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Review

The Evolving Landscape of Systemic Sclerosis Pathogenesis: From Foundational Mechanisms to Organ-Specific Modifiers

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Abstract: Systemic sclerosis (SSc) is a multifaceted autoimmune disease in which the complex interplay of genetic predisposition and environmental factors triggers aberrant immune responses, ultimately leading to vasculopathy and fibrosis. This review offers a comprehensive overview of current perspectives on SSc pathogenesis, integrating classical concepts with recent breakthroughs enabled by advanced analytical techniques. We delve into the foundational trans-organ pathophysiology of SSc, encompassing epigenetic dysregulation, chronic inflammation, vascular injury, vasculopathy, and fibrosis. Furthermore, we explore the organ-specific modifiers that contribute to the heterogeneity of SSc manifestations across different organ systems, including the skin, gastrointestinal tract, lungs, and heart. Recent studies employing single-cell transcriptomics, spatial proteomics, and epigenomic profiling are highlighted, demonstrating how these technologies are revolutionizing our understanding of SSc cellular and molecular pathology. This evolving landscape of SSc pathogenesis research is critical for identifying novel therapeutic targets and advancing personalized medicine approaches for SSc patients.

Keywords: systemic sclerosis; pathogenesis; fibrosis; vasculopathy; immune dysfunction; skin; single-cell analysis; transcriptomics; proteomics; epigenetics

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1. Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disorder of unknown origin, defined by three core pathological features: dysregulated immune activity, vascular injury followed by defective neovascularization and vessel remodeling, and the resulting fibrosis of the skin and various internal organs [1]. The etiology of SSc is still unknown, and there is currently no single hypothesis that uniquely explains the variety of pathophysiologic manifestations of the disease. However, our insight into its pathogenesis is rapidly growing, driven by clinical investigations of patient-derived samples, basic science research with animal models, and progress in targeted molecular treatments. Recent breakthroughs in sophisticated analytical methods, particularly single-cell analysis, have revolutionized the field. These advancements are vital for confirming disease mechanisms in patient tissues and for facilitating the discovery of new therapeutic approaches. This manuscript provides a summary of current perspectives on SSc pathogenesis, with a focus on the latest advancements.

2. Systemic Sclerosis Pathogenesis: Foundational Trans-Organ Pathophysiology

2.1. "Genetics" in SSc

Etiological research suggests that SSc results from a combination of genetic and environmental influences. While family history is the leading risk factor [2], concordance for SSc among twins is low, with comparable rates in both monozygotic (4.2%) and dizygotic (5.6%) pairs. One critical finding, however, is that the concordance for possessing autoantibodies is markedly higher in the unaffected monozygotic twin of an SSc patient (95%), compared to a dizygotic twin (60%, $p < 0.05$) [3]. This observation suggests that genetic factors are associated with autoimmunity, thereby increasing SSc susceptibility, but are insufficient for the development of clinically definite SSc. Consistent with this notion, the majority of SSc susceptibility genes are Human Leukocyte Antigen (HLA) haplotypes and non-HLA genes implicated in immunity and inflammation, which are also implicated in other connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) [4,5]. Beyond influencing susceptibility, genetic factors also determine the severity of SSc. This is demonstrated by multiple case-control and genome-wide association studies showing that variations like single-nucleotide polymorphisms (SNPs) in certain genes correlate with the disease course [6–9]. For instance, a specific SNP linked to lower levels of interferon regulatory factor 5 (IRF5) is more prevalent among SSc patients with less severe clinical manifestations [10].

2.2. "Epigenetics" in SSc

Epigenetics refers to the mechanisms by which cells regulate and transmit gene expression without alterations to the DNA base sequence. It also encompasses the field of study dedicated to these mechanisms. The pathogenesis of SSc is investigated from three perspectives: immune dysregulation, vasculopathy, and fibrosis. However, the ultimate goal of these investigations is to elucidate the mechanisms through which fibroblasts maintain a persistently activated state across various organs. While fibroblast activation is generally considered a response to the cumulative stimuli from the extracellular microenvironment in vivo, fibroblasts isolated from the skin and lungs of SSc patients retain their activated phenotype even after in vitro serial passage. This observation suggests the existence of a mechanism for maintaining a "pathological memory" intrinsic to these cells. Epigenetics is considered to be one such mechanism. DNA methylation, histone acetylation and methylation, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) have been identified as epigenetic modifications implicated in sustaining the activated state of fibroblasts derived from SSc patients.

Focusing on genetic factors, genome-wide association studies, as noted earlier, have identified that most susceptibility genes for SSc are located within the HLA region and in non-HLA immune-related genes. This suggests that genetically determined immune abnormalities play a central role in the development of SSc [5]. Indeed, antinuclear antibodies are detected in over 90% of SSc patients, and numerous other autoantibodies with pathogenic functions have been identified [11,12]. In the lesional skin of patients with early-stage SSc, perivascular lymphocytic infiltration is observed. This inflammation is thought to induce structural abnormalities in blood vessels characteristic of SSc, such as the loss of capillaries and thickening of small artery walls. Furthermore, it activates fibroblasts, leading to fibrosis. Although the precise mechanisms remain to be fully elucidated, it is proposed that SSc-specific phenotypic changes arise in various cells through epigenetic regulation influenced by environmental factors and are potentially shaped by genetic predisposition. These changes result in the breakdown of immune tolerance, excessive inflammatory responses, impaired vascular remodeling, and persistent and aberrant activa-

tion of vascular endothelial cells and fibroblasts. Consequently, these processes contribute to the complex pathogenesis of this disease [13]. Moreover, epigenetic modifications are deeply implicated in the mechanisms by which various cells maintain their pathological phenotypes within the highly fibrotic environment. In summary, epigenetics is considered to be involved in cellular phenotypic changes from two perspectives: the responses to external environmental factors that trigger SSc onset and the mechanisms maintaining pathological homeostasis against the internal microenvironment.

In SSc, the transcription factor FLI1 was the first gene identified as being under epigenetic control of its expression. Wang et al. [14] reported that, in both cultured SSc dermal fibroblasts and lesional SSc skin, CpG methylation is markedly increased in the *FLI1* promoter region. Furthermore, in cultured SSc dermal fibroblasts, significant decreases in histone H3 and H4 acetylation have been observed. Immunohistochemical analysis of skin tissue revealed that FLII expression in fibroblasts and vascular endothelial cells is mildly reduced in non-lesional SSc skin compared to healthy skin. A more pronounced reduction was observed in lesional SSc skin [15]. In the skin of $Fli1^{+/-}$ mice, fibroblasts are constitutively activated and exhibit increased type I collagen production; however, dermal thickening is not histologically apparent. Furthermore, mild structural abnormalities are present in skin microvessels, and phenotypic alterations resembling those in SSc skin vascular endothelial cells are evident at the molecular level [16]. Conversely, when bleomycin-induced SSc model mice are generated using $Fli1^{+/-}$ mice, an exacerbation of SSc-like phenotypes is observed across all aspects: inflammation, vasculopathy, and fibrosis [17]. These findings indicate that reduced FLI1 expression can induce activation of immune cells, vascular endothelial cells, and fibroblasts, molecularly resembling SSc, but this anomaly alone is insufficient to trigger SSc onset.

KLF5 is a crucial transcription factor regulating diverse fibrotic responses, acting as a pro-fibrotic factor in cardiac fibroblasts and a fibrosis-suppressing factor in renal tubular cells [18,19]. DNA microarray analysis has revealed that the expression of this transcription factor is downregulated in lesional SSc skin [20]. A study using cultured SSc dermal fibroblasts has revealed a marked downregulation of KLF5 expression at both the mRNA and protein levels. It was demonstrated that the application of an epigenetic inhibitor could recover KLF5 expression to levels comparable to those in healthy cells. Moreover, increased CpG methylation in the KLF5 promoter region was also detected [16]. These findings elucidate that KLF5 expression is robustly suppressed by epigenetic mechanisms in SSc dermal fibroblasts.

Building upon these findings, $Klf5^{+/-}$; $Fli1^{+/-}$ mice were generated to serve as a model for skin fibrosis. Notably, these mice not only faithfully recapitulated skin and lung fibrosis pathologies of SSc but also mirrored SSc vasculopathy, inflammation, and autoimmunity. Importantly, inflammation and autoimmunity emerged at 4 weeks of age, vasculopathy at 4–8 weeks, and skin fibrosis at 8–12 weeks. The temporal sequence of these major pathologies mirrored that observed in SSc [16]. Thus, $Klf5^{+/-}$; $Fli1^{+/-}$ mice can be considered a novel SSc model that spontaneously develops the three major SSc pathologies in a manner temporally similar to human SSc. This research highlights a significant finding: by focusing on factors governing pathological memory in SSc patient-derived cells, we can potentially identify key players in the pathogenesis of this disease.

Analyses of DNA methylation, histone modifications, miRNAs, and lncRNAs have been conducted in various cell types derived from SSc patients, including fibroblasts, vascular endothelial cells, $CD4^+$ T cells, B cells, and plasmacytoid dendritic cells (pDCs). Consequently, a substantial number of epigenetic aberrations have been reported. Detailed descriptions of individual findings are omitted in this paper, as they are summarized in several review articles; readers are referred to these for further details [21–27].

2.3. Genetic Polymorphisms of FLI1 and SSc Susceptibility

Yamashita et al. [4] conducted a case-control study in a Japanese population, directly genotyping this *FLI1* (GA)*n* microsatellite. Their findings revealed a significant association between extended repeat alleles of the *FLI1* (GA)*n* microsatellite and increased susceptibility to SSc. Specifically, alleles with 22 or more GA repeats (L alleles) were more frequent in SSc patients compared to healthy controls. Furthermore, these L alleles were associated with reduced *FLI1* mRNA levels in healthy individuals, suggesting a functional consequence of this genetic polymorphism on gene expression. This genetic association with *FLI1* further strengthens the evidence implicating *FLI1* as a key player in SSc pathogenesis, acting not only through epigenetic modifications but also through inherent genetic predispositions that influence its expression and potentially its function. These findings suggest that *FLI1* genetic variants, particularly microsatellite polymorphisms, may contribute to the "missing heritability" in SSc.

2.4. Inflammation and Immunological Dysfunction in SSc

As previously described, the interaction between endothelial cells and circulating immune cells, mediated by cell adhesion molecules and chemokines, facilitates the activation of inflammatory cells and their infiltration into SSc-affected organs. Typically, infiltration by T cells, macrophages, and mast cells predominates in SSc-involved skin, whereas B-cell infiltration is comparatively limited [28–31]. In contrast, numerous lymphoid aggregates, characterized by a substantial accumulation of B cells and relatively fewer T cells and macrophages, are commonly observed in the lung tissue of patients with SSc-associated interstitial lung disease (ILD) [32]. Notably, genes associated with activated B cells are upregulated in SSc-involved skin [20], and the B-cell count in the skin correlates with the progression of skin fibrosis [31]. Consequently, while the composition of infiltrating cell types may vary across different affected organs, increased infiltration of B cells, T cells, and innate immune cells is a shared feature in the organs involved in SSc.

Alterations in T cell subsets are a well-documented feature of SSc. The balance of Th1/Th2 and Th17/Treg immune responses is skewed toward Th2 and Th17 dominance [33–36], and regulatory T cell (Treg) function is impaired during the active phase of SSc [37]. In the early stage of diffuse cutaneous SSc (dcSSc), serum levels of interleukin-6 (IL-6) and IL-10 are significantly elevated, whereas they decrease to normal levels in the late stage of dcSSc, which is characterized by the regression of skin sclerosis [38]. The cytokine profile in dcSSc displays dynamic changes over time. Initially, IL-4 levels are normal, and they decline as the skin sclerosis resolves. In contrast, serum IL-12 is low in early dcSSc but rises with disease duration, eventually exceeding normal levels in the late stage [33]. The Th17 pathway is also clearly involved; in early dcSSc skin lesions, the expression of IL-17A, IL-21, and IL-22 is increased, though IL-17F is not [36,39]. Systemically, the frequency of circulating Th17 cells and their IL-17 production are elevated, with Th17 counts corresponding to disease activity [34]. Within the skin, the Treg population is also altered, showing an increased proportion of Th2-like Tregs [30].

Currently, the direct role of SSc-related antinuclear antibodies (ANAs), including antibodies against topoisomerase I (topo I), centromere, and RNA polymerase III (RNAP III) antigens, is not fully understood, although a potential role for anti-topoisomerase I antibodies has been suggested (described below). Nevertheless, the strong correlation of these ANAs with clinical manifestations implies that altered B-cell phenotypes may be associated with the core abnormality driving disease progression.

On the other hand, the potential pathogenic role of so-called functional vascular antibodies, particularly those targeting the angiotensin II type 1 receptor (AT1R) and the endothelin-1 type A receptor (ETAR), has been a subject of discussion. However, compelling

evidence for their direct contribution to pathophysiology is still lacking, and the clinical utility of testing for these antibodies remains unclear [40,41]. The ultimate proof that an antibody is causative is when passive transfer in an animal model (possibly with a specific genetic background) results in disease features.

Aberrant activation of B cells could occur through genetic and epigenetic mechanisms shared across cell types and/or through complex interactions with other immune and non-immune cells. In SSc, B cells are in a state of continuous activation, demonstrated by increased surface expression of the co-receptor CD19 [42] and the activation markers CD80 and CD86 on memory B cells [43]. This is significant because, in addition to producing antibodies, B cells contribute to pathogenesis through cytokine secretion, antigen presentation, and regulation of macrophages and lymphoid tissue [44]. The critical role of B cells is supported by the efficacy of rituximab, an anti-CD20 antibody that improves skin fibrosis and ILD by depleting B cells, as shown in multiple case series and open-label studies [45–48]. Furthermore, several case reports and case series have documented the amelioration of calcinosis, digital ulcers (DUs), and arterial stiffness following rituximab therapy [49–51]. CD19-targeted Chimeric Antigen Receptor (CAR) T-cell therapy is an emerging investigational treatment for severe and refractory SSc. Initial case studies and small series have demonstrated promising clinical responses, including improvements in skin fibrosis, ILD, and cardiac function, often accompanied by reduced autoantibody levels and disease activity. Supporting data show decreased TGF-β levels in dermal biopsies, improved skin elasticity on elastography, and amelioration of lung and heart fibrosis on imaging and through markers like KL-6. These benefits sometimes allow cessation of other immunosuppressive treatments, with generally manageable safety profiles reported [52–55]. Thus, B cells contribute to the activation of vascular and fibrotic processes, in addition to immune system activation in SSc, reinforcing the concept that immune cells are upstream mediators in the SSc-specific disease cascade.

Beyond adaptive immune cells, innate immune cells are also abundantly present in SSc-involved organs. In SSc lesional skin, mast cells secrete excessive levels of transforming growth factor-β (TGF-β) [56]. Moreover, M2 macrophages appear to be critical regulators of tissue fibrosis, as the M2 macrophage-associated gene program, which is upregulated in the skin of early SSc patients, is suppressed in conjunction with the resolution of skin fibrosis following treatment with tocilizumab (an anti-IL-6 receptor antibody) [57].

In SSc-affected skin, a specific sequence of events is thought to drive excess IFN-α production by plasmacytoid dendritic cells (pDCs). First, pDCs are recruited to the area around dermal small vessels by elevated levels of the chemoattractant chemerin [58,59]. Concurrently, endothelial cell death provides a source of self-DNA, which interacts with increased local concentrations of LL-37 [60]. This process forms stimulatory self-DNA/LL-37 complexes that are hypothesized to activate pDCs via TLR7 and 9, resulting in high local production of IFN-α.

Furthermore, disease-associated autoantibodies, particularly anti-topoisomerase I antibodies, may contribute to this process. Anti-topoisomerase I antibodies react with nuclear antigens from endothelial cells, and immune complexes formed with nucleic acids, especially RNA, induce IFN-α production from pDCs [61]. The idea that IFN-α contributes to SSc development is supported by clinical and experimental data. A trial using recombinant IFN-α for SSc reported higher withdrawal rates than placebo, with many discontinuing patients showing worsened ILD [62]. Moreover, administering IFN-α for other disorders, like multiple sclerosis or chronic hepatitis C, can trigger SSc or similar symptoms [63–68]. This may be explained by a self-amplifying cycle in which continuous IFN-α exposure causes endothelial senescence [69], providing self-DNA that stimulates pDCs to produce more IFN-α, thus driving vascular injury and immune activation. Recently, the discovery

of ectopic TLR8 expression on SSc pDCs, a key RNA sensor linked to experimental fibrosis, has added another layer to this mechanism [70]. In addition to their role in IFN-α production, recent findings indicate that pDCs can also contribute to fibrosis through endoplasmic reticulum (ER) stress-mediated mechanisms, as demonstrated by Ferreira et al. [71] who revealed that ER stress induction in pDCs promotes fibroblast activation via direct cell–cell contact, suggesting a novel pathway contributing to fibrosis development in SSc. Collectively, the continuous release of autoantigens from damaged and senescent endothelial cells serves as a fundamental driver of SSc pathology, acting through the induction of chronic inflammation.

2.5. Vascular Injury in SSc

As previously discussed, the pathogenesis of SSc begins with immune dysregulation, while histopathologically detectable structural abnormalities first manifest as vascular damage [72–74]. Indeed, vasculopathy is a critical element in the early clinical picture of SSc, manifesting in patient-reported symptoms such as Raynaud's phenomenon and digital edema [75]. Crucially, the presence of disease-specific autoantibodies, hallmarks of SSc's autoimmune nature, can be detected even before these initial clinical manifestations emerge, highlighting the early involvement of autoimmunity in vascular injury [75–77]. Following this initial vascular insult, the vasculature in SSc undergoes significant structural abnormalities [78]. These changes arise from a combination of dysfunctional vascular remodeling processes and the development of various vascular functional impairments [78].

In the early stages of SSc, capillary fragility leads to capillary dilation, which in turn results in the extravasation of erythrocytes [75]. The observation of dilated and hemorrhaging nailfold capillaries is diagnostically significant, serving as an important early indicator of the disease [76]. As SSc progresses, a progressive loss of capillaries occurs, with capillary numbers gradually diminishing and eventually being replaced by fibrotic tissue [76]. In parallel with this capillary rarefaction and fibrotic replacement, vascular endothelial cells and pericytes, which are crucial components of blood vessels, undergo differentiation into myofibroblasts through processes known as endothelial-to-mesenchymal transition (EndoMT) and pericyte-to-mesenchymal transition (PMT), respectively [78,79]. These transformed cells acquire resistance to apoptosis, or programmed cell death, and exhibit cellular senescence phenotypes. This altered cellular behavior significantly contributes to the establishment and perpetuation of the extensive fibrosis characteristic of SSc [78]. The ensuing loss of capillaries leads to tissue hypoxia, a state of oxygen deficiency, which in turn acts as a potent stimulus for further myofibroblast activation and promotes the fibrotic process across a range of organs, including the skin, lungs, heart, and intestines [78]. In contrast, within arterioles and small to medium-sized arteries, the vascular endothelial cells, when injured, also undergo differentiation into myofibroblasts [78]. Furthermore, the proliferative capacity of vascular smooth muscle cells, another key cell type in blood vessels, and their ability to produce extracellular matrix (ECM) components, are enhanced, culminating in fibrotic stenosis, or narrowing of the blood vessels [78]. The characteristic arterial lesions of SSc arise from an abnormal gathering of myofibroblasts within the vessel wall. This accumulation creates fibroproliferative changes that subsequently impair vascular perfusion [78].

The vascular functional derangements in SSc are multifaceted and encompass a range of abnormalities. These include diminished vascular endothelial function, which refers to the impaired ability of the endothelium to regulate vascular tone and permeability; a reduced capacity for thrombus inhibition, increasing the risk of blood clot formation; impaired physiological anticoagulation mechanisms, further exacerbating the pro-thrombotic state; aberrant expression of cell adhesion molecules and chemokines, which contribute to

chronic inflammation and immune cell recruitment to the vessel wall; and an augmented generation of reactive oxygen species (ROS), leading to oxidative stress and cellular damage [17,80,81]. These functional aberrations play a crucial role in activating fibroblasts, the primary effector cells in fibrosis, mainly by promoting tissue hypoxia and chronic inflammation [17,80–83]. Vasospasm affecting arterioles and arteries, clinically manifested as Raynaud's phenomenon, further exacerbates fibroblast activation through ischemia–reperfusion injury, a process involving tissue damage caused by alternating periods of insufficient blood supply and reperfusion [84]. Fibroblasts themselves undergo phenotypic modulation, acquiring a profibrotic phenotype, and exhibit dysregulated responses to inflammatory signals. Notably, they demonstrate excessive ECM synthesis, contributing to the tissue fibrosis [78]. The cellular origins of myofibroblasts in SSc are diverse, encompassing not only resident tissue fibroblasts but also vascular wall-resident endothelial cells and pericytes, epithelial cells, adipocytes, and bone marrow-derived fibrocytes [78]. Myofibroblasts originating from this heterogeneous array of cellular sources collectively orchestrate the pathogenesis of the extensive fibrosis observed in SSc [78]. The preceding discussion elucidates the fundamental pathophysiology of SSc, highlighting a shared mechanistic basis that operates across various organs affected by fibrosis, and thus can be conceptualized as a foundational trans-organ pathophysiology [72,73].

2.6. Fibrosis in SSc

The key effector cells driving SSc fibrosis are α-smooth muscle actin (α-SMA)-positive myofibroblasts, which secrete excessive ECM in affected tissues. These cells derive from a heterogeneous population of precursors, including local fibroblasts, circulating fibrocytes [85], and cells undergoing epithelial–mesenchymal [86], and endothelial–mesenchymal transition (EndoMT) [87,88], and adipocyte–myofibroblast transdifferentiation [89]. This state of fibroblast activation is the final outcome of the SSc pathogenic process, and the cells maintain their activated phenotype through a combination of intrinsic and extrinsic mechanisms.

A primary growth factor driving dermal fibroblast activation in SSc is TGF-β, which induces the production of ECM components like fibrillar collagens (types I, III, and V). Its expression is high in early, active disease and diminishes in established fibrosis. The localization of its isoforms suggests a role in the disease's inflammatory phase; specifically, TGF-β1 and TGF-β2 are prominently expressed around dermal vessels in connection with perivascular mononuclear infiltrates, while all three isoforms are detectable throughout the ECM [90–92]. Consequently, in the early stages of SSc, TGF-β appears to promote inflammation by recruiting leukocytes through the modulation of cell adhesion molecules and the establishment of chemokine gradients, by activating leukocytes, and by inducing various proinflammatory cytokines and mediators. Conversely, in the sclerotic phase, SSc dermal fibroblasts exhibit constitutive activation with a profibrotic phenotype, resembling that of normal fibroblasts treated with TGF-β1, even when TGF-β expression is diminished or undetectable in the skin [93]. This suggests that SSc fibroblasts possess a self-activation system, one at least partially mediated via autocrine TGF-β signaling. The increased expression of latent TGF-β receptors, including integrin αVβ3, integrin αVβ5, and thrombospondin-1, contributes to this process in SSc fibroblasts [94–98]. These receptors recruit and activate latent TGF-β on the cell surface, efficiently increasing the concentration of active TGF-β in the cellular microenvironment. Further expanding on the mechanisms of TGF-β-driven fibrosis, Meng et al. [99] identified ADAM19 as a significantly upregulated metalloproteinase in SSc skin fibrosis, demonstrating its role in promoting TGF-β-induced ECM deposition and fibroblast activation through the shedding of pro-fibrotic neuregulin-1 (NRG1), thereby contributing to the development of skin fibrosis in SSc. Thus, dermal

fibroblasts are constitutively activated, at least partially, through autocrine TGF-β signaling, in SSc lesional skin.

SSc dermal fibroblasts respond differently to T-cell stimuli, relative to healthy fibroblasts. Normally, collagen production is downregulated by Th1 cells via IFN-γ [100], and by Th2 cells via membrane-associated tumor necrosis factor-α (TNF-α) [101], which counter the profibrotic effect of IL-4. In SSc, however, fibroblasts are resistant to this suppression, especially that from the Th2 cells [100,101]. One proposed reason is the high secretion of progranulin, a TNF receptor antagonist that negates the anti-fibrotic effect of TNF-α [102]. This specific lack of response to Th2-mediated suppression is thought to be a critical driver of fibroblast activation during the early, Th2-polarized phase of dcSSc. Adding to the complexity of fibroblast activation, Bergmann et al. [103] discovered a mutual amplification loop between GLI2/Hedgehog and JUN/AP-1 signaling pathways within SSc fibroblasts, where these pathways synergistically enhance each other's activity, resulting in sustained fibroblast activation and collagen production, highlighting a potential target for combined therapeutic interventions.

The interaction is bidirectional, as SSc dermal fibroblasts also shape the differentiation of inflammatory cells. For example, they direct the transdifferentiation of Tregs into Th2-like cells via IL-33 in the skin [30,104]. By overproducing galectin-9, they also inhibit IFN-γ expression in skin-infiltrating CD4+ T cells, which fosters fibrosis within the Th2/Th17-dominant microenvironment [105]. These findings suggest SSc fibroblasts affect skin immunity more extensively than previously thought.

Collectively, SSc fibroblasts perpetuate their activation through autocrine signaling and feedforward loops with other cells, culminating in the irreversible fibrotic remodeling of multiple organs.

3. Verification of Pathogenesis Hypotheses: Insights from Recent Analytical Innovations

Pathogenesis hypotheses of SSc, as previously outlined, have been largely formulated based on conventional clinical and basic research methodologies, utilizing clinical samples from SSc patients (primarily lesional skin and lung biopsy tissues, and peripheral blood) and animal models. However, recent years have witnessed a transformative shift with the advent of cutting-edge analytical techniques, including single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, imaging mass cytometry, and single-nucleus assay for transposase-accessible chromatin with sequencing (snATAC-seq), particularly in the context of lesional skin analysis. These advanced technologies have provided unprecedented opportunities for the successive validation and refinement of the aforementioned pathogenesis hypotheses. Representative studies employing these innovative approaches are introduced below.

3.1. Scleroderma-Associated Fibroblast (ScAF) Identification via scRNA-Seq Analysis

In a landmark study in 2022, Gur et al. [106] leveraged scRNA-seq to analyze skin tissues from a large cohort comprising 97 patients with SSc and 56 healthy individuals, subsequently publishing transformative findings. Their comprehensive analysis led to the refined classification of skin fibroblasts into 10 distinct cellular subpopulations. Notably, myofibroblasts, which have historically been considered central effector cells in the pathogenesis of SSc, were found to represent only a minor fraction, constituting approximately 1% of the total cellular population. Conversely, the most abundant fibroblast subpopulation was identified as LGR5 (Leucine-rich repeat-containing G-protein coupled Receptor 5)-positive fibroblasts, which account for approximately 30% of the cells in healthy individuals. Gene expression pattern analysis indicated that this LGR5+ fibroblast population plays a

critical homeostatic role in maintaining normal skin architecture. However, a significant reduction in the abundance of this cell population was observed in SSc patients. Furthermore, these Scleroderma-Associated Fibroblasts (ScAFs) exhibited a constellation of molecular characteristics consistent with previously described SSc skin fibroblasts, including the following: 1, pathologically excessive ECM production coupled with suppressed degradation; 2, aberrant activation of Type I interferon signaling, TGF-β pathway, and IL-1 pathway; 3, dysregulation of Wnt signaling and IGF1 signaling, and abnormal expression of CCN1 family proteins; 4, pathologically activated angiogenesis, increased vascular fragility, and enhanced coagulation and platelet aggregation; 5, diminished antioxidation and adipogenesis capacity; and 6, overexpression of CDKN2A (p16) and CDKN1A (p21), indicative of enhanced cellular senescence. Notably, the study also demonstrated a significant inverse correlation between the cellular density of this ScAF population and skin score. These compelling findings suggest that ScAFs, identified as the principal fibroblast subpopulation orchestrating the fibrotic pathology of SSc, may represent promising novel therapeutic targets. Conversely, the investigation also revealed a concomitant increase in vascular endothelial cells and pericytes alongside the progression of skin sclerosis. In particular, RGS5 (Regulator of G-protein Signaling 5)-positive vascular pericytes demonstrated a positive correlation with skin score. These observations may be interpreted as providing support for conventional pathogenesis hypotheses that posit vascular endothelial cells and pericytes as primary cellular origins of pathogenic fibroblasts in SSc.

3.2. Spatial Transcriptomics Analysis

Ma et al. [107] performed an in-depth analysis of SSc pathogenesis using single-cell and spatial transcriptomics. They analyzed scRNA-seq data from skin biopsies of twenty-two SSc patients and eighteen healthy controls, alongside spatial RNA-seq data from four SSc patients, to map disease-associated cells and their interactions within SSc lesions. The study reported four key observations. First, fibroblasts, vascular endothelial cells, and pericytes were diffusely present in fibrotic areas of SSc skin. Second, fibroblasts were classified into seven distinct populations; $SFRP2^+$ fibroblasts activated and differentiated into $COL8A1^+$ fibroblasts (with myofibroblast features) during fibrosis progression. Third, vascular endothelial cells demonstrated heterogeneity, with categorization into seven distinct subpopulations, including arteriolar endothelial cells (EC2) and activated endothelial cells (EC5). EndoMT maturity served as a differentiating factor among these subpopulations, with EC2 identified as the dominant subpopulation within SSc lesions. Fourth, ligand–receptor network analysis indicated that fibroblast–vascular endothelial cell interactions were most pronounced, with EC2 and $COL8A1^+$ myofibroblast-like fibroblasts being the key communicators. These results reinforce existing pathogenesis models implicating vascular wall cells as myofibroblast origins in SSc.

3.3. Integrated Analysis: scRNA-Seq and snATAC-Seq, Focusing on Vascular Endothelial Cells

In their 2024 study, Huang et al. [108] performed a comprehensive analysis using scRNA-seq and snATAC-seq data to investigate SSc vasculopathy. Analyzing skin biopsies from twenty-seven SSc patients and ten healthy controls via scRNA-seq, and snATAC-seq data from eight SSc patients and six controls, they explored the role of transcription factors in SSc-associated vascular pathology. The scRNA-seq analysis of lesional SSc skin revealed two key observations: first, increased apoptosis and decreased cell numbers in arteriolar endothelial cells; and second, an elevation in tip and stalk cell populations, indicative of constitutively enhanced angiogenesis in dermal microvascular endothelial cells. These findings align with established pathogenesis hypotheses of SSc, particularly regarding destructive vasculopathy and angiogenic abnormalities. Furthermore, snATAC-seq analysis

indicated increased chromatin accessibility at the ETS motif in SSc vascular endothelial cells, supporting the involvement of ETS transcription factors, especially FLI1, in SSc vasculopathy, consistent with prior research. These integrated analyses using scRNA-seq and snATAC-seq reinforce the conventional understanding of SSc pathogenesis by highlighting the roles of vascular endothelial cell apoptosis, dysregulated angiogenesis, and ETS transcription factors in the development of SSc vasculopathy (Figure 1).

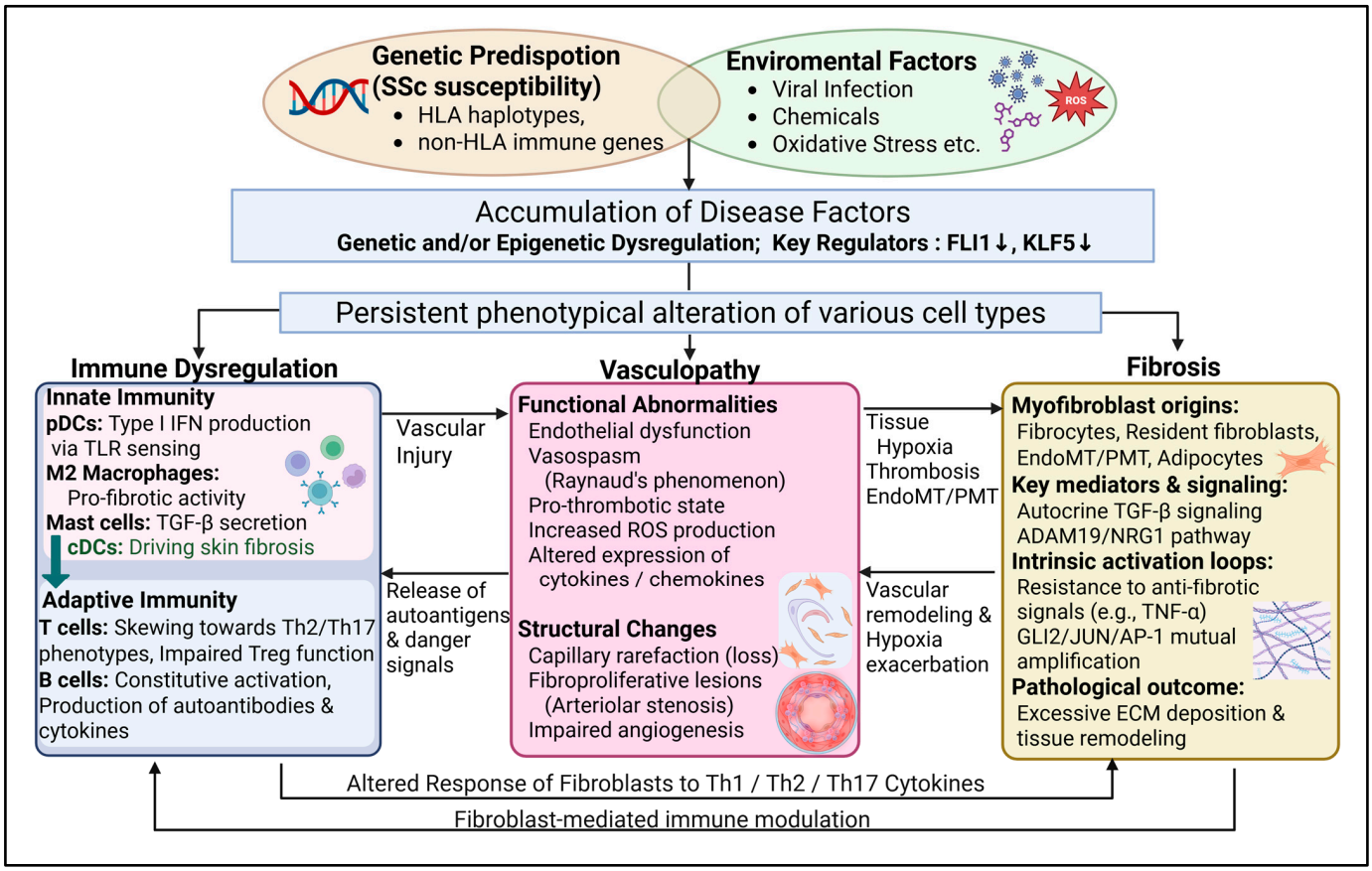

Figure 1. An integrated view of the pathogenesis of systemic sclerosis (SSc). The disease is initiated by genetic predisposition and environmental factors that, via epigenetic dysregulation (e.g., reduced FLI1/KLF5), drive three interconnected pathologies. These are immune dysregulation, involving key innate and adaptive effector cells; vasculopathy, comprising functional and structural abnormalities like endothelial dysfunction and capillary loss; and fibrosis, characterized by activated myofibroblasts and excessive ECM deposition. These pillars are linked by vicious cycles, as depicted by the arrows. Immune-mediated vascular injury is amplified by the subsequent release of autoantigens. Vasculopathy promotes fibrosis through tissue hypoxia and EndoMT/PMT. Activated fibroblasts modulate the immune response, while simultaneously showing an altered response to immune signals, creating a self-perpetuating disease state.

3.4. Vascular Niche Analysis by Spatial Proteomics Using Imaging Mass Cytometry

Rius Rigau et al. [109] employed imaging mass cytometry to conduct a vascular niche analysis in skin samples from 19 SSc patients and 14 healthy individuals. Their spatial proteomics-based approach identified seven subpopulations of vascular endothelial cells based on their unique protein expression profiles. In SSc patients, the researchers reported an increased population of $CD34^+;\alpha SMA^+;CD31^+$ cells alongside a reduction in vascular endothelial progenitor cells. The perivascular microenvironment of $CD34^+;\alpha SMA^+;CD31^+$ cells was characterized by a significant presence of immune cells, predominantly $CD4^+$ T cells and myeloid cells, as well as myofibroblasts. Moreover, $CD34^+;\alpha SMA^+;CD31^+$ cells

exhibited markers of EndoMT, such as SNAI1, SNAI2, TWIST, and ZEB1. The density of $CD34^+$;αSMA^+;$CD31^+$ cells was found to correlate with the clinical progression of skin sclerosis. These observations reinforce the established pathogenesis model wherein vascular endothelial cells contribute to the myofibroblast population through EndoMT in SSc-related fibrosis.

3.5. Novel Pathogenesis Mechanism of SSc Skin Fibrosis Suggested by Epigenetic Analysis Using ATAC-Seq

Liu et al. [110] conducted an epigenetic analysis to explore novel pathogenesis mechanisms in SSc skin fibrosis, employing ATAC-seq. Using flow cytometry, they isolated eight skin-resident cell types—fibroblasts, vascular endothelial cells, epidermal cells, $CD4^+$ T cells, $CD8^+$ T cells, dendritic cells, Langerhans cells, and macrophages—from the healthy, lesional, and non-lesional SSc skin of seven SSc patients and six healthy controls, totaling 19 samples. Leveraging the known enrichment of disease-susceptibility SNPs in non-coding regulatory DNA, they hypothesized that cell-type-specific chromatin accessibility analysis at SSc-associated SNP loci could pinpoint pathogenic cell types. Their analysis revealed significantly increased chromatin accessibility in SSc-associated SNP regions specifically within dendritic cells (DCs), compared to other skin cell types. Re-analysis of time-series RNA-seq data from SSc lesions further supported this, showing a strong positive correlation between the DC gene signature and skin fibrosis score. Specifically, conventional DCs (cDCs) were identified as a key cellular population. Immunohistochemical validation using ZBTB46, a cDC marker, confirmed significant infiltration of $ZBTB46^+$ cells into SSc lesions. These epigenetic findings suggest a previously unappreciated role for cDCs in SSc skin fibrosis, offering a novel perspective on SSc pathogenesis beyond conventional hypotheses. The importance of dendritic cells in the pathogenesis of SSc is also demonstrated in the following articles [111,112]

3.6. Novel Therapeutic Targets Identified by Gene Expression Meta-Analysis of Lung Tissue

Yang et al. [113] published a gene expression meta-analysis of lung tissue, examining 38 patients with SSc-ILD and 18 healthy controls. Their analysis, utilizing three public datasets (GSE48149, GSE81292, GSE76808), identified the activation of epithelial–mesenchymal transition, cellular senescence, coagulation, and DNA repair pathways as characteristic changes in SSc-ILD lung tissue. Consistent with an aging phenotype, telomere length in type II alveolar epithelial cells from SSc-ILD lungs was found to be reduced, indicating enhanced cellular senescence. The current therapeutic development for SSc-ILD primarily targets myofibroblasts and inflammation/autoimmunity. However, this study suggests that cellular senescence and coagulation pathways could offer novel therapeutic avenues for SSc-ILD.

Plasminogen Activator Inhibitor-1 (PAI-1) is a serpin that inhibits tissue-type Plasminogen Activator (tPA) and urokinase-type Plasminogen Activator (uPA), and regulates the plasmin activation and the fibrinolytic system [114]. Emerging research underscores the significance of PAI-1 in regulating cellular senescence, with findings demonstrating that PAI-1 not only serves as a senescence marker but also actively mediates senescence pathways, impacting lifespan and age-related pathologies [115–117]. The tPA, uPA, and PAI-1 are thought to play an important role in the maintenance of endothelial homeostasis, and are associated with the endothelial dysfunction of SSc [118,119]. Therefore, PAI-1 inhibition may be therapeutic for SSc-ILD.

4. Organ-Specific Pathophysiology Modifiers: Refining the Landscape of SSc Organ Involvement

To fully elucidate the organ-specific manifestations of SSc, it is essential to consider organ-specific pathophysiology modifiers, in addition to the broadly acting trans-organ basic pathophysiology. The following sections detail the principal organ-specific modifiers across major organ systems affected by SSc [13].

4.1. Cutaneous Pathology

Epidermal cells and adipocytes function as key pathophysiology modifiers in the skin in SSc (Figure 2).

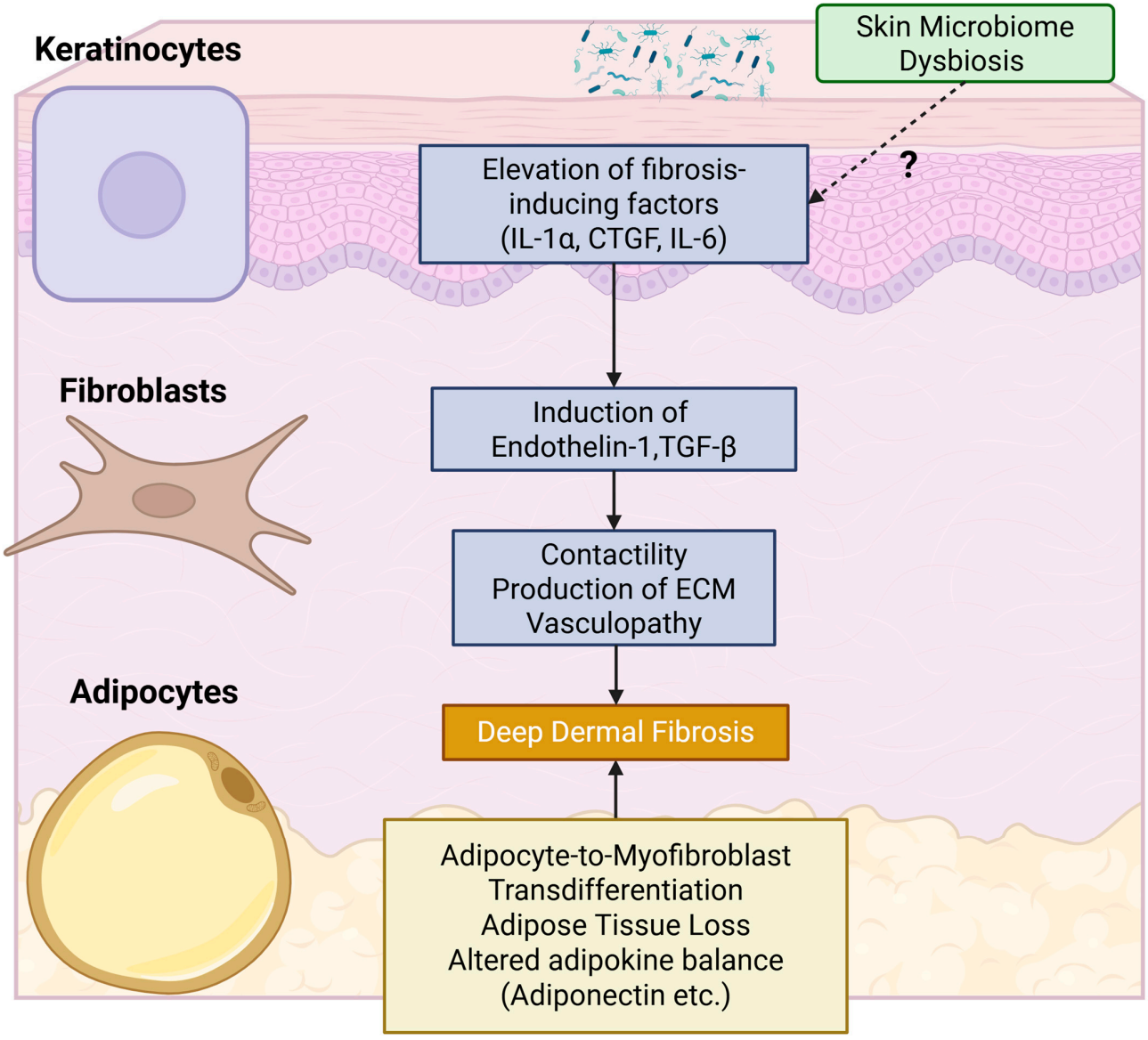

Figure 2. Keratinocytes and adipocytes as key modifiers of skin pathophysiology in systemic sclerosis (SSc). This concept map illustrates the multifaceted roles of keratinocytes and adipocytes in the pathogenesis of SSc skin involvement. Dysfunctional keratinocytes upregulate various disease-associated molecules, contributing to dermal fibroblast activation and fibrosis. Epithelial cell-specific Fli1 deficiency leads to keratinocyte activation, inducing dermal fibrosis, and thymus dysfunction. While the interaction with skin microbiota remains unclear in SSc, it may modulate keratinocyte function and immunity. Adipocytes contribute to dermal fibrosis through adipocyte-to-myofibroblast transition and altered adipokine production, collectively driving SSc skin pathology.

4.1.1. Keratinocytes

The epidermis in SSc is an active participant in the disease process, as evidenced by research identifying the upregulation of numerous molecules in affected skin. These include growth factors (e.g., TGF-β, VEGF, and CTGF), cytokines (e.g., IL-1α, IL-6, and TNF-α), and chemokines (e.g., CCL2, CCL5), in addition to other proteins like endothelin-1, IL-21 receptor, specific keratins, psoriasin, and galectin-7 [120–129]. As several of these molecules—notably IL-1α, CTGF, and IL-6—have strong pro-fibrotic properties, it is probable that SSc keratinocytes play a role in activating dermal fibroblasts.

Experiments using a recently developed mouse model of SSc have suggested a role for various epithelial cells in the disease's development, including keratinocytes, esophageal stratified squamous epithelia, and medullary thymic epithelial cells [130]. Deficiency of the transcription factor Fli1, a potential SSc susceptibility factor [14], induces SSc-like properties in various cell types, including fibroblasts, endothelial cells, keratinocytes, T cells, B cells, cDC, and macrophages [17,130–134]. Notably, epithelial cell-specific *Fli1* knockout mice (*Fli1*$^{flox/flox}$; *K14-Cre*$^{+/-}$ mice), which exhibit SSc-like phenotypic features in epithelial cells, spontaneously develop dermal and esophageal fibrosis due to epithelial cell activation in the skin and esophagus. Furthermore, these mice develop ILD, mediated at least in part by T cells autoreactive to lung antigens, resulting from impaired negative selection and Treg development in the thymus. One component of this impaired central tolerance is attributed to the downregulation of autoimmune regulator (Aire), which modulates the processing and presentation of self-antigens in medullary thymic epithelial cells [135,136]. Importantly, epithelial cell-specific *Fli1* knockout mice lacking an acquired immune system (*Rag1*$^{-/-}$; *Fli1*$^{flox/flox}$; *K14-Cre*$^{+/-}$ mice) spontaneously develop dermal and esophageal fibrosis, along with mast cell infiltration in the skin, but do not develop ILD [137]. This suggests that epithelial cell activation alone can induce tissue fibrosis through the activation of innate immunity. This novel murine model indicates that abnormally activated epithelial cells underlie selective organ fibrosis and autoimmunity in SSc.

Another potential aspect of the keratinocyte-dependent regulation of dermal fibrosis is the interplay between the immune system and the skin microbiota. This area of research has recently garnered significant attention regarding inflammatory skin diseases, such as atopic dermatitis [138] and SLE [139]. This dialogue begins when keratinocytes detect pathogen-associated molecular patterns by the use of microbes using pattern-recognition receptors. This recognition prompts the keratinocytes to release antimicrobial peptides (AMPs), which can kill or inactivate microorganisms and activate other cells like dermal fibroblasts and endothelial cells [140]. The expression of these AMPs can be either constant or temporary, with the latter being regulated by the skin's microbial community. The specific impact of the skin microbiota on keratinocyte function and immunity in SSc is not yet established, but the finding of microbiome dysbiosis in affected skin suggests it may be a contributing factor [141].

4.1.2. Adipocytes

Recently, subcutaneous adipose tissue has been increasingly implicated in the development of skin fibrosis in SSc. This is histologically significant, as the skin is characterized by a large, adjacent layer of fat. The concept that adipose tissue could be a source of fibrotic cells is consistent with the knowledge that myofibroblasts can be derived from non-fibroblast precursors in a pro-fibrotic environment [142]. According to lineage-tracing studies [143], subcutaneous adipocytes are highly plastic cells capable of transdifferentiating into myofibroblasts [144]. Indeed, a significant proportion of activated myofibroblasts in SSc-involved skin appear to derive from adipocytes located adjacent to the deep dermis [89,145].

Adipocytes also influence the disease by producing a range of signaling molecules called adipokines [146]. When adipocyte loss or dysfunction alters the balance of these adipokines, it may contribute to the characteristic inflammation, vasculopathy, and fibrosis of SSc [147–157]. The role of adiponectin, a well-studied example, illustrates this connection; its serum and tissue levels are inversely related to skin score in patients [147,156,158]. Moreover, mice lacking adiponectin show reduced dermal fibrosis after bleomycin challenge [159], and AdipoRon, a drug that inhibits adiponectin signaling, lessens SSc-like features in mouse models [160]. Taken together, these findings indicate that subcutaneous adipose tissue is a significant driver of skin fibrosis in SSc.

4.2. Gastrointestinal Pathology

Affecting approximately 90% of patients, gastrointestinal (GI) issues are a leading cause of morbidity in SSc, stemming from impaired motility and deficient enzyme secretion throughout the digestive system [161–163]. The esophagus is the most commonly affected site, resulting in a high prevalence (70–90%) of upper GI symptoms like GERD and dysphagia. Following the esophagus, the anorectal region, small bowel, stomach, and colon are also frequently involved. This leads to a variety of lower GI symptoms (seen in 20–70% of patients), which can include small intestinal bacterial overgrowth, malabsorption, diarrhea, pseudo-obstruction, and fecal incontinence [164].

Consistent with observations in the skin and other internal organs, the common SSc-specific pathological cascade broadly impacts the GI system, ultimately leading to extensive atrophy and fibrosis of the gastrointestinal smooth muscle [165]. Additionally, SSc exhibits a GI organ-specific pathology relevant to the complex and highly organized enteric nervous system. Vascular structural changes, such as capillary rarefaction and arteriolar stenosis, induce tissue hypoxia throughout the GI tract, resulting in autonomic axonal degeneration [166]. Thus, SSc-associated GI involvement is attributed to the hypomotility and dysmotility stemming from extensive atrophy and fibrosis of the enteric smooth muscle, as well as disturbances in the enteric nervous system. Indeed, SSc-associated esophageal dysfunction comprises three pathological components: (i) reduced lower esophageal sphincter pressure; (ii) ineffective esophageal body peristalsis, particularly in the lower esophagus; and (iii) discoordination of peristaltic and lower esophageal sphincter function [161,165,167–169]. Ultimately, the long-term course of SSc-associated GI involvement often culminates in atrophic and fibrotic changes within the gastrointestinal smooth muscle. The precise temporal dynamics and predisposing factors associated with this progression are complex, with recent evidence suggesting that while esophageal dysfunction can occur early, the overall worsening of GI symptoms over extended periods may be influenced more by characteristics like patient sex and specific autoantibody profiles, such as ACA, rather than strictly by cutaneous subtypes [170].

The neuropathy in SSc-related GI dysfunction may be partly driven by pathogenic autoantibodies. For instance, some patients have antibodies against myenteric neurons [171], including those specific for the muscarinic acetylcholine receptor M3 [172,173]. These are considered pathogenic because they disrupt peristalsis in animal experiments [171,172], and in SSc patients, their levels are associated with more severe GI disease [174], suggesting a pathogenic role for these antibodies in humans. Consistent with this, the motility of the pharynx and proximal esophagus, which is regulated by the somatic nervous system, remains normal in SSc [174,175]. Overall, current evidence supports the concept that a combination of autoimmunity, vasculopathy, and fibrosis underlies GI involvement in SSc.

Drawing a parallel with the skin, the esophagus's stratified squamous epithelia may directly drive fibrosis in SSc. This idea is supported by the *Fli1*$^{flox/flox}$; *K14-Cre*$^{+/-}$ mice, where the esophagus displays SSc-like molecular features, including increased IL-8 and prominent IL-

1β expression. This epithelial dysfunction could also explain symptoms, as epithelium-derived cytokines are thought to cause refractory GERD-related and functional heartburn [176]. This is particularly relevant, because SSc patients' symptoms often do not correlate with objective physiological findings [161,177]. Thus, an abnormal epithelial phenotype is a plausible, though not yet proven, contributor to both fibrosis and heartburn in SSc.

The gut microbiota is also a key component of GI-specific pathology in SSc. It is known to modulate the immune system and is implicated in autoimmune diseases through immune dysfunction [178–180]. In SSc, studies show that the intestinal microbial composition is different from that in healthy individuals, with a decrease in commensal bacteria (e.g., *Faecalibacterium*, *Clostridium*) and an increase in pathobionts (e.g., *Fusobacterium*) [181,182]. It is not yet clear whether these changes are a cause or a consequence of SSc or its treatments. However, a report that fecal microbiota transplantation reduced lower GI symptoms suggests a direct role [183]. More research is needed to clarify the mechanisms by which the gut microbiota interacts with inflammatory and fibrotic pathways in SSc.

In conclusion, the abnormally activated stratified squamous epithelia and enteric nervous system dysfunction constitute organ-specific pathological processes within the GI tract in SSc (Figure 3).

4.3. Pulmonary Pathology

Pulmonary involvement, encompassing ILD and pulmonary hypertension (PH), represents the primary cause of SSc-related mortality [184,185]. ILD in SSc arises from the common SSc-specific pathological cascade and can be further influenced by microaspiration of gastric contents due to GERD. Pulmonary arterial hypertension (PAH) in SSc is attributed to pulmonary arteriolar stenosis resulting from occlusive vascular fibrosis.

The World Health Organization (WHO) classification categorizes PH into five groups: Group 1, PAH characterized by pre-capillary pulmonary vasculopathy involving small pulmonary arterioles; Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia (including ILD); Group 4, PH due to pulmonary artery obstructions (e.g., chronic thromboembolic pulmonary hypertension, CTEPH); and Group 5, PH with unclear multifactorial mechanisms [186]. SSc-associated pulmonary hypertension (SSc-PH) most commonly falls into Group 1 (PAH), Group 2, or Group 3 [187,188]. Additionally, SSc patients with associated antiphospholipid antibody syndrome may be at risk for developing Group 4 PH. It has been observed that PAH (Group 1) is the most frequent form of PH when associated with connective tissue diseases like SSc [189]. These distinct pathologies, particularly PAH and ILD, can indeed coexist to varying extents in SSc patients. The presence of concomitant ILD in PAH-SSc patients has been shown to worsen hemodynamics and pulmonary function tests, making the clinical classification and management more challenging [189]. Such coexistence of PAH and ILD is a significant concern, as these are the two leading causes of mortality in SSc [189].

Historically, SSc-PAH was considered more prevalent in patients with limited cutaneous SSc (lcSSc) and those with ACA [190,191]. However, the understanding of these associations continues to evolve with larger and more contemporary cohort studies. For instance, a meta-analysis by Rubio-Rivas et al. [192] reported an overall PAH prevalence in SSc of 6.4%, with a prevalence of 7.7% in lcSSc and 6.3% in dcSSc, supporting a higher prevalence in lcSSc. Survival for patients with Group 1 SSc-PAH has shown improvement in the most recent decade, potentially due to earlier detection through screening programs and more effective therapeutic strategies, including upfront combination therapy [188,193].

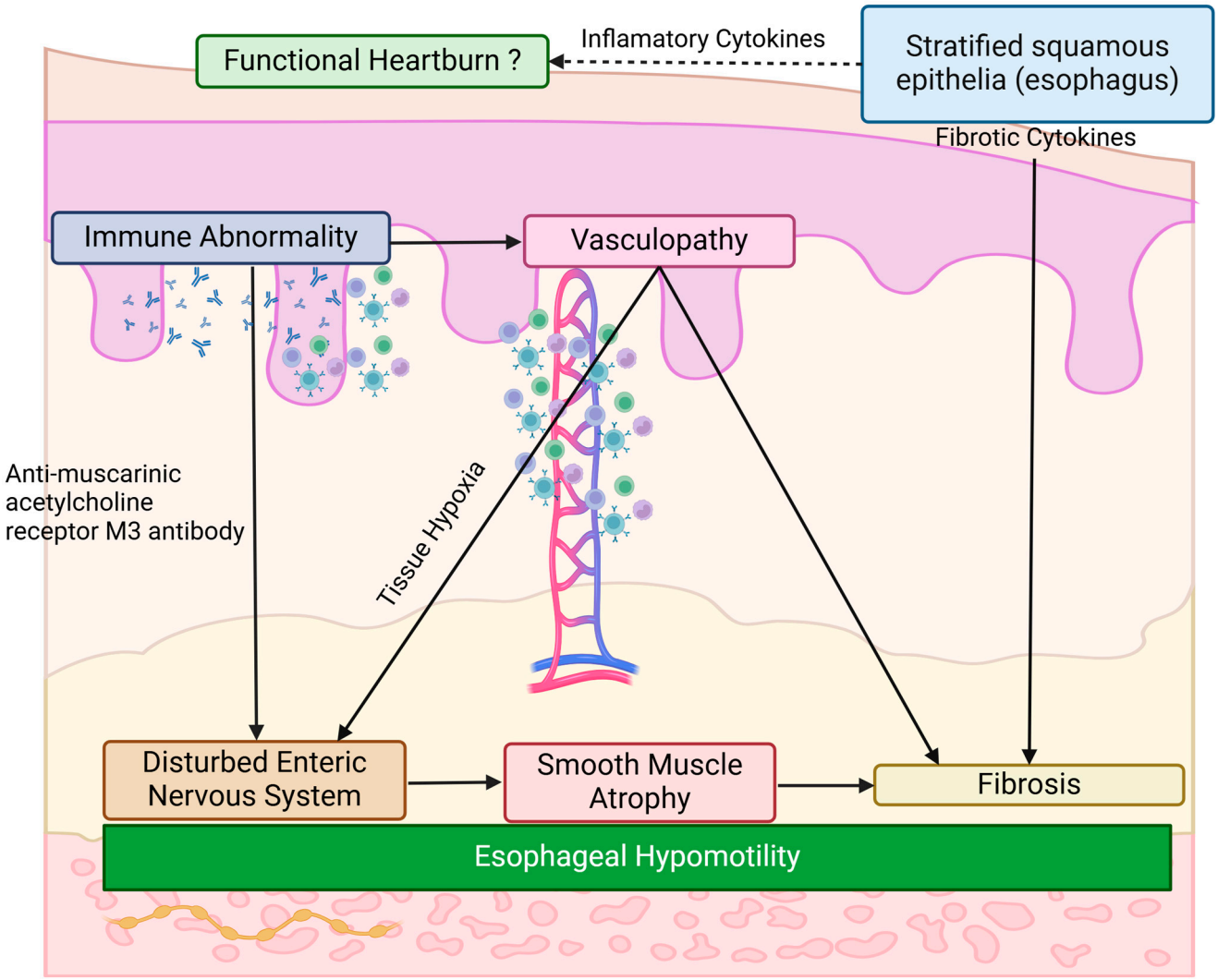

Figure 3. Pathophysiological mechanisms of esophageal involvement in systemic sclerosis (SSc). This schematic illustrates the multi-factorial pathogenesis of gastrointestinal (GI) manifestations in SSc. The cascade is initiated by immune abnormality, including the presence of anti-muscarinic acetylcholine receptor M3 antibodies, and vasculopathy. Both of these pathological processes contribute to disturbed enteric nervous system function, ultimately resulting in esophageal hypomotility. A disturbed enteric nervous system induces smooth muscle atrophy, further contributing to esophageal hypomotility and leading to fibrosis of the esophagus. Esophageal stratified squamous epithelia can produce inflammatory and fibrotic cytokines, further promoting fibrosis. Functional heartburn may also occur, potentially linked to inflammatory cytokines produced by the esophageal stratified squamous epithelia. These interconnected pathways highlight the complex interplay of immune, vascular, epithelial, and neural factors in SSc-related GERD.

In a more focused sense, SSc-PAH is histologically characterized by a proliferative and obliterative vasculopathy predominantly affecting the pulmonary arterioles. This is considered a consequence of the shared SSc-specific pathological cascade involving endothelial dysfunction, inflammation, and fibrotic remodeling [190]. The vascular lesions in SSc-PAH often feature perivascular lymphocytic infiltrates and significant intimal fibrosis. Notably, classical plexiform lesions, which are characteristic of idiopathic PAH, are less commonly observed in SSc-PAH [190].

Furthermore, the clinical picture of SSc-PAH can be frequently complicated by, or mimicked by, conditions such as pulmonary veno-occlusive disease (PVOD) or PAH with overt features of venous/capillaries involvement. PVOD is also classified under WHO

Group 1 PH but represents a distinct pathological entity primarily affecting pulmonary venules and capillaries. PVOD arising in a background of connective tissue disease such as SSc (PVOD-like changes) is a rare but critical condition, often underdiagnosed in SSc due to its symptomatic similarity to PAH. A key distinguishing concern with regard to PVOD-like changes is its particularly poor prognosis and the significant risk of precipitating acute pulmonary edema with the use of PAH-specific vasodilator therapies. Therefore, careful diagnostic evaluation is paramount. High-resolution computed tomography (HRCT) plays a vital role when PVOD-like changes is suspected, with characteristic findings including centrilobular ground-glass opacities, interlobular septal thickening, and mediastinal lymph node enlargement [187,194].

Therefore, understanding and managing SSc-PH necessitates a comprehensive approach that considers all components of the pulmonary circulation. Given that SSc is a disease characterized by multi-organ involvement, a thorough evaluation of all elements related to pulmonary circulation is essential when addressing PH in these patients (Figure 4).

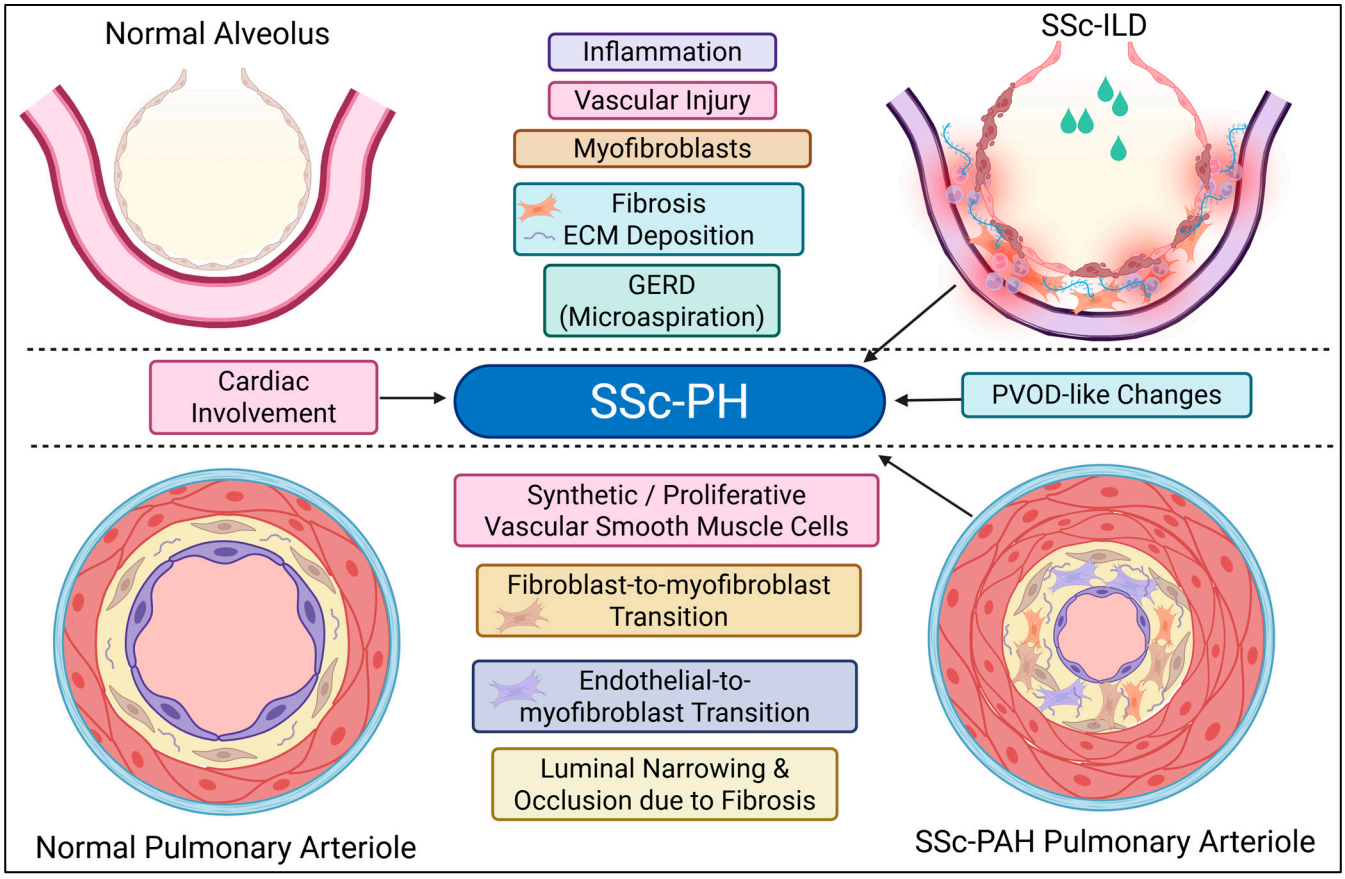

Figure 4. Schematic diagram of the complex pulmonary pathology in SSc, encompassing both ILD and PH. [Upper panel: Interstitial Lung Disease (ILD)] SSc-ILD pathogenesis is driven by the common SSc-specific pathological cascade, leading to distinct histological stages of nonspecific interstitial pneumonia (NSIP), and in some cases, usual interstitial pneumonia (UIP). Gastroesophageal reflux disease (GERD) acts as an organ-specific modifier, potentially exacerbating ILD progression through microaspiration and contributing to centrilobular fibrosis (CLF). [Lower panel: Pulmonary Hypertension (PH)] SSc-PH encompasses pulmonary arterial hypertension (PAH) due to pulmonary arteriolar fibrosis (Group 1 WHO classification), as well as PH related to cardiac involvement (Group 2) or ILD (Group 3). SSc-PAH is characterized by pulmonary arteriole occlusion and may coexist with pulmonary veno-occlusive disease (PVOD)-like changes.

ILD is detectable in 50–60% of SSc patients via HRCT [195,196]. Risk factors for the development of SSc-ILD encompass dcSSc [197], African American ethnicity [198], shorter disease duration [199], older age at disease onset [197], and the presence of anti-topoisomerase I antibody and/or absence of ACA [197]. ILD typically manifests early in the course of dcSSc, particularly within the first 3 years of disease onset [197,199,200], while in lcSSc patients, ILD can arise at any point during the disease course [201]. The clinical trajectory of SSc-ILD is heterogeneous; some patients maintain stable forced vital capacity (FVC), whereas others experience a progressive decline in pulmonary function [202]. ILD progression is generally most pronounced within the initial 4 years following SSc onset, subsequently slowing or ceasing entirely, even without therapeutic intervention [203]. Severe ILD, defined by an FVC decline below 50%, is reported to affect approximately 15% of the total SSc population [203,204]. The predominant histological pattern in SSc-ILD is nonspecific interstitial pneumonia (NSIP), observed in roughly two-thirds of patients [205]. Usual interstitial pneumonia (UIP) is present in a smaller proportion of SSc-ILD cases [205–207] and may correlate with less favorable prognoses [208].

Histologically, nonspecific interstitial pneumonia (NSIP) in SSc-ILD is categorized into four stages [209]:

- * Stage 1 (Initial): Characterized by microvessel overdevelopment with structural abnormalities, and alveolar septal thickening with numerous α-SMA-positive myofibroblasts. The overdeveloped microvessels contain blood cells within their lumina, indicating maintained functional circulation.
- * Stage 2 (Progressive ECM Deposition): Marked by substantial and progressive ECM deposition, irregular and indistinct alveolar septal borders, further structural disorganization of microvessels, and obliteration of larger blood vessels. Disarray or partial loss of the alveolar epithelium is also evident.
- * Stage 3 (Extensive Fibrosis): Progression of fibrosis extensively damages vital lung structures, including alveoli and vasculature.
- * Stage 4 (Final): The lung transforms into a contracted fibrous organ devoid of alveoli and vasculature.

The early microvascular alterations and subsequent progressive fibrotic changes reinforce the concept that SSc-ILD is driven by the common SSc-specific pathological cascade, similar to other organ involvements.

Above pathological findings suggest the presence of foundational trans-organ pathophysiology in the lung tissue.

Microaspiration of gastric contents due to GERD is a potential factor driving the progression of SSc-ILD. Clinical data, histological analyses, and animal studies support this hypothesis. Several clinical studies have shown a positive correlation between increased lung fibrosis severity and more frequent reflux episodes, as well as greater proximal extension of refluxate [210]. In a rat GERD model, pulmonary parenchymal fibrosis was induced by introducing gastric content into the lungs [211]. Analysis of lung biopsy specimens identified a distinct histological pattern of lung disease, centrilobular fibrosis (CLF), particularly prevalent in SSc patients with severe GERD [212]. CLF is characterized by a predominantly bronchocentric distribution of lesions and the presence of intraluminal basophilic material and foreign bodies within the bronchi, sometimes accompanied by multinucleated giant cell reactions. In a prior study examining open lung biopsies from 22 SSc-ILD patients [213], isolated CLF was observed in 21% of cases, and a CLF pattern was present in 84% of patients with a predominant NSIP pattern, suggesting that GERD may exacerbate underlying NSIP in SSc-ILD. Although clinical trial data have not yet demonstrated pulmonary function improvement in SSc-ILD following aggressive GERD

management, aggressive GERD treatment may still benefit the majority of SSc patients. Overall, GERD acts as an organ-specific disease modifier in SSc-ILD (Figure 4).

4.4. Cardiovascular Pathology

Histological examination of autopsy tissues from SSc patients without prior clinical cardiac symptoms reveals evidence of myocardial disease in all cases [214]. Thus, cardiac involvement is nearly ubiquitous in SSc patients, although often clinically silent [215,216]. Once clinically manifest, however, cardiac involvement carries a poor prognosis [215,217–219]. Primary cardiac involvement in SSc encompasses a wide spectrum of clinical manifestations, including arrhythmias, conduction system defects, myocarditis, pericarditis, systolic and diastolic ventricular dysfunction, and heart failure [220,221]. Primary myocardial involvement is estimated to account for approximately 30% of deaths in SSc patients [185,219,222].

In a study employing cardiovascular magnetic resonance (CMR) parametric mapping in SSc patients, Purevsuren et al. [223] demonstrated that native T1 mapping effectively detects early myocardial changes and correlates with left-ventricular diastolic dysfunction, with more pronounced myocardial involvement observed in dcSSc compared to lcSSc. This finding of early diffuse myocardial edema-like lesions on contrast-enhanced MRI mirrors the edematous induration seen in early skin lesions of SSc, suggesting a parallel pathological process, affecting both skin and internal organs, in the initial stages of the disease.

Although the precise molecular mechanisms of SSc-related cardiomyopathy remain incompletely understood [220,224–226], the prevailing consensus attributes a central role to microvascular disease. The proposed mechanism is that structural microvascular defects, including capillary rarefaction and arteriolar stenosis, result in tissue hypoxia. This oxygen deprivation is believed to subsequently trigger inflammation and excessive ECM synthesis by cardiac fibroblasts [215]. This model is supported by histological findings from SSc autopsy specimens, which show increased inflammation, vascular damage, and ECM deposition compared to controls [214]. The microvascular origin is further indicated by the patchy, non-coronary distribution of fibrosis throughout the ventricles [224,227].

In addition to structural damage, abnormal vasoreactivity of small cardiac vessels, known as "myocardial Raynaud's phenomenon," contributes to cardiac involvement in SSc. This concept is supported by multiple lines of evidence. For instance, cold exposure can induce this phenomenon in approximately 30% of SSc patients with a history of Raynaud's, and the effect is preventable with calcium channel blockers (CCBs) [228]. The therapeutic benefit of vasodilators like nifedipine, nicardipine, and captopril, which acutely improve myocardial perfusion and function [229–232], also points to a vasospastic component. Finally, the absence of prior CCB therapy is an independent factor associated with left-ventricular dysfunction.

Thus, from a management perspective, the cardiac involvement in SSc must be viewed as being a result of two distinct categories of vascular change. One category is structural, encompassing capillary rarefaction and arteriolar stenosis, while the other is functional, specifically the myocardial Raynaud's phenomenon.

4.5. Scleroderma Renal Crisis

One frequent form of renal involvement in SSc patients is a subclinical renal vasculopathy, characterized by vascular damage and normal renal function [233]. Scleroderma renal crisis (SRC) complicates the course of 5–10% of SSc patients [234–237], presenting most commonly within the first few years of disease onset, particularly in those with dcSSc [234,236]. Key risk factors include rapidly progressive skin thickening, the presence of anti-RNA

polymerase III antibodies [234,236,238–240], and recent high-dose corticosteroid therapy (>15 mg/day) [234–237,241,242]. While strongly associated with anti-RNA polymerase III antibodies, SRC can rarely occur in patients with lcSSc, including those positive for ACA [239,241,243,244].

Clinically, SRC typically manifests suddenly, with an abrupt onset of accelerated hypertension (often > 150/85 mmHg or a significant rise from baseline) and acute kidney injury (AKI), frequently accompanied by headache, visual changes, or signs of hypertensive encephalopathy or cardiopulmonary failure [234,236,245]. Approximately 10–11% of cases manifest as normotensive SRC, which may be associated with corticosteroid use and has been linked to a poorer prognosis, possibly due to delayed diagnosis or a potentially more severe underlying pathology [234,236,241,245]. Laboratory findings may include microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, features overlapping with hemolytic uremic syndrome (HUS)/thrombotic microangiopathy (TMA) [234,236,241,245].

The core pathogenesis involves endothelial injury in renal arterioles, leading to intimal accumulation of myxoid material, subsequent intimal proliferation resulting in luminal narrowing ("onion-skin" lesions), thrombosis, and fibrinoid necrosis [234,236,241,245]. Renal biopsy findings, such as the extent of vascular thrombosis, severe glomerular ischemic collapse, and peritubular capillary C4d deposits, may predict failure to recover renal function [245]. This vascular damage triggers activation of the renin–angiotensin–aldosterone system (RAAS), causing hyperreninemia and creating a vicious cycle of worsening hypertension and renal ischemia [234,236,241]. Renal vasospasm ("renal Raynaud's") is also thought to contribute significantly to the reduced renal perfusion [234,236]. Historically, it has been reported that SSc patients already on angiotensin-converting enzyme (ACE) inhibitor therapy at the time of SRC onset may experience worse outcomes [236,246,247]. More recently, studies have indicated that prior exposure to ACE inhibitors might not only be associated with poorer SRC prognosis, but could also represent an independent risk factor for the development of SRC itself, particularly in hypertensive SSc patients [248]. These findings have led to the recommendation against the prophylactic use of ACE inhibitors to prevent SRC in patients, without a clear indication for these drugs, such as established hypertension [236,247]. This evolving understanding of the complex relationship between ACE inhibitor use and SRC may offer new insights into the underlying pathogenetic mechanisms of this severe SSc complication.

SRC, along with DUs and SSc-PAH, is considered a manifestation of the systemic, non-organ-specific vasculopathy underlying SSc, primarily driven by arteriolar stenosis affecting different vascular territories [13].

5. Conclusions

The current understanding of SSc pathogenesis, bolstered by advanced analytical methods, has been the focus of this review. The skin's frequent affliction and ease of sampling have made it a cornerstone for pathogenetic investigations. Future research, extending these sophisticated analytical tools to internal organs like the lungs, holds considerable promise for refining our comprehension of the fundamental, widespread pathophysiology and the specific factors that modulate organ involvement in SSc. This improved insight is vital for tailoring more effective treatments, and thereby enhancing disease management and patient prognosis and opening new therapeutic avenues. It is acknowledged that SSc treatment strategies are varied, adapt to specific pathological manifestations, and are the subject of numerous clinical investigations; however, these are not detailed here, and specialized reviews can offer further information [249–252].

Central to deciphering SSc's complex cross-organ impact is the identification of its core pathogenic driver. Although immune dysfunction is characteristic of its autoimmune nature

and "sclerosis" underscores fibrosis, we propose vasculopathy as the pivotal intermediary linking aberrant immunity to fibrotic outcomes. This view is informed by clinical patterns in which vascular alterations are often the first indicators of SSc, as seen with Raynaud's phenomenon, and potentially represent the final opportunity for impactful therapeutic modulation, contrasting with early immune dysregulation, which may be subclinical, and established fibrosis, which is typically irreversible.

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References

1. Denton, C.P.; Khanna, D. Systemic Sclerosis. *Lancet* **2017**, *390*, 1685–1699. [CrossRef]
2. Arnett, F.C.; Cho, M.; Chatterjee, S.; Aguilar, M.B.; Reveille, J.D.; Mayes, M.D. Familial Occurrence Frequencies and Relative Risks for Systemic Sclerosis (Scleroderma) in Three United States Cohorts. *Arthritis Rheum.* **2001**, *44*, 1359–1362. [CrossRef] [PubMed]
3. Feghali-Bostwick, C.; Medsger, T.A., Jr.; Wright, T.M. Analysis of Systemic Sclerosis in Twins Reveals Low Concordance for Disease and High Concordance for the Presence of Antinuclear Antibodies. *Arthritis Rheum.* **2003**, *48*, 1956–1963. [CrossRef]
4. Yamashita, K.; Kawasaki, A.; Matsushita, T.; Furukawa, H.; Kondo, Y.; Okiyama, N.; Nagaoka, S.; Shimada, K.; Sugii, S.; Katayama, M.; et al. Association of Functional (GA)n Microsatellite Polymorphism in the FLI1 Gene with Susceptibility to Human Systemic Sclerosis. *Rheumatology* **2020**, *59*, 3553–3562. [CrossRef]
5. Agarwal, S.K. The Genetics of Systemic Sclerosis. *Discov. Med.* **2010**, *10*, 134–143. [PubMed]
6. Dieudé, P.; Guedj, M.; Wipff, J.; Avouac, J.; Fajardy, I.; Diot, E.; Granel, B.; Sibilia, J.; Cabane, J.; Mouthon, L.; et al. Association between the IRF5 Rs2004640 Functional Polymorphism and Systemic Sclerosis: A New Perspective for Pulmonary Fibrosis. *Arthritis Rheum.* **2009**, *60*, 225–233. [CrossRef]
7. Ito, I.; Kawaguchi, Y.; Kawasaki, A.; Hasegawa, M.; Ohashi, J.; Hikami, K.; Kawamoto, M.; Fujimoto, M.; Takehara, K.; Sato, S.; et al. Association of a Functional Polymorphism in the IRF5 Region with Systemic Sclerosis in a Japanese Population. *Arthritis Rheum.* **2009**, *60*, 1845–1850. [CrossRef]
8. Radstake, T.R.D.J.; Gorlova, O.; Rueda, B.; Martin, J.-E.; Alizadeh, B.Z.; Palomino-Morales, R.; Coenen, M.J.; Vonk, M.C.; Voskuyl, A.E.; Schuerwegh, A.J.; et al. Genome-Wide Association Study of Systemic Sclerosis Identifies CD247 as a New Susceptibility Locus. *Nat. Genet.* **2010**, *42*, 426–429. [CrossRef] [PubMed]
9. Tang, L.; Chen, B.; Ma, B.; Nie, S. Association between IRF5 Polymorphisms and Autoimmune Diseases: A Meta-Analysis. *Genet. Mol. Res.* **2014**, *13*, 4473–4485. [CrossRef]
10. Sharif, R.; Mayes, M.D.; Tan, F.K.; Gorlova, O.Y.; Hummers, L.K.; Shah, A.A.; Furst, D.E.; Khanna, D.; Martin, J.; Bossini-Castillo, L.; et al. IRF5 Polymorphism Predicts Prognosis in Patients with Systemic Sclerosis. *Ann. Rheum. Dis.* **2012**, *71*, 1197–1202. [CrossRef]
11. Benfaremo, D.; Svegliati Baroni, S.; Manfredi, L.; Moroncini, G.; Gabrielli, A. Putative Functional Pathogenic Autoantibodies in Systemic Sclerosis. *Eur. J. Rheumatol.* **2020**, *7*, S181–S186. [CrossRef] [PubMed]
12. Senécal, J.-L.; Hoa, S.; Yang, R.; Koenig, M. Pathogenic Roles of Autoantibodies in Systemic Sclerosis: Current Understandings in Pathogenesis. *J. Scleroderma Relat. Disord.* **2020**, *5*, 103–129. [CrossRef] [PubMed]
13. Asano, Y. The Pathogenesis of Systemic Sclerosis: An Understanding Based on a Common Pathologic Cascade across Multiple Organs and Additional Organ-Specific Pathologies. *J. Clin. Med.* **2020**, *9*, 2687. [CrossRef] [PubMed]
14. Wang, Y.; Fan, P.-S.; Kahaleh, B. Association between Enhanced Type I Collagen Expression and Epigenetic Repression of the FLI1 Gene in Scleroderma Fibroblasts. *Arthritis Rheum.* **2006**, *54*, 2271–2279. [CrossRef]

15. Kubo, M.; Czuwara-Ladykowska, J.; Moussa, O.; Markiewicz, M.; Smith, E.; Silver, R.M.; Jablonska, S.; Blaszczyk, M.; Watson, D.K.; Trojanowska, M. Persistent Down-Regulation of Fli1, a Suppressor of Collagen Transcription, in Fibrotic Scleroderma Skin. *Am. J. Pathol.* **2003**, *163*, 571–581. [CrossRef]
16. Noda, S.; Asano, Y.; Nishimura, S.; Taniguchi, T.; Fujiu, K.; Manabe, I.; Nakamura, K.; Yamashita, T.; Saigusa, R.; Akamata, K.; et al. Simultaneous Downregulation of KLF5 and Fli1 Is a Key Feature Underlying Systemic Sclerosis. *Nat. Commun.* **2014**, *5*, 5797. [CrossRef]
17. Taniguchi, T.; Asano, Y.; Akamata, K.; Noda, S.; Takahashi, T.; Ichimura, Y.; Toyama, T.; Trojanowska, M.; Sato, S. Fibrosis, Vascular Activation, and Immune Abnormalities Resembling Systemic Sclerosis in Bleomycin-Treated Fli-1-Haploinsufficient Mice: SSc Phenotype Induction by Bleomycin in Fli-1+/−Mice. *Arthritis Rheumatol.* **2015**, *67*, 517–526. [CrossRef]
18. Takeda, N.; Manabe, I.; Uchino, Y.; Eguchi, K.; Matsumoto, S.; Nishimura, S.; Shindo, T.; Sano, M.; Otsu, K.; Snider, P.; et al. Cardiac Fibroblasts Are Essential for the Adaptive Response of the Murine Heart to Pressure Overload. *J Clin Investig.* **2010**, *120*, 254–265. [CrossRef]
19. Fujiu, K.; Manabe, I.; Nagai, R. Renal Collecting Duct Epithelial Cells Regulate Inflammation in Tubulointerstitial Damage in Mice. *J. Clin. Investig.* **2011**, *121*, 3425–3441. [CrossRef]
20. Whitfield, M.L.; Finlay, D.R.; Murray, J.I.; Troyanskaya, O.G.; Chi, J.-T.; Pergamenschikov, A.; McCalmont, T.H.; Brown, P.O.; Botstein, D.; Connolly, M.K. Systemic and Cell Type-Specific Gene Expression Patterns in Scleroderma Skin. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12319–12324. [CrossRef]
21. Yu, J.; Tang, R.; Ding, K. Epigenetic Modifications in the Pathogenesis of Systemic Sclerosis. *Int. J. Gen. Med.* **2022**, *15*, 3155–3166. [CrossRef]
22. Riemekasten, G.; Distler, J.H.W. A Broad Look into the Future of Systemic Sclerosis. *Ther. Adv. Musculoskelet. Dis.* **2022**, *14*, 1759720X221109404. [CrossRef]
23. Angiolilli, C.; Marut, W.; van der Kroef, M.; Chouri, E.; Reedquist, K.A.; Radstake, T.R.D.J. New Insights into the Genetics and Epigenetics of Systemic Sclerosis. *Nat. Rev. Rheumatol.* **2018**, *14*, 657–673. [CrossRef] [PubMed]
24. Altorok, N.; Kahaleh, B. Epigenetics and Systemic Sclerosis. *Semin. Immunopathol.* **2015**, *37*, 453–462. [CrossRef]
25. Gao, L.; Lu, Q. The Critical Importance of Epigenetics in Autoimmune-Related Skin Diseases. *Front. Med.* **2023**, *17*, 43–57. [CrossRef] [PubMed]
26. Truchetet, M.E.; Brembilla, N.C.; Chizzolini, C. Current Concepts on the Pathogenesis of Systemic Sclerosis. *Clin. Rev. Allergy Immunol.* **2023**, *64*, 262–283. [CrossRef]
27. Zhang, Y.; Maskan Bermudez, N.; Sa, B.; Maderal, A.D.; Jimenez, J.J. Epigenetic Mechanisms Driving the Pathogenesis of Systemic Lupus Erythematosus, Systemic Sclerosis and Dermatomyositis. *Exp. Dermatol.* **2024**, *33*, e14986. [CrossRef] [PubMed]
28. Higashi-Kuwata, N.; Jinnin, M.; Makino, T.; Fukushima, S.; Inoue, Y.; Muchemwa, F.C.; Yonemura, Y.; Komohara, Y.; Takeya, M.; Mitsuya, H.; et al. Characterization of Monocyte/Macrophage Subsets in the Skin and Peripheral Blood Derived from Patients with Systemic Sclerosis. *Arthritis Res. Ther.* **2010**, *12*, R128. [CrossRef] [PubMed]
29. Yukawa, S.; Yamaoka, K.; Sawamukai, N.; Shimajiri, S.; Kubo, S.; Miyagawa, I.; Sonomoto, K.; Saito, K.; Tanaka, Y. Dermal Mast Cell Density in Fingers Reflects Severity of Skin Sclerosis in Systemic Sclerosis. *Mod. Rheumatol.* **2013**, *23*, 1151–1157. [CrossRef]
30. MacDonald, K.G.; Dawson, N.A.J.; Huang, Q.; Dunne, J.V.; Levings, M.K.; Broady, R. Regulatory T Cells Produce Profibrotic Cytokines in the Skin of Patients with Systemic Sclerosis. *J. Allergy Clin. Immunol.* **2015**, *135*, 946–955.e9. [CrossRef]
31. Bosello, S.; Angelucci, C.; Lama, G.; Alivernini, S.; Proietti, G.; Tolusso, B.; Sica, G.; Gremese, E.; Ferraccioli, G. Characterization of Inflammatory Cell Infiltrate of Scleroderma Skin: B Cells and Skin Score Progression. *Arthritis Res. Ther.* **2018**, *20*, 75. [CrossRef] [PubMed]
32. Lafyatis, R.; O'Hara, C.; Feghali-Bostwick, C.A.; Matteson, E. B Cell Infiltration in Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis Rheum.* **2007**, *56*, 3167–3168. [CrossRef] [PubMed]
33. Matsushita, T.; Hasegawa, M.; Hamaguchi, Y.; Takehara, K.; Sato, S. Longitudinal Analysis of Serum Cytokine Concentrations in Systemic Sclerosis: Association of Interleukin 12 Elevation with Spontaneous Regression of Skin Sclerosis. *J. Rheumatol.* **2006**, *33*, 275–284.
34. Yang, X.; Yang, J.; Xing, X.; Wan, L.; Li, M. Increased Frequency of Th17 Cells in Systemic Sclerosis Is Related to Disease Activity and Collagen Overproduction. *Arthritis Res. Ther.* **2014**, *16*, R4. [CrossRef]
35. Murata, M.; Fujimoto, M.; Matsushita, T.; Hamaguchi, Y.; Hasegawa, M.; Takehara, K.; Komura, K.; Sato, S. Clinical Association of Serum Interleukin-17 Levels in Systemic Sclerosis: Is Systemic Sclerosis a Th17 Disease? *J. Dermatol. Sci.* **2008**, *50*, 240–242. [CrossRef] [PubMed]
36. Zhou, Y.; Hou, W.; Xu, K.; Han, D.; Jiang, C.; Mou, K.; Li, Y.; Meng, L.; Lu, S. The Elevated Expression of Th17-Related Cytokines and Receptors Is Associated with Skin Lesion Severity in Early Systemic Sclerosis. *Hum. Immunol.* **2015**, *76*, 22–29. [CrossRef]
37. Frantz, C.; Auffray, C.; Avouac, J.; Allanore, Y. Regulatory T Cells in Systemic Sclerosis. *Front. Immunol.* **2018**, *9*, 2356. [CrossRef]
38. Sato, S.; Hasegawa, M.; Takehara, K. Serum Levels of Interleukin-6 and Interleukin-10 Correlate with Total Skin Thickness Score in Patients with Systemic Sclerosis. *J. Dermatol. Sci.* **2001**, *27*, 140–146. [CrossRef]

39. Nakashima, T.; Jinnin, M.; Yamane, K.; Honda, N.; Kajihara, I.; Makino, T.; Masuguchi, S.; Fukushima, S.; Okamoto, Y.; Hasegawa, M.; et al. Impaired IL-17 Signaling Pathway Contributes to the Increased Collagen Expression in Scleroderma Fibroblasts. *J. Immunol.* **2012**, *188*, 3573–3583. [CrossRef]
40. Bankamp, L.; Preuß, B.; Pecher, A.-C.; Beucke, N.; Henes, J.; Klein, R. Functionally Active Antibodies to the Angiotensin II Type 1-Receptor Measured by a Luminometric Bioassay Do Not Correlate with Clinical Manifestations in Systemic Sclerosis: A Comparison with Antibodies to Vascular Receptors and Topoisomerase I Detected by ELISA. *Front. Immunol.* **2021**, *12*, 786039.
41. van Oostveen, W.M.; Hoekstra, E.M.; Levarht, E.W.N.; Kotliar, I.B.; Sakmar, T.P.; Toes, R.E.M.; de Vries-Bouwstra, J.K.; Heitman, L.H.; Fehres, C.M. Absence of Functional Autoantibodies Targeting Angiotensin II Receptor Type 1 and Endothelin-1 Type A Receptor in Circulation and Purified IgG from Patients with Systemic Sclerosis. *Arthritis Rheumatol.* **2024**. [CrossRef] [PubMed]
42. Sato, S.; Hasegawa, M.; Fujimoto, M.; Tedder, T.F.; Takehara, K. Quantitative Genetic Variation in CD19 Expression Correlates with Autoimmunity. *J. Immunol.* **2000**, *165*, 6635–6643. [CrossRef]
43. Sato, S.; Fujimoto, M.; Hasegawa, M.; Takehara, K. Altered Blood B Lymphocyte Homeostasis in Systemic Sclerosis: Expanded Naive B Cells and Diminished but Activated Memory B Cells. *Arthritis Rheum.* **2004**, *50*, 1918–1927. [CrossRef]
44. Yoshizaki, A. B Lymphocytes in Systemic Sclerosis: Abnormalities and Therapeutic Targets. *J. Dermatol.* **2016**, *43*, 39–45. [CrossRef]
45. Jordan, S.; Distler, J.H.W.; Maurer, B.; Huscher, D.; van Laar, J.M.; Allanore, Y.; Distler, O.; EUSTAR Rituximab study group. Effects and Safety of Rituximab in Systemic Sclerosis: An Analysis from the European Scleroderma Trial and Research (EUSTAR) Group. *Ann. Rheum. Dis.* **2015**, *74*, 1188–1194. [CrossRef] [PubMed]
46. Daoussis, D.; Melissaropoulos, K.; Sakellaropoulos, G.; Antonopoulos, I.; Markatseli, T.E.; Simopoulou, T.; Georgiou, P.; Andonopoulos, A.P.; Drosos, A.A.; Sakkas, L.; et al. A Multicenter, Open-Label, Comparative Study of B-Cell Depletion Therapy with Rituximab for Systemic Sclerosis-Associated Interstitial Lung Disease. *Semin. Arthritis Rheum.* **2017**, *46*, 625–631. [CrossRef]
47. Bosello, S.L.; De Luca, G.; Rucco, M.; Berardi, G.; Falcione, M.; Danza, F.M.; Pirronti, T.; Ferraccioli, G. Long-Term Efficacy of B Cell Depletion Therapy on Lung and Skin Involvement in Diffuse Systemic Sclerosis. *Semin. Arthritis Rheum.* **2015**, *44*, 428–436. [CrossRef] [PubMed]
48. Ebata, S.; Yoshizaki, A.; Fukasawa, T.; Miura, S.; Takahashi, T.; Sumida, H.; Asano, Y.; Sato, S. Rituximab Therapy Is More Effective than Cyclophosphamide Therapy for Japanese Patients with Anti-Topoisomerase I-Positive Systemic Sclerosis-Associated Interstitial Lung Disease. *J. Dermatol.* **2019**, *46*, 1006–1013. [CrossRef]
49. Daoussis, D.; Antonopoulos, I.; Liossis, S.-N.C.; Yiannopoulos, G.; Andonopoulos, A.P. Treatment of Systemic Sclerosis-Associated Calcinosis: A Case Report of Rituximab-Induced Regression of CREST-Related Calcinosis and Review of the Literature. *Semin. Arthritis Rheum.* **2012**, *41*, 822–829. [CrossRef]
50. Khor, C.-G.; Chen, X.L.-F.; Lin, T.-S.; Lu, C.-H.; Hsieh, S.-C. Rituximab for Refractory Digital Infarcts and Ulcers in Systemic Sclerosis. *Clin. Rheumatol.* **2014**, *33*, 1019–1020. [CrossRef]
51. Maslyanskiy, A.; Lapin, S.; Kolesova, E.; Peñín, I.; Cheshuina, M.D.; Feist, E.; Konradi, A. Effects of Rituximab Therapy on Elastic Properties of Vascular Wall in Patients with Progressive Systemic Sclerosis. *Clin. Exp. Rheumatol.* **2014**, *32*, S-228. [PubMed]
52. Bergmann, C.; Müller, F.; Distler, J.H.W.; Györfi, A.-H.; Völkl, S.; Aigner, M.; Kretschmann, S.; Reimann, H.; Harrer, T.; Bayerl, N.; et al. Treatment of a Patient with Severe Systemic Sclerosis (SSc) Using CD19-Targeted CAR T Cells. *Ann. Rheum. Dis.* **2023**, *82*, 1117–1120. [CrossRef] [PubMed]
53. Müller, F.; Taubmann, J.; Bucci, L.; Wilhelm, A.; Bergmann, C.; Völkl, S.; Aigner, M.; Rothe, T.; Minopoulou, I.; Tur, C.; et al. CD19 CAR T-Cell Therapy in Autoimmune Disease—A Case Series with Follow-Up. *N. Engl. J. Med.* **2024**, *390*, 687–700. [CrossRef] [PubMed]
54. Wang, X.; Wu, X.; Tan, B.; Zhu, L.; Zhang, Y.; Lin, L.; Xiao, Y.; Sun, A.; Wan, X.; Liu, S.; et al. Allogeneic CD19-Targeted CAR-T Therapy in Patients with Severe Myositis and Systemic Sclerosis. *Cell* **2024**, *187*, 4890–4904.e9. [CrossRef]
55. Merkt, W.; Freitag, M.; Claus, M.; Kolb, P.; Falcone, V.; Röhrich, M.; Rodon, L.; Deicher, F.; Andreeva, I.; Tretter, T.; et al. Third-Generation CD19.CAR-T Cell-Containing Combination Therapy in Scl70+ Systemic Sclerosis. *Ann. Rheum. Dis.* **2024**, *83*, 543–546. [CrossRef]
56. Hügle, T.; Hogan, V.; White, K.E.; van Laar, J.M. Mast Cells Are a Source of Transforming Growth Factor β in Systemic Sclerosis. *Arthritis Rheum.* **2011**, *63*, 795–799. [CrossRef]
57. Khanna, D.; Denton, C.P.; Jahreis, A.; van Laar, J.M.; Frech, T.M.; Anderson, M.E.; Baron, M.; Chung, L.; Fierlbeck, G.; Lakshminarayanan, S.; et al. Safety and Efficacy of Subcutaneous Tocilizumab in Adults with Systemic Sclerosis (FaSScinate): A Phase 2, Randomised, Controlled Trial. *Lancet* **2016**, *387*, 2630–2640. [CrossRef]
58. Akamata, K.; Asano, Y.; Taniguchi, T.; Yamashita, T.; Saigusa, R.; Nakamura, K.; Noda, S.; Aozasa, N.; Toyama, T.; Takahashi, T.; et al. Increased Expression of Chemerin in Endothelial Cells Due to Fli1 Deficiency May Contribute to the Development of Digital Ulcers in Systemic Sclerosis. *Rheumatology* **2015**, *54*, 1308–1316. [CrossRef]
59. Duan, H.; Fleming, J.; Pritchard, D.K.; Amon, L.M.; Xue, J.; Arnett, H.A.; Chen, G.; Breen, P.; Buckner, J.H.; Molitor, J.A.; et al. Combined Analysis of Monocyte and Lymphocyte Messenger RNA Expression with Serum Protein Profiles in Patients with Scleroderma. *Arthritis Rheum.* **2008**, *58*, 1465–1474. [CrossRef]

60. Takahashi, T.; Asano, Y.; Nakamura, K.; Yamashita, T.; Saigusa, R.; Ichimura, Y.; Toyama, T.; Taniguchi, T.; Yoshizaki, A.; Tamaki, Z.; et al. A Potential Contribution of Antimicrobial Peptide LL-37 to Tissue Fibrosis and Vasculopathy in Systemic Sclerosis. *Br. J. Dermatol.* **2016**, *175*, 1195–1203. [CrossRef]
61. Kim, D.; Peck, A.; Santer, D.; Patole, P.; Schwartz, S.M.; Molitor, J.A.; Arnett, F.C.; Elkon, K.B. Induction of Interferon-Alpha by Scleroderma Sera Containing Autoantibodies to Topoisomerase I: Association of Higher Interferon-Alpha Activity with Lung Fibrosis. *Arthritis Rheum.* **2008**, *58*, 2163–2173. [CrossRef]
62. Black, C.M.; Silman, A.J.; Herrick, A.I.; Denton, C.P.; Wilson, H.; Newman, J.; Pompon, L.; Shi-Wen, X. Interferon-Alpha Does Not Improve Outcome at One Year in Patients with Diffuse Cutaneous Scleroderma: Results of a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Rheum.* **1999**, *42*, 299–305. [CrossRef] [PubMed]
63. Hügle, T.; Gratzl, S.; Daikeler, T.; Frey, D.; Tyndall, A.; Walker, U.A. Sclerosing Skin Disorders in Association with Multiple Sclerosis. Coincidence, Underlying Autoimmune Pathology or Interferon Induced? *Ann. Rheum. Dis.* **2009**, *68*, 47–50. [CrossRef] [PubMed]
64. Pelidou, S.-H.; Tsifetaki, N.; Giannopoulos, S.; Deretzi, G.; Voulgari, P.; Kyritsis, A. Multiple Sclerosis Associated with Systemic Sclerosis. *Rheumatol. Int.* **2007**, *27*, 771–773. [CrossRef]
65. Spadaro, A.; Sensi, F.; Barrella, M.; Francia, A. Systemic Sclerosis and Multiple Sclerosis. *J. Neurol.* **1999**, *246*, 497–499. [CrossRef]
66. Tahara, H.; Kojima, A.; Hirokawa, T.; Oyama, T.; Naganuma, A.; Maruta, S.; Okada, K.; Ban, S.; Yoshida, K.; Takagi, H.; et al. Systemic Sclerosis after Interferon Alphacon-1 Therapy for Hepatitis C. *Intern. Med.* **2007**, *46*, 473–476. [CrossRef] [PubMed]
67. Esteban, I.; Vilardell, M.R.; Solans, J.A. Bosch. *Clin. Exp. Rheumatol.* **2004**, *22*, 625–628.
68. Beretta, L.; Caronni, M.; Vanoli, M.; Scorza, R. Systemic Sclerosis after Interferon-Alfa Therapy for Myeloproliferative Disorders. *Br. J. Dermatol.* **2002**, *147*, 385–386. [CrossRef]
69. Pammer, J.; Reinisch, C.; Birner, P.; Pogoda, K.; Sturzl, M.; Tschachler, E. Interferon-Alpha Prevents Apoptosis of Endothelial Cells after Short-Term Exposure but Induces Replicative Senescence after Continuous Stimulation. *Lab. Investig.* **2006**, *86*, 997–1007. [CrossRef]
70. Ah Kioon, M.D.; Tripodo, C.; Fernandez, D.; Kirou, K.A.; Spiera, R.F.; Crow, M.K.; Gordon, J.K.; Barrat, F.J. Plasmacytoid Dendritic Cells Promote Systemic Sclerosis with a Key Role for TLR8. *Sci. Transl. Med.* **2018**, *10*, eaam8458. [CrossRef]
71. Ferreira, B.H.; Silva, I.S.; Mendes, A.; Leite-Pinheiro, F.; Paton, A.W.; Paton, J.C.; Duarte, I.F.; Pierre, P.; Almeida, C.R. Promoting ER Stress in a Plasmacytoid Dendritic Cell Line Drives Fibroblast Activation. *Cell Commun. Signal.* **2025**, *23*, 66. [CrossRef]
72. Abraham, D.J.; Krieg, T.; Distler, J.; Distler, O. Overview of Pathogenesis of Systemic Sclerosis. *Rheumatology* **2009**, *48* (Suppl. S3), iii3–iii7. [CrossRef]
73. Asano, Y. Future Treatments in Systemic Sclerosis. *J. Dermatol.* **2010**, *37*, 54–70. [CrossRef]
74. Asano, Y.; Sato, S. Vasculopathy in Scleroderma. *Semin. Immunopathol.* **2015**, *37*, 489–500. [CrossRef]
75. Prescott, R.J.; Freemont, A.J.; Jones, C.J.; Hoyland, J.; Fielding, P. Sequential Dermal Microvascular and Perivascular Changes in the Development of Scleroderma. *J. Pathol.* **1992**, *166*, 255–263. [CrossRef] [PubMed]
76. Sgonc, R.; Gruschwitz, M.S.; Dietrich, H.; Recheis, H.; Gershwin, M.E.; Wick, G. Endothelial Cell Apoptosis Is a Primary Pathogenetic Event Underlying Skin Lesions in Avian and Human Scleroderma. *J. Clin. Investig.* **1996**, *98*, 785–792. [CrossRef] [PubMed]
77. Burbelo, P.D.; Gordon, S.M.; Waldman, M.; Edison, J.D.; Little, D.J.; Stitt, R.S.; Bailey, W.T.; Hughes, J.B.; Olson, S.W. Autoantibodies Are Present before the Clinical Diagnosis of Systemic Sclerosis. *PLoS ONE* **2019**, *14*, e0214202. [CrossRef] [PubMed]
78. Ihn, H. Scleroderma, Fibroblasts, Signaling, and Excessive Extracellular Matrix. *Curr. Rheumatol. Rep.* **2005**, *7*, 156–162. [CrossRef] [PubMed]
79. Romano, E.; Rosa, I.; Fioretto, B.S.; Matucci-Cerinic, M.; Manetti, M. New Insights into Profibrotic Myofibroblast Formation in Systemic Sclerosis: When the Vascular Wall Becomes the Enemy. *Life* **2021**, *11*, 610. [CrossRef]
80. Takahashi, T.; Asano, Y.; Amiya, E.; Hatano, M.; Tamaki, Z.; Takata, M.; Ozeki, A.; Watanabe, A.; Kawarasaki, S.; Taniguchi, T.; et al. Clinical Correlation of Brachial Artery Flow-Mediated Dilation in Patients with Systemic Sclerosis. *Mod. Rheumatol.* **2014**, *24*, 106–111. [CrossRef]
81. Cerinic, M.M.; Valentini, G.; Sorano, G.G.; D'Angelo, S.; Cuomo, G.; Fenu, L.; Generini, S.; Cinotti, S.; Morfini, M.; Pignone, A.; et al. Blood Coagulation, Fibrinolysis, and Markers of Endothelial Dysfunction in Systemic Sclerosis. *Semin. Arthritis Rheum.* **2003**, *32*, 285–295. [CrossRef] [PubMed]
82. Ihn, H. Autocrine TGF-Beta Signaling in the Pathogenesis of Systemic Sclerosis. *J. Dermatol. Sci.* **2008**, *49*, 103–113. [CrossRef] [PubMed]
83. Bhattacharyya, S.; Kelley, K.; Melichian, D.S.; Tamaki, Z.; Fang, F.; Su, Y.; Feng, G.; Pope, R.M.; Budinger, G.R.S.; Mutlu, G.M.; et al. Toll-like Receptor 4 Signaling Augments Transforming Growth Factor-β Responses: A Novel Mechanism for Maintaining and Amplifying Fibrosis in Scleroderma. *Am. J. Pathol.* **2013**, *182*, 192–205. [CrossRef]
84. Kahaleh, M. Raynaud's Phenomenon and Vascular Disease in Scleroderma. *Curr. Opin. Rheumatol.* **1994**, *6*, 621–627. [CrossRef]

85. Tourkina, E.; Bonner, M.; Oates, J.; Hofbauer, A.; Richard, M.; Znoyko, S.; Visconti, R.P.; Zhang, J.; Hatfield, C.M.; Silver, R.M.; et al. Altered Monocyte and Fibrocyte Phenotype and Function in Scleroderma Interstitial Lung Disease: Reversal by Caveolin-1 Scaffolding Domain Peptide. *Fibrogenesis Tissue Repair* **2011**, *4*, 15. [CrossRef]
86. Nikitorowicz-Buniak, J.; Denton, C.P.; Abraham, D.; Stratton, R. Partially Evoked Epithelial-Mesenchymal Transition (EMT) Is Associated with Increased TGFβ Signaling within Lesional Scleroderma Skin. *PLoS ONE* **2015**, *10*, e0134092. [CrossRef]
87. Mendoza, F.A.; Piera-Velazquez, S.; Farber, J.L.; Feghali-Bostwick, C.; Jiménez, S.A. Endothelial Cells Expressing Endothelial and Mesenchymal Cell Gene Products in Lung Tissue from Patients with Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis Rheumatol.* **2016**, *68*, 210–217. [CrossRef]
88. Manetti, M.; Romano, E.; Rosa, I.; Guiducci, S.; Bellando-Randone, S.; De Paulis, A.; Ibba-Manneschi, L.; Matucci-Cerinic, M. Endothelial-to-Mesenchymal Transition Contributes to Endothelial Dysfunction and Dermal Fibrosis in Systemic Sclerosis. *Ann. Rheum. Dis.* **2017**, *76*, 924–934. [CrossRef] [PubMed]
89. Marangoni, R.G.; Korman, B.D.; Wei, J.; Wood, T.A.; Graham, L.V.; Whitfield, M.L.; Scherer, P.E.; Tourtellotte, W.G.; Varga, J. Myofibroblasts in Murine Cutaneous Fibrosis Originate from Adiponectin-Positive Intradermal Progenitors: Adipocyte-Myofibroblast Transition in Skin Fibrosis. *Arthritis Rheumatol.* **2015**, *67*, 1062–1073. [CrossRef]
90. Gruschwitz, M.; Müller, P.U.; Sepp, N.; Hofer, E.; Fontana, A.; Wick, G. Transcription and Expression of Transforming Growth Factor Type Beta in the Skin of Progressive Systemic Sclerosis: A Mediator of Fibrosis? *J. Investig. Dermatol.* **1990**, *94*, 197–203. [CrossRef]
91. Querfeld, C.; Eckes, B.; Huerkamp, C.; Krieg, T.; Sollberg, S. Expression of TGF-Beta 1, -Beta 2 and -Beta 3 in Localized and Systemic Scleroderma. *J. Dermatol. Sci.* **1999**, *21*, 13–22. [CrossRef] [PubMed]
92. Kulozik, M.; Hogg, A.; Lankat-Buttgereit, B.; Krieg, T. Co-Localization of Transforming Growth Factor Beta 2 with Alpha 1(I) Procollagen MRNA in Tissue Sections of Patients with Systemic Sclerosis. *J. Clin. Investig.* **1990**, *86*, 917–922. [CrossRef]
93. Asano, Y.; Ihn, H.; Yamane, K.; Kubo, M.; Tamaki, K. Impaired Smad7-Smurf-Mediated Negative Regulation of TGF-Beta Signaling in Scleroderma Fibroblasts. *J. Clin. Investig.* **2004**, *113*, 253–264. [CrossRef]
94. Asano, Y.; Ihn, H.; Yamane, K.; Jinnin, M.; Mimura, Y.; Tamaki, K. Increased Expression of Integrin Alpha(v)Beta3 Contributes to the Establishment of Autocrine TGF-Beta Signaling in Scleroderma Fibroblasts. *J. Immunol.* **2005**, *175*, 7708–7718. [CrossRef]
95. Asano, Y.; Ihn, H.; Yamane, K.; Kubo, M.; Tamaki, K. Increased Expression Levels of Integrin Alphavbeta5 on Scleroderma Fibroblasts. *Am. J. Pathol.* **2004**, *164*, 1275–1292. [CrossRef] [PubMed]
96. Asano, Y.; Ihn, H.; Yamane, K.; Jinnin, M.; Mimura, Y.; Tamaki, K. Involvement of Alphavbeta5 Integrin-Mediated Activation of Latent Transforming Growth Factor Beta1 in Autocrine Transforming Growth Factor Beta Signaling in Systemic Sclerosis Fibroblasts. *Arthritis Rheum.* **2005**, *52*, 2897–2905. [CrossRef] [PubMed]
97. Asano, Y.; Ihn, H.; Yamane, K.; Jinnin, M.; Tamaki, K. Increased Expression of Integrin Alphavbeta5 Induces the Myofibroblastic Differentiation of Dermal Fibroblasts. *Am. J. Pathol.* **2006**, *168*, 499–510. [CrossRef]
98. Mimura, Y.; Ihn, H.; Jinnin, M.; Asano, Y.; Yamane, K.; Tamaki, K. Constitutive Thrombospondin-1 Overexpression Contributes to Autocrine Transforming Growth Factor-Beta Signaling in Cultured Scleroderma Fibroblasts. *Am. J. Pathol.* **2005**, *166*, 1451–1463. [CrossRef]
99. Meng, Q.; Bao, D.; Liu, S.; Huang, J.; Guo, M.; Dai, B.; Ding, L.; Xie, S.; Meng, M.; Lv, C.; et al. ADAM Metallopeptidase Domain 19 Promotes Skin Fibrosis in Systemic Sclerosis via Neuregulin-1. *Mol. Med.* **2024**, *30*, 269. [CrossRef]
100. Chizzolini, C.; Rezzonico, R.; Ribbens, C.; Burger, D.; Wollheim, F.A.; Dayer, J.M. Inhibition of Type I Collagen Production by Dermal Fibroblasts upon Contact with Activated T Cells: Different Sensitivity to Inhibition between Systemic Sclerosis and Control Fibroblasts. *Arthritis Rheum.* **1998**, *41*, 2039–2047. [CrossRef]
101. Chizzolini, C.; Parel, Y.; De Luca, C.; Tyndall, A.; Akesson, A.; Scheja, A.; Dayer, J.-M. Systemic Sclerosis Th2 Cells Inhibit Collagen Production by Dermal Fibroblasts via Membrane-Associated Tumor Necrosis Factor Alpha: Th2 Cells Inhibit Collagen Synthesis by Dermal Fibroblasts. *Arthritis Rheum.* **2003**, *48*, 2593–2604. [CrossRef] [PubMed]
102. Ichimura, Y.; Asano, Y.; Akamata, K.; Noda, S.; Taniguchi, T.; Takahashi, T.; Toyama, T.; Tada, Y.; Sugaya, M.; Sato, S.; et al. Progranulin Overproduction Due to Fli-1 Deficiency Contributes to the Resistance of Dermal Fibroblasts to Tumor Necrosis Factor in Systemic Sclerosis: THE ROLE OF PROGRANULIN IN SSc. *Arthritis Rheumatol.* **2015**, *67*, 3245–3255. [CrossRef] [PubMed]
103. Bergmann, C.; Chenguiti Fakhouri, S.; Trinh-Minh, T.; Filla, T.; Rius Rigau, A.; Ekici, A.B.; Merlevede, B.; Hallenberger, L.; Zhu, H.; Dees, C.; et al. Mutual Amplification of GLI2/Hedgehog and Transcription Factor JUN/AP-1 Signaling in Fibroblasts in Systemic Sclerosis: Potential Implications for Combined Therapies. *Arthritis Rheumatol.* **2025**, *77*, 92–98. [CrossRef] [PubMed]
104. Saigusa, R.; Asano, Y.; Taniguchi, T.; Hirabayashi, M.; Nakamura, K.; Miura, S.; Yamashita, T.; Takahashi, T.; Ichimura, Y.; Toyama, T.; et al. Fli1-Haploinsufficient Dermal Fibroblasts Promote Skin-Localized Transdifferentiation of Th2-like Regulatory T Cells. *Arthritis Res. Ther.* **2018**, *20*, 23. [CrossRef]
105. Saigusa, R.; Asano, Y.; Nakamura, K.; Hirabayashi, M.; Miura, S.; Yamashita, T.; Taniguchi, T.; Ichimura, Y.; Takahashi, T.; Yoshizaki, A.; et al. Systemic Sclerosis Dermal Fibroblasts Suppress Th1 Cytokine Production via Galectin-9 Overproduction Due to Fli1 Deficiency. *J. Investig. Dermatol.* **2017**, *137*, 1850–1859. [CrossRef]

106. Gur, C.; Wang, S.-Y.; Sheban, F.; Zada, M.; Li, B.; Kharouf, F.; Peleg, H.; Aamar, S.; Yalin, A.; Kirschenbaum, D.; et al. LGR5 Expressing Skin Fibroblasts Define a Major Cellular Hub Perturbed in Scleroderma. *Cell* **2022**, *185*, 1373–1388.e20. [CrossRef]
107. Ma, F.; Tsou, P.-S.; Gharaee-Kermani, M.; Plazyo, O.; Xing, X.; Kirma, J.; Wasikowski, R.; Hile, G.A.; Harms, P.W.; Jiang, Y.; et al. Systems-Based Identification of the Hippo Pathway for Promoting Fibrotic Mesenchymal Differentiation in Systemic Sclerosis. *Nat. Commun.* **2024**, *15*, 210. [CrossRef]
108. Huang, M.; Tabib, T.; Khanna, D.; Assassi, S.; Domsic, R.; Lafyatis, R. Single-Cell Transcriptomes and Chromatin Accessibility of Endothelial Cells Unravel Transcription Factors Associated with Dysregulated Angiogenesis in Systemic Sclerosis. *Ann. Rheum. Dis.* **2024**, *83*, 1335–1344. [CrossRef]
109. Rius Rigau, A.; Li, Y.-N.; Matei, A.-E.; Györfi, A.-H.; Bruch, P.-M.; Koziel, S.; Devakumar, V.; Gabrielli, A.; Kreuter, A.; Wang, J.; et al. Characterization of Vascular Niche in Systemic Sclerosis by Spatial Proteomics. *Circ. Res.* **2024**, *134*, 875–891. [CrossRef]
110. Liu, Q.; Zaba, L.C.; Satpathy, A.T.; Longmire, M.; Zhang, W.; Li, K.; Granja, J.; Guo, C.; Lin, J.; Li, R.; et al. Chromatin Accessibility Landscapes of Skin Cells in Systemic Sclerosis Nominate Dendritic Cells in Disease Pathogenesis. *Nat. Commun.* **2020**, *11*, 5843. [CrossRef]
111. Miura, S.; Asano, Y.; Saigusa, R.; Yamashita, T.; Taniguchi, T.; Takahashi, T.; Ichimura, Y.; Toyama, T.; Yoshizaki, A.; Sato, S.; et al. Regulation of Skin Fibrosis by RALDH1-Producing Dermal Dendritic Cells via Retinoic Acid-Mediated Regulatory T Cell Induction: A Role in Scleroderma. *J. Dermatol. Sci.* **2020**, *97*, 125–134. [CrossRef] [PubMed]
112. Miura, S.; Watanabe, Y.; Saigusa, R.; Yamashita, T.; Nakamura, K.; Hirabayashi, M.; Miyagawa, T.; Yoshizaki, A.; Trojanowska, M.; Sato, S.; et al. Fli1 Deficiency Suppresses RALDH1 Activity of Dermal Dendritic Cells and Related Induction of Regulatory T Cells: A Possible Role in Scleroderma. *Arthritis Res. Ther.* **2021**, *23*, 137. [CrossRef]
113. Yang, M.M.; Lee, S.; Neely, J.; Hinchcliff, M.; Wolters, P.J.; Sirota, M. Gene Expression Meta-Analysis Reveals Aging and Cellular Senescence Signatures in Scleroderma-Associated Interstitial Lung Disease. *Front. Immunol.* **2024**, *15*, 1326922. [CrossRef] [PubMed]
114. Vaughan, D.E.; Rai, R.; Khan, S.S.; Eren, M.; Ghosh, A.K. Plasminogen Activator Inhibitor-1 Is a Marker and a Mediator of Senescence. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 1446–1452. [CrossRef]
115. Rana, T.; Jiang, C.; Liu, G.; Miyata, T.; Antony, V.; Thannickal, V.J.; Liu, R.-M. PAI-1 Regulation of TGF-B1-Induced Alveolar Type II Cell Senescence, SASP Secretion, and SASP-Mediated Activation of Alveolar Macrophages. *Am. J. Respir. Cell Mol. Biol.* **2020**, *62*, 319–330. [CrossRef]
116. Eren, M.; Boe, A.E.; Murphy, S.B.; Place, A.T.; Nagpal, V.; Morales-Nebreda, L.; Urich, D.; Quaggin, S.E.; Budinger, G.R.S.; Mutlu, G.M.; et al. PAI-1-Regulated Extracellular Proteolysis Governs Senescence and Survival in Klotho Mice. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 7090–7095. [CrossRef] [PubMed]
117. Khan, S.S.; Shah, S.J.; Klyachko, E.; Baldridge, A.S.; Eren, M.; Place, A.T.; Aviv, A.; Puterman, E.; Lloyd-Jones, D.M.; Heiman, M.; et al. A Null Mutation in SERPINE1 Protects against Biological Aging in Humans. *Sci. Adv.* **2017**, *3*, eaao1617. [CrossRef]
118. Kanno, Y. The Role of Fibrinolytic Regulators in Vascular Dysfunction of Systemic Sclerosis. *Int. J. Mol. Sci.* **2019**, *20*, 619. [CrossRef] [PubMed]
119. Kanno, Y. The UPA/UPAR System Orchestrates the Inflammatory Response, Vascular Homeostasis, and Immune System in Fibrosis Progression. *Int. J. Mol. Sci.* **2023**, *24*, 1796. [CrossRef]
120. Vancheeswaran, R.; Azam, A.; Black, C.; Dashwood, M.R. Localization of Endothelin-1 and Its Binding Sites in Scleroderma Skin. *J. Rheumatol.* **1994**, *21*, 1268–1276.
121. Rudnicka, L.; Varga, J.; Christiano, A.M.; Iozzo, R.V.; Jimenez, S.A.; Uitto, J. Elevated Expression of Type VII Collagen in the Skin of Patients with Systemic Sclerosis. Regulation by Transforming Growth Factor-Beta. *J. Clin. Investig.* **1994**, *93*, 1709–1715. [CrossRef] [PubMed]
122. Distler, O.; Pap, T.; Kowal-Bielecka, O.; Meyringer, R.; Guiducci, S.; Landthaler, M.; Schölmerich, J.; Michel, B.A.; Gay, R.E.; Matucci-Cerinic, M.; et al. Overexpression of Monocyte Chemoattractant Protein 1 in Systemic Sclerosis: Role of Platelet-Derived Growth Factor and Effects on Monocyte Chemotaxis and Collagen Synthesis. *Arthritis Rheum.* **2001**, *44*, 2665–2678. [CrossRef]
123. Davies, C.A.; Jeziorska, M.; Freemont, A.J.; Herrick, A.L. The Differential Expression of VEGF, VEGFR-2, and GLUT-1 Proteins in Disease Subtypes of Systemic Sclerosis. *Hum. Pathol.* **2006**, *37*, 190–197. [CrossRef]
124. Distler, J.H.W.; Jüngel, A.; Kowal-Bielecka, O.; Michel, B.A.; Gay, R.E.; Sprott, H.; Matucci-Cerinic, M.; Chilla, M.; Reich, K.; Kalden, J.R.; et al. Expression of Interleukin-21 Receptor in Epidermis from Patients with Systemic Sclerosis: Altered Expression Pattern of Keratinocytes in SSc. *Arthritis Rheum.* **2005**, *52*, 856–864. [CrossRef] [PubMed]
125. Aden, N.; Nuttall, A.; Shiwen, X.; de Winter, P.; Leask, A.; Black, C.M.; Denton, C.P.; Abraham, D.J.; Stratton, R.J. Epithelial Cells Promote Fibroblast Activation via IL-1alpha in Systemic Sclerosis. *J. Investig. Dermatol.* **2010**, *130*, 2191–2200. [CrossRef] [PubMed]
126. Nikitorowicz-Buniak, J.; Shiwen, X.; Denton, C.P.; Abraham, D.; Stratton, R. Abnormally Differentiating Keratinocytes in the Epidermis of Systemic Sclerosis Patients Show Enhanced Secretion of CCN2 and S100A9. *J. Investig. Dermatol.* **2014**, *134*, 2693–2702. [CrossRef]

127. McCoy, S.S.; Reed, T.J.; Berthier, C.C.; Tsou, P.-S.; Liu, J.; Gudjonsson, J.E.; Khanna, D.; Kahlenberg, J.M. Scleroderma Keratinocytes Promote Fibroblast Activation Independent of Transforming Growth Factor Beta. *Rheumatology* **2017**, *56*, 1970–1981. [CrossRef]
128. Takahashi, T.; Asano, Y.; Yamashita, T.; Nakamura, K.; Saigusa, R.; Miura, S.; Ichimura, Y.; Toyama, T.; Hirabayashi, M.; Taniguchi, T.; et al. A Potential Contribution of Psoriasin to Vascular and Epithelial Abnormalities and Inflammation in Systemic Sclerosis. *J. Eur. Acad. Dermatol. Venereol.* **2018**, *32*, 291–297. [CrossRef]
129. Saigusa, R.; Yamashita, T.; Miura, S.; Hirabayashi, M.; Nakamura, K.; Miyagawa, T.; Fukui, Y.; Yoshizaki, A.; Sato, S.; Asano, Y. A Potential Contribution of Decreased Galectin-7 Expression in Stratified Epithelia to the Development of Cutaneous and Oesophageal Manifestations in Systemic Sclerosis. *Exp. Dermatol.* **2019**, *28*, 536–542. [CrossRef]
130. Takahashi, T.; Asano, Y.; Sugawara, K.; Yamashita, T.; Nakamura, K.; Saigusa, R.; Ichimura, Y.; Toyama, T.; Taniguchi, T.; Akamata, K.; et al. Epithelial Fli1 Deficiency Drives Systemic Autoimmunity and Fibrosis: Possible Roles in Scleroderma. *J. Exp. Med.* **2017**, *214*, 1129–1151. [CrossRef]
131. Asano, Y.; Stawski, L.; Hant, F.; Highland, K.; Silver, R.; Szalai, G.; Watson, D.K.; Trojanowska, M. Endothelial Fli1 Deficiency Impairs Vascular Homeostasis: A Role in Scleroderma Vasculopathy. *Am. J. Pathol.* **2010**, *176*, 1983–1998. [CrossRef] [PubMed]
132. Asano, Y.; Markiewicz, M.; Kubo, M.; Szalai, G.; Watson, D.K.; Trojanowska, M. Transcription Factor Fli1 Regulates Collagen Fibrillogenesis in Mouse Skin. *Mol. Cell. Biol.* **2009**, *29*, 425–434. [CrossRef] [PubMed]
133. Bujor, A.M.; El Adili, F.; Parvez, A.; Marden, G.; Trojanowska, M. Fli1 Downregulation in Scleroderma Myeloid Cells Has Profibrotic and Proinflammatory Effects. *Front. Immunol.* **2020**, *11*, 800. [CrossRef]
134. Taniguchi, T.; Miyagawa, T.; Toyama, S.; Yamashita, T.; Nakamura, K.; Saigusa, R.; Ichimura, Y.; Takahashi, T.; Toyama, T.; Yoshizaki, A.; et al. CXCL13 Produced by Macrophages Due to Fli1 Deficiency May Contribute to the Development of Tissue Fibrosis, Vasculopathy and Immune Activation in Systemic Sclerosis. *Exp. Dermatol.* **2018**, *27*, 1030–1037. [CrossRef]
135. Anderson, M.S.; Venanzi, E.S.; Klein, L.; Chen, Z.; Berzins, S.P.; Turley, S.J.; von Boehmer, H.; Bronson, R.; Dierich, A.; Benoist, C.; et al. Projection of an Immunological Self Shadow within the Thymus by the Aire Protein. *Science* **2002**, *298*, 1395–1401. [CrossRef]
136. Mathis, D.; Benoist, C. Aire. *Annu. Rev. Immunol.* **2009**, *27*, 287–312. [CrossRef]
137. Saigusa, R.; Asano, Y.; Yamashita, T.; Takahashi, T.; Nakamura, K.; Miura, S.; Ichimura, Y.; Toyama, T.; Taniguchi, T.; Sumida, H.; et al. Systemic Sclerosis Complicated with Localized Scleroderma-like Lesions Induced by Köbner Phenomenon. *J. Dermatol. Sci.* **2018**, *89*, 282–289. [CrossRef] [PubMed]
138. Byrd, A.L.; Belkaid, Y.; Segre, J.A. The Human Skin Microbiome. *Nat. Rev. Microbiol.* **2018**, *16*, 143–155. [CrossRef]
139. Terui, H.; Yamasaki, K.; Wada-Irimada, M.; Onodera-Amagai, M.; Hatchome, N.; Mizuashi, M.; Yamashita, R.; Kawabe, T.; Ishii, N.; Abe, T.; et al. Staphylococcus Aureus Skin Colonization Promotes SLE-like Autoimmune Inflammation via Neutrophil Activation and the IL-23/IL-17 Axis. *Sci. Immunol.* **2022**, *7*, eabm9811. [CrossRef]
140. Grice, E.A.; Segre, J.A. The Skin Microbiome. *Nat. Rev. Microbiol.* **2011**, *9*, 244–253. [CrossRef]
141. Johnson, M.E.; Franks, J.M.; Cai, G.; Mehta, B.K.; Wood, T.A.; Archambault, K.; Pioli, P.A.; Simms, R.W.; Orzechowski, N.; Arron, S.; et al. Microbiome Dysbiosis Is Associated with Disease Duration and Increased Inflammatory Gene Expression in Systemic Sclerosis Skin. *Arthritis Res. Ther.* **2019**, *21*, 49. [CrossRef] [PubMed]
142. Bhattacharyya, S.; Wei, J.; Varga, J. Understanding Fibrosis in Systemic Sclerosis: Shifting Paradigms, Emerging Opportunities. *Nat. Rev. Rheumatol.* **2011**, *8*, 42–54. [CrossRef]
143. Lynch, M.D.; Watt, F.M. Fibroblast Heterogeneity: Implications for Human Disease. *J. Clin. Investig.* **2018**, *128*, 26–35. [CrossRef]
144. Zhang, Z.; Shao, M.; Hepler, C.; Zi, Z.; Zhao, S.; An, Y.A.; Zhu, Y.; Ghaben, A.L.; Wang, M.-Y.; Li, N.; et al. Dermal Adipose Tissue Has High Plasticity and Undergoes Reversible Dedifferentiation in Mice. *J. Clin. Investig.* **2019**, *129*, 5327–5342. [CrossRef]
145. Varga, J.; Marangoni, R.G. Systemic Sclerosis in 2016: Dermal White Adipose Tissue Implicated in SSc Pathogenesis: Systemic Sclerosis in 2016. *Nat. Rev. Rheumatol.* **2017**, *13*, 71–72. [CrossRef] [PubMed]
146. Matsuzawa, Y.; Shimomura, I.; Kihara, S.; Funahashi, T. Importance of Adipocytokines in Obesity-Related Diseases. *Horm. Res.* **2003**, *60* (Suppl. S3), 56–59. [CrossRef] [PubMed]
147. Masui, Y.; Asano, Y.; Shibata, S.; Noda, S.; Aozasa, N.; Akamata, K.; Yamada, D.; Tamaki, Z.; Tada, Y.; Sugaya, M.; et al. Serum Adiponectin Levels Inversely Correlate with the Activity of Progressive Skin Sclerosis in Patients with Diffuse Cutaneous Systemic Sclerosis: Significance of Serum Adiponectin Levels in SSc. *J. Eur. Acad. Dermatol. Venereol.* **2012**, *26*, 354–360. [CrossRef]
148. Masui, Y.; Asano, Y.; Takahashi, T.; Shibata, S.; Akamata, K.; Aozasa, N.; Noda, S.; Taniguchi, T.; Ichimura, Y.; Toyama, T.; et al. Clinical Significance of Monitoring Serum Adiponectin Levels during Intravenous Pulse Cyclophosphamide Therapy in Interstitial Lung Disease Associated with Systemic Sclerosis. *Mod. Rheumatol.* **2013**, *23*, 323–329. [CrossRef]
149. Masui, Y.; Asano, Y.; Shibata, S.; Noda, S.; Akamata, K.; Aozasa, N.; Taniguchi, T.; Takahashi, T.; Ichimura, Y.; Toyama, T.; et al. A Possible Contribution of Visfatin to the Resolution of Skin Sclerosis in Patients with Diffuse Cutaneous Systemic Sclerosis via a Direct Anti-Fibrotic Effect on Dermal Fibroblasts and Th1 Polarization of the Immune Response. *Rheumatology* **2013**, *52*, 1239–1244. [CrossRef]

150. Aozasa, N.; Asano, Y.; Akamata, K.; Noda, S.; Masui, Y.; Yamada, D.; Tamaki, Z.; Tada, Y.; Sugaya, M.; Kadono, T.; et al. Serum Apelin Levels: Clinical Association with Vascular Involvements in Patients with Systemic Sclerosis: Significance of Serum Apelin Levels in SSc. *J. Eur. Acad. Dermatol. Venereol.* **2013**, *27*, 37–42. [CrossRef]
151. Masui, Y.; Asano, Y.; Akamata, K.; Aozasa, N.; Noda, S.; Taniguchi, T.; Takahashi, T.; Ichimura, Y.; Toyama, T.; Sumida, H.; et al. Serum Resistin Levels: A Possible Correlation with Pulmonary Vascular Involvement in Patients with Systemic Sclerosis. *Rheumatol. Int.* **2014**, *34*, 1165–1170. [CrossRef] [PubMed]
152. Toyama, T.; Asano, Y.; Takahashi, T.; Aozasa, N.; Akamata, K.; Noda, S.; Taniguchi, T.; Ichimura, Y.; Sumida, H.; Tamaki, Z.; et al. Clinical Significance of Serum Retinol Binding Protein-4 Levels in Patients with Systemic Sclerosis: Significance of Serum RBP4 Levels in SSc. *J. Eur. Acad. Dermatol. Venereol.* **2013**, *27*, 337–344. [CrossRef] [PubMed]
153. Takahashi, T.; Asano, Y.; Noda, S.; Aozasa, N.; Akamata, K.; Taniguchi, T.; Ichimura, Y.; Toyama, T.; Sumida, H.; Kuwano, Y.; et al. A Possible Contribution of Lipocalin-2 to the Development of Dermal Fibrosis, Pulmonary Vascular Involvement and Renal Dysfunction in Systemic Sclerosis. *Br. J. Dermatol.* **2015**, *173*, 681–689. [CrossRef] [PubMed]
154. Miura, S.; Asano, Y.; Saigusa, R.; Yamashita, T.; Taniguchi, T.; Takahashi, T.; Ichimura, Y.; Toyama, T.; Tamaki, Z.; Tada, Y.; et al. Serum Omentin Levels: A Possible Contribution to Vascular Involvement in Patients with Systemic Sclerosis. *J. Dermatol.* **2015**, *42*, 461–466. [CrossRef]
155. Miura, S.; Asano, Y.; Saigusa, R.; Yamashita, T.; Taniguchi, T.; Takahashi, T.; Ichimura, Y.; Toyama, T.; Tamaki, Z.; Tada, Y.; et al. Serum Vaspin Levels: A Possible Correlation with Digital Ulcers in Patients with Systemic Sclerosis. *J. Dermatol.* **2015**, *42*, 528–531. [CrossRef]
156. Lakota, K.; Wei, J.; Carns, M.; Hinchcliff, M.; Lee, J.; Whitfield, M.L.; Sodin-Semrl, S.; Varga, J. Levels of Adiponectin, a Marker for PPAR-Gamma Activity, Correlate with Skin Fibrosis in Systemic Sclerosis: Potential Utility as Biomarker? *Arthritis Res. Ther.* **2012**, *14*, R102. [CrossRef]
157. Tomčík, M.; Arima, K.; Hulejová, H.; Kuklová, M.; Filková, M.; Braun, M.; Beláček, J.; Novák, M.; Bečvář, R.; Vencovský, J.; et al. Adiponectin Relation to Skin Changes and Dyslipidemia in Systemic Sclerosis. *Cytokine* **2012**, *58*, 165–168. [CrossRef]
158. Arakawa, H.; Jinnin, M.; Muchemwa, F.C.; Makino, T.; Kajihara, I.; Makino, K.; Honda, N.; Sakai, K.; Fukushima, S.; Ihn, H. Adiponectin Expression Is Decreased in the Involved Skin and Sera of Diffuse Cutaneous Scleroderma Patients: Letter to the Editor. *Exp. Dermatol.* **2011**, *20*, 764–766. [CrossRef]
159. Marangoni, R.G.; Masui, Y.; Fang, F.; Korman, B.; Lord, G.; Lee, J.; Lakota, K.; Wei, J.; Scherer, P.E.; Otvos, L.; et al. Adiponectin Is an Endogenous Anti-Fibrotic Mediator and Therapeutic Target. *Sci. Rep.* **2017**, *7*, 4397. [CrossRef]
160. Yamashita, T.; Lakota, K.; Taniguchi, T.; Yoshizaki, A.; Sato, S.; Hong, W.; Zhou, X.; Sodin-Semrl, S.; Fang, F.; Asano, Y.; et al. An Orally-Active Adiponectin Receptor Agonist Mitigates Cutaneous Fibrosis, Inflammation and Microvascular Pathology in a Murine Model of Systemic Sclerosis. *Sci. Rep.* **2018**, *8*, 11843. [CrossRef]
161. Sjogren, R. Gastrointestinal Features of Scleroderma. *Curr. Opin. Rheumatol.* **1996**, *8*, 569–575. [CrossRef] [PubMed]
162. Poirier, T.; Rankin, G. Gastrointestinal Manifestations of Progressive Systemic Scleroderma Based on a Review of 364 Cases. *Am. J. Gastroenterol.* **1972**, *58*, 30–44. [PubMed]
163. Young, M.A.; Rose, S.; Reynolds, J.C. Gastrointestinal Manifestations of Scleroderma. *Rheum. Dis. Clin. N. Am.* **1996**, *22*, 797–823. [CrossRef]
164. Emmanuel, A. Current Management of the Gastrointestinal Complications of Systemic Sclerosis. *Nat. Rev. Gastroenterol. Hepatol.* **2016**, *13*, 461–472. [CrossRef] [PubMed]
165. Lock, G.; Holstege, A.; Lang, B.; Schölmerich, J. Gastrointestinal Manifestations of Progressive Systemic Sclerosis. *Am. J. Gastroenterol.* **1997**, *92*, 763–771.
166. Malandrini, A.; Selvi, E.; Villanova, M.; Berti, G.; Sabadini, L.; Salvadori, C.; Gambelli, S.; De Stefano, R.; Vernillo, R.; Marcolongo, R.; et al. Autonomic Nervous System and Smooth Muscle Cell Involvement in Systemic Sclerosis: Ultrastructural Study of 3 Cases. *J. Rheumatol.* **2000**, *27*, 1203–1206.
167. Lepri, G.; Guiducci, S.; Bellando-Randone, S.; Giani, I.; Bruni, C.; Blagojevic, J.; Carnesecchi, G.; Radicati, A.; Pucciani, F.; Marco, M.-C. Evidence for Oesophageal and Anorectal Involvement in Very Early Systemic Sclerosis (VEDOSS): Report from a Single VEDOSS/EUSTAR Centre. *Ann. Rheum. Dis.* **2015**, *74*, 124–128. [CrossRef]
168. Weston, S.; Thumshirn, M.; Wiste, J.; Camilleri, M. Clinical and Upper Gastrointestinal Motility Features in Systemic Sclerosis and Related Disorders. *Am. J. Gastroenterol.* **1998**, *93*, 1085–1089. [CrossRef]
169. Roman, S.; Hot, A.; Fabien, N.; Cordier, J.-F.; Miossec, P.; Ninet, J.; Mion, F.; Réseau Sclérodermie des Hospices Civils de Lyon. Esophageal Dysmotility Associated with Systemic Sclerosis: A High-Resolution Manometry Study: Systemic Sclerosis and Esophageal HRM. *Dis. Esophagus* **2011**, *24*, 299–304. [CrossRef]
170. van Leeuwen, N.M.; Boonstra, M.; Fretheim, H.; Brunborg, C.; Midtvedt, Ø.; Garen, T.; Molberg, Ø.; Huizinga, T.W.J.; de Vries-Bouwstra, J.K.; Hoffman-Vold, A.-M. Gastrointestinal Symptom Severity and Progression in Systemic Sclerosis. *Rheumatology* **2022**, *61*, 4024–4034. [CrossRef]

171. Eaker, E.Y.; Kuldau, J.G.; Verne, G.N.; Ross, S.O.; Sallustio, J.E. Myenteric Neuronal Antibodies in Scleroderma: Passive Transfer Evokes Alterations in Intestinal Myoelectric Activity in a Rat Model. *J. Lab. Clin. Med.* **1999**, *133*, 551–556. [CrossRef] [PubMed]
172. Kawaguchi, Y.; Nakamura, Y.; Matsumoto, I.; Nishimagi, E.; Satoh, T.; Kuwana, M.; Sumida, T.; Hara, M. Muscarinic-3 Acetylcholine Receptor Autoantibody in Patients with Systemic Sclerosis: Contribution to Severe Gastrointestinal Tract Dysmotility. *Ann. Rheum. Dis.* **2009**, *68*, 710–714. [CrossRef]
173. Singh, J.; Mehendiratta, V.; Del Galdo, F.; Jimenez, S.A.; Cohen, S.; DiMarino, A.J.; Rattan, S. Immunoglobulins from Scleroderma Patients Inhibit the Muscarinic Receptor Activation in Internal Anal Sphincter Smooth Muscle Cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2009**, *297*, G1206–G1213. [CrossRef]
174. Kafaja, S.; Valera, I.; Divekar, A.A.; Saggar, R.; Abtin, F.; Furst, D.E.; Khanna, D.; Singh, R.R. PDCs in Lung and Skin Fibrosis in a Bleomycin-Induced Model and Patients with Systemic Sclerosis. *JCI Insight* **2018**, *3*, e98380. [CrossRef] [PubMed]
175. Dantas, R.O.; Aprile, L.R.O. Esophageal Striated Muscle Contractions in Patients with Gastroesophageal Reflux Symptoms. *Dig. Dis. Sci.* **2002**, *47*, 2586–2590. [CrossRef] [PubMed]
176. Miwa, H.; Kondo, T.; Oshima, T. Gastroesophageal Reflux Disease-Related and Functional Heartburn: Pathophysiology and Treatment. *Curr. Opin. Gastroenterol.* **2016**, *32*, 344–352. [CrossRef]
177. Dessein, P.H.; Joffe, B.I.; Metz, R.M.; Millar, D.L.; Lawson, M.; Stanwix, A.E. Autonomic Dysfunction in Systemic Sclerosis: Sympathetic Overactivity and Instability. *Am. J. Med.* **1992**, *93*, 143–150. [CrossRef]
178. Zhong, D.; Wu, C.; Zeng, X.; Wang, Q. The Role of Gut Microbiota in the Pathogenesis of Rheumatic Diseases. *Clin. Rheumatol.* **2018**, *37*, 25–34. [CrossRef]
179. De Luca, F.; Shoenfeld, Y. The Microbiome in Autoimmune Diseases. *Clin. Exp. Immunol.* **2019**, *195*, 74–85. [CrossRef]
180. Rosser, E.C.; Mauri, C. A Clinical Update on the Significance of the Gut Microbiota in Systemic Autoimmunity. *J. Autoimmun.* **2016**, *74*, 85–93. [CrossRef]
181. Bellocchi, C.; Volkmann, E.R. Update on the Gastrointestinal Microbiome in Systemic Sclerosis. *Curr. Rheumatol. Rep.* **2018**, *20*, 49. [CrossRef] [PubMed]
182. Volkmann, E.R. Intestinal Microbiome in Scleroderma: Recent Progress. *Curr. Opin. Rheumatol.* **2017**, *29*, 553–560. [CrossRef] [PubMed]
183. Fretheim, H.; Chung, B.K.; Didriksen, H.; Bækkevold, E.S.; Midtvedt, Ø.; Brunborg, C.; Holm, K.; Valeur, J.; Tennøe, A.H.; Garen, T.; et al. Fecal Microbiota Transplantation in Systemic Sclerosis: A Double-Blind, Placebo-Controlled Randomized Pilot Trial. *PLoS ONE* **2020**, *15*, e0232739. [CrossRef]
184. Steen, V.D.; Medsger, T.A. Changes in Causes of Death in Systemic Sclerosis, 1972-2002. *Ann. Rheum. Dis.* **2007**, *66*, 940–944. [CrossRef]
185. Elhai, M.; Meune, C.; Boubaya, M.; Avouac, J.; Hachulla, E.; Balbir-Gurman, A.; Riemekasten, G.; Airò, P.; Joven, B.; Vettori, S.; et al. Mapping and Predicting Mortality from Systemic Sclerosis. *Ann. Rheum. Dis.* **2017**, *76*, 1897–1905. [CrossRef]
186. Simonneau, G.; Montani, D.; Celermajer, D.S.; Denton, C.P.; Gatzoulis, M.A.; Krowka, M.; Williams, P.G.; Souza, R. Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension. *Eur. Respir. J.* **2019**, *53*, 1801913. [CrossRef]
187. Duarte, A.C.; Cordeiro, A.; Loureiro, M.J.; Ferreira, F. Pulmonary Veno-Occlusive Disease: A Probably Underdiagnosed Cause of Pulmonary Hypertension in Systemic Sclerosis. *Clin. Rheumatol.* **2020**, *39*, 1687–1691. [CrossRef]
188. Hassan, H.J.; Naranjo, M.; Ayoub, N.; Housten, T.; Hsu, S.; Balasubramanian, A.; Simpson, C.E.; Damico, R.L.; Mathai, S.C.; Kolb, T.M.; et al. Improved Survival for Patients with Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: The Johns Hopkins Registry. *Am. J. Respir. Crit. Care Med.* **2023**, *207*, 312–322. [CrossRef] [PubMed]
189. Guillén-Del-Castillo, A.; Meseguer, M.L.; Fonollosa-Plá, V.; Giménez, B.S.; Colunga-Argüelles, D.; Revilla-López, E.; Rubio-Rivas, M.; Ropero, M.J.C.; Argibay, A.; Barberà, J.; et al. Impact of Interstitial Lung Disease on the Survival of Systemic Sclerosis with Pulmonary Arterial Hypertension. *Sci. Rep.* **2022**, *12*, 5289. [CrossRef]
190. Zamanian, R.T.; Badesch, D.; Chung, L.; Domsic, R.T.; Medsger, T.; Pinckney, A.; Keyes-Elstein, L.; D'Aveta, C.; Spychala, M.; White, R.J.; et al. Safety and Efficacy of B-Cell Depletion with Rituximab for the Treatment of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial. *Am. J. Respir. Crit. Care Med.* **2021**, *204*, 209–221. [CrossRef]
191. Liem, S.I.E.; Boonstra, M.; le Cessie, S.; Riccardi, A.; Airo, P.; Distler, O.; Matucci-Cerinic, M.; Caimmi, C.; Siegert, E.; Allanore, Y.; et al. Sex-Specific Risk of Anti-Topoisomerase Antibodies on Mortality and Disease Severity in Systemic Sclerosis: 10-Year Analysis of the Leiden CCISS and EUSTAR Cohorts. *Lancet Rheumatol.* **2022**, *4*, e699–e709. [CrossRef] [PubMed]
192. Rubio-Rivas, M.; Homs, N.A.; Cuartero, D.; Corbella, X. The Prevalence and Incidence Rate of Pulmonary Arterial Hypertension in Systemic Sclerosis: Systematic Review and Meta-Analysis. *Autoimmun. Rev.* **2021**, *20*, 102713. [CrossRef]
193. Brown, Z.; Proudman, S.; Morrisroe, K.; Stevens, W.; Hansen, D.; Nikpour, M. Screening for the Early Detection of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis: A Systematic Review and Meta-Analysis of Long-Term Outcomes. *Semin. Arthritis Rheum.* **2021**, *51*, 495–512. [CrossRef]

194. Daraban, A.M.; Enache, R.; Predescu, L.; Platon, P.; Constantinescu, T.; Mihai, C.; Coman, I.M.; Ginghina, C.; Jurcuţ, R. Pulmonary Veno-Occlusive Disease: A Rare Cause of Pulmonary Hypertension in Systemic Sclerosis. Case Presentation and Review of the Literature. *Rom. J. Intern. Med.* **2015**, *53*, 175–183. [CrossRef] [PubMed]
195. Steele, R.; Hudson, M.; Lo, E.; Baron, M.; Canadian Scleroderma Research Group. Clinical Decision Rule to Predict the Presence of Interstitial Lung Disease in Systemic Sclerosis. *Arthritis Care Res.* **2012**, *64*, 519–524. [CrossRef] [PubMed]
196. White, B. Interstitial Lung Disease in Scleroderma. *Rheum. Dis. Clin. N. Am.* **2003**, *29*, 371–390. [CrossRef]
197. Nihtyanova, S.I.; Schreiber, B.E.; Ong, V.H.; Rosenberg, D.; Moinzadeh, P.; Coghlan, J.G.; Wells, A.U.; Denton, C.P. Prediction of Pulmonary Complications and Long-Term Survival in Systemic Sclerosis: Pulmonary Complications and Survival in SSc. *Arthritis Rheumatol.* **2014**, *66*, 1625–1635. [CrossRef]
198. Steen, V.; Domsic, R.T.; Lucas, M.; Fertig, N.; Medsger, T.A., Jr. A Clinical and Serologic Comparison of African American and Caucasian Patients with Systemic Sclerosis. *Arthritis Rheum.* **2012**, *64*, 2986–2994. [CrossRef]
199. Jaeger, V.K.; Wirz, E.G.; Allanore, Y.; Rossbach, P.; Riemekasten, G.; Hachulla, E.; Distler, O.; Airò, P.; Carreira, P.E.; Balbir Gurman, A.; et al. Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. *PLoS ONE* **2016**, *11*, e0163894. [CrossRef]
200. Ostojić, P.; Damjanov, N. Different Clinical Features in Patients with Limited and Diffuse Cutaneous Systemic Sclerosis. *Clin. Rheumatol.* **2006**, *25*, 453–457. [CrossRef]
201. Asano, Y.; Ihn, H.; Yamane, K.; Kubo, M.; Tamaki, K. The Prevalence and Clinical Significance of Anti-U1 RNA Antibodies in Patients with Systemic Sclerosis. *J. Investig. Dermatol.* **2003**, *120*, 204–210. [CrossRef]
202. Man, A.; Davidyock, T.; Ferguson, L.T.; Ieong, M.; Zhang, Y.; Simms, R.W. Changes in Forced Vital Capacity over Time in Systemic Sclerosis: Application of Group-Based Trajectory Modelling. *Rheumatology* **2015**, *54*, 1464–1471. [CrossRef] [PubMed]
203. Steen, V.D.; Conte, C.; Owens, G.R.; Medsger, T.A., Jr. Severe Restrictive Lung Disease in Systemic Sclerosis. *Arthritis Rheum.* **1994**, *37*, 1283–1289. [CrossRef] [PubMed]
204. Morgan, C.; Knight, C.; Lunt, M.; Black, C.M.; Silman, A.J. Predictors of End Stage Lung Disease in a Cohort of Patients with Scleroderma. *Ann. Rheum. Dis.* **2003**, *62*, 146–150. [CrossRef]
205. Bouros, D.; Wells, A.U.; Nicholson, A.G.; Colby, T.V.; Polychronopoulos, V.; Pantelidis, P.; Haslam, P.L.; Vassilakis, D.A.; Black, C.M.; du Bois, R.M. Histopathologic Subsets of Fibrosing Alveolitis in Patients with Systemic Sclerosis and Their Relationship to Outcome. *Am. J. Respir. Crit. Care Med.* **2002**, *165*, 1581–1586. [CrossRef]
206. Kim, D.S.; Yoo, B.; Lee, J.S.; Kim, E.K.; Lim, C.M.; Lee, S.D.; Koh, Y.; Kim, W.S.; Kim, W.D.; Colby, T.V.; et al. The Major Histopathologic Pattern of Pulmonary Fibrosis in Scleroderma Is Nonspecific Interstitial Pneumonia. *Sarcoidosis Vasc. Diffuse Lung Dis.* **2002**, *19*, 121–127.
207. Fischer, A.; Swigris, J.J.; Groshong, S.D.; Cool, C.D.; Sahin, H.; Lynch, D.A.; Curran-Everett, D.; Gillis, J.Z.; Meehan, R.T.; Brown, K.K. Clinically Significant Interstitial Lung Disease in Limited Scleroderma: Histopathology, Clinical Features, and Survival. *Chest* **2008**, *134*, 601–605. [CrossRef]
208. Winstone, T.A.; Assayag, D.; Wilcox, P.G.; Dunne, J.V.; Hague, C.J.; Leipsic, J.; Collard, H.R.; Ryerson, C.J. Predictors of Mortality and Progression in Scleroderma-Associated Interstitial Lung Disease: A Systematic Review. *Chest* **2014**, *146*, 422–436. [CrossRef] [PubMed]
209. Beon, M.; Harley, R.A.; Wessels, A.; Silver, R.M.; Ludwicka-Bradley, A. Myofibroblast Induction and Microvascular Alteration in Scleroderma Lung Fibrosis. *Clin. Exp. Rheumatol.* **2004**, *22*, 733–742.
210. Savarino, E.; Bazzica, M.; Zentilin, P.; Pohl, D.; Parodi, A.; Cittadini, G.; Negrini, S.; Indiveri, F.; Tutuian, R.; Savarino, V.; et al. Gastroesophageal Reflux and Pulmonary Fibrosis in Scleroderma: A Study Using PH-Impedance Monitoring: A Study Using PH-Impedance Monitoring. *Am. J. Respir. Crit. Care Med.* **2009**, *179*, 408–413. [CrossRef]
211. Appel, J.Z., 3rd; Lee, S.M.; Hartwig, M.G.; Li, B.; Hsieh, C.-C.; Cantu, E., 3rd; Yoon, Y.; Lin, S.S.; Parker, W.; Davis, R.D. Characterization of the Innate Immune Response to Chronic Aspiration in a Novel Rodent Model. *Respir. Res.* **2007**, *8*, 87. [CrossRef] [PubMed]
212. Christmann, R.B.; Wells, A.U.; Capelozzi, V.L.; Silver, R.M. Gastroesophageal Reflux Incites Interstitial Lung Disease in Systemic Sclerosis: Clinical, Radiologic, Histopathologic, and Treatment Evidence. *Semin. Arthritis Rheum.* **2010**, *40*, 241–249. [CrossRef]
213. de Souza, R.B.C.; Borges, C.T.L.; Capelozzi, V.L.; Parra, E.R.; Jatene, F.B.; Kavakama, J.; Kairalla, R.A.; Bonfá, E. Centrilobular Fibrosis: An Underrecognized Pattern in Systemic Sclerosis. *Respiration* **2009**, *77*, 389–397. [CrossRef] [PubMed]
214. Venalis, P.; Kumánovics, G.; Schulze-Koops, H.; Distler, A.; Dees, C.; Zerr, P.; Palumbo-Zerr, K.; Czirják, L.; Mackevic, Z.; Lundberg, I.E.; et al. Cardiomyopathy in Murine Models of Systemic Sclerosis: Histopathologic Features of Cardiomyopathy in SSc. *Arthritis Rheumatol.* **2015**, *67*, 508–516. [CrossRef]
215. Allanore, Y.; Meune, C. Primary Myocardial Involvement in Systemic Sclerosis: Evidence for a Microvascular Origin. *Clin. Exp. Rheumatol.* **2010**, *28*, S48–S53.

216. Hachulla, A.-L.; Launay, D.; Gaxotte, V.; de Groote, P.; Lamblin, N.; Devos, P.; Hatron, P.-Y.; Beregi, J.-P.; Hachulla, E. Cardiac Magnetic Resonance Imaging in Systemic Sclerosis: A Cross-Sectional Observational Study of 52 Patients. *Ann. Rheum. Dis.* **2009**, *68*, 1878–1884. [CrossRef]
217. Hesselstrand, R.; Scheja, A.; Akesson, A. Mortality and Causes of Death in a Swedish Series of Systemic Sclerosis Patients. *Ann. Rheum. Dis.* **1998**, *57*, 682–686. [CrossRef] [PubMed]
218. Ioannidis, J.P.A.; Vlachoyiannopoulos, P.G.; Haidich, A.-B.; Medsger, T.A., Jr.; Lucas, M.; Michet, C.J.; Kuwana, M.; Yasuoka, H.; van den Hoogen, F.; Te Boome, L.; et al. Mortality in Systemic Sclerosis: An International Meta-Analysis of Individual Patient Data. *Am. J. Med.* **2005**, *118*, 2–10. [CrossRef]
219. Steen, V.D.; Medsger, T.A., Jr. Severe Organ Involvement in Systemic Sclerosis with Diffuse Scleroderma. *Arthritis Rheum.* **2000**, *43*, 2437–2444. [CrossRef]
220. Kahan, A.; Coghlan, G.; McLaughlin, V. Cardiac Complications of Systemic Sclerosis. *Rheumatology* **2009**, *48* (Suppl. S3), iii45–iii48. [CrossRef]
221. Allanore, Y.; Meune, C.; Kahan, A. Outcome Measures for Heart Involvement in Systemic Sclerosis. *Rheumatology* **2008**, *47* (Suppl. S5), v51–v53. [CrossRef] [PubMed]
222. Ferri, C.; Valentini, G.; Cozzi, F.; Sebastiani, M.; Michelassi, C.; La Montagna, G.; Bullo, A.; Cazzato, M.; Tirri, E.; Storino, F.; et al. Systemic Sclerosis: Demographic, Clinical, and Serologic Features and Survival in 1,012 Italian Patients. *Medicine* **2002**, *81*, 139–153. [CrossRef] [PubMed]
223. Purevsuren, M.; Uehara, M.; Ishizuka, M.; Suzuki, Y.; Shimbo, M.; Kakuda, N.; Ishii, S.; Sumida, H.; Miyazaki, M.; Yamashita, T.; et al. Native T1 Mapping in Early Diffuse and Limited Systemic Sclerosis, and Its Association with Diastolic Function. *J. Cardiol.* **2023**, *82*, 100–107. [CrossRef]
224. Bulkley, B.H.; Ridolfi, R.L.; Salyer, W.R.; Hutchins, G.M. Myocardial Lesions of Progressive Systemic Sclerosis. A Cause of Cardiac Dysfunction. *Circulation* **1976**, *53*, 483–490. [CrossRef] [PubMed]
225. Belloli, L.; Carlo-Stella, N.; Ciocia, G.; Chiti, A.; Massarotti, M.; Marasini, B. Myocardial Involvement in Systemic Sclerosis. *Rheumatology* **2008**, *47*, 1070–1072. [CrossRef]
226. Desai, C.S.; Lee, D.C.; Shah, S.J. Systemic Sclerosis and the Heart: Current Diagnosis and Management. *Curr. Opin. Rheumatol.* **2011**, *23*, 545–554. [CrossRef]
227. Tzelepis, G.E.; Kelekis, N.L.; Plastiras, S.C.; Mitseas, P.; Economopoulos, N.; Kampolis, C.; Gialafos, E.J.; Moyssakis, I.; Moutsopoulos, H.M. Pattern and Distribution of Myocardial Fibrosis in Systemic Sclerosis: A Delayed Enhanced Magnetic Resonance Imaging Study. *Arthritis Rheum.* **2007**, *56*, 3827–3836. [CrossRef]
228. Lekakis, J.; Mavrikakis, M.; Emmanuel, M.; Prassopoulos, V.; Papazoglou, S.; Papamichael, C.; Moulopoulou, D.; Kostamis, P.; Stamatelopoulos, S.; Moulopoulos, S. Cold-Induced Coronary Raynaud's Phenomenon in Patients with Systemic Sclerosis. *Clin. Exp. Rheumatol.* **1998**, *16*, 135–140.
229. Meune, C.; Allanore, Y.; Devaux, J.-Y.; Dessault, O.; Duboc, D.; Weber, S.; Kahan, A. High Prevalence of Right Ventricular Systolic Dysfunction in Early Systemic Sclerosis. *J. Rheumatol.* **2004**, *31*, 1941–1945.
230. Kahan, A.; Devaux, J.Y.; Amor, B.; Menkès, C.J.; Weber, S.; Venot, A.; Strauch, G. The Effect of Captopril on Thallium 201 Myocardial Perfusion in Systemic Sclerosis. *Clin. Pharmacol. Ther.* **1990**, *47*, 483–489. [CrossRef]
231. Duboc, D.; Kahan, A.; Maziere, B.; Loc'h, C.; Crouzel, C.; Menkès, C.J.; Amor, B.; Strauch, G.; Guérin, F.; Syrota, A. The Effect of Nifedipine on Myocardial Perfusion and Metabolism in Systemic Sclerosis. A Positron Emission Tomographic Study. *Arthritis Rheum.* **1991**, *34*, 198–203. [CrossRef] [PubMed]
232. Kahan, A.; Jy, D.; Amor, B.; Menkes, C.-J.; Weber, S.; Guerin, F.; Venot, A.; Strauch, G. Pharmacodynamic Effect of Nicardipine on Left Ventricular Function in Systemic Sclerosis. *J. Cardiovasc. Pharmacol.* **1990**, *15*, 249–253. [CrossRef] [PubMed]
233. Gigante, A.; Leodori, G.; Pellicano, C.; Villa, A.; Rosato, E. Assessment of Kidney Involvement in Systemic Sclerosis: From Scleroderma Renal Crisis to Subclinical Renal Vasculopathy. *Am. J. Med. Sci.* **2022**, *364*, 529–537. [CrossRef]
234. Lewandowski, B.; Domysławska, I.; Klimiuk, P.A.; Sierakowski, S. Kidney Crisis in Systemic Sclerosis. *Rocz. Akad. Med. Bialymst.* **2005**, *50* (Suppl. S1), 294–296.
235. Denton, C.P.; Lapadula, G.; Mouthon, L.; Müller-Ladner, U. Renal Complications and Scleroderma Renal Crisis. *Rheumatology* **2009**, *48* (Suppl. S3), iii32–iii35. [CrossRef]
236. Steen, V.D. Kidney Involvement in Systemic Sclerosis. *Presse Med.* **2014**, *43*, e305–e314. [CrossRef]
237. Cole, A.; Ong, V.H.; Denton, C.P. Renal Disease and Systemic Sclerosis: An Update on Scleroderma Renal Crisis. *Clin. Rev. Allergy Immunol.* **2023**, *64*, 378–391. [CrossRef] [PubMed]
238. Chang, M.; Wang, R.J.; Yangco, D.T.; Sharp, G.C.; Komatireddy, G.R.; Hoffman, R.W. Analysis of Autoantibodies against RNA Polymerases Using Immunoaffinity-Purifed RNA Polymerase I, II, and III Antigen in an Enzyme-Linked Immunosorbent Assay. *Clin. Immunol. Immunopathol.* **1998**, *89*, 71–78. [CrossRef]
239. Steen, V.D. Autoantibodies in Systemic Sclerosis. *Semin. Arthritis Rheum.* **2005**, *35*, 35–42. [CrossRef]

240. Santiago, M.; Baron, M.; Hudson, M.; Burlingame, R.W.; Fritzler, M.J. Antibodies to RNA Polymerase III in Systemic Sclerosis Detected by ELISA. *J. Rheumatol.* **2007**, *34*, 1528–1534.
241. Haviv, Y.S.; Safadi, R. Normotensive Scleroderma Renal Crisis: Case Report and Review of the Literature. *Ren. Fail.* **1998**, *20*, 733–736. [CrossRef] [PubMed]
242. Steen, V.D.; Medsger, T.A., Jr. Case-Control Study of Corticosteroids and Other Drugs That Either Precipitate or Protect from the Development of Scleroderma Renal Crisis. *Arthritis Rheum.* **1998**, *41*, 1613–1619. [CrossRef] [PubMed]
243. Sugimoto, T.; Soumura, M.; Danno, K.; Kaji, K.; Kondo, M.; Hirata, K.; Nakazawa, J.; Uzu, T.; Nishio, Y.; Kashiwagi, A. Scleroderma Renal Crisis in a Patient with Anticentromere Antibody-Positive Limited Cutaneous Systemic Sclerosis. *Mod. Rheumatol.* **2006**, *16*, 309–311. [CrossRef]
244. Sugimoto, T.; Sanada, M.; Kashiwagi, A. Is Scleroderma Renal Crisis with Anti-Centromere Antibody-Positive Limited Cutaneous Systemic Sclerosis Overlooked in Patients with Hypertension and/or Renal Dysfunction? *Nephrology* **2008**, *13*, 179–180. [CrossRef] [PubMed]
245. Batal, I.; Domsic, R.T.; Shafer, A.; Medsger, T.A., Jr.; Kiss, L.P.; Randhawa, P.; Bastacky, S. Renal Biopsy Findings Predicting Outcome in Scleroderma Renal Crisis. *Hum. Pathol.* **2009**, *40*, 332–340. [CrossRef]
246. Hudson, M.; Baron, M.; Tatibouet, S.; Furst, D.E.; Khanna, D.; International Scleroderma Renal Crisis Study Investigators. Exposure to ACE Inhibitors Prior to the Onset of Scleroderma Renal Crisis-Results from the International Scleroderma Renal Crisis Survey. *Semin. Arthritis Rheum.* **2014**, *43*, 666–672. [CrossRef]
247. Bose, N.; Chiesa-Vottero, A.; Chatterjee, S. Scleroderma Renal Crisis. *Semin. Arthritis Rheum.* **2015**, *44*, 687–694. [CrossRef]
248. Bütikofer, L.; Varisco, P.A.; Distler, O.; Kowal-Bielecka, O.; Allanore, Y.; Riemekasten, G.; Villiger, P.M.; Adler, S.; EUSTAR collaborators. ACE Inhibitors in SSc Patients Display a Risk Factor for Scleroderma Renal Crisis-a EUSTAR Analysis. *Arthritis Res. Ther.* **2020**, *22*, 59. [CrossRef]
249. Pope, J.E.; Denton, C.P.; Johnson, S.R.; Fernandez-Codina, A.; Hudson, M.; Nevskaya, T. State-of-the-Art Evidence in the Treatment of Systemic Sclerosis. *Nat. Rev. Rheumatol.* **2023**, *19*, 212–226. [CrossRef]
250. Campochiaro, C.; Allanore, Y. An Update on Targeted Therapies in Systemic Sclerosis Based on a Systematic Review from the Last 3 Years. *Arthritis Res. Ther.* **2021**, *23*, 155. [CrossRef]
251. Bukiri, H.; Volkmann, E.R. Current Advances in the Treatment of Systemic Sclerosis. *Curr. Opin. Pharmacol.* **2022**, *64*, 102211. [CrossRef] [PubMed]
252. Volkmann, E.R.; Andréasson, K.; Smith, V. Systemic Sclerosis. *Lancet* **2023**, *401*, 304–318. [CrossRef] [PubMed]

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