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Review article

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Mechanisms of fibrotic tissue remodelling: insights from systemic sclerosis

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Abstract

Systemic sclerosis (SSc) is a prototypical systemic immune-mediated fibrosing disease that affects the skin, the lungs, the heart, the kidneys and the intestinal tract. Similar to many other fibrotic diseases, SSc is associated with high morbidity and mortality and therapeutic options are limited. Fibrosis arises from a complex interplay of vascular damage, inflammation and prolonged, misdirected repair responses. The progressive accumulation of extracellular matrix perturbs the physiological tissue architecture and commonly leads to failure of the affected organs. Understanding the mechanisms of fibrotic tissue remodelling can lead to the identification of preclinical targets. Novel fibrosis-promoting cell subpopulations, the interplay of fibroblasts with B cells and macrophages, the nerve–fibroblast axis, matrikines and matricryptins, senescence, profibrotic transcription factors, developmental pathways and epigenetic tissue memory are all important drivers of fibrotic tissue remodelling that might offer potential for novel therapies to improve outcomes for patients with SSc and possibly other fibrotic conditions.

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Key points

- The pathogenesis of systemic sclerosis (SSc) is characterized by an interplay of vascular damage, autoimmunity-induced inflammation and fibrotic tissue responses.
- These processes are highly interlinked and are active throughout all stages of the disease, although their relative contribution to disease progression can vary at different disease stages and in different patient populations.
- Advances in omics technologies have enabled identification and phenotyping of different cellular subpopulations with diverse functions in the pathogenesis of SSc.
- Interactions between leukocyte subpopulations, such as B cells and macrophages, and fibroblasts have an important role in disease progression.
- Molecular drivers of SSc include, but are not limited to, the nerve–fibroblast axis, matrikines, senescence, JAK–STAT signalling, nuclear receptors and other profibrotic transcription factors, developmental pathways and epigenetic tissue memory.

Introduction

Fibrosis describes the excessive deposition of collagen and other extracellular matrix (ECM) components in tissues. The accumulating ECM disrupts the normal tissue architecture and impairs organ function. Fibrotic tissue remodelling can affect almost every organ system. Moreover, fibrotic tissue responses are not limited to prototypical fibrotic disorders but are also highly prevalent in many chronic diseases, including cardiovascular diseases, chronic inflammatory diseases and cancer[1–3], in which these responses have a crucial impact on disease outcomes. Indeed, up to 45% of all deaths in developed countries might be attributed to fibrotic tissue responses[4]. Thus, fibrosis represents a substantial health care challenge, particularly as the incidence of fibrotic diseases is increasing further[1].

Fibrosis and normal wound healing share many commonalities and fibrotic diseases might be considered an exacerbated, prolonged repair response that is not appropriately terminated[5,6]. Fibrotic tissue remodelling can be divided into different, though overlapping phases: a triggering event in a genetically susceptible individual; an initiating phase, in which the trigger is converted into molecular responses and first histopathological changes; a phase of progression, in which type 2 inflammation and vascular damage promote fibroblast activation and fibrotic remodelling; and a late phase, which is highly variable and can range from mild-to-moderate regression of fibrosis. The latter phase occurs in every tissue; however, this phase is variable. In the skin, this phase can be associated with regression owing to ongoing inflammation-induced remodelling, persistent activation of profibrotic fibroblast subsets and progressive fibrosis driven by endogenous mechanisms independent of overt inflammation. This regression does not occur in the lungs[2,7,8].

Fibrosis can manifest in diverse ways depending on its localization within the tissue, the extent of remodelling[9] and the specific anatomical compartment or organ involved. In the skin, localized fibrotic disorders include lichen sclerosus, which primarily affects the anogenital region and is characterized by fibrosis in the upper layers of the dermis[10], morphea, which is associated with widespread fibrosis in the dermis[11] and types of scarring alopecia, such as discoid lupus erythematosus (fibrosis surrounds hair follicles and often leads to permanent hair loss and fibrosis), or hidradenitis suppurativa (scarring occurs at sites of prior inflammation[12]). By contrast, generalized and diffuse cutaneous fibrosis, often accompanied by internal organ involvement, is characteristic of systemic sclerosis (SSc).

In this Review, we discuss the molecular mechanisms that mediate fibrotic tissue remodelling in SSc as a prototypical immune-mediated systemic fibrotic disease. We focus on mechanisms that promote fibroblast activation at disease initiation and progression, and also on intrinsic mechanisms that can drive fibroblast activation and disease progression at later stages of disease. We highlight intracellular signalling cascades and molecular pathways that have not yet been translated into clinical trials; we do not explore core pathways of fibrosis such as canonical transforming growth factor-β (TGFβ), platelet-derived growth factor (PDGF), interferon or IL-6 signalling, for which molecular targets are currently under investigation in clinical trials and are reviewed elsewhere[2,6,13].

Fibroblasts in fibrotic tissue remodelling

Fibroblasts are key effector cells of fibrotic remodelling as they release the vast majority of ECM components that accumulate in fibrotic tissues[2,14,15]. The differentiation of disease-promoting fibroblast populations and/or different fibroblast states is thought to be initially driven by mediators released from infiltrating immune cells such as B cells, T cells and innate lymphoid cells, activated tissue-resident cells such as macrophages and plasma cells, and also from damaged endothelial cells. However, the role of fibroblasts extends beyond the synthesis of the ECM[16]. Fibroblasts also release mediators that modulate inflammatory responses, which might support the maintenance of chronic, low-grade inflammation in affected tissues. Moreover, fibroblasts can release pro-angiogenic and anti-angiogenic mediators that can modulate angiogenesis and thus alter the outcome of microvascular manifestations of SSc. Last, fibroblasts can release both profibrotic and antifibrotic mediators that can exert autocrine and paracrine effects. Fibroblasts in SSc and other fibrotic diseases are thus not passively converting stimuli from inflammatory cells and vascular cells into ECM production, but they themselves actively modulate the vascular, inflammatory and fibrotic pathogenesis of SSc[2].

Fibroblast heterogeneity in systemic sclerosis

Omics-based phenotyping data have revealed that fibroblasts are a heterogeneous population of phenotypically and functionally distinct subpopulations, even within a given patient and a given tissue[17] (Table 1 and Fig. 1). Certain fibroblast subpopulations are ubiquitous and can be found across all organs, whereas other fibroblast subpopulations and/or fibroblast states are restricted to certain tissues under homeostatic conditions[18]. In disease, the ratios of these individual fibroblast subpopulations can change dramatically, individual populations can show changes in phenotype and additional populations might emerge. Although omics studies have been highly informative and provided insights into fibroblasts biology, these findings are limited by the variations in fibroblast nomenclature used in each study[18–20]; however, efforts have been made to link and standardize nomenclature and definitions of specific fibroblast populations across human tissues[20]. Using skin as a reference tissue, the authors of this study defined six major fibroblast subsets in healthy skin along with three subsets in

Table 1 | Major fibroblast subsets

Subtype	Main markers or genes	Identification method	Localization in tissue	Function	Refs.
Superficial fibroblasts	*COL18A1, COL23A1, SFRP2, WIF1, APCDD1* and *NKD2*	scRNA-seq	Superficial papillary dermis	Possible role in epithelial homeostasis via interactions with the epithelium	20–24,104
Universal fibroblasts	*CD34*, *PI16* and *DPP4*	scRNA-seq	Deep in the skin (reticular dermis)	Found in many tissues and postulated to represent a precursor fibroblast state	17,22–26,28,47
Universal fascial fibroblasts	*CD34, PI16, DPP4, FGF18* and *CCN3*	scRNA-seq	Fascia	High expression of the myofibroblast gene signature and high ECM production	17,20,23, 25,26,28,47
Stroma[+]*PPARG*[+] fibroblasts	*CD34, PI16, CXCL12, APOE, PLA2G2A, C7* and *SFRP2*	scRNA-seq	Deep perivascular immune infiltrate regions and interstitial stroma	The capability to differentiate into adipocytes	20,23,25,26,28, 47,124–126,152
Fibroblastic reticular cell-like fibroblasts	*CCL19, CH25H, IL33, CD74* and *HLA-DR*	scRNA-seq	Found in lymphoid organs and structures, enriched in superficial perivascular regions and adjacent to hair follicles in the skin	Maintenance of T cell populations and facilitation of T cell–dendritic cell interactions	20,26
Schwann-like fibroblasts					
Schwann-like *RAMP1*^{+} fibroblasts	*RAMP1* and *PLEKHA6*	scRNA-seq	Enriched near eccrine (sweat) glands	Possibly form an interface with the nervous system	20
Schwann-like *NGFR*[+] fibroblasts	*NGFR* and *ITGA6*	scRNA-seq	Endoneurium and perineurium of nerve fibres	Nerve-associated fibroblast population	20,99
Myofibroblasts					
Classical myofibroblasts	*COL3A1, COL5A1, COL8A1, POSTN, TNC, ACTA2* and *SPARC*	scRNA-seq	Diffuse in the dermis	Excessive ECM production, typically enriched in skin diseases with high scarring risk and in established fibrosis	20,24
Inflammatory myofibroblasts	*CXCL5, CXCL6, CXCL8, CXCL13, IL11, IL24, MMP1* and *MMP3*	scRNA-seq	Diffuse in the dermis	Recruitment of neutrophils, monocytes and B cells, typically enriched in skin diseases with a high scarring risk, but not in established fibrosis	20,26, 51,63,64
Mechanosensing myofibroblasts	*SFRP4, LRRC17* and *PIEZO2*	scRNA-seq	Precise location remains to be determined	Excessive ECM production, mechanotransduction and associated with disease or wound healing	20
Fascia-like myofibroblasts	*ITGA10, THBS* and *PDLIM3*	scRNA-seq	Precise location remains to be determined	Excessive ECM production, present especially in Dupuytren contracture and associated with disease or wound healing	20
Lung fibroblasts					
Alveolar fibroblasts	*COL13A1, NDNF, TCF21, PDGFRA, FGF10* and *COL13A1*	scRNA-seq	Alveoli	Contribute to the maintenance of alveolar structure and function	35,37,50, 96–98
Hair follicle-associated fibroblasts					
DPEP1[+] dermal sheath fibroblasts	*DPEP1* and *MYL4*	scRNA-seq	Dermal sheath	Precise function remains to be determined	12,20
TNN[+]*COCH*[+] fibroblasts	*CRABP1, RSPO3, COL24A1, TNN, COCH, MKX* and *TNMD*	scRNA-seq	Isthmus (mid-hair shaft)	Precise function remains to be determined	12,20
HHIP[+] dermal papilla fibroblasts	*CRABP1, RSPO3, COL24A1, HHIP* and *RSPO4*	scRNA-seq	Dermal papillae	Precise function remains to be determined	12,20–22
Fibroblasts described in SSc					
LGR5[+] fibroblasts	*LGR5, MMP2* and *CD55*	scRNA-seq	Deep reticular dermis	Associated with several pathogenic features of SSc	28
PI16[+] fibroblasts	*PI16*	scRNA-seq	Diffuse in the dermis	Homeostatic, precursors for other fibroblast subsets	18,26,27,29

Table 1 (continued) | Major Fibroblasts subsets

Subtype	Main markers or genes	Identification method	Localization in tissue	Function	Refs.
Fibroblasts described in SSc (continued)					
CCL19⁺ fibroblasts	*CCL19*, *PTGDS*, *APOE*	scRNA-seq	Perivascular or diffuse in the dermis	Pro-inflammatory	25,27
COL11A1⁺ fibroblasts	*COL11A1*, *TAGLN*, *POSTN*	scRNA-seq	Precise location remains to be determined	Profibrotic	27
SFRP4⁺ *SFRP2*⁺ fibroblasts	*SFRP4*, *MFAP5*, *C1QTNF3*	scRNA-seq	Precise location remains to be determined	Profibrotic	27
PRSS23⁺*SFRP2*⁺ fibroblasts	*PRSS23*, *DPP4*, *STC2* and *CTHRC1*	scRNA-seq	Precise location remains to be determined	Profibrotic	27
COL8A1⁺ fibroblasts	*COL8A1* and *ACTA2*	scRNA-seq	Deep dermis	Profibrotic	25
SFRP2⁺ PapD fibroblasts	*SFRP2*, *COL6A1* and *APCDD1*	scRNA-seq	Papillary dermis	Profibrotic	24–26
SFRP2⁺ RetD fibroblasts	*SFRP2*, *SPAR* and *COL1A1*	cISH	Reticular dermis	Profibrotic	26
CCL19⁺ PV fibroblasts	*CCL19*, *MALAT1* and *CD74*	cISH	Perivascular	Pro-inflammatory	26
CCL19⁺ non-PV fibroblasts	*CCL19*, *PTGDS* and *APOE*	cISH	Diffuse localization in the dermis	Pro-inflammatory	26,27
S1PR⁺ fibroblasts	S1PR	IMC	Diffuse localization in the dermis	Profibrotic	30
Thy1⁺ADAM12^{high}PU.1^{high} fibroblasts	Thy1, ADAM12 and PU.1	IMC	Diffuse localization the dermis	Probably profibrotic	30,124
ADAM12⁺ GLI1⁺ fibroblasts	ADAM12 and GLI1	IMC	Papillary dermis	Probably profibrotic	30
Met^{hi} fibroblasts	Several key enzymes that are involved in glycolysis, the TCA cycle and OXPHOS	IMC	Diffuse localization in the dermis	Profibrotic	30,31

ADAM12, a disintegrin and metalloproteinase domain-containing protein 12; cISH, chromogenic in situ hybridization; ECM, extracellular matrix; GLI, glioma-associated oncogene homologue 1; IMC, imaging mass cytometry; Met, metabolism; OXPHOS, oxidative phosphorylation; PapD, papillary dermis; PV, perivascular; RetD, reticular dermis; S1PR, sphingosine-1-phosphate receptor; scRNA-seq, single-cell RNA sequencing; SSc, systemic sclerosis; TCA, tricarboxylic acid.

inflammatory states that often have distinct distribution in the skin (Table 1 and Fig. 1). These subsets included two major subsets of superficial fibroblasts (often referred to as papillary dermal fibroblasts[21–23]) and universal fibroblasts that are typically located deeper in the skin (often referred to as reticular fibroblasts[23,24]). Other subsets were more specialized and included fibroblastic reticular cells (FRCs), which are found in lymphoid organs, perivascular regions and adjacent to hair follicles. Stromal fibroblasts were found in deeper perivascular and interstitial regions, and hair follicle-associated fibroblasts and Schwann-like fibroblasts were enriched near sweat glands and nerves. The three fibroblast subsets identified in diseased tissues include inflammatory myofibroblasts (which express multiple chemokines, particularly those involved in neutrophil recruitment), myofibroblasts, and fascia-like myofibroblasts. In addition, these fibroblast subsets were used to derive a consensus nomenclature across human tissues, across diverse tissues such as the intestine, lungs, salivary glands, joints and skin[20].

Several subpopulations of fibroblasts have been described in SSc, which differ with regard to their location and function (Table 1). Myofibroblasts in SSc (which express high levels of *COL8A1*) seem to be derived from *SFRP2*⁺ fibroblasts[25], which correspond to either the superficial or universal fibroblast subsets described previously. Two subpopulations of *SFRP2*⁺ fibroblasts have been identified that can be separated based on both their gene expression and that of neighbouring cells using the spatial resolution provided by cyclic in situ hybridization (cISH)[26]. One *SFRP2*⁺ fibroblast subpopulation is located in the papillary dermis, whereas the other is located in the reticular dermis. Although these subpopulations have distinct changes in frequency in SSc, both upregulate profibrotic signalling pathways[26]. Another population of *CCL19*⁺ fibroblasts that have an inflammatory phenotype have been described in SSc and resemble the inflammatory fibroblasts described previously[27]. These *CCL19*⁺ fibroblasts can be segregated by cISH according to their localization to either the perivascular region or diffusely in the dermis[26]. The number of *LGR5*⁺ fibroblasts is lower in patients with diffuse cutaneous SSc (dcSSc) compared with patients who have limited cutaneous SSc (lcSSc) and healthy individuals[28]. In addition to changes in frequency, these fibroblasts also have altered signalling pathways related to fibrosis, vasculopathy and inflammation. Several studies show that *PI16*⁺ fibroblasts are present across several organs, have stem-cell properties and can differentiate into specialized fibroblasts[18,29]. The frequency of *PI16*⁺ fibroblasts is also lower in SSc skin than in healthy skin, as these cells can serve as a potential source of profibrotic fibroblasts, the lower number of these cells in SSc could indicate the differentiation of these cells into profibrotic fibroblasts[26,27].

The annotation of fibroblasts using single-cell RNA sequencing (scRNA-seq) or cISH in SSc has been refined by imaging mass cytometry (IMC), a spatial proteomics technique that has enabled the identification of 13 fibroblast subsets; the frequency of 8 of these subsets was altered in SSc[30]. Of these, a population of sphingosine-1-phosphate receptor (S1PR⁺) fibroblasts had a higher frequency in both the papillary and the reticular dermis in SSc than in healthy individuals. This finding

correlated with the modified Rodnan skin score, particularly when not only the cellular frequency but also the interactions of S1PR$^+$ fibroblasts with other cell types, such as ADAM12$^+$ GLI1$^+$ fibroblasts, were taken into consideration.

In another study, thus far available only as a preprint, IMC enabled the identification of 8 metabolically defined subpopulations of fibroblasts in SSc that differ with regard to their metabolic regulome (composed of over 20 key enzymes across several metabolic pathways)[31]. One subpopulation of Met^{hi} (that is, metabolically active) fibroblasts had high glycolysis, hypoxia, reactive oxygen species signalling and tricarboxylic acid (TCA) and oxidative phosphorylation scores (indicative of the high level of activity of these pathways)[31]. Furthermore, these cells expressed high levels of α-smooth muscle actin (αSMA) and fibroblast activation protein (FAP), and thus had

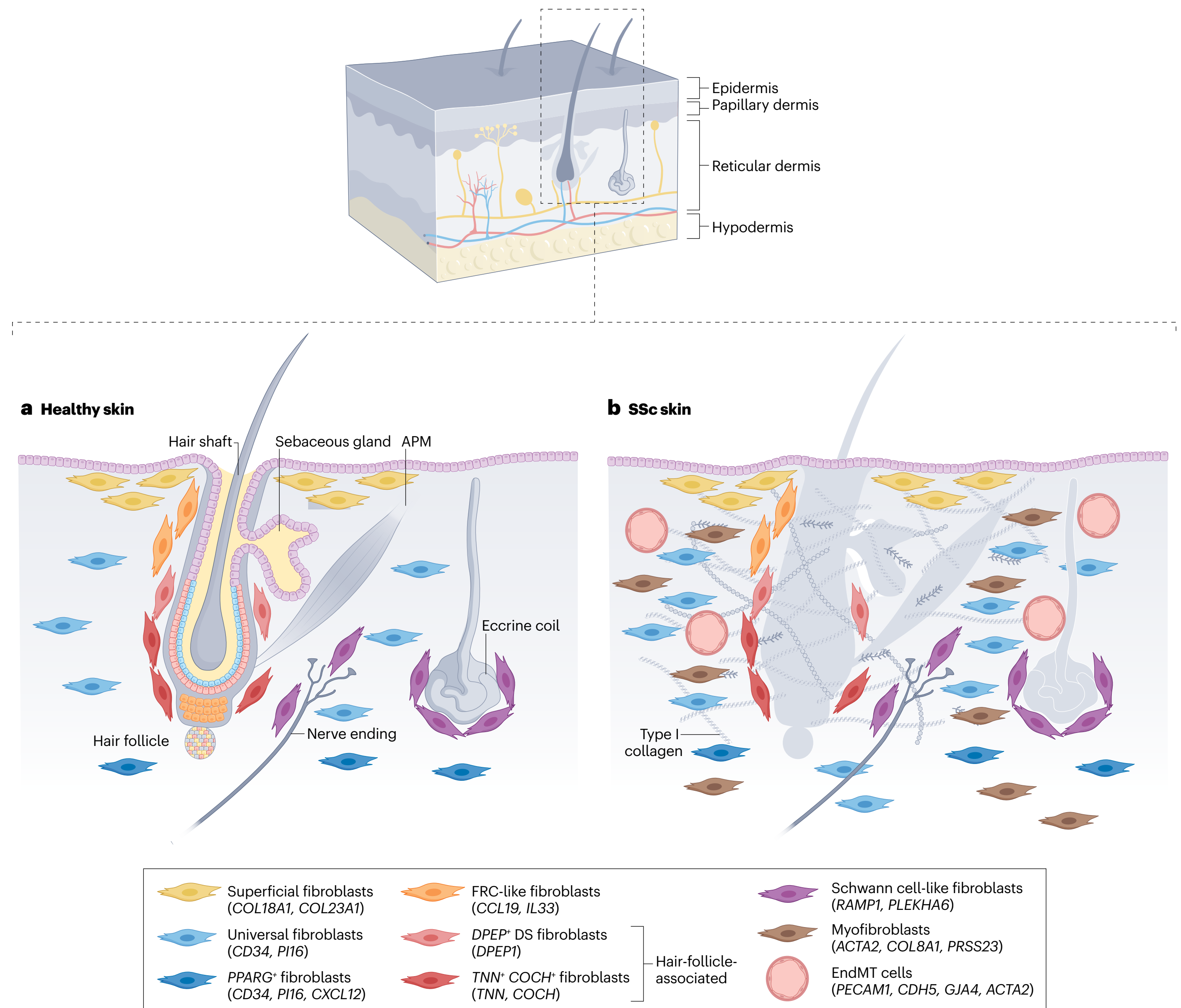

Fig. 1 | Localization and diversity of fibroblast subsets in healthy skin and skin with systemic sclerosis. a, Fibroblast subpopulations in the skin have distinct spatial distributions. Superficial fibroblasts (yellow) are located in the papillary dermis, whereas universal fibroblasts (light blue) are distributed throughout the dermis, with *PPARG*$^+$ fibroblasts (dark blue) enriched in the deeper layers of the dermis. Several fibroblast subsets localize to hair follicles, including fibroblastic reticular cell (FRC)-like fibroblasts (orange) around the follicle opening, and two other subsets (shown in dark red and light red) are located along the follicular shaft and bulge region. Other specialized fibroblasts are found near eccrine glands or nerve endings, such as Schwann cell-like fibroblasts (purple), underscoring the functional and positional heterogeneity of dermal fibroblasts. **b**, In systemic sclerosis (SSc), several fibroblast subsets expand, particularly αSMA$^+$ (α smooth-muscle actin) myofibroblasts (brown) and endothelial-to-mesenchymal transition (EndMT) cells, both of which contribute to type I collagen production and deposition in the skin. Fibrosis in SSc skin is often accompanied by loss of adnexal structures, including hair follicles, sebaceous and eccrine sweat glands. APM, arrector pili muscle; DS, dermal sheath.

a myofibroblast phenotype, but could not be separated from other populations by expression of αSMA and FAP alone. This population is increased in frequency in those patients with SSc and progression of skin fibrosis[31].

The activation of fibroblasts in SSc is driven by a core set of signalling pathways. Traditionally, core signalling pathways of fibroblast activation have been defined as stimuli that can induce a myofibroblast phenotype in resting fibroblasts with upregulation of ECM proteins such as type I collagen and induction of αSMA positive stress fibres that mediate contractility. However, this definition might miss pathways that drive the progression of fibrosis by inducing shifts from homeostatic subpopulations to pro-inflammatory or profibrotic subpopulations and those that promote the differentiation of disease-associated fibroblast populations. Although omics-based profiling shows unique patterns of signalling for each of these fibroblast subpopulations, a deeper understanding of the effects of core fibrosis pathways on individual subpopulations is lacking and how targeting these core pathways affects the numbers and function of fibroblasts remains unclear.

Vasculature–fibroblast crosstalk in systemic sclerosis

The first manifestation of SSc is apoptosis of the microvascular endothelium. Apoptotic microvascular endothelial cells are detected in preclinical models of SSc before the onset of typical clinical manifestations and before inflammatory and fibrotic changes[32]. The precipitating trigger and the molecular mechanisms underlying the induction of apoptosis remain enigmatic. Whether the induction of apoptosis in endothelial cells is a direct consequence of this trigger or a consequence of a misdirected autoimmune response against endothelial cells is unclear; however, autoantibodies directed against different antigens expressed on endothelial cells are reported in SSc[33,34]. These antibodies might maintain chronic vascular injury even after clearance of the trigger. An increase in granzyme-expressing cytotoxic CD4$^+$ and CD8$^+$ T cells colocalizing with apoptotic endothelial cells is described in the skin of patients with early dcSSc, suggesting a direct role of cytotoxic T cells in endothelial cell death[35].

Evidence indicates that vascular injury promotes fibroblast activation in SSc. Platelets are activated at sites of vascular injury in SSc, which leads to the release of platelet granules into the blood. Platelet granules contain large amounts of serotonin (5-hydroxytryptamine (5-HT)) and lower concentrations of other profibrotic mediators including PDGF[36]. 5-HT has been implicated in the pathogenesis of fibrotic tissue remodelling in multiple organs[37]. Stimulating mesenchymal cells with 5-HT in vitro can induce collagen production. These effects are mediated by 5-HT2 receptors, particularly the 5-HT2B receptor, which can activate TGFβ–SMAD3 signalling[38]. Pharmacological or genetic inactivation of the 5-HT2B receptor or knockout of *TPH1*, which encodes tryptophan hydroxylase (the rate-limiting enzyme for 5-HT synthesis in non-neuronal tissues), ameliorates experimental dermal and pulmonary fibrosis[38,39]. Moreover, activated platelets upregulate thymic stromal lymphopoietin (TSLP) in microvascular endothelial cells and might thereby contribute to the increased levels of TSLP found in the blood of patients with SSc[40]. TSLP promotes fibroblast activation, thus providing another link between platelet activation and fibrotic tissue remodelling in SSc.

Increased coagulation might also promote fibrotic tissue remodelling in different organs, although there is no direct evidence of this mechanism in SSc thus far. Thrombin induces the expression of connective tissue growth factor, stimulates proliferation of fibroblasts and promotes fibroblast-to-myofibroblast transition[41]. Moreover, the thrombin inhibitor dabigatran ameliorates experimental fibrosis in multiple organs[42].

The atypical chemokine receptor 1 (ACKR1), also known as Duffy antigen receptor, has been implicated in tissue inflammation across various organs in SSc. ACKR1 is expressed on postcapillary venules and facilitates chemokine transport[43]. Increased ACKR1 expression is found in lesional SSc skin, where it promotes immune cell recruitment[44]. In the bleomycin model of skin fibrosis, elevated ACKR1 levels are associated with immune cell infiltration and fibrosis, whereas ACKR1 inhibition attenuates this effect[44]. Expansion of venous ACKR1$^+$ endothelial cells also occurs in patients with idiopathic pulmonary fibrosis (IPF)[45]. In fibrotic lungs, ACKR1$^+$ endothelial cells are spatially localized within immune cell aggregates, fibroblastic foci and aberrant basaloid cell regions, consistent with their pro-inflammatory and profibrotic functions.

Endothelial-to-mesenchymal transition describes a phenotypic and functional change of endothelial cells, which includes gradual loss of endothelial markers and expression of mesenchymal cell markers. Cells that co-express endothelial cell markers (vascular endothelial-cadherin and von Willebrand factor) and mesenchymal cell markers (αSMA, collagen and fibroblast-specific protein 1 (also known as S100A4)) have been identified in the skin and lungs of people with SSc[46,47]. Cells that undergo endothelial-to-mesenchymal transition are reported to originate from *GJA4*$^+$ arteriolar endothelial cells, and Hippo signalling promotes this transition[25]. Spatial proteomics analyses of SSc skin support these findings, revealing an increase in CD34$^+$ αSMA$^+$ CD31$^+$ triple-positive cells that express markers of endothelial-to-mesenchymal transition in SSc vascular niches[48]. These niches are also enriched in immune cells and myofibroblasts, and the density of these cells correlates with progressive fibrotic remodelling in patients with SSc[48]. Endothelial-to-mesenchymal transition might therefore add to the pool of profibrotic fibroblast populations that drive fibrotic remodelling in SSc.

Pericytes are stromal cells that warp around endothelial cells in capillaries and post-capillary venules, and together with vascular smooth muscle cells make up the mural cells that support blood vessels in tissues. Pericytes are mainly found around pre-capillary, capillary and post-capillary vessels where they regulate vessel tone and integrity, and influence chemotaxis and diapedesis of leukocytes[49]. In people with early SSc, pericytes have an activated phenotype, possibly owing to a PDGF–PDGF receptor-β autocrine or paracrine loop that involves endothelial cells[50,51] Pericytes might also directly contribute to the production of ECM upon acquisition of a myofibroblast phenotype (pericyte-to-myofibroblast transdifferentiation) or indirectly by promoting fibroblast activation via PDGF-AB or PDGF-BB interacting with the PDGFβ receptor[51].

Autoimmune and inflammation-mediated fibroblast activation in systemic sclerosis

Inflammation is thought to be a key driver of fibroblast activation and fibrosis. Although SSc is not a classical inflammatory disease and markers of systemic inflammation, such as C-reactive protein, are not elevated in two-thirds of patients, low-grade inflammation in affected tissues is essential for disease initiation and a central driver of disease progression.

B cells and T cells

Accumulating evidence highlights a central role of B cells in the pathogenesis of SSc. B cell activation is dysregulated in SSc at multiple levels,

including a bias towards effector B cells with an activated phenotype and impaired regulatory B (B_{reg}) cell function[52,53]. B cells promote fibroblast activation and fibrotic remodelling through multiple mechanisms including release of cytokines, chemokines, autoantibodies and direct cellular interactions with fibroblasts and other effector cells[54] (Fig. 2).

In SSc, naive, transitional and $CD21^{low}CD38^{low}$ peripheral B cell subsets are increased, whereas memory B cells, switched memory B cells and IL-10-producing B_{reg} cells are reduced[53,55]. Memory B cells in SSc express increased levels of activation markers such as CD80, CD86 and CD95, and transitional B cells have increased expression of TIM1. Decreased expression of CD22 and elevated CD19 expression further dysregulate B cell receptor signalling[56], skewing B cell populations towards an activated phenotype in SSc.

B cells and plasma cells are increased in tissue samples obtained from the skin, lung and gastrointestinal tract of people with SSc[57,58]. Consistently, pronounced B cell signatures enriched in immunoglobulin genes are observed in SSc skin, particularly in patients with early dcSSc[59]. Dermal B cell extravasation probably involves endothelial E-selectin interacting with cutaneous lymphocyte antigen and α4β1 integrin. In SSc-related interstitial lung disease (SSc-ILD) and pulmonary arterial hypertension $CD19^{+}$ B cells are increased, and some of

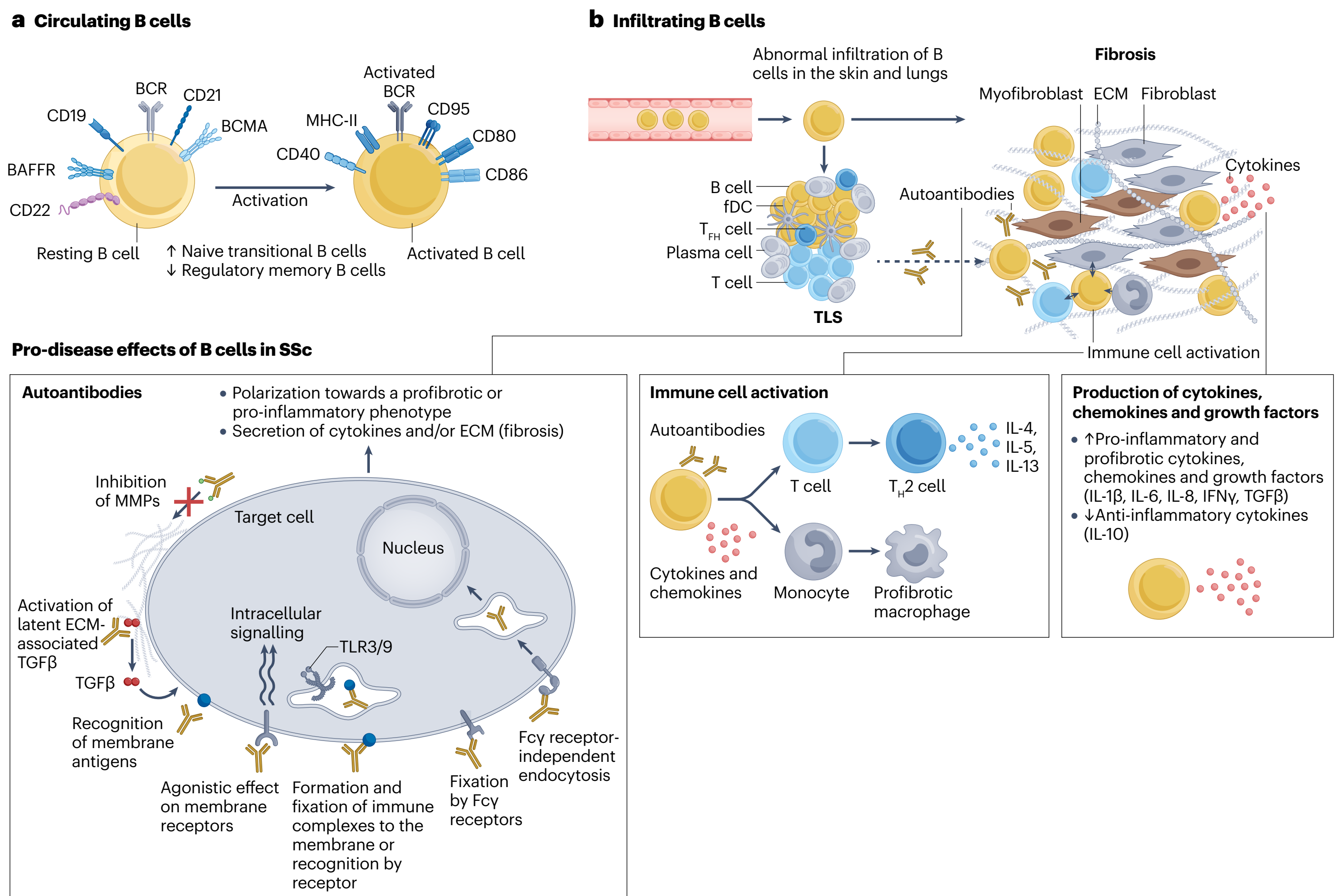

Fig. 2 | Role of B cells in the pathophysiology of systemic sclerosis. **a**, Peripheral B cell populations in systemic sclerosis (SSc) are skewed towards increased naive and transitional B cells, with reduced memory B cells and IL-10-producing regulatory B cells. B cells, particularly memory subsets, exhibit elevated expression of activation markers (CD80, CD86, CD95), decreased regulatory CD22 expression and increased CD19 expression. Those receptors shown in blue are increased on B cells in SSc and those shown in purple are decreased. **b**, Abnormal infiltration of B cells characterizes skin and lung tissues in SSc and these cells can form immune-cell aggregates that might resemble tertiary lymphoid structures (TLSs). In the skin, B cell extravasation probably involves E-selectin expressed on dermal endothelial cells, E-selectin ligands (such as cutaneous lymphocyte antigen) and α4β1 integrin on B cells. Through secretion of pro-inflammatory cytokines (including IL-6, TNF and IL-13) and chemokines, infiltrating B cells activate fibroblasts, endothelial cells and other immune cells. Tissue-resident B cells also interact with non-immune cells, modulating SSc-related fibrosis. Additionally, infiltrating B cells perpetuate disease through autoantibody production. B cells produce autoantibodies, including autoantibodies that activate fibroblasts and polarize them towards profibrotic or pro-inflammatory, disease-promoting phenotypes. B cell and T cell interactions contribute to sustained inflammation and autoimmunity in SSc. B cells present self-antigens and provide co-stimulatory signals to $CD4^{+}$ T cells, promoting a T helper 2 (T_H2) cell immune response characterized by IL-4, IL-5 and IL-13 production. B cells also stimulate macrophages to adopt a profibrotic phenotype. B cells release pro-inflammatory and profibrotic cytokines, chemokines and growth factors that further promote fibrosis. BAFFR, BAFF receptor; BCR, B cell receptor; ECM, extracellular matrix; fDC, follicular dendritic cell; MMPs, matrix metalloproteinases; T_{FH} cell, T follicular helper cell; TGFβ, transforming growth factor-β.

these cells are then organized into tertiary lymphoid structures[60,61]. Lung-resident B cells in SSc include $CD19^{+}CD21^{low/neg}$, IgM^{+} and $CD138^{+}CX3CR1^{+}$ plasma cells[62].

Secretion of cytokines is a central mechanism by which B cells activate fibroblasts and other immune cells. Elevated expression of IL-6 in B cells correlates with progressive fibrotic remodelling, particularly in patients with early SSc[63]. High levels of IL-8, IL-1β, B cell activating factor (BAFF), CXCL13 and granulocyte–macrophage colony-stimulating factor (GM–CSF) are also associated with severe fibrosis[52,64]. Ex vivo studies show that B cells derived from people with SSc can infiltrate healthy skin and induce a pro-inflammatory fibroblast phenotype reminiscent of pro-inflammatory fibroblast subpopulations in SSc skin via TNF signalling[65]. In the lung, B cell–fibroblast interactions promote fibrotic remodelling via cytokines such as TNF and IL-1β[66].

Autoantibodies contribute to the pathophysiology of SSc via multiple mechanisms[67]. Functional autoantibodies that recognize platelet-derived growth factor receptor, endothelin receptor type A or type 1 angiotensin II receptor can bind to cell-surface receptors to activate profibrotic intracellular signalling cascades in fibroblasts and other target cells. Anti-Scl70 antibodies (also known as anti-topoisomerase I antibodies) can disrupt DNA cleavage complexes to promote fibroblast activation[68,69]. Moreover, anti-Scl70 IgG antibody could interfere with the normal interaction between Scl70 autoantigen and CCR7 on fibroblasts[70]. Immune complexes formed by anti-Scl70 antibodies and other autoantibodies can also engage Toll-like receptors on fibroblasts, subsequently triggering pro-inflammatory and profibrotic signalling cascades[71]. Consistent with these findings, IgG anti-Scl70 antibodies from patients with SSc can induce pro-inflammatory and profibrotic transcriptomic and proteomic shifts in healthy fibroblasts[72] and in endothelial cells[73]. Moreover, immunization of mice with human Scl70 antigen and complete Freud's adjuvant induces the production of anti-Scl70 antibodies and subsequent development of dermal and pulmonary fibrosis[74]. B cells with high affinity for Scl70 induce more pronounced upregulation of profibrotic cytokines and more extensive fibrotic remodelling, whereas low-affinity antibodies or inhibition of cytokine production ameliorate fibrosis[75]. Translation of these findings from bench to bedside and clinical trials that target B cells and autoantibodies in SSc have been reviewed elsewhere[13].

T cells also have a key role in SSc. Activated T cells in SSc are predominantly T helper 2 (T_H2) cells, which produce IL-4 and IL-13 and can trigger the activation of adjacent fibroblasts to promote fibrosis[76]. Cytotoxic $CD4^{+}$ T cells accumulate in the skin of patients with SSc and can induce endothelial-cell apoptosis[35]. A heterogeneous subset of effector memory $CD8^{+}KLRB1^{+}IL\text{-}7R^{+}$ cells characterized by increased cytolytic Tc2 and Tc17 effector functions were identified in early dcSSc skin lesions and seemed to induce tissue damage and fibrosis[77]. Although the pathophysiological role of T_H17 cell cytokines is currently less well understood, IL-17 producing T_H17 cells are upregulated in dcSSc, which contributes to the immune imbalance in SSc.

Interactions between B cells and T cells perpetuate inflammation and autoimmunity in SSc. B cells present antigens and provide co-stimulation to $CD4^{+}$ T cells, enhancing follicular helper T (T_{FH}) cell activation, IL-21 secretion and autoantibody production[78]. In SSc, T_{FH} cells are hyperactivated, express elevated levels of immunostimulatory molecules such as inducible T cell co-stimulator (ICOS) and PD-1 and promote type 2 humoral immune responses. A unique $CD4^{+}$ T cell subset characterized by the expression of CXCL13 and IL-21 in addition to a T_{FH} cell-like gene expression signature has been identified using scRNA-seq; this subset seemed poised to promote B cell responses within the inflamed skin of patients with SSc[79].

Thus, B cells and T cells have important roles in the pathophysiology of SSc. In particular, B cell activation and accumulation in organs is key for the activation of resident cells such as fibroblasts and endothelial cells.

Monocytes and macrophages

Activated monocyte and macrophages are key contributors to fibrosis via the release of profibrotic mediators, contact-dependent fibroblast activation and ECM remodelling[80,81] (Fig. 3). Owing to their plasticity, monocytes can dynamically adapt to their tissue environment and exert a broad spectrum of pro-inflammatory and profibrotic responses. Patients with SSc have abnormal circulating monocyte populations characterized by an increased proportion of cells that co-express both pro-inflammatory ($CD80^{+}$ and $CD86^{+}$) and profibrotic ($CD204^{+}$, $CD163^{+}$ and $CD206^{+}$) markers[82]. Notably, patients with SSc and lung involvement exhibit a higher percentage of these abnormal monocytes than those without lung involvement.[83]. Profibrotic macrophage polarization, which is defined by the expression of the scavenger receptor macrophage receptor with collagenous structure (MARCO) and elevated expression of arginase 1, IL-10 and TGFβ, has also been reported in patients with asbestos-induced fibrosis[84]. Experimental studies in mice have confirmed the requirement of MARCO for the development of chrysotile-induced pulmonary fibrosis[84]. Similarly, an increase in $MARCO^{+}$ monocytes and macrophages have been identified in the circulation and lesional skin and lungs of patients with SSc and in the bleomycin-induced mouse model of fibrosis[85]. Preclinical studies further show that administration of poly(lactic-co-glycolic acid) nanoparticles attenuate fibrosis, at least in part, by targeting $MARCO^{+}$ monocytes and macrophages. Although understanding of monocyte and macrophage biology in SSc is still evolving, current studies highlight substantial phenotypic heterogeneity within the myeloid compartment.

The interplay between macrophages and fibroblasts is a central feature of SSc pathogenesis[86]. Soluble mediators present in SSc plasma or secreted via SSc fibroblast-derived exosomes can induce a profibrotic and pro-inflammatory phenotype in monocytes and macrophages[87,88]. Macrophages in turn, particularly those with a profibrotic (formerly referred to as 'M2-like') phenotype, produce cytokines such as TGFβ, IL-6 and CCL2 that activate fibroblasts[87,88]. Circulating monocytes from patients with SSc express low levels of the Friend leukaemia integration 1 (FLI1) transcription factor[89]. FLI1-deficient macrophages can stimulate the expression of collagen in co-cultures with fibroblasts; however, marked phenotypic heterogeneity exists in macrophages, which can make phenotypic classification of these cells challenging.

Activated endothelial cells might also promote macrophage polarization. An increased presence of sialylated IgG that binds to dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin^{+} (DC-SIGN, also known as CD209) and $CD68^{+}$ macrophages has been observed in the perivascular regions of those patients with SSc and a high modified Rodnan skin score[90]. Corresponding in vitro studies show that conditioned medium from IL-1β-treated SSc-derived microvascular endothelial cells induced elevated secretion of IL-6 and endothelin-1. These secreted factors promote the differentiation of monocytes into DC-SIGN^{+} macrophages that produced high levels of CCL2 and CXCL8 but low levels of IL-10. Furthermore, SSc

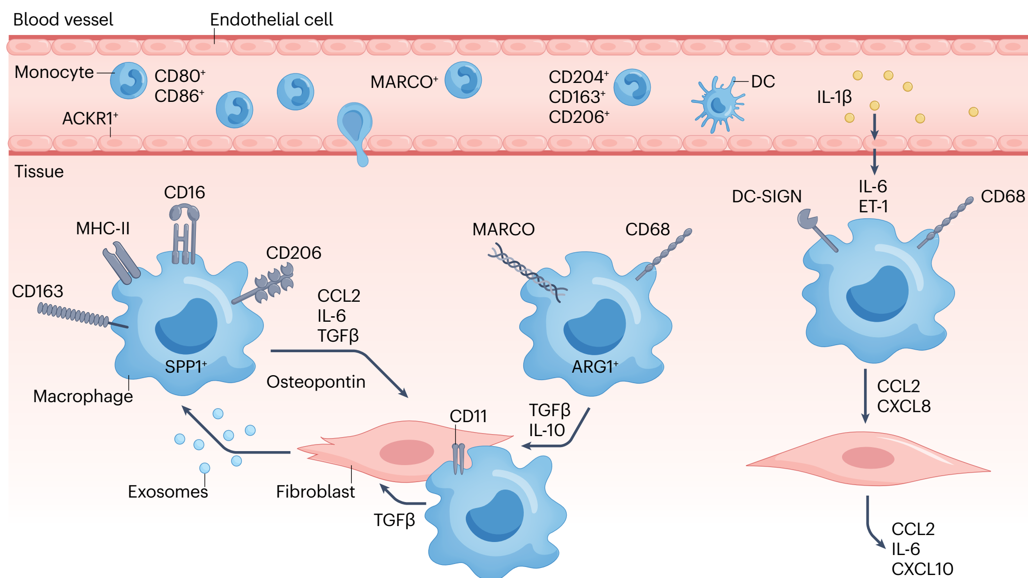

Fig. 3 | Macrophage–fibroblast interactions in fibrotic tissue remodelling in SSc. In systemic sclerosis (SSc), circulating monocytes express both pro-inflammatory (CD80$^+$ and CD86$^+$) and profibrotic (CD204$^+$, CD163$^+$ and CD206$^+$) markers. ACKR1$^+$ endothelial cells facilitate chemokine-mediated recruitment of leukocytes, including monocytes. In tissues, fibroblasts interact with macrophages via direct cell-to-cell contact, as well as soluble mediators. Exosomes derived from SSc fibroblasts stimulate macrophages by increasing surface expression of CD163, CD206, MHC-II and CD16. In turn, activated macrophages (SPP1$^+$ and ARG1$^+$ macrophages) secrete profibrotic cytokines that promote collagen and fibronectin production. Endothelial cells exposed to pro-inflammatory cytokines such as IL-1β also promote differentiation of DC-SIGN$^+$ and CD68$^+$ macrophages, which activate fibroblasts via CCL2 and CXCL8. ACKR1; atypical chemokine receptor 1; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; MARCO, macrophage receptor with collagenous structure.

microvascular endothelial cell-activated DC-SIGN$^+$ macrophages enhanced a pro-inflammatory phenotype in fibroblasts in co-culture experiments[90].

Beyond soluble mediator signalling, macrophages can also activate fibroblasts through direct adhesion via cadherin-11, a transmembrane adhesion molecule expressed on macrophages and fibroblasts in fibrotic skin and lung tissue[91,92]. Cadherin-11 engagement triggers TGFβ signalling, enhancing fibroblast contractility and ECM production.

Several novel monocyte and macrophage subsets associated with SSc have been identified using scRNA-seq. SPP1^{hi} macrophages have emerged as key drivers of fibrosis and immune dysregulation[93–96]. *SPP1* encodes osteopontin, a highly phosphorylated, secreted glycoprotein that can function as both a pro-inflammatory and a profibrotic molecule depending on the disease-specific context. Osteopontin levels are elevated in the serum of patients with SSc and correlate with lung fibrosis and reduced pulmonary function[94]. Notably, a genetic predisposition can contribute to the accumulation of SPP1^{hi} macrophages in SSc. People with SSc who carry a hypofunctional variant of *NCF1*, which encodes the p47phox subunit of the nicotinamide adenine dinucleotide phosphate oxidase complex, are at an increased risk of developing lung fibrosis. Reduced *NCF1* activity is associated with an expansion of SPP1$^+$ macrophages in both patients with SSc and in a bleomycin-induced model of lung fibrosis[96].

Nerve–fibroblast axis

Autonomic and sensory nerves have been studied in the setting of inflammation and immune-cell activation. Noradrenaline produced by the adrenergic nerves in the lungs transmits fibrotic signals to myofibroblasts that express adrenoreceptor α-1D (ADRA1D) in alveolar lung fibrosis in mice[97,98]. This effect can be reversed by administration of the ADRA1D antagonist terazosin. In one study, thus far only available as a preprint, incubation with terazosin also induced the downregulation of fibrotic markers in human precision-cut lung slices[98]. ADRA1D$^+$ alveolar myofibroblasts are detected in lung tissues of patients with SSc-ILD and IPF, and deletion of *Adra1d* in myofibroblasts in vivo in mice attenuates alveolar fibrosis[98]. Netrin-1, derived from macrophages, induces lung fibrosis in mice through neuronal guidance function and by increasing noradrenaline levels, and this profibrotic effect can be blocked by ADRA1D inactivation. Moreover, in a longitudinal IPF cohort, ADRA1D blockade improved patient survival[99]. In addition to noradrenaline, nerve growth factor (NGF) might be implicated in the pathogenesis of fibrosis. NGF enhances fibroblast migration, transition to myofibroblasts and gel contraction (an in vitro model of fibroblast contractibility)[100]; however, NGF can also be antifibrotic as continuous administration of NGF induces myofibroblast apoptosis[100]. In addition, activation of the sympathetic nervous system and production of neuropeptides can indirectly activate fibroblasts by promoting inflammation and production of cytokines from inflammatory cells as shown in cardiac remodelling[101] and other tissues[102,103]. Taken together, these studies implicate sympathetic nerve–fibroblast communication in the pathophysiology of fibrosis.

Matrikines and matricryptins

ECM components including collagens, elastin, fibronectin and laminin are cleaved by different enzymes including cathepsins, matrix metalloproteinases (MMPs), bone morphogenetic proteins and a disintegrin

and metalloproteinases (ADAMs) to release biologically active peptides known as matrikines, which have an important role in tissue remodelling and repair that differs from the role of the parent molecule. The matrikines released as products of partial proteolysis exert pleiotropic effects that modulate cell proliferation, apoptosis, angiogenesis and migration (Supplementary Fig. 1).

Matrikines can exert profibrotic and antifibrotic effects; for example, the cleavage product of collagen type VI, endotrophin, is profibrotic[104], whereas the cleavage product of collagen type XVIII, endostatin, is antifibrotic[105]. Endostatin and an endostatin-derived peptide can reduce fibrosis in experimental dermal and pulmonary fibrosis in mice and in ex vivo cultures of human biopsy-obtained skin and lung samples[105,106]. Although endostatin levels are elevated in the serum of patients with SSc[107], reduced levels of cathepsin L (the main enzyme responsible for cleavage of and also the sequestration of endostatin in extracellular vesicles) might explain why concentrations of endostatin do not reach antifibrotic levels in SSc[108]. Deficiency in certain MMPs that generate matrikines, such as MMP12, might also reduce dermal fibrosis[109]. Thus, targeting pathogenic matrikines using antibodies and/or the enzymes responsible for their generation or boosting the production of beneficial matrikines in fibrosis (such as endostatin) presents a potential novel therapeutic avenue[104].

In addition to the generation of matrikines, enzymatic fragments of ECM molecules can become exposed and bioactive; these sites are referred to as matricryptins[110]. The generation of matricryptins occurs in response to mechanical forces, reactive oxygen species and other processes. Matrikines and matricryptins derived from the same molecule can exert opposite effects; for example, matrikines and matricryptins from SPARC can exert pro-angiogenic and anti-angiogenic effects[110]. To add further complexity, some of these effects are cell-type dependent. Thus, the balance and activity of different matrikines and matricryptins depends on the factors responsible for their release and the tissue and cell context[110].

Senescence

Fibrosis shares features of early or premature senescence. Senescence of activated fibroblasts and myofibroblasts has been described in different fibrosing conditions[111]. Activated fibroblast subpopulations and myofibroblasts can obtain a senescence-associated secretory phenotype (SASP), which includes the release of pro-inflammatory and profibrotic factors (such as IL-1α, IL-1β, IL-6, TGFβ, PDGF and plasminogen activator inhibitor-1)[112]. These factors can promote persistence of the activated fibroblasts by inducing a permissive, profibrotic milieu. Targeted elimination of senescent cells improves pulmonary function in mice[113]. Although the mechanisms leading to the senescent phenotype are incompletely understood, emerging data suggest that senotherapeutics, including senomorphics and senolytics, might be effective for the treatment of fibrosis in SSc. In a study of dasatinib (a multityrosine kinase inhibitor that also has senolytic effects) in patients with SSc, re-analysis of the skin gene-expression profile of those who responded to treatment showed a decrease in the SASP gene signature[114]. Additional research is needed to understand how senescent cells emerge in fibrosis, their exact role in the initiation and/or perpetuation of fibrosis, and the therapeutic potential of eliminating senescent cells in diseased tissues.

Profibrotic transcription factors

Profibrotic signals induce the activation of a network of transcription factors that translate upstream signals into a profibrotic phenotype.

JAK–STAT signalling

Janus kinase 2 (JAK2) has been characterized as a downstream mediator of TGFβ in fibroblasts (Fig. 4). Phosphorylation of JAK2 at 1007/1008 Tyr residues causes fibroblasts to accumulate in skin of patients with SSc. Stimulation of resting fibroblasts with TGFβ induces this JAK2 phosphorylation[115], which provides evidence that TGFβ contributes to the activation of JAK2–signal transducer and activator of transcription 3 (STAT3) signalling in SSc skin. JAK2 activation promotes TGFβ-induced fibroblast-to-myofibroblast transition, which can be prevented by pharmacological or genetic inhibition. Furthermore, inhibiting JAK2 reverses the active phenotype of SSc cells and can also attenuate experimental dermal fibrosis[115]. However, JAK2 can evade inhibition by highly specific JAK2 inhibitors, as JAK1 can *trans*-phosphorylate JAK2, resulting in JAK2 activation. This escape mechanism can be inhibited by using combined JAK1 and JAK2 inhibitors, or selective JAK2 inhibitors in combination with heat shock protein 90 inhibitors, which increase JAK2 degradation[116].

Alternative ways to target TGFβ-induced JAK2–STAT3 signalling in fibrosis might involve the tyrosine phosphatase SHP2 (Src homology 2 domain-containing protein tyrosine phosphatase-2) and the serine-threonine kinase CKII. TGFβ enhances SHP2 recruitment to JAK2 and stimulates tyrosine phosphatase activity, which leads to the dephosphorylation of the inhibitory phosphorylation site Y570 of JAK2 and activation of STAT3. Inactivating SHP2 increases Y570 phosphorylated JAK2, decreases JAK2–STAT3 signalling, suppresses TGFβ-induced fibroblast activation and improves experimental dermal and pulmonary fibrosis[117]. CKII expression is also upregulated in SSc fibroblasts[118]. Inhibiting CKII reduces TGFβ-induced JAK2 phosphorylation and STAT3 accumulation in fibroblasts, which prevents fibroblast-to-myofibroblast transition and experimental fibrosis[118].

STAT3 is an essential downstream mediator of JAK1 and JAK2, but it also integrates signals from other profibrotic kinases such as SMAD3, SRC, ABL and JNK[115,119–122]. Consistently, fibroblast-specific inducible knockout or pharmacological inhibition of STAT3 reduces TGFβ-induced fibroblast-to-myofibroblast transition and collagen release in vitro and ameliorates experimental skin fibrosis[123]. Thus, inhibition of JAK–STAT3 signalling can limit fibroblast activation and fibrotic tissue remodelling in SSc. Translation of these findings into clinical trials is reviewed elsewhere[13].

PU.1

PU.1, also known as SPI1, is a transcription factor of the E26 transformation-specific family. Under homeostatic conditions, the expression of PU.1 is largely restricted to macrophages, and resting fibroblasts lack PU.1 owing to epigenetic repression. However, the tight epigenetic control of PU.1 in fibroblasts is perturbed in fibrotic tissues, such as the skin in SSc, leading to PU.1 expression in certain fibroblast subpopulations. PU.1 induces the expression of profibrotic genes in fibroblasts and promotes fibroblast-to-myofibroblast transition as it can regulate profibrotic gene-expression programmes[124]. Notably, forced overexpression of PU.1 is not only sufficient to induce a fibroblast-to-myofibroblast differentiation in resting fibroblasts but also induces a fibrotic phenotype in inflammatory fibroblasts isolated from inflamed joints of patients with rheumatoid arthritis. Fibroblast-specific, inducible knockout of PU.1 prevents fibroblast-to-myofibroblast transition and ameliorates experimental fibrosis in multiple organs. Small molecule inhibitors of PU.1 can exert potent antifibrotic effects[124]; however, PU.1 inhibitors with sufficient pharmacokinetics for use in humans are currently not available.

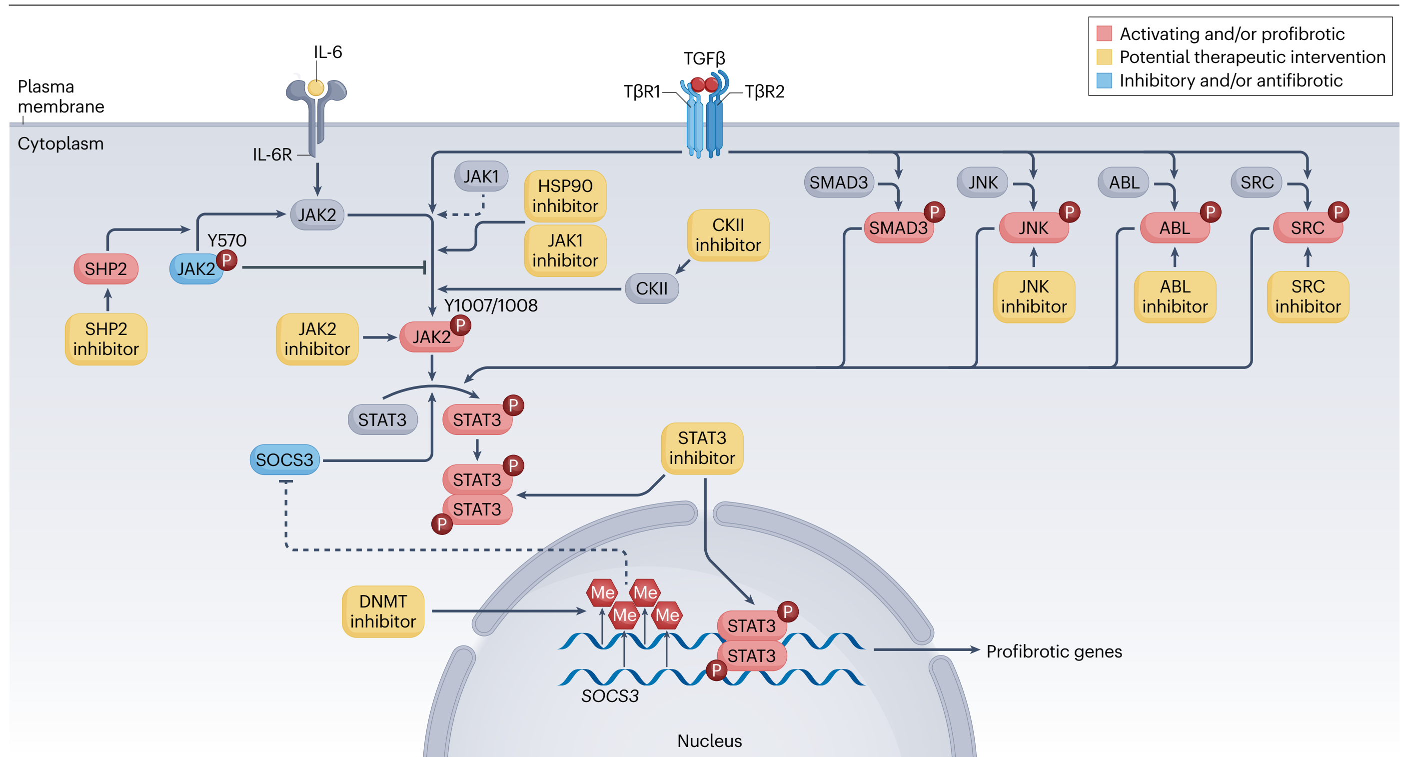

Fig. 4 | Dysregulated JAK–STAT signalling as a core pathway of fibroblast activation in systemic sclerosis. Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling is dysregulated in systemic sclerosis (SSc) fibroblasts on various levels and many potential interventions (shown in yellow) can be used to therapeutically target this dysregulated signalling. JAK1, JAK2, JAK3 and TYK2 together form the JAK family. JAKs are receptor-associated tyrosine kinases that transmit signals of various cytokine and growth-factor receptors. Activation of the upstream receptors (such as the IL-6 receptor (IL-6R) and the transforming growth factor-β (TGFβ) receptors (TβR1 and TβR2)) induces recruitment of JAK proteins and promotes their phosphorylation at 1007/1008 Tyr residues. Activated JAKs then phosphorylate the receptors, thereby generating docking sites for STAT proteins. Upon binding to these phosphorylated binding sites of the receptors, STAT proteins are phosphorylated, dimerize and translocate into the nucleus, where they activate transcription of target genes[212]. DNMT, DNA methyltransferase; HSP90, heat shock protein 90; Me, methyl group; SHP2, Src homology 2 domain-containing protein tyrosine phosphatase-2; SOCS3, suppressor of cytokine signalling 3.

Nuclear receptors

Nuclear receptors, a superfamily of transcriptional regulators, have crucial roles in fibrotic tissue remodelling. Several nuclear receptors can modulate fibrotic tissue remodelling by regulating different molecular pathways and on different cell types (Fig. 5).

NR1C3 (also known as PPARγ) competes with SMAD3 for the coactivator p300, thereby inhibiting SMAD-dependent transcription of profibrotic genes[125]. NR1C3 expression is reduced in fibrotic tissues and cultured fibroblasts from patients with SSc; this downregulation is mediated by TGFβ signalling[126]. In adipocytes, the downregulation of NR1C3 requires the corepressor NCoR[127]. NR1C3 agonists mitigate TGFβ-induced fibroblast activation, collagen secretion and bleomycin-induced fibrosis. Moreover, single-nucleotide polymorphisms in NR1C3 might be implicated in SSc susceptibility; however, a pan-PPAR agonist (lanifibranor) failed to demonstrate efficacy in a phase II study in patients with dcSSc (NCT02921971).

NR4A1 (alternatively known as Nur77 or TR3) also functions as an antifibrotic nuclear receptor, the expression of which is diminished in fibrotic diseases[128,129]. Under normal wound-healing conditions, transient TGFβ signalling upregulates NR4A1, which then represses profibrotic gene expression via SP1-dependent *trans*-repression. In chronic fibrotic states, prolonged TGFβ exposure undermines the inhibitory functions of NR4A1 via histone deacetylase-mediated epigenetic silencing and through AKT-induced phosphorylation[22,128]. NR4A1 agonists have demonstrated antifibrotic properties in multiple models of experimental fibrosis[128,130–132], but small molecules with suitable pharmacokinetic profiles for clinical use have not yet been developed.

NR1I1 (also known as the vitamin D receptor) has a role in fibrotic remodelling in multiple organs[133]. Activation of NR1I1 inhibits TGFβ–SMAD signalling by binding to phosphorylated SMAD3 and preventing its transcriptional activity[134]. This mechanism is particularly relevant to SSc, in which reduced NR1I1 expression in the skin, along with common vitamin D deficiency, might contribute to fibrogenesis.

Other members of the nuclear receptor family that alter TGFβ signalling in fibroblasts and have been implicated in the pathogenesis of SSc are NR0B1 (also known as DAX1), NR2C1 (also known as testicular receptor 4 (TR4)), NR1F1 (also known as RAR-related orphan receptor-α (RORα,)) and NR1I3 (also known as the constitutive androstane receptor (CAR))). The expression of NR0B1, NR2C1 and NR1F1 is upregulated in fibroblasts from patients with SSc[135–137]. NR0B1 and NR2C1 are upregulated in a TGFβ-dependent manner, whereas the expression of NR1F1 is induced by canonical WNT signalling[135–137]. NR0B1, NR2C1 and NR1F1 regulate distinct intracellular pathways in fibroblasts. NR0B1 promotes activation of WNT–β-catenin signalling

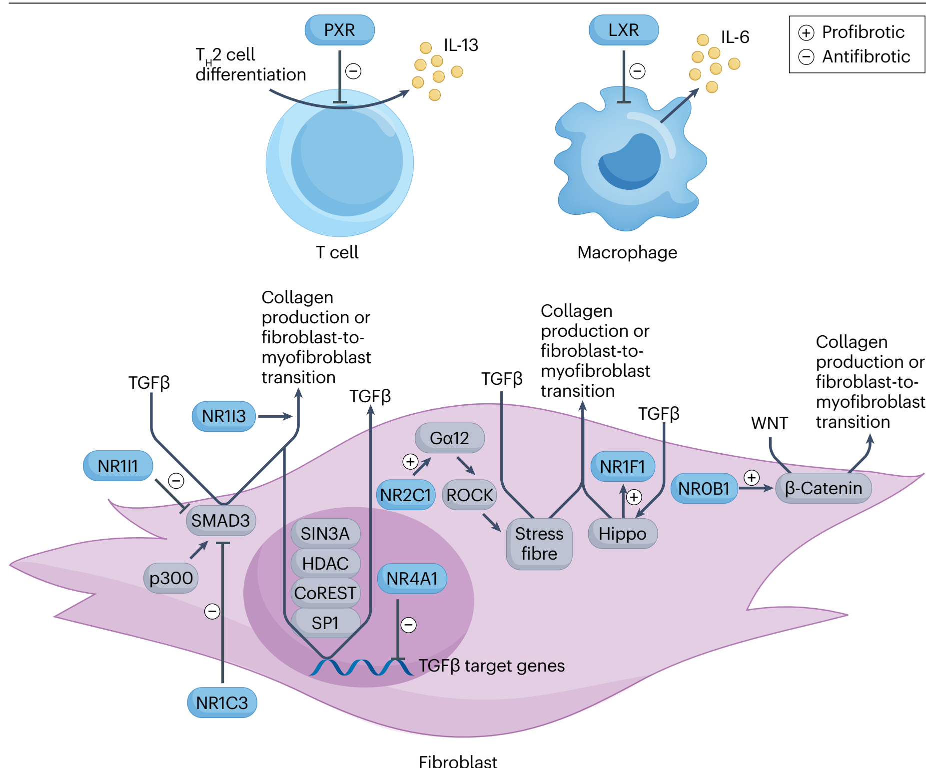

Fig. 5 | The multifaceted roles of nuclear receptors in fibrotic tissue remodelling. Nuclear receptors (shown in blue) function on different target cells (such as T cells, macrophages and fibroblasts) to modulate inflammatory and fibrotic pathways in the pathogenesis of fibrotic tissue remodelling. The expression levels of individual nuclear receptors are often modulated by pro-inflammatory and profibrotic mediators that are commonly implicated in the pathogenesis of systemic sclerosis (SSc). Dysregulation of nuclear receptor signalling in turn regulates core pathways of SSc, including transforming growth factor-β (TGFβ), WNT or IL-6 signalling, to promote fibrotic tissue remodelling. HDAC, histone deacetylase; LXR, liver X receptor; PXR, pregnane X receptor; ROCK, RHO-associated protein kinase; T_H2 cell, T helper 2 cell.

to facilitate fibroblast-to-myofibroblast differentiation[135]. Inactivation of NR0B1 ameliorates collagen release in cultured human dermal fibroblasts, in an in vitro model of human skin and in mouse models of dermal fibrosis[135]. Inhibition of NR0B1 also reduces the expression of disease-relevant genes, including genes associated with WNT–β-catenin signalling in precision-cut slices of skin from patients with SSc[135]. NR2C1 regulates Gα12 and RHO-associated protein kinase (ROCK) signalling to control the expression of numerous genes implicated in cytoskeletal remodelling and thereby promotes fibroblast-to-myofibroblast transition[137]. Inactivation of NR2C1 reduces collagen release and prevents experimental dermal and pulmonary fibrosis in mouse models[137]. NR1F1 is required for TGFβ-induced activation of Hippo signalling in fibroblasts. Inactivation of NR1F1 inhibits Hippo signalling, reduces fibroblast-to-myofibroblast transition and ameliorates experimental dermal, pulmonary and hepatic fibrosis[136]. The role of NR1I3 is less well-defined. Activation of NR1I3 by synthetic NR1I3 agonists fosters activation of canonical TGFβ signalling and exacerbates experimental fibrosis[138]. However, the exact molecular mechanisms and potential therapeutic implications of NR1I3 inhibition have not yet been investigated.

In contrast to the nuclear receptors discussed thus far, liver X receptor (LXR) and pregnane X receptor (PXR) regulate the release of profibrotic mediators from macrophages or T cells, respectively, rather than targeting fibroblasts directly. LXR agonists inhibit macrophage activation and IL-6 release in mouse models of dermal fibrosis[139]. PXR activation inhibits the release of IL-13 from T_H2 cells, which results in reduced fibrotic remoulding in inflammatory mouse models of SSc[140].

Thus, several nuclear receptors have been implicated in the pathogenesis of fibrotic tissue remodelling at different molecular and cellular levels and might offer potential for therapeutic intervention.

Developmental pathways

Hedgehog and WNT signalling pathways are integral to organ development in the embryo and are thus often referred to as developmental pathways. Under physiological conditions, these developmental pathways regulate stem-cell function but are silenced in most other cell types in adults. However, these developmental pathways are reactivated in the context of fibrosis and seem to have crucial roles in tissue remodelling[141].

Hedgehog signalling

The expression levels of the sonic hedgehog (SHH) ligand and the transcription factor GLI2 are increased in skin from patients with SSc and in other fibrotic tissues[142]. Serum levels of SHH are also upregulated in SSc and correlate with the extent of fibrosis[143]. TGFβ contributes to hedgehog pathway activation by inducing SHH expression, upregulating the expression of the hedgehog acyltransferase (also known as skinny hedgehog, which catalyses the attachment of palmitate to SHH, thereby enabling the multimerization of SHH proteins) and also by directly activating the GLI2 promoter in fibroblasts[144–146]. Crosstalk between hedgehog signalling and activator protein 1 signalling might also contribute to aberrant GLI2 activity in SSc[147]. Hedgehog signalling promotes fibroblast-to-myofibroblast differentiation and is sufficient to induce skin fibrosis in mice[144,148]. Moreover, its inactivation, either pharmacologically or genetically, attenuates experimental fibrosis in the skin, lungs and other organs[148–150].

Canonical WNT signalling

Canonical (β-catenin-dependent) WNT signalling is upregulated in various fibrotic conditions including in SSc skin, as indicated by increased expression of WNT ligands, reduced levels of endogenous WNT inhibitors, nuclear accumulation of β-catenin and overexpression

of WNT–β-catenin-regulated target genes[151–155]. Stimulation with recombinant WNT proteins upregulates the expression of myofibroblast markers and the release of collagen in fibroblasts. Moreover, activation of canonical WNT signalling, either by overexpression of WNT ligands (such as WNT10b) or fibroblast-specific, inducible overexpression of β-catenin is sufficient to induce dermal fibrosis in mice[152,156,157]. Targeted inactivation of canonical WNT signalling by several different genetic or pharmacological approaches consistently demonstrated antifibrotic effects in preclinical models[158–163]. TGFβ activates canonical WNT signalling in fibroblasts, promoting nuclear translocation of β-catenin and upregulation of WNT target genes[157]. These stimulatory effects of TGFβ on canonical WNT signalling are at least in part mediated by TGFβ-dependent suppression of the transcription of endogenous WNT antagonists such as Dickkopf-1 (DKK1) and secreted frizzled-related protein 1 (SFRP1) through p38-dependent mechanisms and epigenetic silencing[164], but also by downregulation of axin-2 (ref. 165). The stimulatory effects of TGFβ on canonical WNT signalling contribute to its profibrotic effects as inhibition of canonical WNT signalling ameliorates fibrosis induced by aberrant TGFβ signalling in mice[157]. Collectively, these findings position canonical WNT signalling as a central pathway in fibrotic remodelling (Fig. 6).

Non-canonical WNT signalling

Non-canonical (β-catenin-independent) WNT signalling is defined as signalling events induced by WNT proteins that are transmitted to the nucleus independently of β-catenin. These non-canonical WNT signals are often triggered by specific WNT proteins such as WNT5A. Non-canonical WNT signalling is also perturbed in SSc, with upregulation of WNT5A reported in skin of patients with SSc[166]. Recombinant WNT5A induces collagen release and fibroblast-to-myofibroblast transition in cultured fibroblasts. Overexpression of WNT5A is sufficient to induce fibrosis in organotypic skin models of mouse skin and lungs. These profibrotic effects are mediated by WNT5A-induced activation of latent TGFβ[166]. WNT5A activates JNK and ROCK signalling to induce cytoskeletal rearrangements and clustering of integrin αV, which promotes activation of latent TGFβ stored in large amounts in the ECM. Inhibition of WNT5A or its downstream mediators prevents activation of latent TGFβ, rebalances TGFβ signalling and ameliorates experimental fibrosis[166]. In contrast to canonical WNT signalling and hedgehog signalling, non-canonical signalling via WNT5A is thus an upstream regulator of TGFβ signalling in SSc (Fig. 6).

These findings highlight the close interaction of TGFβ signalling with canonical and non-canonical WNT and hedgehog signalling and

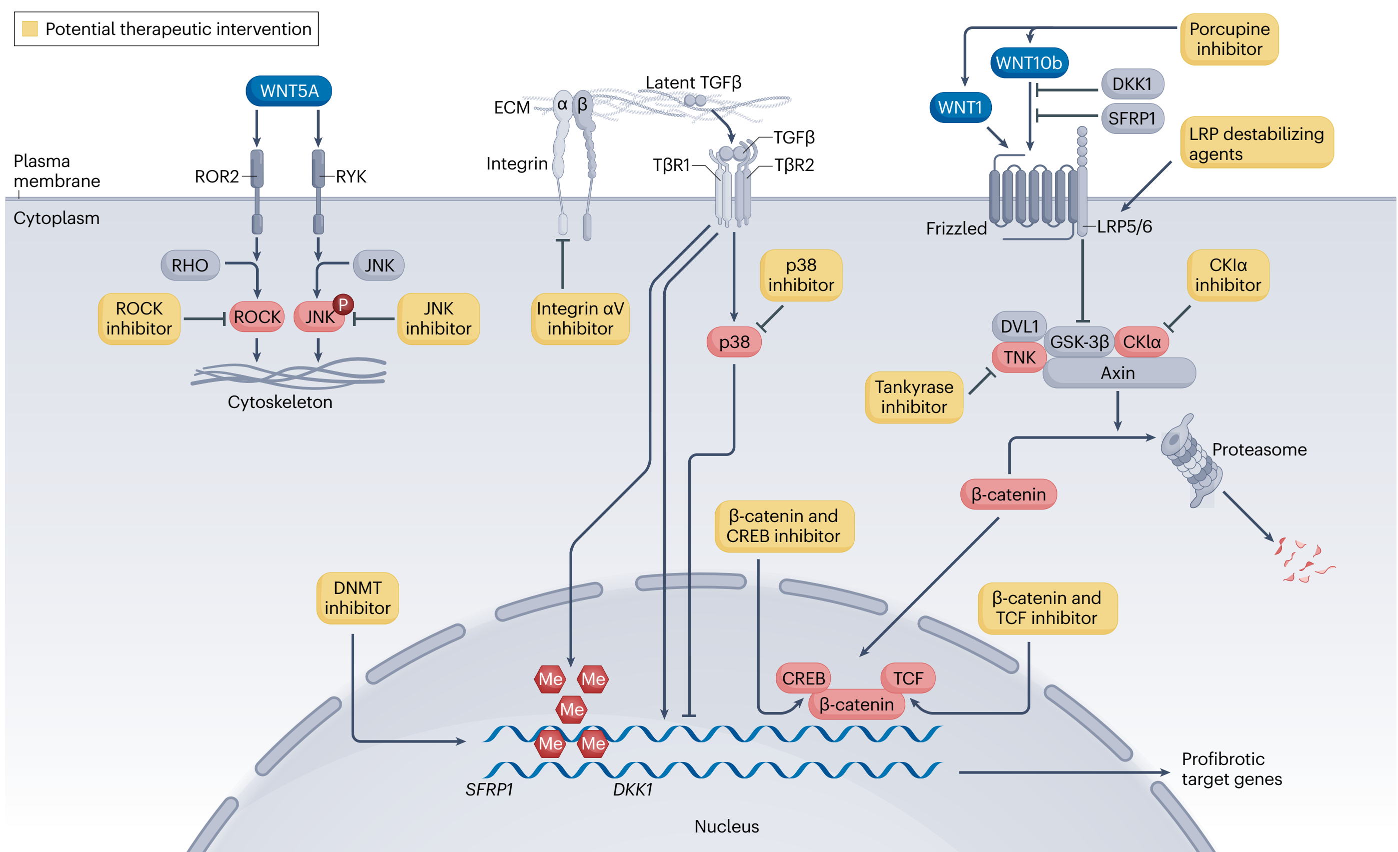

Fig. 6 | Canonical and non-canonical WNT signalling as mediators of fibrotic tissue remodelling in systemic sclerosis. In systemic sclerosis (SSc), WNT signalling in fibroblasts is dysregulated, and molecules within this pathway are potential therapeutic targets (targets are shown in red and potential interventions in yellow). In SSc, changes in the expression of WNT ligands, endogenous inhibitors and intracellular mediators synergize to promote the hyperactivation of canonical as well as non-canonical WNT signalling. The profibrotic effects of WNT signalling can be targeted at multiple levels. CREB, cAMP response element-binding protein; DKK1, Dickkopf 1; DNMT, DNA methyltransferase; ECM, extracellular matrix; LRP, low-density lipoprotein receptor-related protein; Me, methyl group; ROCK, RHO-associated protein kinase; SFRP1, secreted frizzled-related protein 1; TCF, ternary complex factor; TGFβ, transforming growth factor-β; TβR, TGFβ receptor.

provide evidence that these signalling cascades synergize to promote fibrotic tissue remodelling in SSc.

Epigenetic changes and fibrotic tissue memory

Fibroblasts in SSc undergo epigenetic changes as a result of chronic exposure to the profibrotic environment[167]. These epigenetic modifications consolidate the activated phenotype of SSc fibroblasts and render them at least in part independent of external stimuli, such as those delivered by immune cells[168]. This finding is reflected in the chronically active phenotype of SSc fibroblasts with increased release of ECM and elevated expression of myofibroblast markers even after several passages in in vitro monocultures. This stabilization of the activated phenotype of tissue-resident cells by epigenetic modifications is also referred to as 'tissue memory'[169,170]. Tissue memory in SSc is encoded by a complex combination of different epigenetic alterations involving changes in DNA methylation, histone methylation, histone acetylation, epigenetic readers of the bromodomain (BRD) family and non-coding RNAs[164,167,171–187]. We discuss selected examples of DNA and histone modifications that contribute to fibroblast activation; changes in the expression of non-coding RNAs have been reviewed elsewhere[188].

DNA methylation

Three DNA methyltransferases (DNMTs), DNMT1, DNMT3A and DNMT3B, can methylate DNA at position C5 of the pyrimidine ring of cytosine[189]. When methylated cytosine residues are grouped in what are known as CpG islands, binding sites for methyl-CpG-binding domain (MBD) proteins form. MBD protein binding promotes the recruitment of repressor complexes to inhibit transcription[190]. Numerous studies show that fibroblast activation in SSc is promoted by altered DNA methylation[164,186,191–193]. Notably, TGFβ induces the expression of DNMT3A with consecutive increases in DNMT1 in fibroblasts, thereby providing a molecular link between aberrant TGFβ signalling and DNA-methylation-mediated tissue memory[194]. The first target shown to be dysregulated by DNA methylation in SSc was the transcription factor FLI1 (refs. 186,195,196). FLI1 can limit TGFβ signalling[197]; however, in SSc, aberrant DNA methylation silences FLI1 expression. Other targets of DNA methylation are suppressor of cytokine signalling 3 (SOCS3), an endogenous inhibitor of JAK–STAT signalling, and the endogenous WNT antagonists DKK1 and SFRP1. Silencing of SOCS3 expression in fibroblasts facilitates prolonged activation of JAK2–STAT3 signalling and promotes fibroblast activation and tissue remodelling[198]. Silencing of DKK1 and SFRP1 might synergize with overexpression of WNT ligands to induce aberrant WNT signalling in SSc[164]. DNMT inhibitors can partially reverse the activated phenotype of SSc fibroblasts and demonstrate antifibrotic effects across multiple organs[164,199,200].

Methylation analysis of the X chromosome in peripheral blood mononuclear cells (PBMCs) from monozygotic twins discordant for SSc identified differential methylation of genes involved in transcription, proliferation, inflammation, apoptosis and oxidative stress[201]. Global methylation analysis in PBMCs of both monozygotic and dizygotic twins discordant for SSc identified distinct methylation sites in patients with lcSSc compared with those with dcSSc[202]. A global analysis of differential methylation and expression conducted using primary dermal fibroblasts from monozygotic and dizygotic twins with SSc demonstrated the differential regulation of the transcription factor KLF4 (ref. 180). Functional studies in fibroblasts and conditional knockout mice revealed that KLF4 (the expression of which is suppressed in fibroblasts from patients with SSc compared with their healthy twin) regulates *TBX5* and *TFAP2A*, and that lower levels of KLF4 promote fibrosis[180]. Together, these studies highlight the functional impact of differential methylation in SSc, both systemically and in affected tissues, and indicate a potential benefit of using epigenetic modifiers for the treatment of SSc.

Histone acetylation and methylation

TGFβ can also alter the epigenetic memory of SSc fibroblasts by modulating the histone code. Histone modifications include acetylation and methylation. Early reports demonstrated that histone deacetylation inhibitors attenuate the activated phenotype of SSc fibroblasts and ameliorate bleomycin-induced dermal fibrosis in mice[174]. Follow-up studies show that TGFβ downregulates the expression of the H4K16 histone acetyltransferase MYST1 in a SMAD-dependent manner. MYST1 provides epigenetic control of autophagy by suppressing the transcription of core components of the autophagy machinery. Plasmid-induced re-expression of MYST1 abrogates the stimulatory effects of TGFβ on autophagy and ameliorates TGFβ-induced fibroblast activation and experimental fibrosis[203]. Histone modifications are also implicated in the regulation of PU.1 expression[124]. In resting fibroblasts, repressive H3K9me3 and H3K27me3 marks dominate the promoter and upstream regulatory element of the PU.1 gene. In SSc fibroblasts, however, the upstream regulatory element of the PU.1 locus becomes permissive with increased H3K27 acetylation and loss of H3K9me3 and H3K27me3, thereby facilitating transcription of PU.1 (ref. 124). Histone modifications are thus a central component of the profibrotic tissue memory.

Other epigenetic modifications

Epigenetic modifications with an open chromatin state also maintain constitutive activation of a *TGFB2* enhancer in SSc fibroblasts[179]. Although most other in vitro studies in SSc use recombinant TGFβ1, this study demonstrated that the upregulation of TGFβ2 signalling might contribute to endogenous activation of SSc fibroblasts in a BRD4-dependent manner. Inhibition of the epigenetic reader protein BRD4 alleviated the hyperactivation of the *TGFB2* enhancer, mitigated profibrotic gene expression in fibroblasts and ameliorated dermal fibrosis in explant cultures of the skin of patients with SSc.

Epigenetic modifications are not restricted to fibroblasts in SSc but also contribute to the activated phenotype of other cell types such as macrophages. Combined scRNA-seq and single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) of SSc-ILD and healthy lungs revealed that the opening of chromatin promotes the activation of a specific set of transcription factors that promote SPP1 macrophage differentiation in SSc-ILD[204].

Although some epigenetic modulators such as histone deacetylase inhibitors or DNMT inhibitors are already in clinical use in oncology and thus offer potential for direct translation to SSc, the use of others such as bromodomain and extra terminal domain protein inhibitors is limited by adverse events. Cell-type specific delivery, such as coupling to antibodies or topical application, might offer opportunities for translation of those therapies to the clinic, but these are currently unavailable.

Other self-maintaining activation loops

The excessive deposition of ECM alters the biomechanical properties of fibrotic tissues, resulting in increased stiffness. Moreover, fibrotic tissues in SSc are hypoxic. Such changes, which are highly conserved across different fibrotic organs, trigger molecular signals that promote fibroblast activation and generate matricryptins, and might thus drive disease progression, particularly in later disease stages.

Tissue stiffness

Stiff substrates promote fibroblast activation, as evidenced by increased expression of contractile proteins and collagen production of fibroblasts cultured on stiff surfaces (such as standard cell culture dishes)[205]. Integrin receptors have a major role in how cells sense mechanical cues from the ECM, including changes in stiffness, and can convert them into intracellular signals that influence cell behaviour. Many of the downstream signalling pathways of integrin receptors are implicated in fibrosis[206]. The transcriptional coactivators Yes-associated protein-1 (YAP1) and transcriptional coactivator with PDZ-binding motif (TAZ) are key downstream effectors of the Hippo pathway. They function as mechanosensors and have central roles in transducing stiffness into cellular responses[207]. Inhibition of YAP–TAZ signalling attenuates both stiffness-induced and TGFβ-induced fibroblast-to-myofibroblast transformation, whereas constitutive YAP activation drives fibroblast activation and ECM synthesis[205]. Additional factors such as p300 and α6 integrin might also be implicated in stiffness-induced myofibroblast differentiation.

Hypoxia

Hypoxia-inducible factor 1α (HIF-1α) is the principal mediator of cellular responses to low oxygen levels[208]. Under normoxic conditions, HIF-1α undergoes hydroxylation and acetylation, which promotes its proteasomal degradation. In hypoxic environments, the lack of oxygen prevents HIF-1α hydroxylation, enabling its accumulation, nuclear translocation, dimerization with HIF-1β (also known as aryl hydrocarbon receptor nuclear translocator) and subsequent activation of target genes with hypoxia-responsive elements[209]. Hypoxia promotes fibroblast-to-myofibroblast differentiation and enhances ECM protein transcription via HIF-1α-dependent and -independent mechanisms[210]. The stimulatory effects of hypoxia on fibroblasts and ECM release are in part mediated by TGFβ[211]. Thus, hypoxia can promote fibroblast activation and progression of fibrosis, particularly in later stages of SSc with advanced vasculopathy and excessive accumulation of ECM.

Conclusions

The pathogenesis of SSc is characterized by a complex interplay of vascular injury, inflammation and misdirected tissue repair, which interact at multiple levels to drive disease progression. The intense crosstalk also makes defining of individual pathways such as drivers, amplifiers or modulators of disease challenging. Despite advances in understanding of fibrotic tissue remodelling, the pathogenesis of SSc remains incompletely understood; for example, the early, disease-initiating mechanisms remain largely unknown, mechanisms of disease progression in the absence of inflammation are understudied and specific cellular niches and localized differences in signalling activity within affected tissues are unclear. This lack of understanding is partly due to preclinical models that do not fully recapitulate the diverse features of SSc. Emerging human model systems, such as organoids, organ-on-chip platforms and ex vivo tissue cultures combined with unbiased multi-level omics approaches, hold promise for uncovering novel molecular and cellular targets for the treatment of SSc. Therapies aimed at disrupting the self-sustaining cycle of vasculopathy, inflammation and fibrosis offer potential for development of truly disease-modifying therapeutics that target not only certain manifestations but also the underlying core pathophysiology to treat the full spectrum of manifestations of SSc and other fibrotic diseases.

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References

1. Rieder, F. et al. Fibrosis: cross-organ biology and pathways to development of innovative drugs. *Nat. Rev. Drug Discov.* **24**, 543–569 (2025).
2. Distler, J. H. W. et al. Shared and distinct mechanisms of fibrosis. *Nat. Rev. Rheumatol.* **15**, 705–730 (2019).
3. Thannickal, V. J. et al. Fibrosis: ultimate and proximate causes. *J. Clin. Invest.* **124**, 4673–4677 (2014).
4. Wynn, T. A. Cellular and molecular mechanisms of fibrosis. *J. Pathol.* **214**, 199–210 (2008).
5. Dees, C., Chakraborty, D. & Distler, J. H. W. Cellular and molecular mechanisms in fibrosis. *Exp. Dermatol.* **30**, 121–131 (2021).
6. Truchetet, M. E., Brembilla, N. C. & Chizzolini, C. Current concepts on the pathogenesis of systemic sclerosis. *Clin. Rev. Allergy Immunol.* **64**, 262–283 (2023).
7. Volkmann, E. R., Andréasson, K. & Smith, V. Systemic sclerosis. *Lancet* **401**, 304–318 (2023).
8. Distler, J. H. et al. Review: frontiers of antifibrotic therapy in systemic sclerosis. *Arthritis Rheumatol.* **69**, 257–267 (2017).
9. Limandjaja, G. C. et al. Hypertrophic scars and keloids: overview of the evidence and practical guide for differentiating between these abnormal scars. *Exp. Dermatol.* **30**, 146–161 (2021).
10. De Luca, D. A. et al. Lichen sclerosus: the 2023 update. *Front. Med.* **10**, 1106318 (2023).
11. Keum, H. et al. Incidence and prevalence of morphea. *JAMA Dermatol.* **160**, 1128–1130 (2024).
12. van Straalen, K. R. et al. Single-cell sequencing reveals Hippo signaling as a driver of fibrosis in hidradenitis suppurativa. *J. Clin. Invest.* **134**, e169225 (2024).
13. Distler, J. H. W. et al. Emerging therapies for the treatment of systemic sclerosis. *Nat. Rev. Rheumatol.* **21**, 612–625 (2025).
14. Leask, A., Naik, A. & Stratton, R. J. Back to the future: targeting the extracellular matrix to treat systemic sclerosis. *Nat. Rev. Rheumatol.* **19**, 713–723 (2023).
15. Ho, Y. Y. et al. Fibrosis — a lethal component of systemic sclerosis. *Nat. Rev. Rheumatol.* **10**, 390–402 (2014).
16. Davidson, S. et al. Fibroblasts as immune regulators in infection, inflammation and cancer. *Nat. Rev. Immunol.* **21**, 704–717 (2021).
17. Pradhan, R. N. et al. A bird's eye view of fibroblast heterogeneity: a pan-disease, pan-cancer perspective. *Immunol. Rev.* **302**, 299–320 (2021).
18. Buechler, M. B. et al. Cross-tissue organization of the fibroblast lineage. *Nature* **593**, 575–579 (2021).
19. Gao, Y. et al. Cross-tissue human fibroblast atlas reveals myofibroblast subtypes with distinct roles in immune modulation. *Cancer Cell* **42**, 1764–1783.e10 (2024).
20. Steele, L. et al. A single-cell and spatial genomics atlas of human skin fibroblasts reveals shared disease-related fibroblast subtypes across tissues. *Nat. Immunol.* **26**, 1807–1820 (2025).
21. Sole-Boldo, L. et al. Single-cell transcriptomes of the human skin reveal age-related loss of fibroblast priming. *Commun. Biol.* **3**, 188 (2020).
22. Philippeos, C. et al. Spatial and single-cell transcriptional profiling identifies functionally distinct human dermal fibroblast subpopulations. *J. Invest. Dermatol.* **138**, 811–825 (2018).
23. Korosec, A. et al. Lineage identity and location within the dermis determine the function of papillary and reticular fibroblasts in human skin. *J. Invest. Dermatol.* **139**, 342–351 (2019).
24. Tabib, T. et al. SFRP2/DPP4 and FMO1/LSP1 define major fibroblast populations in human skin. *J. Invest. Dermatol.* **138**, 802–810 (2018).
25. Ma, F. et al. Systems-based identification of the hippo pathway for promoting fibrotic mesenchymal differentiation in systemic sclerosis. *Nat. Commun.* **15**, 210 (2024).
26. Li, Y. N. et al. Spatially informed phenotyping by cyclic-in-situ-hybridisation identifies novel fibroblast populations and their pathogenic niches in systemic sclerosis. *Ann. Rheum. Dis.* **84**, 1852–1864 (2025).
27. Zhu, H. et al. Fibroblast subpopulations in systemic sclerosis: functional implications of individual subpopulations and correlations with clinical features. *J. Invest. Dermatol.* **144**, 1251–1261.e13 (2024).
28. Gur, C. et al. LGR5 expressing skin fibroblasts define a major cellular hub perturbed in scleroderma. *Cell* **185**, 1373–1388.e20 (2022).
29. Merrick, D. et al. Identification of a mesenchymal progenitor cell hierarchy in adipose tissue. *Science* **364**, eaav2501 (2019).
30. Rius Rigau, A. et al. Imaging mass cytometry-based characterization of fibroblast subsets and their cellular niches in systemic sclerosis. *Ann. Rheum. Dis.* https://doi.org/10.1136/ard-2024-226336 (2024).
31. Devakumar, V. et al. Single cell mapping of the metabolic landscape of skin fibrosis in systemic sclerosis. Preprint at *bioRxiv* https://doi.org/10.1101/2025.04.14.648761 (2025).
32. Sgonc, R. et al. Endothelial cell apoptosis is a primary pathogenetic event underlying skin lesions in avian and human scleroderma. *J. Clin. Invest.* **98**, 785–792 (1996).
33. Riemekasten, G. et al. Involvement of functional autoantibodies against vascular receptors in systemic sclerosis. *Ann. Rheum. Dis.* **70**, 530–536 (2011).
34. Sgonc, R. et al. Endothelial cell apoptosis in systemic sclerosis is induced by antibody-dependent cell-mediated cytotoxicity via CD95. *Arthritis Rheum.* **43**, 2550–2562 (2000).
35. Maehara, T. et al. Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis. *J. Clin. Invest.* **130**, 2451–2464 (2020).
36. Gremmel, T., Frelinger, A. L. 3rd & Michelson, A. D. Platelet physiology. *Semin. Thromb. Hemost.* **42**, 191–204 (2016).

37. Mann, D. A. & Oakley, F. Serotonin paracrine signaling in tissue fibrosis. *Biochim. Biophys. Acta* **1832**, 905–910 (2013).
38. Dees, C. et al. Platelet-derived serotonin links vascular disease and tissue fibrosis. *J. Exp. Med.* **208**, 961–972 (2011).
39. Trinh-Minh, T. et al. Antifibrotic effects of specific targeting of the 5-hydroxytryptamine 2B receptor (5-HT_{2B}R) in murine models and ex vivo models of scleroderma skin. *Arthritis Rheumatol.* **77**, 1063–1076 (2025).
40. Truchetet, M. E. et al. Platelets induce thymic stromal lymphopoietin production by endothelial cells: contribution to fibrosis in human systemic sclerosis. *Arthritis Rheumatol.* **68**, 2784–2794 (2016).
41. Howell, D. C. et al. Direct thrombin inhibition reduces lung collagen, accumulation, and connective tissue growth factor mRNA levels in bleomycin-induced pulmonary fibrosis. *Am. J. Pathol.* **159**, 1383–1395 (2001).
42. de Ridder, G. G., Lundblad, R. L. & Pizzo, S. V. Actions of thrombin in the interstitium. *J. Thromb. Haemost.* **14**, 40–47 (2016).
43. Crawford, K. S. & Volkman, B. F. Prospects for targeting ACKR1 in cancer and other diseases. *Front. Immunol.* **14**, 1111960 (2023).
44. Huang, Y. et al. Atypical chemokine receptor 1-positive endothelial cells mediate leucocyte infiltration and synergize with secreted frizzled-related protein 2/asporin-positive fibroblasts to promote skin fibrosis in systemic sclerosis. *Br. J. Dermatol.* **191**, 964–978 (2024).
45. Raslan, A. A. et al. Lung injury-induced activated endothelial cell states persist in aging-associated progressive fibrosis. *Nat. Commun.* **15**, 5449 (2024).
46. Romano, E. et al. Recent insights into cellular and molecular mechanisms of defective angiogenesis in systemic sclerosis. *Biomedicines* **12**, 1331 (2024).
47. Piera-Velazquez, S., Mendoza, F. A. & Jimenez, S. A. Endothelial to mesenchymal transition (EndoMT) in the pathogenesis of human fibrotic diseases. *J. Clin. Med.* **5**, 45 (2016).
48. Rius Rigau, A. et al. Characterization of vascular niche in systemic sclerosis by spatial proteomics. *Circ. Res.* **134**, 875–891 (2024).
49. Talotta, R. et al. Certainties and uncertainties concerning the contribution of pericytes to the pathogenesis of systemic sclerosis. *J. Scleroderma Relat. Disord.* **3**, 14–20 (2018).
50. Iwayama, T. & Olson, L. E. Involvement of PDGF in fibrosis and scleroderma: recent insights from animal models and potential therapeutic opportunities. *Curr. Rheumatol. Rep.* **15**, 304 (2013).
51. Rajkumar, V. S. et al. Activation of microvascular pericytes in autoimmune Raynaud's phenomenon and systemic sclerosis. *Arthritis Rheum.* **42**, 930–941 (1999).
52. Sanges, S. et al. Soluble markers of B cell activation suggest a role of B cells in the pathogenesis of systemic sclerosis-associated pulmonary arterial hypertension. *Front. Immunol.* **13**, 954007 (2022).
53. Forestier, A. et al. Altered B lymphocyte homeostasis and functions in systemic sclerosis. *Autoimmun. Rev.* **17**, 244–255 (2018).
54. Sanges, S. et al. Role of B cells in the pathogenesis of systemic sclerosis. *Rev. Med. Interne* **38**, 113–124 (2017).
55. Matsushita, T. et al. Decreased levels of regulatory B cells in patients with systemic sclerosis: association with autoantibody production and disease activity. *Rheumatology* **55**, 263–267 (2016).
56. Melissaropoulos, K. & Liossis, S. N. Decreased CD22 expression and intracellular signaling aberrations in B cells of patients with systemic sclerosis. *Rheumatol. Int.* **38**, 1225–1234 (2018).
57. Le Maitre, M. et al. Beyond circulating B cells: characteristics and role of tissue-infiltrating B cells in systemic sclerosis. *Autoimmun. Rev.* **24**, 103782 (2025).
58. Bosello, S. et al. Characterization of inflammatory cell infiltrate of scleroderma skin: B cells and skin score progression. *Arthritis Res. Ther.* **20**, 75 (2018).
59. Whitfield, M. L. et al. Systemic and cell type-specific gene expression patterns in scleroderma skin. *Proc. Natl Acad. Sci.* **100**, 12319–12324 (2003).
60. Lafyatis, R. et al. B cell infiltration in systemic sclerosis-associated interstitial lung disease. *Arthritis Rheum.* **56**, 3167–3168 (2007).
61. Sanges, S. et al. B-cells in pulmonary arterial hypertension: friend, foe or bystander? *Eur. Respir. J.* **63**, 2301949 (2024).
62. Hoffmann-Vold, A. M. et al. Augmented concentrations of CX3CL1 are associated with interstitial lung disease in systemic sclerosis. *PLoS ONE* **13**, e0206545 (2018).
63. Taher, T. E. et al. Association of defective regulation of autoreactive interleukin-6-producing transitional B lymphocytes with disease in patients with systemic sclerosis. *Arthritis Rheumatol.* **70**, 450–461 (2018).
64. Thoreau, B., Chaigne, B. & Mouthon, L. Role of B-cell in the pathogenesis of systemic sclerosis. *Front. Immunol.* **13**, 933468 (2022).
65. Le Maitre, M. et al. Characteristics and impact of infiltration of B-cells from systemic sclerosis patients in a 3D healthy skin model. *Front. Immunol.* **15**, 1373464 (2024).
66. Kondo, K. et al. Establishment and characterization of a human B cell line from the lung tissue of a patient with scleroderma; extraordinary high level of IL-6 secretion by stimulated fibroblasts. *Cytokine* **13**, 220–226 (2001).
67. Benfaremo, D. et al. Putative functional pathogenic autoantibodies in systemic sclerosis. *Eur. J. Rheumatol.* **7**, S181–S186 (2020).
68. Chepy, A. et al. Autoantibodies in systemic sclerosis: From disease bystanders to pathogenic players. *J. Transl. Autoimmun.* **10**, 100272 (2025).
69. Chepy, A. et al. Can antinuclear antibodies have a pathogenic role in systemic sclerosis? *Front. Immunol.* **13**, 930970 (2022).
70. Arcand, J. et al. The autoantigen DNA topoisomerase I interacts with chemokine receptor 7 and exerts cytokine-like effects on dermal fibroblasts. *Arthritis Rheum.* **64**, 826–834 (2012).
71. Raschi, E. et al. Immune complexes containing scleroderma-specific autoantibodies induce a profibrotic and proinflammatory phenotype in skin fibroblasts. *Arthritis Res. Ther.* **20**, 187 (2018).
72. Chepy, A. et al. Effects of immunoglobulins g from systemic sclerosis patients in normal dermal fibroblasts: a multi-omics study. *Front. Immunol.* **13**, 904631 (2022).
73. Chepy, A. et al. Immunoglobulins G from patients with systemic sclerosis modify the molecular signatures of endothelial cells. *RMD Open* **11**, e004290 (2025).
74. Yoshizaki, A. et al. Immunization with DNA topoisomerase I and Freund's complete adjuvant induces skin and lung fibrosis and autoimmunity via interleukin-6 signaling. *Arthritis Rheum.* **63**, 3575–3585 (2011).
75. Fukasawa, T. et al. Single-cell-level protein analysis revealing the roles of autoantigen-reactive B lymphocytes in autoimmune disease and the murine model. *eLife* **10**, e67209 (2021).
76. Sakkas, L. I., Chikanza, I. C. & Platsoucas, C. D. Mechanisms of Disease: the role of immune cells in the pathogenesis of systemic sclerosis. *Nat. Clin. Pract. Rheumatol.* **2**, 679–685 (2006).
77. Gaydosik, A. M. et al. Dysfunctional KLRB1$^+$CD8$^+$ T-cell responses are generated in chronically inflamed systemic sclerosis skin. *Ann. Rheum. Dis.* **84**, 798–809 (2025).
78. Ricard, L. et al. Circulating follicular helper T cells are increased in systemic sclerosis and promote plasmablast differentiation through the IL-21 pathway which can be inhibited by ruxolitinib. *Ann. Rheum. Dis.* **78**, 539–550 (2019).
79. Gaydosik, A. M. et al. Single-cell transcriptome analysis identifies skin-specific T-cell responses in systemic sclerosis. *Ann. Rheum. Dis.* **80**, 1453–1460 (2021).
80. Al-Adwi, Y. et al. Macrophages as determinants and regulators of fibrosis in systemic sclerosis. *Rheumatology* **62**, 535–545 (2023).
81. Toledo, D. M. & Pioli, P. A. Macrophages in systemic sclerosis: novel insights and therapeutic implications. *Curr. Rheumatol. Rep.* **21**, 31 (2019).
82. Soldano, S. et al. Increase in circulating cells coexpressing M1 and M2 macrophage surface markers in patients with systemic sclerosis. *Ann. Rheum. Dis.* **77**, 1842–1845 (2018).
83. Trombetta, A. C. et al. A circulating cell population showing both M1 and M2 monocyte/macrophage surface markers characterizes systemic sclerosis patients with lung involvement. *Respir. Res.* **19**, 186 (2018).
84. Murthy, S. et al. Alternative activation of macrophages and pulmonary fibrosis are modulated by scavenger receptor, macrophage receptor with collagenous structure. *FASEB J.* **29**, 3527–3536 (2015).
85. Xu, D. et al. PLG nanoparticles target fibroblasts and MARCO+ monocytes to reverse multiorgan fibrosis. *JCI Insight* **7**, e151037 (2022).
86. Taroni, J. N. et al. A novel multi-network approach reveals tissue-specific cellular modulators of fibrosis in systemic sclerosis. *Genome Med.* **9**, 27 (2017).
87. Bhandari, R. et al. Profibrotic activation of human macrophages in systemic sclerosis. *Arthritis Rheumatol.* **72**, 1160–1169 (2020).
88. Bhandari, R. et al. Human dermal fibroblast-derived exosomes induce macrophage activation in systemic sclerosis. *Rheumatology* **62**, SI114–SI124 (2023).
89. Bujor, A. M. et al. Fli1 downregulation in scleroderma myeloid cells has profibrotic and proinflammatory effects. *Front. Immunol.* **11**, 800 (2020).
90. Laurent, P. et al. Interleukin-1β-activated microvascular endothelial cells promote DC-SIGN-positive alternatively activated macrophages as a mechanism of skin fibrosis in systemic sclerosis. *Arthritis Rheumatol.* **74**, 1013–1026 (2022).
91. To, S. & Agarwal, S. K. Macrophages and cadherins in fibrosis and systemic sclerosis. *Curr. Opin. Rheumatol.* **31**, 582–588 (2019).
92. Lodyga, M. et al. Cadherin-11-mediated adhesion of macrophages to myofibroblasts establishes a profibrotic niche of active TGF-β. *Sci. Signal.* **12**, eaao3469 (2019).
93. Ouyang, J. F. et al. Systems level identification of a matrisome-associated macrophage polarisation state in multi-organ fibrosis. *eLife* **12**, e85530 (2023).
94. Gao, X. et al. Osteopontin links myeloid activation and disease progression in systemic sclerosis. *Cell Rep. Med.* **1**, 100140 (2020).
95. Morse, C. et al. Proliferating SPP1/MERTK-expressing macrophages in idiopathic pulmonary fibrosis. *Eur. Respir. J.* **54**, 1802441 (2019).
96. Yuan, X. et al. Human hypofunctional NCF1 variants promote pulmonary fibrosis in the bleomycin-induced mouse model and patients with systemic sclerosis via expansion of SPP1$^+$ monocytes-derived macrophages. *Ann. Rheum. Dis.* **84**, 294–306 (2025).
97. Ishikawa, G. et al. α1 Adrenoreceptor antagonism mitigates extracellular mitochondrial DNA accumulation in lung fibrosis models and in patients with idiopathic pulmonary fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol* **324**, L639–L651 (2023).
98. Ishikawa, G. et al. A nerve-fibroblast axis in mammalian lung fibrosis. Preprint at *bioRxiv* https://doi.org/10.1101/2024.09.09.611003 (2025).
99. Gao, R. et al. Macrophage-derived netrin-1 drives adrenergic nerve-associated lung fibrosis. *J. Clin. Invest.* **131**, e136542 (2021).
100. Micera, A. et al. New insights on the involvement of nerve growth factor in allergic inflammation and fibrosis. *Cytokine Growth Factor. Rev.* **14**, 369–374 (2003).
101. Levick, S. P. et al. Sympathetic nervous system modulation of inflammation and remodeling in the hypertensive heart. *Hypertension* **55**, 270–276 (2010).
102. Pongratz, G. & Straub, R. H. The sympathetic nervous response in inflammation. *Arthritis Res. Ther.* **16**, 504 (2014).
103. Koenecke, A. et al. Alpha-1 adrenergic receptor antagonists to prevent hyperinflammation and death from lower respiratory tract infection. *eLife* **10**, e61700 (2021).
104. An, Y. A. et al. Endotrophin neutralization through targeted antibody treatment protects from renal fibrosis in a podocyte ablation model. *Mol. Metab.* **69**, 101680 (2023).

105. Yamaguchi, Y. et al. A peptide derived from endostatin ameliorates organ fibrosis. *Sci. Transl. Med.* **4**, 136ra71 (2012).
106. Sharma, S. et al. E4 engages uPAR and enolase-1 and activates urokinase to exert antifibrotic effects. *JCI Insight* **6**, e144935 (2021).
107. Hebbar, M. et al. Increased concentrations of the circulating angiogenesis inhibitor endostatin in patients with systemic sclerosis. *Arthritis Rheum.* **43**, 889–893 (2000).
108. Mouawad, J. E. et al. Reduced Cathepsin L expression and secretion into the extracellular milieu contribute to lung fibrosis in systemic sclerosis. *Rheumatology* **62**, 1306–1316 (2023).
109. Stawski, L. et al. MMP-12 deficiency attenuates angiotensin II-induced vascular injury, M2 macrophage accumulation, and skin and heart fibrosis. *PLoS ONE* **9**, e109763 (2014).
110. Ricard-Blum, S. & Salza, R. Matricryptins and matrikines: biologically active fragments of the extracellular matrix. *Exp. Dermatol.* **23**, 457–463 (2014).
111. O'Reilly, S., Tsou, P. S. & Varga, J. Senescence and tissue fibrosis: opportunities for therapeutic targeting. *Trends Mol. Med.* **30**, 1113–1125 (2024).
112. Merkt, W. et al. Senotherapeutics: targeting senescence in idiopathic pulmonary fibrosis. *Semin. Cell Dev. Biol.* **101**, 104–110 (2020).
113. Schafer, M. J. et al. Cellular senescence mediates fibrotic pulmonary disease. *Nat. Commun.* **8**, 14532 (2017).
114. Martyanov, V., Whitfield, M. L. & Varga, J. Senescence signature in skin biopsies from systemic sclerosis patients treated with senolytic therapy: potential predictor of clinical response? *Arthritis Rheumatol.* **71**, 1766–1767 (2019).
115. Dees, C. et al. JAK-2 as a novel mediator of the profibrotic effects of transforming growth factor β in systemic sclerosis. *Arthritis Rheum.* **64**, 3006–3015 (2012).
116. Zhang, Y. et al. JAK1-dependent transphosphorylation of JAK2 limits the antifibrotic effects of selective JAK2 inhibitors on long-term treatment. *Ann. Rheum. Dis.* **76**, 1467–1475 (2017).
117. Zehender, A. et al. The tyrosine phosphatase SHP2 controls TGFβ-induced STAT3 signaling to regulate fibroblast activation and fibrosis. *Nat. Commun.* **9**, 3259 (2018).
118. Zhang, Y. et al. Inhibition of casein kinase II reduces TGFβ induced fibroblast activation and ameliorates experimental fibrosis. *Ann. Rheum. Dis.* **74**, 936–943 (2015).
119. Pedroza, M. et al. Role of STAT3 in skin fibrosis and transforming growth factor beta signalling. *Rheumatology* **57**, 1838–1850 (2017).
120. Skhirtladze, C. et al. Src kinases in systemic sclerosis: central roles in fibroblast activation and in skin fibrosis. *Arthritis Rheum.* **58**, 1475–1484 (2008).
121. Akhmetshina, A. et al. Dual inhibition of c-abl and PDGF receptor signaling by dasatinib and nilotinib for the treatment of dermal fibrosis. *FASEB J.* **22**, 2214–2222 (2008).
122. Reich, N. et al. Jun N-terminal kinase as a potential molecular target for prevention and treatment of dermal fibrosis. *Ann. Rheum. Dis.* **71**, 737–745 (2012).
123. Chakraborty, D. et al. Activation of STAT3 integrates common profibrotic pathways to promote fibroblast activation and tissue fibrosis. *Nat. Commun.* **8**, 1130 (2017).
124. Wohlfahrt, T. et al. PU.1 controls fibroblast polarization and tissue fibrosis. *Nature* **566**, 344–349 (2019).
125. Wei, J. et al. PPARγ downregulation by TGFβ in fibroblast and impaired expression and function in systemic sclerosis: a novel mechanism for progressive fibrogenesis. *PLoS ONE* **5**, e13778 (2010).
126. Wei, J. et al. Regulation of matrix remodeling by peroxisome proliferator-activated receptor-gamma: a novel link between metabolism and fibrogenesis. *Open. Rheumatol. J.* **6**, 103–115 (2012).
127. Korman, B. et al. Adipocyte-specific repression of PPAR-gamma by NCoR contributes to scleroderma skin fibrosis. *Arthritis Res. Ther.* **20**, 145 (2018).
128. Palumbo-Zerr, K. et al. Orphan nuclear receptor NR4A1 regulates transforming growth factor-β signaling and fibrosis. *Nat. Med.* **21**, 150–158 (2015).
129. Chen, J. et al. Nur77 deficiency exacerbates cardiac fibrosis after myocardial infarction by promoting endothelial-to-mesenchymal transition. *J. Cell Physiol.* **236**, 495–506 (2021).
130. Pulakazhi Venu, V. K. et al. Nr4A1 modulates inflammation-associated intestinal fibrosis and dampens fibrogenic signaling in myofibroblasts. *Am. J. Physiol. Gastrointest. Liver Physiol.* **321**, G280–G297 (2021).
131. Tao, Y. et al. Nr4a1 promotes renal interstitial fibrosis by regulating the p38 MAPK phosphorylation. *Mol. Med.* **29**, 63 (2023).
132. Ma, M. F. et al. Orphan nuclear receptor 4 A1 involvement in transforming growth factor beta1-induced myocardial fibrosis in diabetic mice. *J. Physiol. Pharmacol.* https://doi.org/10.26402/jpp.2023.6.04 (2023).
133. Shany, S., Sigal-Batikoff, I. & Lamprecht, S. Vitamin D and myofibroblasts in fibrosis and cancer: at cross-purposes with TGF-β/SMAD signaling. *Anticancer. Res.* **36**, 6225–6234 (2016).
134. Zerr, P. et al. Vitamin D receptor regulates TGF-β signalling in systemic sclerosis. *Ann. Rheum. Dis.* **74**, e20 (2015).
135. Shen, L. et al. POS0007 The nuclear receptor Dax1 regulates Wnt/B-catenin signaling to promote fibroblast activation and skin fibrosis in systemic sclerosis. *Ann. Rheumatic Dis.* **83**, 286 (2024).
136. Tran-Manh, C. et al. POS1013 Retinoic acid-related orphan receptor-a as an upstream regulator of Hippo signaling and a therapeutic target in fibrotic tissue remodeling. *Ann. Rheumatic Dis.* **84**, 1121 (2025).
137. Shen, L. et al. POS0476 The nuclear receptor tr4 orchestrates cytoskeletal organization in a gα12/rock-dependent manner to promote myofibroblast differentiation and tissue fibrosis in systemic sclerosis. *Ann. Rheumatic Dis.* **81**, 492–493 (2022).
138. Avouac, J. et al. The nuclear receptor constitutive androstane receptor/NR1I3 enhances the profibrotic effects of transforming growth factor β and contributes to the development of experimental dermal fibrosis. *Arthritis Rheumatol.* **66**, 3140–3150 (2014).
139. Beyer, C. et al. Activation of liver X receptors inhibits experimental fibrosis by interfering with interleukin-6 release from macrophages. *Ann. Rheum. Dis.* **74**, 1317–1324 (2015).
140. Beyer, C. et al. Activation of pregnane X receptor inhibits experimental dermal fibrosis. *Ann. Rheum. Dis.* **72**, 621–625 (2013).
141. Beyer, C., Dees, C. & Distler, J. H. Morphogen pathways as molecular targets for the treatment of fibrosis in systemic sclerosis. *Arch. Dermatol. Res.* **305**, 1–8 (2013).
142. Beyer, C. & Distler, J. H. Morphogen pathways in systemic sclerosis. *Curr. Rheumatol. Rep.* **15**, 299 (2013).
143. Beyer, C. et al. Elevated serum levels of sonic hedgehog are associated with fibrotic and vascular manifestations in systemic sclerosis. *Ann. Rheum. Dis.* **77**, 626–628 (2018).
144. Horn, A. et al. Hedgehog signaling controls fibroblast activation and tissue fibrosis in systemic sclerosis. *Arthritis Rheum.* **64**, 2724–2733 (2012).
145. Liang, R. et al. The transcription factor GLI2 as a downstream mediator of transforming growth factor-β-induced fibroblast activation in SSc. *Ann. Rheum. Dis.* **76**, 756–764 (2017).
146. Liang, R. et al. Acyltransferase skinny hedgehog regulates TGFβ-dependent fibroblast activation in SSc. *Ann. Rheum. Dis.* **78**, 1269–1273 (2019).
147. Bergmann, 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.* **77**, 92–98 (2025).
148. Horn, A. et al. Inhibition of hedgehog signalling prevents experimental fibrosis and induces regression of established fibrosis. *Ann. Rheum. Dis.* **71**, 785–789 (2012).
149. Distler, A. et al. Combined inhibition of morphogen pathways demonstrates additive antifibrotic effects and improved tolerability. *Ann. Rheum. Dis.* **73**, 1264–1268 (2014).
150. Zerr, P. et al. Inhibition of hedgehog signaling for the treatment of murine sclerodermatous chronic graft-versus-host disease. *Blood* **120**, 2909–2917 (2012).
151. Bergmann, C. & Distler, J. H. Canonical Wnt signaling in systemic sclerosis. *Lab. Invest.* **96**, 151–155 (2016).
152. Wei, J. et al. Canonical Wnt signaling induces skin fibrosis and subcutaneous lipoatrophy: a novel mouse model for scleroderma? *Arthritis Rheum.* **63**, 1707–1717 (2011).
153. Zhang, Y. et al. Targeting of canonical WNT signaling ameliorates experimental sclerodermatous chronic graft-versus-host disease. *Blood* **137**, 2403–2416 (2021).
154. Fakhouri, S. C. et al. Disturbed spatial WNT activation — a potential driver of the reticularized skin phenotype in systemic sclerosis. *Arthritis Rheumatol.* **77**, 740–749 (2025).
155. Daoussis, D. et al. Dickkopf-1 is downregulated early and universally in the skin of patients with systemic sclerosis despite normal circulating levels. *Clin. Exp. Rheumatol.* **36**, 45–49 (2018).
156. Bergmann, C. et al. Inhibition of glycogen synthase kinase 3β induces dermal fibrosis by activation of the canonical Wnt pathway. *Ann. Rheum. Dis.* **70**, 2191–2198 (2011).
157. Akhmetshina, A. et al. Activation of canonical Wnt signalling is required for TGF-β-mediated fibrosis. *Nat. Commun.* **3**, 735 (2012).
158. Bergmann, C. et al. X-linked inhibitor of apoptosis protein (XIAP) inhibition in systemic sclerosis (SSc). *Ann. Rheum. Dis.* **80**, 1048–1056 (2021).
159. Beyer, C. et al. Blockade of canonical Wnt signalling ameliorates experimental dermal fibrosis. *Ann. Rheum. Dis.* **72**, 1255–1258 (2013).
160. Distler, A. et al. Inactivation of tankyrases reduces experimental fibrosis by inhibiting canonical Wnt signalling. *Ann. Rheum. Dis.* **72**, 1575–1580 (2013).
161. Beyer, C. et al. β-catenin is a central mediator of pro-fibrotic Wnt signaling in systemic sclerosis. *Ann. Rheum. Dis.* **71**, 761–767 (2012).
162. Chen, C. W. et al. Pharmacological inhibition of porcupine induces regression of experimental skin fibrosis by targeting Wnt signalling. *Ann. Rheum. Dis.* **76**, 773–778 (2017).
163. Distler, A. et al. Inactivation of evenness interrupted (EVI) reduces experimental fibrosis by combined inhibition of canonical and non-canonical Wnt signalling. *Ann. Rheum. Dis.* **73**, 624–627 (2014).
164. Dees, C. et al. The Wnt antagonists DKK1 and SFRP1 are downregulated by promoter hypermethylation in systemic sclerosis. *Ann. Rheum. Dis.* **73**, 1232–1239 (2014).
165. Gillespie, J. et al. Transforming growth factor β activation primes canonical wnt signaling through down-regulation of axin-2. *Arthritis Rheumatol.* **70**, 932–942 (2018).
166. Trinh-Minh, T. et al. Noncanonical WNT5A controls the activation of latent TGF-β to drive fibroblast activation and tissue fibrosis. *J. Clin. Invest.* **134**, e159884 (2024).
167. Tsou, P. S., Varga, J. & O'Reilly, S. Advances in epigenetics in systemic sclerosis: molecular mechanisms and therapeutic potential. *Nat. Rev. Rheumatol.* **17**, 596–607 (2021).
168. Henderson, J., Distler, J. & O'Reilly, S. The role of epigenetic modifications in systemic sclerosis: a druggable target. *Trends Mol. Med.* **25**, 395–411 (2019).
169. Tsou, P. S. Epigenetic control of scleroderma: current knowledge and future perspectives. *Curr. Rheumatol. Rep.* **21**, 69 (2019).
170. Bergmann, C. & Distler, J. H. Epigenetic factors as drivers of fibrosis in systemic sclerosis. *Epigenomics* **9**, 463–477 (2017).
171. Pachera, E. et al. Long noncoding RNA H19X is a key mediator of TGF-β-driven fibrosis. *J. Clin. Invest.* **130**, 4888–4905 (2020).
172. Kramer, M. et al. Inhibition of H3K27 histone trimethylation activates fibroblasts and induces fibrosis. *Ann. Rheum. Dis.* **72**, 614–620 (2013).
173. Bergmann, C. et al. The histone demethylase Jumonji domain-containing protein 3 (JMJD3) regulates fibroblast activation in systemic sclerosis. *Ann. Rheum. Dis.* **77**, 150–158 (2018).
174. Huber, L. C. et al. Trichostatin a prevents the accumulation of extracellular matrix in a mouse model of bleomycin-induced skin fibrosis. *Arthritis Rheum.* **56**, 2755–2764 (2007).

175. Maurer, B. et al. MicroRNA-29, a key regulator of collagen expression in systemic sclerosis. *Arthritis Rheum.* **62**, 1733–1743 (2010).
176. Ramahi, A., Altorok, N. & Kahaleh, B. Epigenetics and systemic sclerosis: an answer to disease onset and evolution? *Eur. J. Rheumatol.* **7**, S147–S156 (2020).
177. Abd-Elmawla, M. A. et al. Deregulation of long noncoding RNAs ANCR, TINCR, HOTTIP and SPRY4-IT1 in plasma of systemic sclerosis patients: SPRY4-IT1 as a novel biomarker of scleroderma and its subtypes. *Cytokine* **133**, 155124 (2020).
178. Martinez-Lopez, J. et al. A strong dysregulated myeloid component in the epigenetic landscape of systemic sclerosis: an integrated DNA methylome and transcriptome analysis. *Arthritis Rheumatol.* **77**, 439–449 (2025).
179. Shin, J. Y. et al. Epigenetic activation and memory at a TGFB2 enhancer in systemic sclerosis. *Sci. Transl. Med.* **11**, eaaw0790 (2019).
180. Malaab, M. et al. Antifibrotic factor KLF4 is repressed by the miR-10/TFAP2A/TBX5 axis in dermal fibroblasts: insights from twins discordant for systemic sclerosis. *Ann. Rheum. Dis.* **81**, 268–277 (2022).
181. Tsou, P. S. et al. Histone deacetylase 5 is overexpressed in scleroderma endothelial cells and impairs angiogenesis via repression of proangiogenic factors. *Arthritis Rheumatol.* **68**, 2975–2985 (2016).
182. Ciechomska, M. et al. Histone demethylation and Toll-like receptor 8-dependent cross-talk in monocytes promotes transdifferentiation of fibroblasts in systemic sclerosis Via Fra-2. *Arthritis Rheumatol.* **68**, 1493–1504 (2016).
183. Li, T. et al. Epigenomics and transcriptomics of systemic sclerosis CD4+ T cells reveal long-range dysregulation of key inflammatory pathways mediated by disease-associated susceptibility loci. *Genome Med.* **12**, 81 (2020).
184. Lu, T. et al. Whole-genome bisulfite sequencing in systemic sclerosis provides novel targets to understand disease pathogenesis. *BMC Med. Genomics* **12**, 144 (2019).
185. van der Kroef, M. et al. Histone modifications underlie monocyte dysregulation in patients with systemic sclerosis, underlining the treatment potential of epigenetic targeting. *Ann. Rheum. Dis.* **78**, 529–538 (2019).
186. 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.* **54**, 2271–2279 (2006).
187. Ghosh, A. K. et al. p300 is elevated in systemic sclerosis and its expression is positively regulated by TGF-β: epigenetic feed-forward amplification of fibrosis. *J. Invest. Dermatol.* **133**, 1302–1310 (2013).
188. Liu, Y. et al. The roles of noncoding RNAs in systemic sclerosis. *Front. Immunol.* **13**, 856036 (2022).
189. Razin, A. & Riggs, A. D. DNA methylation and gene function. *Science* **210**, 604–610 (1980).
190. Nan, X. et al. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature* **393**, 386–389 (1998).
191. Chen, X. et al. Suppression of SUN2 by DNA methylation is associated with HSCs activation and hepatic fibrosis. *Cell Death Dis.* **9**, 1021 (2018).
192. Sanders, Y. Y. et al. Thy-1 promoter hypermethylation: a novel epigenetic pathogenic mechanism in pulmonary fibrosis. *Am. J. Respir. Cell Mol. Biol.* **39**, 610–618 (2008).
193. Zhang, Y. et al. Poly(ADP-ribose) polymerase-1 regulates fibroblast activation in systemic sclerosis. *Ann. Rheum. Dis.* **77**, 744–751 (2018).
194. Asano, Y., Czuwara, J. & Trojanowska, M. Transforming growth factor-β regulates DNA binding activity of transcription factor Fli1 by p300/CREB-binding protein-associated factor-dependent acetylation. *J. Biol. Chem.* **282**, 34672–34683 (2007).
195. Noda, S. et al. Simultaneous downregulation of KLF5 and Fli1 is a key feature underlying systemic sclerosis. *Nat. Commun.* **5**, 5797 (2014).
196. Asano, Y., Bujor, A. M. & Trojanowska, M. The impact of Fli1 deficiency on the pathogenesis of systemic sclerosis. *J. Dermatol. Sci.* **59**, 153–162 (2010).
197. Asano, Y. & Trojanowska, M. Fli1 represses transcription of the human α2(I) collagen gene by recruitment of the HDAC1/p300 complex. *PLoS ONE* **8**, e74930 (2013).
198. Dees, C. et al. TGF-β-induced epigenetic deregulation of SOCS3 facilitates STAT3 signaling to promote fibrosis. *J. Clin. Invest.* **130**, 2347–2363 (2020).
199. Zhao, S. et al. 5-aza-2′-deoxycytidine inhibits the proliferation of lung fibroblasts in neonatal rats exposed to hyperoxia. *Pediatr. Neonatol.* **58**, 122–127 (2017).
200. Bechtel, W. et al. Methylation determines fibroblast activation and fibrogenesis in the kidney. *Nat. Med.* **16**, 544–550 (2010).
201. Selmi, C. et al. X chromosome gene methylation in peripheral lymphocytes from monozygotic twins discordant for scleroderma. *Clin. Exp. Immunol.* **169**, 253–262 (2012).
202. Ramos, P. S. et al. Integrative analysis of DNA methylation in discordant twins unveils distinct architectures of systemic sclerosis subsets. *Clin. Epigenetics* **11**, 58 (2019).
203. Zehender, A. et al. TGFβ promotes fibrosis by MYST1-dependent epigenetic regulation of autophagy. *Nat. Commun.* **12**, 4404 (2021).
204. Papazoglou, A. et al. Epigenetic regulation of profibrotic macrophages in systemic sclerosis-associated interstitial lung disease. *Arthritis Rheumatol.* **74**, 2003–2014 (2022).
205. Liu, F. et al. Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol* **308**, L344–L357 (2015).
206. Conroy, K. P., Kitto, L. J. & Henderson, N. C. αv integrins: key regulators of tissue fibrosis. *Cell Tissue Res.* **365**, 511–519 (2016).
207. Panciera, T. et al. Mechanobiology of YAP and TAZ in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **18**, 758–770 (2017).
208. Choudhry, H. & Harris, A. L. Advances in hypoxia-inducible factor biology. *Cell Metab.* **27**, 281–298 (2018).
209. Beyer, C. et al. Hypoxia. Hypoxia in the pathogenesis of systemic sclerosis. *Arthritis Res. Ther.* **11**, 220 (2009).
210. Distler, J. H. et al. Hypoxia-induced increase in the production of extracellular matrix proteins in systemic sclerosis. *Arthritis Rheum.* **56**, 4203–4215 (2007).
211. Xiong, A. & Liu, Y. Targeting hypoxia inducible factors-1α as a novel therapy in fibrosis. *Front. Pharmacol.* **8**, 326 (2017).
212. Baker, S. J., Rane, S. G. & Reddy, E. P. Hematopoietic cytokine receptor signaling. *Oncogene* **26**, 6724–6737 (2007).

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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