Chapter 14
Overview: Pathogenesis Integrated

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Keywords Autoimmunity • Fibroblast • Fibrosis • Integrated view • Overview • Pathogenesis • Reciprocal cross-modulation

The pathogenesis of scleroderma is complex, multifactorial and incompletely understood. Evidence of vascular injury, immune dysfunction and tissue remodeling can be detected in every patient with scleroderma. These processes do not occur in isolation but are interrelated and reciprocally modulate each other, as illustrated in Fig. 14.1 and discussed in the following chapters. The triad of vasculopathy, autoimmunity/inflammation and connective tissue remodeling underlies the protean clinical and laboratory manifestations of scleroderma, ranging from Raynaud phenomenon to autoantibody production to pulmonary fibrosis. However, the relative contributions of these distinct pathophysiological processes to the individual disease phenotype, and their roles in driving the natural history of disease vary greatly from one patient to another. This individual variability, which is not well understood but might be genetically determined, accounts for the strikingly heterogeneous clinical picture of scleroderma. Vascular injury and endothelial damage are early and probably primary events in the evolution of the disease, and can be detected at initial evaluation in a majority of patients. While initially vascular injury is associated with reversible functional changes, over time progressive and irreversible structural vascular alterations accrue. Progressive vascular damage with obliteration of small and medium-sized arteries in multiple vascular beds, and associated activation of thrombotic and coagulation cascades follow. Reduced vascular supply leads to tissue hypoxia, ischemia and its myriad complications. In addition, generation of reactive oxygen species contributes to increased oxidative stress and associated damage to protein and lipid macromolecules. Vascular injury also plays a role in activation of the innate and adaptive immune systems, and contributes directly and indirectly to tissue fibrosis.

Immune dysfunction is prominent and also occurs early in the course of the disease, possibly even preceding clinical symptoms and signs. Highly specific autoantibodies are generated and can be readily detected in the circulation. The scleroderma-associated autoantibodies are distinct from those seen in other autoimmune diseases. Moreover, not only are they unique to scleroderma, but they tend to be mutually exclusive (i.e., do not coexist with other scleroderma-specific autoantibodies) in any individual patient. The mechanisms responsible for generating specific antigen-directed humoral autoimmune responses in scleroderma are unknown, and their contribution to tissue damage and disease manifestations has not been convincingly demonstrated to date. It is becoming clear that innate immune responses are prominent in scleroderma, and may be linked to adaptive immunity through dendritic cells, toll-like receptors and interferons. Innate immunity also appears to be important in initiating and propagating the fibrotic process.

Aberrant fibroblast activation in most parenchymal tissues and around blood vessels leads to excessive matrix synthesis and deposition that disrupt normal tissue architecture and organ function. Fibrosis affects the skin, lungs, heart, intestinal tract and musculoskeletal soft tissues, and plays a tremendous role in the morbidity and mortality associated with scleroderma. Factors triggering fibroblast activation include soluble cytokines, chemokines and bioactive lipids, products of intravascular coagulation, hypoxia and reactive oxygen species, and biomechanical forces generated from a stiff matrix. While fibroblast activation is an integral feature of the normal wound healing response, in scleroderma, fibroblast activation

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J. Varga et al. (eds.), *Scleroderma: From Pathogenesis to Comprehensive Management*,
DOI 10.1007/978-1-4419-5774-0_14, © Springer Science+Business Media, LLC 2012

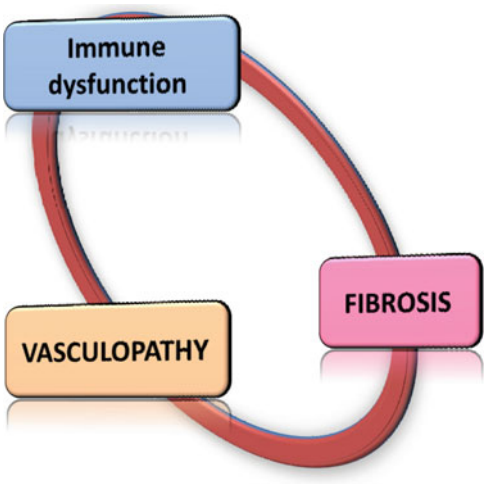

Fig. 14.1 Reciprocal cross-modulation of the pathogenetic processes underlying scleroderma

is excessive, and becomes constitutive and sustained due to the loss of endogenous anti-fibrotic control mechanisms, coupled with the development of powerful self-amplifying feed-forward mechanisms driven by tissue hypoxia and matrix stiffness. Unrestrained fibroblast activity invariably leads to more matrix deposition, tissue damage, and progressive and intractable fibrosis. The chapters in this section provide an in-depth examination of current understanding of each of these processes and their interrelationships in the context of scleroderma.