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# Is antiendothelial cell antibody the murder weapon in systemic sclerosis ?

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Systemic sclerosis (SSc) is presumably an autoimmune disease encompassing a wide spectrum of clinical settings (1). Humoral autoimmunity is there expressed as a group of antibodies reacting with nuclear and cytoplasmic structures, such as the kinetochore targeted by anticentromere antibodies in a number of patients with limited SSc (lSSc) and the topoisomerase I recognized by anti-Scl70 antibodies in certain patients with diffuse SSc (dSSc). Vascular endothelial cell (EC) damage appears, however, to be one of the earliest events in the pathophysiology of the disease, so that the structural basis of such an injury has been the subject of much study over the past decade. Therefore, it is not surprising that anti-EC antibodies (AECA) have been described in patients with SSc (2).

Herein lies a problem since a consensus on the prevalence of AECA in SSc has not yet been reached. The proportion of AECA-positive sera ranges from 28% (3) to 71% (4). As usual, the discrepancies may be ascribed to variations in patient selection and the tests used in different laboratories. The main message emerging from this awareness is thus the crucial need for standardization (5). Such a programme is currently in progress, and this should provide new insights into our understanding of the AECA-EC system.

Meanwhile, to clarify the question as to whether there was actually a difference between the results obtained in different studies depending on the cells used as the substrate, Renaudineau et *al.* (submitted) examined 477 sera from unselected SSc patients to establish that the binding activity was significantly higher to microvessel than to macrovessel EC in this disorder. That is, EC vary among and within tissues (6) and AECA represent an extremely heterogeneous family of autoantibodies (7), of which subgroups might be specific for a given disease.

Evidence has long been lacking that they are pathogenic. This was first suggested by the observation that AECA levels fluctuate with disease activity. The test can indeed identify subsets of SSc with differing prognoses (8), inasmuch as AECA were shown to be present in 3 of 13 patients with primary Raynaud's phenomenon (23%), 16 of 36 patients with lSSc (44%) and 26 of 31 patients with dSS (84%). Would then AECA be only another potential disease marker? Probably no, because AECA are complicated by pulmonary arterial hypertension (3) and alveolo-capillary dysfunction in SSc (9). Additional evidence for a pathogenic role of these autoantibodies has been provided by Damianovich e*t al.* (10), who induced the production of murine AECA by injecting human AECA into mice.

Serum from patients with SSc has the capacity to kill human umbilical vein EC (HUVEC), possibly through autoantibodies (11). Cytotoxicity has, however, been attributed by previous investigators to a protease-like factor (12). Some AECA cause complement-mediated lysis of EC in systemic lupus erythematosus but not in SSc (13), or induce antibody-dependent cellular cytotoxicity in Wegener's granulomatosis but not in SSc (14). More recently, speculation about the mechanism of vascular damage has focused on the enhanced expression of adhesion molecules by EC. Again, the serum of patients with SSc has not been examined in these experiments.

Nonetheless, several effects of AECA in SSc are being unraveled with the benefit of new data. In particular, EC programmed death is emerging as a central participant in the pathophysiology of vascular injury (15). Surprisingly, AECA and antiphospholipid (PL) antibodies (aPL) coexist in approximately one-third of the patients with non-organ-specific autoimmune diseases, while cationic cofactors - mainly $\beta_2$-glycoprotein I ($\beta_2$ GPI) - bind to the cells (16, 17). For this to occur, it follows that plasma membrane anionic PL must become accessible, since they are sequestered in the leaflet facing the cytosol.

The recent finding that EC apoptosis is a primary pathogenic event underlying skin lesions in avian and human SSc (18) may be highly relevant to this phenomenon. In this respect, we have shown that AECA derived from six of eight patients with SSc led to the translocation of anionic PL to the surface of the cells (19). The redistribution of plasma membrane anionic PL (most notably phosphatidylserine) preceded other events associated

with apoptosis. As a result, AECA binding made negatively-charged PL accessible to the relevant autoantibodies (20). Some of them may even have the potential to induce the production of aPL.
In brief, not only do they show promise as a sensitive indicator of disease activity, but some AECA have also the ability to initiate the exposure of anionic PL. A subgroup of AECA may actually represent a normal response to dispose of unwanted EC and counteract excessive thrombin formation. Important studies are in progress to identify the cell surface epitopes that apoptosis-inducing AECA recognize.

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