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References


Endothelial cell antibodies: pathogenetic or epiphenomenon?

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Introduction

Endothelial cells line the entire circulatory system of the body and are positioned well to interact intimately with circulating immunoglobulins. Antibodies against endothelial cell surface antigens (AECA) have been described in diverse conditions, those relevant to the kidney include renal allograft rejection, connective tissue diseases, vasculitis and haemolytic-uraemic syndrome. The endothelial cell molecules that are recognized by AECA have been defined in very few instances; one example is recognition of endothelial phospholipids by antiphospholipid antibodies in patients with lupus anticoagulant [1], another that of recognition of endothelial proteinase-3 by antibodies developing in vasculitis [2]. Vascular endothelial cells are not homogeneous but show structural heterogeneity; for example, renal glomerular endothelial cells are fenestrated. Further, they are able to alter their surface phenotype, for example in response to inflammatory mediators such as thrombin and histamine, or cytokines such as IL-1, TNF or IFN-γ. This heterogeneity provides AECA with the potential to bind to specific vessels within specific organs or only to those endothelial cells that have been activated by inflammatory mediators or cytokines. Binding of AECA to cytokine-activated but not unactivated endothelial cells has been described in Kawasaki disease [3], while there is loss of AECA binding after cytokine activation in the haemolytic-uraemic syndrome [4].

How can endothelial cell antibodies be measured?

Several approaches have been adopted to detect human AECA. Direct staining for antibody bound to vascular endothelial cells in tissue biopsy sections has the advantage of detecting tissue-specific AECA but in practice this approach is relatively insensitive and has been successful only in some cases of AECA associated with renal allograft rejection [5]. A more common approach has been to set up cell-based ELISAs where cultured endothelial cells are incubated with diluted test sera. Such systems are very sensitive but their specificity is restricted by the use of endothelial cells that have been isolated from large vessels and serially passaged in culture, so that their ability to detect microvascular-specific AECA is limited and the phenotype of the cells may change with time in culture. Conversely, when AECA are detected using such *in vitro* systems, one has to be cautious when interpreting their potential significance in culture since binding to human umbilical vein endothelial cells in culture (a common source of endothelial cells) may not be synonymous with binding to renal arterioles or capillaries. Further, the endothelium in *in vivo* is in contact with plasma and immunoglobulins, and relevant AECA that have a sufficiently high binding constant would require to be present in gross antibody excess. *In vitro* assays may detect antibodies of relatively low binding constant, which may be of little pathophysiologial significance.

How may endothelial cell antibodies interact with their target cells?

Antibodies binding to endothelial cell surfaces are important only if they subvert the normal function of the endothelial cell or injure it. Endothelial cells do
not normally express receptors for immunoglobulin Fc, so that it is likely that most direct AECA binding occurs via antigen-specific variable Fab regions. Two broad types of interactive mechanisms between AECA and endothelial cells may be proposed. First, Fc may engage and direct effector systems such as complement or Fc-receptor-bearing cytotoxic cells, to the endothelial surface. Second, the bound Fab portion of the antibody may interfere with the function of or initiate functional changes within endothelial cells. There are examples for all of these. Thus, AECA activation of complement has been described in Kawasaki disease [3], while AECA engagement of Fc-receptor-bearing cytotoxic cells has been described in scleroderma [6] and vasculitis [7]. Phospholipid-binding AECA interfere with the anticoagulant properties of endothelial cells by preventing the inactivation of factor Va by activated protein C, thereby encouraging the intravascular coagulation that characterizes the course of patients with antiphospholipid antibodies [1]. The AECA in sera from patients with systemic lupus erythematosus have been reported also to enhance endothelial expression of procoagulant tissue factor. Recently, binding of antibodies to endothelial cells has been reported to enhance their surface expression of the leukocyte adhesion molecules E-selectin, ICAM-1, and VCAM-1. Thus antibodies from patients with Wegener’s granulomatosis appear to induce E-selectin expression and neutrophil binding [2], while AECA from patients with scleroderma enhance levels of all three adhesion molecules and the adhesion of the monocyte cell line, U937 [8].

Are endothelial cell antibodies relevant in human disease?

How applicable are these findings to human disease? Studies demonstrating complement-mediated lysis that have used non-human sources of complement may be legitimate for demonstrating AECA binding, but since human endothelial cells express an array of molecules (CD59, decay accelerating factor, membrane cofactor protein) that protect them against lysis by activated autologous complement, the ability of AECA to cause injury in vivo via this mechanism may be rather limited. Engagement of effector cytotoxic cells has been demonstrated only in small numbers of individuals with scleroderma [6], vasculitis [7] or occasionally in patients undergoing renal allograft rejection [5]. None of the in-vitro studies has been performed under flow conditions which, particularly on the arterial side of the circulatory system, might tend to reduce the number of effective lytic encounters between circulating leukocytes and endothelial cells.

The ability of AECA to alter the functional properties of endothelial cells is a rather newer concept that needs to be more fully evaluated in larger numbers of patients and in different disease groups. Preliminary data in scleroderma suggest that AECA mediate their effects by stimulating endothelial cell cytokine release [8] but whether this is a response to a specific receptor-mediated event or a generalized response to perturbation of the endothelial cell membrane remains to be established. Another approach that has been used to evaluate the role of AECA in disease is to correlate circulating titres with disease activity. In systemic lupus erythematosus there is evidence that AECA are associated with active renal lesions [9]. Correlations between AECA and disease activity have been described sporadically also in vasculitis, rheumatoid arthritis, and scleroderma. Experimentally, infusion of anti-angiotensin-converting enzyme into animal models induces lung and glomerular injury [10], suggesting that if and when antibodies develop to endothelial surface antigens, they do have the potential to mediate tissue injury.

In summary, some AECA such as antiphospholipid antibodies may be linked closely to defined pathogenetic functional changes in endothelial cells. However, in most disorders where AECA have been described, their pathogenetic potential in vivo remains undefined, they may contribute to tissue injury in individual patients but thus far central roles in pathogenesis have not been demonstrated conclusively.

References