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Immunobiology 210 (2005) 789–797
Immunobiology
www.elsevier.de/imbio

REVIEW

New target antigens for antiendothelial cell antibodies

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Received 30 July 2005; accepted 30 August 2005

Abstract

Numerous connective tissue diseases, such as systemic lupus erythematosus (SLE), and infectious states, such as leprosy, are characterized by early vascular endothelial cell (EC) damage. There is substantial interest in the role of anti-EC antibodies (AECA) in such an injury. Due to the diversity of AECA-associated conditions, these autoantibodies are likely to be heterogeneous, and, therefore, identification of their antigens (Ag) to be difficult. They may be classified into three groups: membrane components, ligand–receptor complexes and Ag derived from the blood and attached to the cell surface. New technologies have been developed to sort it out, such as expression libraries and two-dimensional electrophoresis. A handful of Ag have hitherto been recognized viz. heat-shock protein 60 in SLE and leprosy, or plasminogen activator inhibitor-1 in SLE and Wegener granulomatosis. In reality, most of the target Ag for AECA remain to be identified.

Keywords: Antiendothelial cell antibody; Endothelial cell; Systemic lupus erythematosus

Contents

Abbreviations: Ab, antibody; AECA, antiendothelial cell Ab; Ag, antigen; ANCA, anti-neutrophil cytoplasmic Ab; BD, Behçet disease; CMV, cytomegalovirus; CS, Churg Strauss vasculitis; HS, heparan sulfate; HSP, heat-shock protein; HUS, hemolytic uremic syndrome; HUVEC, human umbilical vein EC; IFN, interferon; IL, interleukin; KS, Kawasaki syndrome; PR3, proteinase 3; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TA, Takayasu's arteritis; TM, thrombomodulin; TNF, tumor necrosis factor; TPP, thrombotic thrombocytopenic purpura; WG, Wegener granulomatosis

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doi:10.1016/j.imbio.2005.10.011

Introduction

Endothelial cells (EC) lining the vasculature contribute to the development of inflammatory responses. Because they have long proved to be a target for immune-mediated assault (Youinou, 1995; Meroni et al., 1996; Meroni and Youinou, 1996), it could have been predicted that damage of these vessels occurs through antibodies (Ab) to EC antiendothelial cell Ab

Table 1. Prevalence of anti-endothelial cell antibodies in systemic disease

Disease	% of positive sera
Systemic lupus erythematosus	15–85
Rheumatoid arthritis	0–87
Systemic sclerosis	15–84
Mixed connective tissue disease	45
Polyarteritis nodosa	56
Polymyositis	44
Microscopic polyarteritis	2–60
Wegener's granulomatosis	19–80
Behçet's disease	18–80
Takayasu's arteritis	95
Anti-phospholipid syndrome	60–63
Kawasaki syndrome	65
Churg-Strauss syndrome	69
Thrombotic thrombocytopenic purpura	13–100
Hemolytic uremic syndrome	93
Diabetes mellitus type I	35

(AECA). Such autoreactivity was originally described by indirect immunofluorescence analysis, with tissue sections as the substrate in sera from patients with systemic lupus erythematosus (SLE). The reliability of this staining was then settled (Cines et al., 1984), using $F(ab')_2$ fragments. The impetus was thus provided for a host of studies to assess AECA in a number of settings delineated only by widespread vascular lesions. These include autoimmune conditions, such as SLE, rheumatoid arthritis (RA), systemic sclerosis (SSc), Wegener granulomatosis (WG), as well as infectious states, such as Kawasaki syndrome (KS), Behçet disease (BD), leprosy and cytomegalovirus (CMV) infection.

One may infer from the impressive diversity of conditions involved (Table 1) that AECA represent a mixed family of autoAb. Moreover, it may be stated that natural AECA exist, on the basis that they are produced by coculture of Epstein-Barr virus-infected B cells with EC. Furthermore, endothelium varies in phenotype (Fukuda et al., 1986), biology (Maruyama, 1998) and pathophysiologic implications (Belmont et al., 1996). This view is further supported by the finding that sera apparently negative on a given EC type become positive if appropriate substrate cells are used (Renaudineau et al., 2004).

The corollary of such a diversity is that the target antigens (Ag) differ from one group of AECA to another (Youinou et al., 1995; Praprotnick et al., 2001; Meroni et al., 2001; Castillo et al., 2001). Still, we are unable to identify most of them, and, even worse, the Ag status of endothelium from different sites is far from being completed. It has even been established that cytokines render EC immunogenic, whilst similar resting cells are not. Some AECA damage EC from capillaries and other bind to macrovascular EC. Not only would their in-depth analysis bring about new insights into the understanding of their pathogenesis, but their availability might provide a new asset for the clinician in the optimal management of inflammatory autoimmune conditions.

Cell membrane reactivity

Though the target Ag for AECA are poorly deciphered, we assume that they are not directed toward HLA class I molecules or ABO blood group polysaccharides, because AECA react in a similar manner with EC from different HLA and ABO unrelated donors (Meroni and Youinou, 1996). Neither do they recognize HLA class II molecules which can be expressed by EC following interferon (IFN)γ activation. AECA allotypic systems had been described in the earliest reports (Wood et al., 1988), but this notion has since been detracted. Cryptic AECA-binding structures (Leung et al., 1988) have also been shown to be unmasked upon activation with interleukin (IL)-1 or tumor necrosis factor (TNF)-α in KS. However, not only have other investigators established that AECA can be cytotoxic to EC without cytokine tickling (Kaneko et al., 1994), but the absence of AECA has been claimed by different groups (Nash et al., 1995). Intriguingly, the reverse phenomenon does also occur in hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopemic purpura (TPP). The expression of membrane Ag exquisitely recognized by a subset of AECA has been inhibited (Leung et al., 1986, 1988) by incubating the target cells with IFNγ prior to the assay. Inasmuch as the phenomenon has never been confirmed, it remains at issue.

AECA-positive sera react with human EC eluted from large arteries, namely the aorta, as well as large veins, namely human umbilical vein EC (HUVEC). Other AECA (presumably a different subset of autoAb) recognize EC eluted from the microsvasculature, particularly in SSc (Salojin et al., 1997). According to the type of EC used for detection, the prevalence of AECA ranges from 20% to 40% of the cases of SSc (Renaudineau et al., 1999). In view of the overwhelming variability in the Ag pattern of EC from one cord to another, one must admit that there is a crucial need for several EC lines (Youinou et al., 1995; Le Tonquèze et al., 1996; Praprotnick et al., 2001) to be established.

These findings do not imply that AECA are specific for EC. Such a concept is substantiated by the demonstration that AECA cross-react with human fibroblasts (Koenig et al., 1993), and by partial inhibition of this reactivity by absorption of the AECA-containing sera with mononuclear cells. It has also been found that a 55 kDa structure which is shared by platelets and EC is recognized by a subset of AECA