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Review

Anti-endothelial cell antibodies in vasculitis: A systematic review

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ABSTRACT

Anti-endothelial cell antibodies (AECAs) are those that can bind to endothelial cells (ECs) via variable region-specific interactions. The identification and quantification of AECAs varies depending on the technique used. The best approach would be to combine at least two different methods. Thus, AECA measurement cannot be considered a diagnostic tool, but the detection and titers of AECAs are associated with disease activity in various systemic vasculitis diseases. AECAs have been described in almost all primary systemic vasculitis diseases but also in many secondary vasculitis diseases, with the identification of various antigens. AECAs may play a pathogenic role in vasculitis, both in vitro and in vivo, mainly via EC activation and induction of apoptosis. We used a systematic review of the literature to better define the prevalence, clinical association, targeted antigens, possible pathophysiologic role and clinical usefulness of AECAs in various types of vasculitis.

Contents

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1. Introduction

The anti-endothelial cell antibodies (AECAs) can bind specifically to the membrane of endothelial cells (ECs) via variable region-specific interactions. However, this definition is probably too restrictive, and in fact, intracellular antigens could also be recognized by AECAs.

ECs are localized at the interface between blood and tissues; they line the vasculature and interact with circulating blood cells, particularly inflammatory cells [1]. AECAs are a heterogeneous group of antibodies directed against ECs. They were described for the first time in the early 1970s by indirect immunofluorescence as human antibodies binding to rat kidney ECs [2]. Since then, AECAs reacting with human ECs have been identified in a number of conditions mainly characterized by vascular inflammation, including systemic lupus erythematosus (SLE) [3], anti-phospholipid syndrome (APLS), systemic vasculitis, rheumatoid arthritis, systemic sclerosis (SSc) and solid organ transplantation. Usually, AECAs do not bind specifically to a single antigenic molecule but are directed toward a wide variety of target antigens including extracellular matrix proteins [5] as well as molecules that adhere to ECs such as deoxyribonucleic acid (DNA) in SLE [4] and β2-glycoprotein I (β2GPI) or phospholipids in APLS [6]. AECAs are commonly of the immunoglobulin G (IgG) isotype, but IgM and IgA AECAs have been described [6].

EC injury has been long known to play a crucial role in the pathogenesis of systemic vasculitis [7,8]. According to the Chapel Hill nomenclature, vasculitis features inflammation of the vessel walls [9]. The term vasculitis includes a wide diversity of diseases sharing common pathophysiological features such as EC damage and vessel-wall leukocyte infiltrates.

The potential pathogenic role of AECAs in diseases involving the vascular system remains controversial [10]. First, natural AECAs present in healthy individuals may be protective; such AECAs may participate in the host defense against pathogens by opsonization, contribute to the clearance of senescent cells and immune complexes, and/or exert anti-inflammatory properties [1]. Circulating autoantibodies fulfilling the AECA definition are present in therapeutic preparations of normal human IgG (IVIg) and are internalized and induce an anti-inflammatory EC functional phenotype both on resting and activated ECs [11].

AECAs can activate ECs; they may induce apoptosis and might contribute to the pathogenesis of systemic vasculitis [14,12], for example, by triggering the release of the 60-kDa heat shock protein (Hsp60) [13,15]. In addition, AECAs may trigger an inflammatory process via complement- or antibody-dependent cellular cytotoxicity; they may upregulate the expression of adhesion molecules by ECs, including E-selectin and intercellular adhesion molecule 1 (ICAM-1) as well as cytokines and chemokines [15].

Here we report a systematic review of the published literature on AECAs in vasculitis.

2. Sources of endothelial cells

Several types of ECs tested as sources of autoantigens to detect AECAs include ECs from large arteries (aorta) and veins (umbilical cord veins, saphenous veins) as well as small vessels such as renal, skin, omental and brain microvasculature, or lineage ECs.

2.1. Macrovascular ECs

Human umbilical vein ECs (HUVECs) are commonly used as a substrate, but antigen patterns of ECs differ among other ECs, by passage number and by culture conditions. The properties of HUVECs cannot be guaranteed beyond three culture passages. Perfusion of the human umbilical cord vein with collagenase results in a pure preparation of the single layer of ECs that lines this vessel [16]. HUVECs have provided a critical in vitro model for major breakthroughs in molecular medicine, including seminal insights into cellular and molecular events in the pathophysiology of atherosclerosis and plaque formation as well as mechanisms for the control of angiogenesis or neovascularization in response to hypoxia and inflammation in tumors and ischemic tissue and in embryogenesis [17].

2.2. Microvascular ECs

ECs from microvasculature are extracted from several tissues: bone marrow, kidney, skin, omental or brain. Particularly, human dermal microvascular ECs (HDMECs), derived from the foreskins of newborns, or bone-marrow ECs are sources of microvascular ECs [18]. The advantage of bone-marrow ECs has been demonstrated by Renaudineau et al., who compared four EC sources in a study of AECAs in patients with SSc [18]. Microvascular ECs up to passage 6 could be used.

2.3. Lineage ECs

EC hybridoma (EA.hy 926), a mixed endothelial–epithelial cell line, and Kaposi sarcoma ECs have been used. However, a higher prevalence of AECA reactivity was found when combining bone-marrow ECs with other types of cells [18].

Simian virus-40 (SV 40) T-antigen–transfected human umbilical ECs obtained by lentiviral transduction of telomerase reverse transcriptase and SV 40 T antigen in HUVEC primary culture allowed for great stability even at a high culture passage number [19].

3. Methods to detect AECAs

3.1. Indirect immunofluorescence (IIF)

In 1971, Lindqvist and Osterland used IIF for the first time to detect AECAs [2]. The authors initially used frozen mouse kidney sections as a substrate for detection and found AECAs in sera from patients with a wide variety of diseases, with high incidence in chronic pulmonary tuberculosis (26.6%). IIF revealed up to 14% AECA incidence in healthy blood donors [2] (Fig. 1).

3.2. Enzyme-linked immunosorbent assay (ELISA)

In 1987, Hashemi et al. used ELISA to detect AECAs directed against HUVECs [20] with sera from patients with SLE or SSc. Since then, cell-based ELISA with HUVECs is one of the major approaches for AECA detection [21]. Cell-based ELISA with EC suspension (in the absence of