in SSc, large-scale epidemiologic investigations found no evidence of increased prevalence of SSc.

PATHOGENESIS

The following three cardinal pathophysiologic processes account for the protean clinical manifestations of SSc: (1) diffuse microangiopathy, (2) inflammation and autoimmunity, and (3) visceral and vascular fibrosis in multiple organs (Fig. 382-1). Autoimmunity and altered vascular reactivity are early manifestations. Complex and dynamic interplay between these processes initiates and then amplifies the fibrotic process.

ANIMAL MODELS OF DISEASE

No single animal model of SSc fully reproduces the three cardinal processes that underlie the pathogenesis, but some recapitulate selected aspects of the human disease, including fibrosis, microvascular involvement, and autoimmunity. Tight-skin mice (Tsk1) develop spontaneous skin thickening due to a mutation in the fibrillin-1 gene. The mutant fibrillin-1 protein disrupts extracellular matrix assembly and causes aberrant activation of transforming growth factor β (TGF-β). Fibrillin-1 mutations are associated with Marfan's disease as well as the stiff skin syndrome but not SSc. Skin and lung fibrosis can be induced in mice by injection of bleomycin, HOCl, or double-stranded RNA or by transplantation of human leukocyte antigen (HLA)–mismatched bone marrow or spleen cells. Targeted genetic modifications in mice give rise to new disease models for dissecting the pathogenetic roles of individual molecules, cell types, and networks. For example, mice lacking Smad3, an intracellular TGF-β signal transducer, adiponectin, or the nuclear receptor peroxisome proliferator-activated receptor (PPAR) γ or overexpressing Wnt10b or adiponectin were either resistant or hypersensitive to chemically induced experimental scleroderma. These mouse models have potential utility in preclinical evaluation of potential therapies.

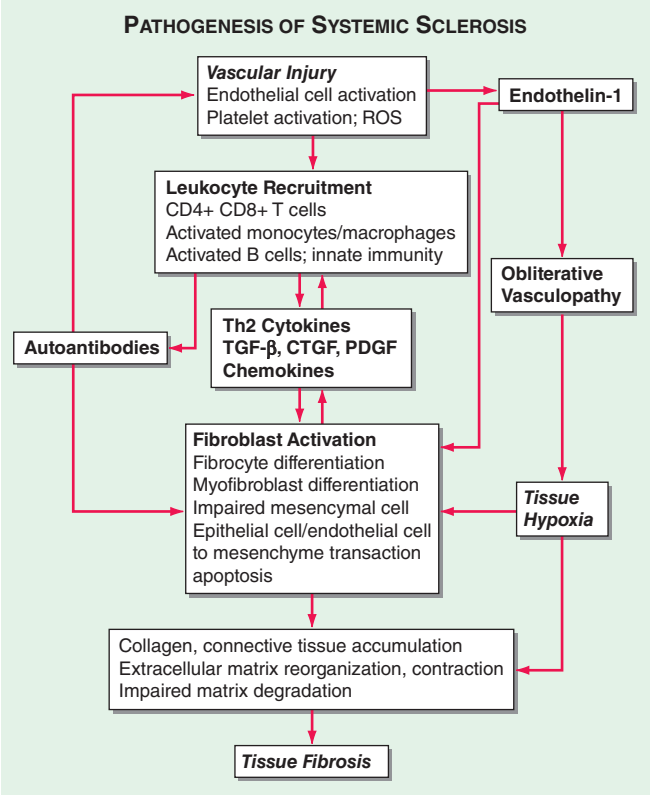

FIGURE 382-1 Initial vascular injury in a genetically susceptible individual leads to functional and structural vascular alterations, inflammation, and autoimmunity. The inflammatory and immune responses initiate and sustain fibroblast activation and differentiation, resulting in pathologic fibrogenesis and irreversible tissue damage. Vascular damage results in tissue ischemia that further contributes to progressive fibrosis and atrophy. CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β.

MICROANGIOPATHY

Involvement of small blood vessels in SSc affects multiple vascular beds and has important clinical sequelae including Raynaud's phenomenon, ischemic digital ulcers, scleroderma renal crisis, and PAH. Raynaud's phenomenon, an early disease manifestation, is characterized by an altered blood-flow response to cold challenge. This initially reversible functional abnormality is associated with autonomic and peripheral nervous system alterations, including impaired production of the neuropeptide calcitonin gene-related peptide from sensory afferent nerves and heightened sensitivity of α_2-adrenergic receptors on vascular smooth-muscle cells. Isolated (primary) Raynaud's phenomenon is extremely common and generally benign and nonprogressive. In contrast, SSc-associated Raynaud's phenomenon is often progressive and complicated by irreversible structural changes, culminating in ischemic digital ulcers and loss of digits. Viruses, vascular cytotoxic factors, thrombogenic microparticles, complement and autoantibodies to phospholipids, β2 glycoprotein I (β2GPI), and endothelial cells are suspected triggers of endothelial cell injury in SSc. Endothelial injury results in dysregulated production of endothelium-derived vasodilatory (nitric oxide and prostacyclin) and vasoconstricting (endothelin-1) substances, as well as increased expression of intercellular adhesion molecule 1 (ICAM-1) and other surface adhesion molecules. Microvessels show enhanced permeability and transendothelial leukocyte diapedesis, abnormal activation of coagulation cascades, elevated thrombin production, and impaired fibrinolysis. Spontaneous platelet aggregation causes release of serotonin, platelet-derived growth factor (PDGF), and platelet alpha granules including thromboxane, a potent vasoconstrictor. Smooth-muscle cell–like myointimal cells proliferate, the basement membrane is thickened and reduplicated, and fibrosis of the adventitial layers develops. The vasculopathic process affects capillaries, as well as arterioles, and even large vessels in many organs, resulting in reduced blood flow and tissue ischemia. Progressive luminal occlusion due to intimal and medial hypertrophy, combined with persistent endothelial cell damage and adventitial fibrosis, establish a vicious cycle that culminates in the striking absence of blood vessels (rarefaction) in late-stage disease. Recurrent ischemia-reperfusion generates reactive oxygen species (ROS) that further damage the endothelium through peroxidation of membrane lipids. Paradoxically, the process of revascularization that normally reestablishes blood flow to ischemic tissue is defective in SSc despite elevated levels of vascular endothelial growth factor (VEGF) and other angiogenic factors. Moreover, the number of bone marrow–derived circulating endothelial progenitor cells is reduced. Thus, widespread capillary loss, obliterative vasculopathy of small and medium-sized arteries, and failure to repair damaged vessels are hallmarks of SSc.

IMMUNE DYSREGULATION

Cellular Immunity The following observations highlight the autoimmune nature of SSc: presence of circulating autoantibodies; familial clustering of SSc with other autoimmune diseases; detection of immune cells, including T cells with oligoclonal antigen receptors, in target organs; elevated circulating levels and spontaneous secretion from blood mononuclear cells of inflammatory cytokines and chemokines such as interleukin (IL) 1, IL-4, IL-10, IL-17, IL-33, CCL2, and CXCL4; and the association with variants in genes functionally implicated in immune responses. Genetic studies in SSc reveal strong and consistent associations with major histocompatibility locus alleles, as well as non-HLA-linked genes encoding mediators of both adaptive and innate immune responses (*CD247*, *STAT4*, *IRF5*, *CD226*, and *TNFSF4*). In early SSc, mononuclear inflammatory cell infiltrates comprised of activated T cells, monocytes/macrophages, and dendritic cells can be seen in skin, lungs, and other affected organs prior to appearance of fibrosis or vascular damage. Dendritic cells and T cells can often be found in close proximity to activated fibroblasts and myofibroblasts. Tissue-infiltrating T cells express CD45 and HLA-DR activation markers and display restricted T cell receptor signatures indicative of oligoclonal expansion in response to (unknown) antigen.