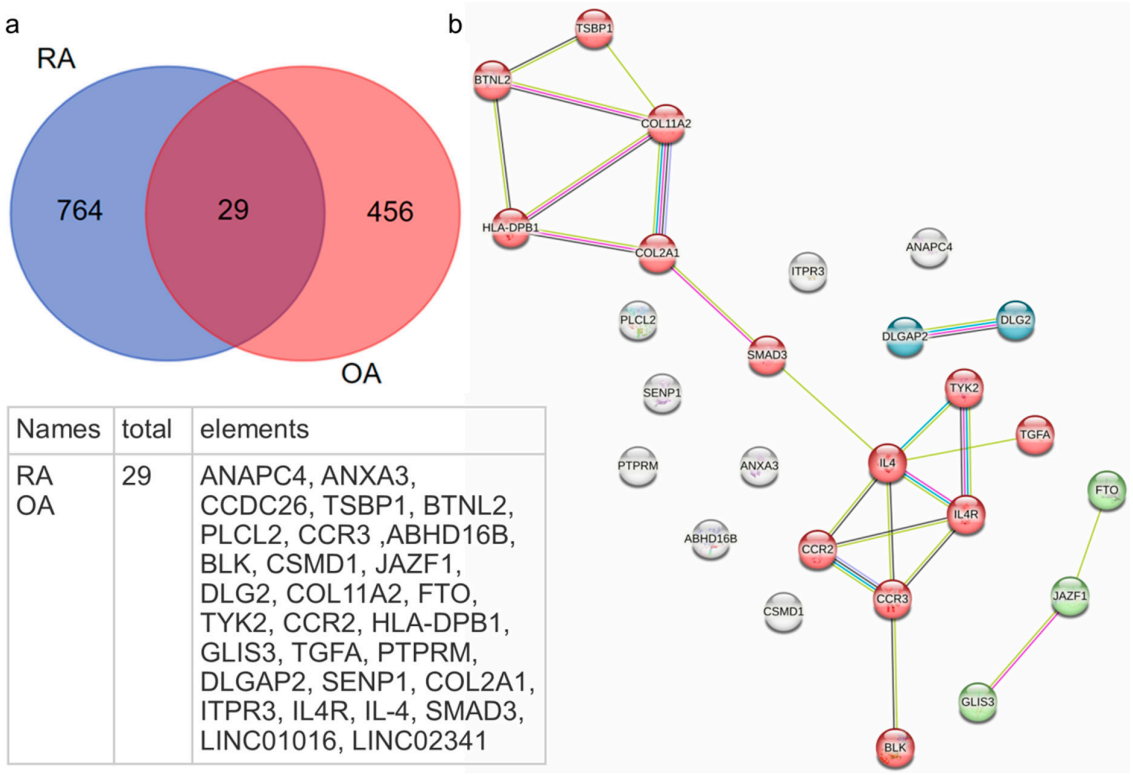
Ideas regarding different variants of OA are still in the hypothesis development stage. The following options may be suggested: post-traumatic OA with probable disturbances in repair processes after joint injury; mechanical variants due to the chronic microtrauma of the joint, aggravated by excess weight and other environmental and individual factors [14,15]; and primary hand erosive osteoarthritis with a probable major contribution of immunological mechanisms in its pathogenesis (in particular, the frequent presence of lymphoid follicles in joint tissues, which brings it closer to RA) [16].

So, even a cursory glance allows one to see a certain similarity between OA and RA. These diseases may share not only the arena in which they unfold but also some pathogenic mechanisms. Therefore, it appears reasonable to consider the interweaving of OA and RA pathological mechanisms, which, to some extent, may lead to the convergence of their clinical features.

Accordingly, we will consider the similarities and differences of (i) genetic factors predisposing to the development of OA and RA, (ii) individual and environmental triggers of diseases, as well as (iii) the processes of disease development in joint tissues.

2. Comparison of RA and OA Genetic Backgrounds

Genome-wide association studies (GWASs) have provided significant insights into the shared genetic underpinnings of RA and OA. Several single-nucleotide polymorphisms (SNPs) have been identified that are common to both diseases, suggesting overlapping genetic factors that influence susceptibility to joint diseases (Figure 1). Within the 1249 genes identified, 29 genes were found to be common to both pathologies (Figure 1a).



Names	total	elements
RA OA	29	ANAPC4, ANXA3, CCDC26, TSBP1, BTNL2, PLCL2, CCR3 ,ABHD16B, BLK, CSMD1, JAZF1, DLG2, COL11A2, FTO, TYK2, CCR2, HLA-DPB1, GLIS3, TGFA, PTPRM, DLGAP2, SENP1, COL2A1, ITPR3, IL4R, IL-4, SMAD3, LINC01016, LINC02341

Figure 1. Coincidences of genetic background in OA and RA. (**a**) Shared mutated genes (GWAS). (**b**) Clusters of shared genes (STRING). Rheumatoid arthritis (RA); osteoarthritis (OA); Genome-wide association studies (GWASs); Search Tool for the Retrieval of Interacting Genes/Proteins (STRING); anaphase-promoting complex subunit 4 (ANAPC4); annexin A3 (ANXA3); CCDC26 long non-coding RNA (CCDC26); testis-expressed basic protein 1 (TSBP1); butyrophilin-like 2 (BTNL2); phospholipase C-like 2 (PLCL2); C-C motif chemokine receptor 3 (CCR3); abhydrolase domain-containing 16B (ABHD16B); BLK proto-oncogene, Src family tyrosine kinase (BLK); CUB and Sushi Multiple Domains 1 (CSMD1); JAZF zinc finger 1 (JAZF1); discs large MAGUK scaffold protein 2 (DLG2); collagen type XI (COL11A2); FTO alpha-ketoglutarate-dependent dioxygenase (FTO); tyrosine kinase 2 (TYK2); C-C motif chemokine receptor 2 (CCR2); major histocompatibility complex, class II, DPbeta 1 (HLA-DPB1); GLIS family zinc finger 3, (GLIS3); transforming growth factor alpha (TGFA); protein tyrosine phosphatase receptor type M (PTPRM); transforming growth factor alpha; DLG-associated protein 2 (DLGAP2); SUMO-specific peptidase 1 (SENP1); type II collagen (COL2A1); inositol 1,4,5-trisphosphate receptor type 3 (ITPR3); interleukin 4 receptor (IL4R); interleukin 4 (IL-4); SMAD family member 3 (SMAD3); long intergenic non-protein coding RNA 1016 (LINC01016); long intergenic non-protein coding RNA 2341 (LINC02341).

A number of these genes—type II collagen *(COL2A1)*, type XI collagen *(COL11A2)*, and CUB and Sushi Multiple Domains 1 (*CSMD1*)—play crucial roles in cartilage integrity and extracellular matrix formation. Type II collagen is the main extracellular matrix (ECM protein), while the inclusion of a minor type, XI collagen, is due to some physical properties of mature ECM [17]. Interestingly, XI collagen is used in a rat model for the induction of chronic arthritis [18]. CSMD1 is, in particular, a transmembrane inhibitor of the classical and lectin complement pathways [19] involved in modulating cartilage immune environment due to aggravating of its degradation [20]. SMAD family member 3 (*SMAD3*) and transforming growth factor alpha (*TGFA*)-coded molecules are the factors of TGF signaling pathways, which, being overactivated both in OA and RA, are involved in ECM neogenesis as well as in other pathological processes (neoangiogenesis, apoptosis, and osteoblast differentiation; Figure 2).

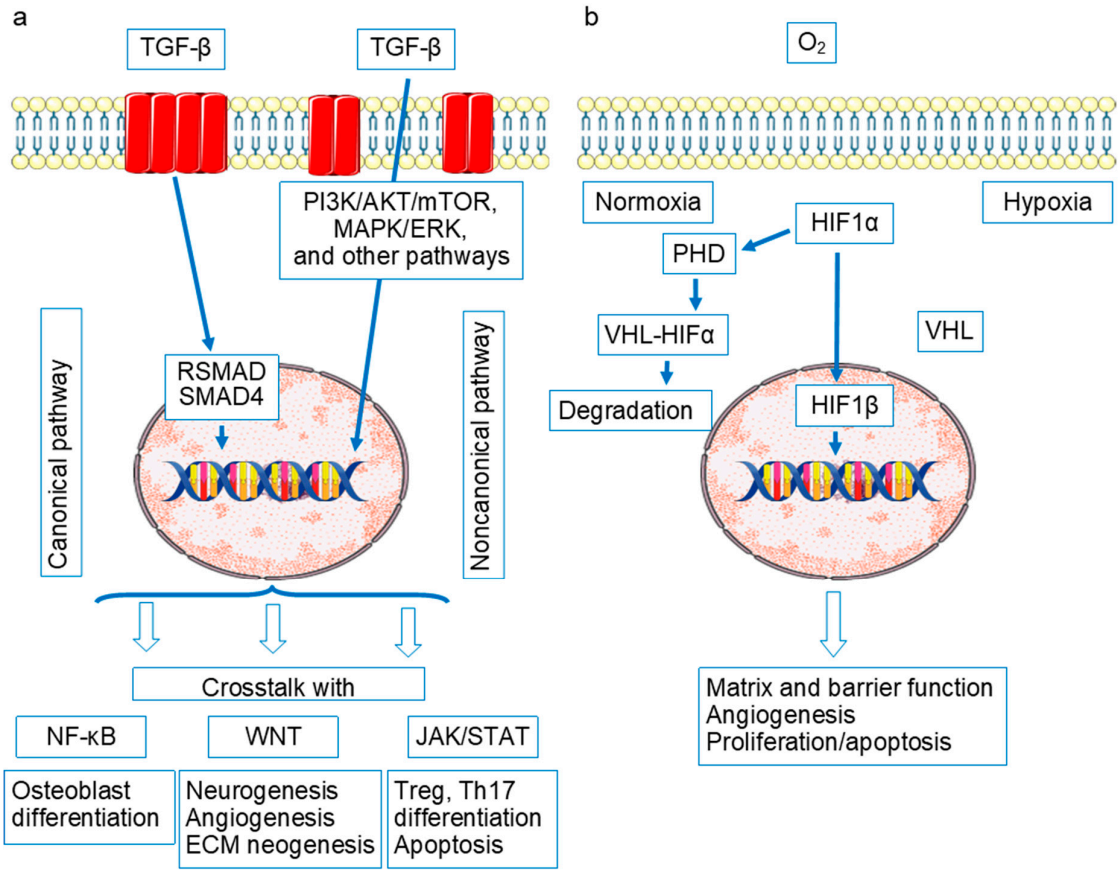


Figure 2. Schematic representation of the activation of signaling pathways and the influence on the pathogenesis of OA and RA. (**a**) Canonical and non-canonical activation of TGFβ signaling pathways. In canonical activation, 2 types of receptors form a hetero-tetrameric complex. Type I cell surface receptor phosphorylates intracellular receptor-regulated SMADS (R-SMADS), such as SMAD2 or SMAD3. The phosphorylated R-SMADS then binds to SMAD4. RSMAD/SMAD complexes act as transcription factors. Non-canonical, nonSMAD pathways are activated without formation of a hetero-tetrameric complex. These nonSMAD pathways include various branches of the ERK/MAPK and PI3K/AKT/mTOR pathways. (**b**) Transcriptional activity of HIF1 depends on the oxygen level. Under normoxia, the VHL-mediated ubiquitin protease pathway degrades HIF1A. Enzymes prolyl hydroxylase (PHD) and HIF prolyl hydroxylase (HPH) are involved in specific post-translational modification of HIF1A proline residues, which allow for VHL association with HIF1A. Under hypoxia, HIF1A protein degradation is prevented, and HIF1A associates with HIF1B to exert transcriptional effects on target genes. Transforming growth factor (TGF); phosphatidylinositol-3-kinase (PI3K); SMAD family member (SMAD); receptor-regulated SMADs (RSMADs); extracellular signal-regulated kinases (ERK); mitogen-activated protein kinases (MAPK); mammalian target of rapamycin (mTOR); protein kinase B (AKT); nuclear factor Kb (NF-κB); Wnt family member (Wnt); Janus kinase (JAK); signal transducer and activator of transcription (STAT); hypoxia-inducible factor 1 (HIF-1); prolyl hydroxylase (PHD); von Hippel–Lindau tumor suppressor (VHL); extracellular matrix (ECM). The information about signaling pathways was obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG).

Additionally, anaphase-promoting complex subunit 4 (ANAPC4), SUMO-specific peptidase 1 (SENP1), DLG-associated protein 2 (DLGAP2), BLK proto-oncogene, Src family tyrosine kinase (BLK), and *PTPRM*-coded factors are implicated in the dysregulation of apoptotic pathways, disrupting cell cycle regulation in synovial cells, causing increased apoptosis in chondrocytes contributing to cartilage loss in OA and disturbed cell cycling in synovial fibroblasts, and promoting hyperplasia in RA (Supplementary Table S1). The *ANXA3*-coded molecule collaborates with RANK in acceleration of osteoblast differentia-

tion [21] and contributes to cell proliferation and angiogenesis via the HIF-VEGF signaling pathway [22]. TYK2 as well as CSMD1 code factors modulating the JAK/STAT cascade (KEGG-obtained data) [20,23], overactivated in both OA and RA *DLG2* and *ITPR3* gene-coding factors, interfering with calcium-dependent signaling pathways regulating ion channel functioning (PRR signaling and inflammasome formation as examples) [24]. FTO Alpha-ketoglutarate-dependent dioxygenase (FTO) is involved in repair of alkylation lesions in DNA, RNA, and nucleoprotein complexes, regulating adipogenic pathways (in particular in pre-adipocyte differentiation) and inflammation-associated vascular endothelial dysfunction [25–27]. Besides the more thoroughly studied function of FTO/IRX3 is the involvement in adipocyte precursor development and obesity and diabetes pathogenesis [28–30]. A meta-analysis revealed association of *FTO* gene SNPs with hip/knee OA, collagen formation, and extracellular matrix organization biological pathways [31,32]. In addition, it was demonstrated that FTO overexpression alleviates OA progression [33,34]. In RA, FTO SNPs were associated with joint damage, due to the inflammation activity [35]. Increased FTO expression in RA synovial cells enhanced their proliferation and migration and decreased senescence and apoptosis [36].

Two chemokine gene SNPs—C-C motif chemokine receptor 3 (*CCR3*) and C-C motif chemokine receptor 2 (*CCR2*)—may be involved due to the attraction of leucocytes in inflammatory joint loci both in OA and RA, and together with SNPs of the *IL4* gene and its receptor, as discussed above, a SNP of *TYK2*-coding protein associated with the cytoplasmic domain of type I and type II cytokine receptors, and being a part of IFN type I and type III signaling pathways (NCBI), demonstrates the involvement of the immune system not only in RA but in OA as well. Additional notable coincidences are gene mutations that may be important for the development of the adoptive immune response both in OA and RA genes of molecules involved in B-cell development and B-cell receptor signaling—phospholipase C like 2 (*PLCL2*), BLK proto-oncogene, Src family tyrosine kinase (*BLK*) and the two genes located in MHC, class II–butyrophilin like 2 (*BTNL2*), encoding type I transmembrane protein involved in immune surveillance, serving as a negative T-cell regulator by decreasing T-cell proliferation and cytokine release, and *HLA-DPB1* (major histocompatibility complex, class II, DP beta 1) presenting peptides derived from extracellular proteins by B lymphocytes, dendritic cells, and macrophages (NCBI) [31,37–42]. The above-mentioned CSMD1 factor promotes both B-lymphocyte receptor signaling and pathways related to antigen presentation [20].

Involved in both pathologies, long non-coding RNAs—LINC02341 and LINC01016 (lncRNAs)—are involved in regulation of processes of cell survival, apoptosis, and lipid metabolism [43–45].

STRING analyses (Search Tool for the Retrieval of Interacting Genes/Proteins) of genes showed a distinct clustering of genes involved in both RA and OA with associated SNPs. STRING identifies functional associations between gene products and predicted protein–protein interactions. The analyses visualize (Figure 1b) complex interaction networks by integrating data taken from GWASs. STRING integrates proteins encoded by genes associated with SNPs (Supplementary Table S1) to infer how genetic variations might affect protein interactions and pathways [46]. The biggest clustering was obtained for 13 gene products (HLA-DPB1, BTNL2, TSBPI, COL2A1, COL11A2, SMAD3, TYK2, TGFA, CCR2, CCR3, IL-4, IL-4R, and BLK) having protein–protein interactions and associated with biological processes including Th17 cell differentiation and the regulation of leukocyte degranulation. The presence of gene products such as HLA-DPB1, BTNL2, TYK2, CCR2, CCR3, and IL-4R supports immune inflammatory mechanisms that are central to both RA and OA. Numerous studies have emphasized the important role of Th17 cells in driving autoimmune responses in animal models of autoimmune arthritis. In humans, it was shown

that Th17 cells correlate with the disease activity [47]. Despite this, recent studies have reported the presence of Th17 cells in the synovial fluid and synovial membranes of OA patients, although in smaller quantities compared to those found in RA joints [48]. Notably, HLA-DPB1 and BTNL2 are involved in antigen presentation and T-cell activation, further underscoring the role of immune responses in joint disease progression. Gene products such COL2A1 (type II collagen, a primary collagen found in cartilage) and COL11A2 (type XI collagen, a minor component of cartilage collagen, working with COL2A1 to maintain ECM stability) play crucial roles in cartilage integrity and extracellular matrix formation. Both RA and OA, despite their distinct pathophysiologies, are significantly implicated in cartilage damage, and the alterations in these proteins across RA and OA indicate a convergence of molecular pathways, particularly those involved cartilage degradation. SMAD3 and TGFA regulate ECM production and repair, contributing to cartilage repair dysfunction in OA and fibrosis in RA.

The second cluster, containing FTO, GLIS3, and JAZF1, is a smaller cluster but highly relevant to the regulation of metabolic processes and cellular function. Particularly, FTO is associated with body mass index (BMI) and obesity, which are known risk factors for OA and potentially for RA. GLIS3 and JAZF1 are associated with gene regulation and metabolic processes, suggesting that metabolic dysregulation may contribute to the development of both RA and OA, albeit through different mechanisms.

The third cluster comprises two gene products, DLGAP2 and DLG2. While the exact roles of DLGAP1 and DLG2 are involved in regulation of apoptosis and calcium-depended signaling cascades, including inflammasome formation—the processes undoubtedly being important links in the pathogenesis of both RA and OA.

The clustering analysis suggests that the shared genetic factors and their products could provide new insights into the pathogenesis of these diseases. Further research is needed to validate these findings and determine how these shared genes contribute to disease onset and progression in RA and OA.

3. Signaling Pathways in RA and OA Pathogenesis

The following signaling pathways are considered fundamental in RA and OA pathogenesis: NF-κB, Wnt, Jak/STAT/SOCS, OPG/RANKL/RANK, TGFβ/BMP, and HIFs-PHDs [49–51] (Figures 2–4).

As shown in Figure 2, created on the basis of the schematics presented in Wikipedia with the addition of KEGG information, these signaling pathways are closely intertwined and interact in the process of modulating precisely those mechanisms, which, when disrupted, play a role in the pathogenesis of both OA and RA. We attempted to analyze the participation in OA and RA pathogenesis from the point of view of the progression of destructive processes in OA and RA joints.

Osteoarthritis. Excessive NF-κB signaling in synovial tissue samples has been detected already in the early stages of OA, and it is probably not limited to the synovium, but extends at least to cartilage and subchondral bone with chondrocyte macrophages, synoviocytes, and osteoblasts in a vicious circle of mutual potentiation of proinflammatory activities [51–57]. Overactivation of NFkB and of interdependent signaling pathways is triggered by abnormal mechanical pressure and hypoxia and interaction of crystals, cartilage fibronectin, hyaluronan, biglycan, tenascin c, syndecan-4, and type II collagen and aggrecan fragments with PPRs [51,58,59]. The abnormal excessive signaling in OA might be due to TLR9 and TLR3 SNPs, associated with OA risk [60,61], numerous gene mutations of the factors of TGF cascade associated with cartilage thickness, erosive hand OA or hip minimal joint space width (PIK3R1, SMAD3, CEMIP (KIAA1199) BMP6, and NOG) partly

presented in Supplementary Table S1 [62–65] and probably HIF SNP (contradictory data) associated with OA and RA disease risk [66,67].

Excessively activated NFkB cascade acting directly or in collaboration with overstimulated JAK/STAT, RANKL/RANK, a branch of HIFs-PHDs (HIF-2α) and WNT, dysregulated TGFβ/BMP is due to increased production of matrix metalloproteinases (MMP1, MMP2, MMP3, MMP7, MMP8, MMP9, MMP13), ADAMTS4 and ADAMTS5, degrading articular cartilage. Various inflammatory molecules (prostaglandin E2, nitric oxide synthase and nitric oxide, cyclooxygenase-2), induced by hyperactivated NFkB cascade promote chondrocyte apoptosis in the inflammatory focus. The abnormal signaling in a tangle of RANKL/RANK, HIFs-PHDs, JAK/STAT, TGFβ/BMP, and WNT pathways results in chondrocyte dedifferentiation and loss of functions—decreased expression of COLII, aggrecan, Sox-9, collagen I collagen, and X collagen [50,51,68–72]. Abnormal RANKL/RANK and WNT signaling in OA proinflammatory osteoblasts is due to subchondral bone loss and bone sclerosis development [51]. Another subchondral event—osteophyte formation—occurs with chondrocyte TGF cascade participation [73,74]. Neoangiogenesis in subchondral bone with vessel penetration into normally avascular cartilage and synovia is due to proinflammatory signaling in the discussed cascades with the HIF pathway first of all. Proinflammatory cytokines stimulate synovial macrophages, abnormal OA osteoblasts, and chondrocytes to produce vascular endothelial growth factor (VEGF)—a major actor of neovascularization [75,76].

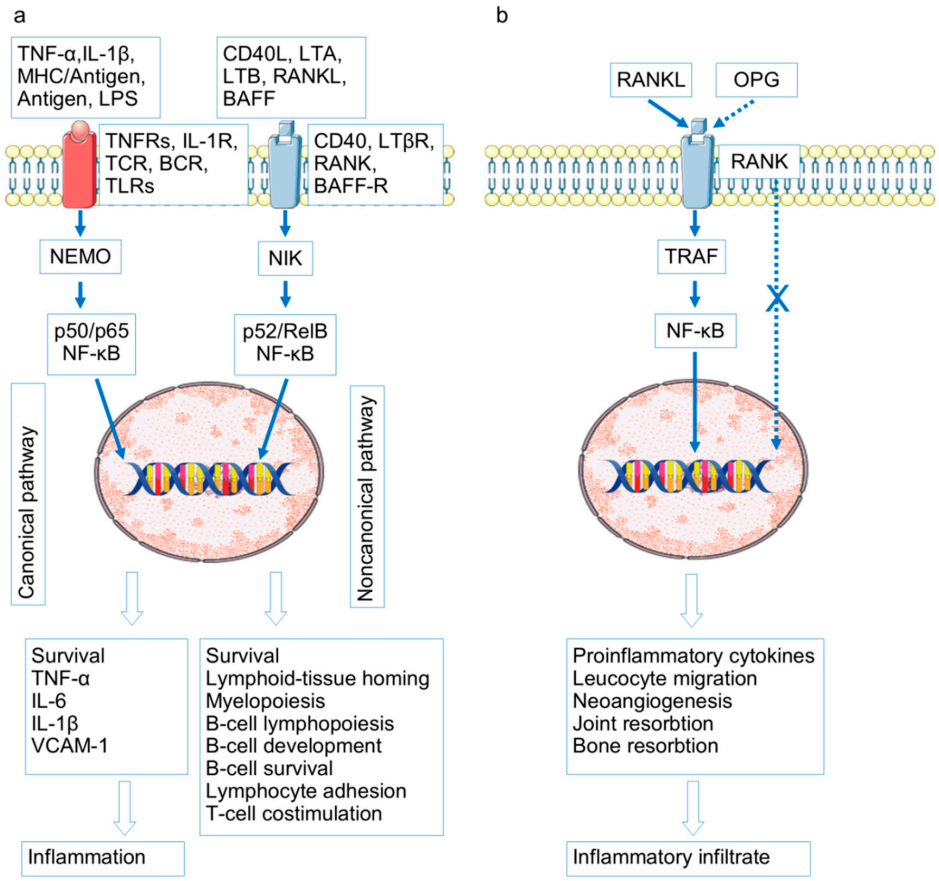


Figure 3. Schematic representation of the activation of signaling pathways and their influence on the pathogenesis of OA and RA. (**a**) Canonical and non-canonical activation of NF-κB signaling pathway. In canonical NEMO-dependent activation, the dimer regulating transcription—p50/p65. In non-canonical NIK -dependent activation, the dimer—p52/RelB. (**b**) Activation of the RANKL /RANK/OPG pathway.

RANKL binds to RANK as its receptor and eventually leads to osteoclast precursor maturation. OPG is known as a decoy receptor for RANKL that prevents RANKL-RANK binding and the subsequent reactions. Osteoarthritis (OA); rheumatoid arthritis (RA); nuclear factor κB (NF-κB); NF-κB essential modulator (NEMO); NF-κB-inducing kinase (NIK); receptor activator for nuclear factor κB ligand (RANKL); receptor activator for nuclear factor κB (RANK); osteoprotegerin (OPG); tumor necrosis factor (TNF); TNF receptor-associated factor (TRAF); major histocompatibility complex (MHC); interleukin 1 beta (IL-1b); lipopolysaccharide (LPS); cluster of differentiation 40/cluster of differentiation 40 ligand (CD40/CD40L); lymphotoxins alpha and beta (LTA/LTB); lymphotoxin beta receptor (LTBR); B-cell activating factor receptor (BAFFR); B-cell activating factor (BAFF); interleukin 6 (IL-6); vascular cell adhesion molecule 1 (VCAM-1). The information about signaling pathways was obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG).

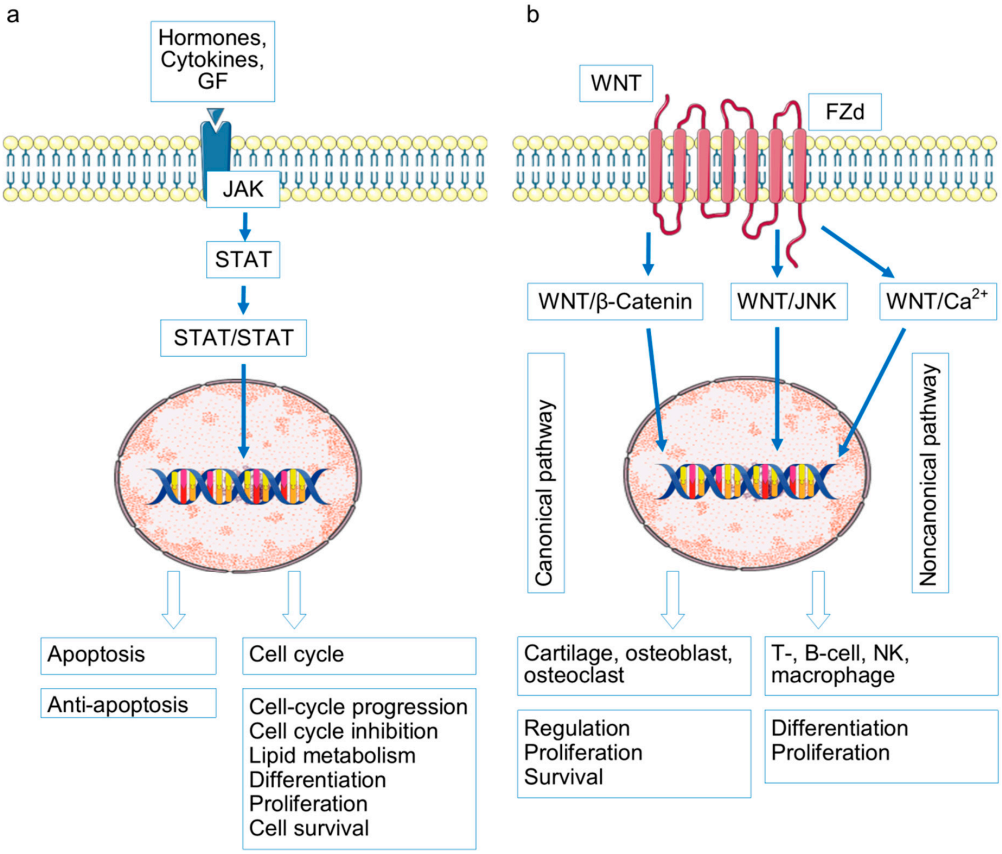


Figure 4. Schematic representation of the activation of signaling pathways and their influence on the pathogenesis of OA and RA. (**a**) Activation of the JAK/STAT pathway. JAK/STAT signaling involves three main proteins: cell surface receptors, JAKs, and STATs. After a ligand binds to a receptor, JAKs phosphorylate the receptor. This attracts STAT proteins, which are also phosphorylated and bind to form a dimer. The dimer translocates into the nucleus, binds to DNA, and induces gene transcription. (**b**) Activation of Wnt signaling pathways: the canonical Wnt pathway, the non-canonical planar cell polarity pathway, and the non-canonical Wnt/calcium pathway. All pathways are activated by binding of a Wnt protein ligand to a receptor of the Frizzled family. The canonical pathway involves the protein beta-catenin, while the non-canonical pathways act independently. Janus kinase (JAK); signal transducer and activator of transcription (STAT); growth factor (GF); Wnt family member (Wnt); Frizzled family receptor (FZd); c-Jun N-terminal kinases (JNK); natural killer (NK). The information about signaling pathways was obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG).

Rheumatoid arthritis. The accumulation of gene polymorphisms of factors of the discussed signaling pathways, with the possible exception of the HIF cascade, is noteworthy [40,77–86]. OA-associated SNPs in signaling pathways have been found significantly less frequently, or this aspect of OA pathogenesis has been less studied. In addition, RA is

characterized by a number of mutations in TLR genes [87]. Signaling from overexpressed PRRs, in particular in fibroblast-like synoviocytes, macrophages, and other joint tissues [87], in combination with SNP signaling pathway factors, lead to a rampant proinflammatory reaction in the joints. It is probably more pronounced than in the OA activation of the same tangle of signaling pathways and leads to practically the same consequences—increased production of matrix metalloproteinases and ADAMTs, chondrocyte degradation/survival, ECM degradation, osteoclastogenesis, subchondral bone loss and bone sclerosis development, neoangiogenesis, fibroblast proliferation, and fibrosis [84,88–104].

Thus, there is a clear similarity between the role of overactivation of signaling pathways and the consequences of this activation for joint tissues in RA and OA. The signaling pathways being RA hallmark and the application points of its modern biologic and targeted therapy are the drivers OA as well. Overactivation of these signaling pathways is associated with the involvement of inflammation and immune processes in the pathogenesis of both diseases (indications of immune system involvement in the pathogenesis of OA are discussed below). Yet there is an obvious difference. RA is an immune inflammatory disease characterized by a powerful systemic inflammatory process [105,106]. OA is characterized by low-grade inflammation, which is not always determined outside the joint tissues and has less pronounced signs of innate and cellular immune mechanism involvement [107].

4. Individual and Environmental RA and OA Triggers

As reported in other multifactorial diseases, both RA and OA are provoked by interaction of external factors with the unique genetic features of the diseases. As it was mentioned above, there are two well-identified RA variants—ACCP-positive and ACCP-negative—with the discussion below focusing on some essential differences of their genetic backgrounds and early-stage pathogenic mechanisms, while OA variants are currently discussed mainly at the level of analyzing clinical data and developing therapy without depending on the differences in the intimate pathogenic mechanisms, which are now beginning to be intensively studied [108–110].

Therefore, we tried to compare the influence of the main non-genetic triggers on the development of OA and two variants of RA—ACCP-positive and -negative—using PubMed as a source of information. The following key words were selected: “disease, trigger, statistical indicator” (Supplementary Table S2).

It should be noted that the different contributions of non-genetic factors to the development of OA and ACCP-positive and -negative RA variants primarily can only be assumed based on the noticeable differences in OR/HR/RR values, as we failed to find any publications with a rigorous analysis of this hypothesis (Supplementary Table S3).

The risks of both RA variants in the presence of these diseases in the family history were increased [111–113]. The authors did not conduct a direct comparison of the family risk in the ACCP-positive and ACCP-negative RA cohorts depending on the age of onset of the disease; however, upon detailed consideration of the presented data, the following hypotheses arise. First, the risk of developing RA in the presence of a relative with ACCP-positive RA in the family is higher than in the presence of ACCP-negative cases in the family history [111]. Second, in both cohorts, the risk of developing RA is the highest if the disease develops in the proband at an age of less than 40 years.

If there are cases of OA in the family, the risk of developing this disease in relatives is also significant [112,113].

Risk of both ACCP-positive and -negative RA onset increases with age, yet one could notice some difference. The risk of ACCP-positive cases was the highest at the age of 50–59 years and then appears to decrease, while in the ACCP-negative cohort, it was high

at the age of 45 years and increased with age until at least 60–64 years [114]. The incidence of OA also increased steadily with age [115].

Women are more prone than men to develop RA and/or OA [113,116–119]. Yet, only a modest role of gender differences in OA and even the absence of a reliable difference in the frequency of hand OA, in contrast to hip and knee involvement, were revealed [118,119]. Perhaps this is one of the arguments for the existence of different variants of OA with specific triggers, mechanisms of progression and, possibly, requiring different therapeutic approaches.

Gender preferences and the link of both RA and OA with the corresponding age ranges evoke a natural assumption that the changes in sex hormone levels in pre- and perimenopause and later on may provoke the diseases. However a trigger role of this factor was demonstrated for OA and ACCP-negative RA, but not for the ACCP-positive one [114,120,121]. The results of the analysis of the postmenopausal replacement hormone therapy link with ACCP-negative and -positive RA and OA cohorts were contradictory, which may be due to the differences in pill compositions, doses, duration of the therapy, and, as OA, localization of the process presented in the analysis [114,120,122–126].

The triggering role of parous in RA risk may depend on the number of children as well as on the normal/adverse pregnancy data [127]. Yet the analysis revealed that being parous increased ACCP-negative RA risk with no impact on ACCP-positive one [128]. In addition, being parous was a predictor of a more severe RA among ACCP-negative younger women [129]. OA risk also increased in parous vs. non-parous women and depended on the number of children [130,131]. Breastfeeding association with RA depended on its duration and may have a protective effect for ACCP-positive cases, with no impact on ACCP-negative cases [132–135]. Few publications demonstrated a provoking effect of breastfeeding on OA risk [130,136]. The analysis of oral contraceptive usage impact on ACCP-positive RA risk yielded contradictory results and revealed no effect on ACCP-negative RA and OA [124,131–133].

Smoking by the parent during pregnancy (in utero exposure) increased the risk of ACCP-positive RA with no impact on the risk of ACCP-negative cases (no data were available regarding the link with OA risk) [137]. Larger gestational age birth weight increased RA risk regardless of ACCP status, while smaller gestational age birth weight appeared to be protective [135,138,139]. The opposite pattern was found for OA [140–142].

The curious patterns of BMI links with the risks of OA and RA variants were revealed. Being overweight had no impact on the risk of ACCP-positive RA cases or even had a protective effect [117,132,143], while it was associated with the risk of ACCP-negative RA cases [132,143,144]. Risk of knee and hip OA, as expected, increased with overweight (conflicting data regarding hip OA), due to the overload of the lower limb joints [113,145–148] However, being overweight has also been associated with an increased risk of hand OA, which clearly suggests a more complex relationship than excess joint loading [148,149].

Coffee (more than 10 cups per day) in a dose-dependent pattern increased the risk of ACCP-positive cases and had no effect in ACCP-negative cases [132]. Only marginally significant evidence of the link of low daily coffee doses and OA risk and not in all studies was revealed [150,151]. Consumption of $\geq$7 cup of coffee was linked with increased OA link in men, but not in women [151].

Alcohol consumption dose-dependently reduced the risk of developing ACCP-positive RA, but was associated with an increased risk of developing its ACCP-negative variants in patients with >15 drinks per week [117,144,152] and was a risk factor for severe erosive hand OA [153,154].

Smoking was definitely associated with an increased risk of ACCP-positive RA especially in shared epitope (SE) carriers [132,155,156]. Analyses revealed a possible protective effect of smoking on the risk of ACCP-negative cases without SE in the genome and no

link with that in SE carriers [132,155,156]. A possible protective effect of smoking was demonstrated for knee OA as well [157–159].

Mental stress prior to RA onset was definitely a trigger, and antidepressant use had a protective effect [160,161]. However, upon further examination, it was found that mental stress was associated with the development of ACCP-negative RA, but not the ACCP-positive one [162]. Mental stress was associated with the severity of radiographic features of knee/hip OA, but the study design did not allow us to understand whether mental stress was a risk factor for OA progression, or whether symptoms due to progressive joint disease were the cause of stress [163,164].

Ten years of high and even slight physical activity wer a risk factor for ACCP-negative but not for ACCP-positive RA [132]. And the various variants of work and everyday physical activity were a major risk factor for OA [113,165,166].

So, two RA variants and OA are predominantly "female" family-aggregated age-related diseases. Yet their links with non-genetic triggers appeared to have certain differences, probably reflecting the difference in the contribution of concrete pathogenetic mechanisms to their development.

Some patterns emerge when comparing the lists of RA and OA triggers. Family clustering has a complex nature, including shared genetics; infections; microbiome; lifestyle; and ecology [167]. Familial aggregation of RA and OA may be due to different triggers from this list.

The peak risk of developing both RA and OA occurs in the age range of 50–60 years. The well-known molecular mechanisms of aging are the same for OA and RA with a greater or lesser contribution to their development. Imbalance in production and inactivation of reactive oxygen species due to chondrocyte cell death and ECM degradation [168,169]. Oxidative stress is due to DNA, lipid, and protein damage, leading to synovial inflammation, essential for the both diseases [170]. Reactive oxygen species are involved in the process of carbamylation, which provokes the production of antibodies to carbamylated peptides, which have diagnostic and prognostic significance in RA [171,172]. Oxidative stress might trigger joint symptoms in patients at preclinic RA stages [173]. Immune system aging results in proinflammatory shift of immune reactions [174]. Tissue damage and increased proinflammatory potential of immune system predisposes for chronic-persistent inflammation.

Common sense would expect traditional lifestyle differences and gender-based occupational characteristics certainly contribute to the female/male disparities in RA and OA. Yet, it is noteworthy that the ACCP-negative RA variant appeared to be more dependent on fluctuations in estrogen levels than the ACCP-positive cases. The same trend was observed in OA. Indeed, menopause is characterized by a decrease in estrogen and progesterone levels, and a weakening of their anti-inflammatory effects [167]. Being parous is associated with OA and ACCP-negative RA, but not with ACCP-positive cases. Normal pregnancy is characterized by increased estrogen and progesterone levels and Th1→Th2 immune responses, and with the delivery process, there is a powerful explosion of Th1 responses against the background of decreasing estrogen and progesterone levels. So, repetitive surges of a Th1 response at each delivery might ultimately trigger a persistent immune inflammatory process, characteristic primarily of ACCP-negative RA and, perhaps, to some extent, of OA. Breastfeeding is characterized by high levels of prolactin supporting a Th1 response by reduced levels of estrogen and prolactin compared to the period before pregnancy (which quickly return to normal in the absence of breastfeeding). So, this situation, if repeated, is also fraught with the possibility of provoking a chronic immune-inflammatory response. This is a very simplified speculative scheme of the possible involvement of sex hormone-associated processes in provocation of ACCP-negative RA and OA. Further stud-

ies are needed to clarify the possible gender-dependent differences between ACCP-positive and ACCP-negative disease variants.

Obesity and mental stress, which can increase risk for OA and ACCP-negative RA, but not ACCP-positive RA risk, also have proinflammatory potential [167]. Another trigger of OA and ACCP-negative, but not ACCP-positive RA is physical activity, which may impact the diseases via repetitive joint tissue microtrauma and concomitant inflammation. The scheme of the greater importance of non-specific proinflammatory triggers of OA and ACCP-negative, but not ACCP-positive RA, contradicts the links between smoking, which provokes ACCP-positive RA, but possibly has a protective effect in ACCP-negative cases and OA, and alcohol consumption, which reduces the risk of developing ACCP-positive RA and provokes ACCP-negative cases and OA. The provoking effect of smoking in ACCP-positive RA was expected given its well-known association with ACCP production [132,155,156]; however, its other known mechanisms are proinflammatory [167]. The protective effect of alcohol consumption on RA development is usually associated with its anti-inflammatory effect [167]. However, it is not clear why this effect occurs in ACCP-positive cases but not in ACCP-negative RA or OA.

Despite the obvious contradictions, possibly related to the lack of data analyzing the differences in the connections of triggers with ACCP-positive and ACCP-negative RA and OA, a certain trend is visible—the lists of triggers for OA and ACCP-negative OA are similar.

Adipose tissue was recognized to be an important player in OA pathogenesis. In addition to the obvious impact of obesity as a trigger for the development and progression of the disease, there are also less obvious connections. In particular, interesting data were obtained in experiments on mice with lipodystrophy, protected from spontaneous and posttraumatic OA even in the presence of known trigger factors—obesity, systemic inflammation, and high-fat diet [175]. Implantation of adipose tissue or fibroblast-derived adipocytes restored susceptibility of the mice to post-traumatic OA. Adipocytes produce a number of well-studied adipokine modulators of various processes in the body. They interact with sex hormones, interfere with immune processes and inflammation, and interact with chondrocytes (Table 1). These functions make them undoubted participants in the pathogenesis of OA and RA.

In terms of OA and RA pathogenesis, and of the various functions of adipokines, their pro/anti-inflammatory potential and effect on cartilage are of interest. When analyzing the influence on various immune processes, adipokines are very conditionally divided into predominantly proinflammatory (adipsin, leptin, resistin, visfatin, chemerin), with those discussed above obviously promoting both RA and OA progression; anti-inflammatory (apelin, vaspin); and multidirectional (adiponectin, omentin). All the analyzed adipokines with proinflammatory effects as well as adiponectin promoted ECM degradation via various mechanisms. Anti-inflammatory apelin demonstrated a multidirectional yet mainly catabolic effect—stimulated chondrocyte proliferation, yet increased expression of MMP and IL-1beta and decreased collagen II level. Omentin and vaspin contributed to the replenishment of cartilage tissue or, at least, prevented its degradation.

Due to their participation in modulation of inflammation and cartilage processes, adpokines play a significant role in the both RA and OA pathogenesis. Promoting cartilage degradation, blood and synovial fluid proinflammatory adipokines and multidirectional adiponectin were increased and correlated with RA activity and OA progression. Oppositely acting vaspin and omentin were decreased in blood and synovial fluid and inversely correlated with RA activity and OA progression.

Recognized as an anti-inflammatory adipokine, apelin, again, does not fit into these patterns. Although its level was reduced in RA, it promoted neoangiogenesis, being a

major component of joint damage. In OA, increased apelin levels were demonstrated due to the joint damage progression via the same mechanism, neoangiogenesis promotion.

Adipokines undoubtedly are the major players in obesity, play role in aging, and interplay with sex hormones, and so, participate in the implementation of the trigger role gender and gender-associated risk factors (Table 1). So, they might be involved in implementation of OA and RA triggers. Proinflammatory adipokine levels were directly associated with weight gain, while the link of adiponectin and omentin with BMI was inverse. Contrary to expectations, levels of anti-inflammatory adipokines also increased with weight increasing, possibly regardless of their impact on the inflammatory process. Despite the ambiguous patterns, adipokines are clearly powerful players in the pathogenesis of obesity and undoubtedly promote the implementation of the role of obesity in OA and RA provocation. Proinflammatory adipokine, adiponectin, and omentin expression was associated with aging or at least age-associated diseases. Anti-inflammatory vaspin demonstrated the same pattern, while apelin was inversely associated with age. So, the age-associated dynamic of proinflammatory adipokines and adiponectin is in good agreement with the role of age in the provocation of RA and OA and the relationship of these factors with the parameters of these diseases. The inverse association of apelin with age, its anti-inflammatory functions, and clear link with RA and OA are also in good agreement with each other. Omentin and vaspin expression in aging and their link with OA and RA parameters, at first glance, appear paradoxical. Perhaps this might be due to the change in tissue sensitivity to these factors (in particular, the age-dependent change in the expression of receptors to them).

Analysis of gender disparities of adipokine levels in connection with sex hormones led to ambiguous results. Leptin, adipsin, chemerin, and adiponectin levels in females were higher than that in males, and these findings agree with their role in OA and RA pathogenesis as well as with the fact that these diseases show a female bias. In addition, adiponectin, adipsin, leptin, and chemerin expressions were in direct connection with estrogen and inversely with testosterone levels. However, gender disparity links with sex hormones were not so straightforward. Omentin demonstrated an inverse correlation with gender dependence, which is consistent with its interference with OA and RA mechanisms, yet its levels were in direct correlation with estrogen. Apelin and visfatin were also in direct connection with estrogen and inversely with testosterone levels, yet no sexual dimorphism of these adipokines was revealed. The same patterns were demonstrated for resistin. On the contrary, vaspin levels were independent from estrogen and progesterone, yet they were higher in females vs. males.

The ambiguous picture of the connections of adipokines with sex differences, contradicting their impact to the parameters of "female" diseases of OA and RA, is likely to be due to the following reasons: (i) gender dependence of these diseases has a comprehensive nature—at least lifestyle, eating habits, and professional differences undoubtedly contribute to their provocation; (ii) as discussed above, sex hormones, regardless of their connection with adipokines, modulate immune reactions; (iii) interplay of adipokines and hormones and their interference in the mechanisms of development of the diseases under discussion might be of different value in OA and RA phenotypes.

Another important factor is that the polymorphisms of genes of some adipokines may affect to susceptibility to rheumatoid arthritis and osteoarthritis. It is worth noting that heterogeneity between the study's results was observed in the analysis (Table 2).

Discordant results are common among genetic studies on complex diseases. Possible explanations for controversial results include clinical heterogeneity, ethnic differences, real genetic heterogeneity, and small sample sizes. Geographical regions may be the source of heterogeneity in studies of polymorphisms of adipokines and RA/OA susceptibility.

Table 1. Adipokines role in RA and OA.

Adipokine	Immune Functions	Cartilage	Estrogens/ Testosterone	Female/ Male	Age	Lean/Obese	RA	OA
Adiponectin	Multidirectional [176]	Promoted aggrecan degradation [177]	⇑/⇓ [178–180]	f > m [178–181]	⇑ 66–80 years vs. 51–65 years = 36–50 years [182]	⇓/⇑ [183] ⇑/⇓ [184,185]	⇑ CRP and ESR [186–188]	⇑ cartilage damage [177,189]
Omentin	Multidirectional (⇑ IL-4, ⇑ IL-1β) [190]	Blocks cartilage degradation, bone erosion, chondrocyte senescence via suppressing the proinflammatory cytokines [191,192]	⇑/? [193]	f < m [194]	⇑ [195]	⇑/⇓ [190,196,197]	⇓ MMP-3 levels, RA activity CDAI, ESR [198]	⇓ in synovia [199] ⇓ OA progression [191]
Apelin	Anti-inflammatory [200,201]	In total catabolic: stimulated chondrocyte proliferation, yet increased expression of MMP and IL-1beta and decreased collagen II level [202]	⇑/⇓ apelin and APJ expression are up-regulated by estrogen [203] Inverse association with testosterone levels [204]	No sexual dimorphism [205]	⇓ apelin and its receptor (APJ) expression [206,207]	⇑/⇓ No difference [183] ⇓/⇑ [208,209]	⇓ [210] Promotes neoangio-genesis [211]	⇑ progression via stimulation of neoangio-genesis [212]
Vaspin	Anti-inflammatory [213]	Promoted differentiation and chondrocyte survival, and ECM formation [214]	No association [215]	f > m [216,217]	⇑ [182]	⇓/⇑ [217]	⇓ eRA activity (DAS28), ESR, CRP levels [218]	⇓ in serum ⇑ in synovia [219]
Adipsin	Proinflammatory [190]	Promoted cartilage volume loss [220]	⇑/? expression of adipsin gene [221]	f > m [222]	⇑ [223,224]	⇓/⇑ [223]	⇑ clinical activity in early RA [225]	⇑ +OA progression [220]
Leptin	Proinflammatory [190]	Promoted chondrocyte apoptosis [226], degradation ECM [227], cartilage volume loss [228]	⇑/⇓ [193,229,230]	f > m [180,231–233]	⇑ In male ? In female leptin resistance due to reduced expression of leptin receptor [234]	⇓/⇑ [185,190,235]	⇑ [186,187] Direct link with CRP levels [188]	⇑ [193] Prediction of early-onset post-traumatic OA [236]
Resistin	Proinflammatory [190]	Promoted proteoglycan loss due to inhibition of proteoglycan synthesis in chondrocytes [237,238]	⇑/⇓ [215,239]	f < m [240] f = m [241]	Associated with combination of age-related comorbidities but not with age itself [242,243]	⇓/⇑ [190,244]	⇑ [186] Direct link with CRP levels [188]	⇑ [193,245] Prediction of early-onset post-traumatic OA [236]

Table 1. *Cont.*

Adipokine	Immune Functions	Cartilage	Estrogens/ Testosterone	Female/ Male	Age	Lean/Obese	RA	OA
Visfatin	Proinflammatory [190]	Promoted collagen II and aggrecan degradation [246]	⇑/⇑ [247,248]	f = m [249,250]	⇑ In female [250]	⇓/⇑ [190,251]	⇑ Direct link with DAS28 and CRP [187,252]	⇑ [193] Direct link joint damage [246] Prediction of early-onset post-traumatic OA [236]
Chemerin	Proinflammatory [190]	ECM degradation due to stimulation of pro-catabolic cytokine and metalloproteinase production [253]	⇑/? [193,254]	f > m [254] f < m [255] f = m [256]	⇑ [257]	⇓/⇑ [190,235,258]	⇑ Direct link with DAS28, ESR, CRP [259]	⇑ [193,245] Prediction of early-onset post-traumatic OA [236]

⇑—under the influence of the factor, the adipokine level decreased; ⇓—under the influence of the factor, the adipokine level increased; ?—no data.

Table 2. The influence of polymorphisms of some adipokines genes on susceptibility to RA/OA.

	RA	OA
Adiponectin	Polymorphisms rs266729, rs2241766, rs2082940, and rs1063539 in the adiponectin gene—no association with RA. Adiponectin gene rs1063539 locus was possibly associated with anti-CCP in RA female patients [260]. No significant genetic correlation between adiponectin levels and RA [261].	The ADIPOQ gene rs1501299 (+276G/T) polymorphism was not associated with KOA severity or vulnerability [262]. Polymorphisms +45T/G and +276G/T of the ADIPOQ gene might not be responsible for OA susceptibility among Thais [263]. The SNP rs182052 in the ADIPOQ gene may potentially modify individual susceptibility to knee OA in the Chinese population [264]. Associations may exist between ADIPOQ rs2241766 and knee OA in Asians' DOI [265]. The ADIPOQ gene rs1501299 polymorphism intensifies the risk of knee OA in this Chinese Han population [266].
Omentin	Revealed the association between omentin rs2274907 and RA susceptibility [267].	The Val109Asp polymorphism of the omentin-1 gene may not be the primary pathogenic factor of KOA in Chinese individuals. The Val/Val genotype can be regarded as a potential biomarker for the risk of KOA progression [268]. ITLN1 (intelectin-1, also known as omentin) polymorphism rs2274908 was related to KOA risk in the Han population [269].
Leptin	Leptin gene (rs10244329, rs2071045, and rs2167270) polymorphisms are not associated with RA genetic susceptibility and its clinical features in the Chinese population [270].	In normal weight and overweight Han Chinese individuals, LEP polymorphisms (three SNPs of leptin—rs11761556, rs12706832, rs2071045) were associated with knee OA [271].

Table 2. *Cont.*

	RA	OA
Resistin	There were no significant differences for the distribution of allele and genotype frequencies of three resistin SNPs (rs1862513, rs3745368, and rs3745367) between RA patients and normal controls (all $p > 0.05$). The genotype effects of dominant and recessive models were also analyzed, and no significant association was detected (all $p > 0.05$). Haplotype analysis suggested that the frequency of haplotype GAA was notably lower in RA patients in comparison with normal controls. Thus, resistin gene polymorphisms might affect the genetic predisposition of RA in the Chinese population [272]. C allele of the resistin SNP rs7408174 as well as those with the AG allele or who had at least one A allele of the SNP rs3219175 are at greater risk of developing RA disease compared with wild-type carriers [273].	Weak associations between resistin genes and hand OA in Finnish women, and that the associations are modified by BMI [274]. Resistin −420/+299 alleles haplotype analysis demonstrated that mutant alleles were more prevalent in knee OA-affected individuals compared to healthy subjects ($p < 0.05$) in Pakistani population [275]. SNP rs3745368 from resistin was identified as being related to an increased risk of HOA [276].
Visfatin	X	SNP rs4730153 was significantly associated with decreased risk of OA in an additive genetic model ($p < 0.05$), while rs16872158 showed an increased risk of developing OA ($p < 0.05$) in the Chinese population [277]. Limited data revealed that associations may exist between visfatin rs4730153 and knee OA in Asians, and between visfatin rs16872158 and knee OA in Asians [265].
Chemerin	Chemerin rs17173608 polymorphism were associated with increased susceptibility to RA [267].	X
Apelin	No association between apelin rs2235306 and RA [267].	X

X—no data.

5. Comparison of Pathogenesis of ACCP-Positive and ACCP-Negative RA and OA Through the Prism of Joint Tissue Processes

5.1. ACCP-Positive RA: Initial Processes

ACCP-positive RA is a classical 'antigen-driven' pathology [278]. The cornerstone of its development is cyclic citrullinated peptide (CCP) interaction with the immune system. Initially, CCP portions appear in inflamed oral, lung, and presumably gut mucosa at preclinical stages [279,280]. Presentation of these neo-epitopes by antigen-presenting cells in secondary lymphoid organs, being a common non-specific event, becomes critical in persons at risk of ACCP-positive RA due to a well-known interplay of CCP with T-cell receptors in SE carriers, supported by a vast number of gene SNPs, involved in the shaping selection, maturation, and functioning of T and B cells [281]. Perinatal epigenetic events might also play a role. At least in utero nicotine exposure increased the risk of ACCP-positive RA but not in ACCP-negative cases [137].

The next step in RA promotion is associated with ACCP and specific lymphocyte clones. Studies at the preclinical stage demonstrated that specific CD3+ T lymphocytes with highly proliferative, tissue-invasive, and proinflammatory effector cells non-stochastically migrate into synovia, instead of leading to relatively quiescent memory T cells; ACCP stochastic migration also takes place [282]. A subsequent trigger might lead to synovia infiltration by oligoclonal B cells, together with macrophages, developing a local germinal center (GC), and accumulation of other B-lymphocyte subsets, attracted to synovia by unknown mechanisms [283,284].

Notably, at the preclinical stage, ACCP and lymphocyte oligoclones are found in synovia with no signs of inflammatory processes and vascular bed foreign cell infiltration [282]. These processes develop as a consequence of the ACCP and lymphocyte impact on joint tissues. ACCP deposited in joint tissues may activate osteoclast precursors expressing citrullinating enzymes and surface CCPs [285], due to bone loss and joint pain [286–288]. Infiltrating oligoclonal T and B lymphocytes produced proinflammatory factors that become drivers of synovial inflammation [289].

5.2. ACCP-Negative RA: Initial Processes

According to Pratt's model [278], the key node of ACCP-negative RA pathogenesis is dysregulation of CD4+lymphocytes due to SNPs in a number of genes mainly *ANKRD55* and *STAT4*, genes of components of the IL6 signaling pathway strongly associated specifically with this phenotype. Due to the proinflammatory skewing of immune reactions, any non-specific events provoke local inflammation. Unlike ACCP-positive RA, in ACCP-negative cases, a wide range of non-specific cytokine-activated T lymphocytes of various antigen specificity attracted to synovia was demonstrated [290]. In addition to wide T-cell clone numbers, another remarkable peculiarity of synovial processes in ACCP-negative RA is an increased number of dysfunctional cells with lower cytotoxic gene expression and increased expression of exhausted genes [291], and lower antigen processing and presentation activity in synovial B cells than that in the ACCP-positive variant [292–294].

Proinflammatory cytokines, predominantly of macrophage origin, with differences in biologic efficiency suggest a greater proportion of myeloid pauci-immune patterns in ACCP-negative synovia vs. lympho-myeloid pattern in ACCP-positive cases [295].

Early-stage ACCP-negative RA demonstrates a greater contribution of innate immune mechanisms [295,296], namely pathogen-associated molecular patterns (PAMPs), TLRs, Nod-like receptors, inflammasomes, complement system, monocytes/macrophages, granulocytes, natural killers, and dendritic cells [297].

Of fundamental importance is that, unlike ACCP-positive RA, ACCP-negative cases start as an immune response to a synovial injury with subsequent inflammation, due to exposure to non-specific factors (trauma, infection) [295].

5.3. OA: Initial Processes

Initial events are cartilage damage, decrease in chondrocyte functional activity, and a shift from anabolic to catabolic processes in cartilage tissue due to external influences, namely joint injury or joint tissue microtrauma with repeated loads or overweight, hormonal imbalance, accidental entry fragments, and products of commensal bacteria translocated from mucous membranes to joint tissues with inflammatory focus formation or other triggers of aseptic inflammation [298–301]. Gene SNPs of the factors involved in ECM formation [15,302] may aggravate these events.

Inflammation may be a trigger factor for functional asthenia of chondrocytes, or it may conjoin later due to proinflammatory factors produced by these cells in unfavorable conditions [303]. At the early stage with minimal radiographic signs of cartilage damage, synovia is involved with signs of ongoing inflammatory and fibrotic processes and perhaps autoimmune reactions—mononuclear infiltrates, diffuse fibrosis, lining layer thickening, macrophage appearance, and neoangiogenesis [304–306]. Intensive exchange of proinflammatory signals between degrading chondrocytes and activated synovial cells creates a vicious cycle. Crosstalk between chondrocytes, synoviocytes, osteocytes, osteoblasts, osteoclasts, and endotheliocytes is due to early-stage subchondral bone loss and late-stage bone sclerosis, subchondral bone cysts, bone marrow oedema-like lesions, and osteophyte formation [307,308].

So, despite the obvious dissimilarities of the starting points, chondrocytes and cartilage in OA and synovia in RA, there are some similarities in initial processes in OA and ACCP-negative RA.

6. ACCP-Positive and ACCP-Negative RA in Full Swing

Regardless of the characteristics of the initial stages of synovitis development in ACCP-positive and ACCP-negative variants of RA, further events develop in many respects in the same way. The process includes recruitment from the vascular bed and local M1 macrophages and synovial fibroblasts undergoing de-differentiation in response to activating stimuli, mainly originating from tissue-invasive T cells undergoing pyroptosis [309]. Other major players of synovitis development and perpetuation are recruited by cytokines, blood granulocytes, and macrophage. Granulocytes form neutrophil extracellular traps (NETs) [310–312], and together with synovial macrophages, endotheliocytes, and fibroblasts, release a bulk of toxic proinflammatory agonists into the surroundings, synergistically destroying synovial cells, cartilage, and bone [313–316].

The well-known feature of RA synovia is the presence of ectopic lymphoid structures (germinal centers), resembling secondary lymphoid organs with plasma cells, macrophages, B- and T-lymphocyte compartments, follicular T helpers, lymphatic vessels, and high endothelial venules [317,318]. It is important to note that these tertiary lymphoid tissues are not specific for RA, but develop in non-lymphoid tissues in response to chronic inflammation. The cells of lymphoid aggregates produce cytokines and adhesion molecules locally in the joint tissues with a subsequent increase in peripheral blood [318–320]. Germinal center cells might produce autoantibodies. The ongoing somatic hypermutation and class-switch recombination of Ig genes and ACCP production by germinal center lymphocytes has been demonstrated [321,322]. B cells differentiated within synovial ectopic lymphoid structures target deiminated proteins that could be generated during NETosis [323,324]. RF production in synovial germinal centers was also assumed [325]. However, these results

are contradictory with the fact that the presence of lymphoid aggregates is associated with the inflammation intensity, but not with the ACCP-positive RA phenotype [326–328].

It should be specified that lymphoid neogenesis was demonstrated in RA in no more than 30–50% of synovial samples and the presence of follicular dendritic cells as an attribute of a germinal center in less than 10% of RA biopsies [318,329].

RA synovia has some features of a local neoplastic process, such as significantly expressed angiogenesis and aggressive expansion of dedifferentiated fibroblasts with abnormal overexpression of embryonic genes (wnt5A as an example [330]). The leading role in pannus formation is played by fibroblasts with the participation of synovial macrophages. Fibroblasts are effectors of cartilage and bone destruction due to unique invasive abilities, the production of large numbers of matrix-degrading enzymes, and resistance to apoptosis. RA is characterized by an increase in the amount of antiapoptotic proteins, Bcl-2 and Mcl-1, SUMO1, FLIP, as well as by somatic mutation of the p53 protein gene, which probably contributes to the inhibition of synoviocyte apoptosis [331–333].

Another well-known feature of both ACCP-positive and ACCP-negative RA variants is development of secondary OA due to the negative impact of inflammation on chondrocytes, osteoblasts, and fibroblasts [305,334–336]. OA incidence in a Russian cohort of 620 RA patients was 70%, whereas in the non-RA population, it was 21% [4,337]. The main risk factors for OA progression in RA patients were high RA activity (DAS28), RA experience for more than 10 years, age more of than 45 years, BMI of more than 25 kg/m^2, and glucocorticosteroid intra-articular injection 6 months or more before the study [4].

Despite the convergence of pathoimmunological mechanisms, some differences are revealed in ACCP-positive and ACCP-negative RA advanced stages. Synovial tissue from ACCP-positive patients had a higher number of infiltrating lymphocytes, less extensive fibrosis, and a thinner synovial lining layer compared with synovial tissue from ACCP-negative patients [338]. The samples of ACCP-negative patients showed an increased extent of fibrosis and a thicker synovial lining layer. These specific features of ACCP-positive and -negative RA synovitis were the same in the 31 synovial samples of the same patients obtained 3–4 years earlier (including those obtained at an early disease stage). The authors also noted that samples of ACCP-positive patients were more likely to have germinal centers, although there were no significant differences in this indicator, probably due to the small number of samples. It should be specified that attempts to link the presence of lymphocytic infiltrates with ACCP-positive RA yielded conflicting results. On the one hand, it was demonstrated that synovial tissues with lymphocyte aggregates contained significantly elevated RF-IgM and anti-CCP IgG compared to tissues with diffuse lymphoid infiltration [322]. On the other hand, it was revealed that lymphoid neogenesis was linked to a higher RA activity but not with the ACCP or RF phenotype [318]. ACCP-positive RA is likely linked with the more pronounced secondary OA progression, assessed using the Kellgren/Lawrence scale or serum levels of cartilage oligomeric matrix protein and other markers of cartilage turnover [338,339]. The pronounced cartilage degradation due to the inhibitory effect of ACCP on collagen IIA formation was assumed [339]. However, according to some data, cartilage degradation can be caused not only by the presence of ACCP, but also by high RA activity [5,339].

Regardless of the presence or absence of ACCP, the study of synovial biopsy specimens reveals a variety of synovitis variants. Histologic, cellular, and gene expression analyses revealed the following synovial ‘pathotypes’—lymphoid with diffuse or follicular lymphoid infiltrates and germinal centers, myeloid with less abundant lymphoid aggregates, and presence of macrophages, pauci-immune (‘low inflammatory’) pathotype with minimal infiltrating immune cells, and fibroid variants with hyperplastic processes in the absence of lymphoid aggregates and with minimal lymphoid infiltration [294,340].

It is noteworthy that the drivers of fibroid pathotype—highly activated fibroblast-like synoviocytes—are involved in pannus formation and cartilage and bone destruction [341]. Gene expression analysis in the RA joint tissues of patients undergoing total joint replacement surgery allowed van der Pouw Kraan et al. [342] to identify the following vastly different pathotypes—first group with a high inflammatory gene expression signature, including those indicating the specific activity of B and T cells, genes of cytokine receptors, cytokine/stat-activation pathway factors, HLA class II-encoding genes, and other IFNg-induced genes, a number of genes that are required for lymph node development. Upon further analysis, this group split into subgroup A, with high expression of immunoglobulin genes and genes involved in the adaptive immune response, and another one (B) with the signs of activation of the classical pathway of complement activation and high expression of genes involved in the production and degradation of extracellular matrix components. The second group included the samples with a lower expression of genes involved in inflammation and complement activation but with higher expression of genes indicative for fibroblast dedifferentiation, as well as collagen genes, with type II and XI collagen most exclusively in the RA. In the samples of both the second group and first (B) subgroup, tissues expressed genes that are involved in tissue remodeling. The association of the samples with ACCP-positive or -negative RA phenotypes was not analyzed.

7. OA in Full Swing

Despite the initial fundamentally different origins of RA and OA, a significant number of studies have demonstrated data suggesting possible shared mechanisms in the pathogenesis of these diseases [343,344].

In the discordance of data, caused in particular by differences in approaches to the formation of cohorts and the selection of research methods, some probable patterns emerge.

First, the well-known RA hallmark of citrullinated peptides and ACCP turned out to be not strictly specific. The citrullinated peptides (epitopes) of proteoglycan aggrecan were found in normal articular cartilage and were the target for ACCP [345]. In early OA patients, plasma citrullinated protein levels detected by spectrometric methods was five times higher than those in healthy controls and even higher than those in early RA (eRA) serum (4-fold increase), and unlike eRA patients, persons with early OA were ACCP-negative in this cohort [346]. However, it seems that as OA progresses, autoABs of post-translationally modified proteins are revealed, though less often than in RA. Xie and coauthors (2021) obtained serum ACCP in 5.9% of advanced OA patients (70%—in advanced (a)RA); antibodies against carbamylated peptides (aCarp), in as many as 18% of patients (47.8—in aRA); RF in 5.9% in the OA group (63.1—in aRA); and in synovial fluid, ACCP in 45.9% (71.4 in RA) and aCarp in 1.9% in OA (23.8% in RA), both cohorts consisting of patients with reliable diagnoses [347]. Unfortunately, there are very few publications on this issue, and we failed to find publications with results comparing the frequency of ACCP antibodies in the early and advanced stages of OA within the same study. We can assume several options for the relationship between OA and ACCP: (1) these antibodies are exclusively sanitary with the function of removing modified proteins; (2) involvement of adaptive immunity in the progression of OA leads to transformation into an autoimmune response; (3) and, less likely, despite the compliance of the cases included in the study with the diagnostic criteria for OA, the presence of ACCP is due to a combination with mild and unrecognized RA.

Second, both innate and adaptive immune systems were found to be involved in OA pathogenesis. It seems that, as the disease progresses, the predominance of innate immune responses is replaced by adaptive ones, although both are present at all stages of OA.

The current model of OA development assumes the following logic of events—local damage to the articular cartilage leads to appearance of danger-associated molecular pat-

terns (DAMPs), due to macrophage activation and production of proinflammatory cytokine and chemokines, which in turn attract a new recruitment of macrophages as well as lymphocytes to the joint. A rampage of proinflammatory cytokines and chemokines also leads to an increase in angiogenesis, chondrocyte dysregulation, and release of metalloproteinases. In a vicious cycle of these events, the release of more proinflammatory cytokines and prostaglandins induces more cartilage destruction [348,349]. Inflammatory cell infiltrate with CD68 and CD4+ cells, neoangiogenesis, and expression of proinflammatory cytokines were demonstrated in synovial tissue samples of patients with knee pain, normal radiographs, and cartilage destruction revealed at arthroscopy at the very-early OA stage, and were significantly less pronounced in late OA synovial samples [336]. In another study, when comparing synovial biopsies obtained from patients with different OA experiences, it was found that, in the samples of early OA patients (knee pain for at least one year, no Xray OA), there were signs of thickening of the lining layer, proliferation of the lining cells, and mononuclear infiltration principally with macrophages present especially in areas of chondral defects, while in late OA samples, the thickening of the lining layer and proliferation of lining cells were not necessarily localized to areas of chondral defects and tended to be diffuse, and lymphoid cell infiltrates near newly formed vessels instead of macrophage infiltration was found [304]. Proinflammatory cytokines TNF alpha, IL1 beta, and IL6 were found in both early and late OA synovia using various methods, though there are discrepancies in the results of comparing the expression of these cytokines at an early and late stage of the disease [350,351]. Increased levels of IL-6 and TNF alpha and their association with cartilage loss were demonstrated in OA sera [352,353]. According to Barker et al. (2014), TNF-α levels were higher in early OA compared to late OA patients [354].

In the study of both early and late OA synovial samples, attributes of activation of the innate mechanisms of inflammation were found—the expression of pattern recognition receptors, matrix metalloproteinases (MMP), and Nod-like receptor pyrin domain 3 (NLRP3) inflammasomes, creating vicious cycles with pro-inflammatory cytokines [355–361]. It is noteworthy that, for example, when comparing RA and OA synovial samples, no differences were found in the expression of TLR 1 and 4 and adapters (domain-containing adapter protein MyD88 adapter-like, and TIR domain-containing adapter-inducing interferon/TIR-containing adapter molecule-1 adapters) predominantly in myeloid and plasmacytoid dendritic cells, and, to a lesser extent, in CD68+ type A lining cells/macrophages [356]. Noteworthily, when looking for matches of RA and OA pathogenesis, OA-associated gene SNPs of some innate immunity factors were revealed—of TNF α-308G/A gene related to excessive TNF α levels in synovia and individual susceptibility to and severity of early-onset knee OA in Egyptian females [362,363]; several SNPs of IL1 gene clusters, associated with erosive interphalangeal as well as with severe hip and knee OA [364–366]; several SNPs of IL6 gene, associated with radiographic hand osteoarthritis [367]; SNPs of several MMP genes associated with knee OA risk [368]; SNPs of various PRRs related with increased OA risk [61,369–372]; and excessive TLR expression in OA articular chondrocytes [60].

Other innate immunity players presented in both early and late OA synovia in significant numbers are CD8+ natural killers (nearly 30% of the CD45+ mononuclear cell infiltrate in late OA synovia) [373]. Yet the functional status of these cells was demonstrated to be different in early and late stages. In early OA samples, the cells with pro-inflammatory IFN-γ and IL-17A-producing phenotype dominated, while in late OA samples, a significant increase in CD8+IL4+ was revealed, with the phenotype consistent with postactivation exhaustion [373,374]. Other researchers revealed that the expression of perforin and granzyme B in late OA cells (CD56brightCD16(−) cells) was low and correlated with a poor cytotoxic potential against K562-sensitive target cells [375]. This is the difference between NKs in OA and highly aggressive cells in much greater numbers infiltrating RA synovia [376,377].

Lymphoid nodular aggregates are a sign that brings together synovial lesions in OA and RA. They seem to be more characteristic of late RA, in which they were found in 30% of samples (up to 65% of samples with severe disease) [378,379], while in early OA synovial specimens, they were rare or absent [350]. According to some researchers, the histological features of the most severe inflamed late OA synovial samples were identical to those found in the synovia of RA patients [378]. In particular, lymphocytic nodular aggregates, distributed around blood vessels (as in RA) according to some features, were similar to those in RA synovia [380].

Krenn and coauthors (1999) described an inflammatory infiltration of OA synovia as aggregates of cells either as small perivascular lymphoid clusters with plasma cells surrounding the lymphocytes or as small groups of plasma cells, located in the vicinity of small blood vessels [381]. Immunohistochemical analysis demonstrated CD20+ B and CD4+ and CD8+ T lymphocytes in the cluster center, surrounded by IgG (predominantly) or IgA and IgM plasma cells. The absence of proliferating Ki-67-positive cells and follicular dendritic cells in these clusters indicated that they were not ectopic germinal centers—a hallmark of RA synovia [283]. The absence of germinal centers in OA synovia was confirmed by several researchers [378].

On the other hand, full-fledged ectopic germinal centers were found not in all, but in 10–23% of RA synovia samples with a high inflammatory grade [326,382,383]. Analysis of OA B-cell V(H) gene repertoire sequence demonstrated a high number of somatic mutations and high ratios of replacement to silent mutations of synovial B lymphocytes. Additionally, V(H) gene repertoire was mismatched in synovial and blood B cells. Based on these results, Krenn and coauthors assumed that the cells underwent germinal center reactions at different sites [381]. So, according to the authors, OA memory B cells underwent germinal center reaction at different sites and migrated into the synovial tissue with subsequent differentiation into plasma cells but without further V gene diversification (accumulative type—probably a single one typical for OA). Unlike OA, the V(H) gene repertoire sequence analysis of RA synovial germinal centers and blood B cells demonstrated both accumulative and maturative (immigration of naïve B lymphocytes into synovial tissue, a local proliferation and somatic mutation of V genes in germinal centers) patterns of B-cell activation [283]. Apparently, RA is characterized by local production of autoantibodies in the synovium, in particular, of RF and antibodies to a number of organ-specific antigens; as for OA, this issue needs further investigation [283].

The most abundant cell population in OA synovial infiltrates (after macrophages—65% of the immune cells) are T lymphocytes—up 22% of the infiltrate [379]. It should be noted that T-cell infiltration was found not only in late OA synovial samples, but in early OA ones as well [384]. CD3+ cells were found to be CD4+ helpers, expressing memory/activity markers—CD28; or complex CD45RO, HLA-DR, and CD69; or complex CD69, CD25, HLA class II, CD38, CD43, and CD45RO [48,376,380]; and remarkable Th1 marker expression (CXCR3+, CCR5+) [385] and proinflammatory cytokines and their receptors [384,386]. Synovial CCR5+ and CCR3+ CD3+CD4+CD8-Th1 cell infiltration was associated with knee OA severity [385].

The comparison of the profiles of T-lymphocyte late OA and RA of the synovium led a number of researchers to the conclusion that the difference between CD4 T cells infiltrating synovia was not qualitative, but a quantitative aspect [48] with a similar distribution in synovia, but a smaller number of infiltrating CD4+ cells in OA [386].

In particular, CD+3 T cells in late OA lymphocytic nodular aggregates were stained for the activation antigens (CD69, CD25, HLA class II, CD38, CD43, and CD45RO); according to some researchers, they were localized around blood vessels as in RA, and in some instances, were indistinguishable from those found in RA, though in OA, the number of

these cells and expression of activation molecules were expressed to a lesser extent than in RA synovia [380].

Most of the T cells in OA synovial aggregates are T-helper/inducer cells, whereas cytotoxic/suppressor T cells located in the periphery were found sparsely, unlike RA, in which these cells are in abundance and extremely aggressive [387]. Nevertheless, both OA and RA blood T-cell responses were induced by cartilage proteoglycan aggrecan epitopes—amino acid regions 16–39 and 263–282 [388]. Autologous chondrocytes as a whole were also shown to serve as targets for OA blood T lymphocytes, and this effect was partially blocked by antibodies against HLA class I, class II, CD4, or CD8 [389].

Another subpopulation of T cells presented both in OA and RA synovial infiltrate are Treg. The results of testing their number and activation profiles are contradictory, as well as the role of these cells in OA pathogenesis, which might be due to the cohort peculiarities [48,385,390]. Some publications point out that only minor differences were found in this subpopulation in RA and OA synovial infiltrates [391].

It is curious that few and conflicting data indicated the possible involvement of follicular helper T cells, inducing B cells to produce immunoglobulins in lymph nodes in OA pathogenesis [392]. Increased numbers of these cells and their production of IL21 in blood and synovia were found to be due to RA progression [393–395]. In a single publication, it was specified that Tfh cells ((CD4(+)CXCR5(+)ICOS(+)T cells)) found in RA synovia samples were absent in those of OA patients [393]. However, in this publication, a single synovia sample of a patient with unknown OA parameters and two RA samples were studied. At that time, Shan et al. (2017) demonstrated increased numbers of CXCR5+CD4+ cells, PD 1+CXCR5+CD4+, ICOS+CXCR5+CD4+, and IL 21+CXCR5+CD4+ blood T cells and increased serum IL-21 levels in 40 newly diagnosed OA patients (Kellgren and Lawrence grades II–IV) compared to healthy controls [396].

Third. It is well known that RA synovia has some features of a local neoplastic process, such as significantly expressed angiogenesis and aggressive expansion of dedifferentiated fibroblasts with abnormal overexpression of embryonic genes (wnt5A as an example [330]). The leading role in pannus formation is played by fibroblasts with the participation of synovial macrophages. Fibroblasts are effectors of cartilage and bone destruction due to unique invasive abilities, with production of large amounts of matrix-degrading enzymes and resistance to apoptosis. RA is characterized by an increase in the amount of antiapoptotic proteins, Bcl-2 and Mcl-1, SUMO1, FLIP, as well as by somatic mutation of the p53 protein gene, which probably contributes to the inhibition of synovicyte apoptosis [331–333,397].

However, pannuses did not appear to be a unique RA feature; in particular, they are a common finding in OA articular tissues, though with a lesser degree of fibroblast hyperplasia, fibrosis, and lymphocyte infiltration and a significantly lower rate of plasma cell infiltration and a milder vascular proliferation than that in RA pannus [398]. The authors of the cited publication stated pannus in OA synovia under microscopic examination was indistinguishable from that in RA.

Shibakawa et al. [399] revealed pannus-like tissue of vascular fibrous types in 90% of 15 late OA knee and hip synovia. Immunostaining revealed a predominant number of IL-1beta and MMP3 and few CD68-positive cells. The same pannus types, and additionally, with similar qualitative metabolic characteristics and pro-inflammatory cytokine response (IL-1beta, IL-8, IL-10, IL-12, TNF-alpha, IFN-gamma determined in supernatants of tissue cultures and COMP, type II collagen, TNF-alpha, IL-10, and Ki-67 expression detected by immunohistochemistry), were described by Furuzawa-Carballeda et al. in synovial samples of late OA and RA obtained during arthroplasty [400]. With a pronounced similarity of pannus in these diseases, there was a difference that was quite natural from the point of view of their pathogenesis—OA cartilage, synovial tissue, and pannus had

a lower production of proteoglycans, type II collagen, and IL-1beta. The hallmark of RA pannus—neovascularization studied by testing of vascular endothelial growth factor Ets 1—was less expressed in OA samples vs. RA ones [401]. Another endothelial growth factor—VEGF—was also expressed both in RA and to a lesser extent in OA synovial samples [402]. Another important sign of pannus expression of antiapoptotic and prooncogenic factors demonstrated both in RA and OA synovial samples—in particular, oncofetal glycosylated Fn in correlation with hyperplasia [403]; Ki-67 both in RA (26.6-fold vs. histologically normal synovium) and OA (3.9-fold) pannuses [404]; and metastasis-associated protein S100A4 in RA and OA synovial tissues, in contrast with normal synovium [405].

Studies of OA synovial biopsies reveal synovial lining hyperplasia, macrophage and lymphocytic infiltration, neoangiogenesis, and fibrosis detected in varying degrees in early and late OA, and often entirely indistinguishable from those in RA [16,406]. Given the initial mechanisms of OA development, it is not surprising that synovitis in OA occurred primarily in association with the zones of cartilage and bone lesion being due to the activation of proinflammatory factors and matrix metalloproteinases by detritus [406,407]. Oehler et al. identified the following synovial variants in early and late disease stages: hyperplastic (with synovial lining and villous hyperplasia as a single process), fibrotic (with activated fibroblasts as the major players), detritus-rich (with fragments of cartilage and bone), and inflammatory (diffuse or perivascular aggregated lymphocyte and plasma cell infiltration independent on detritus presence) [408].

OA, like RA, is a multifactorial disease and also probably has different phenotypes due to the peculiarities of pathogenesis with a greater or lesser contribution of genetic factors, with the peculiarities of maturation of chondrocytes in the perinatal period, with the influence of certain non-genetic factors (trauma, obesity, etc.). This potentially leaves an imprint on the histological features of OA synovia. In particular synovial lymphoid aggregates were demonstrated to be more typical for patients with a “mechanical” than for post-traumatic OA [16]. Also, inflammatory-like OA is close to a true inflammatory arthritis and OA with cartilage remodeling features [409].

8. The Efficiency of Conventional Synthetic and Biologic DMARDs in RA and OA

The analysis revealed a convergence of several of pathogenic mechanisms in RA and OA, including inflammation as a key driver of both diseases. It is natural to compare the efficiency of the widely used and largely effective RA therapy with conventional or biological disease-modifying antirheumatic drugs in these two diseases. The widely used methotrexate for RA and anti-inflammatory cytokine antibodies along were tried and analyzed for OA therapy [410].

Methotrexate and anti-inflammatory cytokine antibodies, widely used in RA and tried for OA therapy, were analyzed.

Erosive hand OA (EHOA) seemed to be an obvious target for MTX/Biologic therapy due to the striking similarities with RA—a greater contribution of inflammation to erosion progression compared to other OA phenotypes, pain syndrome, and functional disability comparable to that in RA. The results of few histological studies of biopsy material demonstrated pathological changes in the synovium indistinguishable from those in RA [411–415].

Transferring ideas from RA therapy to OA application, despite seemingly obvious premises, led to disappointing results. EULAR experts concluded that “Patients with hand OA should not be treated with conventional or biological disease-modifying antirheumatic drugs” (level of agreement 8.8 out of 10, grade of recommendation “A”) [416]. Without disputing such a professional conclusion, we tried to understand the reasons for the failures.

An analysis of publications on this issue revealed the following (Table 3).

Methotrexate or biologic DMARD therapy was carried out in cohorts of individuals resistant to standard OA therapy. In the most studies, the indicator of drug effectiveness was the impact on pain syndrome and functional disability in comparison with common OA therapy. Most studies were conducted in advanced OA cohorts.

Patients with severe pain syndrome and advanced stages of joint damage were selected for such an aggressive therapy. The reasons for the experimental immunosuppressive and anti-inflammatory DMARD therapy failure might be the following. In addition to the inflammatory process, well-known causes of pain and functional disability in advanced OA might be destruction of articular cartilage with exposure of subchondral bone and decreased ability of articular surfaces to withstand loads. This leads to increased pressure on the bone, bending of bone beams towards the spongy bone, and their microfractures. Of certain importance are fibrosis of the capsule with compression of nerve endings and the reaction of ligaments and tendons (secondary periarthritis), which manifests itself when they are stretched during movements in the affected joint [417]. So, it would be unlikely to expect any impact from the therapy being tested. Additionally, in such cases, a significant, perhaps the major, contribution to the pain syndrome is made by sensitization of the nervous system and cognitive mechanisms. Some authors distinguish such cases into a separate OA phenotype of "chronic pain" [418]. The argument in favor of this understanding of the situation is the efficiency of therapy with anti-NGF (nerve growth factor) antibodies [419,420]. It should be noted that similar mechanisms—sensitization of the nervous system and degeneration of articular tissues—were indicated as one of the causes of refractory RA as well [421].

Another endpoint evaluated in some clinical trials was the therapy impact on the number of swollen joints and/or ultrasound or MRI signs of synovitis (effusion, synovial hypertrophy) and progression of eroding in affected joints. Contrary to expectations, conflicting data were obtained on the impact of the therapy on these indicators.

Continuing the comparison of the two analyzed diseases, it should be noted that the efficiency of conventional or biological disease-modifying antirheumatic drugs was evaluated by their ability to suppress the inflammatory process. Undoubtedly, the contribution of powerful inflammation to the pain syndrome and functional insufficiency in RA is enormous compared to low-grade inflammation in OA. Undoubtedly, the contribution of powerful inflammation to the pain syndrome and functional disability in RA is enormous compared to low-grade inflammation in OA. Moreover, unlike OA, this is a systemic, pronounced process, the monitoring of which is carried out using a well-developed system of clinical and laboratory indicators. However, when the tools used in clinical trials to assess the anti-inflammatory effect in OA cohorts were applied to assess the effectiveness of RA therapy, it turned out that, in patients with clinical remission or significant reduction in RA activity under infliximab therapy, MRI signs of low-grade inflammation in the affected joints persisted [422,423].

A significant proportion of RA patients are non-responders to conventional or biological DMARD drugs. Predictors of non-responsiveness were RA duration, erosive process in the joints, and poor functional status. In a cohort of patients with 10 years of RA experience, the percentage of non-responders/poor responders to MTX was as much as 42.6% [424]. Moreover, the same dependence of the effectiveness of MTX therapy on the duration of symptoms in months was found in the eRA cohort [425]. In early seronegative RA cohort, the starting of conventional synthetic DMARDs within 3 months after the first joint swelling led to good/moderate EULAR response in 66% patients, while erosions and poor functional status were predictors of non-responsiveness [426].

The term "Difficult-to treat RA patient" (D2T) is used in the cases of non-responsiveness to biological therapy, being the second line after failed MTX therapy. As much as 40% of RA patients did not respond to biologic therapy [421]. The predictors of D2T appeared

to be the same—inadequately late start of MTX therapy, impaired physical function, and presence of erosions at baseline [427–431].

So, if the characteristic of non-responsiveness patterns in RA can be applied to OA, patients included in clinical trials had all chances of becoming non-responders to MTX and biologic therapy (Table 3). The exception is the cohort with inclusion of OA patients with a less pronounced erosive process in the joints (67% patients with knee OA with the Kellgren and Lawrence grade II). And incomplete but reliable effect of MTX on ultrasound signs of joint inflammation was demonstrated [432].

So, it might make sense to continue research into the efficacy of conventional or biological DMARD drugs in OA, by thoroughly rethinking the inclusion criteria for clinical trial cohorts and, what is an even more difficult problem, by selecting adequate tools to assess the effect of therapy.

Table 3. Application of conventional synthetic (methotrexate) and biologic DMARDs to the treatment of OA patients.

OA Phenotype	Efficacy
Methotrexate	
symptomatic, radiographic (Kellgren–Lawrence grades 3 to 4), painful inadequate response to current medication Knee OA, *n* = 207, 6 months, up to 25 mg [433]	⇓ pain, MS, ⇑ function
Knee OA, *n* = 160, 6 months, up to 25 mg radiograph (X-ray) tibiofemoral OA within the last 2 years, Kellgren–Lawrence grades 3 to 4 [11]	⇓ pain
Knee OA, *n* = 58, 4 months, 7.5 mg DS OA 2 years, Kellgren–Lawrence 2–3, synovitis [434]	no effect on pain, no difference in paracetamol consumption
Knee OA with insufficient pain relief from, or inability to tolerate, traditional analgesics including NSAIDs and opioids with synovitis, average duration 4 year, K/L score 1–4 (*n* = 20 II score 67%, *n* = 3 III score—10%), *n* = 24 weeks, up to 20 mg Erosions, 51.6; osteophytes, 68.9% [432]	13/30 (43%) achieved ≥30% reduction in pain VAS, 7 (23%) achieved ≥50% reduction, and 4 (13%) had worsened. All had synovitis (effusion or synovial hypertrophy 52 mm) at baseline and 25/30 demonstrated both pathologies. US at the final study visit (including three participants who withdrew after 12 weeks) demonstrated synovitis in 22 people. There was a median (IQR) reduction in total synovial thickness of 1.3 mm (0.7 to 3.8) (*n* = 26) and a median (IQR) reduction in total effusion measurement of 0.6 mm (1.3 to 3.6) (*n* = 26) ($p > 0.05$). Baseline synovitis or effusion (whether total values summated across the three knee compartments or maximum individual compartment scores) were not substantively correlated with baseline pain or change in 48-h pain VAS at 24 weeks ($r < 0.2$). Changes in synovitis and effusion at 24 weeks were similarly not substantively correlated with changes in pain.
Moderate to severe knee OA, Kellgren–Lawrence score of III to IV, *n* = 100, 6 months, 7.5 mg up to 15 mg [435]	reduced pain severity and improved functional status and quality of life
Clinical and radiographic knee OA, *n* = 155, 50% K-L grade 3–4, 12 months, 10 mg up to 25 mg [436]	⇓ pain (contradictory results) and stiffness, ⇑ function No change in synovial volume (MRI)
Knee OA with pain resistant to paracetamol, Kellgren–Lawrence II–III, *n* = 58, experience 2 years, 4 months, 7.5 mg [434]	no amelioration of symptoms functional status, tendency to reduce consumption of analgesics
Knee OA with effusion-synovitis, *n* = 215, Kellgren–Lawrence score II-22 (21%), III-39 (37%), IV-44 (42%), 52 weeks, up to 15 mg [437]	VAS pain and effusion-synovitis and maximal area, cartilage defects—no difference with placebo
Knee and hand OA, *n* = 465, 6 months, metanalysis [438]	reduced knee and hand stiffness at the end of follow-up knee and hand stiffness at 6 months of follow-up

Table 3. *Cont.*

OA Phenotype	Efficacy
Erosive hand OA, n = 64, 6 and 12 months, 10 mg [10] Verbruggen–Veys anatomical score [439] and Ghent University Score System (GUSS) scores [440]	Comparable effect of MTX and placebo on pain, functional disability, joint damage progression vs. placebo Joints with space loss appeared to be eroding less in the MTX group compared to the placebo group. Only serum IL-6 level and presence of synovitis at inclusion (but not pain, sex, age adipokines) were associated with a higher risk of erosive evolution in the non-erosive joints using the GUSS score at 12 months in the entire population.
Hand OA, n = 202, Kellgren and Lawrence grade $\geq$ 2 with synovitis, experience 6 years, 6 months, 20 mg [441]	moderate effect on reducing pain, but not function
Hand OA refractory to usual treatments [10]	
Erosive hand OA, 2 months, 10 mg [11]	decreased pain and morning stiffness, but not functional indices, number of tender and swollen joints
Biologics	
Tocilizumab anti-IL6 receptor	
Symptomatic hand OA with synovitis, Kellgren–Lawrence grade $\geq$ 2, experience 9 years, n = 104 [9]	no more effective than placebo for pain relief, number of painful and swollen joints, duration of morning stiffness, patients' and physicians' global assessment and function scores
Hip, knee, and hand OA (late in the most analyzed studies) Meta-analysis [13]	**Anti-TNFa**, n = 427, experience 6–14 (Anakinra, Adalimumab, Etanercept, Infliximab) no effect on pain and function
	Anti-IL-1, n = 404, experience (when specified) 5–11 years (AMG108, Canakinumab, ABT981, Lutikizumab) no effect on pain and function
	Anti-NGF (nerve growth factor), n = 1749, experience 3–7 (Tanezumab, Fulranumab, Fasinumab, AMG403) ⇓ pain; ⇑ function
Anti-IL-1	
Knee OA, n = 1240, Kellgren–Lawrence grades II–III (50/50%, when specified) meta-analysis [442]	superior to placebo in terms of pain relief and functional improvement (ABT981, AMG 108, Orthokine, ABT-981, Anakinra, Canakinumab, Diacerein)
Diacerein Knee OA n = 1277 meta-analysis [443]	pain and function—short-term residual effectiveness
Diacerein Knee OA n = 1732 meta-analysis [444]	⇓ pain
Diacerein Knee OA n = 1533 [445]	⇑ function
Diacerein knee and/or hip meta-analysis [446]	⇓ pain, ⇑ function, ⇑ escape medication use
TNF inhibitors	
Adalimumab	
Hand OA, n = 276, erosive inflammatory phenotype Meta-analysis (Etanercept, Adalimumab), n = 276 [447]	no effect on pain at 4–6 weeks and 24–26 weeks and on grip strength at 12 months reducing progression of structural outcomes (X-ray, ultrasonography, or MRI) in hand OA with of inflammation but not in those without inflammation at 12 months
hand OA refractory to analgesics, n = 85, 13 years [448] Kellgren–Lawrence grade and Verbruggen–Veys anatomical scores—progression was not analyzed in dynamic	no difference to placebo for pain decrease in the number of swollen joints adalimumab group

Table 3. *Cont.*

OA Phenotype	Efficacy
erosive hand OA with synovitis, n = 43, MRI-detected synovitis [449]	No effect pain, function, and stiffness subscales from baseline to 4, 8 and 12 weeks, no effect on MRI-detected synovitis and bone marrow lesions pain and inflammation are not responsive to TNF α inhibition
erosive hand OA (on radiology), n = 60, experience > 6 years [450] Verbruggen–Veys anatomical scores Exploration of potential risk factors for more erosive disease—disease duration, palpable effusion at baseline	Effect on progression of joint damage in joints with soft tissue swelling compared to placebo. Risk factors for progression were then identified and the presence of palpable soft tissue swelling at baseline was recognized as the strongest predictor for erosive progression. In this subpopulation at risk, statistically significant less erosive evolution on the radiological image (3.7%) was seen in the adalimumab treated group compared to the placebo group
Etanercept	
symptomatic erosive inflammatory hand osteoarthritis, n = 90, experience 8 years [451] Verbruggen–Veys score and MRI	did not relieve pain effectively after 24 weeks in erosive osteoarthritis. Small subgroup analyses showed a signal for effects on subchondral bone in actively inflamed joints, but future studies to confirm this are warranted less MRI bone marrow lesions in more pronounced inflammatory joint group
erosive (≥ 1 IPJ with radiographic pre(erosive) anatomical phase ("J"/"E") according to Verbruggen–Veys system) inflammatory (≥1 IPJ with soft swelling/erythema and with positive power Doppler at US) symptomatic (VAS pain > 30/100 on NSAID use, flare after NSAID washout) OA were included [452] quantitative Ghent University Scoring System	No effect-VAS pain, hand function (FIHOA), quality of life (SF-36), no. of tender joints and grip strength, radiographic progression after 4, 8, 12, 24, 36 weeks, and 1 year Symptomatic and inflammatory patients completing the study ETN was superior over placebo both on pain and structural damage assessed by GUSS; ETN was especially effective in joints with signs of inflammation

⇓—decrease in indicator; ⇑—increase in indicator.

9. Synthesis of the Key Findings on RA and OA Convergence and Divergence of the Pathogenetic Mechanisms

We analyzed three initially different pathologies developing in joint tissues: ACCP-positive RA, classical 'antigen-driven' pathology, developing in synovia with no signs of inflammatory process; ACCP-negative RA, starting with synovial inflammation triggered by nonspecific factors that becomes a chronic process due to inherited innate immune factor peculiarities; and OA, starting with inadequate chondrocyte functioning and cartilage degradation with inflammation as a driving force (Figure 5).

However, notable coincidences in RA and OA development were revealed:

1. Shared mutations of 29 genes, encoding molecules involved in immunoinflammatory processes and ECM production.
2. Unidirectional association of non-genetic factors with OA and ACCP-negative RA; signaling pathway overactivation with the same consequences for RA and OA.
3. Serum ACCPs were rarely detected in OA (ACCP-negative RA exists as well!).
4. For a clearer understanding, studies of OA variants with potentially different mechanisms are needed. Erosive hand OA is especially interesting.
5. Innate and adaptive immune responses (although less aggressive than in RA) are involved in OA development.
6. Identical to those in RA, lymphoid nodular aggregates (but not GCs) were revealed in 30% of OA synovial samples. On the other hand, GCs were not revealed in all RA synovial 'pathotypes', but only in lymphoid ones, while myeloid and especially pauci-immune and fibroid pathotypes look quite acceptable for OA.
7. Indistinguishable from that in RA, pannuses were found in OA articular tissues.

8. The identified list of coincidences may be evidence of evolution of some variants of OA in RA, especially from the point of view of some researchers, RA may be a syndrome developed as a result of a number of different diseases [453,454].

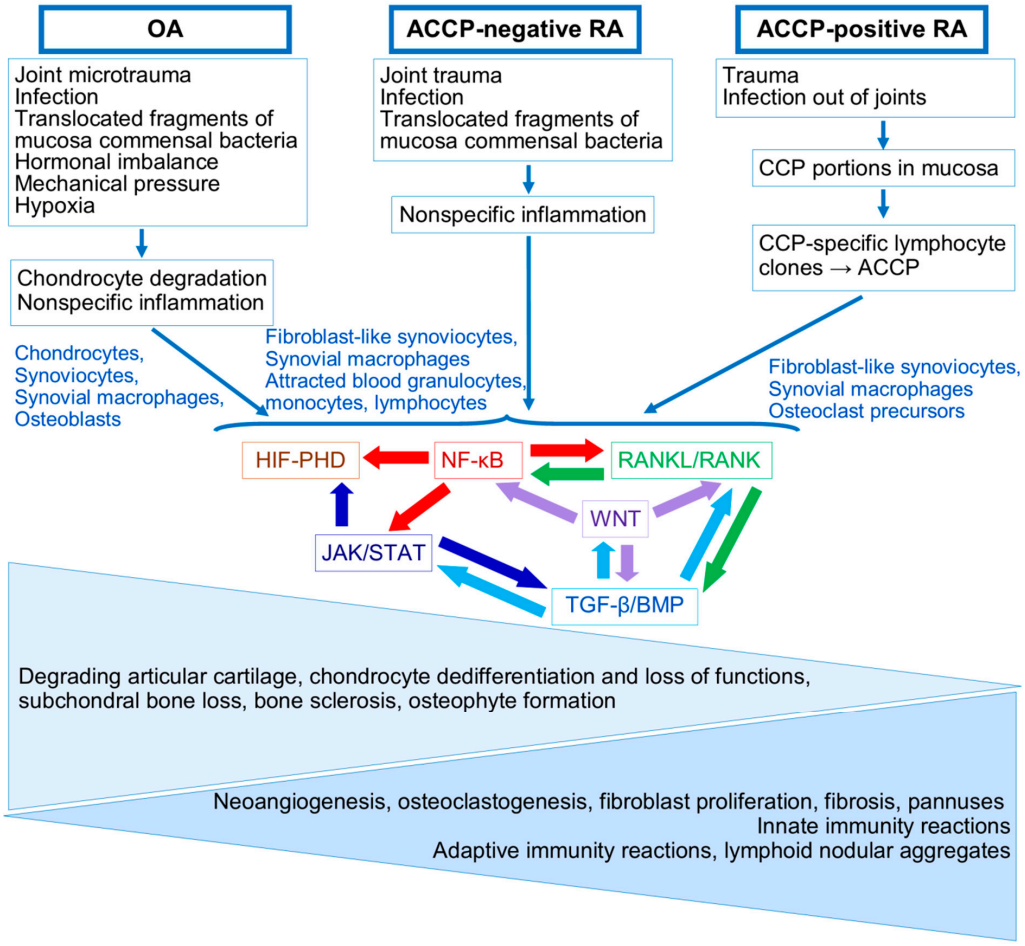


Figure 5. Main nodes of OA and ACCP-positive and ACCP-negative RA pathogenesis: similarities and differences. OA and ACCP-negative RA: nonspecific factors trigger inflammation and degradation of joint tissues. ACCP-positive RA: CCPs provoke ACCP production and CCP-specific lymphocyte clones in MALT, infiltrating healthy joints and generating chronic inflammation and joint tissue degradation. At early stages, a tangle of overactivated interdependent signaling pathways is the same in OA and RA joint cells; however, the lists of major players differ. In advanced OA and RA stages, signs of damage to joint tissues exhibit remarkable similarities yet differ in the intensity of certain processes. Osteoarthritis (OA); rheumatoid arthritis (RA); cyclic citrullinated peptides (CCPs); anti-CCP antibodies (ACCP); mucosa-associated lymphoid tissue (MALT). The information about interdependence of signaling pathways was obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms26178742/s1.

Author Contributions: Conceptualization: M.I.A.; investigation: M.O.K., G.M. and M.I.A.; methodology: M.I.A.; project administration: M.I.A.; supervision: M.I.A.; visualization: M.O.K. and A.R.V.; writing—original draft: M.O.K., A.R.V., I.F.A., W.B., Y.R., G.M. and M.I.A.; writing—review and editing: W.B. and M.I.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Sanchez-Lopez, E.; Coras, R.; Torres, A.; Lane, N.E.; Guma, M. Synovial inflammation in osteoarthritis progression. *Nat. Rev. Rheumatol.* **2022**, *18*, 258–275. [CrossRef]
2. McInnes, I.B.; Schett, G. The Pathogenesis of Rheumatoid Arthritis. *N. Engl. J. Med.* **2011**, *365*, 2205–2219. [CrossRef]
3. Roškar, S.; Hafner-Bratkovič, I. The Role of Inflammasomes in Osteoarthritis and Secondary Joint Degeneration Diseases. *Life* **2022**, *12*, 731. [CrossRef] [PubMed]
4. Starodubtseva, I.A. Prevalence of secondary osteoarthritis in patients with rheumatoid arthritis and risk factors for its progression. *Adv. Gerontol.* **2014**, *27*, 693–698. [PubMed]
5. Fujikawa, K.; Kawakami, A.; Tamai, M.; Uetani, M.; Takao, S.; Arima, K.; Iwamoto, N.; Aramaki, T.; Kawashiri, S.; Ichinose, K.; et al. High Serum Cartilage Oligomeric Matrix Protein Determines the Subset of Patients with Early-Stage Rheumatoid Arthritis with High Serum C-Reactive Protein, Matrix Metalloproteinase-3, and MRI-Proven Bone Erosion. *J. Rheumatol.* **2009**, *36*, 1126–1129. [CrossRef] [PubMed]
6. Niki, Y.; Takeuchi, T.; Nakayama, M.; Nagasawa, H.; Kurasawa, T.; Yamada, H.; Toyama, Y.; Miyamoto, T. Clinical Significance of Cartilage Biomarkers for Monitoring Structural Joint Damage in Rheumatoid Arthritis Patients Treated with Anti-TNF Therapy. *PLoS ONE* **2012**, *7*, e37447. [CrossRef] [PubMed]
7. Serdyuk, I.L.; Valeeva, A.R.; Korovina, M.O.; Renaudineau, Y.; Arleevskaya, M.I. Triggering role of environmental and individual factors in rheumatoid arthritis and preclinical joint symptoms. *Kazan Med. J.* **2024**, *106*, 51–61. [CrossRef]
8. Wenham, C.Y.J.; Hensor, E.M.A.; Grainger, A.J.; Hodgson, R.; Balamoody, S.; Dore, C.J.; Emery, P.; Conaghan, P.G. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology* **2012**, *51*, 2286–2294. [CrossRef]
9. Richette, P.; Latourte, A.; Sellam, J.; Wendling, D.; Piperno, M.; Goupille, P.; Pers, Y.-M.; Eymard, F.; Ottaviani, S.; Ornetti, P.; et al. Efficacy of tocilizumab in patients with hand osteoarthritis: Double blind, randomised, placebo-controlled, multicentre trial. *Ann. Rheum. Dis.* **2021**, *80*, 349–355. [CrossRef]
10. Ferrero, S.; Wittoek, R.; Allado, E.; Cruzel, C.; Fontas, E.; Breuil, V.; Ziegler, L.; Kremer, J.; Loeuille, D.; Roux, C.H. Methotrexate treatment in hand osteoarthritis refractory to usual treatments: A randomised, double-blind, placebo-controlled trial. *Semin. Arthritis Rheum.* **2021**, *51*, 831–838. [CrossRef]
11. Kingsbury, S.R.; Tharmanathan, P.; Arden, N.K.; Batley, M.; Birrell, F.; Cocks, K.; Doherty, M.; Edwards, C.J.; Garrood, T.; Grainger, A.J.; et al. Pain reduction with oral methotrexate in knee osteoarthritis, a pragmatic phase iii trial of treatment effectiveness (PROMOTE): Study protocol for a randomized controlled trial. *Trials* **2015**, *16*, 77. [CrossRef]
12. Schieker, M.; Conaghan, P.G.; Mindeholm, L.; Praestgaard, J.; Solomon, D.H.; Scotti, C.; Gram, H.; Thuren, T.; Roubenoff, R.; Ridker, P.M. Effects of Interleukin-1β Inhibition on Incident Hip and Knee Replacement: Exploratory Analyses from a Randomized, Double-Blind, Placebo-Controlled Trial. *Ann. Intern. Med.* **2020**, *173*, 509–515. [CrossRef] [PubMed]
13. Meng, F.; Li, H.; Feng, H.; Long, H.; Yang, Z.; Li, J.; Wang, Y.; Xie, D. Efficacy and safety of biologic agents for the treatment of osteoarthritis: A meta-analysis of randomized placebo-controlled trials. *Ther. Adv. Musculoskelet.* **2022**, *14*, 1759720X221080377. [CrossRef]
14. Nwankwo, E.C.; Labaran, L.A.; Athas, V.; Olson, S.; Adams, S.B. Pathogenesis of Posttraumatic Osteoarthritis of the Ankle. *Orthop. Clin. N. Am.* **2019**, *50*, 529–537. [CrossRef] [PubMed]
15. Jiménez, G.; Cobo-Molinos, J.; Antich, C.; López-Ruiz, E. Osteoarthritis: Trauma vs Disease. In *Osteochondral Tissue Engineering*; Oliveira, J.M., Pina, S., Reis, R.L., San Roman, J., Eds.; Advances in Experimental Medicine and Biology; Springer International Publishing: Cham, Switzerland, 2018; Volume 1059, pp. 63–83. ISBN 978-3-319-76734-5.
16. Revell, P.A.; Mayston, V.; Lalor, P.; Mapp, P. The synovial membrane in osteoarthritis: A histological study including the characterisation of the cellular infiltrate present in inflammatory osteoarthritis using monoclonal antibodies. *Ann. Rheum. Dis.* **1988**, *47*, 300–307. [CrossRef] [PubMed]
17. Luo, Y.; Sinkeviciute, D.; He, Y.; Karsdal, M.; Henrotin, Y.; Mobasheri, A.; Önnerfjord, P.; Bay-Jensen, A. The minor collagens in articular cartilage. *Protein Cell* **2017**, *8*, 560–572. [CrossRef]
18. Czarny-Ratajczak, M.; Lohiniva, J.; Rogala, P.; Kozlowski, K.; Perälä, M.; Carter, L.; Spector, T.D.; Kolodziej, L.; Seppänen, U.; Glazar, R.; et al. A Mutation in COL9A1 Causes Multiple Epiphyseal Dysplasia: Further Evidence for Locus Heterogeneity. *Am. J. Hum. Genet.* **2001**, *69*, 969–980. [CrossRef]
19. Escudero-Esparza, A.; Kalchishkova, N.; Kurbasic, E.; Jiang, W.G.; Blom, A.M. The novel complement inhibitor human CUB and Sushi multiple domains 1 (CSMD1) protein promotes factor I-mediated degradation of C4b and C3b and inhibits the membrane attack complex assembly. *FASEB J.* **2013**, *27*, 5083–5093. [CrossRef]
20. Huang, T.; Liang, Y.; Zhang, H.; Chen, X.; Wei, H.; Sun, W.; Wang, Y. CSMD1 Mutations Are Associated with Increased Mutational Burden, Favorable Prognosis, and Anti-Tumor Immunity in Gastric Cancer. *Genes* **2021**, *12*, 1715. [CrossRef]
21. Lin, S.; Li, M.; Zhou, Y.; Chen, L.; Wang, Y.; Zhuang, Z.; Zhao, H.; Yang, R. Annexin A3 accelerates osteoclast differentiation by promoting the level of RANK and TRAF6. *Bone* **2023**, *172*, 116758. [CrossRef]

22. Chen, Y.; Di, M.; Tang, Y.; Zhao, J.; Wang, Q.; Guo, Z.; Li, Y.; Ouyang, D.; Yang, J.; Chen, H.; et al. Epstein-Barr virus causes vascular abnormalities in epithelial malignancies through upregulating ANXA3-HIF-1α-VEGF pathway. *Oncogene* **2024**, *43*, 2143–2159. [CrossRef]
23. Loo, W.J.; Turchin, I.; Prajapati, V.H.; Gooderham, M.J.; Grewal, P.; Hong, C.; Sauder, M.; Vender, R.B.; Maari, C.; Papp, K.A. Clinical Implications of Targeting the JAK-STAT Pathway in Psoriatic Disease: Emphasis on the TYK2 Pathway. *J. Cutan. Med. Surg.* **2023**, *27*, 3S–24S. [CrossRef]
24. Li, W.; Cao, T.; Luo, C.; Cai, J.; Zhou, X.; Xiao, X.; Liu, S. Crosstalk between ER stress, NLRP3 inflammasome, and inflammation. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 6129–6140. [CrossRef]
25. Marcinkowski, M.; Pilžys, T.; Garbicz, D.; Steciuk, J.; Zugaj, D.; Mielecki, D.; Sarnowski, T.J.; Grzesiuk, E. Human and Arabidopsis alpha-ketoglutarate-dependent dioxygenase homolog proteins—New players in important regulatory processes. *IUBMB Life* **2020**, *72*, 1126–1144. [CrossRef] [PubMed]
26. Azzam, S.K.; Alsafar, H.; Sajini, A.A. FTO m6A Demethylase in Obesity and Cancer: Implications and Underlying Molecular Mechanisms. *Int. J. Mol. Sci.* **2022**, *23*, 3800. [CrossRef] [PubMed]
27. Zhou, C.; She, X.; Gu, C.; Hu, Y.; Ma, M.; Qiu, Q.; Sun, T.; Xu, X.; Chen, H.; Zheng, Z. FTO fuels diabetes-induced vascular endothelial dysfunction associated with inflammation by erasing m6A methylation of TNIP1. *J. Clin. Investig.* **2023**, *133*, e160517. [CrossRef]
28. Bjune, J.-I.; Lawrence-Archer, L.; Røsland, G.V.; Tronstad, K.J.; Njølstad, P.R.; Sagen, J.V.; Dankel, S.N.; Mellgren, G. The homeobox factor Irx3 maintains adipogenic identity. *Metabolism* **2020**, *103*, 154014. [CrossRef]
29. Sanghera, D.K.; Ortega, L.; Han, S.; Singh, J.; Ralhan, S.K.; Wander, G.S.; Mehra, N.K.; Mulvihill, J.J.; Ferrell, R.E.; Nath, S.K.; et al. Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF2BP2, TCF7L2 and FTOvariants confer a significant risk. *BMC Med. Genet.* **2008**, *9*, 59. [CrossRef]
30. Hunt, L.E.; Noyvert, B.; Bhaw-Rosun, L.; Sesay, A.K.; Paternoster, L.; Nohr, E.A.; Davey Smith, G.; Tommerup, N.; Sørensen, T.I.A.; Elgar, G. Complete re-sequencing of a 2Mb topological domain encompassing the FTO/IRXB genes identifies a novel obesity-associated region upstream of IRX5. *Genome Med.* **2015**, *7*, 126. [CrossRef]
31. Tachmazidou, I.; Hatzikotoulas, K.; Southam, L.; Esparza-Gordillo, J.; Haberland, V.; Zheng, J.; Johnson, T.; Koprulu, M.; Zengini, E.; Steinberg, J.; et al. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. *Nat. Genet.* **2019**, *51*, 230–236. [CrossRef]
32. Boer, C.G.; Hatzikotoulas, K.; Southam, L.; Stefánsdóttir, L.; Zhang, Y.; Coutinho De Almeida, R.; Wu, T.T.; Zheng, J.; Hartley, A.; Teder-Laving, M.; et al. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell* **2021**, *184*, 4784–4818.e17. [CrossRef] [PubMed]
33. Cai, D.; Zhang, J.; Yang, J.; Lv, Q.; Zhong, C. Overexpression of FTO alleviates osteoarthritis by regulating the processing of miR-515-5p and the TLR4/MyD88/NF-κB axis. *Int. Immunopharmacol.* **2023**, *114*, 109524. [CrossRef] [PubMed]
34. Liu, W.; Jiang, T.; Zheng, W.; Zhang, J.; Li, A.; Lu, C.; Lin, Z. FTO-mediated m6A demethylation of pri-miR-3591 alleviates osteoarthritis progression. *Arthritis Res. Ther.* **2023**, *25*, 53. [CrossRef]
35. Massey, J.; Plant, D.; Hyrich, K.; Morgan, A.W.; Wilson, A.G.; Spiliopoulou, A.; Colombo, M.; McKeigue, P.; Isaacs, J.; Cordell, H.; et al. Genome-wide association study of response to tumour necrosis factor inhibitor therapy in rheumatoid arthritis. *Pharmacogenom. J.* **2018**, *18*, 657–664. [CrossRef]
36. Jin, L.; Chen, Q.; Hu, K.; Fan, D.; Zhang, H.; Deng, J.; Qi, W.; Yu, Q. The FTO-CMPK2 Pathway in Fibroblast-like Synoviocytes Modulates Rheumatoid Arthritis Synovial Inflammation and Cartilage Homeostasis via mtDNA Regulation. *Int. J. Biol. Sci.* **2024**, *20*, 1617–1633. [CrossRef]
37. Henkel, C.; Styrkársdóttir, U.; Thorleifsson, G.; Stefánsdóttir, L.; Björnsdóttir, G.; Banasik, K.; Brunak, S.; Erikstrup, C.; Dinh, K.M.; Hansen, T.F.; et al. Genome-wide association meta-analysis of knee and hip osteoarthritis uncovers genetic differences between patients treated with joint replacement and patients without joint replacement. *Ann. Rheum. Dis.* **2023**, *82*, 384–392. [CrossRef]
38. McDonald, M.-L.N.; Lakshman Kumar, P.; Srinivasasainagendra, V.; Nair, A.; Rocco, A.P.; Wilson, A.C.; Chiles, J.W.; Richman, J.S.; Pinson, S.A.; Dennis, R.A.; et al. Novel genetic loci associated with osteoarthritis in multi-ancestry analyses in the Million Veteran Program and UK Biobank. *Nat. Genet.* **2022**, *54*, 1816–1826. [CrossRef]
39. Nakajima, M.; Takahashi, A.; Kou, I.; Rodriguez-Fontenla, C.; Gomez-Reino, J.J.; Furuichi, T.; Dai, J.; Sudo, A.; Uchida, A.; Fukui, N.; et al. New Sequence Variants in HLA Class II/III Region Associated with Susceptibility to Knee Osteoarthritis Identified by Genome-Wide Association Study. *PLoS ONE* **2010**, *5*, e9723. [CrossRef]
40. Saevarsdottir, S.; Stefansdottir, L.; Sulem, P.; Thorleifsson, G.; Ferkingstad, E.; Rutsdottir, G.; Glintborg, B.; Westerlind, H.; Grondal, G.; Loft, I.C.; et al. Multiomics analysis of rheumatoid arthritis yields sequence variants that have large effects on risk of the seropositive subset. *Ann. Rheum. Dis.* **2022**, *81*, 1085–1095. [CrossRef]
41. Ishigaki, K.; Sakaue, S.; Terao, C.; Luo, Y.; Sonehara, K.; Yamaguchi, K.; Amariuta, T.; Too, C.L.; Laufer, V.A.; Scott, I.C.; et al. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. *Nat. Genet.* **2022**, *54*, 1640–1651. [CrossRef]

42. Liu, R.; Shang, X.; Fu, Y.; Wang, Y.; Wang, P.; Yan, S. Shared genetic architecture between hypothyroidism and rheumatoid arthritis: A large-scale cross-trait analysis. *Mol. Immunol.* **2024**, *168*, 17–24. [CrossRef]
43. Sun, Y.; Zhang, H.; Ma, R.; Guo, X.; Zhang, G.; Liu, S.; Zhu, W.; Liu, H.; Gao, P. ETS-1-activated LINC01016 over-expression promotes tumor progression via suppression of RFFL-mediated DHX9 ubiquitination degradation in breast cancers. *Cell Death Dis.* **2023**, *14*, 507. [CrossRef] [PubMed]
44. Song, P.; Li, W.; Wu, X.; Qian, Z.; Ying, J.; Gao, S.; He, J. Integrated analysis of single-cell and bulk RNA-sequencing identifies a signature based on B cell marker genes to predict prognosis and immunotherapy response in lung adenocarcinoma. *Cancer Immunol. Immunother.* **2022**, *71*, 2341–2354. [CrossRef] [PubMed]
45. Alfaisal University; Dvornyk, V. Integrated in-depth bioinformatic analysis suggests RELCH/KIAA1468, LINC02341, and AKAP11 as candidate genes for ages at menarche and menopause. *RRB* **2021**, *7*, 220–231. [CrossRef]
46. Franceschini, A.; Szklarczyk, D.; Frankild, S.; Kuhn, M.; Simonovic, M.; Roth, A.; Lin, J.; Minguez, P.; Bork, P.; Von Mering, C.; et al. STRING v9.1: Protein-protein interaction networks, with increased coverage and integration. *Nucleic Acids Res.* **2012**, *41*, D808–D815. [CrossRef]
47. Vitales-Noyola, M.; Hernández-Castro, B.; Alvarado-Hernández, D.; Baranda, L.; Bernal-Silva, S.; Abud-Mendoza, C.; Niño-Moreno, P.; González-Amaro, R. Levels of Pathogenic Th17 and Th22 Cells in Patients with Rheumatoid Arthritis. *J. Immunol. Res.* **2022**, *2022*, 5398743. [CrossRef]
48. Yamada, H.; Nakashima, Y.; Okazaki, K.; Mawatari, T.; Fukushi, J.-I.; Oyamada, A.; Fujimura, K.; Iwamoto, Y.; Yoshikai, Y. Preferential Accumulation of Activated Th1 Cells Not Only in Rheumatoid Arthritis But Also in Osteoarthritis Joints. *J. Rheumatol.* **2011**, *38*, 1569–1575. [CrossRef]
49. Yao, Q.; Wu, X.; Tao, C.; Gong, W.; Chen, M.; Qu, M.; Zhong, Y.; He, T.; Chen, S.; Xiao, G. Osteoarthritis: Pathogenic signaling pathways and therapeutic targets. *Sig. Transduct. Target. Ther.* **2023**, *8*, 56. [CrossRef]
50. Liu, S.; Ma, H.; Zhang, H.; Deng, C.; Xin, P. Recent advances on signaling pathways and their inhibitors in rheumatoid arthritis. *Clin. Immunol.* **2021**, *230*, 108793. [CrossRef]
51. Kovács, B.; Vajda, E.; Nagy, E.E. Regulatory Effects and Interactions of the Wnt and OPG-RANKL-RANK Signaling at the Bone-Cartilage Interface in Osteoarthritis. *Int. J. Mol. Sci.* **2019**, *20*, 4653. [CrossRef]
52. Ostojic, M.; Zevrnja, A.; Vukojevic, K.; Soljic, V. Immunofluorescence Analysis of NF-κB and iNOS Expression in Different Cell Populations during Early and Advanced Knee Osteoarthritis. *Int. J. Mol. Sci.* **2021**, *22*, 6461. [CrossRef]
53. Sohn, D.H.; Sokolove, J.; Sharpe, O.; Erhart, J.C.; Chandra, P.E.; Lahey, L.J.; Lindstrom, T.M.; Hwang, I.; Boyer, K.A.; Andriacchi, T.P.; et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. *Arthritis Res. Ther.* **2012**, *14*, R7. [CrossRef]
54. Horváth, E.; Sólyom, Á.; Székely, J.; Nagy, E.E.; Popoviciu, H. Inflammatory and Metabolic Signaling Interfaces of the Hypertrophic and Senescent Chondrocyte Phenotypes Associated with Osteoarthritis. *Int. J. Mol. Sci.* **2023**, *24*, 16468. [CrossRef]
55. Zhang, H.; Cai, D.; Bai, X. Macrophages regulate the progression of osteoarthritis. *Osteoarthr. Cartil.* **2020**, *28*, 555–561. [CrossRef]
56. Arra, M.; Swarnkar, G.; Ke, K.; Otero, J.E.; Ying, J.; Duan, X.; Maruyama, T.; Rai, M.F.; O'Keefe, R.J.; Mbalaviele, G.; et al. LDHA-mediated ROS generation in chondrocytes is a potential therapeutic target for osteoarthritis. *Nat. Commun.* **2020**, *11*, 3427. [CrossRef]
57. Liu, B.; Xian, Y.; Chen, X.; Shi, Y.; Dong, J.; Yang, L.; An, X.; Shen, T.; Wu, W.; Ma, Y.; et al. Inflammatory Fibroblast-Like Synoviocyte-Derived Exosomes Aggravate Osteoarthritis via Enhancing Macrophage Glycolysis. *Adv. Sci.* **2024**, *11*, 2307338. [CrossRef]
58. Van Den Bosch, M.H.J. Inflammation in osteoarthritis: Is it time to dampen the alarm(in) in this debilitating disease? *Clin. Exp. Immunol.* **2019**, *195*, 153–166. [CrossRef]
59. Sokolove, J.; Lepus, C.M. Role of inflammation in the pathogenesis of osteoarthritis: Latest findings and interpretations. *Ther. Adv. Musculoskelet.* **2013**, *5*, 77–94. [CrossRef] [PubMed]
60. Yang, H.; Lee, H.; Lee, C.; Fang, W.; Chen, H.; Salter, D.M.; Su, S. Association of a functional polymorphism in the promoter region of TLR-3 with osteoarthritis: A two-stage case–control study. *J. Orthop. Res.* **2013**, *31*, 680–685. [CrossRef] [PubMed]
61. Yi, X.; Xu, E.; Xiao, Y.; Cai, X. Evaluation of the Relationship Between Common Variants in the *TLR-9* Gene and Hip Osteoarthritis Susceptibility. *Genet. Test. Mol. Biomark.* **2019**, *23*, 373–379. [CrossRef] [PubMed]
62. Gao, S.-T.; Lv, Z.-T.; Sheng, W.-B. The association between rs12901499 polymorphism in SMAD3 gene and risk of osteoarthritis: A meta-analysis. *Ther. Clin. Risk Manag.* **2018**, *14*, 929–936. [CrossRef] [PubMed]
63. Faber, B.G.; Frysz, M.; Boer, C.G.; Evans, D.S.; Ebsim, R.; Flynn, K.A.; Lundberg, M.; Southam, L.; Hartley, A.; Saunders, F.R.; et al. The identification of distinct protective and susceptibility mechanisms for hip osteoarthritis: Findings from a genome-wide association study meta-analysis of minimum joint space width and Mendelian randomisation cluster analyses. *eBioMedicine* **2023**, *95*, 104759. [CrossRef] [PubMed]
64. Styrkarsdottir, U.; Stefansdottir, L.; Thorleifsson, G.; Stefansson, O.A.; Saevarsdottir, S.; Lund, S.H.; Rafnar, T.; Hoshijima, K.; Novak, K.; Oreiro, N.; et al. Meta-analysis of erosive hand osteoarthritis identifies four common variants that associate with relatively large effect. *Ann. Rheum. Dis.* **2023**, *82*, 873–880. [CrossRef] [PubMed]

65. Cui, X.; Wang, S.; Cai, H.; Lin, Y.; Zheng, X.; Zhang, B.; Xia, C. Overexpression of microRNA-634 suppresses survival and matrix synthesis of human osteoarthritis chondrocytes by targeting PIK3R1. *Sci. Rep.* **2016**, *6*, 23117. [CrossRef]
66. Nakajima, M.; Shi, D.; Dai, J.; Tsezou, A.; Zheng, M.; Norman, P.E.; Chou, C.; Lee, M.T.M.; Hwang, J.; Kim, D.; et al. A large-scale replication study for the association of rs17039192 in HIF-2α with knee osteoarthritis. *J. Orthop. Res.* **2012**, *30*, 1244–1248. [CrossRef]
67. Fernández-Torres, J.; Hernández-Díaz, C.; Espinosa-Morales, R.; Camacho-Galindo, J.; Galindo-Sevilla, N.D.C.; López-Macay, Á.; Zamudio-Cuevas, Y.; Martínez-Flores, K.; Santamaría-Olmedo, M.G.; Pineda, C.; et al. Polymorphic variation of hypoxia inducible factor-1 A (HIF1A) gene might contribute to the development of knee osteoarthritis: A pilot study. *BMC Musculoskelet. Disord.* **2015**, *16*, 218. [CrossRef]
68. Philip, A. TGF-b signaling in cartilage homeostasis and osteoarthritis. *Front. Biosci.* **2012**, *S4*, 251–268. [CrossRef]
69. Thielen, N.; Van Der Kraan, P.; Van Caam, A. TGFβ/BMP Signaling Pathway in Cartilage Homeostasis. *Cells* **2019**, *8*, 969. [CrossRef]
70. Zhai, G.; Doré, J.; Rahman, P. TGF-β signal transduction pathways and osteoarthritis. *Rheumatol. Int.* **2015**, *35*, 1283–1292. [CrossRef]
71. Chan, B.Y.; Fuller, E.S.; Russell, A.K.; Smith, S.M.; Smith, M.M.; Jackson, M.T.; Cake, M.A.; Read, R.A.; Bateman, J.F.; Sambrook, P.N.; et al. Increased chondrocyte sclerostin may protect against cartilage degradation in osteoarthritis. *Osteoarthr. Cartil.* **2011**, *19*, 874–885. [CrossRef]
72. Guo, H.; Huang, J.; Liang, Y.; Wang, D.; Zhang, H. Focusing on the hypoxia-inducible factor pathway: Role, regulation, and therapy for osteoarthritis. *Eur. J. Med. Res.* **2022**, *27*, 288. [CrossRef] [PubMed]
73. Blaney Davidson, E.N.; Vitters, E.L.; Van Der Kraan, P.M.; Van Den Berg, W.B. Expression of transforming growth factor-β (TGFβ) and the TGFβ signalling molecule SMAD-2P in spontaneous and instability-induced osteoarthritis: Role in cartilage degradation, chondrogenesis and osteophyte formation. *Ann. Rheum. Dis.* **2006**, *65*, 1414–1421. [CrossRef]
74. Van Der Kraan, P.M.; Van Den Berg, W.B. Osteophytes: Relevance and biology. *Osteoarthr. Cartil.* **2007**, *15*, 237–244. [CrossRef] [PubMed]
75. Su, W.; Liu, G.; Liu, X.; Zhou, Y.; Sun, Q.; Zhen, G.; Wang, X.; Hu, Y.; Gao, P.; Demehri, S.; et al. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. *JCI Insight* **2020**, *5*, e135446. [CrossRef]
76. Ashraf, S.; Walsh, D.A. Angiogenesis in osteoarthritis. *Curr. Opin. Rheumatol.* **2008**, *20*, 573–580. [CrossRef]
77. Roman-Blas, J.A.; Jimenez, S.A. Targeting NF-κB: A Promising Molecular Therapy in Inflammatory Arthritis. *Int. Rev. Immunol.* **2008**, *27*, 351–374. [CrossRef]
78. De Rooy, D.P.C.; Yeremenko, N.G.; Wilson, A.G.; Knevel, R.; Lindqvist, E.; Saxne, T.; Krabben, A.; Leijsma, M.K.; Daha, N.A.; Tsonaka, S.; et al. Genetic studies on components of the Wnt signalling pathway and the severity of joint destruction in rheumatoid arthritis. *Ann. Rheum. Dis.* **2013**, *72*, 769–775, Correction in *Ann. Rheum. Dis.* **2014**, *74*, 319. https://doi.org/10.1136/annrheumdis-2012-202184corr1. [CrossRef]
79. Ruyssen-Witrand, A.; Degboé, Y.; Cantagrel, A.; Nigon, D.; Lukas, C.; Scaramuzzino, S.; Allanore, Y.; Vittecoq, O.; Schaeverbeke, T.; Morel, J.; et al. Association between *RANK*, *RANKL* and *OPG* polymorphisms with ACPA and erosions in rheumatoid arthritis: Results from a meta-analysis involving three French cohorts. *RMD Open* **2016**, *2*, e000226. [CrossRef]
80. Wielińska, J.; Kolossa, K.; Świerkot, J.; Dratwa, M.; Iwaszko, M.; Bugaj, B.; Wysoczańska, B.; Chaszczewska-Markowska, M.; Jeka, S.; Bogunia-Kubik, K. Polymorphisms within the RANK and RANKL Encoding Genes in Patients with Rheumatoid Arthritis: Association with Disease Progression and Effectiveness of the Biological Treatment. *Arch. Immunol. Ther. Exp.* **2020**, *68*, 24. [CrossRef]
81. Furuya, T.; Hakoda, M.; Ichikawa, N.; Higami, K.; Nanke, Y.; Yago, T.; Kamatani, N.; Kotake, S. Associations between HLA-DRB1, RANK, RANKL, OPG, and IL-17 genotypes and disease severity phenotypes in Japanese patients with early rheumatoid arthritis. *Clin. Rheumatol.* **2007**, *26*, 2137–2141. [CrossRef]
82. Iriyoda, T.M.V.; Flauzino, T.; Costa, N.T.; Lozovoy, M.A.B.; Reiche, E.M.V.; Simão, A.N.C. TGFB1 (rs1800470 and rs1800469) variants are independently associated with disease activity and autoantibodies in rheumatoid arthritis patients. *Clin. Exp. Med.* **2022**, *22*, 37–45. [CrossRef]
83. Hussein, Y.M.; Mohamed, R.H.; El-Shahawy, E.E.; Alzahrani, S.S. Interaction between TGF-β1 (869C/T) polymorphism and biochemical risk factor for prediction of disease progression in rheumatoid arthritis. *Gene* **2014**, *536*, 393–397. [CrossRef]
84. Paradowska-Gorycka, A.; Romanowska-Próchnicka, K.; Haladyj, E.; Manczak, M.; Maslinski, S.; Olesinska, M. Association of the Smad3 and NFATc2 gene polymorphisms and their serum levels with susceptibility to rheumatoid arthritis in Polish cohorts. *Clin. Exp. Immunol.* **2015**, *179*, 444–453. [CrossRef]
85. Elshazli, R.; Settin, A. Association of PTPN22 rs2476601 and STAT4 rs7574865 polymorphisms with rheumatoid arthritis: A meta-analysis update. *Immunobiology* **2015**, *220*, 1012–1024. [CrossRef]
86. Bravo-Villagra, K.M.; Muñoz-Valle, J.F.; Baños-Hernández, C.J.; Cerpa-Cruz, S.; Navarro-Zarza, J.E.; Parra-Rojas, I.; Aguilar-Velázquez, J.A.; García-Arellano, S.; López-Quintero, A. STAT4 Gene Variant rs7574865 Is Associated with Rheumatoid Arthritis Activity and Anti-CCP Levels in the Western but Not in the Southern Population of Mexico. *Genes* **2024**, *15*, 241. [CrossRef] [PubMed]

87. Arleevskaya, M.I.; Larionova, R.V.; Brooks, W.H.; Bettacchioli, E.; Renaudineau, Y. Toll-Like Receptors, Infections, and Rheumatoid Arthritis. *Clin. Rev. Allergy Immunol.* **2020**, *58*, 172–181. [CrossRef]
88. Wada, T.; Nakashima, T.; Hiroshi, N.; Penninger, J.M. RANKL–RANK signaling in osteoclastogenesis and bone disease. *Trends Mol. Med.* **2006**, *12*, 17–25. [CrossRef]
89. Schett, G.; Zwerina, J.; David, J.-P. The role of Wnt proteins in arthritis. *Nat. Rev. Rheumatol.* **2008**, *4*, 473–480. [CrossRef]
90. Sen, M.; Reifert, J.; Lauterbach, K.; Wolf, V.; Rubin, J.S.; Corr, M.; Carson, D.A. Regulation of fibronectin and metalloproteinase expression by Wnt signaling in rheumatoid arthritis synoviocytes. *Arthritis Rheum.* **2002**, *46*, 2867–2877. [CrossRef]
91. Sen, M.; Lauterbach, K.; El-Gabalawy, H.; Firestein, G.S.; Corr, M.; Carson, D.A. Expression and function of wingless and frizzled homologs in rheumatoid arthritis. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2791–2796. [CrossRef]
92. Strunk, J. A new approach to studying angiogenesis in rheumatoid arthritis by means of power Doppler ultrasonography and measurement of serum vascular endothelial growth factor. *Rheumatology* **2004**, *43*, 1480–1483. [CrossRef]
93. Wang, S.-Y.; Liu, Y.-Y.; Ye, H.; Guo, J.-P.; Li, R.; Liu, X.; Li, Z.-G. Circulating Dickkopf-1 Is Correlated with Bone Erosion and Inflammation in Rheumatoid Arthritis. *J. Rheumatol.* **2011**, *38*, 821–827. [CrossRef]
94. Kong, Y.-Y.; Feige, U.; Sarosi, I.; Bolon, B.; Tafuri, A.; Morony, S.; Capparelli, C.; Li, J.; Elliott, R.; McCabe, S.; et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* **1999**, *402*, 304–309. [CrossRef]
95. Lubberts, E.; Van Den Bersselaar, L.; Oppers-Walgreen, B.; Schwarzenberger, P.; Coenen-de Roo, C.J.J.; Kolls, J.K.; Joosten, L.A.B.; Van Den Berg, W.B. IL-17 Promotes Bone Erosion in Murine Collagen-Induced Arthritis Through Loss of the Receptor Activator of NF-κB Ligand/Osteoprotegerin Balance. *J. Immunol.* **2003**, *170*, 2655–2662. [CrossRef] [PubMed]
96. Mao, X.; Wu, W.; Nan, Y.; Sun, W.; Wang, Y. SMAD2 inhibits pyroptosis of fibroblast-like synoviocytes and secretion of inflammatory factors via the TGF-β pathway in rheumatoid arthritis. *Arthritis Res. Ther.* **2023**, *25*, 144. [CrossRef] [PubMed]
97. Ba, X.; Huang, Y.; Shen, P.; Huang, Y.; Wang, H.; Han, L.; Lin, W.J.; Yan, H.J.; Xu, L.J.; Qin, K.; et al. WTD Attenuating Rheumatoid Arthritis via Suppressing Angiogenesis and Modulating the PI3K/AKT/mTOR/HIF-1α Pathway. *Front. Pharmacol.* **2021**, *12*, 696802. [CrossRef] [PubMed]
98. Hayer, S.; Pundt, N.; Peters, M.A.; Wunrau, C.; Kühnel, I.; Neugebauer, K.; Striethолt, S.; Zwerina, J.; Korb, A.; Penninger, J.; et al. PI3Kγ regulates cartilage damage in chronic inflammatory arthritis. *FASEB J.* **2009**, *23*, 4288–4298. [CrossRef]
99. Xu, X.; Zheng, L.; Bian, Q.; Xie, L.; Liu, W.; Zhen, G.; Crane, J.L.; Zhou, X.; Cao, X. Aberrant Activation of TGF-β in Subchondral Bone at the Onset of Rheumatoid Arthritis Joint Destruction. *J. Bone Miner. Res.* **2015**, *30*, 2033–2043. [CrossRef]
100. Guo, X.; Chen, G. Hypoxia-Inducible Factor Is Critical for Pathogenesis and Regulation of Immune Cell Functions in Rheumatoid Arthritis. *Front. Immunol.* **2020**, *11*, 1668. [CrossRef]
101. Guan, S.-Y.; Leng, R.-X.; Tao, J.-H.; Li, X.-P.; Ye, D.-Q.; Olsen, N.; Zheng, S.G.; Pan, H.-F. Hypoxia-inducible factor-1α: A promising therapeutic target for autoimmune diseases. *Expert Opin. Ther. Targets* **2017**, *21*, 715–723. [CrossRef]
102. Ibrahim, S.S.A.; Huttunen, K.M. Orchestrated modulation of rheumatoid arthritis via crosstalking intracellular signaling pathways. *Inflammopharmacology* **2021**, *29*, 965–974. [CrossRef]
103. Traylor, M.; Knevel, R.; Cui, J.; Taylor, J.; Harm-Jan, W.; Conaghan, P.G.; Cope, A.P.; Curtis, C.; Emery, P.; Newhouse, S.; et al. Genetic associations with radiological damage in rheumatoid arthritis: Meta-analysis of seven genome-wide association studies of 2,775 cases. *PLoS ONE* **2019**, *14*, e0223246. [CrossRef]
104. Hu, L.; Liu, R.; Zhang, L. Advance in bone destruction participated by JAK/STAT in rheumatoid arthritis and therapeutic effect of JAK/STAT inhibitors. *Int. Immunopharmacol.* **2022**, *111*, 109095. [CrossRef] [PubMed]
105. Goldblatt, F.; O'Neill, S.G. Clinical aspects of autoimmune rheumatic diseases. *Lancet* **2013**, *382*, 797–808. [CrossRef]
106. Wang, L.; Wang, F.; Gershwin, M.E. Human autoimmune diseases: A comprehensive update. *J. Intern. Med.* **2015**, *278*, 369–395. [CrossRef] [PubMed]
107. Robinson, W.H.; Lepus, C.M.; Wang, Q.; Raghu, H.; Mao, R.; Lindstrom, T.M.; Sokolove, J. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* **2016**, *12*, 580–592. [CrossRef] [PubMed]
108. Marshall, M.; Watt, F.E.; Vincent, T.L.; Dziedzic, K. Hand osteoarthritis: Clinical phenotypes, molecular mechanisms and disease management. *Nat. Rev. Rheumatol.* **2018**, *14*, 641–656. [CrossRef]
109. Dório, M.; Deveza, L.A. Phenotypes in Osteoarthritis. *Clin. Geriatr. Med.* **2022**, *38*, 273–286. [CrossRef]
110. Ye, J.; Xie, D.; Li, X.; Lu, N.; Zeng, C.; Lei, G.; Wei, J.; Li, J. Phenotypes of osteoarthritis-related knee pain and their transition over time: Data from the osteoarthritis initiative. *BMC Musculoskelet. Disord.* **2024**, *25*, 173. [CrossRef]
111. Frisell, T.; Holmqvist, M.; Källberg, H.; Klareskog, L.; Alfredsson, L.; Askling, J. Familial Risks and Heritability of Rheumatoid Arthritis: Role of Rheumatoid Factor/Anti–Citrullinated Protein Antibody Status, Number and Type of Affected Relatives, Sex, and Age. *Arthritis Rheum.* **2013**, *65*, 2773–2782. [CrossRef]
112. Riyazi, N.; Meulenbelt, I.; Kroon, H.M.; Ronday, K.H.; Hellio Le Graverand, M.-P.; Rosendaal, F.R.; Breedveld, F.C.; Slagboom, P.E.; Kloppenburg, M. Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: The GARP study. *Ann. Rheum. Dis.* **2005**, *64*, 438–443. [CrossRef] [PubMed]

113. Khan, B.; Khan, O.Y.; Zehra, S.; Azhar, A.; Fatima, S. Association between obesity and risk of knee osteoarthritis. *Pak. J. Pharm. Sci.* **2020**, *33*, 295–298. [PubMed]
114. Bengtsson, C.; Malspeis, S.; Orellana, C.; Sparks, J.A.; Costenbader, K.H.; Karlson, E.W. Association Between Menopausal Factors and the Risk of Seronegative and Seropositive Rheumatoid Arthritis: Results from the Nurses' Health Studies. *Arthritis Care Res.* **2017**, *69*, 1676–1684. [CrossRef] [PubMed]
115. Bikbov, M.M.; Kazakbaeva, G.M.; Gilmanshin, T.R.; Zainullin, R.M.; Rakhimova, E.M.; Fakhretdinova, A.A.; Tuliakova, A.M.; Rusakova, I.A.; Panda-Jonas, S.; Nuriev, I.F.; et al. Prevalence and associated factors of osteoarthritis in the Ural Eye and Medical Study and the Ural Very Old Study. *Sci. Rep.* **2022**, *12*, 12607. [CrossRef]
116. Scublinsky, D.; Venarotti, H.; Citera, G.; Messina, O.D.; Scheines, E.; Rillo, O.; Arturi, A.; Hofman, J.; Somma, L.F.; Casado, G.; et al. The Prevalence of Rheumatoid Arthritis in Argentina: A Capture-Recapture Study in a City of Buenos Aires Province. *JCR J. Clin. Rheumatol.* **2010**, *16*, 317–321. [CrossRef]
117. Ro, J.; Kim, S.H.; Kim, H.-R.; Lee, S.-H.; Min, H.K. Impact of lifestyle and comorbidities on seropositive rheumatoid arthritis risk from Korean health insurance data. *Sci. Rep.* **2022**, *12*, 2201. [CrossRef]
118. Srikanth, V.K.; Fryer, J.L.; Zhai, G.; Winzenberg, T.M.; Hosmer, D.; Jones, G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthr. Cartil.* **2005**, *13*, 769–781. [CrossRef]
119. Haugen, I.K.; Englund, M.; Aliabadi, P.; Niu, J.; Clancy, M.; Kvien, T.K.; Felson, D.T. Prevalence, incidence and progression of hand osteoarthritis in the general population: The Framingham Osteoarthritis Study. *Ann. Rheum. Dis.* **2011**, *70*, 1581–1586, Correction in *Ann. Rheum. Dis.* **2018**, *77*, 1546. https://doi.org/10.1136/ard.2011.150078corr1. [CrossRef]
120. Parazzini, F. Menopausal status, hormone replacement therapy use and risk of self-reported physician-diagnosed osteoarthritis in women attending menopause clinics in Italy. *Maturitas* **2003**, *46*, 207–212. [CrossRef]
121. Tan, X.; Mei, Y.; Zhou, Y.; Liao, Z.; Zhang, P.; Liu, Y.; Han, Y.; Wang, D. Causal association of menstrual reproductive factors on the risk of osteoarthritis: A univariate and multivariate Mendelian randomization study. *PLoS ONE* **2024**, *19*, e0307958. [CrossRef]
122. Orellana, C.; Saevarsdottir, S.; Klareskog, L.; Karlson, E.W.; Alfredsson, L.; Bengtsson, C. Postmenopausal hormone therapy and the risk of rheumatoid arthritis: Results from the Swedish EIRA population-based case-control study. *Eur. J. Epidemiol.* **2015**, *30*, 449–457. [CrossRef]
123. Jung, J.H.; Bang, C.H.; Song, G.G.; Kim, C.; Kim, J.-H.; Choi, S.J. Knee osteoarthritis and menopausal hormone therapy in postmenopausal women: A nationwide cross-sectional study. *Menopause* **2019**, *26*, 598–602. [CrossRef] [PubMed]
124. Sandmark, H.; Hogstedt, C.; Lewold, S.; Vingård, E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. *Ann. Rheum. Dis.* **1999**, *58*, 151–155. [CrossRef] [PubMed]
125. Lee, J.L.; Seo, J.; Shin, Y.; Han, G.H.; Yoon, S.-H.; Noh, J.H.; Kim, M.H.; Yuk, J.-S. Menopausal Hormone Therapy and Osteoarthritis Risk: Retrospective Population-Based Study in South Korea. *J. Menopausal. Med.* **2024**, *30*, 78. [CrossRef] [PubMed]
126. Von Mühlen, D.; Morton, D.; Von Mühlen, C.A.; Barrett-Connor, E. Postmenopausal Estrogen and Increased Risk of Clinical Osteoarthritis at the Hip, Hand, and Knee in Older Women. *J. Women's Health Gend.-Based Med.* **2002**, *11*, 511–518. [CrossRef]
127. Jørgensen, K.T.; Pedersen, B.V.; Jacobsen, S.; Biggar, R.J.; Frisch, M. National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: A role for hyperemesis, gestational hypertension and pre-eclampsia? *Ann. Rheum. Dis.* **2010**, *69*, 358–363. [CrossRef]
128. Orellana, C.; Wedrén, S.; Källberg, H.; Holmqvist, M.; Karlson, E.W.; Alfredsson, L.; Bengtsson, C. Parity and the risk of developing rheumatoid arthritis: Results from the Swedish Epidemiological Investigation of Rheumatoid Arthritis study. *Ann. Rheum. Dis.* **2014**, *73*, 752–755. [CrossRef]
129. Pikwer, M.; Orellana, C.; Källberg, H.; Pikwer, A.; Turesson, C.; Klareskog, L.; Alfredsson, L.; Saevarsdottir, S.; Bengtsson, C. Parity influences the severity of ACPA-negative early rheumatoid arthritis: A cohort study based on the Swedish EIRA material. *Arthritis Res. Ther.* **2015**, *17*, 358. [CrossRef]
130. Ham, D.; Bae, S. Associations of breastfeeding duration and the total number of children breastfed with self-reported osteoarthritis in Korea women 50 years and older: A cross-sectional study. *Epidemiol. Health* **2023**, *45*, e2023044. [CrossRef]
131. Wang, A.; Zawadzki, N.; Hedlin, H.; LeBlanc, E.; Budrys, N.; Van Horn, L.; Gass, M.; Westphal, L.; Stefanick, M. Reproductive history and osteoarthritis in the Women's Health Initiative. *Scand. J. Rheumatol.* **2021**, *50*, 58–67. [CrossRef]
132. Pedersen, M.; Jacobsen, S.; Klarlund, M.; Pedersen, B.V.; Wiik, A.; Wohlfahrt, J.; Frisch, M. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. *Arthritis Res. Ther.* **2006**, *8*, R133. [CrossRef] [PubMed]
133. Orellana, C.; Saevarsdottir, S.; Klareskog, L.; Karlson, E.W.; Alfredsson, L.; Bengtsson, C. Oral contraceptives, breastfeeding and the risk of developing rheumatoid arthritis: Results from the Swedish EIRA study. *Ann. Rheum. Dis.* **2017**, *76*, 1845–1852. [CrossRef] [PubMed]
134. Karlson, E.W.; Mandl, L.A.; Hankinson, S.E.; Grodstein, F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis?: Results from the Nurses' Health Study. *Arthritis Rheum.* **2004**, *50*, 3458–3467. [CrossRef] [PubMed]
135. Jacobsson, L.T.H. Perinatal characteristics and risk of rheumatoid arthritis. *BMJ* **2003**, *326*, 1068–1069. [CrossRef]

136. Kim, M.-Y.; Kim, H.-J.; Noh, J.-H.; Kim, S.-A.; Hwang, D.-S.; Lee, C.-H.; Ha, I.-H. Relationship of breastfeeding duration with joint pain and knee osteoarthritis in middle-aged Korean women: A cross-sectional study using the Korea National Health and Nutrition Examination Survey. *BMC Women's Health* **2020**, *20*, 213. [CrossRef]
137. Yoshida, K.; Wang, J.; Malspeis, S.; Marchand, N.; Lu, B.; Prisco, L.C.; Martin, L.W.; Ford, J.A.; Costenbader, K.H.; Karlson, E.W.; et al. Passive Smoking Throughout the Life Course and the Risk of Incident Rheumatoid Arthritis in Adulthood Among Women. *Arthritis Rheumatol.* **2021**, *73*, 2219–2228. [CrossRef]
138. Carlens, C.; Jacobsson, L.; Brandt, L.; Cnattingius, S.; Stephansson, O.; Askling, J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. *Ann. Rheum. Dis.* **2009**, *68*, 1159–1164. [CrossRef]
139. Mandl, L.A.; Costenbader, K.H.; Simard, J.F.; Karlson, E.W. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. *Ann. Rheum. Dis.* **2009**, *68*, 514–518. [CrossRef]
140. Jordan, K.M.; Syddall, H.; Dennison, E.M.; Cooper, C.; Arden, N.K. Birthweight, vitamin D receptor gene polymorphism, and risk of lumbar spine osteoarthritis. *J. Rheumatol.* **2005**, *32*, 678–683.
141. Hussain, S.M.; Wang, Y.; Wluka, A.E.; Shaw, J.E.; Magliano, D.J.; Graves, S.; Cicuttini, F.M. Association of Low Birth Weight and Preterm Birth with the Incidence of Knee and Hip Arthroplasty for Osteoarthritis. *Arthritis Care Res.* **2015**, *67*, 502–508. [CrossRef]
142. Clynes, M.A.; Parsons, C.; Edwards, M.H.; Jameson, K.A.; Harvey, N.C.; Aihie Sayer, A.; Cooper, C.; Dennison, E.M. Further evidence of the developmental origins of osteoarthritis: Results from the Hertfordshire Cohort Study. *J. Dev. Orig. Health Dis.* **2014**, *5*, 453–458. [CrossRef] [PubMed]
143. Wesley, A.; Bengtsson, C.; Elkan, A.; Klareskog, L.; Alfredsson, L.; Wedrén, S.; for the Epidemiological Investigation of Rheumatoid Arthritis Study Group. Association between body mass index and anti–citrullinated protein antibody–positive and anti–citrullinated protein antibody–negative rheumatoid arthritis: Results from a population-based case–control study. *Arthritis Care Res.* **2013**, *65*, 107–112. [CrossRef]
144. Lahiri, M.; Luben, R.N.; Morgan, C.; Bunn, D.K.; Marshall, T.; Lunt, M.; Verstappen, S.M.M.; Symmons, D.P.M.; Khaw, K.-T.; Wareham, N.; et al. Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register—The EPIC-2-NOAR Study). *Ann. Rheum. Dis.* **2014**, *73*, 219–226. [CrossRef] [PubMed]
145. Jiang, L.; Rong, J.; Wang, Y.; Hu, F.; Bao, C.; Li, X.; Zhao, Y. The relationship between body mass index and hip osteoarthritis: A systematic review and meta-analysis. *Jt. Bone Spine* **2011**, *78*, 150–155. [CrossRef]
146. Jiang, L.; Tian, W.; Wang, Y.; Rong, J.; Bao, C.; Liu, Y.; Zhao, Y.; Wang, C. Body mass index and susceptibility to knee osteoarthritis: A systematic review and meta-analysis. *Jt. Bone Spine* **2012**, *79*, 291–297. [CrossRef]
147. Holliday, K.L.; McWilliams, D.F.; Maciewicz, R.A.; Muir, K.R.; Zhang, W.; Doherty, M. Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. *Osteoarthr. Cartil.* **2011**, *19*, 37–43. [CrossRef]
148. Grotle, M.; Hagen, K.B.; Natvig, B.; Dahl, F.A.; Kvien, T.K. Obesity and osteoarthritis in knee, hip and/or hand: An epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet. Disord.* **2008**, *9*, 132. [CrossRef]
149. Jiang, L.; Xie, X.; Wang, Y.; Wang, Y.; Lu, Y.; Tian, T.; Chu, M.; Shen, Y. Body mass index and hand osteoarthritis susceptibility: An updated meta-analysis. *Int. J. Rheum. Dis.* **2016**, *19*, 1244–1254. [CrossRef]
150. Zhang, Y.; Fan, J.; Chen, L.; Xiong, Y.; Wu, T.; Shen, S.; Wang, X.; Meng, X.; Lu, Y.; Lei, X. Causal Association of Coffee Consumption and Total, Knee, Hip and Self-Reported Osteoarthritis: A Mendelian Randomization Study. *Front. Endocrinol.* **2021**, *12*, 768529. [CrossRef]
151. Bang, C.H.; Kim, C.; Kim, J.-H.; Choi, S.J.; Song, G.G.; Jung, J.H. Is knee osteoarthritis related to coffee drinking? A nationwide cross-sectional observational study. *Clin. Rheumatol.* **2019**, *38*, 817–825. [CrossRef]
152. Sundström, B.; Johansson, I.; Rantapää-Dahlqvist, S. Diet and alcohol as risk factors for rheumatoid arthritis: A nested case–control study. *Rheumatol. Int.* **2015**, *35*, 533–539. [CrossRef] [PubMed]
153. Magnusson, K.; Mathiessen, A.; Hammer, H.; Kvien, T.; Slatkowsky-Christensen, B.; Natvig, B.; Hagen, K.; Østerås, N.; Haugen, I. Smoking and alcohol use are associated with structural and inflammatory hand osteoarthritis features. *Scand. J. Rheumatol.* **2017**, *46*, 388–395. [CrossRef] [PubMed]
154. Haugen, I.K.; Magnusson, K.; Turkiewicz, A.; Englund, M. The Prevalence, Incidence, and Progression of Hand Osteoarthritis in Relation to Body Mass Index, Smoking, and Alcohol Consumption. *J. Rheumatol.* **2017**, *44*, 1402–1409. [CrossRef] [PubMed]
155. Klareskog, L.; Stolt, P.; Lundberg, K.; Källberg, H.; Bengtsson, C.; Grunewald, J.; Rönnelid, J.; Erlandsson Harris, H.; Ulfgren, A.; Rantapää-Dahlqvist, S.; et al. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA–DR (shared epitope)–restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* **2006**, *54*, 38–46. [CrossRef]
156. Yahya, A.; Bengtsson, C.; Lai, T.C.; Larsson, P.T.; Mustafa, A.N.; Abdullah, N.A.; Muhamad, N.; Hussein, H.; Klareskog, L.; Alfredsson, L.; et al. Smoking is associated with an increased risk of developing ACPA-positive but not ACPA-negative rheumatoid arthritis in Asian populations: Evidence from the Malaysian MyEIRA case–control study. *Mod. Rheumatol.* **2012**, *22*, 524–531. [CrossRef]

157. Zhang, Y.; Zeng, C.; Li, H.; Yang, T.; Deng, Z.; Yang, Y.; Ding, X.; Xie, D.; Wang, Y.; Lei, G. Relationship between cigarette smoking and radiographic knee osteoarthritis in Chinese population: A cross-sectional study. *Rheumatol. Int.* **2015**, *35*, 1211–1217. [CrossRef]
158. Kong, L.; Wang, L.; Meng, F.; Cao, J.; Shen, Y. Association between smoking and risk of knee osteoarthritis: A systematic review and meta-analysis. *Osteoarthr. Cartil.* **2017**, *25*, 809–816. [CrossRef]
159. Kim, J.W.; Lee, S.Y. Correlation between radiographic knee osteoarthritis and lifetime cigarette smoking amount in a Korean population: A cross-sectional study. *Medicine* **2020**, *99*, e20839. [CrossRef]
160. Olsson, Å.R.; Skogh, T.; Wingren, G. Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann. Rheum. Dis.* **2001**, *60*, 934–939, Correction in *Ann. Rheum. Dis.* **2001**, *60*, 1161. https://doi.org/10.1136/ard.60.12.1161. [CrossRef]
161. Vallerand, I.A.; Lewinson, R.T.; Frolkis, A.D.; Lowerison, M.W.; Kaplan, G.G.; Swain, M.G.; Bulloch, A.G.M.; Patten, S.B.; Barnabe, C. Depression as a risk factor for the development of rheumatoid arthritis: A population-based cohort study. *RMD Open* **2018**, *4*, e000670. [CrossRef]
162. Sparks, J.A.; Malspeis, S.; Hahn, J.; Wang, J.; Roberts, A.L.; Kubzansky, L.D.; Costenbader, K.H. Depression and Subsequent Risk for Incident Rheumatoid Arthritis Among Women. *Arthritis Care Res.* **2021**, *73*, 78–89. [CrossRef]
163. Jung, J.H.; Seok, H.; Kim, J.; Song, G.G.; Choi, S.J. Association between osteoarthritis and mental health in a Korean population: A nationwide study. *Int. J. Rheum. Dis.* **2018**, *21*, 611–619. [CrossRef]
164. Park, H.; Kim, H.; Lee, Y. Knee osteoarthritis and its association with mental health and health-related quality of life: A nationwide cross-sectional study. *Geriatr. Gerontol. Int.* **2020**, *20*, 379–383. [CrossRef] [PubMed]
165. Yoshimura, N.; Sasaki, S.; Iwasaki, K.; Danjoh, S.; Kinoshita, H.; Yasuda, T.; Tamaki, T.; Hashimoto, T.; Kellingray, S.; Croft, P.; et al. Occupational lifting is associated with hip osteoarthritis: A Japanese case-control study. *J. Rheumatol.* **2000**, *27*, 434–440. [PubMed]
166. Coggon, D.; Croft, P.; Kellingray, S.; Barrett, D.; McLaren, M.; Cooper, C. Occupational physical activities and osteoarthritis of the knee. *Arthritis Rheum.* **2000**, *43*, 1443–1449. [CrossRef] [PubMed]
167. Arleevskaya, M.; Takha, E.; Petrov, S.; Kazarian, G.; Renaudineau, Y.; Brooks, W.; Larionova, R.; Korovina, M.; Valeeva, A.; Shuralev, E.; et al. Interplay of Environmental, Individual and Genetic Factors in Rheumatoid Arthritis Provocation. *Int. J. Mol. Sci.* **2022**, *23*, 8140. [CrossRef]
168. Bolduc, J.A.; Collins, J.A.; Loeser, R.F. Reactive oxygen species, aging and articular cartilage homeostasis. *Free Radic. Biol. Med.* **2019**, *132*, 73–82. [CrossRef]
169. Loeser, R.F. Aging and osteoarthritis: The role of chondrocyte senescence and aging changes in the cartilage matrix. *Osteoarthr. Cartil.* **2009**, *17*, 971–979. [CrossRef]
170. Zamudio-Cuevas, Y.; Martínez-Flores, K.; Martínez-Nava, G.A.; Clavijo-Cornejo, D.; Fernández-Torres, J.; Sánchez-Sánchez, R. Rheumatoid arthritis and oxidative stress, a review of a decade. *Cell. Mol. Biol.* **2022**, *68*, 174–184. [CrossRef]
171. Darrah, E.; Andrade, F. Editorial: Citrullination, and Carbamylation, and Malondialdehyde-Acetaldehyde! Oh My! Entering the Forest of Autoantigen Modifications in Rheumatoid Arthritis. *Arthritis Rheumatol.* **2015**, *67*, 604–608. [CrossRef]
172. Verheul, M.K.; Böhringer, S.; Van Delft, M.A.M.; Jones, J.D.; Rigby, W.F.C.; Gan, R.W.; Holers, V.M.; Edison, J.D.; Deane, K.D.; Janssen, K.M.J.; et al. Triple Positivity for Anti–Citrullinated Protein Autoantibodies, Rheumatoid Factor, and Anti–Carbamylated Protein Antibodies Conferring High Specificity for Rheumatoid Arthritis: Implications for Very Early Identification of At-Risk Individuals. *Arthritis Rheumatol.* **2018**, *70*, 1721–1731. [CrossRef]
173. Takha, E.A.; Larionova, R.V.; Petrov, S.V.; Kazarian, G.G.; Valeeva, A.R.; Korovina, M.O.; Shamaev, N.D.; Pipchenko, A.P.; Renaudineau, Y.; Kravtsova, O.A.; et al. Possible mechanism of the implementing the trigger role of air pollution in rheumatoid arthritis (preliminary data). *Hyg. Sanit.* **2022**, *101*, 139–145. [CrossRef]
174. Weyand, C.M.; Goronzy, J.J. Aging of the Immune System. Mechanisms and Therapeutic Targets. *Ann. Am. Thorac. Soc.* **2016**, *13*, S422–S428. [CrossRef] [PubMed]
175. Collins, K.H.; Lenz, K.L.; Pollitt, E.N.; Ferguson, D.; Hutson, I.; Springer, L.E.; Oestreich, A.K.; Tang, R.; Choi, Y.-R.; Meyer, G.A.; et al. Adipose tissue is a critical regulator of osteoarthritis. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2021096118. [CrossRef] [PubMed]
176. Choi, H.M.; Doss, H.M.; Kim, K.S. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 1219. [CrossRef]
177. Hao, D.; Li, M.; Wu, Z.; Duan, Y.; Li, D.; Qiu, G. Synovial fluid level of adiponectin correlated with levels of aggrecan degradation markers in osteoarthritis. *Rheumatol. Int.* **2011**, *31*, 1433–1437. [CrossRef]
178. Xu, A.; Chan, K.W.; Hoo, R.L.C.; Wang, Y.; Tan, K.C.B.; Zhang, J.; Chen, B.; Lam, M.C.; Tse, C.; Cooper, G.J.S.; et al. Testosterone Selectively Reduces the High Molecular Weight Form of Adiponectin by Inhibiting Its Secretion from Adipocytes. *J. Biol. Chem.* **2005**, *280*, 18073–18080. [CrossRef]
179. Nishizawa, H.; Shimomura, I.; Kishida, K.; Maeda, N.; Kuriyama, H.; Nagaretani, H.; Matsuda, M.; Kondo, H.; Furuyama, N.; Kihara, S.; et al. Androgens Decrease Plasma Adiponectin, an Insulin-Sensitizing Adipocyte-Derived Protein. *Diabetes* **2002**, *51*, 2734–2741. [CrossRef]

180. Laughlin, G.A.; Barrett-Connor, E.; May, S. Sex–specific association of the androgen to oestrogen ratio with adipocytokine levels in older adults: The Rancho Bernardo Study. *Clin. Endocrinol.* **2006**, *65*, 506–513. [CrossRef]
181. Boyne, M.S.; Bennett, N.R.; Cooper, R.S.; Royal-Thomas, T.Y.; Bennett, F.I.; Luke, A.; Wilks, R.J.; Forrester, T.E. Sex-differences in adiponectin levels and body fat distribution: Longitudinal observations in Afro-Jamaicans. *Diabetes Res. Clin. Pract.* **2010**, *90*, e33–e36. [CrossRef]
182. Xu, X.; Wen, J.; Lu, Y.; Ji, H.; Zhuang, J.; Su, Y.; Liu, B.; Li, H.; Xu, Y. Impact of age on plasma vaspin concentration in a group of normal Chinese people. *J. Endocrinol. Investig.* **2017**, *40*, 143–151. [CrossRef]
183. Bellissimo, M.P.; Hsu, E.; Hao, L.; Easley, K.; Martin, G.S.; Ziegler, T.R.; Alvarez, J.A. Relationships between plasma apelin and adiponectin with normal weight obesity, body composition, and cardiorespiratory fitness in working adults. *J. Clin. Transl. Endocrinol.* **2021**, *24*, 100257. [CrossRef]
184. Cruz-Mejía, S.; Durán López, H.H.; Navarro Meza, M.; Xochihua Rosas, I.; De La Peña, S.; Arroyo Helguera, O.E. Body mass index is associated with interleukin-1, adiponectin, oxidative stress and ioduria levels in healthy adults. *Nutr. Hosp.* **2018**, *35*, 841. [CrossRef] [PubMed]
185. Li, G.; Feng, D.; Qu, X.; Fu, J.; Wang, Y.; Li, L.; Li, L.; Han, L.; Esangbedo, I.C.; Li, M.; et al. Role of adipokines FGF21, leptin and adiponectin in self-concept of youths with obesity. *Eur. Neuropsychopharmacol.* **2018**, *28*, 892–902. [CrossRef] [PubMed]
186. Vasileiadis, G.K.; Lundell, A.-C.; Zhang, Y.; Andersson, K.; Gjertsson, I.; Rudin, A.; Maglio, C. Adipocytokines in Untreated Newly Diagnosed Rheumatoid Arthritis: Association with Circulating Chemokines and Markers of Inflammation. *Biomolecules* **2021**, *11*, 325. [CrossRef]
187. Otero, M.; Lago, R.; Gomez, R.; Lago, F.; Dieguez, C.; Gómez-Reino, J.J.; Gualillo, O. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **2006**, *65*, 1198–1201. [CrossRef]
188. Yoshino, T.; Kusunoki, N.; Tanaka, N.; Kaneko, K.; Kusunoki, Y.; Endo, H.; Hasunuma, T.; Kawai, S. Elevated Serum Levels of Resistin, Leptin, and Adiponectin are Associated with C-reactive Protein and also Other Clinical Conditions in Rheumatoid Arthritis. *Intern. Med.* **2011**, *50*, 269–275. [CrossRef] [PubMed]
189. Nugzar, O.; Zandman-Goddard, G.; Oz, H.; Lakstein, D.; Feldbrin, Z.; Shargorodsky, M. The role of ferritin and adiponectin as predictors of cartilage damage assessed by arthroscopy in patients with symptomatic knee osteoarthritis. *Best Pract. Res. Clin. Rheumatol.* **2018**, *32*, 662–668. [CrossRef] [PubMed]
190. Taylor, E.B. The complex role of adipokines in obesity, inflammation, and autoimmunity. *Clin. Sci.* **2021**, *135*, 731–752. [CrossRef]
191. Ko, C.-Y.; Lin, Y.-Y.; Achudhan, D.; Chang, J.-W.; Liu, S.-C.; Lai, C.-Y.; Huang, Y.-L.; Tsai, C.-H.; Fong, Y.-C.; Chen, H.-T.; et al. Omentin-1 ameliorates the progress of osteoarthritis by promoting IL-4-dependent anti-inflammatory responses and M2 macrophage polarization. *Int. J. Biol. Sci.* **2023**, *19*, 5275–5289. [CrossRef]
192. Chai, B.; Zheng, Z.-H.; Liao, X.; Li, K.-Y.; Liang, J.-S.; Huang, Y.-X.; Tong, C.-J.; Ou, D.-J.; Lu, J. The protective role of omentin-1 in IL-1β-induced chondrocyte senescence. *Artif. Cells Nanomed. Biotechnol.* **2020**, *48*, 8–14. [CrossRef] [PubMed]
193. Economou, A.; Mallia, I.; Fioravanti, A.; Gentileschi, S.; Nacci, F.; Bellando Randone, S.; Lepri, G.; Guiducci, S. The Role of Adipokines between Genders in the Pathogenesis of Osteoarthritis. *Int. J. Mol. Sci.* **2024**, *25*, 10865. [CrossRef] [PubMed]
194. Valencak, T.G.; Osterrieder, A.; Schulz, T.J. Sex matters: The effects of biological sex on adipose tissue biology and energy metabolism. *Redox Biol.* **2017**, *12*, 806–813. [CrossRef] [PubMed]
195. Alissa, E.M.; Al-Salmi, M.M.; Alama, N.A.; Ferns, G.A. Role of omentin-1 and C-reactive protein in obese subjects with subclinical inflammation. *J. Clin. Transl. Endocrinol.* **2016**, *3*, 7–11. [CrossRef]
196. Çimen, A. Serum Omentin-1 Levels and Endothelial Dysfunction in Obesity. *Acta Endo.* **2017**, *13*, 138–143. [CrossRef]
197. Oświęcimska, J.; Suwała, A.; Świętochowska, E.; Ostrowska, Z.; Gorczyca, P.; Ziora-Jakutowicz, K.; Machura, E.; Szczepańska, M.; Kukla, M.; Stojewska, M.; et al. Serum Omentin Levels in Adolescent Girls with Anorexia Nervosa and Obesity. *Physiol. Res.* **2015**, *64*, 701–709. [CrossRef]
198. Robinson, C.; Tsang, L.; Solomon, A.; Woodiwiss, A.J.; Gunter, S.; Millen, A.M.E.; Norton, G.R.; Fernandez-Lopez, M.J.; Hollan, I.; Dessein, P.H. Omentin concentrations are independently associated with those of matrix metalloproteinase-3 in patients with mild but not severe rheumatoid arthritis. *Rheumatol. Int.* **2017**, *37*, 3–11. [CrossRef]
199. Li, Z.-G.; Zhao, D.-W.; Xia, C.-J.; Wang, T.-N.; Liu, Y.-P.; Zhang, Y.; Wang, B.-J. Decreased synovial fluid omentin-1 concentrations reflect symptomatic severity in patients with knee osteoarthritis. *Scand. J. Clin. Lab. Investig.* **2012**, *72*, 623–628. [CrossRef]
200. Chi, Y.; Chai, J.; Xu, C.; Luo, H.; Zhang, Q. Apelin inhibits the activation of the nucleotide-binding domain and the leucine-rich, repeat-containing family, pyrin-containing 3 (NLRP3) inflammasome and ameliorates insulin resistance in severely burned rats. *Surgery* **2015**, *157*, 1142–1152. [CrossRef]
201. Wang, X.; Zhang, L.; Li, P.; Zheng, Y.; Yang, Y.; Ji, S. Apelin/APJ system in inflammation. *Int. Immunopharmacol.* **2022**, *109*, 108822. [CrossRef]
202. Hu, P.-F.; Chen, W.-P.; Tang, J.-L.; Bao, J.-P.; Wu, L.-D. Apelin plays a catabolic role on articular cartilage: In vivo and in vitro studies. *Int. J. Mol. Med.* **2010**, *26*, 357–363. [CrossRef]

203. Anima, B.; Gurusubramanian, G.; Roy, V.K. Hormonal dependent expression of apelin and apelin receptor in the ovary and uterus of mice. *Reprod. Biol.* **2024**, *24*, 100918. [CrossRef] [PubMed]
204. Tekin, S.; Erden, Y.; Sandal, S.; Etem Onalan, E.; Ozyalin, F.; Ozen, H.; Yilmaz, B. Effects of apelin on reproductive functions: Relationship with feeding behavior and energy metabolism. *Arch. Physiol. Biochem.* **2017**, *123*, 9–15. [CrossRef] [PubMed]
205. Butruille, L.; Drougard, A.; Knauf, C.; Moitrot, E.; Valet, P.; Storme, L.; Deruelle, P.; Lesage, J. The apelinergic system: Sexual dimorphism and tissue-specific modulations by obesity and insulin resistance in female mice. *Peptides* **2013**, *46*, 94–101. [CrossRef]
206. Zhou, Q.; Chen, L.; Tang, M.; Guo, Y.; Li, L. Apelin/APJ system: A novel promising target for anti-aging intervention. *Clin. Chim. Acta* **2018**, *487*, 233–240. [CrossRef]
207. Rai, R.; Ghosh, A.K.; Eren, M.; Mackie, A.R.; Levine, D.C.; Kim, S.-Y.; Cedernaes, J.; Ramirez, V.; Procissi, D.; Smith, L.H.; et al. Downregulation of the Apelinergic Axis Accelerates Aging, whereas Its Systemic Restoration Improves the Mammalian Healthspan. *Cell Rep.* **2017**, *21*, 1471–1480. [CrossRef]
208. Soriguer, F.; Garrido-Sanchez, L.; Garcia-Serrano, S.; Garcia-Almeida, J.M.; Garcia-Arnes, J.; Tinahones, F.J.; Garcia-Fuentes, E. Apelin Levels Are Increased in Morbidly Obese Subjects with Type 2 Diabetes Mellitus. *Obes. Surg.* **2009**, *19*, 1574–1580. [CrossRef]
209. Castan-Laurell, I.; Vítkova, M.; Daviaud, D.; Dray, C.; Kováčiková, M.; Kovacova, Z.; Hejnova, J.; Stich, V.; Valet, P. Effect of hypocaloric diet-induced weight loss in obese women on plasma apelin and adipose tissue expression of apelin and APJ. *Eur. J. Endocrinol.* **2008**, *158*, 905–910. [CrossRef]
210. Di Franco, M.; Spinelli, F.R.; Metere, A.; Gerardi, M.C.; Conti, V.; Boccalini, F.; Iannuccelli, C.; Ciciarello, F.; Agati, L.; Valesini, G. Serum Levels of Asymmetric Dimethylarginine and Apelin as Potential Markers of Vascular Endothelial Dysfunction in Early Rheumatoid Arthritis. *Mediat. Inflamm.* **2012**, *2012*, 347268. [CrossRef]
211. Chang, T.-K.; Zhong, Y.-H.; Liu, S.-C.; Huang, C.-C.; Tsai, C.-H.; Lee, H.-P.; Wang, S.-W.; Hsu, C.-J.; Tang, C.-H. Apelin Promotes Endothelial Progenitor Cell Angiogenesis in Rheumatoid Arthritis Disease via the miR-525-5p/Angiopoietin-1 Pathway. *Front. Immunol.* **2021**, *12*, 737990. [CrossRef]
212. Wang, Y.-H.; Kuo, S.-J.; Liu, S.-C.; Wang, S.-W.; Tsai, C.-H.; Fong, Y.-C.; Tang, C.-H. Apelin Affects the Progression of Osteoarthritis by Regulating VEGF-Dependent Angiogenesis and miR-150-5p Expression in Human Synovial Fibroblasts. *Cells* **2020**, *9*, 594. [CrossRef] [PubMed]
213. Heiker, J.T. Vaspin (serpinA12) in obesity, insulin resistance, and inflammation: Molecular mechanisms of vaspin function. *J. Pept. Sci.* **2014**, *20*, 299–306. [CrossRef]
214. Wang, J.; Zhang, K.; Zhang, S.; Guan, Z. Vaspin promotes chondrogenic differentiation of BMSCs via Akt activation in osteoarthritis. *BMC Musculoskelet. Disord.* **2022**, *23*, 344. [CrossRef] [PubMed]
215. Wyskida, K.; Franik, G.; Wikarek, T.; Owczarek, A.; Delroba, A.; Chudek, J.; Sikora, J.; Olszanecka-Glinianowicz, M. The levels of adipokines in relation to hormonal changes during the menstrual cycle in young, normal-weight women. *Endocr. Connect.* **2017**, *6*, 892–900. [CrossRef] [PubMed]
216. Esteghamati, A.; Mousavizadeh, M.; Noshad, S.; Zandieh, A.; Zarei, H.; Nakhjavani, M. Gender-dependent Effects of Metformin on Vaspin and Adiponectin in Type 2 Diabetes Patients: A Randomized Clinical Trial. *Horm. Metab. Res.* **2012**, *45*, 319–325. [CrossRef]
217. Youn, B.-S.; Klöting, N.; Kratzsch, J.; Lee, N.; Park, J.W.; Song, E.-S.; Ruschke, K.; Oberbach, A.; Fasshauer, M.; Stumvoll, M.; et al. Serum Vaspin Concentrations in Human Obesity and Type 2 Diabetes. *Diabetes* **2008**, *57*, 372–377. [CrossRef]
218. Chamorro-Melo, Y.; Calixto, O.-J.; Bello-Gualtero, J.; Bautista-Molano, W.; Beltran-Ostos, A.; Romero-Sánchez, C. Evaluation of the adipokine profile (adiponectin, resistin, adipsin, vaspin, and leptin) in patients with early rheumatoid arthritis and its correlation with disease activity. *Reumatologia* **2022**, *60*, 192–199. [CrossRef]
219. Bao, J.-P.; Jiang, L.-F.; Chen, W.-P.; Hu, P.-F.; Wu, L.-D. Expression of vaspin in the joint and the levels in the serum and synovial fluid of patients with osteoarthritis. *Int. J. Clin. Exp. Med.* **2014**, *7*, 3447–3453.
220. Martel-Pelletier, J.; Raynauld, J.-P.; Dorais, M.; Abram, F.; Pelletier, J.-P. The levels of the adipokines adipsin and leptin are associated with knee osteoarthritis progression as assessed by MRI and incidence of total knee replacement in symptomatic osteoarthritis patients: Apost hocanalysis. *Rheumatology* **2016**, *55*, 680–688. [CrossRef]
221. Bitirim, C.V.; Ozer, Z.B.; Akcali, K.C. Estrogen receptor alpha regulates the expression of adipogenic genes genetically and epigenetically in rat bone marrow-derived mesenchymal stem cells. *PeerJ* **2021**, *9*, e12071. [CrossRef]
222. Ramirez, M.F.; Pan, A.S.; Parekh, J.K.; Owunna, N.; Courchesne, P.; Larson, M.G.; Levy, D.; Murabito, J.M.; Ho, J.E.; Lau, E.S. Sex Differences in Protein Biomarkers and Measures of Fat Distribution. *J. Am. Heart Assoc.* **2024**, *13*, e000223. [CrossRef]
223. Milek, M.; Moulla, Y.; Kern, M.; Stroh, C.; Dietrich, A.; Schön, M.R.; Gärtner, D.; Lohmann, T.; Dressler, M.; Kovacs, P.; et al. Adipsin Serum Concentrations and Adipose Tissue Expression in People with Obesity and Type 2 Diabetes. *Int. J. Mol. Sci.* **2022**, *23*, 2222. [CrossRef]
224. Maity, S.K.; Das Sharma, A.; Sarkar, J.; Chaudhuri, T.; Tantia, O.; Chakrabarti, P. Adipose tissue–derived adipsin marks human aging in non-type 2 diabetes population. *BMJ Open Diab. Res. Care* **2024**, *12*, e004179. [CrossRef] [PubMed]

225. Romero-Sánchez, C.; De Avila, J.; Ramos-Casallas, A.; Chila-Moreno, L.; Delgadillo, N.A.; Chalem-Choueka, P.; Pacheco-Tena, C.; Bello-Gualtero, J.M.; Bautista-Molano, W. High Levels of Leptin and Adipsin Are Associated with Clinical Activity in Early Rheumatoid Arthritis Patients with Overweight and Periodontal Infection. *Diagnostics* **2023**, *13*, 1126. [CrossRef] [PubMed]
226. Cordero-Barreal, A.; González-Rodríguez, M.; Ruiz-Fernández, C.; Eldjoudi, D.A.; AbdElHafez, Y.R.F.; Lago, F.; Conde, J.; Gómez, R.; González-Gay, M.A.; Mobasheri, A.; et al. An Update on the Role of Leptin in the Immuno-Metabolism of Cartilage. *Int. J. Mol. Sci.* **2021**, *22*, 2411. [CrossRef] [PubMed]
227. Koskinen, A.; Vuolteenaho, K.; Nieminen, R.; Moilanen, T.; Moilanen, E. Leptin enhances MMP-1, MMP-3 and MMP-13 production in human osteoarthritic cartilage and correlates with MMP-1 and MMP-3 in synovial fluid from OA patients. *Clin. Exp. Rheumatol.* **2011**, *29*, 57–64.
228. Berry, P.A.; Jones, S.W.; Cicuttini, F.M.; Wluka, A.E.; Maciewicz, R.A. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. *Arthritis Rheum.* **2011**, *63*, 700–707. [CrossRef]
229. Luukkaa, V.; Pesonen, U.; Huhtaniemi, I.; Lehtonen, A.; Tilvis, R.; Tuomilehto, J.; Koulu, M.; Huupponen, R. Inverse Correlation between Serum Testosterone and Leptin in Men1. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 3243–3246. [CrossRef]
230. Elbers, J.M.H.; Asscheman, H.; Seidell, J.C.; Frölich, M.; Meinders, A.E.; Gooren, L.J.G. Reversal of the Sex Difference in Serum Leptin Levels upon Cross-Sex Hormone Administration in Transsexuals. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 3267–3270. [CrossRef]
231. Guerra, B.; Fuentes, T.; Delgado-Guerra, S.; Guadalupe-Grau, A.; Olmedillas, H.; Santana, A.; Ponce-Gonzalez, J.G.; Dorado, C.; Calbet, J.A.L. Gender Dimorphism in Skeletal Muscle Leptin Receptors, Serum Leptin and Insulin Sensitivity. *PLoS ONE* **2008**, *3*, e3466. [CrossRef]
232. Seyfart, T.; Friedrich, N.; Kische, H.; Bülow, R.; Wallaschofski, H.; Völzke, H.; Nauck, M.; Keevil, B.G.; Haring, R. Association of sex hormones with physical, laboratory, and imaging markers of anthropometry in men and women from the general population. *PLoS ONE* **2018**, *13*, e0189042. [CrossRef]
233. Hellström, L.; Wahrenberg, H.; Hruska, K.; Reynisdottir, S.; Arner, P. Mechanisms behind gender differences in circulating leptin levels. *J. Intern. Med.* **2000**, *247*, 457–462. [CrossRef]
234. Roszkowska-Gancarz, M.; Jonas, M.; Owczarz, M.; Kurylowicz, A.; Polosak, J.; Franek, E.; Slusarczyk, P.; Mossakowska, M.; Puzianowska-Kuznicka, M. Age-related changes of leptin and leptin receptor variants in healthy elderly and long-lived adults. *Geriatr. Gerontol. Int.* **2015**, *15*, 365–371. [CrossRef] [PubMed]
235. Würfel, M.; Breitfeld, J.; Gebhard, C.; Scholz, M.; Baber, R.; Riedel-Heller, S.G.; Blüher, M.; Stumvoll, M.; Kovacs, P.; Tönjes, A. Interplay between adipose tissue secreted proteins, eating behavior and obesity. *Eur. J. Nutr.* **2022**, *61*, 885–899. [CrossRef] [PubMed]
236. Kluzek, S.; Arden, N.K.; Newton, J. Adipokines as potential prognostic biomarkers in patients with acute knee injury. *Biomarkers* **2015**, *20*, 519–525. [CrossRef]
237. Lee, J.H.; Ort, T.; Ma, K.; Picha, K.; Carton, J.; Marsters, P.A.; Lohmander, L.S.; Baribaud, F.; Song, X.-Y.R.; Blake, S. Resistin is elevated following traumatic joint injury and causes matrix degradation and release of inflammatory cytokines from articular cartilage in vitro. *Osteoarthr. Cartil.* **2009**, *17*, 613–620. [CrossRef]
238. Zhao, C.-W.; Song, W.-X.; Liu, B.; Gao, Y.-H.; Ding, L.; Huang, Y.-F.; Qi, X. Resistin induces chemokine and matrix metalloproteinase production via CAP1 receptor and activation of p38-MAPK and NF-κB signalling pathways in human chondrocytes. *Pathog. Rheum. Arthritis One Year Rev.* **2022**, *40*, 501–513. [CrossRef]
239. Siemińska, L.; Cichoń-Lenart, A.; Kajdaniuk, D.; Kos-Kudła, B.; Marek, B.; Lenart, J.; Nowak, M. Sex hormones and adipocytokines in postmenopausal women. *Pol. Merkur. Lek.* **2006**, *20*, 727–730.
240. Massengale, M.; Lu, B.; Pan, J.J.; Katz, J.N.; Solomon, D.H. Adipokine Hormones and Hand Osteoarthritis: Radiographic Severity and Pain. *PLoS ONE* **2012**, *7*, e47860. [CrossRef]
241. Presle, N.; Pottie, P.; Dumond, H.; Guillaume, C.; Lapicque, F.; Pallu, S.; Mainard, D.; Netter, P.; Terlain, B. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. *Osteoarthr. Cartil.* **2006**, *14*, 690–695. [CrossRef]
242. Ohmori, R.; Momiyama, Y.; Kato, R.; Taniguchi, H.; Ogura, M.; Ayaori, M.; Nakamura, H.; Ohsuzu, F. Associations Between Serum Resistin Levels and Insulin Resistance, Inflammation, and Coronary Artery Disease. *J. Am. Coll. Cardiol.* **2005**, *46*, 379–380. [CrossRef] [PubMed]
243. Vozarova De Courten, B.; Degawa-Yamauchi, M.; Considine, R.V.; Tataranni, P.A. High Serum Resistin Is Associated with an Increase in Adiposity But Not a Worsening of Insulin Resistance in Pima Indians. *Diabetes* **2004**, *53*, 1279–1284, Erratum in *Diabetes* **2004**, *53*, 2518. https://doi.org/10.2337/diabetes.53.9.2518. [CrossRef] [PubMed]
244. Onyemelukwe, O.U.; Ogoina, D.; Onyemelukwe, G.C. Effect of Obesity on Resistin Concentrations in Normal, Pre-Obese and Obese Apparently Healthy Nigerian-Africans. *West Afr. J. Med.* **2022**, *39*, 702–791.
245. Vasileva, E.; Stankova, T.; Batalov, K.; Staynova, R.; Nonchev, B.; Bivolarska, A.; Karalilova, R. Association of serum and synovial adipokines (chemerin and resistin) with inflammatory markers and ultrasonographic evaluation scores in patients with knee joint osteoarthritis—A pilot study. *Rheumatol. Int.* **2024**, *44*, 1997–2005. [CrossRef]

246. Duan, Y.; Hao, D.; Li, M.; Wu, Z.; Li, D.; Yang, X.; Qiu, G. Increased synovial fluid visfatin is positively linked to cartilage degradation biomarkers in osteoarthritis. *Rheumatol. Int.* **2012**, *32*, 985–990. [CrossRef]
247. Annie, L.; Gurusubramanian, G.; Roy, V.K. Estrogen and progesterone dependent expression of visfatin/NAMPT regulates proliferation and apoptosis in mice uterus during estrous cycle. *J. Steroid Biochem. Mol. Biol.* **2019**, *185*, 225–236. [CrossRef]
248. Rempuia, V.; Gurusubramanian, G.; Roy, V.K. Intra-testicular visfatin inhibition disrupts androgen and estrogen signalling in the mouse testis. *Reprod. Biol.* **2024**, *24*, 100956. [CrossRef]
249. Chen, W.; Bao, J.; Feng, J.; Hu, P.; Shi, Z.; Wu, L. Increased serum concentrations of visfatin and its production by different joint tissues in patients with osteoarthritis. *Clin. Chem. Lab. Med.* **2010**, *48*, 1141–1145. [CrossRef]
250. Jurdana, M.; Petelin, A.; Černelič Bizjak, M.; Bizjak, M.; Biolo, G.; Jenko-Pražnikar, Z. Increased serum visfatin levels in obesity and its association with anthropometric/biochemical parameters, physical inactivity and nutrition. *e-SPEN J.* **2013**, *8*, e59–e67. [CrossRef]
251. Ugur, K.; Erman, F.; Turkoglu, S.; Aydin, Y.; Aksoy, A.; Lale, A.; Karagöz, Z.K.; Ugur, İ.; Akkoc, R.F.; Yalniz, M. Asprosin, visfatin and subfatin as new biomarkers of obesity and metabolic syndrome. *Eur. Rev. Med. Pharmacol. Sci.* **2022**, *26*, 2124–2133. [CrossRef]
252. Lee, Y.H.; Bae, S. Circulating adiponectin and visfatin levels in rheumatoid arthritis and their correlation with disease activity: A meta-analysis. *Int. J. Rheum. Dis.* **2018**, *21*, 664–672. [CrossRef] [PubMed]
253. Iannone, F.; Lapadula, G. Chemerin/ChemR23 pathway: A system beyond chemokines. *Arthritis Res. Ther.* **2011**, *13*, 104. [CrossRef] [PubMed]
254. Li, L.; Ma, P.; Huang, C.; Liu, Y.; Zhang, Y.; Gao, C.; Xiao, T.; Ren, P.-G.; Zabel, B.A.; Zhang, J.V. Expression of chemerin and its receptors in rat testes and its action on testosterone secretion. *J. Endocrinol.* **2014**, *220*, 155–163. [CrossRef] [PubMed]
255. Han, L.; Zhang, Y.; Wan, S.; Wei, Q.; Shang, W.; Huang, G.; Fang, P.; Min, W. Loss of chemerin triggers bone remodeling in vivo and in vitro. *Mol. Metab.* **2021**, *53*, 101322. [CrossRef]
256. Stejskal, D.; Karpisek, M.; Hanulova, Z.; Svestak, M. Chemerin is an independent marker of the metabolic syndrome in a caucasian population—A pilot study. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub.* **2008**, *152*, 217–221. [CrossRef]
257. Aronis, K.N.; Sahin-Efe, A.; Chamberland, J.P.; Spiro, A.; Vokonas, P.; Mantzoros, C.S. Chemerin levels as predictor of acute coronary events: A case–control study nested within the veterans affairs normative aging study. *Metabolism* **2014**, *63*, 760–766. [CrossRef]
258. Chang, S.; Eisenberg, D.; Zhao, L.; Adams, C.; Leib, R.; Morser, J.; Leung, L. Chemerin activation in human obesity. *Obesity* **2016**, *24*, 1522–1529. [CrossRef]
259. Dessein, P.H.; Tsang, L.; Woodiwiss, A.J.; Norton, G.R.; Solomon, A. Circulating Concentrations of the Novel Adipokine Chemerin Are Associated with Cardiovascular Disease Risk in Rheumatoid Arthritis. *J. Rheumatol.* **2014**, *41*, 1746–1754. [CrossRef]
260. Zhao, Y.-L.; Zhang, T.-P.; Wu, J.; Li, B.-Z.; Li, X.-M.; Pan, H.-F.; Ye, D.-Q. Association of adiponectin and adiponectin receptor gene polymorphisms with rheumatoid arthritis in a Chinese population. *Postgrad. Med. J.* **2020**, *96*, 149–155. [CrossRef]
261. Chen, H.; Mi, S.; Zhu, J.; Jin, W.; Li, Y.; Wang, T.; Li, Y.; Fan, C. No Causal Association Between Adiponectin and the Risk of Rheumatoid Arthritis: A Mendelian Randomization Study. *Front. Genet.* **2021**, *12*, 670282. [CrossRef]
262. Elnemr, R.; El Hamid, M.M.A.; Taleb, R.S.Z.; Khalil, N.F.W.; El-Sherif, S.M. Study of adiponectin gene (rs1501299) polymorphism and serum adiponectin level in patients with primary knee osteoarthritis. *Hum. Genom.* **2024**, *18*, 105. [CrossRef]
263. Zhan, D.; Thumtecho, S.; Tanavalee, A.; Yuktanandana, P.; Anomasiri, W.; Honsawek, S. Association of adiponectin gene polymorphisms with knee osteoarthritis. *World J. Orthop.* **2017**, *8*, 719. [CrossRef] [PubMed]
264. Jiang, L.; Zhu, X.; Rong, J.; Xing, B.; Wang, S.; Liu, A.; Chu, M.; Huang, G. Obesity, osteoarthritis and genetic risk: The rs182052 polymorphism in the ADIPOQ gene is potentially associated with risk of knee osteoarthritis. *Bone Jt. Res.* **2018**, *7*, 494–500. [CrossRef] [PubMed]
265. Wang, Y.; Meng, F.; Wu, J.; Long, H.; Li, J.; Wu, Z.; He, H.; Wang, H.; Wang, N.; Xie, D. Associations between adipokines gene polymorphisms and knee osteoarthritis: A meta-analysis. *BMC Musculoskelet. Disord.* **2022**, *23*, 166. [CrossRef]
266. Shang, H.; Hao, Y.; Hu, W.; Hu, X.; Jin, Q. Association between ADIPOQ gene variants and knee osteoarthritis in a Chinese population. *Biosci. Rep.* **2019**, *39*, BSR20182104. [CrossRef]
267. Wahba, A.S.; Ibrahim, M.E.; Abo-elmatty, D.M.; Mehanna, E.T. Association of the Adipokines Chemerin, Apelin, Vaspin and Omentin and Their Functional Genetic Variants with Rheumatoid Arthritis. *J. Pers. Med.* **2021**, *11*, 976. [CrossRef]
268. Chen, R.; Zhang, Y.; Xu, H.; Hu, H.; Chen, M.; Shuai, Z. Val109Asp Polymorphism of the Omentin-1 Gene and Incidence of Knee Osteoarthritis in a Chinese Han Population: A Correlation Analysis. *Drug Des. Dev. Ther.* **2021**, *15*, 5075–5086. [CrossRef]
269. Wang, C.; Zhang, R. The effect of ITLN1, XCL2 and DOT1L variants on knee osteoarthritis risk in the Han population. *Arch. Orthop. Trauma. Surg.* **2023**, *143*, 4821–4831. [CrossRef]
270. Tao, S.-S.; Dan, Y.-L.; Wu, G.-C.; Zhang, Q.; Zhang, T.-P.; Fan, Y.-G.; Pan, H.-F. Association of *Leptin* Gene Polymorphisms with Rheumatoid Arthritis in a Chinese Population. *BioMed Res. Int.* **2020**, *2020*, 3789319. [CrossRef]
271. Qin, J.; Shi, D.; Dai, J.; Zhu, L.; Tsezou, A.; Jiang, Q. Association of the leptin gene with knee osteoarthritis susceptibility in a Han Chinese population: A case–control study. *J. Hum. Genet.* **2010**, *55*, 704–706. [CrossRef]
272. Li, H.; Zhang, T.; Li, X.; Pan, H.; Ma, D. Association of single nucleotide polymorphisms in *resistin* gene with rheumatoid arthritis in a Chinese population. *Clin. Lab. Anal.* **2018**, *32*, e22595. [CrossRef] [PubMed]

273. Wang, L.; Tang, C.-H.; Lu, T.; Sun, Y.; Xu, G.; Huang, C.-C.; Yang, S.-F.; Su, C.-M. Resistin polymorphisms are associated with rheumatoid arthritis susceptibility in Chinese Han subjects. *Medicine* **2018**, *97*, e0177. [CrossRef] [PubMed]
274. Hämäläinen, S.; Solovieva, S.; Vehmas, T.; Hirvonen, A.; Leino-Arjas, P. Adipokine genes and radiographic hand osteoarthritis in Finnish women: A cross-sectional study. *Scand. J. Rheumatol.* **2018**, *47*, 71–78. [CrossRef] [PubMed]
275. Naqvi, S.K.B.; Murtaza, I.; Javed, Q. Role of resistin genetic variations in knee osteoarthritis pathogenesis, a cross sectional study. *Mol. Biol. Rep.* **2019**, *46*, 2657–2663. [CrossRef]
276. Yan, S.; Liu, H.; Nie, H.; Bu, G.; Yuan, W.; Wang, S. Common variants of RARRES2 and RETN contribute to susceptibility to hand osteoarthritis and related pain. *Biomark. Med.* **2022**, *16*, 731–738. [CrossRef]
277. Chu, M.; Rong, J.; Wang, Y.; Zhu, L.; Xing, B.; Tao, Y.; Zhuang, X.; Zhao, Y.; Jiang, L. Strong association of the polymorphisms in PBEF1 and knee OA risk: A two-stage population-based study in China. *Sci. Rep.* **2016**, *6*, 19094. [CrossRef]
278. Pratt, A.G.; Isaacs, J.D. Seronegative rheumatoid arthritis: Pathogenetic and therapeutic aspects. *Best Pract. Res. Clin. Rheumatol.* **2014**, *28*, 651–659. [CrossRef]
279. Malmström, V.; Catrina, A.I.; Klareskog, L. The immunopathogenesis of seropositive rheumatoid arthritis: From triggering to targeting. *Nat. Rev. Immunol.* **2017**, *17*, 60–75, Correction in *Nat. Rev. Immunol.* **2022**, *22*, 459. https://doi.org/10.1038/s41577-022-00741-0. [CrossRef]
280. Arleevskaya, M.; Takha, E.; Petrov, S.; Kazarian, G.; Novikov, A.; Larionova, R.; Valeeva, A.; Shuralev, E.; Mukminov, M.; Bost, C.; et al. Causal risk and protective factors in rheumatoid arthritis: A genetic update. *J. Transl. Autoimmun.* **2021**, *4*, 100119. [CrossRef]
281. Arleevskaya, M.I.; Kravtsova, O.A.; Lemerle, J.; Renaudineau, Y.; Tsibulkin, A.P. How Rheumatoid Arthritis Can Result from Provocation of the Immune System by Microorganisms and Viruses. *Front. Microbiol.* **2016**, *7*, 1296. [CrossRef]
282. De Hair, M.J.H.; Van De Sande, M.G.H.; Ramwadhdoebe, T.H.; Hansson, M.; Landewé, R.; Van Der Leij, C.; Maas, M.; Serre, G.; Van Schaardenburg, D.; Klareskog, L.; et al. Features of the Synovium of Individuals at Risk of Developing Rheumatoid Arthritis: Implications for Understanding Preclinical Rheumatoid Arthritis. *Arthritis Rheumatol.* **2014**, *66*, 513–522. [CrossRef]
283. Magalhães, R.; Stiehl, P.; Morawietz, L.; Berek, C.; Krenn, V. Morphological and molecular pathology of the B cell response in synovitis of rheumatoid arthritis. *Virchows Arch.* **2002**, *441*, 415–427. [CrossRef] [PubMed]
284. Musters, A.; Balzaretti, G.; Van Schaik, B.D.C.; Jongejan, A.; Van Der Weele, L.; Tas, S.W.; Van Kampen, A.H.C.; De Vries, N. In rheumatoid arthritis inflamed joints share dominant patient-specific B-cell clones. *Front. Immunol.* **2022**, *13*, 915687. [CrossRef] [PubMed]
285. Krishnamurthy, A.; Ytterberg, A.J.; Sun, M.; Sakuraba, K.; Steen, J.; Joshua, V.; Tarasova, N.K.; Malmström, V.; Wähämaa, H.; Réthi, B.; et al. Citrullination Controls Dendritic Cell Transdifferentiation into Osteoclasts. *J. Immunol.* **2019**, *202*, 3143–3150. [CrossRef] [PubMed]
286. Wigerblad, G.; Bas, D.B.; Fernades-Cerqueira, C.; Krishnamurthy, A.; Nandakumar, K.S.; Rogoz, K.; Kato, J.; Sandor, K.; Su, J.; Jimenez–Andrade, J.M.; et al. Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism. *Ann. Rheum. Dis.* **2016**, *75*, 730–738, Erratum in *Ann. Rheum. Dis.* **2019**, *78*, 865. https://doi.org/10.1136/annrheumdis-2015-208094corr1. [CrossRef]
287. Krishnamurthy, A.; Joshua, V.; Haj Hensvold, A.; Jin, T.; Sun, M.; Vivar, N.; Ytterberg, A.J.; Engström, M.; Fernandes-Cerqueira, C.; Amara, K.; et al. Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss. *Ann. Rheum. Dis.* **2016**, *75*, 721–729; Correction in *Ann. Rheum. Dis.* **2019**, *78*, 866 [CrossRef]
288. Harre, U.; Georgess, D.; Bang, H.; Bozec, A.; Axmann, R.; Ossipova, E.; Jakobsson, P.-J.; Baum, W.; Nimmerjahn, F.; Szarka, E.; et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. *J. Clin. Investig.* **2012**, *122*, 1791–1802. [CrossRef]
289. Romão, V.C.; Fonseca, J.E. Disease mechanisms in preclinical rheumatoid arthritis: A narrative review. *Front. Med.* **2022**, *9*, 689711. [CrossRef]
290. Cantaert, T.; Brouard, S.; Thurlings, R.M.; Pallier, A.; Salinas, G.F.; Braud, C.; Klarenbeek, P.L.; De Vries, N.; Zhang, Y.; Soulillou, J.; et al. Alterations of the synovial T cell repertoire in anti–citrullinated protein antibody–positive rheumatoid arthritis. *Arthritis Rheum.* **2009**, *60*, 1944–1956. [CrossRef]
291. Wu, X.; Liu, Y.; Jin, S.; Wang, M.; Jiao, Y.; Yang, B.; Lu, X.; Ji, X.; Fei, Y.; Yang, H.; et al. Single-cell sequencing of immune cells from anticitrullinated peptide antibody positive and negative rheumatoid arthritis. *Nat. Commun.* **2021**, *12*, 4977. [CrossRef]
292. Floudas, A.; Canavan, M.; McGarry, T.; Mullan, R.; Nagpal, S.; Veale, D.J.; Fearon, U. ACPA Status Correlates with Differential Immune Profile in Patients with Rheumatoid Arthritis. *Cells* **2021**, *10*, 647. [CrossRef]
293. Alivernini, S.; Bruno, D.; Tolusso, B.; Bui, L.; Petricca, L.; Gigante, M.R.; Birra, D.; Fedele, A.L.; Peluso, G.; Federico, F.; et al. Differential synovial tissue biomarkers among psoriatic arthritis and rheumatoid factor/anti-citrulline antibody-negative rheumatoid arthritis. *Arthritis Res. Ther.* **2019**, *21*, 116. [CrossRef] [PubMed]
294. Dennis, G.; Holweg, C.T.; Kummerfeld, S.K.; Choy, D.F.; Setiadi, A.F.; Hackney, J.A.; Haverty, P.M.; Gilbert, H.; Lin, W.Y.; Diehl, L.; et al. Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. *Arthritis Res. Ther.* **2014**, *16*, R90. [CrossRef] [PubMed]

295. De Stefano, L.; D'Onofrio, B.; Manzo, A.; Montecucco, C.; Bugatti, S. The Genetic, Environmental, and Immunopathological Complexity of Autoantibody-Negative Rheumatoid Arthritis. *Int. J. Mol. Sci.* **2021**, *22*, 12386. [CrossRef] [PubMed]
296. McGonagle, D.; Watad, A.; Savic, S. Mechanistic immunological based classification of rheumatoid arthritis. *Autoimmun. Rev.* **2018**, *17*, 1115–1123. [CrossRef]
297. Geng, Y.; Zhang, Z. Comparative study on the level of B lymphocyte stimulator (B ly S) and frequency of lymphocytes between sero-negative and sero-positive rheumatoid arthritis patients. *Int. J. Rheum. Dis.* **2012**, *15*, 478–485. [CrossRef]
298. Grunz, J.-P.; Gietzen, C.H.; Christopoulos, G.; Van Schoonhoven, J.; Goehtz, F.; Schmitt, R.; Hesse, N. Osteoarthritis of the Wrist: Pathology, Radiology, and Treatment. *Semin. Musculoskelet. Radiol.* **2021**, *25*, 294–303. [CrossRef]
299. Gleason, B.; Chisari, E.; Parvizi, J. Osteoarthritis Can Also Start in the Gut: The Gut–Joint Axis. *Indian J. Orthop.* **2022**, *56*, 1150–1155. [CrossRef]
300. Andersson, J.K.; Hagert, E.; Brittberg, M. Cartilage Injuries and Posttraumatic Osteoarthritis in the Wrist: A Review. *Cartilage* **2021**, *13*, 156S–168S. [CrossRef]
301. Watt, F.E. Hand osteoarthritis, menopause and menopausal hormone therapy. *Maturitas* **2016**, *83*, 13–18. [CrossRef]
302. Egloff, C.; Hügle, T.; Valderrabano, V. Biomechanics and pathomechanisms of osteoarthritis. *Swiss Med. Wkly.* **2012**, *142*, w13583. [CrossRef]
303. Goldring, M.B.; Otero, M. Inflammation in osteoarthritis. *Curr. Opin. Rheumatol.* **2011**, *23*, 471–478. [CrossRef]
304. Ene, R.; Sinescu, R.D.; Ene, P.; Cîrstoiu, M.M.; Cîrstoiu, F.C. Synovial inflammation in patients with different stages of knee osteoarthritis. *Rom. J. Morphol. Embryol.* **2015**, *56*, 169–173.
305. Sellam, J.; Berenbaum, F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat. Rev. Rheumatol.* **2010**, *6*, 625–635. [CrossRef]
306. Ponchel, F.; Burska, A.N.; Hensor, E.M.A.; Raja, R.; Campbell, M.; Emery, P.; Conaghan, P.G. Changes in peripheral blood immune cell composition in osteoarthritis. *Osteoarthr. Cartil.* **2015**, *23*, 1870–1878. [CrossRef]
307. Hu, W.; Chen, Y.; Dou, C.; Dong, S. Microenvironment in subchondral bone: Predominant regulator for the treatment of osteoarthritis. *Ann. Rheum. Dis.* **2021**, *80*, 413–422. [CrossRef]
308. Li, G.; Yin, J.; Gao, J.; Cheng, T.S.; Pavlos, N.J.; Zhang, C.; Zheng, M.H. Subchondral bone in osteoarthritis: Insight into risk factors and microstructural changes. *Arthritis Res. Ther.* **2013**, *15*, 223. [CrossRef]
309. Li, Y.; Shen, Y.; Jin, K.; Wen, Z.; Cao, W.; Wu, B.; Wen, R.; Tian, L.; Berry, G.J.; Goronzy, J.J.; et al. The DNA Repair Nuclease MRE11A Functions as a Mitochondrial Protector and Prevents T Cell Pyroptosis and Tissue Inflammation. *Cell Metab.* **2019**, *30*, 477–492.e6. [CrossRef] [PubMed]
310. Khandpur, R.; Carmona-Rivera, C.; Vivekanandan-Giri, A.; Gizinski, A.; Yalavarthi, S.; Knight, J.S.; Friday, S.; Li, S.; Patel, R.M.; Subramanian, V.; et al. NETs Are a Source of Citrullinated Autoantigens and Stimulate Inflammatory Responses in Rheumatoid Arthritis. *Sci. Transl. Med.* **2013**, *5*, 178ra40. [CrossRef] [PubMed]
311. Zec, K.; Schonfeldova, B.; Ai, Z.; Van Grinsven, E.; Pirgova, G.; Eames, H.L.; Berthold, D.L.; Attar, M.; Compeer, E.B.; Arnon, T.I.; et al. Macrophages in the synovial lining niche initiate neutrophil recruitment and articular inflammation. *J. Exp. Med.* **2023**, *220*, e20220595. [CrossRef] [PubMed]
312. O'Neil, L.J.; Oliveira, C.B.; Sandoval-Heglund, D.; Barrera-Vargas, A.; Merayo-Chalico, J.; Aguirre-Aguilar, E.; Kaplan, M.J.; Carmona-Rivera, C. Anti-Carbamylated LL37 Antibodies Promote Pathogenic Bone Resorption in Rheumatoid Arthritis. *Front. Immunol.* **2021**, *12*, 715997. [CrossRef]
313. Wright, H.L.; Moots, R.J.; Edwards, S.W. The multifactorial role of neutrophils in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **2014**, *10*, 593–601. [CrossRef]
314. Feldman, M.; Ginsburg, I. A Novel Hypothetical Approach to Explain the Mechanisms of Pathogenicity of Rheumatic Arthritis. *Mediterr. J. Rheumatol.* **2021**, *32*, 112. [CrossRef]
315. Bromley, M.; Woolley, D.E. Histopathology of the rheumatoid lesion. *Arthritis Rheum.* **1984**, *27*, 857–863. [CrossRef]
316. Kraan, M.C.; Haringman, J.J.; Post, W.J.; Versendaal, J.; Breedveld, F.C.; Tak, P.P. Immunohistological analysis of synovial tissue for differential diagnosis in early arthritis. *Rheumatology* **1999**, *38*, 1074–1080. [CrossRef] [PubMed]
317. Bery, A.I.; Shepherd, H.M.; Li, W.; Krupnick, A.S.; Gelman, A.E.; Kreisel, D. Role of tertiary lymphoid organs in the regulation of immune responses in the periphery. *Cell. Mol. Life Sci.* **2022**, *79*, 359. [CrossRef] [PubMed]
318. Thurlings, R.M.; Wijbrandts, C.A.; Mebius, R.E.; Cantaert, T.; Dinant, H.J.; Van Der Pouw-Kraan, T.C.T.M.; Verweij, C.L.; Baeten, D.; Tak, P.P. Synovial lymphoid neogenesis does not define a specific clinical rheumatoid arthritis phenotype. *Arthritis Rheum.* **2008**, *58*, 1582–1589. [CrossRef] [PubMed]
319. Klimiuk, P.A.; Sierakowski, S.; Latosiewicz, R.; Cylwik, J.P.; Cylwik, B.; Skowronski, J.; Chwiecko, J. Soluble adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and vascular endothelial growth factor (VEGF) in patients with distinct variants of rheumatoid synovitis. *Ann. Rheum. Dis.* **2002**, *61*, 804–809. [CrossRef]
320. Klimiuk, P.A.; Goronzy, J.J.; Björnsson, J.; Beckenbaugh, R.D.; Weyand, C.M. Tissue cytokine patterns distinguish variants of rheumatoid synovitis. *Am. J. Pathol.* **1997**, *151*, 1311–1319.

321. Humby, F.; Bombardieri, M.; Manzo, A.; Kelly, S.; Blades, M.C.; Kirkham, B.; Spencer, J.; Pitzalis, C. Ectopic Lymphoid Structures Support Ongoing Production of Class-Switched Autoantibodies in Rheumatoid Synovium. *PLoS Med.* **2009**, *6*, e1. [CrossRef]
322. Rosengren, S.; Wei, N.; Kalunian, K.C.; Zvaifler, N.J.; Kavanaugh, A.; Boyle, D.L. Elevated autoantibody content in rheumatoid arthritis synovia with lymphoid aggregates and the effect of rituximab. *Arthritis Res. Ther.* **2008**, *10*, R105. [CrossRef] [PubMed]
323. Corsiero, E.; Bombardieri, M.; Carlotti, E.; Pratesi, F.; Robinson, W.; Migliorini, P.; Pitzalis, C. Single cell cloning and recombinant monoclonal antibodies generation from RA synovial B cells reveal frequent targeting of citrullinated histones of NETs. *Ann. Rheum. Dis.* **2016**, *75*, 1866–1875. [CrossRef] [PubMed]
324. Corsiero, E.; Jagemann, L.; Perretti, M.; Pitzalis, C.; Bombardieri, M. Characterization of a Synovial B Cell–Derived Recombinant Monoclonal Antibody Targeting Stromal Calreticulin in the Rheumatoid Joints. *J. Immunol.* **2018**, *201*, 1373–1381. [CrossRef] [PubMed]
325. Randen, I.; Mellbye, O.J.; Førre, Ø.; Natvig, J.B. The Identification of Germinal Centres and Follicular Dendritic Cell Networks in Rheumatoid Synovial Tissue. *Scand. J. Immunol.* **1995**, *41*, 481–486. [CrossRef]
326. Krenn, V.; Morawietz, L.; Häupl, T.; Neidel, J.; Petersen, I.; König, A. Grading of Chronic Synovitis—A Histopathological Grading System for Molecular and Diagnostic Pathology. *Pathol.-Res. Pract.* **2002**, *198*, 317–325. [CrossRef]
327. Klaasen, R.; Thurlings, R.M.; Wijbrandts, C.A.; Van Kuijk, A.W.; Baeten, D.; Gerlag, D.M.; Tak, P.P. The relationship between synovial lymphocyte aggregates and the clinical response to infliximab in rheumatoid arthritis: A prospective study. *Arthritis Rheum.* **2009**, *60*, 3217–3224. [CrossRef]
328. Tak, P.P.; Smeets, T.J.M.; Daha, M.R.; Kluin, P.M.; Meijers, K.A.E.; Brand, R.; Meinders, A.E.; Breedveld, F.C. Analysis of the synovial cell infiltrate in early rheumatoid synovial tissue in relation to local disease activity. *Arthritis Rheum.* **1997**, *40*, 217–225. [CrossRef]
329. Cañete, J.D.; Celis, R.; Moll, C.; Izquierdo, E.; Marsal, S.; Sanmartí, R.; Palacín, A.; Lora, D.; De La Cruz, J.; Pablos, J.L. Clinical significance of synovial lymphoid neogenesis and its reversal after anti-tumour necrosis factor α therapy in rheumatoid arthritis. *Ann. Rheum. Dis.* **2009**, *68*, 751–756. [CrossRef]
330. Sen, M.; Chamorro, M.; Reifert, J.; Corr, M.; Carson, D.A. Blockade of Wnt-5A/Frizzled 5 signaling inhibits rheumatoid synoviocyte activation. *Arthritis Rheum.* **2001**, *44*, 772–781. [CrossRef]
331. Korb-Pap, A.; Bertrand, J.; Sherwood, J.; Pap, T. Stable activation of fibroblasts in rheumatic arthritis—Causes and consequences. *Rheumatology* **2016**, *55*, ii64–ii67. [CrossRef]
332. Bustamante, M.F.; Garcia-Carbonell, R.; Whisenant, K.D.; Guma, M. Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. *Arthritis Res. Ther.* **2017**, *19*, 110. [CrossRef]
333. Jamora, C.; Fuchs, E. Intercellular adhesion, signalling and the cytoskeleton. *Nat. Cell. Biol.* **2002**, *4*, E101–E108. [CrossRef]
334. Sutton, S.; Clutterbuck, A.; Harris, P.; Gent, T.; Freeman, S.; Foster, N.; Barrett-Jolley, R.; Mobasheri, A. The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis. *Vet. J.* **2009**, *179*, 10–24. [CrossRef] [PubMed]
335. Rahmati, M.; Mobasheri, A.; Mozafari, M. Inflammatory mediators in osteoarthritis: A critical review of the state-of-the-art, current prospects, and future challenges. *Bone* **2016**, *85*, 81–90. [CrossRef] [PubMed]
336. Benito, M.J.; Veale, D.J.; FitzGerald, O.; Van Den Berg, W.B.; Bresnihan, B. Synovial tissue inflammation in early and late osteoarthritis. *Ann. Rheum. Dis.* **2005**, *64*, 1263–1267. [CrossRef] [PubMed]
337. Galushko, E.A.; Bolshakova, T.Y.; Vinogradova, I.B.; Ivanova, O.N.; Lesnyak, O.M.; Menshikova, L.V.; Petrachkova, T.N.; Erdes, S.F. Structure of rheumatic diseases among adult population of Russia according to data of an epidemiological study (preliminary results). *Rheumatol. Sci. Pract.* **2009**, *47*, 11–17. [CrossRef]
338. Van Oosterhout, M.; Bajema, I.; Levarht, E.W.N.; Toes, R.E.M.; Huizinga, T.W.J.; Van Laar, J.M. Differences in synovial tissue infiltrates between anti–cyclic citrullinated peptide–positive rheumatoid arthritis and anti–cyclic citrullinated peptide–negative rheumatoid arthritis. *Arthritis Rheum.* **2008**, *58*, 53–60. [CrossRef]
339. Christensen, A.F.; Lindegaard, H.; Hørslev-Petersen, K.; Hetland, M.L.; Ejbjerg, B.; Stengaard-Pedersen, K.; Jacobsen, S.; Lottenburger, T.; Ellingsen, T.; Andersen, L.S.; et al. Cartilage Oligomeric Matrix Protein Associates Differentially with Erosions and Synovitis and Has a Different Temporal Course in Cyclic Citrullinated Peptide Antibody (Anti-CCP)-positive versus Anti-CCP-negative Early Rheumatoid Arthritis. *J. Rheumatol.* **2011**, *38*, 1563–1568. [CrossRef]
340. Pitzalis, C.; Kelly, S.; Humby, F. New learnings on the pathophysiology of RA from synovial biopsies. *Curr. Opin. Rheumatol.* **2013**, *25*, 334–344. [CrossRef]
341. Kasperkovitz, P.V.; Timmer, T.C.G.; Smeets, T.J.; Verbeet, N.L.; Tak, P.P.; Van Baarsen, L.G.M.; Baltus, B.; Huizinga, T.W.J.; Pieterman, E.; Fero, M.; et al. Fibroblast-like synoviocytes derived from patients with rheumatoid arthritis show the imprint of synovial tissue heterogeneity: Evidence of a link between an increased myofibroblast-like phenotype and high-inflammation synovitis. *Arthritis Rheum.* **2005**, *52*, 430–441. [CrossRef]
342. Van Der Pouw Kraan, T.C.T.M.; Van Gaalen, F.A.; Huizinga, T.W.J.; Pieterman, E.; Breedveld, F.C.; Verweij, C.L. Discovery of distinctive gene expression profiles in rheumatoid synovium using cDNA microarray technology: Evidence for the existence of multiple pathways of tissue destruction and repair. *Genes Immun.* **2003**, *4*, 187–196. [CrossRef] [PubMed]

343. Van Delft, M.A.M.; Van Beest, S.; Kloppenburg, M.; Trouw, L.A.; Ioan-Facsinay, A. Presence of Autoantibodies in Erosive Hand Osteoarthritis and Association with Clinical Presentation. *J. Rheumatol.* **2019**, *46*, 101–105. [CrossRef] [PubMed]
344. Dolzani, P.; Assirelli, E.; Pulsatelli, L.; Addimanda, O.; Mancarella, L.; Peri, G.; Mantovani, A.; Facchini, A.; Meliconi, R. Systemic inflammation and antibodies to citrullinated peptides in hand osteoarthritis. *Clin. Exp. Rheumatol.* **2011**, *29*, 1006–1009. [PubMed]
345. Glant, T.T.; Ocsko, T.; Markovics, A.; Szekanecz, Z.; Katz, R.S.; Rauch, T.A.; Mikecz, K. Characterization and Localization of Citrullinated Proteoglycan Aggrecan in Human Articular Cartilage. *PLoS ONE* **2016**, *11*, e0150784. [CrossRef]
346. Ahmed, U.; Anwar, A.; Savage, R.S.; Costa, M.L.; Mackay, N.; Filer, A.; Raza, K.; Watts, R.A.; Winyard, P.G.; Tarr, J.; et al. Biomarkers of early stage osteoarthritis, rheumatoid arthritis and musculoskeletal health. *Sci. Rep.* **2015**, *5*, 9259. [CrossRef]
347. Xie, X.; Van Delft, M.A.M.; Shuweihdi, F.; Kingsbury, S.R.; Trouw, L.A.; Doody, G.M.; Conaghan, P.G.; Ponchel, F. Auto-antibodies to post-translationally modified proteins in osteoarthritis. *Osteoarthr. Cartil.* **2021**, *29*, 924–933. [CrossRef]
348. Lopes, E.B.P.; Filiberti, A.; Husain, S.A.; Humphrey, M.B. Immune Contributions to Osteoarthritis. *Curr. Osteoporos. Rep.* **2017**, *15*, 593–600. [CrossRef]
349. Berenbaum, F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthr. Cartil.* **2013**, *21*, 16–21. [CrossRef]
350. Smith, M.D.; Triantafillou, S.; Parker, A.; Youssef, P.P.; Coleman, M. Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. *J. Rheumatol.* **1997**, *24*, 365–371.
351. Orita, S.; Koshi, T.; Mitsuka, T.; Miyagi, M.; Inoue, G.; Arai, G.; Ishikawa, T.; Hanaoka, E.; Yamashita, K.; Yamashita, M.; et al. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. *BMC Musculoskelet. Disord.* **2011**, *12*, 144. [CrossRef]
352. Livshits, G.; Zhai, G.; Hart, D.J.; Kato, B.S.; Wang, H.; Williams, F.M.K.; Spector, T.D. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford study. *Arthritis Rheum.* **2009**, *60*, 2037–2045. [CrossRef]
353. Stannus, O.; Jones, G.; Cicuttini, F.; Parameswaran, V.; Quinn, S.; Burgess, J.; Ding, C. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. *Osteoarthr. Cartil.* **2010**, *18*, 1441–1447. [CrossRef] [PubMed]
354. Barker, T.; Rogers, V.E.; Henriksen, V.T.; Aguirre, D.; Trawick, R.H.; Rasmussen, G.L.; Momberger, N.G. Serum cytokines are increased and circulating micronutrients are not altered in subjects with early compared to advanced knee osteoarthritis. *Cytokine* **2014**, *68*, 133–136. [CrossRef] [PubMed]
355. Barreto, G.; Sandelin, J.; Salem, A.; Nordström, D.C.; Waris, E. Toll-like receptors and their soluble forms differ in the knee and thumb basal osteoarthritic joints. *Acta Orthop.* **2017**, *88*, 326–333. [CrossRef] [PubMed]
356. Tamaki, Y.; Takakubo, Y.; Hirayama, T.; Konttinen, Y.T.; Goodman, S.B.; Yamakawa, M.; Takagi, M. Expression of Toll-like Receptors and Their Signaling Pathways in Rheumatoid Synovitis. *J. Rheumatol.* **2011**, *38*, 810–820. [CrossRef]
357. Takakubo, Y.; Barreto, G.; Konttinen, Y.T.; Oki, H.; Takagi, M. Role of Innate Immune Sensors, TLRs, and NALP3 in Rheumatoid Arthritis and Osteoarthritis. *J. Long Term Eff. Med. Implant.* **2014**, *24*, 243–251. [CrossRef]
358. Fernandes, J.C.; Martel-Pelletier, J.; Pelletier, J.-P. The role of cytokines in osteoarthritis pathophysiology. *Biorheology* **2002**, *39*, 237–246. [CrossRef]
359. Rosenberg, J.H.; Rai, V.; Dilisio, M.F.; Agrawal, D.K. Damage-associated molecular patterns in the pathogenesis of osteoarthritis: Potentially novel therapeutic targets. *Mol. Cell. Biochem.* **2017**, *434*, 171–179. [CrossRef]
360. Chen, Z.; Zhong, H.; Wei, J.; Lin, S.; Zong, Z.; Gong, F.; Huang, X.; Sun, J.; Li, P.; Lin, H.; et al. Inhibition of Nrf2/HO-1 signaling leads to increased activation of the NLRP3 inflammasome in osteoarthritis. *Arthritis Res. Ther.* **2019**, *21*, 300. [CrossRef]
361. Yan, Z.; Qi, W.; Zhan, J.; Lin, Z.; Lin, J.; Xue, X.; Pan, X.; Zhou, Y. Activating Nrf2 signalling alleviates osteoarthritis development by inhibiting inflammasome activation. *J. Cell. Mol. Med.* **2020**, *24*, 13046–13057. [CrossRef]
362. Abdel Galil, S.M.; Ezzeldin, N.; Fawzy, F.; El-Boshy, M. The single-nucleotide polymorphism (SNP) of tumor necrosis factor α −308G/A gene is associated with early-onset primary knee osteoarthritis in an Egyptian female population. *Clin. Rheumatol.* **2017**, *36*, 2525–2530. [CrossRef]
363. Fernandes, M.T.P.; Fernandes, K.B.P.; Anibal, F.F.; Shimoya-Bittencourt, W.; Santos, V.M.; De Oliveira Perrucini, P.D.; Poli-Frederico, R.C. Functional status and severity of osteoarthritis in elderly is associated to the polymorphism of TNFA gene. *Adv. Rheumatol.* **2019**, *59*, 25. [CrossRef]
364. Stern, A.G.; De Carvalho, M.R.C.; Buck, G.A.; Adler, R.A.; Rao, T.P.S.; Disler, D.; Moxley, G. Association of erosive hand osteoarthritis with a single nucleotide polymorphism on the gene encoding interleukin-1 beta. *Osteoarthr. Cartil.* **2003**, *11*, 394–402. [CrossRef] [PubMed]
365. Solovieva, S.; Kämäräinen, O.-P.; Hirvonen, A.; Hämäläinen, S.; Laitala, M.; Vehmas, T.; Luoma, K.; Näkki, A.; Riihimäki, H.; Ala-Kokko, L.; et al. Association Between Interleukin 1 Gene Cluster Polymorphisms and Bilateral Distal Interphalangeal Osteoarthritis. *J. Rheumatol.* **2009**, *36*, 1977–1986. [CrossRef] [PubMed]
366. Moxley, G.; Meulenbelt, I.; Chapman, K.; Van Diujn, C.M.; Eline Slagboom, P.; Neale, M.C.; Smith, A.J.P.; Carr, A.J.; Loughlin, J. Interleukin-1 region meta-analysis with osteoarthritis phenotypes. *Osteoarthr. Cartil.* **2010**, *18*, 200–207. [CrossRef] [PubMed]

367. Blumenfeld, O.; Williams, F.M.K.; Valdes, A.; Hart, D.J.; Malkin, I.; Spector, T.D.; Livshits, G. Association of interleukin-6 gene polymorphisms with hand osteoarthritis and hand osteoporosis. *Cytokine* **2014**, *69*, 94–101. [CrossRef]
368. Milaras, C.; Lepetsos, P.; Dafou, D.; Potoupnis, M.; Tsiridis, E. Association of Matrix Metalloproteinase (MMP) Gene Polymorphisms with Knee Osteoarthritis: A Review of the Literature. *Cureus* **2021**, *13*, e18607. [CrossRef]
369. Vrgoc, G.; Vrbanec, J.; Eftedal, R.K.; Dembic, P.L.; Balen, S.; Dembic, Z.; Jotanovic, Z. Interleukin-17 and Toll-like Receptor 10 genetic polymorphisms and susceptibility to large joint osteoarthritis. *J. Orthop. Res.* **2018**, *36*, 1684–1693. [CrossRef]
370. Zheng, M.; Shi, S.; Zheng, Q.; Wang, Y.; Ying, X.; Jin, Y. Association between *TLR-9* gene rs187084 polymorphism and knee osteoarthritis in a Chinese population. *Biosci. Rep.* **2017**, *37*, BSR20170844. [CrossRef]
371. Xi, X.; Mehmood, A.; Niu, P.; Yang, J.; Wang, Y.; Zhou, H.; Han, X.; Ma, L.; Jin, S.; Wu, Y. Association of X-linked TLR-7 gene polymorphism with the risk of knee osteoarthritis: A case–control study. *Sci. Rep.* **2022**, *12*, 7243. [CrossRef]
372. Stefik, D.; Vranic, V.; Ivkovic, N.; Velikic, G.; Maric, D.M.; Abazovic, D.; Vojvodic, D.; Maric, D.L.; Supic, G. Potential Impact of Polymorphisms in Toll-like Receptors 2, 3, 4, 7, 9, miR-146a, miR-155, and miR-196a Genes on Osteoarthritis Susceptibility. *Biology* **2023**, *12*, 458. [CrossRef] [PubMed]
373. Huss, R.S.; Huddleston, J.I.; Goodman, S.B.; Butcher, E.C.; Zabel, B.A. Synovial tissue–infiltrating natural killer cells in osteoarthritis and periprosthetic inflammation. *Arthritis Rheum.* **2010**, *62*, 3799–3805. [CrossRef] [PubMed]
374. Platzer, H.; Trauth, R.; Nees, T.A.; Tripel, E.; Gantz, S.; Schiltenwolf, M.; Moradi, B.; Rosshirt, N. CD8+ T Cells in OA Knee Joints Are Differentiated into Subsets Depending on OA Stage and Compartment. *J. Clin. Med.* **2022**, *11*, 2814. [CrossRef] [PubMed]
375. Jaime, P.; García-Guerrero, N.; Estella, R.; Pardo, J.; García-Álvarez, F.; Martinez-Lostao, L. CD56+/CD16− Natural Killer cells expressing the inflammatory protease granzyme A are enriched in synovial fluid from patients with osteoarthritis. *Osteoarthr. Cartil.* **2017**, *25*, 1708–1718. [CrossRef]
376. Pawłowska, J.; Mikosik, A.; Soroczynska-Cybula, M.; Jóźwik, A.; Łuczkiewicz, P.; Mazurkiewicz, S.; Lorczyński, A.; Witkowski, J.M.; Bryl, E. Different distribution of CD4 and CD8 T cells in synovial membrane and peripheral blood of rheumatoid arthritis and osteoarthritis patients. *Folia Histochem. Cytobiol.* **2010**, *47*, 627–632. [CrossRef]
377. Yamin, R.; Berhani, O.; Peleg, H.; Aamar, S.; Stein, N.; Gamliel, M.; Hindi, I.; Scheiman-Elazary, A.; Gur, C. High percentages and activity of synovial fluid NK cells present in patients with advanced stage active Rheumatoid Arthritis. *Sci. Rep.* **2019**, *9*, 1351. [CrossRef]
378. Haywood, L.; McWilliams, D.F.; Pearson, C.I.; Gill, S.E.; Ganesan, A.; Wilson, D.; Walsh, D.A. Inflammation and angiogenesis in osteoarthritis. *Arthritis Rheum.* **2003**, *48*, 2173–2177. [CrossRef]
379. Pessler, F.; Chen, L.X.; Dai, L.; Gomez-Vaquero, C.; Diaz-Torne, C.; Paessler, M.E.; Scanzello, C.; Çakir, N.; Einhorn, E.; Schumacher, H.R. A histomorphometric analysis of synovial biopsies from individuals with Gulf War Veterans' Illness and joint pain compared to normal and osteoarthritis synovium. *Clin. Rheumatol.* **2008**, *27*, 1127–1134. [CrossRef]
380. Sakkas, L.I.; Scanzello, C.; Johanson, N.; Burkholder, J.; Mitra, A.; Salgame, P.; Katsetos, C.D.; Platsoucas, C.D. T Cells and T-Cell Cytokine Transcripts in the Synovial Membrane in Patients with Osteoarthritis. *Clin. Diagn. Lab. Immunol.* **1998**, *5*, 430–437. [CrossRef]
381. Krenn, V.; Hensel, F.; Kim, H.J.; Souto Carneiro, M.M.; Starostik, P.; Ristow, G.; König, A.; Vollmers, H.P.; Müller-Hermelink, H.K. Molecular IgV(H) analysis demonstrates highly somatic mutated B cells in synovialitis of osteoarthritis: A degenerative disease is associated with a specific, not locally generated immune response. *Lab. Investig.* **1999**, *79*, 1377–1384.
382. Kouskoff, V.; Lacaud, G.; Nemazee, D. T Cell-Independent Rescue of B Lymphocytes from Peripheral Immune Tolerance. *Science* **2000**, *287*, 2501–2503. [CrossRef] [PubMed]
383. Takemura, S.; Braun, A.; Crowson, C.; Kurtin, P.J.; Cofield, R.H.; O'Fallon, W.M.; Goronzy, J.J.; Weyand, C.M. Lymphoid Neogenesis in Rheumatoid Synovitis. *J. Immunol.* **2001**, *167*, 1072–1080. [CrossRef] [PubMed]
384. Rosshirt, N.; Trauth, R.; Platzer, H.; Tripel, E.; Nees, T.A.; Lorenz, H.-M.; Tretter, T.; Moradi, B. Proinflammatory T cell polarization is already present in patients with early knee osteoarthritis. *Arthritis Res. Ther.* **2021**, *23*, 37. [CrossRef] [PubMed]
385. Nees, T.A.; Rosshirt, N.; Zhang, J.A.; Platzer, H.; Sorbi, R.; Tripel, E.; Reiner, T.; Walker, T.; Schiltenwolf, M.; Lorenz, H.-M.; et al. T Helper Cell Infiltration in Osteoarthritis-Related Knee Pain and Disability. *J. Clin. Med.* **2020**, *9*, 2423. [CrossRef]
386. Deleuran, B.W.; Chu, C.Q.; Field, M.; Brennan, F.M.; Katsikis, P.; Feldmann, M.; Maini, R.N. Localization of interleukin-1α, type 1 interleukin-1 receptor and interleukin-1 receptor antagonist in the synovial membrane and cartilage/pannus junction in rheumatoid arthritis. *Rheumatology* **1992**, *31*, 801–809. [CrossRef]
387. Johnell, O.; Hulth, A.; Henricson, A. T-Lymphocyte Subsets and HLA-DR-Expressing Cells in the Osteoarthritic Synovialis. *Scand. J. Rheumatol.* **1985**, *14*, 259–264. [CrossRef]
388. De Jong, H.; Berlo, S.E.; Hombrink, P.; Otten, H.G.; Van Eden, W.; Lafeber, F.P.; Heurkens, A.H.M.; Bijlsma, J.W.J.; Glant, T.T.; Prakken, B.J. Cartilage proteoglycan aggrecan epitopes induce proinflammatory autoreactive T-cell responses in rheumatoid arthritis and osteoarthritis. *Ann. Rheum. Dis.* **2010**, *69*, 255–262. [CrossRef]
389. Sakata, M.; Masuko-Hongo, K.; Nakamura, H.; Onuma, H.; Tsuruha, J.I.; Aoki, H.; Nishioka, K.; Kato, T. Osteoarthritic articular chondrocytes stimulate autologous T cell responses in vitro. *Clin. Exp. Rheumatol.* **2003**, *21*, 704–710.

390. Nees, T.A.; Zhang, J.A.; Platzer, H.; Walker, T.; Reiner, T.; Tripel, E.; Moradi, B.; Rosshirt, N. Infiltration Profile of Regulatory T Cells in Osteoarthritis-Related Pain and Disability. *Biomedicines* **2022**, *10*, 2111. [CrossRef]
391. Moradi, B.; Schnatzer, P.; Hagmann, S.; Rosshirt, N.; Gotterbarm, T.; Kretzer, J.P.; Thomsen, M.; Lorenz, H.-M.; Zeifang, F.; Tretter, T. $CD4^+CD25^{+/high}CD127^{low/-}$ regulatory T cells are enriched in rheumatoid arthritis and osteoarthritis joints—Analysis of frequency and phenotype in synovial membrane, synovial fluid and peripheral blood. *Arthritis Res. Ther.* **2014**, *16*, R97. [CrossRef]
392. Ueno, H.; Banchereau, J.; Vinuesa, C.G. Pathophysiology of T follicular helper cells in humans and mice. *Nat. Immunol.* **2015**, *16*, 142–152. [CrossRef]
393. Chu, Y.; Wang, F.; Zhou, M.; Chen, L.; Lu, Y. A preliminary study on the characterization of follicular helper T (Tfh) cells in rheumatoid arthritis synovium. *Acta Histochem.* **2014**, *116*, 539–543. [CrossRef]
394. Liu, R.; Zhao, P.; Zhang, Q.; Che, N.; Xu, L.; Qian, J.; Tan, W.; Zhang, M. Adiponectin promotes fibroblast-like synoviocytes producing IL-6 to enhance T follicular helper cells response in rheumatoid arthritis. *Clin. Exp. Rheumatol.* **2020**, *38*, 11–18. [PubMed]
395. Murray-Brown, W.; Guo, Y.; Small, A.; Lowe, K.; Weedon, H.; Smith, M.D.; Lester, S.E.; Proudman, S.M.; Rao, N.L.; Hao, L.-Y.; et al. Differential expansion of T peripheral helper cells in early rheumatoid arthritis and osteoarthritis synovium. *RMD Open* **2022**, *8*, e002563. [CrossRef] [PubMed]
396. Shan, Y.; Qi, C.; Liu, Y.; Gao, H.; Zhao, D.; Jiang, Y. Increased frequency of peripheral blood follicular helper T cells and elevated serum IL-21 levels in patients with knee osteoarthritis. *Mol. Med. Rep.* **2017**, *15*, 1095–1102. [CrossRef]
397. Chichasova, N.V. Cartilage destruction in rheumatoid arthritis, its association with functional impairments. *Mod. Rheumatol. J.* **2014**, *8*, 60–71. [CrossRef]
398. Chen, Y.; Qiu, F.; Zhu, X.; Mo, H.; Wu, Z.; Xiao, C. Pannus does not occur only in rheumatoid arthritis: A pathological observation of pannus of knee osteoarthritis. *Nan Fang Yi Ke Da Xue Xue Bao* **2019**, *39*, 747–750. [CrossRef]
399. Shibakawa, A.; Aoki, H.; Masuko-Hongo, K.; Kato, T.; Tanaka, M.; Nishioka, K.; Nakamura, H. Presence of pannus-like tissue on osteoarthritic cartilage and its histological character. *Osteoarthritis. Cartil.* **2003**, *11*, 133–140. [CrossRef]
400. Furuzawa-Carballeda, J.; Macip-Rodríguez, P.M.; Cabral, A.R. Osteoarthritis and rheumatoid arthritis pannus have similar qualitative metabolic characteristics and pro-inflammatory cytokine response. *Clin. Exp. Rheumatol.* **2008**, *26*, 554–560.
401. Wernert, N.; Justen, H.-P.; Rothe, M.; Behrens, P.; Dreschers, S.; Neuhaus, T.; Florin, A.; Sachinidis, A.; Vetter, H.; Ko, Y. The Ets 1 transcription factor is upregulated during inflammatory angiogenesis in rheumatoid arthritis. *J. Mol. Med.* **2002**, *80*, 258–266. [CrossRef]
402. Wang, C.; Chen, L.; Zhu, P.; Fan, C.; Wang, Y.; Jia, J. CD147 stimulates the angiogenesis in rheumatoid synovium via the activation of vascular endothelial growth factor. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* **2007**, *23*, 426–428.
403. Kriegsmann, J.; Berndt, A.; Hansen, T.; Borsi, L.; Zardi, L.; Bräuer, R.; Petrow, P.K.; Otto, M.; Kirkpatrick, C.J.; Gay, S.; et al. Expression of fibronectin splice variants and oncofetal glycosylated fibronectin in the synovial membranes of patients with rheumatoid arthritis and osteoarthritis. *Rheumatol. Int.* **2004**, *24*, 25–33. [CrossRef] [PubMed]
404. Pessler, F.; Ogdie, A.; Diaz-Torne, C.; Dai, L.; Yu, X.; Einhorn, E.; Gay, S.; Schumacher, H.R. Subintimal Ki-67 as a synovial tissue biomarker for inflammatory arthropathies. *Ann. Rheum. Dis.* **2008**, *67*, 162–167. [CrossRef] [PubMed]
405. Šenolt, L.; Grigorian, M.; Lukanidin, E.; Simmen, B.; Michel, B.A.; Pavelka, K.; Gay, R.E.; Gay, S.; Neidhart, M. S100A4 is expressed at site of invasion in rheumatoid arthritis synovium and modulates production of matrix metalloproteinases. *Ann. Rheum. Dis.* **2006**, *65*, 1645–1648. [CrossRef] [PubMed]
406. Lindblad, S.; Hedfors, E. Arthroscopic and immunohistologic characterization of knee joint synovitis in osteoarthritis. *Arthritis Rheum.* **1987**, *30*, 1081–1088. [CrossRef]
407. Homandberg, G.A.; Hui, F. Association of Proteoglycan Degradation with Catabolic Cytokine and Stromelysin Release from Cartilage Cultured with Fibronectin Fragments. *Arch. Biochem. Biophys.* **1996**, *334*, 325–331. [CrossRef]
408. Oehler, S.; Neureiter, D.; Meyer-Scholten, C.; Aigner, T. Subtyping of osteoarthritic synoviopathy. *Clin. Exp. Rheumatol.* **2002**, *20*, 633–640.
409. Wood, M.J.; Leckenby, A.; Reynolds, G.; Spiering, R.; Pratt, A.G.; Rankin, K.S.; Isaacs, J.D.; Haniffa, M.A.; Milling, S.; Hilkens, C.M.U. Macrophage proliferation distinguishes 2 subgroups of knee osteoarthritis patients. *JCI Insight* **2019**, *4*, e125325. [CrossRef]
410. McInnes, I.B.; Schett, G. Pathogenetic insights from the treatment of rheumatoid arthritis. *Lancet* **2017**, *389*, 2328–2337. [CrossRef]
411. Favero, M.; Perino, G.; Valente, M.L.; Tiengo, C.; Ramonda, R. Radiological and histological analysis of two replaced interphalangeal joints with active subchondral bone resorption in erosive hand osteoarthritis: A novel mechanism? *Skelet. Radiol.* **2017**, *46*, 385–391. [CrossRef]
412. Wittoek, R.; Cruyssen, B.V.; Verbruggen, G. Predictors of functional impairment and pain in erosive osteoarthritis of the interphalangeal joints: Comparison with controlled inflammatory arthritis. *Arthritis Rheum.* **2012**, *64*, 1430–1436. [CrossRef]
413. Zhang, Y. Prevalence of Symptomatic Hand Osteoarthritis and Its Impact on Functional Status among the Elderly: The Framingham Study. *Am. J. Epidemiol.* **2002**, *156*, 1021–1027. [CrossRef]
414. Kidd, K.L.; Peter, J.B. Erosive Osteoarthritis. *Radiology* **1966**, *86*, 640–647. [CrossRef]

415. Favero, M.; Belluzzi, E.; Ortolan, A.; Lorenzin, M.; Oliviero, F.; Doria, A.; Scanzello, C.R.; Ramonda, R. Erosive hand osteoarthritis: Latest findings and outlook. *Nat. Rev. Rheumatol.* **2022**, *18*, 171–183. [CrossRef]
416. Kloppenburg, M.; Kroon, F.P.; Blanco, F.J.; Doherty, M.; Dziedzic, K.S.; Greibrokk, E.; Haugen, I.K.; Herrero-Beaumont, G.; Jonsson, H.; Kjeken, I.; et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann. Rheum. Dis.* **2019**, *78*, 16–24. [CrossRef]
417. Dahaghin, S.; Bierma-zeinstra, S.M.A.; Hazes, J.M.W.; Koes, B.W. Clinical burden of radiographic hand osteoarthritis: A systematic appraisal. *Arthritis Rheum.* **2006**, *55*, 636–647. [CrossRef]
418. Dell'Isola, A.; Allan, R.; Smith, S.L.; Marreiros, S.S.P.; Steultjens, M. Identification of clinical phenotypes in knee osteoarthritis: A systematic review of the literature. *BMC Musculoskelet. Disord.* **2016**, *17*, 425. [CrossRef] [PubMed]
419. Hochberg, M.C.; Carrino, J.A.; Schnitzer, T.J.; Guermazi, A.; Walsh, D.A.; White, A.; Nakajo, S.; Fountaine, R.J.; Hickman, A.; Pixton, G.; et al. Long-Term Safety and Efficacy of Subcutaneous Tanezumab Versus Nonsteroidal Antiinflammatory Drugs for Hip or Knee Osteoarthritis: A Randomized Trial. *Arthritis Rheumatol.* **2021**, *73*, 1167–1177. [CrossRef] [PubMed]
420. Sanga, P.; Katz, N.; Polverejan, E.; Wang, S.; Kelly, K.M.; Haeussler, J.; Thipphawong, J. Efficacy, safety, and tolerability of fulranumab, an anti-nerve growth factor antibody, in the treatment of patients with moderate to severe osteoarthritis pain. *Pain* **2013**, *154*, 1910–1919, Erratum in *Pain* **2014**, *155*, 204. https://doi.org/10.1016/j.pain.2013.10.020. [CrossRef]
421. Buch, M.H. Defining refractory rheumatoid arthritis. *Ann. Rheum. Dis.* **2018**, *77*, 966–969. [CrossRef]
422. Fonseca, J.E.; Canhão, H.; Tavares, N.J.; Cruz, M.; Branco, J.; Queiroz, M.V. Persistent low grade synovitis without erosive progression in magnetic resonance imaging of rheumatoid arthritis patients treated with infliximab over 1 year. *Clin. Rheumatol.* **2009**, *28*, 1213–1216. [CrossRef]
423. Forslind, K.; Svensson, B. MRI evidence of persistent joint inflammation and progressive joint damage despite clinical remission during treatment of early rheumatoid arthritis. *Scand. J. Rheumatol.* **2016**, *45*, 99–102. [CrossRef] [PubMed]
424. Majorczyk, E.; Mazurek-Mochol, M.; Pawlik, A.; Kuśnierczyk, P. Clinical Factors and the Outcome of Treatment with Methotrexate in Rheumatoid Arthritis: Role of Rheumatoid Factor, Erosive Disease and High Level of Erythrocyte Sedimentation Rate. *J. Clin. Med.* **2022**, *11*, 6078. [CrossRef] [PubMed]
425. Saevarsdottir, S.; Wallin, H.; Seddighzadeh, M.; Ernestam, S.; Geborek, P.; Petersson, I.F.; Bratt, J.; Van Vollenhoven, R.F. Predictors of response to methotrexate in early DMARD naïve rheumatoid arthritis: Results from the initial open-label phase of the SWEFOT trial. *Ann. Rheum. Dis.* **2011**, *70*, 469–475. [CrossRef] [PubMed]
426. Lukas, C.; Mary, J.; Debandt, M.; Daïen, C.; Morel, J.; Cantagrel, A.; Fautrel, B.; Combe, B. Predictors of good response to conventional synthetic DMARDs in early seronegative rheumatoid arthritis: Data from the ESPOIR cohort. *Arthritis Res. Ther.* **2019**, *21*, 243. [CrossRef]
427. Watanabe, R.; Okano, T.; Gon, T.; Yoshida, N.; Fukumoto, K.; Yamada, S.; Hashimoto, M. Difficult-to-treat rheumatoid arthritis: Current concept and unsolved problems. *Front. Med.* **2022**, *9*, 1049875. [CrossRef]
428. Novella-Navarro, M.; Plasencia, C.; Tornero, C.; Navarro-Compán, V.; Cabrera-Alarcón, J.L.; Peiteado-López, D.; Nuño, L.; Monjo-Henry, I.; Franco-Gómez, K.; Villalba, A.; et al. Clinical predictors of multiple failure to biological therapy in patients with rheumatoid arthritis. *Arthritis Res. Ther.* **2020**, *22*, 284. [CrossRef]
429. Khader, Y.; Beran, A.; Ghazaleh, S.; Lee-Smith, W.; Altorok, N. Predictors of remission in rheumatoid arthritis patients treated with biologics: A systematic review and meta-analysis. *Clin. Rheumatol.* **2022**, *41*, 3615–3627. [CrossRef]
430. Jung, J.-Y.; Lee, E.; Kim, J.-W.; Suh, C.-H.; Shin, K.; Kim, J.; Kim, H.-A. Unveiling difficult-to-treat rheumatoid arthritis: Long-term impact of biologic or targeted synthetic DMARDs from the KOBIO registry. *Arthritis Res. Ther.* **2023**, *25*, 174. [CrossRef]
431. Hecquet, S.; Combier, A.; Steelandt, A.; Pons, M.; Wendling, D.; Molto, A.; Miceli-Richard, C.; Allanore, Y.; Avouac, J. Characteristics of patients with difficult-to-treat rheumatoid arthritis in a French single-centre hospital. *Rheumatology* **2023**, *62*, 3866–3874. [CrossRef]
432. Wenham, C.Y.J.; Grainger, A.J.; Hensor, E.M.A.; Caperon, A.R.; Ash, Z.R.; Conaghan, P.G. Methotrexate for pain relief in knee osteoarthritis: An open-label study. *Rheumatology* **2013**, *52*, 888–892. [CrossRef]
433. Kingsbury, S.R.; Tharmanathan, P.; Keding, A.; Watt, F.E.; Scott, D.L.; Roddy, E.; Birrell, F.; Arden, N.K.; Bowes, M.; Arundel, C.; et al. Pain Reduction with Oral Methotrexate in Knee Osteoarthritis: A Randomized, Placebo-Controlled Clinical Trial. *Ann. Intern. Med.* **2024**, *177*, 1145–1156. [CrossRef] [PubMed]
434. Holanda, H.T.D.; Pollak, D.F.; Pucinelli, M.L.C. Baixa dose de methotrexate comparado a placebo em osteoartrite de joelho. *Rev. Bras. Reumatol.* **2007**, *47*, 334–340. [CrossRef]
435. Enteshari-Moghaddam, A.; Isazadehfar, K.; Habibzadeh, A.; Hemmati, M. Efficacy of Methotrexate on Pain Severity Reduction and Improvement of Quality of Life in Patients with Moderate to Severe Knee Osteoarthritis. *Anesth. Pain Med.* **2019**, *9*, e89990. [CrossRef] [PubMed]
436. Kingsbury, S.R.; Tharmanathan, P.; Keding, A.; Corbacho, B.; Watt, F.E.; Scott, D.L.; Roddy, E.; Birrell, F.; Arden, N.K.; Bowes, M.A.; et al. Significant pain reduction with oral methotrexate in knee osteoarthritis; results from the promote randomised controlled phase iii trial of treatment effectiveness. *Osteoarthr. Cartil.* **2019**, *27*, S84–S85. [CrossRef]

437. Zhu, Z.; Yu, Q.; Leng, X.; Xu, J.; Ren, L.; Wang, K.; Huang, C.; Pan, Y.; Zhao, Y.; Li, T.; et al. Low-Dose Methotrexate for the Treatment of Inflammatory Knee Osteoarthritis: A Randomized Clinical Trial. *JAMA Intern. Med.* **2025**, *185*, 808. [CrossRef]
438. Queiroz, I.; Pimentel, T.; Gallo Ruelas, M.; Tavares, A.H.; Barbosa, L.M.; Defante, M.L.R.; Leandro, G.N.; Monteiro, A.R.; Pimentel, F.N. Methotrexate for osteoarthritis: A systematic review meta-analysis of randomized controlled trials. *Inflammopharmacology* **2025**, *33*, 135–144. [CrossRef]
439. Verbruggen, G.; Veys, E.M. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum.* **1996**, *39*, 308–320. [CrossRef]
440. Verbruggen, G.; Wittoek, R.; Cruyssen, B.V.; Elewaut, D. Morbid anatomy of 'erosive osteoarthritis' of the interphalangeal finger joints: An optimised scoring system to monitor disease progression in affected joints. *Ann. Rheum. Dis.* **2010**, *69*, 862–867. [CrossRef]
441. Wang, Y.; Jones, G.; Keen, H.I.; Hill, C.L.; Wluka, A.E.; Kasza, J.; Teichtahl, A.J.; Antony, B.; O'Sullivan, R.; Cicuttini, F.M. Methotrexate to treat hand osteoarthritis with synovitis (METHODS): An Australian, multisite, parallel-group, double-blind, randomised, placebo-controlled trial. *Lancet* **2023**, *402*, 1764–1772. [CrossRef]
442. Yu, L.; Luo, R.; Qin, G.; Zhang, Q.; Liang, W. Efficacy and safety of anti-interleukin-1 therapeutics in the treatment of knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *J. Orthop. Surg. Res.* **2023**, *18*, 100. [CrossRef]
443. Li, G.; Zhang, Z.; Ye, Y.; Li, H.; Luo, H.; Tang, K.; Lai, Y. Efficacy, residual effectiveness and safety of diacerein in the treatment of knee osteoarthritis: A meta-analysis of randomized placebo-controlled trials. *Medicine* **2022**, *101*, e31700. [CrossRef] [PubMed]
444. Zeng, F.; Wang, K.; Duan, H.; Xu, X.; Kuang, G.; Lu, M. Diacerein versus non-steroidal anti-inflammatory drugs in the treatment of knee osteoarthritis: A meta-analysis. *J. Orthop. Surg. Res.* **2023**, *18*, 308. [CrossRef] [PubMed]
445. Bartels, E.M.; Bliddal, H.; Schøndorff, P.K.; Altman, R.D.; Zhang, W.; Christensen, R. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: A meta-analysis of randomized placebo-controlled trials. *Osteoarthr. Cartil.* **2010**, *18*, 289–296. [CrossRef] [PubMed]
446. Rintelen, B.; Neumann, K.; Leeb, B.F. A Meta-analysis of Controlled Clinical Studies with Diacerein in the Treatment of Osteoarthritis. *Arch. Intern. Med.* **2006**, *166*, 1899. [CrossRef]
447. Estee, M.M.; Cicuttini, F.M.; Page, M.J.; Wluka, A.E.; Wang, Y. Efficacy of tumor necrosis factor inhibitors in hand osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *Osteoarthr. Cartil. Open* **2023**, *5*, 100404. [CrossRef]
448. Chevalier, X.; Ravaud, P.; Maheu, E.; Baron, G.; Rialland, A.; Vergnaud, P.; Roux, C.; Maugars, Y.; Mulleman, D.; Lukas, C.; et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: A randomised, multicentre, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **2015**, *74*, 1697–1705. [CrossRef]
449. Aitken, D.; Laslett, L.L.; Pan, F.; Haugen, I.K.; Otahal, P.; Bellamy, N.; Bird, P.; Jones, G. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis—The HUMOR trial. *Osteoarthr. Cartil.* **2018**, *26*, 880–887. [CrossRef]
450. Verbruggen, G.; Wittoek, R.; Cruyssen, B.V.; Elewaut, D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: A double blind, randomised trial on structure modification. *Ann. Rheum. Dis.* **2012**, *71*, 891–898. [CrossRef]
451. Kloppenburg, M.; Ramonda, R.; Bobacz, K.; Kwok, W.-Y.; Elewaut, D.; Huizinga, T.W.J.; Kroon, F.P.B.; Punzi, L.; Smolen, J.S.; Vander Cruyssen, B.; et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): A multicentre, randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **2018**, *77*, 1757–1764. [CrossRef]
452. Kloppenburg, M.; Ramonda, R.; Kwok, W.-Y.; Bobacz, K.; Elewaut, D.; Frallonardo, P.; Huizinga, T.W.; Kroon, F.; Smolen, J.; Vander Cruyssen, B.; et al. OP0095 Randomized, Placebo-Controlled Trial to Evaluate Clinical Efficacy and Structure Modifying Properties of Subcutaneous Etanercept (ETN) in Patients with Erosive Inflammatory Hand Osteoarthritis (OA). *Ann. Rheum. Dis.* **2016**, *75*, 90–91. [CrossRef]
453. Jonsson, H.; Helgason, J. Rheumatoid Arthritis in an Icelandic Textbook from 1782. *Scand. J. Rheumatol.* **1996**, *25*, 134–137. [CrossRef]
454. Weyand, C.M.; Klimiuk, P.A.; Goronzy, J.J. Heterogeneity of rheumatoid arthritis: From phenotypes to genotypes. *Springer Semin. Immunopathol.* **1998**, *20*, 5–22. [CrossRef]