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Role of anti-receptor autoantibodies in pathophysiology of scleroderma

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ABSTRACT

The pathophysiology of SSc-mediated organ damage is complex and not well understood. Hallmarks of the disease include skin thickening, vasculopathy and gastrointestinal dysmotility. Diverse anti-nuclear antibodies can be used as biomarkers for classification and prognosis, but their role in producing tissue pathology/organ dysfunction is not established. In contrast, antibodies against cell surface receptors for platelet derived growth factor, angiotensin II, endothelin A, ICAM-1, and type 3 muscarinic acetyl choline receptors may play a major role in skin thickening, vasoconstriction/pulmonary and renal hypertension, ischemia and gastrointestinal dysmotility, respectively. In addition, antibodies to an inhibitory B-lymphocyte surface molecule, CD 22, may allow increased production of other autoantibodies. Each of these types of antibodies have been reported in some SSc patients, and laboratory studies suggest signaling pathways and mechanisms by which they may contribute to disease activity. However, we are far from a consensus on their importance. Additional epidemiologic, mechanistic and physiologic studies are needed. Confirmation of the roles of anti-receptor antibodies and identification of the signaling pathways by which they alter cellular functions would have major implications for treatment of SSc, both in terms of targeting autoantibodies and the cells that produce them, and in the use of small molecules which inhibit their pernicious effects.

Contents

1. Introduction

Systemic sclerosis (SSc) is a serious but poorly understood disease. Because virtually all patients have multiple autoantibodies, it is

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considered an autoimmune disease, but the immune effector mechanisms remain ill-defined [1,2]. In both the limited and diffuse cutaneous forms of SSc, the cardinal manifestations seem to result from two major processes: vasculopathy and net increased production of fibrotic extracellular matrix. In turn, these processes account for the skin thickening, Raynaud's phenomenon and other peripheral vascular problems which are the hallmark of the disease. The most serious forms of internal organ involvement, affecting the lungs, kidneys, and in many cases the heart, are also likely sequelae of vasculopathy and fibrosis. In contrast, GI dysmotility may precede significant fibrosis or structural changes and often presents before other changes in the viscera [3]. SSc differs from other connective tissue diseases in that there is a relative lack of frank inflammation.

In common with other autoimmune connective tissue diseases, SSc patients have multiple different types of anti-nuclear antibodies which are useful in diagnosis, classification and prognostication [4–8]. However, the actual pathological effects of these antibodies are unknown. In addition to the antinuclear antibodies like anti-topoisomerase I (Scl-70), anti-centromere and anti-RNA polymerase, SSc patients frequently have antibodies that target cell surface molecules such as G-protein- or tyrosine kinase- coupled receptors, which can alter their functions in stimulatory or inhibitory ways. Identification of autoantibodies as key effectors of pathophysiology *per se* would suggest that neutralizing or removing these antibodies and/or decreasing their production might have important therapeutic effects. In this article, we evaluate the hypothesis that functionally important anti-receptor antibodies play major roles in the organ dysfunction and tissue damage that characterize SSc.

2. Clinical characteristics of SSc

2.1. Limited and diffuse cutaneous SSc

"Scleroderma" is a broad category that encompasses multiple different syndromes including localized conditions such as morphea and linear scleroderma as well as systemic sclerosis (SSc). SSc itself is extremely varied, both in the extent of skin affected as well as the range of internal organ involvement. Skin changes are most common, although GI dysmotility and other internal organ involvement are frequent accompaniments. SSc is often divided into two subsets based on the extent of skin involvement, limited cutaneous (lcSSc) and diffuse cutaneous (dc) SSc. LcSSc involves cutaneous sclerosis distal to the elbows and knees. Nailfold capillary abnormalities, telangiectases and Raynaud's phenomenon may be more severe in this form of SSc than in dcSSc, and pulmonary arterial hypertension is more common, suggesting a predominance of small vessel involvement. Gastrointestinal dysfunction and pulmonary fibrosis also occur in lcSSc. DcSSc is the more severe form, and is characterized by cutaneous sclerosis proximal to the elbow as well as gastrointestinal, pulmonary, and cardiac fibrosis, and renal vascular disease. In both types of systemic sclerosis, the most common manifestation is Raynaud's, followed by skin involvement, characterized by thickening. Impairment of gastrointestinal function is the most common internal organ involvement.

3. Pathology and pathophysiology

3.1. Overview

The pathology and pathophysiology underlying SSc-mediated organ damage is complex and not completely understood. The incidence of SSc in monozygotic and dizygotic twins is similar, suggesting that genetic factors do not play a major role, although some data suggests that epigenetic modifications contribute [9,10]. Environmental factors may be more likely than genetics to play a significant role in development of autoimmunity in SSc, and a number of infections, as well as exposure to non-infectious agents, have been implicated in the development of the disease. The complex pathophysiology of SSc seems to involve interactions between the immune system, endothelial cells and fibroblasts [1,2,11].

Pro-fibrotic cytokines, chemokines and changes in the balance between reactive oxygen species (ROS) and antioxidant defenses have been implicated in the tissue damage and vascular dysfunction which characterize SSc [11,12]. The etiology of the gastrointestinal involvement in SSc is not clear. Many feel it begins as an ischemic process of the myenteric nerves leading to dysmotility [13–18]. However, accumulating data suggests that dysmotility may be mediated by autoantibodies which impede muscarinic receptor signaling [19–23]. In any case, GI problems could be exacerbated by ROS-mediated fibrosis and endothelial cell damage. Moreover, antibodies against lymphocytes [24] and alterations in B- and T-cell subpopulations and dendritic cells have also been reported in SSc, suggesting that the immune system may induce and/or exacerbate other tissue- or organ-specific pathogenic mechanisms.

SSc is characterized by abnormal vascular tone and capillary structure, endothelial cell apoptosis and loss of barrier function, and increased permeability of blood vessels. Microvascular dysfunction contributes to end-organ damage in the heart, lungs and kidneys. An increase in circulating endothelin-1 levels may also contribute to vasoconstriction and vascular damage [23].

3.2. Skin disease

In SSc, increased accumulation of collagen in the dermis occurs primarily due to fibroblast activation and excessive production along with increases in other matrix proteins [11,12]. Antibody-mediated inhibition of matrix metalloproteases may also play a role [25]. Fibroblasts from the skin of SSc patients have been shown to have activated signaling through *Ras* and MAP kinase pathways, including extracellular signal regulated kinases (ERK) 1 and 2, increased production of ROS, and increased transcription of collagen genes [12]. In addition, increased transcription of smooth muscle α-actin is associated with conversion to a myofibroblast phenotype [26]. Dysregulation of transforming growth factor β (TGF-β) secretion and signaling may play a key role through several mechanisms including increasing expression of PDGF receptors [26]. In turn, excessive activation of PDGF signaling pathways by agonistic anti-receptor antibodies may lead to the excessive proliferation of fibroblasts and differentiation into myofibroblasts. The resulting net increase in accumulation of collagen and other extracellular matrix components (ECM) is a hallmark of SSc.

4. Classical autoantibodies as diagnostic and prognostic markers

The presence of auto-antibodies is one of the most common manifestations in SSc, being observed in more than 90% of patients [4–8]. A number of autoantibody biomarkers have traditionally been recognized for their value in diagnosis of SSc, clinical subset classification, and for predicting organ involvement (Table 1). They vary in different populations, depending on genetics and ethnicity [27,28]. African-Americans have a very different frequency of some of these antibodies, which may contribute to the difference in long term outcomes [27,28]. Antibody to DNA topoisomerase I (ATA), also known as anti-Scl-70, is seen mostly in dcSSc although 25 to 30% of patients may have lcScc disease. ATA is associated with severe fibrosis, interstitial lung disease, and digital ulceration regardless of the extent of skin disease [4–8]. It is possible that peptide fragments of topoisomerase 1, presumably released from apoptotic or damaged cells, can bind to other proteins on the surface of fibroblasts, which are then activated when these surface proteins are cross-linked by anti Scl70 antibodies [5].

Anti-centromere antibodies (ACA) are the most common marker for lcSSc, reported in 45–50% of patients compared with ~10% of patients with dcSSc, and may be associated with pulmonary arterial hypertension. Notably, ATAs and ACAs are only rarely observed together in the