PRIMEVIEW

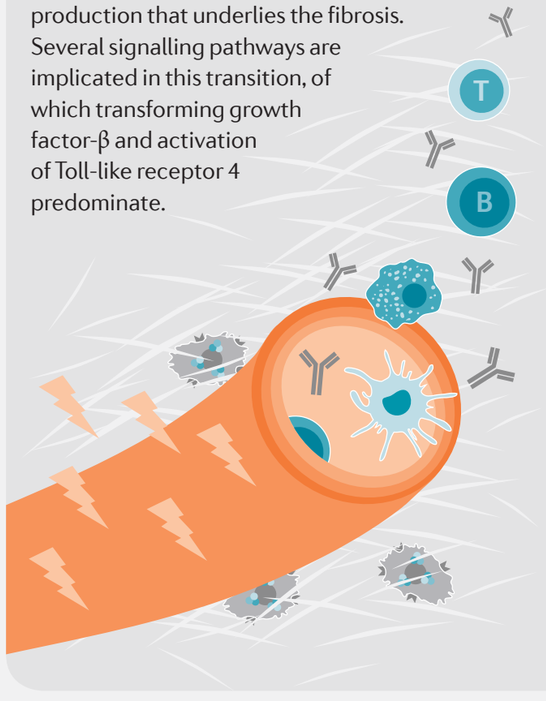
SYSTEMIC SCLEROSIS

nature REVIEWS DISEASE PRIMERS

Systemic sclerosis is an autoimmune disease characterized by microvascular damage and progressive fibrosis of the skin and visceral organs that might result in life-threatening complications, including renal crisis.

MECHANISMS

The exact cause of systemic sclerosis remains enigmatic but involves an interplay between genetic factors and environmental events (such as viral infections). Initially, pathogenesis is dominated by microvascular injury, which leads to endothelial cell activation and platelet aggregation. The resulting hypoxia and chemokine release trigger an uncontrolled inflammatory reaction, infiltration of immune cells and secretion of autoantibodies. As a consequence, resident fibroblasts undergo differentiation into myofibroblasts, which are responsible for the excessive extracellular matrix production that underlies the fibrosis. Several signalling pathways are implicated in this transition, of which transforming growth factor-β and activation of Toll-like receptor 4 predominate.

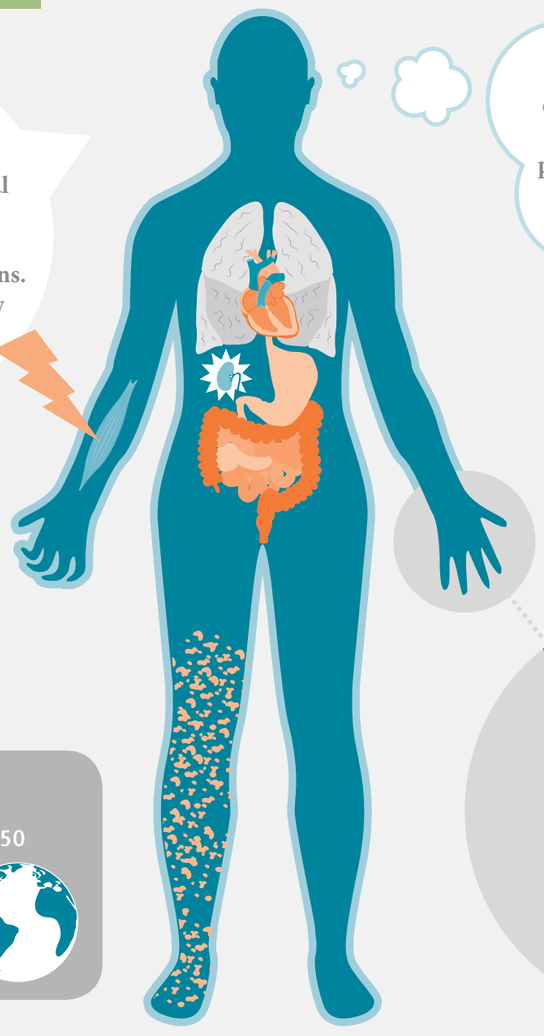


QUALITY OF LIFE

Scarring of the skin and organs leads to interstitial lung disease, pulmonary arterial hypertension, renal crisis, and musculoskeletal and gastrointestinal complications. Patients' hands often show Raynaud phenomenon and ulcers

? ! ?

Although clinical depression is not prevalent, many patients develop psychological complications such as anxiety and body image concerns

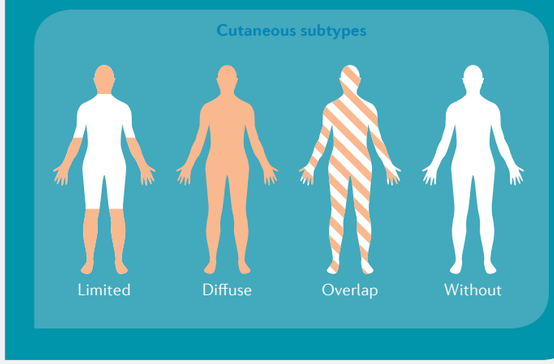


♀ Women are five times more prone to develop systemic sclerosis than men

! The prevalence and incidence vary geographically: 150–450 per million and 10–20 per million per year, respectively

DIAGNOSIS

In general, patients are classified on the basis of the location of skin fibrosis, as illustrated below. However, the high interpatient variability makes diagnosis particularly challenging. In 2013, new criteria that take into account accompanying complications and biomarkers were proposed, although these still lack sensitivity to classify the disease early. Early detection and accurate disease subset definitions are urgently needed to identify patients at risk for specific complications or rapid progression.



MANAGEMENT

Clinically, systemic sclerosis manifests as vascular, immune and fibrotic anomalies. Treatments include immunomodulation (such as immune suppression and haematopoietic stem cell transplantation), as well as complication-specific therapies. For example, vasodilating agents are used to treat hypertension, angiotensin-converting enzyme inhibitors to prevent renal crisis, and endothelin receptor antagonists to treat digital ulcers.

OUTLOOK

A better understanding of the triggers, cell types and pathways involved in systemic sclerosis will clear the way for the design of new, targeted medication and the repurposing of existing therapies. In addition, not only is the identification of specific and reliable biomarkers essential to improve early diagnosis, but it will also help to optimize and standardize clinical trial design. The latter is urgently needed to validate potential therapies but is difficult to implement because of confounding factors — including the natural amelioration of symptoms over time and the lack of robust subgroup definitions.

doi:10.1038/nrdp.2015.2; published online 23 April 2015

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