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Anti-annexin V antibodies: are they prothrombotic?

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Abstract

Annexin V inhibits prothrombin activation and is able to prevent thrombus formation under normal venous and arterial blood flow conditions. Antibodies to annexin V have been identified in association with several pathological conditions, including systemic lupus erythematosus (SLE) with or without anti-phospholipid syndrome, recurrent spontaneous abortions and systemic sclerosis (SSc). These antibodies are suspected to exert a detrimental role and interfere with annexin V function. Thus, they have been associated with the occurrence of foetal loss and venous and/or arterial thrombosis in SLE patients, as well as digital ischemia in SSc patients. However, their true pathogenic role remains to be proven.

Keywords: Systemic lupus erythematosus; Anti-phospholipid syndrome; Systemic sclerosis; Recurrent spontaneous abortion; Thrombosis; Anti-annexin V antibodies

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Abbreviations: Ab, antibody; ACL, anti-cardiolipin; aPL, anti-phospholipid Abs; APLS, anti-phospholipid syndrome; ELISA, enzyme-linked immunosorbent assay; kDA, kiloDalton; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; lSSc, limited SSc; dSSc, diffuse SSc; PAH, pulmonary arterial hypertension; SRC, scleroderma renal crisis.

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1. Introduction

Annexins belong to a family of proteins that are able to bind to negatively charged phospholipids and membrane bilayers through calcium dependent interactions [1]. Though their fine structure has been well described [1], the function(s) of annexins are not clearly identified yet [1]. With others, annexins constitute a group of ubiquitous cytoplasmic proteins involved in signal transduction. Annexins have been shown to exhibit putative binding sites for protein kinase C (PKC). However, only annexin V possesses a potential pseudo-substrate site that might modulate the activity of PKC [2]. Annexin V is a 320-amino acid-residue, 36 kDa protein [3] that is folded into a planar cyclic arrangement of four repeats with each repeat composed of five alpha-helical segments [4]. Upon analysis of the crystal structure of annexin V [4,5], a prominent hydrophilic pore was identified that might constitute an ion pathway. The annexin V gene is located on human chromosome 4q26–q28 and spans a region of 28 kb DNA containing 13 exons and 12 introns [6].

2. Biological effects of annexin V

Annexin V has a wide tissue distribution since it has been detected mainly in placenta [7] and vascular endothelium [8], but also in cardiac and striated muscle myocytes [9], chondrocytes [10], osteoblasts [10], glial cells [11], Schwann cells [11], optic nerve [11], hepatocytes and bronchi [11]. The potent anticoagulant activity of annexin V is derived from its inhibitory effect on prothrombin activation [12] and its ability to effectively prevent thrombus formation under normal venous and arterial blood flow conditions [13]. Annexin V's preferential binding partner is phosphatidylserine (PS), which is prominently located in membrane leaflets. It has recently been shown that the molecular machinery that is responsible for the expression of PS onto cell surface is present in any cell type and activated during apoptosis [14]. Thus, once PS is exposed at the cell surface, annexin V might bind to PS and inhibit its procoagulant and pro-inflammatory activities. These findings, together with the characterization of annexin V in the extracellular space, provide evidence for a new physiological function of annexin V [15].

3. Anti-annexin V antibodies

Anti-annexin V antibodies (Ab) have been detected for the first time 10 years ago in patients with systemic lupus erythematosus (SLE). Since then, these Ab have been associated with the occurrence of thrombotic events and/or recurrent abortions in patients with SLE and anti-phospholipid syndrome (APLS) as well as digital ischemia in patients with systemic sclerosis (SSc) (Table 1). Although the mechanisms leading to the occurrence of anti-annexin V Ab have not been completely elucidated, it has been proposed that in the context of increased apoptosis, extracellular/membrane annexin V might constitute an antigenic stimulus for specific Ab production. Moreover, it is suspected that anti-annexin V Ab may interfere with annexin V function(s) and exert a detrimental role leading to thrombosis and/or vascular occlusion [16] (Fig. 1).

3.1. Systemic lupus erythematosus

SLE is considered as the prototypic systemic autoimmune disease, characterized by a huge diversity of clinical manifestations and serum IgG autoantibodies to nuclear components. Although significant progresses have been made in the understanding of the pathogenesis of the disease, the fine mechanisms that lead to the aberrant autoimmune responses are not clearly understood. Anti-phospholipid (aPL) Abs are