

## 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  $\beta$ , 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 anti-topoisomerase I (Scl70), anticentromere, anti-RNA polymerase III, anti-U3-fibrillar, 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

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### Abbreviations

<b>AECA</b>	antiendothelial cell antibody
<b>ANA</b>	antinuclear autoantibody
<b>ECM</b>	extracellular matrix
<b>FBN1</b>	fibrillin-1
<b>HLA</b>	human leukocyte antigen
<b>MMP</b>	matrix metalloproteinase
<b>PDGFR</b>	platelet-derived growth factor receptor
<b>SSc</b>	systemic sclerosis

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**Table 1 Putative new pathogenic autoantibodies in systemic sclerosis**

Autoantibodies	Specific for SSc	Frequency in SSc	Pathogenetic roles in SSc
Antiendothelial cell antibodies (AECAs)	No	>90%	Induce endothelial cell apoptosis via caspase 3 pathway and induce fibrillin-1 expression in apoptotic endothelial cells
Antifibrillin-1 (FBN1) antibodies	Yes	>50%	Activate normal fibroblasts into pro-fibrotic phenotype via causing release of sequestered TGF $\beta$ in the ECM
Anti-matrix metalloproteinases (MMPs) 1 and 3	Yes	High percentage	Prevent degradation of excessive collagen and other fibrotic ECM components
Antiplatelet-derived growth factor receptor (PDGFR) antibodies	Yes	100%	Stimulate normal fibroblasts via Ha-Ras-ERK1/2 pathways and generate reactive oxygen species cascades to induce collagen I production, and convert resting fibroblasts into activated myofibroblasts

SSc, systemic sclerosis; TGF, transforming growth factor; ECM, extracellular matrix.

proliferation in small arteries which is characteristic of SSc. Evidence recently presented supports a role for induction of the caspase 3 apoptotic pathway by AECAs by both anticentromere and antitopoisomerase 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)- $\beta$  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 TGF $\beta$  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 matricellular 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-PDGFR 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 PDGFR, 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 Sjogren'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 origin of this disease rather than its downstream effects on the vasculature 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

- 1 Arnett FC. HLA and autoimmunity in scleroderma (systemic sclerosis). In: Korn JH, LeRoy EC, editors. *Immuno-pathogenesis of scleroderma*. Internat Rev Immunol 1995; 12:107-128.

- 2 Cepeda EJ, Reveille JD. Autoantibodies in systemic sclerosis and fibrosing syndromes: clinical indications and relevance. *Curr Opin Rheumatol* 2004; 16:723–732.
- 3 Bordron A, Dueymes M, Levy Y, *et al*. The binding of some human anti-endothelial cell antibodies induces endothelial apoptosis. *J Clin Invest* 1996; 101:2029–2035.
- 4 Ahmed SS, Tan FK, Arnett FC, *et al*. Scleroderma sera containing endothelial cell antibodies induce apoptosis and fibrillin-1 in human dermal endothelial cells. *Arthritis Rheum* 2006; 54:2250–2262.
- 5 Lunardi C, Bason C, Navone R, *et al*. Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells. *Nat Med* 2000; 6:1183–1186.
- 6 Tan FK, Arnett FC, Reveille JD, *et al*. Autoantibodies to fibrillin-1 in systemic sclerosis: ethnic differences in antigen recognition and lack of correlation with specific clinical features or HLA alleles. *Arthritis Rheum* 2000; 43:2464–2471.
- 7 Zhou X, Tan FK, Wallis D, *et al*. Autoantibodies to fibrillin-1 activate normal human fibroblasts in culture through the TGF beta pathway and recapitulate the 'scleroderma phenotype'. *J Immunol* 2005; 175:4555–4560.
- 8 Sato S, Hayakawa I, Hasegawa M, *et al*. Function blocking autoantibodies against matrix metalloproteinase-1 in patients with systemic sclerosis. *J Invest Dermatol* 2003; 120:542–547.
- 9 Nishijima C, Hayakawa I, Matsushita T, Komura K, *et al*. Autoantibody against matrix metalloproteinase-3 patients with systemic sclerosis. *Clin Exp Immunol* 2004; 138:357–363.
- 10 Svegliati Baroni S, Santillo M, Bevilacqua F, Luchetti M, *et al*. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. *N Engl J Med* 2006; 354:2667–2676.
- 11 Tan FK. Autoantibodies against PDGF receptor in scleroderma [editorial]. *N Engl J Med* 2006; 354:2709–2711.
- 12 Sisto M, Lisi S, Castellana D, Scagliusi P, *et al*. Autoantibodies from Sjogren's syndrome induce activation of both the intrinsic and extrinsic apoptotic pathways in human salivary gland cell line A-253. *J Autoimmun* 2006; June 20 [Epub ahead of print]