Systemic sclerosis

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Abstract | Systemic sclerosis is a complex autoimmune disease characterized by a chronic and frequently progressive course and by extensive patient-to-patient variability. Like other autoimmune diseases, systemic sclerosis occurs more frequently in women, with a peak of onset in the fifth decade of life. The exact cause of systemic sclerosis remains elusive but is likely to involve environmental factors in a genetically primed individual. Pathogenesis is dominated by vascular changes; evidence of autoimmunity with distinct autoantibodies and activation of both innate and adaptive immunity; and fibrosis of the skin and visceral organs that results in irreversible scarring and organ failure. Intractable progression of vascular and fibrotic organ damage accounts for the chronic morbidity and high mortality. Early and accurate diagnosis and classification might improve patient outcomes. Screening strategies facilitate timely recognition of life-threatening complications and initiation of targeted therapies to halt their progression. Effective treatments of organ-based complications are now within reach. Discovery of biomarkers — including autoantibodies that identify patient subsets at high risk for particular disease complications or rapid progression — is a research priority. Understanding the key pathogenetic pathways, cell types and mediators underlying disease manifestations opens the door for the development of targeted therapies with true disease-modifying potential. For an illustrated summary of this Primer, visit: http://go.nature.com/lchkcA

Systemic sclerosis is an autoimmune disease that is characterized by the distinctive pathogenetic triad of microvascular damage, dysregulation of innate and adaptive immunity, and generalized fibrosis in multiple organs. Although skin fibrosis is the distinguishing hallmark, the pathological changes in the lungs, gastrointestinal tract, kidneys and heart determine the clinical outcome. In general, the extent of skin involvement and its rate of progression reflect the severity of visceral organ complications[1,2].

A striking feature of systemic sclerosis is its patient-to-patient variability, and heterogeneity has been observed in clinical manifestations, autoantibody profiles, tempo of disease progression, response to treatment and survival (TABLE 1). On the basis of the extent of their skin involvement, patients are grouped into limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) subsets[3]. In lcSSc, skin fibrosis is restricted to the fingers (sclerodactyly), distal extremities and face, whereas in dcSSc, the trunk and proximal extremities are also affected. In patients with lcSSc, Raynaud phenomenon (BOX 1) typically precedes skin involvement and other disease manifestations by months to years, whereas patients with dcSSc have rapid disease progression with extensive skin changes and early development of visceral organ complications. Autoantibodies are particularly helpful in systemic sclerosis for both diagnosis and classification. lcSSc is commonly associated with centromere-specific antibodies, whereas dcSSc is more often associated with topoisomerase I- or RNA polymerase III-specific antibodies[4]. However, not all patients with systemic sclerosis fall clearly into one of these two disease subsets, and some can change their subset assignment over time. Furthermore, some individuals present with hallmark clinical and serological features of systemic sclerosis in the absence of detectable skin involvement (systemic sclerosis *sine* scleroderma); others manifest features of another connective tissue disease, such as rheumatoid arthritis or polymyositis, in overlap with systemic sclerosis (overlap syndrome).

In 2013, revised classification criteria — the American College of Rheumatology (ACR)–European League Against Rheumatism (EULAR) criteria — were proposed to address some of the difficulties in classification[5,6]. However, none of the currently used classification schemes adequately captures disease complexity and heterogeneity in systemic sclerosis, suggesting that a clinically useful, new taxonomy based on genetic or molecular disease determinants needs to be developed and implemented in future clinical practice and trials.

In this Primer, we describe the epidemiology and genetic risks of systemic sclerosis, current views of pathogenesis, and approaches to screening, diagnosis and

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prevention of organ complications. We end by presenting an outlook for the future.

Epidemiology

Prevalence and incidence estimates of systemic sclerosis around the world vary substantially. Lower estimates of prevalence (<150 per million) and incidence (<10 per million per year) have been observed in northern Europe and Japan, whereas higher estimates of prevalence (276–443 per million) and incidence (14–21 per million per year) have been reported in southern Europe, North America and Australia[7]. The 2013 ACR–EULAR classification criteria are more sensitive than the criteria published in the 1980s because they include patients who are positive for centromere-specific antibodies and who have limited cutaneous involvement[8]. As a consequence, the estimated prevalence of systemic sclerosis based on the ACR–EULAR classification criteria (for example, 88 per million in men, 514 per million in women and overall 305 per million in Sweden) was much higher than previously published estimates[7,8].

The development of systemic sclerosis is sex dependent and, as is true for all connective tissue diseases, is much more common in women (FIG. 1). However, the EULAR Scleroderma Trials and Research (EUSTAR) cohort (see the EUSTAR website) has revealed some unusual features in men[9]. In a cross-sectional study of 9,182 patients with systemic sclerosis, including 1,321 men, male sex was independently associated with a higher risk of dcSSc (odds ratio (OR) 1.68; 95% CI 1.45–1.94; $P<0.001$), a higher frequency of digital ulcers (OR 1.28; 95% CI 1.11–1.47; $P<0.001$) and pulmonary arterial hypertension (PAH; OR 3.01; 95% CI 1.47–6.20; $P<0.003$). In a longitudinal study (mean follow-up 4.9 ± 2.7 years), male sex was predictive of new onset of PAH (hazard ratio (HR) 2.70; 95% CI 1.38–5.29; $P=0.004$), heart failure (HR 2.15; 95% CI 1.03–4.48; $P=0.04$) and all-cause mortality (HR 1.48; 95% CI 1.19–1.84; $P<0.001$). Male sex has been consistently shown to be a poor prognostic factor in systemic sclerosis.

As in other connective tissue disorders such as systemic lupus erythematosus, ethnicity has a role in systemic sclerosis. A large US study[10] showed that African American patients presented at a younger mean age than white patients (47 years versus 53 years; $P<0.001$). Furthermore, two-thirds of white patients exhibited lcSSc, whereas the majority of black patients had dcSSc ($P<0.001$). The race differential was mirrored by the finding that African Americans with systemic sclerosis were more likely to have antibodies against topoisomerase I and less likely to be positive for centromere-specific antibodies. In addition, African American patients experienced an increase in risk of mortality (relative risk (RR) 1.8; 95% CI 1.4–2.2) after adjustment for age at disease onset and disease duration. Thus, race is related to a distinct phenotypic profile, and there is a trend towards less favourable outcomes in African American patients.

The overlap between systemic sclerosis and other connective tissue disorders has been recognized for some time. The links between connective tissue diseases are further supported by the results from genome-wide association studies (GWASs) that highlight the critical role of shared autoimmunity. The co-occurrence of another autoimmune disease with systemic sclerosis was investigated in a meta-analysis of 6,102 patients with systemic sclerosis obtained from 10 studies[11]. Of these patients, 1,432 had one or more additional autoimmune disease corresponding to a weighted prevalence of poly-autoimmunity of 26% (95% CI 20–32%). Thus, these results confirm that poly-autoimmunity is frequent in systemic sclerosis, affecting 25% of patients. It remains to be determined how this finding might affect

Table 1 | **Clinical subsets in systemic sclerosis**

Clinical subset	Clinical manifestations	Primary targets of autoantibodies	Disease course
Limited cutaneous systemic sclerosis	• Distal skin fibrosis, sclerodactyly, telangiectasia and calcinosis cutis may be prominent • Severe interstitial lung disease and scleroderma renal crisis are very rare	Centromere proteins	• Raynaud phenomenon may precede other manifestations • Slow progression with late development of PAH
Diffuse cutaneous systemic sclerosis	• Proximal skin fibrosis up to elbows and knees, including trunk • Tendon friction rubs may be present	Topoisomerase I and RNA polymerase III	• Rapidly progressive skin fibrosis • Early occurrence of renal, cardiac and pulmonary complications
Systemic sclerosis *sine* scleroderma	No detectable skin involvement	Nuclear and centromere proteins	Raynaud phenomenon, nailfold capillary abnormalities and PAH
Overlap syndrome	Features of another connective tissue disease in the setting of systemic sclerosis	U1 RNP, PM–Scl, Ro and La	• Prominent musculoskeletal involvement • Lung fibrosis and scleroderma renal crisis are uncommon

PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein.

Box 1 | **Raynaud phenomenon**

- Raynaud phenomenon refers to reversible vasospasm of arteries, such as digital arteries
- In systemic sclerosis, the vasospasms are accompanied by progressive structural damage, including proliferation of the arterial intima, adventitial fibrosis and collagen deposition
- Vasodilators target vasospasm, especially calcium channel blockers, phosphodiesterase 5 inhibitors and prostacyclins

the outcomes and how it could be used to guide the choice of treatments and also the positioning of potential biologic agents.

Mechanisms/pathophysiology

Systemic sclerosis is thought to be caused by environmental events in a genetically susceptible individual that trigger a chronic and self-amplifying multifocal process characterized by vascular alterations, inflammation and autoimmunity, and fibrosis[12] (FIG. 2). Cell types prominently implicated in the disease process include endothelial cells, platelets, structural cells (pericytes, vascular smooth muscle cells, fibroblasts and myofibroblasts) and immune cells (T cells, B cells, monocytes, macrophages and dendritic cells). Prominent mediators of cell activation include transforming growth factor-β (TGFβ), platelet-derived growth factor (PDGF), IL-6 and IL-13, endothelin 1, angiotensin II, lipid mediators and autoantibodies, along with reactive oxygen species (ROS) and numerous other biologically active substances[13]. Still poorly understood is the pathogenetic basis for female predominance, the disease heterogeneity and variable outcomes, the nature of environmental triggers and their interplay with the genetic background, and the precise contribution of these interactions to disease susceptibility and phenotype.

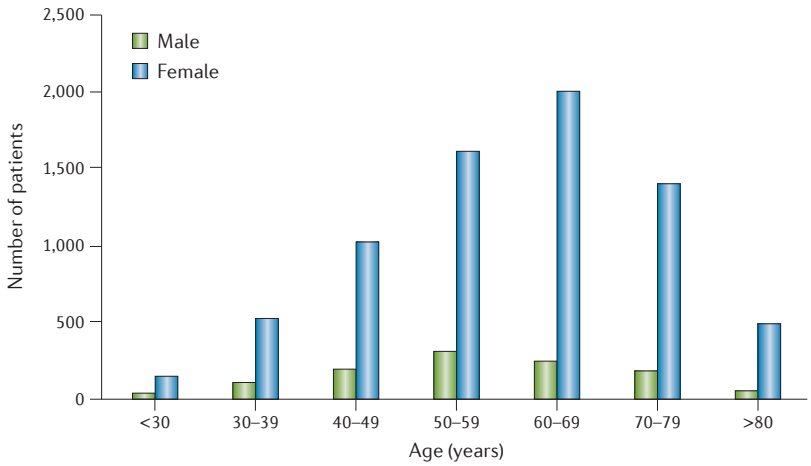

Figure 1 | **Characteristics of the EUSTAR cohort.** Figure shows the gender and age distribution of the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) cohort in 2013. The EUSTAR registry contains baseline and yearly follow-up data of approximately 10,000 patients with systemic sclerosis from about 200 centres. However, inclusion and exclusion criteria may vary between studies, which leads to differences in sample size. More information on cohort characteristics and quality control is available at www.eustar.org.

Vascular injury and microangiopathy

Microvascular injury and endothelial cell activation that results in vascular damage are the earliest, and possibly primary, events in systemic sclerosis[14]. Progressive vascular damage causes a reduction in the number of capillaries (rarefaction), thickening of the vessel wall due to intimal and smooth muscle cell proliferation, and luminal narrowing, which lead to tissue hypoxia and oxidative stress[14]. In addition, activated endothelial cells show increased expression of the adhesion molecules vascular cell adhesion protein 1 (VCAM1), intercellular adhesion molecule (ICAM) and E-selectin, resulting in recruitment of inflammatory cells. They also secrete endothelin 1, connective tissue growth factor (CTGF; also known as CCN2) and other profibrotic factors that stimulate vascular smooth muscle cell proliferation and extracellular matrix production. Inflammatory cell infiltration in the lesions can be prominent in patients with early-stage disease, and inflammatory and immune cells are an important source of TGFβ, PDGF, IL-1, IL-6 and other profibrotic mediators (FIG. 2).

Inflammation and immune response

Dysregulation of both innate and adaptive immunity plays a prominent part in systemic sclerosis. Evidence of (auto)immunity includes the presence of inflammatory cells and inflammatory signatures in target tissues such as the skin and lungs; alterations in the number and function of circulating immune cells; the presence of a prominent type I interferon (IFN) signature in circulating and tissue-infiltrating immune cells; and characteristic and distinct serum autoantibodies detected in most patients. Furthermore, genetic studies identified that polymorphisms of *IRF5* (interferon regulatory factor 5) and *STAT4* (signal transducer and activator of transcription 4), along with several other immune pathway genes, are prominently associated with systemic sclerosis[15].

Cellular response. Circulating and tissue-infiltrating monocytes and macrophages, plasmacytoid dendritic cells and stromal cells show a type I IFN signature, defined by increased expression of IFN-regulated genes, which reflects activation of Toll-like receptor (TLR)-mediated immune signalling[16–18]. TLR activation in these cells is thought to be triggered by endogenous ligands, such as nucleic acid-containing immune complexes, as well as by damage-associated molecular patterns (DAMPs), such as variants of extracellular matrix components generated during tissue injury.

Fibrotic tissue also displays prominent infiltration of bone marrow-derived immune cells that include $CD4^+$ T cells, macrophages, activated B cells, plasmacytoid dendritic cells and mast cells. Among $CD4^+$ T cells, type 2 T helper (T_H2) cells — characterized by secretion of IL-4 and IL-13 — predominate over T_H1 cells, which primarily secrete anti-fibrotic IFNγ[19]. The role of T_H17 cells remains to be defined, with some

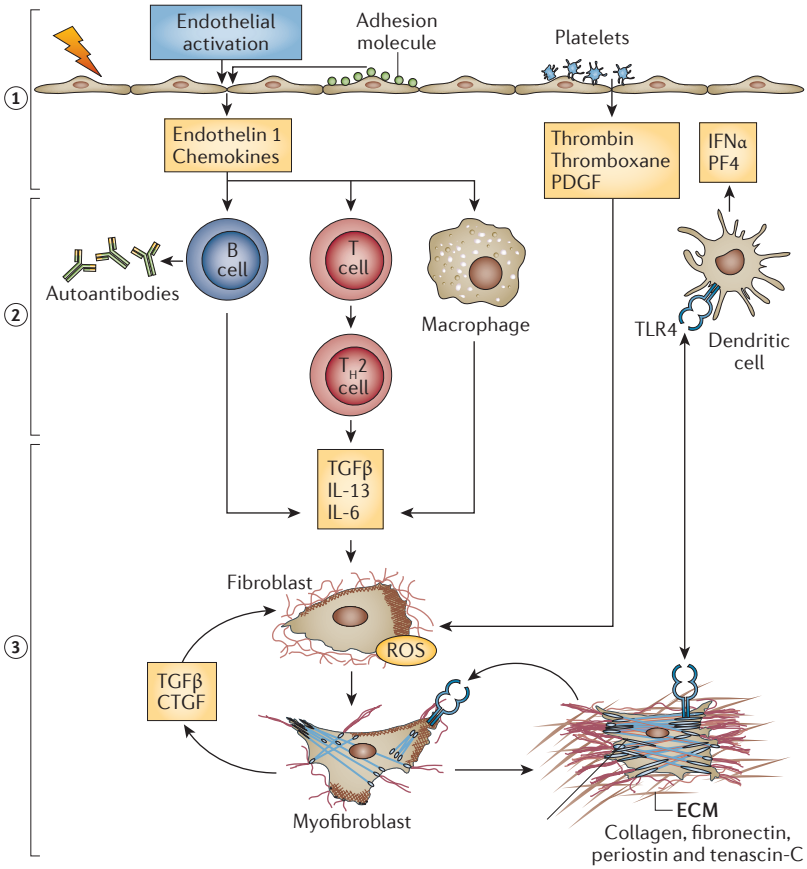

Figure 2 | **The disease process in systemic sclerosis.** The fibroblast activation and fibrosis underlying systemic sclerosis are induced by vascular injury and endothelial activation, leading to an uncontrolled inflammatory reaction. Step 1: the vascular response to injury consists of endothelial activation; production of endothelin 1 and chemokines; increased expression of adhesion molecules; and platelet activation. Step 2: in response to chemokines and adhesion receptors, several types of inflammatory cells are recruited. Activated type 2 T helper (T_H2) cells secrete TGFβ and IL-13; B cells produce autoantibodies and IL-6; macrophages release transforming growth factor-β (TGFβ); and dendritic cells secrete interferon-α (IFNα) and platelet factor 4 (PF4). Step 3: resident fibroblasts, activated by this cytokine 'cocktail', generate reactive oxygen species (ROS) and undergo differentiation into myofibroblasts, which are responsible for the excessive extracellular matrix (ECM) production. Activation of Toll-like receptor 4 (TLR4) on immune cells and myofibroblasts by the ECM further exacerbates this reaction. CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor.

studies implicating IL-17 in fibrosis and other studies indicating an anti-fibrotic effect[20]. Finally, emerging evidence suggests an important pathogenetic role of tissue macrophages with an 'alternatively activated' M2 phenotype. Levels of soluble CD163, a marker for M2 macrophages, are elevated in the sera of patients with systemic sclerosis, as well as on macrophages in the affected skin and lungs[21–24]. The mechanisms of how these polarized macrophages are differentiated — as well as how they contribute to the induction, progression and possibly resolution of vascular damage and tissue fibrosis — remain to be determined.

Cytokines and chemokines. T_H2 cytokines, including IL-4 and IL-13, have prominent roles in the pathogenesis of systemic sclerosis. The levels of T_H2 cytokines are increased in the serum and fibrotic tissue, and they stimulate fibroblast proliferation and extracellular matrix synthesis in cell cultures[25]. These findings are supported by studies in animal models, as illustrated by the attenuation of fibrosis in mice with the genetic deletion of *Il13*, whereas targeted overexpression of *Il13* results in pulmonary fibrosis[26].

Of special interest in systemic sclerosis is IL-6, a multifunctional cytokine produced by T cells and B cells, fibroblasts, fibrocytes and endothelial cells. IL-6 signals through the widely expressed GP130 receptor that forms a heterodimer with IL-6 receptor subunit-α, which activates the JAK/STAT and mitogen-activated protein kinase (MAPK) pathways and induces T_H2-dominant immunity, inflammation and fibrotic responses. High levels of IL-6 in systemic sclerosis correlate with the extent of skin involvement and portend poor long-term outcomes[27]. *In vitro*, an antibody against human IL-6 reduced type I collagen levels in fibroblasts derived from patients with systemic sclerosis, whereas mice with the genetic deletion of *Il-6* had reduced inflammation and fibrosis after a profibrotic challenge (bleomycin). Moreover, administration of an IL-6 receptor-specific antibody in mice prevented development of fibrosis induced either by bleomycin or by immunization with topoisomerase I[28,29]. These observations provide the rationale for ongoing clinical trials of IL-6 receptor-specific antibody (tocilizumab) in systemic sclerosis (ClinicalTrials.gov identifier NCT01532869).

Chemokines have important roles in angiogenesis, wound healing and fibrosis. Serum and tissue levels of C-C motif chemokine 2 (CCL2; also known as MCP1), CCL3 (also known as MIP1α), IL-8 and CCL18 are increased in patients with systemic sclerosis, correlate with disease severity and can predict progression[30–32]. Plasmacytoid dendritic cells from patients were found to secrete markedly elevated amounts of the small chemokine platelet factor 4 (PF4; also known as CXCL4); under physiological conditions, PF4 is primarily localized in α-granules of activated platelets[33]. Levels of PF4 were elevated in the sera and skin from patients with systemic sclerosis and were good predictors of the risk of pulmonary complications, including lung fibrosis and PAH[33].

Autoantibodies. Nearly all patients with systemic sclerosis have highly specific circulating autoantibodies (TABLE 2). Most commonly, these autoantibodies are directed against intracellular nuclear and nucleolar components, but they can also be directed against cell surface receptors and extracellular antigens, including fibrillin 1, matrix metalloprotease 1 (MMP1) and MMP3 (REF. 34). Although the diagnostic importance of nuclear- and nucleolar-specific antibodies in systemic sclerosis is well recognized, their potential role in contributing to pathogenesis and tissue damage is not. However, of interest is that patients with systemic sclerosis have been reported to have circulating autoantibodies to cell surface receptors for acetylcholine (the muscarinic acetylcholine receptor M3), PDGF,

Table 2 | **Selected autoantibodies linked to complications in systemic sclerosis**

Primary target of autoantibody	Immunofluorescence pattern	Clinical association
Diffuse cutaneous systemic sclerosis		
DNA topoisomerase I	Speckled	Interstitial lung disease
RNA polymerase III	Speckled	Renal crisis and cancer
Fibrillarin (ribonucleolarprotein; targets U3 RNP)	Nucleolar	PAH and myositis
Limited cutaneous systemic sclerosis		
Centromere proteins	Centromeric	Ischaemic digital ulcers and telangiectasia
Th/To ribonucleoprotein	Nucleolar	Interstitial lung disease

PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein.

endothelin 1 and angiotensin II, among others. These autoantibodies have been shown in some studies to be functional, as they were capable of triggering receptor activation and eliciting profibrotic responses[35,36].

Fibrosis

The distinguishing hallmark of systemic sclerosis is progressive tissue accumulation of fibrous matrix composed of collagen, elastin, glycosaminoglycan and fibronectin. The process leads to permanent scarring and replacement of normal tissue architecture with compact, mechanically stressed, rigid connective tissue[13]. Excessive accumulation of extracellular matrix results from a combination of increased synthesis by activated stromal cells; enhanced assembly and crosslinking catalysed by prolyl and lysyl oxidase and transglutaminase 2; and defective degradation[37].

Fibrotic tissue is characterized by the presence of α-smooth muscle actin-positive, apoptosis-resistant myofibroblasts. These contractile cells secrete not only matrix molecules but also TGFβ and other profibrotic mediators, further promoting extracellular matrix accumulation and remodelling. The origin of activated mesenchymal cells in fibrosis is of great research interest and has therapeutic implications[38]. Monocyte-derived circulating mesenchymal progenitor cells (fibrocytes) — as well as tissue-specific transdifferentiation from pericytes, telocytes and endothelial cells — might each contribute to expansion of the reservoir of disease-causing myofibroblasts. A recent study using lineage tracing indicates that the majority of myofibroblasts in the fibrotic dermis in mice arise from intradermal adipocyte progenitors[39].

Fibroblast differentiation, recruitment, proliferation and activation in systemic sclerosis are controlled by a combination of mechanical factors and paracrine and/or autocrine mediators (FIG. 3). Excessive collagen deposition and crosslinking increases tissue stiffness and reduces elasticity of affected organs, resulting in mechanical stress. Fibroblasts sense and respond to mechanical forces in their environment through a process of mechanotransduction that involves cell surface integrins and changes in cytoskeletal tension mediated by focal adhesion kinase (FAK) and RHO-associated kinase. These signals activate the downstream effectors YAP (Yes-associated protein) and TAZ (transcriptional co-activator with PDZ-binding motif), which perpetuate fibroblast activation and further exacerbate the fibrotic process[40].

In addition, high levels of alternatively spliced isoforms of extracellular matrix molecules such as fibronectin (fibronectin-EDA (Fn^{EDA})) and tenascin-C are known to accumulate within fibrotic lesions. One study demonstrated that these isoforms can directly bind to TLR4 on stromal cells and induce fibroblast activation and myofibroblast differentiation[41]. Blocking TLR4 signalling might therefore represent a novel therapeutic opportunity for halting fibrosis.

Of the multitude of soluble mediators implicated in systemic sclerosis, TGFβ is commonly viewed as the master regulator of fibrosis[42]. This pleiotropic cytokine is secreted from macrophages and other cells as an inactive precursor complexed to latent TGFβ-binding protein and deposited within the extracellular matrix; it is converted to its biologically active form via integrin-mediated activation. Canonical TGFβ signalling involves sequential phosphorylation of the type I TGFβ receptor (TGFR1; also known as ALK5), activation of cytosolic signal transducers SMAD2–SMAD3, and their binding to a consensus SMAD-binding element found in TGFβ-inducible profibrotic genes. The SMAD pathway is positively and negatively regulated by various factors, including SMAD7, which blocks SMAD signalling, and the nuclear receptor NR4A1, which promotes SMAD7 degradation and modulates TGFβ signalling[43,44]. Fibrotic TGFβ responses can also be mediated via the transcription factor early growth response 1 (EGR1), the non-receptor tyrosine kinases ABL1 (previously known as c-ABL) and FAK, and potentiated via inactivation of transcriptional repressors such as peroxisome proliferator-activated receptor-γ (PPARγ), friend leukaemia integration 1 (FLI1) and krüppel-like factor (KLF) family members[13]. Fibroblasts derived from patients with systemic sclerosis show constitutive FAK activation, which integrates TGFβ signalling and integrin-mediated mechanotransduction to drive persistent myofibroblast differentiation and ROS generation[45]. Other identified intracellular TGFβ signalling pathways implicated in systemic sclerosis include MAPK1 and MAPK3 (also known as ERK2 and ERK1, respectively), p38, phosphatidylinositol 3-kinase (PI3K), AKT and TGFβ-activated kinase 1 (TAK)[42]. As integrins, ABL1, FAK and other TGFβ mediators can all be selectively targeted by pharmacological inhibitors, they represent potential therapeutic targets.

CTGF is a cysteine-rich matricellular protein that functions in conjunction with TGFβ to enhance fibrotic responses. CTGF is expressed at low levels in normal tissues but is markedly increased in the sera of patients with systemic sclerosis, and levels correlate with the extent of skin and pulmonary fibrosis[46]. TGFβ, endothelin 1 and angiotensin II are potent inducers of CTGF[47].

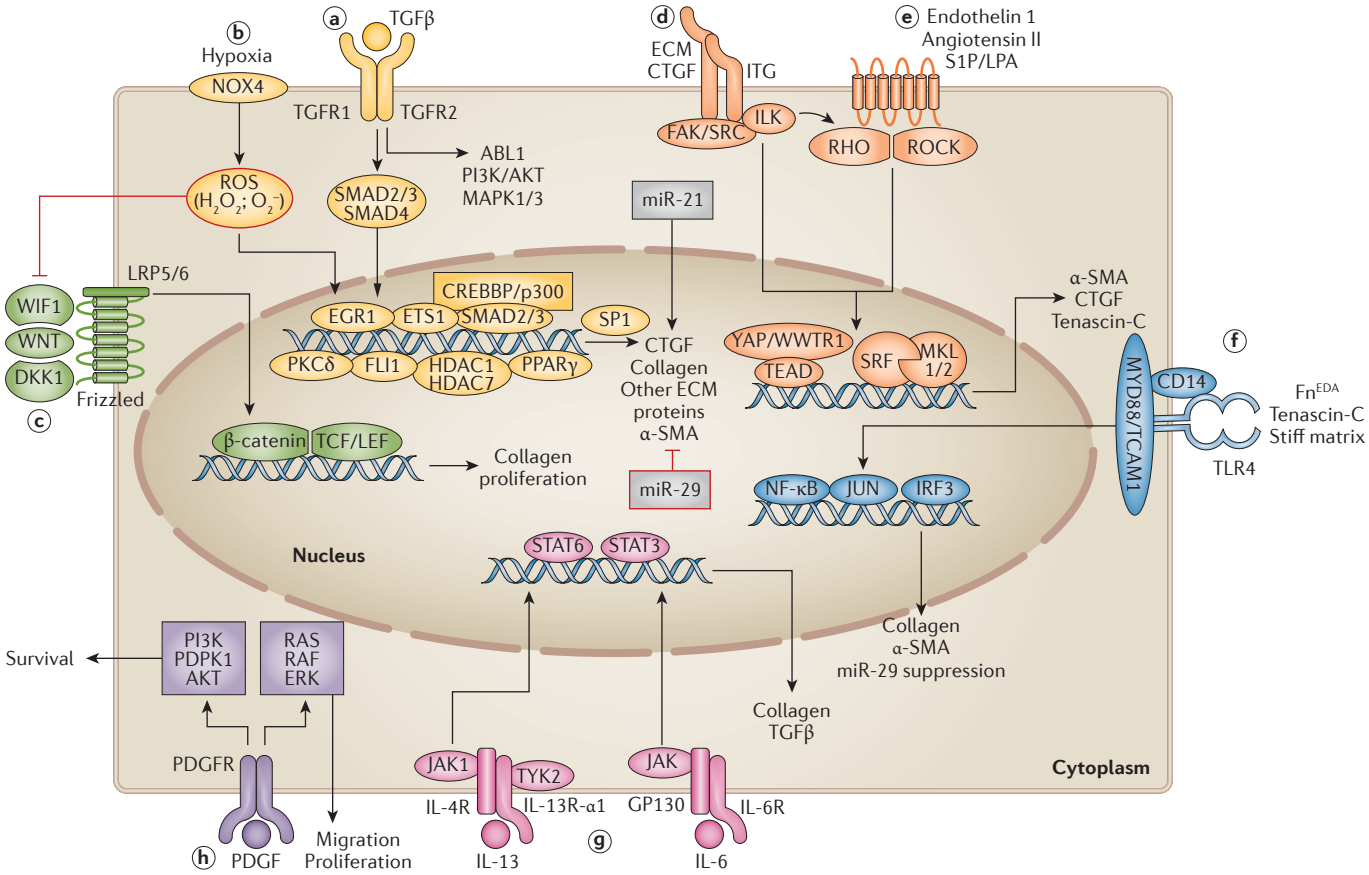

Figure 3 | **Molecular mechanisms of fibroblast activation in systemic sclerosis.** Fibroblast activation and their transdifferentiation to myofibroblasts are regulated by various paracrine and/or autocrine molecules and mechanical stimuli, and this process involves a highly complex and interconnected intracellular signalling cascade[50]. **a** | Transforming growth factor-β (TGFβ) signalling has a central role by inducing profibrotic gene expression through activation of canonical (SMAD2–SMAD3 (SMAD2/3)- and SMAD4-dependent) and non-canonical pathways, and through crosstalk with other intracellular signalling pathways. SMAD2/3 cooperates with other transcriptional activators (for example, ETS1) to induce the expression of connective tissue growth factor (CTGF), collagen and other profibrotic genes[189–191]. Of note, the transcription co-activators p300 (a histone acetyltransferase) and CREB-binding protein (CREBBP), which are also present in the transcriptional complex at the promoter region of these genes, are constitutively elevated in fibroblasts isolated from patients with systemic sclerosis[67]. In addition, TGFβ signalling promotes profibrotic gene expression by inactivating the transcriptional repressors friend leukaemia integration 1 (FLI1) and peroxisome proliferator-activated receptor-γ (PPARγ)[144,192]. Non-canonical TGFβ signalling pathways with relevance to fibrosis include focal adhesion kinase (FAK), ABL1, phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase 1 (MAPK1)–MAPK3 (MAPK1/3), p38, endoglin and SMAD1 pathways[193]. The ABL1 pathway, for example, regulates the profibrotic transcription factor early growth response 1 (EGR1)[194]. **b** | TGFβ and hypoxia converge on EGR1 to stimulate NADPH oxidase 4 (NOX4) expression, leading to reactive oxygen species (ROS) generation[194]. **c** | In addition to TGFβ, canonical WNT signalling promotes fibrosis. This pathway is found to be hyperactivated in fibrotic lesions[53]. WNT3A induces a fibrogenic response in dermal fibroblasts[53]. WNT inhibitory factor 1 (WIF1) is a ROS target and is constitutively downregulated in fibroblasts derived from patients with systemic sclerosis[50]. **d** | Mechanical stress, sensed by integrins (ITGs), also has a pivotal role in the formation of myofibroblasts through induction of α-smooth muscle actin (α-SMA), CTGF and tenascin-C, among others. Mechanical stimulation triggers the formation of an intracellular multiprotein signalling complex composed of FAK, SRC, MEK, integrin-linked protein kinase (ILK), RHOA and F-actin[195]. Moreover, the profibrotic effects of CTGF are mediated through the ITG and SRC in dermal fibroblasts[196]. Two known transcriptional regulatory pathways mediate the cellular response to mechanical signals: myocardin-related transcription factors, MKL/myocardin-like protein 1 (MKL1), MKL2 and serum response factor (SRF); and the components of the Hippo pathway, YAP1 and WW domain-containing transcription regulator protein 1 (WWTR1)[197]. **e** | Alternatively, this pathway can be stimulated by RHO small GTPase and F-actin signalling, which is activated by endothelin 1, angiotensin II and sphingosine 1 phosphate/lysophosphatidic acid (S1P/LPA). **f** | Connective tissue molecules, such as an alternately spliced variant of fibronectin (Fn^{EDA}) and tenascin-C, which are induced by TGFβ and constitutively upregulated in systemic sclerosis, represent damage-associated molecular patterns (DAMPs) that serve as endogenous ligands of Toll-like receptor 4 (TLR4)[41]. The TLR4-mediated profibrotic pathway is not yet fully understood, but it might involve suppression of anti-fibrotic microRNA-29 (miR-29). Of note, miR-21 is suggested to be involved in promoting the fibrotic response by suppressing an inhibitor of the TGFβ non-canonical pathway — specifically, SMAD7 (REF. 68). **g** | IL-6 and IL-13 are pleiotropic cytokines, which directly or indirectly through TGFβ, drive collagen production and promote fibrotic matrix deposition[198,199]. **h** | Finally, platelet-derived growth factor (PDGF) signalling stimulates fibroblast migration, proliferation, survival and matrix gene expression[48]. DKK1, dickkopf WNT signalling pathway inhibitor 1; ECM, extracellular matrix; GP130, envelope glycoprotein 130; HDAC, histone deacetylase; IL-4R, IL-4 receptor; IRF3, interferon regulatory factor 3; LEF, lymphoid enhancer-binding factor; LRP, low-density lipoprotein receptor-related protein; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; PDGFR, PDGF receptor; PDPK1, 3-phosphoinositide-dependent protein kinase 1; PKCγ, protein kinase C-γ; ROCK, RHO-associated protein kinase; STAT, signal transducer and activator of transcription; TCAM1, TIR domain-containing adaptor molecule 1; TCF, transcription factor; TEAD, transcriptional enhancer factor; TGFR, TGF receptor.

PDGFs also have a role in fibrosis. PDGFs are heterodimeric peptides secreted by platelets, macrophages, endothelial cells and fibroblasts that function as potent mitogens and chemo-attractants for mesenchymal cells[48]. Transgenic mice expressing a constitutively active PDGF receptor-α (*Pdgfra*) develop fibrosis in multiple organs[49]. Patients with systemic sclerosis show increased expression of PDGFRα and PDGFRβ in the skin and bronchoalveolar lavage fluid and, as noted above, have circulating antibodies that trigger PDGFR-mediated fibroblast activation and ROS generation[35]. Explanted systemic sclerosis fibroblasts constitutively produce ROS, which might directly contribute to persistent fibrosis via DNA damage and autocrine amplification of TGFβ, as well as to WNT-mediated fibrotic responses in these cells[50].

The evolutionarily conserved WNT signalling network controls developmental processes and the maintenance of adult tissue homeostasis. Through the canonical β-catenin intracellular signalling pathways, WNT proteins elicit fibrotic responses both directly and through TGFβ[51]. Aberrantly elevated expression of nuclear (activated) β-catenin and its target gene *AXIN2* occur in the skin and lungs of patients with systemic sclerosis, as well as in animal models of the disease[52,53]. Microarray studies of skin biopsy samples provide further evidence for activated WNT–β-catenin pathways in systemic sclerosis, suggesting that therapeutic blockade of WNT signalling might be a possible therapeutic approach.

Genetic factors

Although the exact cause that triggers the onset of the microvascular damage and the associated immune response and fibrosis remains elusive, interplay between genetic factors and environmental events is likely to play a part. Although systemic sclerosis is not considered to be a Mendelian disorder, in a study of 703 families, first-degree relatives of patients with systemic sclerosis had a RR of 13 (95% CI 2.9–48.6; $P < 0.001$) for developing systemic sclerosis[54]; they are also more likely to develop Raynaud phenomenon, systemic lupus erythematosus and other autoimmune diseases[55].

Single-nucleotide polymorphisms. GWASs and immunoChIP (chromatin immunoprecipitation) analyses have identified single-nucleotide polymorphisms (SNPs) at multiple loci that are associated with susceptibility to systemic sclerosis in general, and with specific clinical and autoantibody-defined disease subsets. In particular,

Table 3 | **Selected genetic variants identified as risk factors for systemic sclerosis***

Gene	Clinical association	Putative function of encoded proteins	Study approach	Refs
Major histocompatibility region genes (*HLA-DQ1B*, *HLA-DQA1*, *DBP1*, *DRB1* and *NOTCH4*)	Systemic sclerosis positive for topoisomerase I- and/or centromere-specific antibodies	Histocompatibility complex and immune regulation	GWAS and immunoChIP	15
IRF5‡	Systemic sclerosis	Transcription factor regulating inflammatory gene expression	GWAS and immunoChIP	200
CD247	Systemic sclerosis	T cell receptor and antigen recognition	GWAS and immunoChIP	201
STAT4‡	Systemic sclerosis	Signal transducer for type I interferon signalling in T cells	GWAS and immunoChIP	200
BANK1	dcSSc	Scaffolding for B cell signalling	Candidate gene study	202
A20-binding inhibitor of NF-κB activation (*TNIP1*)‡	Systemic sclerosis	Blocks NF-κB	ImmunoChIP	203
TNFAIP3‡	Systemic sclerosis positive for centromere-specific antibodies	Blocks NF-κB activation	ImmunoChIP	204
PTPN22‡	Systemic sclerosis positive for topoisomerase I-specific antibodies	Intracellular protein tyrosine phosphatase and negative regulator of T cell activation; variants show increased phosphatase activity that enhances T cell receptor signalling	ImmunoChIP and meta-analysis	205
PPARG	Systemic sclerosis	Controls adipogenesis and suppresses fibrotic responses	GWAS, meta-analysis and candidate gene study	206
MECP2 (located on the X chromosome)	dcSSc	DNA methylation	Meta-analysis	207
IRAK1 (located on the X chromosome)‡	dcSSc and interstitial lung disease	Intracellular IL-1 receptor signalling and inflammation	Meta-analysis	208

BANK1, B cell scaffold protein with ankyrin repeats 1; ChIP, chromatin immunoprecipitation; dcSSc, diffuse cutaneous systemic sclerosis; GWAS, genome-wide association study; *HLA*, human leukocyte antigen; *IRAK1*, IL-1 receptor-associated kinase 1; *IRF5*, interferon regulatory factor 5; *MECP2*, methyl CpG-binding protein 2; NF-κB, nuclear factor-κB; *PPARG*, peroxisome proliferator-activated receptor gamma; *PTPN22*, tyrosine protein phosphatase non-receptor type 22; *STAT4*, signal transducer and activator of transcription 4; *TNFAIP3*, tumour necrosis factor α-induced protein 3; *TNIP1*, TNFAIP3-interacting protein 1. *Genetic abnormalities associated with systemic sclerosis and identified by GWASs, meta-analyses, candidate gene studies and ChIP analyses. ‡Loci also associated with systemic lupus erythematosus.

SNPs in the major histocompatibility complex (MHC) class II region showed strong associations[56]. In addition, high-density SNP genotyping of autoimmune disease-associated loci identified multiple non-MHC susceptibility loci (TABLE 3). A majority of these genetic variants are functionally implicated in immune regulation. However, as most SNPs were located outside gene-coding or regulatory regions, their causal role remains to be established. In addition, these studies show that systemic sclerosis is a complex multigenic disease that shares genetic risk factors with systemic lupus erythematosus and other autoimmune diseases[12], and indicate that immune dysregulation and autoimmunity are fundamental in the pathogenesis. A major unanswered question is why patients with systemic sclerosis and systemic lupus erythematosus, despite their genetic overlap, display such markedly different phenotypes. Moreover, the direct contribution of the genetic variants to disease susceptibility and manifestations, as well as the underlying mechanisms, remains largely unknown. Environmental events and consequent epigenetic changes are likely to have a major role.

Epigenetic modifications. The relatively modest genetic contribution to disease susceptibility has increasingly drawn attention to the role of environmentally induced epigenetic modifications that stably influence gene expression without changes in the genetic code. Best studied among these are DNA methylation, histone modifications and non-coding RNAs. Several of these epigenetic abnormalities have been found in systemic sclerosis[57,58]. A genome-wide DNA methylation analysis revealed a large number of differentially methylated CpG sites in fibroblasts derived from patients with systemic sclerosis[59]. Two transcription factors shown to inhibit fibrotic gene expression, KLF5 and FLI1, were simultaneously repressed at the epigenetic level owing to promoter methylation and silencing[60]. The pathogenetic significance of altered regulation of these two genes was highlighted by the observation that transgenic mice with deletions of a single copy of *Klf5* and *Fli1* spontaneously developed a phenotype that recapitulated all three key features of systemic sclerosis: skin fibrosis, vasculopathy and B cell activation with autoantibody production. Moreover, fibroblasts isolated from patients with systemic sclerosis had elevated levels of methylation-regulating genes and global DNA hypermethylation coupled with transcriptional silencing of dickkopf WNT signalling pathway inhibitor 1 (*DKK1*), WNT inhibitory factor 1 (*WIF1*) and secreted frizzled-related protein 1 (*SFRP1*), genes that are involved in WNT signalling[61,62]. $CD4^+$ T cells isolated from patients showed a generalized reduction of DNA methylation and of methylation-regulating genes such as DNA (cytosine-5)-methyltransferase 1 (*DNMT1*)[63]. By contrast, forkhead box P3 (*FOXP3*), which encodes a transcription factor controlling $CD4^+$ regulatory T (T_{Reg}) cell differentiation, was hypermethylated[64]. Post-translational histone modifications, including acetylation, deacetylation and methylation, are also implicated in systemic sclerosis. Although levels of histone deacetylases (HDACs) have been reported to be either elevated or reduced, pharmacological HDAC inhibition in wild-type fibroblasts resulted in suppression of fibrotic responses[65,66]. Indeed, the acetyltransferase p300 has been shown to promote fibrotic responses by enhancing collagen transcription. Importantly, p300 levels are elevated in systemic sclerosis fibroblasts[67].

MicroRNAs (miRNAs) are non-coding RNAs of 18–23 nucleotides in length that function as intracellular regulators of gene expression. Of particular interest in systemic sclerosis are miR-21 and miR-29, which show aberrant expression in patients and might contribute to pathogenesis. On the one hand, miR-21, the level of which is elevated in fibrotic fibroblasts, suppresses the expression of anti-fibrotic SMAD7, thereby promoting expression of profibrotic genes[68]. On the other hand, miR-29 has inhibitory effects on fibrotic gene expression; its levels are suppressed by fibrotic stimuli and are lower in fibroblasts isolated from patients with systemic sclerosis than in those from healthy controls[69,70]. miRNAs can be detected in the circulation and exert biological activities when incorporated into microvesicles. Although much remains to be learned about the spectrum and mechanisms of action of aberrantly regulated miRNAs in systemic sclerosis, these regulatory non-coding RNAs might be used as biomarkers and therapeutic targets in the future.

Environmental factors

Little is known about the environmental, dietary and lifestyle exposures that might trigger the onset of systemic sclerosis in genetically susceptible individuals. Although smoking and alcohol have not been shown to increase disease risk, occupational exposures to silica dust, vinyl chloride and organic solvents might play a part. However, the absence of robust temporal or spatial disease clusters argues against the importance of these environmental factors in the pathogenesis of systemic sclerosis[71–73].

Viruses and other infectious agents might be involved and have been investigated as potential environmental triggers. Some patients have serum antibodies specific to the UL94 epitope of the herpesvirus cytomegalovirus. Viral infection might have a causal role in systemic sclerosis by inducing vascular damage and fibroblast proliferation[74]. In addition, RNA from Epstein–Barr virus, another member of the Herpesviridae family, has been found in fibroblasts and myofibroblasts within fibrotic lesions[75].

Diagnosis, screening and prevention

Classification

Classification criteria for systemic sclerosis, first published in the 1980s, had the primary goal of achieving a highly specific definition[76]. These criteria have been used for several decades for inclusion of patients into clinical and experimental studies. However, in clinical practice and in studies not aiming at treating patients with established or advanced-stage disease, these criteria lacked adequate sensitivity, particularly in (non-advanced) patients with limited or no skin fibrosis[77].

These obvious limitations led to the aforementioned joint effort of the ACR and EULAR to

Table 4 | **The ACR–EULAR criteria for classification of systemic sclerosis***

Item	Sub-item	Weight or score‡
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints§	NA	9
Skin thickening of the fingers‖	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the interphalangeal joints)	4
Fingertip lesions‖	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	NA	2
Abnormal nailfold capillaries	NA	2
Lung involvement	PAH and/or interstitial lung disease	2
Raynaud phenomenon	NA	3
Scleroderma-related autoantibodies	Any of centromere-, topoisomerase I- and RNA polymerase III-specific antibodies	3

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NA, not applicable; PAH, pulmonary arterial hypertension. *These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (that is, nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromelalgia, porphyria, lichen sclerosus, graft-versus-host disease and diabetic cheiroarthropathy). ‡A summary score of ≥9 is sufficient to fulfil the criteria. §Sufficient criterion. ‖The higher of the two is counted. Table reproduced from *Ann. Rheum. Dis.*, Van den Hoogen, F. *et al.*, **72**, 1747–1755, 2013 with permission from BMJ Publishing Group Ltd, and from REF. 5, © 2013 by the American College of Rheumatology.

develop more-sensitive criteria that considered modern diagnostic measures[5,6] (TABLE 4). The 2013 ACR–EULAR criteria showed high sensitivity and specificity (0.91 and 0.92, respectively) in an international multicentre validation cohort of patients with systemic sclerosis and scleroderma-like disorders. This level of sensitivity and specificity was improved over previously published classification criteria and has been confirmed in a recent analysis from the Canadian Scleroderma Research Group cohort, which pointed to the importance of including Raynaud phenomenon and puffy fingers as criteria[78].

There are several important considerations when applying the 2013 criteria. First, the classification items are cumulative, and past medical history must therefore be considered. Second, the criteria should not be applied to patients with skin thickening that spares the fingers or those who have a scleroderma-like disorder such as scleromyxedema or generalized morphea that better explains the skin manifestations. Most importantly, the classification criteria are not meant to be diagnostic. For example, although the 2013 criteria in a patient cohort enriched for early or mild systemic sclerosis clearly outperformed the 1980 criteria, 44% of patients with early and mild forms of the disease (according to expert consensus) were still not classified[79]. These results show that, although the diagnosis is often straightforward when the disease is advanced and severe, it remains challenging in individuals with early or mild disease.

As definite criteria for early diagnosis are still lacking, EUSTAR launched the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) initiative[80,81]. The results from their Delphi exercise with a group of international experts suggested that individuals who had Raynaud phenomenon in combination with puffy fingers, characteristic nailfold or systemic sclerosis-specific antibodies (or, alternatively, more than one of these items in the absence of Raynaud phenomenon) should be referred to an expert centre for further evaluation. These consensus data were supported by a long-term, single-centre Canadian study, which revealed that 65% of patients with Raynaud phenomenon, who have an abnormal pattern on capillaroscopy and/or specific antibodies, developed definite systemic sclerosis at 5-year follow-up. By contrast, <1% of the patients who only had Raynaud phenomenon progressed to definite systemic sclerosis[82]. This finding is supported by additional studies[83] and has important implications for clinical practice. Measurement of systemic sclerosis-specific antibodies and nailfold capillaroscopy is advisable in patients with new-onset Raynaud phenomenon, particularly when additional features such as puffy fingers are present.

Considering the high prevalence of Raynaud phenomenon (up to 5.4% in males and 7.5% in females in European populations)[84], it might be argued that such an approach is too costly and might lead to overdiagnosis of mild cases that might never develop severe organ and life-threatening complications. However, some data underline that patients with early-stage disease have increased prevalence of digital ulcers, gastrointestinal dysmobility, abnormal heart function parameters on echocardiograms and a compromised diffusing lung capacity for carbon monoxide (DLCO) below 80%[85,86]. In addition, severe complications of the kidneys, heart, lungs, and gastrointestinal tract generally develop within 3 years of disease onset, particularly in patients with dcSSc[87]. These observations highlight the need for prompt referral of patients with suspected systemic sclerosis to specialized centres and the need for criteria to identify patients with early systemic sclerosis who are at risk for developing dcSSc and/or major internal organ involvement.

Screening and diagnosis

Similar to other rheumatic diseases, early diagnosis of organ involvement enables timely therapeutic intervention to prevent irreversible organ damage and to improve prognosis (FIG. 4). For example, patients with PAH identified through a systematic screening programme showed less-severe PAH at baseline than those identified by routine clinical practice, which led to improved survival for screened patients[88]. Although these observations might be confounded by potential lead time bias, the results are consistent with beneficial effects of early treatment of patients with PAH[89]. In patients at high risk for scleroderma renal crisis, including those with early-stage (<4 years from onset) or progressive disease courses and RNA polymerase III-specific antibodies, regular blood pressure screening is appropriate. However, conclusive evidence showing that this approach is associated with improved patient outcomes is still lacking. Unfortunately, the situation in

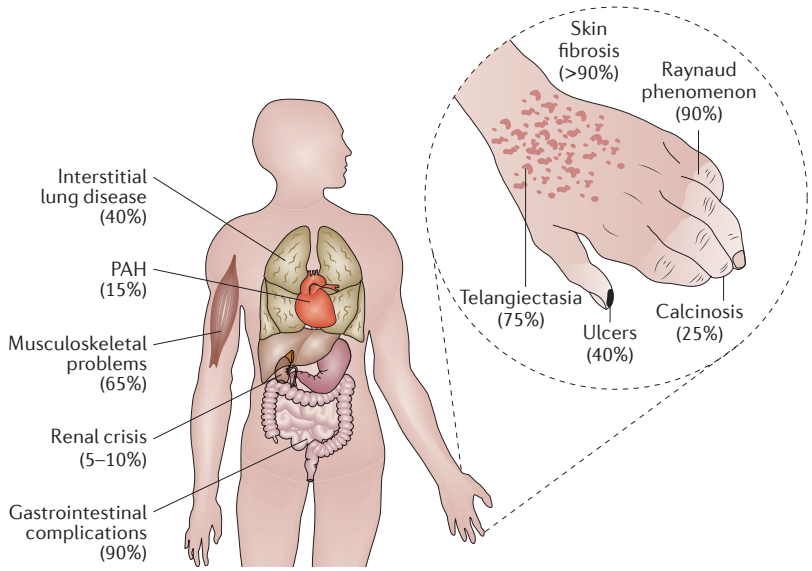

Figure 4 | **Organ complications associated with systemic sclerosis.** The uncontrolled fibrosis and scaring of the skin and internal organs in systemic sclerosis leads to severe and sometimes life-threatening complications. The average frequency of the specific complications is indicated in parentheses. PAH, pulmonary arterial hypertension.

systemic sclerosis is more complex than other rheumatic diseases. As different patient subgroups develop organ complications at different stages during disease progression, screening algorithms need to be adapted for each of the organ manifestations.

Skin fibrosis. The extent of skin fibrosis is often quantified using the modified Rodnan skin score (mRSS), which assesses skin thickness at 17 body surface areas with a scale of 0 (normal) to 3 (severe) and has a maximum total score of 51. Measurements using ultrasonography and durometer have been tested, but the mRSS remains established as the most feasible approach[90,91]. Although the mRSS is routinely used and has been found to be reliable, valid and responsive to change, its substantial interobserver variability limits its utility[91].

In patients with dcSSc, the natural course of skin fibrosis is generally characterized by a rapid increase, followed by a stabilization (plateau) period, after which skin fibrosis slowly ameliorates. Although this disease course has been confirmed in many clinical trials for the overall dcSSc population, the characteristics of the distinct stages show a high interindividual variability[92]. For example, the time between disease onset and progression to peak skin score might vary from a few months to several years. Similarly, the maximum mRSS ranges from mild to severe fibrosis associated with contracture of large joints and chest wall restriction. To date, attempts to enrich clinical studies with patients who have the same disease trajectory to control for experimental design have been unsuccessful[92]. Indeed, the spontaneous regression of skin fibrosis in late-stage disease creates challenges for both clinical trial design and clinical practice. Patients in whom the disease is still progressing require therapeutic intervention, whereas patients with (spontaneous) regression or stabilization might not; that is, any clinical study of skin fibrosis that does not also include a control group with the disease has to be interpreted with great caution, as improvement might simply reflect the natural course of the disease rather than therapy-specific effects.

A recent analysis of the EUSTAR cohort has created evidence-based criteria to identify patients with dcSSc at high risk for progression of skin involvement[93]. This study identified short disease duration (<15 months) and a low mRSS at baseline (<22) as independent predictors of later skin worsening. These results are of importance for both clinical practice and clinical study design, as they indicate a therapeutic window of opportunity in early dcSSc before severe skin fibrosis has occurred.

Pulmonary arterial hypertension. PAH, a life-threatening complication of systemic sclerosis, occurs in approximately 15% of patients, especially in those with lcSSc, long-standing Raynaud phenomenon and prominent vascular manifestations[94,95]. Risk factors include longer disease duration, presence of centromere-specific antibodies and high telangiectasia burden[96].

Recommendations for PAH screening in systemic sclerosis have been proposed by respiratory medicine and cardiology societies. These recommendations generally rely on symptoms and abnormal echocardiograms[97,98]. However, symptoms associated with PAH are nonspecific and generally occur late in the disease course. In addition, although echocardiography alone can identify later, clinically manifest disease stages, it is not sensitive enough to detect early, preclinical conditions. Thus, appropriate indicators (identified by expert consensus) are now available for referring patients for right heart catheterization when PAH is suspected[99,100]. The recommendations suggest that right heart catheterization is appropriate for patients with unexplained or progressive dyspnoea, disproportionately low DLCO, echocardiographic evidence of elevated pulmonary artery pressures and/or evidence of right ventricular volume overload, such as increase in serum levels of amino-terminal pro-brain natriuretic peptide (NT pro-BNP).

These recommendations are supported by considerable evidence from clinical studies. For example, the Cochin risk prediction score considered simple clinical measures such as forced vital capacity (FVC), DLCO and age to classify patients at high risk for the development of PAH — calculated using the formula 0.0001107 (age) + 0.0207818(100 – FVC) + 0.04905(150 – DLCO/alveolar volume)[101]. Values >2.73 put patients at risk of PAH during 24-month follow-up[101]. The DETECT study is the only one that used right heart catheterization in all patients to confirm the diagnosis of PAH. The DETECT score (see the DETECT website) is validated in patients with a disease duration of >3 years and DLCO of <60%[102]. It recommends a two-step approach with clinical and laboratory measures in the first stage. If a certain score is passed, patients are referred to echocardiography for evaluation of the right atrial area and tricuspid regurgitant jet velocity. Patients deemed to be

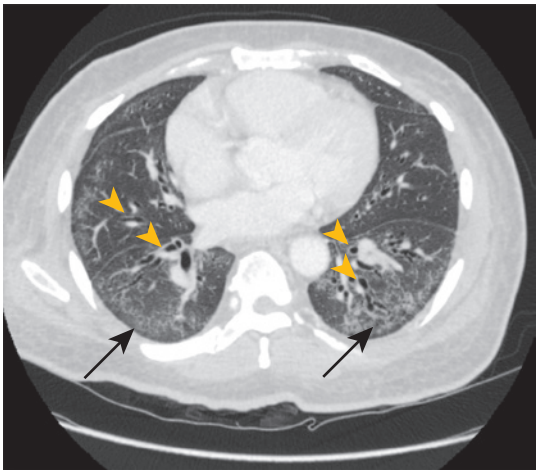

Figure 5 | **Early systemic sclerosis-associated interstitial lung disease.** High-resolution chest CT scan of a patient with diffuse cutaneous systemic sclerosis is shown. Of note are extensive bilateral subpleural ground glass opacities (indicated by black arrows), and early fibrosis and traction bronchiectasis (indicated by yellow arrow heads) at the lung bases. These findings are characteristic of nonspecific interstitial pneumonia.

at risk are further tested by right heart catheterization. The DETECT algorithm outperformed current consensus-based society guidelines on the identification of PAH and on the resources spend on catheterization.

Interstitial lung disease. Interstitial lung disease is clinically significant in approximately 40% of patients and accounts, together with PAH, for approximately 50% of all systemic sclerosis deaths[103]. Screening tools used in current clinical practice, such as pulmonary function tests (spirometry and DLCO) and 6-minute walking distance, have low sensitivity to detect systemic sclerosis-associated interstitial lung disease. For example, in a recent analysis, >50% of patients who have systemic sclerosis and interstitial lung disease had normal lung function parameters[104]. High-resolution CT scanning detects interstitial lung disease in most patients with abnormal lung function parameters. At disease onset, 'ground glass opacification' is observed on high-resolution CT images of the chest that can progress to 'honeycomb' changes and traction bronchiectasis[105] (FIG. 5). The clinical presentation is nonspecific interstitial pneumonitis with predominantly basilar involvement[106]. Repeat CT imaging should be limited owing to the radiation dose. Novel approaches that show promise include ultrasonography and high-resolution CT with lower radiation exposure using reduced number of slices[107–109]. Bronchoalveolar lavage and lung biopsy have not been shown to have diagnostic or predictive value and are consequently rarely indicated.

In many patients with systemic sclerosis, interstitial lung disease remains mild. Thus, identification of those who might show progression towards organ failure is an important clinical challenge. Early-stage dcSSc (disease duration <3–4 years), extensive fibrosis on high-resolution CT (>20% of lung volume) and clinically meaningful fibrosis with low-lung-function parameters were associated with worse prognosis in several studies[1,110–112]. The presence of topoisomerase I-specific antibodies is an additional risk factor[113,114]. Worsening of lung function parameters such as FVC might also be a negative prognostic factor, but this has not been documented in systemic sclerosis.

Digital ischaemic ulcers. Approval in Europe of an endothelin receptor antagonist (bosentan) for the prevention of digital ulcers presented a need for prediction algorithms to identify patients who are at risk for developing new digital ulcers. Several studies showed that previous or current digital ulcers are one of the strongest risk factors for recurrent ulcers[115]. In addition, nailfold capillaroscopy-based indices of microvascular alterations have been developed for systemic sclerosis. The capillaroscopic index (CSURI index) is based on the number and maximum diameter of megacapillaries and capillaries, and is validated in independent cohorts[115,116]. Its utility is limited by the fact that megacapillaries have to be present for calculating the index.

Management

Systemic sclerosis involves a wide spectrum of clinical features that encompass vascular, immune and fibrotic manifestations, and affects many organs. No single approach to treatment has proved uniformly effective, and clinical trials are limited by the lack of adequate outcome measures and the variable course of the disease. Current therapeutic approaches include general immunosuppression and complication-specific therapies. Future studies show promise to use potentially more-sensitive and more-specific biomarkers in the assessment of optimal therapeutic approaches.

The initial approach to optimal management of systemic sclerosis is to determine the disease phenotype and disease stage[117]. Phenotype assessment is important in determining potential complications that differ between the two principal systemic phenotypes of the disease (that is, lcSSc and dcSSc)[118,119]. For example, renal disease tends to be much more common in dcSSc, whereas PAH tends to be observed more frequently in lcSSc. Observational studies have demonstrated that rapid progression of organ involvement predominantly occurs in the earlier stages of disease. In late-stage disease, fibrosis in patients with both lcSSc and dcSSc might remain quite stable and, therefore, not require intervention[117].

Immunosuppression and immunomodulation

Immunomodulation is the 'centrepiece' of current therapeutic approaches and is based on the rationale that this resets the immune system. More-targeted therapies are currently not yet available.

Immunomodulatory approaches with myelosuppression or myeloablation followed by autologous haematopoietic stem cell (HSC) transplantation have been evaluated as a therapeutic strategy in systemic sclerosis. As an example, the ASSIST trial was an open-label, randomized Phase II trial, in which patients with

Table 5 | **Selected clinical trials in systemic sclerosis**

Therapeutic agent	Mechanism of action	Trial status	ClinicalTrials.gov identifier
Interstitial lung disease			
Mycophenylate mofetil	Immunosuppressive	Ongoing randomized trial versus cyclophophosphamide (SLS II)	NCT00883129
Pirfenidone	Anti-fibrotic	Open-label safety trial completed	NCT01933334
Palmolidomide	Anti-fibrotic	Open-label safety trial in progress	NCT01559129
Overall disease			
Fresolimumab	Anti-fibrotic (TGFβ-specific antibody)	Open-label safety trial completed	NCT01284322
Rilonacept	IL-1 inhibitor	Randomized trial in progress	NCT01538719
Tocilizumab	IL-6 receptor-specific antibody	Randomized trial in progress	NCT01532869
Abatacept	T cell activation inhibitor	Randomized trial in progress	NCT02161406

TGFβ, transforming growth factor-β.

dcSSc and pulmonary involvement were treated with intravenous cyclophosphamide followed by either HSC transplantation (treatment arm) or monthly pulse intravenous cyclophosphamide (control arm). At 12-month follow-up, all 10 patients who received HSC transplantation showed improvement in skin score (mRSS decreased by at least 25%) and in lung function (FVC increased by at least 10%) compared with none of the 9 patients in the control arm[120]. Results from a multicentre European trial (ASTIS) showed that high-dose immunosuppressive therapy and autologous HSC transplantation in patients with early dcSSc who had poor prognoses (most of whom had either interstitial lung disease or a history of scleroderma renal crisis) experienced a survival benefit over conventional immunosuppression[121]. In this study, 156 patients were randomly assigned either to conventional immune suppression with monthly intravenous cyclophosphamide or to high-dose cyclophosphamide followed by autologous HSC transplantation. At a median of 5.8 years of follow-up, there was a significant event-free (event defined as death or irreversible organ failure) survival benefit in the transplantation group[121]. Although this approach is clearly of benefit for patients with a poor prognosis, it is not for all patients, as 10% of all treatment-related mortality occurred with HSC transplantation. Thus, HSC transplantation should be viewed as a potential therapeutic option for patients with aggressive systemic sclerosis but should not be considered a standard of care. Additional trials have also been initiated. For example, a large multicentre trial comparing monthly intravenous cyclophosphamide to myeloablation with cyclophosphamide and total body irradiation (SCOT) has completed enrolment, but results are not yet available (ClinicalTrials.gov identifier NCT00114530). Another multicentre clinical trial (STAT) of myeloablation followed by HSC transplantation and long-term immunosuppression (mycophenylate) for dcSSc is currently recruiting subjects (ClinicalTrials.gov identifier NCT01413100).

Given the modest benefit of conventional immunosuppressants, which are associated with risks and the efficacy of which decreases over time, targeted immunosuppressive or immune ablation treatments are urgently needed. No such therapy currently exists, but there are several promising therapies in development that target potential drivers of disease pathogenesis. These agents include tocilizumab (which targets IL-6), abatacept (T cell activation inhibitor), fresolimumab (which targets TGFβ) and rilonacept (IL-1 inhibitor) (TABLE 5).

Interstitial lung disease

The standard of care for systemic sclerosis-associated interstitial lung disease includes assessment of disease stage and chronology — more specifically, stability or progression using high-resolution CT and assessment of changes in pulmonary functions with spirometry and DLCO. Immunosuppressive therapy might be appropriate for patients who show evidence of progression or early-stage disease. For patients with end-stage disease, lung transplantation can be considered[122].

Several clinical trials have provided evidence to support the use of immunosuppressive agents in the management of systemic sclerosis-associated interstitial lung disease. One randomized clinical trial compared placebo to oral cyclophosphamide over a 12-month period (Scleroderma Lung Study I[123]) and showed a significant benefit in lung function parameters (FVC) in the experimental arm. However, a follow-up study showed that this benefit decreased after 2 years, suggesting a transient response[124]. Post-hoc analysis revealed that patients with more-extensive lung fibrosis at baseline had greater improvement in FVC than those with modest lung fibrosis. Of note, patients with diffuse skin fibrosis had a greater reduction in skin scores than patients with less skin involvement. Another randomized, placebo-controlled trial explored monthly intravenous cyclophosphamide administration (for 6 months) followed by oral azathioprine (for 6 months) and showed a trend towards improvement in the treated group with changes in FVC and DLCO as the primary outcomes[125]. Other therapies currently under evaluation include mycophenylate mofetil (immunosuppressive), pirfenidone (anti-fibrotic), palmolidomide (anti-fibrotic) and rituximab (which targets CD20) (TABLE 5).

Pulmonary arterial hypertension

Therapy of systemic sclerosis-associated PAH has undergone considerable advances over the past decade. First-line therapy includes vasodilating, rather than immunosuppressive, agents. Almost all therapeutic trials of PAH included patients with systemic sclerosis; however, only one randomized trial has so far exclusively examined systemic sclerosis-associated PAH[126]. The pharmacological approaches to PAH include blocking the vasoconstrictive effects of endothelin 1 (ET1 antagonists) or enhancing the vasodilatory effects of nitric oxide (phosphodiesterase (PDE) and guanylate cyclase inhibitors) and prostacyclin (epoprostenol and treprostinil). Endothelin antagonists (including bosentan, ambrisentan and macitentan), PDE inhibitors (sildenafil and tadalafil) and guanylate cyclase inhibitors (riociguat) have shown marked haemodynamic and symptomatic improvement in PAH[127]. However, only the most recent ET1 inhibitor, macitentan, has shown a significant improvement in event-free (event defined as death or hospitalization from PAH) survival in a trial of predominately idiopathic and connective tissue disease-associated PAH compared with placebo[128]. Early evidence suggests that combination oral therapies — for example, ET1 antagonists combined with PDE5 inhibitors — might be more effective than single agents[129].

The current standard of care for symptomatic patients with NYHA (New York Heart Association) functional class II (mild to moderate impairment) is to start with ET1 or PDE5 inhibitors. For patients with advanced-stage disease or NYHA functional classes III–IV, continuous intravenous infusion with prostacyclin derivatives, such as epoprostenol, can be considered[130]. Lung transplantation is an option for some patients with end-stage disease[122].

Skin fibrosis

The assessment of skin disease, a cardinal manifestation of systemic sclerosis, is hampered by the lack of sensitive and specific outcome measures, and by the varying natural history of the disease. No single therapy has yet been shown to be conclusively effective. In patients with dcSSc, the mRSS typically decreases over time, complicating the assessment of the skin as an outcome in clinical trials[131]. A multicentre trial of methotrexate versus placebo showed a trend towards improvement in the methotrexate arm at 24 months[132]. In the SLS I trial, a modest but significant improvement in mRSS was observed in cyclophosphamide-treated patients with dcSSc compared with controls[123].

Scleroderma renal crisis

Scleroderma renal crisis occurs in approximately 5% of patients, most commonly in those with dcSSc and early-stage (<4 years) disease. The use of steroids is recognized as a risk factor, as is the presence of RNA polymerase III-specific antibodies[133]. Renal crisis onset is generally heralded by the sudden development of hypertension, progressive renal insufficiency, proteinuria and evidence of microangiopathy[134]. Prior to the introduction of angiotensin-converting enzyme (ACE) inhibitors, scleroderma renal crisis was associated with progression to end-stage renal disease and high mortality. ACE inhibitors have substantially improved outcomes, although the risk of progression to end-stage renal disease remains 50% even with early use of these drugs[133,135]. Approximately 30% of patients who require renal replacement therapy are able to discontinue haemodialysis within 1 year with continued ACE inhibitor treatment[136]. The use of ACE inhibitors to prevent renal crisis is paradoxically associated with worse renal outcomes and increased mortality, perhaps because new or worsening hypertension is masked by incomplete inhibition of the renin–angiotensin system[137].

Digital ulcers and Raynaud phenomenon

Raynaud phenomenon and digital ischaemic ulcers occur in approximately 90% and 40% of patients with systemic sclerosis, respectively, and account for substantial morbidity with pain and limitation of hand function[138,139]. First-line therapy for symptomatic Raynaud phenomenon commonly includes calcium channel blockade. Resistant or severe Raynaud phenomenon can be treated with PDE5 inhibitors such as tadalafil or sildenafil, which have also shown to be of benefit for digital ischaemic ulcers[140,141]. Endothelin antagonists seem to be helpful in preventing digital ischaemic ulcers but not in healing established ulcers[142,143]. Other treatment options reported to be effective include topical nitrates (Raynaud phenomenon), intradigital injections of botulinum toxin (severe digital ischaemia and ulceration) and intravenous prostanoids (threatened digital ischaemia)[144].

Musculoskeletal complications

A notable proportion of patients with systemic sclerosis develop arthropathy or myositis, which may contribute substantially to extremity dysfunction and disability. Physical and occupational therapy to maintain finger mobility and extremity function are important adjunctive therapies. Low-dose prednisone can provide symptomatic and functional benefit for both inflammatory arthritis and myositis. Prednisone at doses >15 mg daily is generally avoided in patients with dcSSc owing to concern about precipitating renal crisis[145]. Weekly methotrexate treatment can be used for musculoskeletal complications. Open-label studies of TNF-blocking agents, abatacept and tocilizumab suggest that these agents may be of benefit in some cases[117,146].

Gastrointestinal involvement

Upper gastrointestinal involvement occurs in approximately 90% of patients with systemic sclerosis. The most common complication is gastroesophageal reflux disease owing to disordered oesophageal motility and to incompetence of the lower oesophageal sphincter, which results in oesophagitis, oesophageal strictures and Barrett oesophagus. Varying degrees of gastrointestinal dysmotility can occur almost anywhere along the gastrointestinal tract and lead to aspiration, pseudo-obstruction and bacterial overgrowth[147,148]. Gastric antral venous ectasia can be a cause of gastrointestinal haemorrhage[149].

Treatment of gastrointestinal complications remains largely symptomatic. In addition to anti-acid treatment, pro-motility agents (such as metchlopramide, domperidone, octreotide and erythromycin), antibiotics for bacterial overgrowth and argon laser ablation for lesions are occasionally effective[147].

Calcinosis cutis

Tumoral calcinosis or calcinosis cutis occurs in up to 25% of patients with systemic sclerosis. Calcinosis has a broad spectrum of severity ranging from tiny asymptomatic lesions detected as incidental radiologic findings, to large bulky deposits associated with severe symptoms[150,151]. No treatment has been shown to be uniformly effective. Surgical removal or debulking may be options for patients with especially troublesome lesions[152]. The development of a validated radiographic scoring system to evaluate calcinosis may facilitate the systematic assessment of therapeutic options[153].

Quality of life

Systemic sclerosis is associated with an increase in mortality, but this has been improving during the past few decades[154]. As systemic sclerosis is a multisymptomatic disease, quality of life of patients may be severely affected[147]. A review on how to measure quality of life in systemic sclerosis is beyond the scope of this Primer but has been covered elsewhere[139,155,156]. Overall, general health, as measured by the SF-36 health survey, is reduced in systemic sclerosis compared with the age- and sex-matched controls[157]. Patients with systemic sclerosis also have poor quality of life as measured by a reduced patient global assessment of health, chronic pain, fatigue and sleep disturbance[157–159]. Functional impairment often worsens over time (as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI))[160].

Many symptoms affect quality of life in systemic sclerosis — for example, pain[161], gastrointestinal symptoms, pruritus (itch)[162], fatigue, sleep problems, work disability[163] and sexual dysfunction[164]. Work disability in systemic sclerosis is higher than in rheumatoid arthritis[165]. The pain experience can have many causes, such as skin inflammation, Raynaud phenomenon, digital ulcers, inflamed calcinosis and joint and/or tendon swelling. Pain scores averaged around four out of ten on a visual analogue scale in a population of patients with systemic sclerosis on treatment (outpatients who were attending a follow-up visits)[157]. Pain management comprises chronic pain medication (pregabalin, gabapentin, serotonin–noradrenaline reuptake inhibitor (duloxetine) and selective serotonin reuptake inhibitors), as well as treatments targeting the underlying cause. Gastrointestinal complications impair quality of life substantially[166]. Symptoms include faecal incontinence, choking, aspiration, bloating, gas, constipation, diarrhoea, early satiety and gastric dumping. Treatment directed at the pathology can help and includes treatment of small-bowel overgrowth with antibiotics, stool softeners, laxatives and pro-motility agents for severe constipation. A validated instrument to measure various gastrointestinal symptoms is often used[167,168]. Itch is more difficult to treat, and options consist of antihistamines, lubrication of the skin, less bathing to prevent the skin from drying out, heat, massage and exercise. Fatigue is usually multifactorial. If it is associated with iron deficiency, treating the underlying cause can provide relief: erosive oesophagitis can be treated with proton pump inhibitors and pro-motility agents, whereas repeated laser therapy can alleviate the gastric antral vascular ectasia. Administration of iron or blood transfusions might be necessary. Anaemia caused by chronic disease is likely to improve upon suppression of inflammation. In 15% of patients, secondary Sjögren syndrome develops with dry eyes and mouth, which can be treated with artificial tears and frequent dental visits[169]. Most men with systemic sclerosis experience erectile dysfunction[164].

The increased risk of malignancy is a concern in systemic sclerosis, as is the case in other chronic inflammatory conditions. A meta-analysis showed that the pooled standardized incidence ratio (SIR) for cancer in patients with systemic sclerosis was 1.41 (95% CI 1.18–1.68)[170]. The most common were lung, liver, haematological and bladder cancers, although absolute risk is lower than the general population. Of note, men are at higher risk than women for developing cancers. In both groups, the presence of RNA polymerase III-specific antibodies seems to be associated with an increased risk for cancers, particularly those developing at an early stage in the natural history of systemic sclerosis[171,172]. Moreover, patients with RNA polymerase III-specific antibodies who have developed cancers often have somatic alterations in the *POLR3A* gene, which encodes RNA polymerase III[173], and show specific immune responses directed against the mutated RNA polymerase III subunit (RPC1) antigen. These findings suggest that the mutations triggered cellular immunity and cross-reactive humoral immune responses that might have a role in disease pathogenesis.

In addition to these physical morbidities, many patients develop psychological complications, including symptoms of depression, anxiety, fear of disease progression and dying, and body image concerns from disfigurement[174,175]. Clinical depression is not prevalent, but depressive symptoms are increased compared with the general population; this is a common feature of chronic diseases in which chronic pain occurs[176,177]. If there is clinical depression in systemic sclerosis, the usual treatment would be similar to other people diagnosed with depression, such as use of antidepressants[177]. As systemic sclerosis often causes visible changes to the patient's face — for example, telangiectasia, tight skin, increased wrinkles around the mouth when skin softens, small upper lip, and loss of subcutaneous fat around the cheeks and nose — a stigma is associated with systemic sclerosis. There is a questionnaire that has been developed for patients with systemic sclerosis with respect to their appearance[178]. Patients also experience tightening of their hands, with swollen fingers or contractures, or with ulcers or digital loss. All of these changes may have an impact on self-esteem and can enhance a fear of dying in the patient. Trials are underway to improve hand function, body image and mood

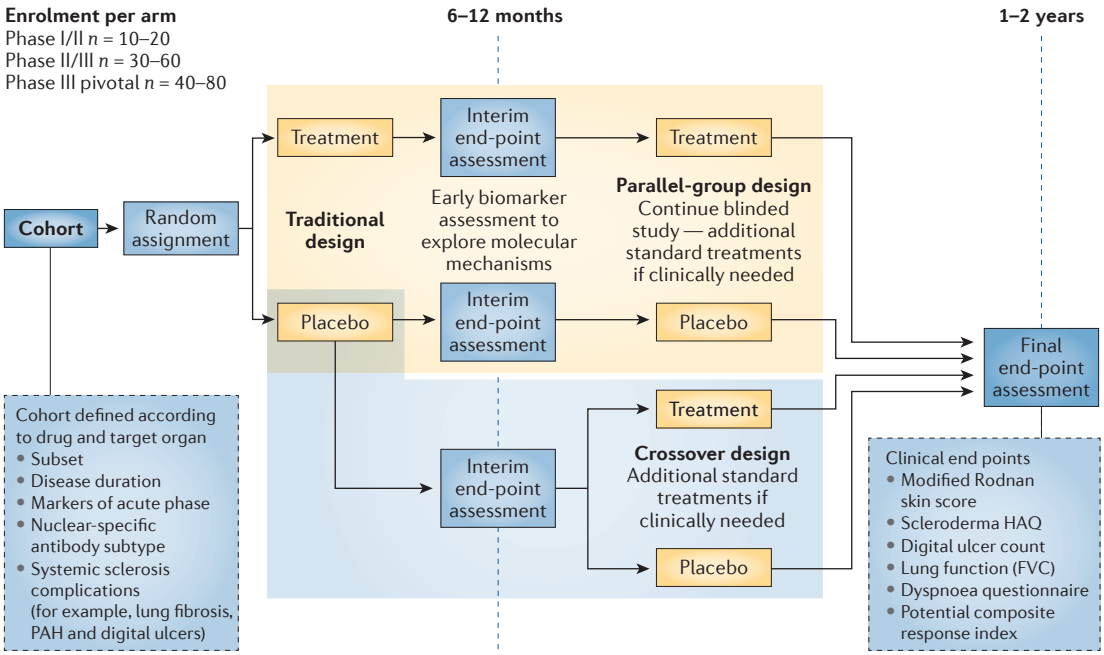

Figure 6 | **Future of clinical trial design in systemic sclerosis.** The validation of potential medications or treatment strategies to tackle systemic sclerosis requires the development of a novel and robust clinical trial design. Essential parameters to implement such a novel scheme include an improved definition of patient subgroups, biomarker validation and better end-point assessment. The strategy proposed here is still speculative and might have to be refined in the future, but it illustrates several key areas in which progress is feasible. First, study cohorts should be defined in greater detail to enrich for the population that has progressive disease or that has the specific complication under evaluation. Second, the inclusion of a placebo control arm would reduce difficulties in evaluating variable clinical outcomes. Third, implementation of a crossover design in which patients are randomly assigned to active drug treatment after a placebo phase will strengthen data emerging from Phase I/II studies. Last, traditional clinical end-point assessment — such as examination of skin, digital ulcerations, lung fibrosis and other potential aspects of systemic sclerosis — requires updating. Possible tools that can be used are disease-specific patient-reported outcomes and composite disease response indices that incorporate multiple end points such as skin score, lung function and a health assessment questionnaire (HAQ), and may be more responsive than individual outcomes. For interim end points, biomarker validation in the blood and/or skin biopsy is preferred over clinical parameters. Interim end points can be assessed early for evidence of pharmacodynamic effects or biomarker assessment: at 6 months in early-phase trials (Phase I/II) or 12 months for later studies (Phase II/III). A follow-up by a crossover or an open-label study for an additional 6 months can enhance the power of the interim trial. If required, adding additional standard treatments for the skin or lung will help to sustain the parallel-grouped, blinded, placebo-controlled design for at least 12 months, which is likely to be the minimum timeframe to obtain clinically meaningful benefits for these conditions. FVC, forced vital capacity; PAH, pulmonary arterial hypertension.

through an innovative Internet network (Scleroderma Patient-centered Intervention Network (SPIN))[179].

Outlook

Although systemic sclerosis remains a major clinical and research challenge, there are reasons to be optimistic about progress in the next few years. Substantial advances in the past decade have demonstrated the feasibility of progress and pointed to new avenues for future success in understanding the disease process and in improving clinical outcomes. Below, we focus our discussion on areas in which we envision progress.

Advances in clinical trials

After many years of frustration in developing feasible and robust clinical studies, the outlook finally shows promise. Clinical trials are being completed that are able to differentiate active treatment from placebo owing to better design and understanding of the trial set-up, as well as to the nature of the agents tested. The development of a standard design for clinical trials in systemic sclerosis is still required and proves to be difficult (FIG. 6). Standardization is important because, by analogy with other areas of rheumatology, establishment of a reliable trial template will enable drug development to progress, which will be central to improvements in disease management[180].

Recent studies show that high-intensity immunosuppression is a key addition to evidence-based treatment in systemic sclerosis[121]. Nonetheless, finding better and less-toxic ways of achieving the same therapeutic outcome is essential[121]. Research should also focus on regenerative medicine and prevention of complications. Indeed, the non-lethal burden of systemic sclerosis is considerable and will only increase as treatments that target lethal complications improve. Research on clinical outcomes needs to be re-evaluated to take this eventuality into account, and better clinical strategies to treat

calcinosis, ulcerations, gut disease and fatigue need to be developed.

Triage of new potential therapies can be facilitated by the development of molecular markers and predictive scores that can be applied in the clinic[1]. Biomarkers are important, as there are many promising therapeutic avenues to explore; however, there are limited numbers of patients available for trials, and centres with the essential infrastructure and capacity to perform such trials. The number of new therapies, together with the potential repurposing of existing drugs, is likely to lead to an inevitable 'bottleneck' for early-phase studies. Although the development of better assessment tools, such as validated biomarkers and composite clinical scores, is challenging, it is essential for countering this problem[181].

Better definition of disease subgroups

Systemic sclerosis is characterized by a very heterogeneous array of symptoms, even within the currently classified subgroups. Indeed, although certain complications are more frequent in dcSSc, this is not always the case. Moreover, it remains unknown why some manifestations such as gastroesophageal reflux or secondary Raynaud phenomenon are universal in systemic sclerosis, whereas others affect only a proportion of patients. Novel classification criteria are required to better predict the risk of complications and to justify early monitoring and preventive treatment strategies, in addition to tailoring treatment and stratifying patients for inclusion in clinical trials[182,183]. Subgroups are likely to be defined, to a large extent, on the basis of autoantibody subtypes, either in isolation or in combination with clinical or other variables. For example, topoisomerase I- and RNA polymerase III-specific antibodies seem to be strong predictors of lung fibrosis and scleroderma renal crisis, respectively, and are now included in the 2013 classification criteria. Other antibodies associated with disease subtypes are likely to be identified through the use of proteomic and other molecular approaches, and these might complement gene or protein expression-based systemic sclerosis subsets.

Molecular basis of disease

A better understanding of the disease process and connection between the complications in the different organs will help to better tailor treatments to individual patients. Although deciphering the link between cutaneous involvement and internal organ complications is prominent, it remains an important challenge. Research efforts of consortia aim to have sufficient biological samples linked to clinical annotation, which will lead to better insights of the autoimmune process, including the intriguing link between cancer and systemic sclerosis[172,173]. Furthermore, elucidating the impact of the microbiome and the potential role of infection or colonization in triggering or progressing the pathology might herald new therapeutic options.

We envision additional focus on epigenetics, which will complement the advances in genetics. Challenges are the identification of disease-specific features and the determination of, for example, whether they are susceptibility factors or phenotype modifiers. Antibody-based subgroups will also help to define disease subsets and elucidate pivotal biological mechanisms, including the potential role of autoantibodies that target relevant cell surface proteins and receptors.

Moreover, despite similarities between organ-based pathologies — such as pulmonary fibrosis, PAH and accelerated hypertension occurring outside the context of systemic sclerosis — there remain key differences that have yet to be understood. Better insights in the disease process will be important when considering translation or repurposing of emerging or existing therapies. Advances in the past two decades have already improved the overall survival of patients with dcSSc, including a more systematic approach to monitoring that enables earlier detection of significant complications that may be treated; use of specific therapies for complications such as PAH or scleroderma renal crisis; and advances in chronic supportive care.

Dysfunctional tissue remodelling

Progress in understanding the biology of systemic sclerosis has depended on drawing appropriate analogies from other areas of science, especially developmental biology and genetics. It is compelling to view systemic sclerosis as an almost inevitable consequence of having a connective tissue repair pathway that is essential for survival. It is intriguing that this might have some selective advantage in the population. In addition, this may provide an explanation for the persistence of the trait and the observed ethnic and racial differences.

Furthermore, the pathological mechanisms are likely to be shared with other conditions, including other autoimmune diseases and other forms of fibrosis. Key questions are how these processes in systemic sclerosis differ from other conditions and what the triggers or aetiopathological factors are. Moreover, the advances in reparative niche microenvironments, plasticity of progenitor cells and location-specific cellular programming will help to better understand the role of progenitor and stem cells in systemic fibrosis[41]. Indeed, delineating the disease process might be sufficient to progress therapy, especially in an era of targeted biological approaches.

Bidirectional research translation

Animal models have been useful to extending our knowledge of the pathophysiology of systemic sclerosis, but it is likely that optimal use of patient samples will have more potential to lead to bidirectional research translation[184]. The disease process and its similarity to the human pathology need to be validated in animal models. If these models are validated, they will become platforms for preclinical evaluation of novel treatments of specific complications such as PAH[185]. Thus, it is likely that as the understanding of disease biology in systemic sclerosis grows, substantial clinical development will follow. Ultimately, the non-lethal burden of systemic sclerosis might gain increasing importance because patients will survive longer. In addition, disease management could be improved through use of targeted therapeutics that may differentially benefit

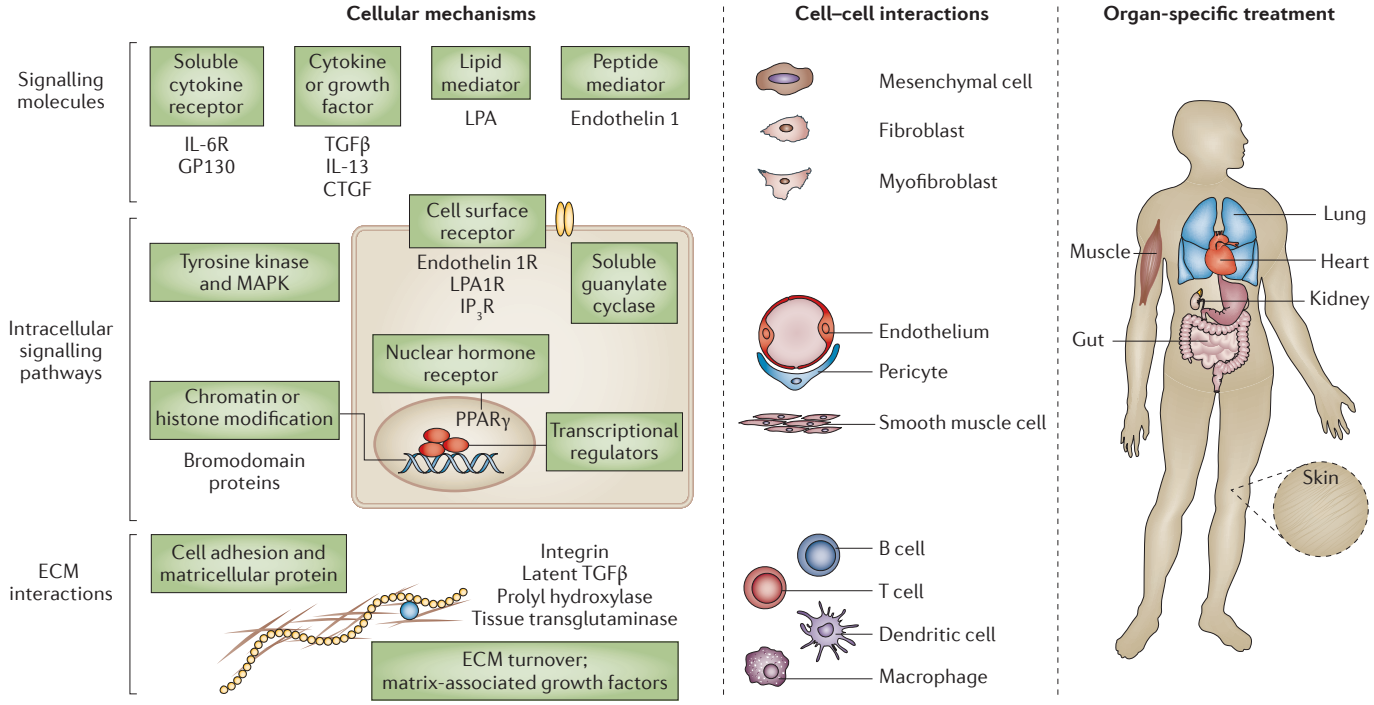

Figure 7 | **Putative therapeutic targets in systemic sclerosis.** The design of new therapeutic interventions will rely on a greater understanding of relevant signalling molecules, pathways and extracellular matrix (ECM) interactions implicated in the development and/or progression of systemic sclerosis. Unravelling the key target cells and cellular interactions between the different cell types involved in the pathology may also lead to new lines of inquiry. Finally, we may be able to capitalize on our knowledge of existing organ-based treatments that may be useful in systemic sclerosis-specific complications. CTGF, connective tissue growth factor; GP130, envelope glycoprotein 130; IL-6R, IL-6 receptor; IP_3R, inositol trisphosphate receptor; LPA, lipoprotein; MAPK, mitogen-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor-γ; TGFβ, transforming growth factor-β.

different aspects of the condition. It is encouraging that novel biological interventions are demonstrating treatment effect for skin fibrosis[186].

Targeted disease-modifying therapy

Historically, major therapeutic advances in systemic sclerosis have arisen through the management of specific, organ-based complications. Acid-suppressive medication has transformed the impact and consequences of severe gastro-oesophageal reflux disease. Targeted therapies for PAH have benefitted functional outcomes and survival, and routine use of ACE inhibitors in scleroderma renal crisis means that this complication is no longer almost always lethal[187]. Other organ-based treatment advances are likely, but the real challenge and opportunity are for targeted and logical disease-modifying therapy. As outlined above, better patient stratification, advances in biological understanding, availability of candidate therapeutics and improved clinical trial design make the prospect feasible, and the first tentative steps towards this have already been taken[188]. It seems more likely than not that at least one effective novel therapy will emerge in the next decade (FIG. 7). This, together with a better understanding of disease impact and risk stratification, will make systemic sclerosis much more manageable. The remaining challenge then will be a health-economical one, as treatments and longer survival are likely to increase the costs, which will need to be addressed by health-care systems and policy makers.

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Author contributions
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