organoids

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Review

Meniscus Repair: From In Vitro Research to Patients

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Abstract: Walking, running, jumping, or even just standing up are habits that we all have to perform in our everyday lives. However, defects in tissues composing the knee joint can drastically alter our ability to complete those simple actions. The knee joint is made up of the interaction between bones (femur, tibia, and patella), tendons, ligaments, and the two menisci (lateral and medial) in order to ensure smooth body movements. The meniscus corresponds to a crescent-shaped fibrocartilaginous tissue, which is found in the knee joint between the femoral condyles and the tibial plateau. It plays a key role in the stability of the knee joint. However, it is quite vulnerable and therefore tears can occur within this tissue and compromise the proper function of the knee. Recently, numerous efforts have been made in order to find solutions to repair and regenerate the meniscus, supported by both bioengineering researchers and orthopedic surgeons. However, due to its poor healing capacity and its complex structure, the reconstruction of the meniscus remains particularly challenging. In this review, the current treatment options will be explained and the possibility of using organoids as building blocks for implant formation or as an in vitro three-dimensional model will be highlighted.

Keywords: meniscus; fibrocartilage; osteoarthritis; regeneration; organoids

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1. The Meniscus: Microarchitecture, Functions, and the Occurrence of Injuries

1.1. Microarchitecture

Anatomically, the meniscus has a fairly complex geometry with a crescent shape and a triangular cross-section (Figure 1A,B). The two menisci are distinct in shape with the medial meniscus having an open C-shape whereas the lateral meniscus has a more closed C-shape. The human medial meniscus is 46.8 ± 3.7 mm long, 31.6 ± 3 mm wide, and 9.3 ± 1.4 mm high whereas the human lateral meniscus is 35.3 ± 2.8 mm long, 31.7 ± 3.7 mm wide, and 9.9 ± 1.4 mm high [1]. At both extremities of the crescent, the anterior and posterior horns are somewhat asymmetrical (the posterior horn being slightly larger than the anterior horn) [2,3] and are anchored into the tibial plateau.

Regarding its microstructure, the meniscus is composed of different kinds of cells, making a gradient phenotype of fibrocartilage with more oval-shaped fibroblast-like cells in the outer region and rounded chondrocyte-like cells in the inner region (Figure 1B). In terms of cellularity (number of cells per area), it was found to decrease from the outer region towards the inner region and was also found to be lower in the anterior part of the meniscus compared with the midbody or posterior parts [4]. The cells are responsible for extracellular matrix (ECM) production, which therefore also has a region-specific organization. It mainly contains collagen that accounts for 22% of the meniscus wet weight [5]. It is predominantly fibrillar collagen type I in the outer region and a mixture of fibrillar collagen type II (at 60%) and fibrillar collagen type I (at 40%) in the inner region [6,7] (Figure 1C). Therefore, the inner region is more reflective of a hyaline cartilage-like region. In addition to histologic disparities between the inner and outer regions, the organization

of the fibers is also distinct. Within the outer and middle region of the meniscus, collagen fibril bundles have a circumferential orientation all around the periphery [8] (Figure 1D). Some radial fibers, known as "Tie" fibers, are also present within the tissue and arborize from the outer edge towards the inner edge [8] (Figure 1D). On top of collagen, the ECM also contains proteoglycans such as small leucine-rich proteoglycans (SLRPs) as well as larger proteoglycans that are important regulators of collagen fibrillogenesis [9]. Their localization within the fibrocartilage is region-dependent (Figure 1D). Sulfated glycosaminoglycans (GAGs) that correspond to the side chains of proteoglycans are mainly found, histologically, in the deep zone of the human meniscus, at least 600 µm away from the meniscus surface [10]. Within the inner region of the meniscus, it is mostly the SLRPs biglycan (most abundant SLRP in the meniscus tissue) and fibromodulin that are present [9]. In the outer region, it is mostly decorin which is found [9]. The large proteoglycan aggrecan and versican are expressed throughout the whole tissue but the expression of aggrecan is enriched in the inner region and on the contrary the expression of versican is enriched in the outer region [9,11]. These two proteoglycans are able to bind hyaluronic acid (G1 domain) but also through their C-terminal domain (G3 domain) to directly interact with epidermal growth factors or to entrap growth factors such as transforming tissue growth factor β (TGFβ) or Bone Morphogenic Proteins (BMPs) via the formation of supramolecular structures [12]. Even though the total content of proteoglycans present within the meniscus is low (around 0.5% wet weight) compared with articular cartilage (around 15% wet weight), it is strongly involved in the visco-elastic properties of the tissue, the maintenance of the collagen network, as well as the function of the fibrocartilage [13].

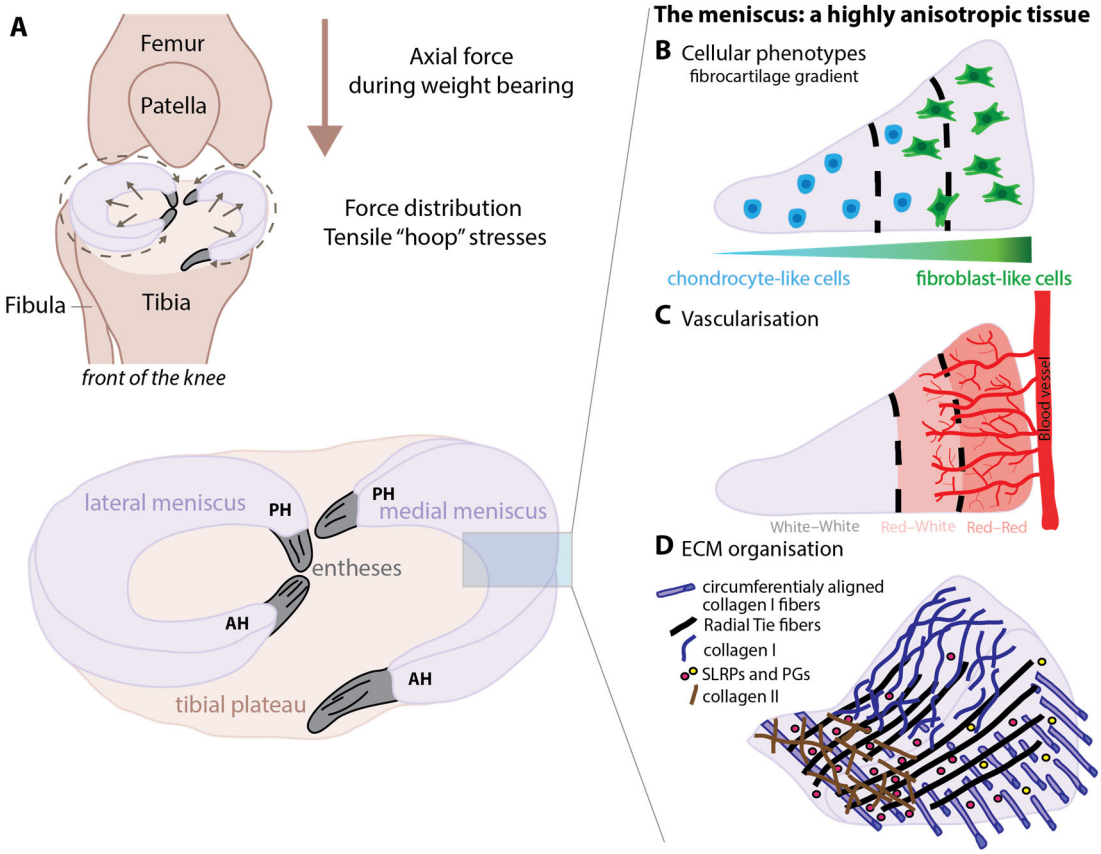

Figure 1. Meniscus localization and composition. (**A**) The two menisci are found in between the femur and tibia and are anchored into the tibial plateau through their entheses. During weight loading, the femur exerts an axial force onto the meniscus. The meniscus distributes this force to avoid too high stresses within the joint and generates tensile hoop stresses throughout the structure. AP = anterior horn, PH = posterior horn. (**B**) Gradient of fibrocartilage throughout the meniscus.

(**C**) Only the outer periphery of the meniscus is vascularized (Red–Red zone). The middle Red–White zone is partially vascularized and the inner White–White zone is completely avascular. (**D**) ECM spatial organization is highly complex with circumferentially oriented collagen I fibers in the deep zone of the meniscus. Radial Tie fibers circulate from the periphery towards the inner region. Collagen II is mainly found in the inner avascular region with chondrocyte-like cells. SLRPs and PGs are throughout the structure but are different between the inner/outer regions. ECM = extracellular matrix, SLRPs = small leucine-rich proteoglycans, PGs = proteoglycans.

It is interesting to note that during embryonic development, the whole fibrocartilage tissue is vascularized [14]. However, after the onset of mechanical loading following birth (in the first two years of life), the meniscus gets progressively less and less vascularized in the inner zone [14]. This has been shown to be driven by biochemical factors that are influenced by mechanical factors: the expression of the anti-angiogenic factor endostatin ENDO (which opposes the angiogenic effects of VEGF) early in development [15–17] as well as the anti-angiogenic factor Chondromodulin-I, which prevents endothelial cell proliferation [18], both expressed within the inner regions of the meniscus. In adulthood, only 10 to 25% of the meniscus periphery remains vascularized [19]. Therefore, heterogeneity is also found in terms of vascularization of the adult tissue, and the vascularized outer periphery is referred to as the red–red zone, which contains nerves (Figure 1C). The middle region is called the red–white zone and then there is the innermost region, called the white–white region, which is completely avascular and aneural (Figure 1C).

Therefore, the meniscus tissue has a highly anisotropic nature with region-specific disparities in terms of cellular phenotypes, vascularization, and ECM biochemical composition. In total, a recent study that used mass spectrometry to decipher the proteome of the human meniscus revealed that 170 proteins are differently expressed between the inner and outer zones of the meniscus [11]. The genes that are expressed inside the avascular region are being more and more characterized and this will help the development of tissue-engineered strategies [20].

This anisotropy makes it very complicated to mimic a meniscus in vitro. However, it is key to reproduce as much as possible its specific micro-structure as it is essential for the functions and mainly mechanical properties of the meniscus.

1.2. Mechanical Properties

The mechanical properties of the meniscus are crucial for the proper function of the knee biomechanics encountered during weight bearing, flexion, and extension of the leg. It protects the articular cartilage of the femur and tibia from excessive impact damage and its multiple functions highly rely on its curved shape [21] and the heterogeneous architecture of its ECM. Indeed, within the body, depending on the regions, the meniscus does not experience the same types of forces. Its inner region is mostly exposed to compression forces whereas the outer region sustains mostly tensile loads.

One of its key functions is to transfer the axial compressive force exerted by weight bearing from the femur into circumferential tensile "hoop" stresses [7] (Figure 1A). This is made possible by the presence of the circumferentially aligned collagen I fibers all around the structure. A recent inverse finite element analysis characterized the mechanical properties of those circumferentially oriented collagen fibers based on experiments performed on porcine menisci and simulations [22].

The meniscus can also be seen to act as a cushion that absorbs shocks inside the knee joint. In this sense, the presence of proteoglycans is primordial, as due to their numerous negative charges, they will attract positively charged ions that will result in the attraction of water (osmotic swelling of the tissue). Therefore, their presence contributes to the fact that the meniscus is a highly hydrated tissue (80% of wet weight). This hydration is important as it exerts pressure that counteracts the compressive forces exerted onto the tissue during weight bearing. From a mechanical point of view, as fluid water disperses the sudden stress, while entrapped within a macromolecule network, it allows molecular mobility

(plasticizing effect) leading to a more strain-resistant and dissipative elastic environment. Aggrecan, which is the most represented large proteoglycan within the meniscus, is key to resisting compression forces within the inner region and has been proposed to be important for the sliding of tensile loads within the outer region [9]. Mahmood et al., tested the ionic contribution of the proteoglycans by exposing human meniscus discs to different ionic concentrations (from deionized water to high ionic concentration) and submitted them to compression into a chamber [23]. They observed that, in physiological ionic concentration, the quantified Young modulus, reflecting the mechanical stiffness of the meniscus, is 58% higher compared to meniscus discs exposed to deionized water [23]. However, too-high hydration of the meniscus tissue is associated with degeneration, and an exploratory study recently quantified that the ability of the meniscus to dissipate energy decreases when the amount of water increases within the tissue [22,24].

Indentation creep tests revealed no significant differences of the elasticity between the anterior, central, and posterior regions of the meniscus (porcine meniscus, E of approximatively 0.24 MPa) [25]. Nevertheless, these assessments have been performed at the surface of the tissue. Maritz et al., sliced the meniscus to study the central body of the meniscus comparing the tibial, the internal, and the femoral zone of the tissue. The viscoelastic outputs revealed a higher elasticity of the femoral and tibial area (105 MPa and 189 MPa, respectively) in contrast to the internal tissue (34 MPa) [26]. These results mean that the tissue has in fact a soft core covered with harder strata. The study also revealed two modes of stress relaxation. This has to be linked to the microstructure reported by Agustoni et al., which described the presence of microchannels within the tissue [27]. These channels allow fluid movement and permit quick relaxation, whereas the collagen fibers are responsible for the slower relaxation process. On top of this, the meniscus is important for increasing knee joint congruency [28] for proper load distribution and stress reduction within the joint, as well as a stabilizer [29] and for joint lubrication and proprioception [19].

Altogether, these characteristics maintain optimal stress absorption and dissipation. Engineering tissues that can recapitulate these spatial specifications and variations in order to reproduce key biomechanical functions remains a challenge that has to be overcome to develop fully appropriate implants.

1.3. Meniscus Tears

Since the meniscus has to withstand high forces during a lifetime, it is highly vulnerable and exposed to the risk of tear formation that corresponds to a common musculoskeletal injury.

There are two different types of possible injuries:

- Traumatic meniscus injuries, due to an acute trauma in usually young and sportive patients and generally caused by a too high loading or twisting of the knee, often resulting in the onset of pain. Knee injuries correspond to approximately 40% of sport-related injuries and among them around 11% to medial meniscus injuries (more exposed to biomechanical forces compared to the lateral meniscus) and around 4% to lateral meniscus injuries [30]. Sports that are mainly at risk were reported to be: soccer, gymnastics, dancing, tennis, and jogging [30].
- Degenerative meniscus injuries caused by slow degradation of the tissue in older patients.

In a study performed on cadaver knees of young (below 40 years old) and older (more than 65 years old) persons subjected to cyclic uniaxial tensile loads, the older menisci were found to be less resistant (led before to failure) at high-stress magnitude but had similar resistance as the younger menisci at low-stress magnitude [31]. This underlines the effect of aging on repeated loads.

Importantly, meniscal injuries are a common healthcare issue and affect proper knee joint function. Arthroscopic destabilization of the medial meniscus is used as a model for meniscus injury and induces the onset of osteoarthritis in mice and Yucatan minipigs after 4 weeks [32,33]. So, if the meniscus injuries are left untreated, they can lead to the early development of degenerative osteoarthritis. In fact, around 50% of patients will develop osteoarthritis within 10 to 20 years following diagnosis of the injury [34]. Osteoarthritis

(OA), characterized by a progressive loss of the articular cartilage, is a degenerative joint disease that represents a highly important societal issue worldwide. In fact, knee OA has a prevalence of around 16% in people aged 15 years and over and around 23% in people aged 40 years and over [35]. In 2020, around 654 million people over the age of 40 had knee OA worldwide [35].

Different kinds of meniscus injuries can occur either in the inner region, outer region, or both, and can be either vertical (longitudinal (bucket handle), radial (transverse), oblique (parrot beak)) or horizontal (flap or cleavage) [36]. Radial tears are problematic because they are perpendicular to circumferentially aligned collagen fibers and therefore disrupt the ability for hoop stress generation. It is also quite frequent that those injuries occur in the inner region of the meniscus and due to the fact that this region is completely avascular, it has a poor spontaneous self-healing capacity. Therefore, repairing those injuries via sutures is not working, whereas it can work for the red–white or red–red zone [37]. However, instead of simple sutures, a system of cross tie-grip sutures seems to work better in the case of radial tears as recently shown in a porcine model [38], but surgical repair remains ineffective for a lot of meniscal tears. Therefore, efficient treatment options need to be found to treat and repair those tears.

2. Therapeutic Options: From Meniscectomy to Preservative Therapies

2.1. Meniscectomy/Partial Meniscectomy

The meniscus was considered for a long time as a non-essential structure inside the knee joint. Therefore, if any defects or increased pain were observed in some patients, it was relatively common to remove the entire tissue through total surgical meniscectomy (Figure 2A). Now that the meniscus' essential biomechanical functions are well recognized, surgeons try to keep as much healthy tissue as possible and perform an arthroscopic partial meniscectomy (APM). Its goal is mainly symptomatic relief in order to decrease patients' pain and improve knee function, and therefore the quality of life. However, this procedure is not trivial and can lead in some rare cases to the occurrence of pulmonary embolisms or infections [39]. On top of that, total or partial meniscectomy both have an impact on the contact area between the femur and tibia (20% contact area decrease for a 50% partial meniscectomy and 54% contact area decrease for a total meniscectomy compared to an intact meniscus) leading to a mean contact stress increase (24% for a partial meniscectomy and 134% for a total meniscectomy compared with an intact meniscus) [40]. This overload onto the articular cartilage is known to lead to cartilage degeneration that ultimately results in the onset of OA. Following a partial meniscectomy, incident osteoarthritis often occurs within 1-year post-surgery, and it can also increase the risk of worsening the cartilage damage [41].

A recent clinical trial investigated the long-term effects and long-term efficacy of this common orthopedic procedure [42]. A slightly increased risk of progression of knee OA has been reported in patients who underwent a partial meniscectomy, based on radiographic outcomes [42]. Moreover, partial meniscectomy was unable to confer benefits in the long term as there was no difference in pain and functions compared with the placebo surgery [42]. Therefore, this technique offers no clinically-relevant benefits in the long term, as evidenced in other studies [43,44]. However, it is still one of the most commonly performed orthopedic procedures. In France, between 2005 and 2017, 1,564,461 meniscectomies were performed [45]. However, this tendency started to change as the meniscectomy rate decreased (21.4% reduction in 2017 compared to 2005) and the meniscus repair rate increased drastically (320% increase in 2017 compared to 2005) [45]. Therefore, this highlights that the current surgical procedures try to turn towards more conservative techniques. In fact, keeping the integrity of the whole meniscus seems essential in order to prevent the development of early OA. There is approximately a 25 to 50% less risk to consult for the development of knee OA after meniscus repair compared to APM [46]. The European Society for Sports Traumatology, Knee Surgery, and Arthroscopy (ESSKA) consensus agrees on the fact that preservation of the meniscus is considered the main goal in the management

of traumatic meniscus tears [47]. In order to conserve the integrity of the meniscus, it is necessary to try to repair the meniscus or to develop a synthetic or biological replacement of the meniscus. There are already some replacement strategies that are in use and can help to reach better clinical outcomes following total or partial meniscectomy in order to stop or slow down the development of OA. However, as we saw previously in this review, the low intrinsic healing capacity of this fibrocartilaginous tissue and its complex microarchitecture renders its reconstruction for clinics highly challenging.

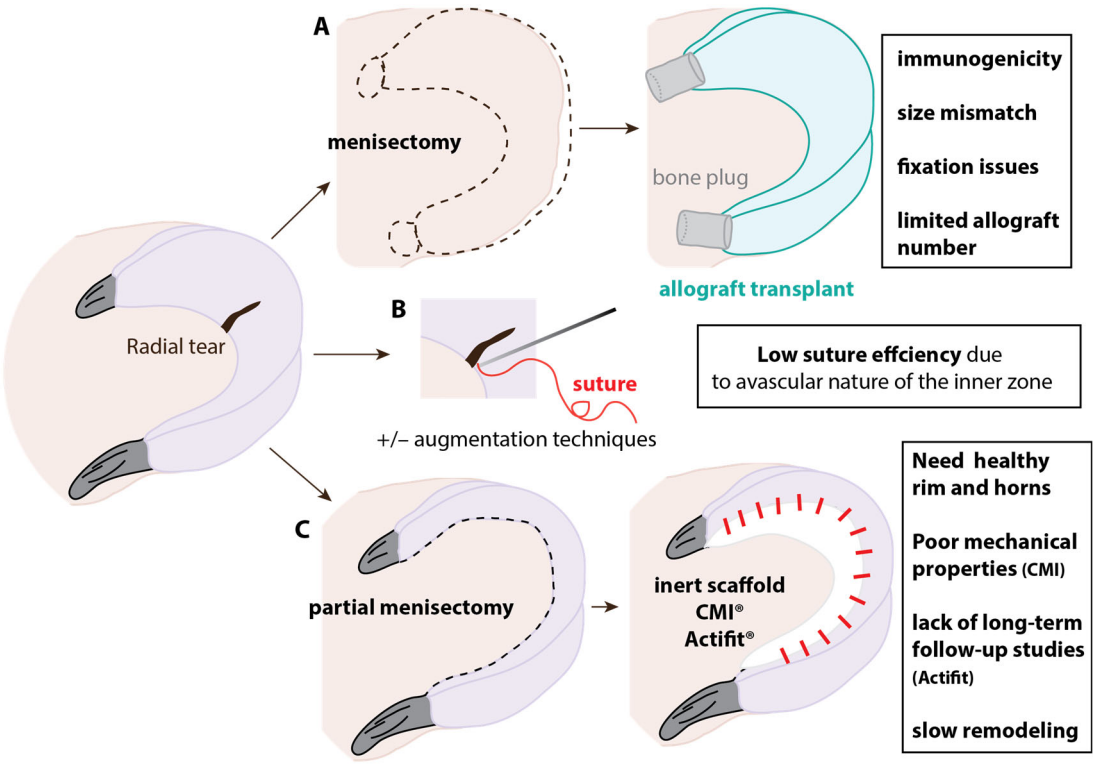

Figure 2. Current clinical treatment options for meniscal tears. (**A**) Following a full meniscectomy, where the damaged meniscus is taken off, it is possible to perform meniscal allograft transplantation. (**B**) Local treatment of closing the tears with sutures and waiting for healing of the tissue is possible but does not have a high success rate in the inner region of the meniscus which is avascular. (**C**) Partial meniscectomy enables removal of the zone that comprises the meniscus injury and this zone can be replaced with an inert scaffold either the CMI (CMI = collagen meniscus implant) or Actifit. For each treatment option presented in this figure, the major limitations are highlighted in the right boxes.

2.2. Meniscal Allograft Transplantation (MAT)

In order to completely replace the damaged meniscus following a total meniscectomy, the only available procedure consists of meniscal allograft transplantation (MAT) (Figure 2A). The first one was performed in Munich (Germany) in 1989 [48]. However, one of the main issues is the size mismatch that can exist between the donor and the recipient. If it is undersized this will induce a low congruence between the femur and tibia, whereas in contrast, if it is oversized it will lead to the extrusion from its proper site [49]. Recently, methods are developed in order to properly select the most suitable size within the allograft bank for matching to the patients, based on 3D magnetic resonance imaging (MRI) scan of the contralateral side [50]. However, this involves additional costs in the process of meniscus replacement. MAT has been shown to survive up to seven years [51]. However, the long-term survival of allograft transplantation has been tested and does not seem to be adapted especially to young patients as it is only around 50–70% [52]. Another issue apart from size mismatch is the possibility to transmit dangerous biological pathogens

from the donor to the recipient. Additionally, the possibility of transplant rejection due to immunologic reactions is quite high.

Additionally, the allograft transplant needs to be secured inside the knee joint and thus needs to have a proper fixation. Studies have shown that suturing the meniscal allograft transplant directly to the remaining host meniscal rim, corresponding to soft tissue, is often not enough and can result in transplant extrusion [53,54]. Therefore, a common procedure consists of adding 3D allograft bone plugs in order to anchor it properly to the tibial plateau. A recent study highlights a novel mini-arthrotomy technique where they added 10 mm × 8 mm bone plugs both anteriorly and posteriorly to the allograft transplant and they also added a third bone tunnel located posteromedially (2 cm from the posterior root) [55]. This is currently under investigation in clinical studies, but it should improve the strength of fixation, avoid the implant's extrusion, and should also improve the distribution of the load throughout the tissue [55]. However, it involves additional surgical risks (greater blood loss and pain post-surgery) and results in additional costs [55].

One of the main drawbacks of MATs is that the number of allografts is very limited, and the demands are constantly increasing. In addition, the allografts need to be stored frozen, and once integrated, only a few cells can re-popularize it, and therefore it can affect the viability of the MAT. This last point could be improved by injecting allogeneic mesenchymal stromal/stem cells in the transplant, as suggested recently in a proof-of-concept study [56]. As we saw here, MAT is quite intensive and it is therefore not routinely used except for patients with a completely damaged meniscus. Most of the time, MAT is indicated only in the case of relatively young patients (under 50 years old) that do not suffer from advanced OA [57]. Therefore, for all the different reasons described before, allograft transplantation cannot be the only option to replace the meniscus and it is needed to develop efficient approaches with better long-term survivorship and fewer risks of immunological reactions.

Instead of using the intact allograft meniscus, studies have shown that keeping just the ECM from those allografts can be a promising and safer approach.

2.3. Meniscus-Derived Scaffolds

Acellularized meniscus allografts are often becoming used as scaffolds in recent research and development studies of meniscus repair. In fact, they are promising as removing all the cells from the matrix reduces the chances of immunological reactions to the graft. Interestingly, decellularizing the tissue through the use of a detergent (such as SDS 2%) kept the native ECM components and did not affect the organization of the collagen bundles as validated by phase-contrast microscopy and immunostaining [58]. Moreover, Standmann et al., investigated the biomechanical properties of such scaffolds via a repetitive ball indentation test and found that their properties (stiffness, compression, and residual forces) were really close to the native human meniscus [58]. If taken from different regions (inner/outer), those decellularized scaffolds can drive the differentiation of human bone marrow mesenchymal stem cells into more fibroblasts for the scaffolds of the outer region (expression of type I collagen) and into more fibrochondrocytes for the scaffolds of the inner region (expression of type II collagen and aggrecan) [59]. However, the biggest drawback of this technology comes from the fact that the ECM of the meniscus is a highly dense network of collagen and proteoglycans and therefore inhibits proper cell migration into the scaffold (sterical limitation) [60]. Therefore, one solution to obtain a porous microenvironment that still contains the meniscus-specific growth factors consists of reducing the meniscus-derived matrix (MDM) into powder and then reconstructing it into 8% MDM scaffolds [61]. This approach enables an improved migration of endogenous meniscus cells in an in vitro meniscus repair model system [61]. To go further, the McNulty lab tested different cross-linking strategies (physical or chemical) in order to improve the scaffold and its biomechanical properties. Adding 16% genipin to cross-link the scaffold gave the best results of integrative meniscus repair (better attraction of endogenous meniscus cells, better production of GAG and collagen) [62]. Therefore, this strategy could serve in clinics, in the

following years, in order to repair a damaged region and therefore re-assemble two pieces of the meniscus together.

In the following section, biological augmentation strategies and inert acellular implants that can be used as alternatives for meniscus replacement will be presented.

2.4. Biological Augmentation Strategies and Synthetic Meniscus Scaffolds

The capacity of the meniscus to regenerate can also be augmented by several biological augmentation approaches such as platelet-rich plasma (PRP), fibrin glue, or fibrin clots [63] (Figure 2B). In fact, placing a graft of a fibrin clot (assembly of fibrin and platelets) helps the healing of the damaged region [64]. This can be added on top of suturing the horizontal meniscal tear [65] or longitudinal tears [66]. However, the delivery is not easy and the fibrin has the tendency to dissolve too quickly. Adding a polyglycolic acid (PGA) sheet can help to regulate the dissolution as well as increase the coagulation time of the fibrin clot but it also complicates the process of graft fabrication [67]. However, all those different enhancement techniques are not recommended to be used in clinics by the ESSKA [47]:

- for the fibrin glue as well as fibrin clots, it has been reported that scientific evidence studies are still lacking to evaluate the efficiency of this procedure.
- for PRP, its use does not seem to help meniscus repair as reported in a clinical study in which surgeries were performed with or without the addition of PRP [68]. In both the treated and control groups, there were similar functional outcomes and no difference in reoperation rate [68].

On top of those strategies that can be added to normal repair techniques (sutures. . .) (Figure 2B), some acellular and porous implants are already used in orthopedic clinics for partial meniscus replacements [69] (Figure 2C). Those implants are placed at the injury site following a partial meniscectomy. For instance, the Collagen Meniscus Implant (CMI®) commercialized by Stryker corporation (Kalamazoo, MI, USA) had its first clinical trial in 1997 and was FDA-approved in 2008 in the United States [70] (Figure 2C). It is composed of type I collagen fibers that are derived from bovine Achilles tendons and glycosaminoglycans. There is also the Actifit® scaffold (Orteq Sports Medicine Ltd., London, UK), which arose more recently onto the market [71] (Figure 2C). This one is composed of a synthetic hybrid of polycaprolactone (PCL) at 80% and polyurethane (PU) at 20%. These two scaffolds are bioresorbable and lead to colonization by endogenous cells that differentiate and regenerate the fibrocartilage. A recent meta-analysis highlighted that both lead to good clinical outcomes (in terms of improvement of the symptoms and meniscus function) and have a relatively low failure rate (7% for the CMI® and 9% for Actifit®) [72]. However, some issues remain. The CMI® has poorer mechanical properties compared with the native meniscus and its implantation inside the body is difficult to handle as it is quite fragile [73,74]. It has been reported that its remodeling once implanted is slow and that the overall structure of the CMI® is still visible 6-month post-implantation [75]. Often, the invasion by endogenous cells is poor and one solution to try to speed up this process and the whole regeneration could be conducted by the addition of autologous cells into the CMI scaffold prior to implantation [73]. This leads to the increased formation of ECM. Additionally, neither the CMI® nor Actifit® can be used to replace the whole meniscus structure as in order for endogenous cells to invade the implant the meniscus rim (vascularized portion) still needs to be present. Therefore, only partial meniscal lesions can be repaired with those implants. In addition, both the anterior and posterior horns should not be damaged so that the meniscus is still well-fixed inside the knee joint. For the Actifit® scaffold, long-term follow-up data are still lacking to properly evaluate its efficiency [72]. Contrary to the CMI, where only collagen is used and is known to have a too-fast degradation rate, coaxially electrospun nanofibers with a core of polylactic acid (PLA) to enhance mechanical properties and still collagen to improve the biocompatibility of the fibers was tested in vitro [76]. Interestingly, this led to higher mechanical properties and better capacity for differentiation in comparison to PLA scaffolds alone [76].

An alternative to the whole meniscus replacement, under FDA clinical trials, consists of the non-resorbable NUsurface® implant (Active Implants LLC, Memphis, TN, USA) made of polyethylene and reinforced all around with polycarbonate urethane to support high traction forces. This scaffold is particularly interesting as it recapitulates the proper biomechanical properties of the meniscus with the natural contact pattern pressure [77]. However, the drawback is that it is not fixed within the knee joint and therefore it can move freely and potentially result in knee lock-up [78].

Some strategies also consist of mimicking the anisotropic organization of the collagen fibers by weaving a 3D matrix of freeze-dried collagen reinforced by a network of synthetic polymer fibers [79]. However, on top of being heavy in terms of manufacturing, it is also not possible to do personalized medicine with this implant as cutting it will not retain the weaving of the fibers.

Overall, meniscus scaffolds represent an interesting strategy to replace damaged parts of the meniscus or the whole meniscus. When part of the meniscus structure is compromised, the mechanical function of the tissue is impaired and therefore the scaffolds furnish mechanical stability. Other kinds of biomaterials have also been used recently: polyglycolic acid [80] and polyurethane-gellan gum-hyaluronic acid-glucosamine [81]. Growth factors can also be incorporated [82], helping the differentiation of endogenous cells or stem cells.

However, the degradation of the components of the scaffolds can lead to toxicity, and there are also some issues with proper tissue remodeling. The thing is that those scaffolds have most of the time good mechanical properties tested in vitro before implantation, and it corresponds to the moment where they are the most performant. However, once put in place they can degrade (completely or partially) fairly quickly (depending on the nature of their components) over time, or break and therefore get weaker. Additionally, the constraints are imposed by the chosen material composing the scaffold or hydrogel. Out of all the different scaffolds developed, only two have reached the phase of application in the clinics.

Alternatively, a strategy combining a collagen scaffold with autologous human iliac crest bone marrow-derived mesenchymal stem cells has been tested in five patients but led to meniscectomy in two of them following 15 months post-implantation [83].

For the moment, except for the synthetic scaffolds used in clinics, there is no other clinical impact of tissue-engineered menisci to recover the meniscus function impaired by injury. This can be largely understandable by the high difficulty to recapitulate the microstructure of the meniscus, its ECM composition, and its natural mechanical properties. On top of all the treatments that currently exist, there is a medical need to obtain in vitro 3D models to test and develop new therapeutic options. In addition, one should not forget that the meniscus is embedded into the whole articulation of the knee, and recapitulating the whole knee joint with compartmentalized specific cell types and physiological mechanical properties would represent an important tool for the research and development of new therapies and the characterization of rheumatologic diseases or orthopedic pathologies.

3. Tissue Engineering of the Meniscus and at a Larger Scale the Whole Knee Joint

In order to develop a cell-based implant (Section 3.1) or to go further in the understanding of disease development and to test new therapies against joint diseases (Section 3.4), it would be of great interest to build up 3D cell-based structures of the meniscus and the whole knee joint. For that, the 3D culture of cells leading to the formation of an organoid that contains numerous organ-specific cells differentiated from progenitor cells that aggregate together according to the principle of cellular self-assembly could be used. 3D culture recently became the gold standard to build up tissues and whole organs for the purposes of in vitro modeling, drug screening, developmental biology, the development of biomarkers, or for regeneration [84–92]. Within the spheroids, cells are producing their own 3D microenvironment, which is physiologically more relevant compared to 2D culture. For regenerative purposes, it is of great interest as it enables recapitulation of the 3D conditions

found during embryonic development (organogenesis), and cells are also known to better communicate with each other and maintain their phenotypic lineage differentiation in comparison with the 2D culture [88].

3.1. Cell-Based Biofabrication of Knee Joint Tissue Implants

Instead of trying to regenerate the whole meniscus tissue, local repair treatments with Adipose-derived stem cells (ADSCs), and spheroids have been tested in vivo with a rabbit model with meniscal defect [93]. It consists in using approximately 400–500 ADSC spheroids that are put into a handmade cylindrical Teflon mold with perforations at the bottom for medium circulation (Figure 3A). Inside, the spheroids adhere and fuse with each other to form what they called a "high-density mesenchymal stem cell scaffold-free allograft construct" (HDMACs) [93]. After implantation of these cylindrical plugs into a 1.5 mm avascular meniscus defect, this resulted in histological healing [93].

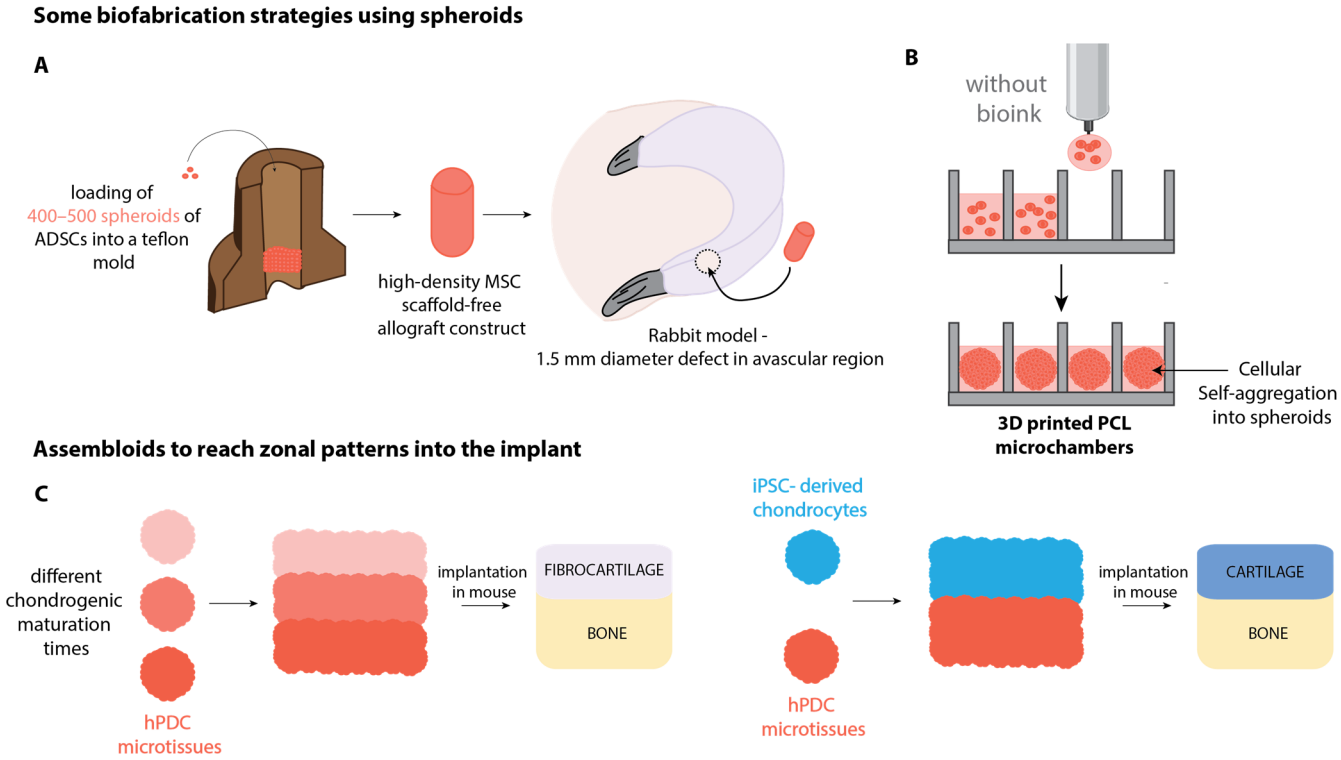

Figure 3. Examples of tissue engineering techniques based on the use of spheroids. (**A**) Scheme of the Teflon mold inspired from [94]. The high-density MSC scaffold-free allograft construct successfully healed a defect of 1.5 mm in the avascular region of the anterior horn in a rabbit model [93]. ADSCs = adipose-derived stem cells. (**B**) A biofabrication strategy that is based on the use of spheroids that form inside PCL chambers. PCL = polycaprolactone. (**C**) Using distinct spheroid populations in order to build up specific zonal patterns within the in vitro-produced tissue in order to obtain specific and functional regions following in vivo implantation. hPDC = human periosteum derived cells, Ipsc = induced pluripotent stem cells.

To produce larger cell-based implants, one technology that has become more common is 3D bioprinting, which allows the patterned deposition of cells by a layer-by-layer assembling process. This field has grown a lot in the past years and current 3D bioprinting approaches for meniscus regeneration have been discussed in detail elsewhere [95]. With this technology, it is possible to precisely control the architectural geometry, and therefore it is suitable for on-demand product design for personalized medicine. This presents a considerable advantage as measurements of numerous cadaveric menisci present a high variability between donors [96]. For reconstructing a patient's exact meniscus, 3D med-

ical image datasets from magnetic resonance imaging (MRI) or computed tomography (CT) can be used to design the shape of the product [97]. Recently, spheroids combined with the technology of 3D printing have been used for purposes of articular cartilage regeneration. Using spheroids is interesting in that context as it enables recapitulation of the cell interactions that happen during early developmental mesenchymal condensation. Daly et al., established a novel biofabrication strategy where a cell suspension of BM-MSCs and chondrocytes (ratio of 3:1) is ink-jetted into 3D-printed biodegradable thermoplastic poly (ε-caprolactone) (PCL) microchambers [98] (Figure 3A). Inside the hydrophobic chambers, the mixed-cell population is able to self-assemble, leading to spheroids that grow and can fuse with their adjacent spheroids. Interestingly, the boundary conditions provided by the microchambers are able to guide the growth of the spheroids and collagen fiber anisotropy. Recently, they updated this technology by building up the microchambers with PCL fibers thanks to an electric field through melt electrowriting [98]. This technology produces lower fiber diameter which is more accurate for biomimetic implants. The produced hybrid synthetic–biological implant provides tensile stiffness through the PCL fibers and also resistance to compression after 8 weeks in culture. Therefore, it is really promising and could be envisioned to be used for fibrocartilaginous tissue implants. However, here, the bio-printed tissue is homogenous and therefore does not recapitulate the zonal complexity that is found, for instance in a native meniscus tissue.

3.2. Recapitulating the Zonal Complexity of Tissues

As we saw in the previous sections of this review, one of the biggest challenges in trying to tissue engineer a meniscus in vitro is coming from the anisotropy of the tissue, with its highly organized architecture enabling proper meniscus function. Some existing strategies have recently been developed in order to grow knee joint cellular structures with different stable zonal patterns that could inspire future work to build up meniscus implants.

In the context of articular cartilage repair, a bizonal (with a non-mineralized hyaline cartilage region and at the bottom a mineralizing calcified cartilage region) structure was biofabricated [99]. To do so, the bottom layer was made up of mesenchymal stromal cell (MSC)-derived cell disks, and on top articular chondrocytes embedded into a starPEG/heparin hydrogel (preventing mineralization) were placed. Depending on the regions, specific differentiation mediums were applied.

On top of cartilage defects, osteochondral lesions are also found, involving both defects in cartilage and bone. For that purpose, Nilsson Hall et al., engineered osteochondral assembloids to recapitulate the whole osteochondral unit made up of a gradient of specific layers going from avascular cartilage to mineralized cartilage and subchondral bone [100]. They were inspired by trying to recapitulate processes found during embryonic development. Cell-based microtissues and organoids from different origins (either from human periosteum-derived cells (hPDCs) or induced pluripotent stem cells (iPSCs)) were used as building blocks that are assembled into a multilayered structure (Figure 3B). The goal of their study is the formation of cartilaginous intermediate implants that possess zone-specific characteristics resulting in both bone and cartilage formation after implantation subcutaneously. They cultured the different microtissues into agarose microwells and then fused them together to obtain the proper zonal patterns into macro wells [100]. To obtain different populations subtypes with hPDCs, they could play on the time of chondrogenesis maturation, the more they left the microtissues the more they mature into mineralization to give up the specific bone part [100]. To obtain the proper differentiation for the meniscus, it is important to know the steps of its morphogenesis and the involved regulatory pathways during embryonic development. It is known that, as the articular cartilage, the meniscus originates from the condensation of mesenchymal cells. Then, the Interzone cells (within the intermediate layer of the condensate) progressively morph into the specific meniscus shape between the 7th and 10th week of gestation [101,102]. Not much is understood about the controlling molecular pathways but TGF-beta signaling has been revealed to be important and IGF-1 signaling seems also to be involved specifically in the meniscus mor-

phogenesis (for the specification as well as the maintenance of meniscal progenitors [103]. Those developmental studies can help to engineer meniscus tissue in vitro.

On top of getting the appropriate cell differentiation in each region, validated by histological stainings and gene expression analyses, it is also key to recapitulate the proper ECM fiber alignment found in every tissue in order to be as close as possible to the native mechanical properties.

3.3. Optimization of the Mechanical Properties

One major challenge for engineering a functional meniscus implant is to develop a robust biomimetic-aligned collagen fibrillar network organization in order to withstand the strong forces present in the in vivo environment. Simply seeding chondrocytes in the inner region and a 50/50 co-culture of chondrocytes and meniscal cells in the outer two-thirds of a mold spatially already results in distinct biomechanical properties (the inner region being more resistant to compression and the outer region more resistant to tension) [104]. However, this study did not investigate if the fibers recapitulate the circumferential alignment. More recently, by also using a molding technique inside a high-density collagen gel, Puetzer et al., could show that recapitulating the mechanical attachments of the meniscus by its horns, through clamping the hydrogel, results in the development of organized circumferential and radial fibers by the fibrochoncytes and also on tissue size maintenance (avoiding tissue retraction) [105]. To go further, the same authors submitted this clamped scaffold-free meniscus implant to physiological axial loading inside a bioreactor [106]. This led to an increase in the production of ECM components (collagen, GAG) and importantly to a more pronounced zonal alignment of the fibers, both circumferentially and radially, leading to an increase in the mechanical properties closer to the native properties [106]. Additionally, applying a biaxial plastic compression instead of the usually applied uniaxial compression enables the generation of a highly aligned microstructure along a single axis, whereas, in the case of uniaxial compression, the alignment remains isotropic [107].

To enhance the neotissue biomechanical properties instead of biomechanical loading, stimulation of the cells with biochemical stimuli is also an option. The use of lysophosphatidic acid (LPA) in combination with TCL (comprising TGFβ1, GAG-cleaving enzyme chondroitinase ABC and lysyl-oxidase like 2 (LOXL2)) enables the increase of the tensile and compressive properties of a self-assembled tissue with chondrocytes and meniscus cells [108,109]. Lysyl oxidase (LOX)-induced cross-linking of the collagen fibers can also be naturally promoted by hypoxia culture conditions 2% (vol/vol) O_2 leading to an increase in the engineered tissue mechanical properties (5-fold more robust) [110]. Studies also used a combinatorial approach with mechanical stimuli (compression-tension strains) as well as the application of growth factors to properly induce anisotropic differentiation of bone-marrow-derived MSCs in a wedge-shaped scaffold of PCL [111].

Altogether, the addition of boundary conditions to mimic the anchoring of the meniscus into the bone, the application of physiological biomechanical forces, as well as bioactive stimuli can help to reach native biomechanical properties.

Targeting the cell's mechanotransduction to decrease inflammation and/or increase repair capacities can also be an option. Mechanotransduction corresponds to the ability of the cells to sense mechanical stimuli and respond by leading to chemical information within the cells and the expression of specific genes.

Following meniscus injury, it has been shown that an inflammatory response is induced, as can be seen by the presence of several cytokines within the synovial fluid such as interleukin 1 (IL-1) [112]. IL-1 participates in the onset of OA as it leads to the expression of nitric oxide, matrix metalloproteinases that degrade the ECM of the meniscus tissue, and inhibits the proper mechanical properties as well as the repair of the fibrocartilage [113]. Interestingly, a recent study performed on meniscal explants of the inner and outer regions as well as isolated meniscus cells submitted to physiological mechanical loading (compression and cyclic tensile stretch), revealed that mechanical stimulation can strongly

modulate the transcriptomic profile that is activated by IL-1, and can decrease the expression of genes involved in inflammatory signaling and OA development [114]. These new results open the hope of increasing the capacity of the meniscus for repair by targeting the meniscus mechanotransduction.

In addition, the process of mechanotransduction was revealed essential for the cell-signaling events underlying the mechanism of collagen fiber alignments [115]. Some Ca^{2+} oscillations in MSCs are observed during fibrillar collagen assembly and the authors could show that inhibiting the mechanosensitive channel transient receptor potential vanilloid 4 (TRPV4) (through a chemical inhibitor GSK205) abolishes those oscillations and disrupts the alignment of the collagen fibers, whereas activating this channel (though the chemical agonist GSK101) accelerates the alignment of the fibers [115]. TRPV4 activity is necessary to regulate cell-generated tension forces at cell-matrix adhesions for proper matrix assembly by the MSCs. Therefore, for robust cell differentiation it would also be possible to play with the properties of the cells to sense the physical forces and transmit them.

Instead of targeting mechanosensitive channels, finding ways to directly target key transcription factors is also an option. In a recent study, Lee et al., found out that both in the human and mouse menisci, the Forkhead box O (FoxOs) transcription factors are almost suppressed in the context of the osteoarthritic degenerative meniscus [116]. However, both are essential regulators of meniscus development and cellular homeostasis, therefore targeting them so that they are accurately expressed in injured situations, could serve as a new therapeutic approach.

3.4. Building Up an In Vitro 3D-Organoid Model of the Knee Joint

For the purpose of designing an organotypic model for recapitulating the knee joint, the challenge consists in being able to reconstitute the specific nature of the tissues composing the knee joint (cartilage, bone, fibrocartilage for the meniscus, synoviocytes that compose the synovial membrane and produce the synovial fluid) offering the possibility to investigate the crosstalk between them. The advantage of this approach is that it can be personalized (if based on patient-specific human cells) and it can be an alternative to the use of the animal model to characterize or perform pre-clinical studies of a specific disease.

Some attempts have already been made in vitro. Sun et al., biofabricated a human cartilage organoid [117]. Synovial mesenchymal stromal cells self-aggregated into organoids that showed ectopic chondrogenesis that could serve as a model for osteoarthritis and testing of a possible treatment. However, here, the authors construct a model composed solely of cartilage. Since osteoarthritis is a degenerative joint disease that causes damage to the cartilage but also the subchondral bone, we have developed in our laboratory a revolutionary model to regenerate both the cartilage and the subchondral bone [92,118,119]. Therefore, it is interesting to biofabricate a model with an interaction between these two tissue cell types. This has been achieved by building up organoids from murine-induced pluripotent stem cells and exposing them in a sequentially time-controlled way to growth factors such as transforming growth factor β3 (TGFβ3) (to stimulate chondrogenesis) and bone morphogenetic protein 2 (BMP2) (to stimulate osteogenesis) [120]. This is very promising as they started from a single cell source but reached an organoid composed of both cartilage and bone that can be used as in vitro model for the study of osteoarthritis [120].

Recently, new techniques called organ-on-a-chip have emerged and allow the mimicking of specific organ functions but at a micro-scale. Thanks to these advances, cartilage-on-a-chip [121,122] have been developed, comprising microfluidics chips containing chondrocytes permanently exposed to a well-controlled medium. This approach is really interesting for testing the toxicity and efficiency of new compound treatment, for exposing cells to deleterious signals known to be involved in the development of a pathology, characterizing cell behaviors, or observing the cell's response to physiological/pathophysiological mechanical stimuli. For instance, using their cartilage-on-a-chip platform, Paggi et al., were able to exert multi-directional mechanical stimuli onto the chondrocytes, reflecting the different types of forces that chondrocytes experience in vivo (both compressive forces and shear

strain) [123]. This work highlights the importance of mechanical cues in the production of essential cartilaginous ECM markers such as aggrecan and collagen type II. It shows the importance of applying adequate mechanical stimuli to the cells in order for them to produce and secrete a matrix close to the native matrix found in vivo.

In vitro 3D models also enables us to study the cross-talks between different tissues composing the knee joint. Recently Rothbauer et al., took advantage of the microfluidic joint-on-a-chip technology to study the cross-talk between a coculture with a human synovial organoid (made from Rheumatoid Arthritis patient-derived primary fibroblast-like synoviocytes) and a human chondral organoid with the perspective to develop a model for arthritic diseases [124] (Figure 3C). In their design, the two organoids were embedded within hydrogels. They could show that, in the presence of synovial organoids, the chondral organoids exhibited an improved phenotype of chondrocytes. Therefore, this article emphasizes that it is very important to consider the interactions between tissues in the modeling of musculoskeletal diseases and that joint-on-a-chip techniques offer those abilities.

Overall, current technologies allow researchers to obtain those types of in vitro models. However, it is still a great challenge to allow different tissues that are spatially co-existing and interacting with each other to mimic the whole knee-joint architecture and function; especially the mechanical functions which, as we have seen for the meniscus, are very important.

4. Conclusions

In conclusion, this review highlights current therapies and some prospects for treating meniscal tears. It remains a challenge to try to mimic the sophisticated structure and composition of the meniscus to be as close as possible to the native mechanical properties. However, research in this area is highly active and hopefully, new treatments will appear soon in the clinics. Developing in vitro personalized 3D model of the meniscus and a larger scale of the entire knee joint would represent a great advance in the research and development of new therapies.

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References

1. Beeler, S.; Jud, L.; Von Atzigen, M.; Sutter, R.; Fürnstahl, P.; Fucentese, S.F.; Vlachopoulos, L. Three-Dimensional Meniscus Allograft Sizing-a Study of 280 Healthy Menisci. *J. Orthop. Surg. Res.* **2020**, *15*, 74. [CrossRef]
2. Aman, Z.S.; DePhillipo, N.N.; Storaci, H.W.; Moatshe, G.; Chahla, J.; Engebretsen, L.; LaPrade, R.F. Quantitative and Qualitative Assessment of Posterolateral Meniscal Anatomy: Defining the Popliteal Hiatus, Popliteomeniscal Fascicles, and the Lateral Meniscotibial Ligament. *Am. J. Sports Med.* **2019**, *47*, 1797–1803. [CrossRef] [PubMed]
3. DePhillipo, N.N.; Moatshe, G.; Chahla, J.; Aman, Z.S.; Storaci, H.W.; Morris, E.R.; Robbins, C.M.; Engebretsen, L.; LaPrade, R.F. Quantitative and Qualitative Assessment of the Posterior Medial Meniscus Anatomy: Defining Meniscal Ramp Lesions. *Am. J. Sports Med.* **2019**, *47*, 372–378. [CrossRef] [PubMed]
4. Pereira, H.; Caridade, S.G.; Frias, A.M.; Silva-Correia, J.; Pereira, D.R.; Cengiz, I.F.; Mano, J.F.; Oliveira, J.M.; Espregueira-Mendes, J.; Reis, R.L. Biomechanical and Cellular Segmental Characterization of Human Meniscus: Building the Basis for Tissue Engineering Therapies. *Osteoarthr. Cartil.* **2014**, *22*, 1271–1281. [CrossRef] [PubMed]
5. Herwig, J.; Egner, E.; Buddecke, E. Chemical Changes of Human Knee Joint Menisci in Various Stages of Degeneration. *Ann. Rheum. Dis.* **1984**, *43*, 635–640. [CrossRef]
6. Cheung, H.S. Distribution of Type I, II, III and V in the Pepsin Solubilized Collagens in Bovine Menisci. *Connect. Tissue Res.* **1987**, *16*, 343–356. [CrossRef] [PubMed]

7. Fox, A.J.S.; Bedi, A.; Rodeo, S.A. The Basic Science of Human Knee Menisci: Structure, Composition, and Function. *Sports Health* **2012**, *4*, 340–351. [CrossRef]
8. Zhu, S.; Tong, G.; Xiang, J.P.; Qiu, S.; Yao, Z.; Zhou, X.; Lin, L.J. Microstructure Analysis and Reconstruction of a Meniscus. *Orthop. Surg.* **2021**, *13*, 306. [CrossRef]
9. Lopez, S.G.; Bonassar, L.J. The Role of SLRPs and Large Aggregating Proteoglycans in Collagen Fibrillogenesis, Extracellular Matrix Assembly, and Mechanical Function of Fibrocartilage. *Connect. Tissue Res.* **2022**, *63*, 269–286. [CrossRef]
10. Moyer, J.T.; Priest, R.; Bouman, T.; Abraham, A.C.; Haut Donahue, T.L. Indentation Properties and Glycosaminoglycan Content of Human Menisci in the Deep Zone. *Acta Biomater.* **2013**, *9*, 6624. [CrossRef]
11. Folkesson, E.; Turkiewicz, A.; Rydén, M.; Hughes, H.V.; Ali, N.; Tjörnstrand, J.; Önnerfjord, P.; Englund, M. Proteomic Characterization of the Normal Human Medial Meniscus Body Using Data-independent Acquisition Mass Spectrometry. *J. Orthop. Res.* **2020**, *38*, 1735. [CrossRef] [PubMed]
12. Aspberg, A. The Different Roles of Aggrecan Interaction Domains. *J. Histochem. Cytochem.* **2012**, *60*, 987–996. [CrossRef] [PubMed]
13. Chen, S.; Fu, P.; Wu, H.; Pei, M. Meniscus, Articular Cartilage, and Nucleus Pulposus: A Comparative Review of Cartilage-like Tissues in Anatomy, Development, and Function. *Cell Tissue Res.* **2017**, *370*, 53. [CrossRef] [PubMed]
14. Petersen, W.; Tillmann, B. Age-Related Blood and Lymph Supply of the Knee Menisci. A Cadaver Study. *Acta Orthop. Scand.* **1995**, *66*, 308–312. [CrossRef] [PubMed]
15. Pufe, T.; Petersen, W.; Kurz, B.; Tsokos, M.; Tillmann, B.; Mentlein, R. Mechanical Factors Influence the Expression of Endostatin—An Inhibitor of Angiogenesis—In Tendons. *J. Orthop. Res.* **2003**, *21*, 610–616. [CrossRef]
16. Pufe, T.; Petersen, W.J.; Miosge, N.; Goldring, M.B.; Mentlein, R.; Varoga, D.J.; Tillmann, B.N. Endostatin/Collagen XVIII—An Inhibitor of Angiogenesis—Is Expressed in Cartilage and Fibrocartilage. *Matrix Biol.* **2004**, *23*, 267–276. [CrossRef]
17. Di Giancamillo, A.; Deponti, D.; Modina, S.; Tessaro, I.; Domeneghini, C.; Peretti, G.M. Age-related Modulation of Angiogenesis-regulating Factors in the Swine Meniscus. *J. Cell. Mol. Med.* **2017**, *21*, 3066. [CrossRef]
18. Fujii, M.; Furumatsu, T.; Yokoyama, Y.; Kanazawa, T.; Kajiki, Y.; Abe, N.; Ozaki, T. Chondromodulin-I Derived from the Inner Meniscus Prevents Endothelial Cell Proliferation. *J. Orthop. Res.* **2013**, *31*, 538–543. [CrossRef]
19. Makris, E.A.; Hadidi, P.; Athanasiou, K.A. The Knee Meniscus: Structure-Function, Pathophysiology, Current Repair Techniques, and Prospects for Regeneration. *Biomaterials* **2011**, *32*, 7411–7431. [CrossRef]
20. Grogan, S.P.; Duffy, S.F.; Pauli, C.; Lotz, M.K.; D'Lima, D.D. Gene Expression Profiles of the Meniscus Avascular Phenotype: A Guide for Meniscus Tissue Engineering. *J. Orthop. Res.* **2018**, *36*, 1947–1958. [CrossRef]
21. Meakin, J.R.; Shrive, N.G.; Frank, C.B.; Hart, D.A. Finite Element Analysis of the Meniscus: The Influence of Geometry and Material Properties on Its Behaviour. *Knee* **2003**, *10*, 33–41. [CrossRef]
22. De Rosa, M.; Filippone, G.; Best, T.M.; Jackson, A.R.; Travascio, F. Mechanical Properties of Meniscal Circumferential Fibers Using an Inverse Finite Element Analysis Approach. *J. Mech. Behav. Biomed. Mater.* **2022**, *126*, 105073. [CrossRef] [PubMed]
23. Mahmood, M.F.; Clarke, M.J.; Riches, D.P. Proteoglycans Exert a Significant Effect on Human Meniscal Stiffness through Ionic Effects. *Clin. Biomech.* **2020**, *77*, 105028. [CrossRef] [PubMed]
24. Morejon, A.; Mantero, A.M.A.; Best, T.M.; Jackson, A.R.; Travascio, F. Mechanisms of Energy Dissipation and Relationship with Tissue Composition in Human Meniscus. *Osteoarthr. Cartil.* **2022**, *30*, 605–612. [CrossRef]
25. Abdelgaied, A.; Stanley, M.; Galfe, M.; Berry, H.; Ingham, E.; Fisher, J. Comparison of the Biomechanical Tensile and Compressive Properties of Decellularised and Natural Porcine Meniscus. *J. Biomech.* **2015**, *48*, 1389–1396. [CrossRef]
26. Maritz, J.; Agustoni, G.; Dragnevski, K.; Bordas, S.P.A.; Barrera, O. The Functionally Grading Elastic and Viscoelastic Properties of the Body Region of the Knee Meniscus. *Ann. Biomed. Eng.* **2021**, *49*, 2421–2429. [CrossRef]
27. Agustoni, G.; Maritz, J.; Kennedy, J.; Bonomo, F.P.; Bordas, S.P.A.; Barrera, O. High Resolution Micro-Computed Tomography Reveals a Network of Collagen Channels in the Body Region of the Knee Meniscus. *Ann. Biomed. Eng.* **2021**, *49*, 2273–2281. [CrossRef]
28. Walker, P.S.; Erkman, M.J. The Role of the Menisci in Force Transmission across the Knee. *Clin. Orthop. Relat. Res.* **1975**, *109*, 184–192. [CrossRef]
29. Arno, S.; Hadley, S.; Campbell, K.A.; Bell, C.P.; Hall, M.; Beltran, L.S.; Recht, M.P.; Sherman, O.H.; Walker, P.S. The Effect of Arthroscopic Partial Medial Meniscectomy on Tibiofemoral Stability. *Am. J. Sports Med.* **2013**, *41*, 73–79. [CrossRef]
30. Majewski, M.; Susanne, H.; Klaus, S. Epidemiology of Athletic Knee Injuries: A 10-Year Study. *Knee* **2006**, *13*, 184–188. [CrossRef]
31. Henderson, B.S.; Cudworth, K.F.; Wale, M.E.; Siegel, D.N.; Lujan, T.J. Tensile Fatigue Strength and Endurance Limit of Human Meniscus. *J. Mech. Behav. Biomed. Mater.* **2022**, *127*, 105057. [CrossRef] [PubMed]
32. Bansal, S.; Miller, L.M.; Patel, J.M.; Meadows, K.D.; Eby, M.R.; Saleh, K.S.; Martin, A.R.; Stoeckl, B.D.; Hast, M.W.; Elliott, D.M.; et al. Transection of the Medial Meniscus Anterior Horn Results in Cartilage Degeneration and Meniscus Remodeling in a Large Animal Model. *J. Orthop. Res.* **2020**, *38*, 2696–2708. [CrossRef] [PubMed]
33. Glasson, S.S.; Blanchet, T.J.; Morris, E.A. The Surgical Destabilization of the Medial Meniscus (DMM) Model of Osteoarthritis in the 129/SvEv Mouse. *Osteoarthr. Cartil.* **2007**, *15*, 1061–1069. [CrossRef] [PubMed]
34. Lohmander, L.S.; Englund, P.M.; Dahl, L.L.; Roos, E.M. The Long-Term Consequence of Anterior Cruciate Ligament and Meniscus Injuries: Osteoarthritis. *Am. J. Sports Med.* **2007**, *35*, 1756–1769. [CrossRef] [PubMed]
35. Cui, A.; Li, H.; Wang, D.; Zhong, J.; Chen, Y.; Lu, H. Global, Regional Prevalence, Incidence and Risk Factors of Knee Osteoarthritis in Population-Based Studies. *eClinicalMedicine* **2020**, *29*, 100587. [CrossRef] [PubMed]

36. Kwon, H.; Brown, W.E.; Lee, C.A.; Wang, D.; Paschos, N.; Hu, J.C.; Athanasiou, K.A. Surgical and Tissue Engineering Strategies for Articular Cartilage and Meniscus Repair. *Nat. Rev. Rheumatol.* **2019**, *15*, 550–570. [CrossRef] [PubMed]
37. Barber-Westin, S.D.; Noyes, F.R. Clinical Healing Rates of Meniscus Repairs of Tears in the Central-Third (Red-White) Zone. *Arthroscopy* **2014**, *30*, 134–146. [CrossRef] [PubMed]
38. Nakanishi, Y.; Hoshino, Y.; Nagamune, K.; Yamamoto, T.; Nagai, K.; Araki, D.; Kanzaki, N.; Matsushita, T.; Kuroda, R. Radial Meniscal Tears Are Best Repaired by a Modified "Cross" Tie-Grip Suture Based on a Biomechanical Comparison of 4 Repair Techniques in a Porcine Model. *Orthop. J. Sport. Med.* **2020**, *8*, 2325967120935810. [CrossRef]
39. Abram, S.G.F.; Judge, A.; Beard, D.J.; Price, A.J. Adverse Outcomes after Arthroscopic Partial Meniscectomy: A Study of 700 000 Procedures in the National Hospital Episode Statistics Database for England. *Lancet* **2018**, *392*, 2194–2202. [CrossRef]
40. Lee, S.J.; Aadalen, K.J.; Malaviya, P.; Lorenz, E.P.; Hayden, J.K.; Farr, J.; Kang, R.W.; Cole, B.J. Tibiofemoral Contact Mechanics after Serial Medial Meniscectomies in the Human Cadaveric Knee. *Am. J. Sports Med.* **2006**, *34*, 1334–1344. [CrossRef]
41. Roemer, F.W.; Kwoh, C.K.; Hannon, M.J.; Hunter, D.J.; Eckstein, F.; Grago, J.; Boudreau, R.M.; Englund, M.; Guermazi, A. Partial Meniscectomy Is Associated with Increased Risk of Incident Radiographic Osteoarthritis and Worsening Cartilage Damage in the Following Year. *Eur. Radiol.* **2017**, *27*, 404–413. [CrossRef] [PubMed]
42. Sihvonen, R.; Paavola, M.; Malmivaara, A.; Itälä, A.; Joukainen, A.; Kalske, J.; Nurmi, H.; Kumm, J.; Sillanpaä, N.; Kiekara, T.; et al. Arthroscopic Partial Meniscectomy for a Degenerative Meniscus Tear: A 5 Year Follow-up of the Placebo-Surgery Controlled FIDELITY (Finnish Degenerative Meniscus Lesion Study) Trial. *Br. J. Sports Med.* **2020**, *54*, 1332–1339. [CrossRef] [PubMed]
43. Katz, J.N.; Shrestha, S.; Losina, E.; Jones, M.H.; Marx, R.G.; Mandl, L.A.; Levy, B.A.; MacFarlane, L.A.; Spindler, K.P.; Silva, G.S.; et al. Five-Year Outcome of Operative and Nonoperative Management of Meniscal Tear in Persons Older Than Forty-Five Years. *Arthritis Rheumatol.* **2020**, *72*, 273–281. [CrossRef]
44. Collins, J.E.; Losina, E.; Marx, R.G.; Guermazi, A.; Jarraya, M.; Jones, M.H.; Levy, B.A.; Mandl, L.A.; Martin, S.D.; Wright, R.W.; et al. Early Magnetic Resonance Imaging-Based Changes in Patients with Meniscal Tear and Osteoarthritis: Eighteen-Month Data from a Randomized Controlled Trial of Arthroscopic Partial Meniscectomy Versus Physical Therapy. *Arthritis Care Res.* **2020**, *72*, 630–640. [CrossRef]
45. Jacquet, C.; Pujol, N.; Pauly, V.; Beaufils, P.; Ollivier, M. Analysis of the Trends in Arthroscopic Meniscectomy and Meniscus Repair Procedures in France from 2005 to 2017. *Orthop. Traumatol. Surg. Res.* **2019**, *105*, 677–682. [CrossRef] [PubMed]
46. Persson, F.; Turkiewicz, A.; Bergkvist, D.; Neuman, P.; Englund, M. The Risk of Symptomatic Knee Osteoarthritis after Arthroscopic Meniscus Repair vs Partial Meniscectomy vs the General Population. *Osteoarthr. Cartil.* **2018**, *26*, 195–201. [CrossRef] [PubMed]
47. Kopf, S.; Beaufils, P.; Hirschmann, M.T.; Rotigliano, N.; Ollivier, M.; Pereira, H.; Verdonk, R.; Darabos, N.; Ntagiopoulos, P.; Dejour, D.; et al. Management of Traumatic Meniscus Tears: The 2019 ESSKA Meniscus Consensus. *Knee Surg. Sports Traumatol. Arthrosc.* **2020**, *28*, 1177–1194. [CrossRef]
48. Milachowski, K.A.; Weismeier, K.; Wirth, C.J. Homologous Meniscus Transplantation. *Int. Orthop.* **1989**, *13*, 1–11. [CrossRef] [PubMed]
49. Rodeo, S.A. Meniscal Allografts—Where Do We Stand? *Am. J. Sports Med.* **2001**, *29*, 246–261. [CrossRef]
50. Beeler, S.; Vlachopoulos, L.; Jud, L.; Sutter, R.; Fürnstahl, P.; Fucentese, S.F. Contralateral MRI Scan Can Be Used Reliably for Three-Dimensional Meniscus Sizing—Retrospective Analysis of 160 Healthy Menisci. *Knee* **2019**, *26*, 954–961. [CrossRef]
51. Stone, K.R.; Walgenbach, A.W.; Turek, T.J.; Freyer, A.; Hill, M.D. Meniscus Allograft Survival in Patients with Moderate to Severe Unicompartmental Arthritis: A 2- to 7-Year Follow-Up. *Arthroscopy* **2006**, *22*, 469–478. [CrossRef] [PubMed]
52. Figueroa, F.; Figueroa, D.; Calvo, R.; Vaisman, A.; Espregueira-Mendes, J. Meniscus Allograft Transplantation: Indications, Techniques and Outcomes. *EFORT Open Rev.* **2019**, *4*, 115–120. [CrossRef] [PubMed]
53. Abat, F.; Gelber, P.E.; Erquicia, J.I.; Pelfort, X.; Gonzalez-Lucena, G.; Monllau, J.C. Suture-Only Fixation Technique Leads to a Higher Degree of Extrusion than Bony Fixation in Meniscal Allograft Transplantation. *Am. J. Sports Med.* **2012**, *40*, 1591–1596. [CrossRef] [PubMed]
54. Ambra, L.F.; Mestriner, A.B.; Ackermann, J.; Phan, A.T.; Farr, J.; Gomoll, A.H. Bone-Plug Versus Soft Tissue Fixation of Medial Meniscal Allograft Transplants: A Biomechanical Study. *Am. J. Sports Med.* **2019**, *47*, 2960–2965. [CrossRef]
55. Teo, S.J.; Tan, M.W.P.; Koh, D.T.S.; Lee, K.H. Medial Meniscal Allograft Transplantation with Bone Plugs Using a 3-Tunnel Technique. *Arthrosc. Tech.* **2022**, *11*, e217–e222. [CrossRef]
56. Struijk, C.; Van Genechten, W.; Verdonk, P.; Krych, A.J.; Dietz, A.B.; van Wijnen, A.J.; Saris, D.B.F. Human Meniscus Allograft Augmentation by Allogeneic Mesenchymal Stromal/Stem Cell Injections. *J. Orthop. Res.* **2022**, *40*, 712–726. [CrossRef]
57. Noyes, F.; Barber-Westin, S.D. Meniscus Transplantation: Indications, Techniques, Clinical Outcomes. *AAOS Instr. Course Lect.* **2005**, *54*, 341.
58. Sandmann, G.H.; Eichhorn, S.; Vogt, S.; Adamczyk, C.; Aryee, S.; Hoberg, M.; Milz, S.; Imhoff, A.B.; Tischer, T. Generation and Characterization of a Human Acellular Meniscus Scaffold for Tissue Engineering. *J. Biomed. Mater. Res. Part A* **2009**, *91*, 567–574. [CrossRef]
59. Shimomura, K.; Rothrauff, B.B.; Tuan, R.S. Region-Specific Effect of the Decellularized Meniscus Extracellular Matrix on Mesenchymal Stem Cell-Based Meniscus Tissue Engineering. *Am. J. Sports Med.* **2017**, *45*, 604–611. [CrossRef]
60. Qu, F.; Guilak, F.; Mauck, R.L. Cell Migration: Implications for Repair and Regeneration in Joint Disease. *Nat. Rev. Rheumatol.* **2019**, *15*, 167–179. [CrossRef]

61. Ruprecht, J.C.; Waanders, T.D.; Rowland, C.R.; Nishimuta, J.F.; Glass, K.A.; Stencel, J.; DeFrate, L.E.; Guilak, F.; Weinberg, J.B.; McNulty, A.L. Meniscus-Derived Matrix Scaffolds Promote the Integrative Repair of Meniscal Defects. *Sci. Rep.* **2019**, *9*, 8719. [CrossRef] [PubMed]
62. Lyons, L.P.; Perea, S.H.; Weinberg, J.B.; Wittstein, J.R.; McNulty, A.L. Meniscus-Derived Matrix Bioscaffolds: Effects of Concentration and Cross-Linking on Meniscus Cellular Responses and Tissue Repair. *Int. J. Mol. Sci.* **2020**, *21*, 44. [CrossRef] [PubMed]
63. Ghazi Zadeh, L.; Chevrier, A.; Farr, J.; Rodeo, S.A.; Buschmann, M.D. Augmentation Techniques for Meniscus Repair. *J. Knee Surg.* **2018**, *31*, 99–116. [CrossRef] [PubMed]
64. Chahla, J.; Kennedy, N.I.; Geeslin, A.G.; Moatshe, G.; Cinque, M.E.; DePhillipo, N.N.; LaPrade, R.F. Meniscal Repair with Fibrin Clot Augmentation. *Arthrosc. Tech.* **2017**, *6*, e2065–e2069. [CrossRef] [PubMed]
65. Laidlaw, M.S.; Gwathmey, F.W. Circumferential Suture Repair of Isolated Horizontal Meniscal Tears Augmented with Fibrin Clot. *Arthrosc. Tech.* **2017**, *6*, e1567–e1572. [CrossRef] [PubMed]
66. Desai, T.; Babu, S.S.; Lal, J.V.; Kaushik, Y.S.; Lukose, A.M.; Sandesh, G.M.; Amaravathi, R.S. Fibrin Clot Augmented Repair of Longitudinal Tear of Medial Meniscus. *Arthrosc. Tech.* **2021**, *10*, e2449–e2455. [CrossRef] [PubMed]
67. Yamanashi, Y.; Kato, T.; Akao, M.; Takata, T.; Kobayakawa, K.; Deie, M. Meniscal Repair Using Fibrin Clots Made from Bone Marrow Blood Wrapped in a Polyglycolic Acid Sheet. *Arthrosc. Tech.* **2021**, *10*, e2541–e2546. [CrossRef]
68. Griffin, J.W.; Hadeed, M.M.; Werner, B.C.; Diduch, D.R.; Carson, E.W.; Miller, M.D. Platelet-Rich Plasma in Meniscal Repair: Does Augmentation Improve Surgical Outcomes? *Clin. Orthop. Relat. Res.* **2015**, *473*, 1665–1672. [CrossRef]
69. Kluyskens, L.; Debieux, P.; Wong, K.L.; Krych, A.J.; Saris, D.B.F. Biomaterials for Meniscus and Cartilage in Knee Surgery: State of the Art. *J. ISAKOS* **2022**, *7*, 67–77. [CrossRef]
70. Steadman, J.R.; Rodkey, W.G. Tissue-Engineered Collagen Meniscus Implants: 5- to 6-Year Feasibility Study Results. *Arthroscopy* **2005**, *21*, 515–525. [CrossRef]
71. Baynat, C.; Andro, C.; Vincent, J.P.; Schiele, P.; Buisson, P.; Dubrana, F.; Gunepin, F.X. Actifit Synthetic Meniscal Substitute: Experience with 18 Patients in Brest, France. *Orthop. Traumatol. Surg. Res.* **2014**, *100*, S385–S389. [CrossRef] [PubMed]
72. Reale, D.; Previtali, D.; Andriolo, L.; Grassi, A.; Candrian, C.; Zaffagnini, S.; Filardo, G. No Differences in Clinical Outcome between CMI and Actifit Meniscal Scaffolds: A Systematic Review and Meta-Analysis. *Knee Surg. Sports Traumatol. Arthrosc.* **2022**, *30*, 328–348. [CrossRef] [PubMed]
73. Martinek, V.; Ueblacker, P.; Bräun, K.; Nitschke, S.; Mannhardt, R.; Specht, K.; Gansbacher, B.; Imhoff, A.B. Second Generation of Meniscus Transplantation: In-Vivo Study with Tissue Engineered Meniscus Replacement. *Arch. Orthop. Trauma Surg.* **2006**, *126*, 228–234. [CrossRef] [PubMed]
74. Bulgheroni, E.; Grassi, A.; Campagnolo, M.; Bulgheroni, P.; Mudhigere, A.; Gobbi, A. Comparative Study of Collagen versus Synthetic-Based Meniscal Scaffolds in Treating Meniscal Deficiency in Young Active Population. *Cartilage* **2016**, *7*, 29–38. [CrossRef]
75. Reguzzoni, M.; Manelli, A.; Ronga, M.; Raspanti, M.; Grassi, F.A. Histology and Ultrastructure of a Tissue-Engineered Collagen Meniscus before and after Implantation. *J. Biomed. Mater. Res. B Appl. Biomater.* **2005**, *74*, 808–816. [CrossRef]
76. Baek, J.; Lotz, M.K.; D'Lima, D.D. Core-Shell Nanofibrous Scaffolds for Repair of Meniscus Tears. *Tissue Eng. Part A* **2019**, *25*, 1577–1590. [CrossRef]
77. Shemesh, M.; Asher, R.; Zylberberg, E.; Guilak, F.; Linder-Ganz, E.; Elsner, J.J. Viscoelastic Properties of a Synthetic Meniscus Implant. *J. Mech. Behav. Biomed. Mater.* **2014**, *29*, 42–55. [CrossRef]
78. Elsner, J.J.; Portnoy, S.; Zur, G.; Guilak, F.; Shterling, A.; Linder-Ganz, E. Design of a Free-Floating Polycarbonate-Urethane Meniscal Implant Using Finite Element Modeling and Experimental Validation. *J. Biomech. Eng.* **2010**, *132*, 095001. [CrossRef]
79. Balint, E.; Gatt, C.J.; Dunn, M.G. Design and Mechanical Evaluation of a Novel Fiber-Reinforced Scaffold for Meniscus Replacement. *J. Biomed. Mater. Res. A* **2012**, *100*, 195–202. [CrossRef]
80. Cojocaru, D.G.; Hondke, S.; Krüger, J.P.; Bosch, C.; Croicu, C.; Florescu, S.; Lazarescu, A.; Patrascu, J.M.; Patrascu, J.M.; Dauner, M.; et al. Meniscus-Shaped Cell-Free Polyglycolic Acid Scaffold for Meniscal Repair in a Sheep Model. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2020**, *108*, 809–818. [CrossRef]
81. Amiri, F.; Babaei, M.; Jamshidi, N.; Agheb, M.; Rafienia, M.; Kazemi, M. Fabrication and Assessment of a Novel Hybrid Scaffold Consisted of Polyurethane-Gellan Gum-Hyaluronic Acid-Glucosamine for Meniscus Tissue Engineering. *Int. J. Biol. Macromol.* **2022**, *203*, 610–622. [CrossRef] [PubMed]
82. Baek, J.; Lee, K.I.; Ra, H.J.; Lotz, M.K.; D'Lima, D.D. Collagen Fibrous Scaffolds for Sustained Delivery of Growth Factors for Meniscal Tissue Engineering. *Nanomedicine* **2022**, *17*, 77–93. [CrossRef] [PubMed]
83. Whitehouse, M.R.; Howells, N.R.; Parry, M.C.; Austin, E.; Kafienah, W.; Brady, K.; Goodship, A.E.; Eldridge, J.D.; Blom, A.W.; Hollander, A.P. Repair of Torn Avascular Meniscal Cartilage Using Undifferentiated Autologous Mesenchymal Stem Cells: From In Vitro Optimization to a First-in-Human Study. *Stem Cells Transl. Med.* **2017**, *6*, 1237. [CrossRef] [PubMed]
84. Fennema, E.; Rivron, N.; Rouwkema, J.; van Blitterswijk, C.; De Boer, J. Spheroid Culture as a Tool for Creating 3D Complex Tissues. *Trends Biotechnol.* **2013**, *31*, 108–115. [CrossRef] [PubMed]
85. Boucherit, N.; Gorvel, L.; Olive, D. 3D Tumor Models and Their Use for the Testing of Immunotherapies. *Front. Immunol.* **2020**, *11*, 603640. [CrossRef]

86. Rivron, N.C.; Frias-Aldeguer, J.; Vrij, E.J.; Boisset, J.C.; Korving, J.; Vivié, J.; Truckenmüller, R.K.; Van Oudenaarden, A.; Van Blitterswijk, C.A.; Geijsen, N. Blastocyst-like Structures Generated Solely from Stem Cells. *Nature* **2018**, *557*, 106–111. [CrossRef]
87. Mironov, V.; Visconti, R.P.; Kasyanov, V.; Forgacs, G.; Drake, C.J.; Markwald, R.R. Organ Printing: Tissue Spheroids as Building Blocks. *Biomaterials* **2009**, *30*, 2164–2174. [CrossRef]
88. McDermott, A.M.; Herberg, S.; Mason, D.E.; Collins, J.M.; Pearson, H.B.; Dawahare, J.H.; Tang, R.; Patwa, A.N.; Grinstaff, M.W.; Kelly, D.J.; et al. Recapitulating Bone Development through Engineered Mesenchymal Condensations and Mechanical Cues for Tissue Regeneration. *Sci. Transl. Med.* **2019**, *11*, eaav7756. [CrossRef]
89. Yang, Q.; Xue, S.L.; Chan, C.J.; Rempfler, M.; Vischi, D.; Maurer-Gutierrez, F.; Hiiragi, T.; Hannezo, E.; Liberali, P. Cell Fate Coordinates Mechano-Osmotic Forces in Intestinal Crypt Formation. *Nat. Cell Biol.* **2021**, *23*, 733–744. [CrossRef]
90. Lukonin, I.; Zinner, M.; Liberali, P. Organoids in Image-Based Phenotypic Chemical Screens. *Exp. Mol. Med.* **2021**, *53*, 1495–1502. [CrossRef]
91. Favreau, H.; Pijnenburg, L.; Seitlinger, J.; Fioretti, F.; Keller, L.; Scipioni, D.; Adriaensen, H.; Kuchler-Bopp, S.; Ehlinger, M.; Mainard, D.; et al. Osteochondral Repair Combining Therapeutics Implant with Mesenchymal Stem Cells Spheroids. *Nanomedicine* **2020**, *29*, 102253. [CrossRef] [PubMed]
92. Keller, L.; Wagner, Q.; Schwinté, P.; Benkirane-Jessel, N. Double Compartmented and Hybrid Implant Outfitted with Well-Organized 3D Stem Cells for Osteochondral Regenerative Nanomedicine. *Nanomedicine* **2015**, *10*, 2833–2845. [CrossRef] [PubMed]
93. Toratani, T.; Nakase, J.; Numata, H.; Oshima, T.; Takata, Y.; Nakayama, K.; Tsuchiya, H. Scaffold-Free Tissue-Engineered Allogenic Adipose-Derived Stem Cells Promote Meniscus Healing. *Arthrosc. J. Arthrosc. Relat. Surg.* **2017**, *33*, 346–354. [CrossRef] [PubMed]
94. Ishihara, K.; Nakayama, K.; Akieda, S.; Matsuda, S.; Iwamoto, Y. Simultaneous Regeneration of Full-Thickness Cartilage and Subchondral Bone Defects In vivo Using a Three-Dimensional Scaffold-Free Autologous Construct Derived from High-Density Bone Marrow-Derived Mesenchymal Stem Cells. *J. Orthop. Surg. Res.* **2014**, *9*, 98. [CrossRef] [PubMed]
95. Klarmann, G.J.; Gaston, J.; Ho, V.B. A Review of Strategies for Development of Tissue Engineered Meniscal Implants. *Biomater. Biosyst.* **2021**, *4*, 100026. [CrossRef]
96. Patel, J.M.; Brzezinski, A.; Ghodbane, S.A.; Tarapore, R.; Lu, T.M.; Gatt, C.J.; Dunn, M.G. Personalized Fiber-Reinforcement Networks for Meniscus Reconstruction. *J. Biomech. Eng.* **2020**, *142*, 051008. [CrossRef]
97. Filardo, G.; Petretta, M.; Cavallo, C.; Roseti, L.; Durante, S.; Albisinni, U.; Grigolo, B. Patient-Specific Meniscus Prototype Based on 3D Bioprinting of Human Cell-Laden Scaffold. *Bone Jt. Res.* **2019**, *8*, 101–106. [CrossRef] [PubMed]
98. Daly, A.C.; Kelly, D.J. Biofabrication of Spatially Organised Tissues by Directing the Growth of Cellular Spheroids within 3D Printed Polymeric Microchambers. *Biomaterials* **2019**, *197*, 194–206. [CrossRef]
99. Kunisch, E.; Knauf, A.-K.; Hesse, E.; Freudenberg, U.; Werner, C.; Bothe, F.; Diederichs, S.; Richter, W. StarPEG/Heparin-Hydrogel Based in Vivo Engineering of Stable Bizonal Cartilage with a Calcified Bottom Layer. *Biofabrication* **2018**, *11*, 015001. [CrossRef]
100. Hall, G.N.; Tam, W.L.; Andrikopoulos, K.S.; Casas-Fraile, L.; Voyiatzis, G.A.; Geris, L.; Luyten, F.P.; Papantoniou, I. Patterned, Organoid-Based Cartilaginous Implants Exhibit Zone Specific Functionality Forming Osteochondral-like Tissues in Vivo. *Biomaterials* **2021**, *273*, 120820. [CrossRef]
101. Gardner, E.; O'Rahilly, R. The Early Development of the Knee Joint in Staged Human Embryos. *J. Anat.* **1968**, *102*, 289–299. [PubMed]
102. Uhthoff, H.K.; Kumagai, J. Embryology of Human Meniscus. In *Trends in Research and Treatment of Joint Diseases*; Hirohata, K., Mizuno, K., Matsubara, T., Eds.; Springer: Tokyo, Japan, 1992; pp. 135–141. ISBN 9784431681922.
103. Pazin, D.E.; Gamer, L.W.; Capelo, L.P.; Cox, K.A.; Rosen, V. Gene Signature of the Embryonic Meniscus. *J. Orthop. Res.* **2014**, *32*, 46–53. [CrossRef] [PubMed]
104. Higashioka, M.M.; Chen, J.A.; Hu, J.C.; Athanasiou, K.A. Building an Anisotropic Meniscus with Zonal Variations. *Tissue Eng. Part A* **2014**, *20*, 294–302. [CrossRef] [PubMed]
105. Puetzer, J.L.; Koo, E.; Bonassar, L.J. Induction of Fiber Alignment and Mechanical Anisotropy in Tissue Engineered Menisci with Mechanical Anchoring. *J. Biomech.* **2015**, *48*, 1436–1443. [CrossRef] [PubMed]
106. Puetzer, J.L.; Bonassar, L.J. Physiologically Distributed Loading Patterns Drive the Formation of Zonally Organized Collagen Structures in Tissue-Engineered Meniscus. *Tissue Eng. Part A* **2016**, *22*, 907–916. [CrossRef] [PubMed]
107. Zitnay, J.L.; Reese, S.P.; Tran, G.; Farhang, N.; Bowles, R.D.; Weiss, J.A. Fabrication of Dense Anisotropic Collagen Scaffolds Using Biaxial Compression. *Acta Biomater.* **2018**, *65*, 76–87. [CrossRef] [PubMed]
108. Gonzalez-Leon, E.A.; Bielajew, B.J.; Hu, J.C.; Athanasiou, K.A. Engineering Self-Assembled Neomenisci through Combination of Matrix Augmentation and Directional Remodeling. *Acta Biomater.* **2020**, *109*, 73–81. [CrossRef]
109. MacBarb, R.F.; Makris, E.A.; Hu, J.C.; Athanasiou, K.A. A Chondroitinase-ABC and TGF-B1 Treatment Regimen for Enhancing the Mechanical Properties of Tissue-Engineered Fibrocartilage. *Acta Biomater.* **2013**, *9*, 4626–4634. [CrossRef]
110. Makris, E.A.; Responte, D.J.; Paschos, N.K.; Hu, J.C.; Athanasiou, K.A. Developing Functional Musculoskeletal Tissues through Hypoxia and Lysyl Oxidase-Induced Collagen Cross-Linking. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E4832–E4841. [CrossRef]
111. Zhang, Z.-Z.; Chen, Y.-R.; Wang, S.-J.; Zhao, F.; Wang, X.-G.; Yang, F.; Shi, J.-J.; Ge, Z.-G.; Ding, W.-Y.; Yang, Y.-C.; et al. Orchestrated Biomechanical, Structural, and Biochemical Stimuli for Engineering Anisotropic Meniscus. *Sci. Transl. Med.* **2019**, *11*, eaao0750. [CrossRef]

112. Bigoni, M.; Turati, M.; Sacerdote, P.; Gaddi, D.; Piatti, M.; Castelnuovo, A.; Franchi, S.; Gandolla, M.; Pedrocchi, A.; Omeljaniuk, R.J.; et al. Characterization of Synovial Fluid Cytokine Profiles in Chronic Meniscal Tear of the Knee. *J. Orthop. Res.* **2017**, *35*, 340–346. [CrossRef] [PubMed]
113. McNulty, A.L.; Estes, B.T.; Wilusz, R.E.; Weinberg, J.B.; Guilak, F. Dynamic Loading Enhances Integrative Meniscal Repair in the Presence of Interleukin-1. *Osteoarthr. Cartil.* **2010**, *18*, 830–838. [CrossRef] [PubMed]
114. Andress, B.D.; Irwin, R.M.; Puranam, I.; Hoffman, B.D.; McNulty, A.L. A Tale of Two Loads: Modulation of IL-1 Induced Inflammatory Responses of Meniscal Cells in Two Models of Dynamic Physiologic Loading. *Front. Bioeng. Biotechnol.* **2022**, *10*, 837619. [CrossRef] [PubMed]
115. Gilchrist, C.L.; Leddy, H.A.; Kaye, L.; Case, N.D.; Rothenberg, K.E.; Little, D.; Liedtke, W.; Hoffman, B.D.; Guilak, F. TRPV4-Mediated Calcium Signaling in Mesenchymal Stem Cells Regulates Aligned Collagen Matrix Formation and Vinculin Tension. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 1992–1997. [CrossRef]
116. Lee, K.I.; Choi, S.; Matsuzaki, T.; Alvarez-Garcia, O.; Olmer, M.; Grogan, S.P.; D'Lima, D.D.; Lotz, M.K. FOXO1 and FOXO3 Transcription Factors Have Unique Functions in Meniscus Development and Homeostasis during Aging and Osteoarthritis. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 3135–3143. [CrossRef]
117. Sun, Y.; Wu, Q.; Dai, K.; You, Y.; Jiang, W. Generating 3D-Cultured Organoids for Pre-Clinical Modeling and Treatment of Degenerative Joint Disease. *Signal Transduct. Target. Ther.* **2021**, *6*, 380. [CrossRef]
118. Keller, L.; Pijnenburg, L.; Idoux-Gillet, Y.; Bornert, F.; Benameur, L.; Tabrizian, M.; Auvray, P.; Rosset, P.; María Gonzalo-Daganzo, R.; Gómez Barrena, E.; et al. Preclinical Safety Study of a Combined Therapeutic Bone Wound Dressing for Osteoarticular Regeneration. *Nat. Commun.* **2019**, *10*, 2156. [CrossRef]
119. Keller, L.; Schwinté, P.; Gomez-Barrena, E.; Arruebo, M.; Benkirane-Jessel, N. Smart Implants as a Novel Strategy to Regenerate Well-Founded Cartilage. *Trends Biotechnol.* **2017**, *35*, 8–11. [CrossRef]
120. O'Connor, S.K.; Katz, D.B.; Oswald, S.J.; Groneck, L.; Guilak, F. Formation of Osteochondral Organoids from Murine Induced Pluripotent Stem Cells. *Tissue Eng. Part A* **2021**, *27*, 1099–1109. [CrossRef]
121. Paggi, C.; Venzac, B.; Leijten, J.; Teixeira Leijten, L.M.; Le Gac, S.; Karperien, M. Cartilage-on-Chip: A Multi-Modal Platform to Study Human Chondrocyte's Response to Mechanical Stimuli. *Osteoarthr. Cartil.* **2020**, *28*, S176–S177. [CrossRef]
122. Collison, J. Cartilage-on-a-Chip to Aid OA Drug Development. *Nat. Rev. Rheumatol.* **2019**, *15*, 511. [CrossRef] [PubMed]
123. Paggi, C.A.; Hendriks, J.; Karperien, M.; Le Gac, S. Emulating the Chondrocyte Microenvironment Using Multi-Directional Mechanical Stimulation in a Cartilage-on-Chip. *Lab Chip* **2022**, *22*, 1815–1828. [CrossRef] [PubMed]
124. Rothbauer, M.; Byrne, R.A.; Schobesberger, S.; Calvo, I.O.; Fischer, A.; Reihs, E.I.; Spitz, S.; Bachmann, B.; Sevelda, F.; Holinka, J.; et al. Establishment of a Human Three-Dimensional Chip-Based Chondro-Synovial Coculture Joint Model for Reciprocal Cross Talk Studies in Arthritis Research. *Lab Chip* **2021**, *21*, 4128–4143. [CrossRef] [PubMed]