Is scleroderma an autoantibody mediated disease?
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Purpose of review
Research into the pathogenesis of systemic sclerosis and other fibrotic conditions is becoming increasingly broad and sophisticated. In the past year, several provocative studies have presented evidence that autoantibodies may actually cause the vascular damage and fibrosis characteristic of systemic sclerosis. These autoantibodies include antiendothelial cell, antifibrillin-1, anti-matrix metalloproteinases 1 and 3, and antiplatelet-derived growth factor β, each having its own unique mechanism. Such reports provide novel avenues to pursue in understanding this enigmatic disease.

Keywords
autoantibodies, endothelial cells, fibrillin, matrix metalloproteinases, platelet-derived growth factor, systemic sclerosis

Introduction
Scleroderma or systemic sclerosis (SSc) is a multisystem disorder characterized by prominent small blood vessel and capillary damage, fibroblast activation leading to overt fibrosis in connective tissues, especially the skin, and a myriad of circulating antinuclear autoantibodies (ANAs), the majority of which are disease-specific and mutually exclusive. These autoantibodies include antitopoisorserase I (Scl70), anticentromere, anti-RNA polymerase III, anti-U3-fibrillarin, and others. It is intriguing that each of these ANA specificities is associated with distinctive clinical subsets of SSc characterized by extent and rapidity of cutaneous involvement (diffuse versus limited), patterns of organ involvement, ethnicity and sex differences, and prognosis [1,2]. It should be noted, however, that the clinical auto-antibody subset correlations are not absolute, and many patients follow clinical courses which defy such categorization. In addition, each of these disease-specific nuclear ANAs appears to be genetically influenced by different major histocompatibility complex (MHC) or human leukocyte antigen (HLA) class II alleles or haplotypes [1,2]. There appears to be no overriding HLA association with SSc itself. Despite these SSc clinical, autoantibody and HLA subsets, compelling evidence that any of the scleroderma ANAs actually cause disease manifestations is lacking.

Recently, several additional autoantibodies directed against nonnuclear antigens have been described in scleroderma sera, which may actually play demonstrable pathogenetic roles in vascular damage and in tissue fibrosis (Table 1). Several such ‘new’ autoantibodies deserve highlighting because strong experimental evidence is accumulating supporting their roles in tissue damage. They include antiendothelial cell antibodies (AECAs), although most of their target endothelial autoantigens have not yet been identified; antifibrillin-1 (anti-FBN1) antibodies; antibodies against matrix metalloproteinases (MMP), such as MMP1 (interstitial collagenase) and MMP3 (stromelysin); and, most recently, anti-platelet-derived growth factor receptor (PDGFR) antibodies.

AECAs have been long suspected but only recently proven to be potentially relevant to the vascular damage of SSc [3,4]. It is now clear that AECAs induce apoptosis of endothelial cells in vitro which could lead in vivo to the widespread loss of capillaries and obliterative intimal
Evidence recently presented supports a role for induction of the caspase 3 apoptotic pathway by AECAs by both anticitrullinomerase and antiproteinase I positive SSc sera, and specifically by its IgG fraction [4]. Moreover, apoptotic endothelial cells so induced were found to express FBN1, another SSc-specific autoantigen (see below), which is not typically expressed by normal adult endothelial cells [4]. The aberrant expression and degradation of FBN1 by these apoptotic endothelial cells theoretically could reveal cryptic epitopes leading to an autoimmune response (see below). Also of possible importance in the origin of AECAs has been the finding that some of these antibodies bind to human cytomegalovirus late protein UL94, an antigen from a putative viral trigger of SSc [5].

FBN1 is a 350 kDa glycoprotein which is the major constituent of microfibrils in the extracellular matrix (ECM) (see article by Lafyatis). Beyond their structural importance for ECM integrity, microfibrils also sequester transforming growth factor (TGF)-β in its latent form. Circulating autoantibodies to FBN1 have been found in the majority of scleroderma patients and are specific for the disease [6]. Recent in-vitro studies using purified human anti-FBN1 antibodies have shown that they activate normal fibroblasts, resulting in increased production of collagens and other ECM components [7]. These studies suggest that anti-FBN1 antibodies may either prevent the proper sequestration of TGFβ in the ECM or promote its release from latent stores in the ECM, which can then activate fibroblasts and promote tissue fibrosis.

Antibodies to MMP1 and MMP3, whose functions are to break down collagens and other matrixcellular components, have been reported and also appear to be specific for SSc sera [8,9]. Such antibodies have been proposed to cause a failure of degradation of those ECM components that accumulate as fibrotic material in the ECM of patients with scleroderma.

Anti-PDGF-α autoantibodies have been described most recently and were detected in all of 46 SSc patients but in no normal controls or rheumatoid arthritis, primary Raynaud’s phenomenon, or lupus sera [10,11]. These IgG antibodies were shown to activate PDGF-α, thus inducing the Ha-Ras–ERK1/2 pathways leading to increased synthesis of reactive oxygen species which stimulated type I collagen gene expression and promoted the conversion of normal human fibroblasts into myofibroblasts.

Many questions regarding these ‘new’ and potentially pathogenic SSc autoantibodies arise. First, can all of these be confirmed by other groups in additional SSc patients and control populations? Second, how might they relate to the various SSc clinical-autoantibody–HLA subsets noted above? Third, how might they relate to each other? It seems unlikely that four or more seemingly different autoimmune responses are required to produce both the vascular and fibrotic phenotypes which we view clinically as scleroderma, although such a similar situation appears to apply to another multisystem autoimmune disease characterized by many different autoantibodies, namely systemic lupus erythematosus. Also, there are certainly precedents for stimulatory autoantibodies to receptors, such as in Graves’ disease, as well as structure altering autoantibodies, such as in bullous skin diseases, including pemphigus. Apoptosis inducing autoantibodies recently were reported in Sjögren’s syndrome [12].

Finally, should one or more of these autoantibodies prove to be responsible for all or most of the lesions of scleroderma, should not our investigative attention and therapeutic strategies be aimed more at the immunologic or vascular and ECM?

Certainly, this latter question cannot reasonably be addressed until additional and more definitive research clearly defines the pathogenetic roles (if any) of both ‘old’ and ‘new’ autoantibodies in scleroderma.

References


