36 Annexins in Antiphospholipid Syndrome

Jacob H. Rand and Xiao-Xuan Wu

Introduction

Annexin A5 is a potent anticoagulant protein that binds to anionic phospholipid containing bilayers with high affinity. The protein has potent anticoagulant properties that are a consequence of its forming two-dimensional crystals that shield the bilayers from being available for critical coagulation enzyme reactions. Autoantibodies against phospholipid binding proteins or against annexin A5 itself may disrupt the crystallization of the annexin A5 shield, expose anionic phospholipids (PL), and thereby make them available for phospholipid dependent coagulation reactions. This interference with annexin A5 crystallization may be a mechanism for pregnancy losses and thrombosis in antiphospholipid syndrome (APS) – a condition that is also known as the Hughes syndrome.

Anticoagulant Effect of Annexin A5

The various annexins were isolated from different tissues, characterized by different research groups, and given different names prior to their becoming recognized to be a homologous family of proteins in 1990 [1]. The family is composed of several thousand different proteins that have been identified in eukaryotic phyla [2]. Their canonical structure consists of repetitive homologous domains of about 70 amino acids, with almost all of the annexins having 4 of these domains. The unique amino terminal tails are thought to contribute to each of the protein's unique properties. The protein forms highly ordered two-dimensional crystalline arrays over the bilayers [3–5] [Fig. 36.1(A)]. The monomer of annexin A5 is a concave disk, with the phospholipid membrane binding domain and calcium binding domains located on the convex surface. These monomers assembles into large, slightly convex crystals on membranes that, when added to large spherical phospholipid vesicles, form planar facets that transform the vesicles into polyhedrons [6]. Annexin A5 appears to be synthesized ubiquitously, but is especially highly expressed by cells that serve a barrier function between tissues and an extracellular fluid [7], such as vascular endothelial cells, placental trophoblasts, proximal renal tubules, and bile ductules.

As mentioned above, the anticoagulant properties of annexin A5 result from its shielding phospholipids from availability for coagulation reactions. Phospholipids are critically required for the sequence of blood coagulation reactions from their

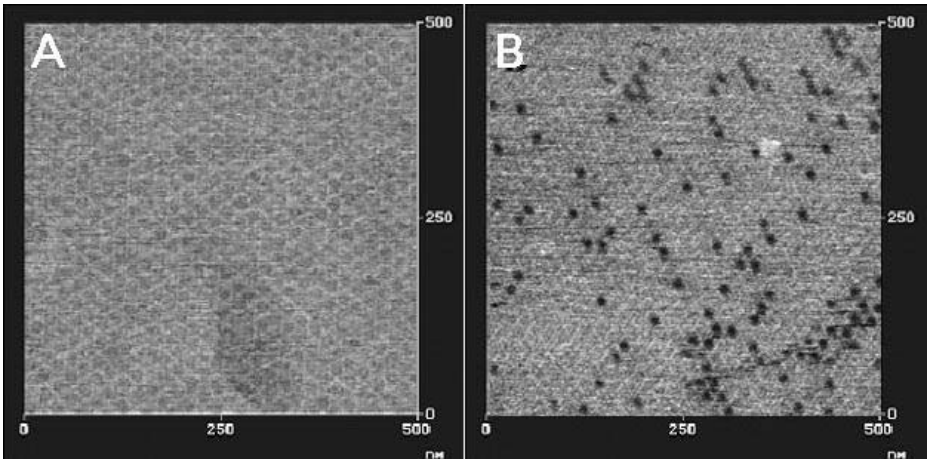

Figure 36.1. Crystal structure of annexin A5 and its disruption by monoclonal aPL. (A) An atomic force image of annexin A5 that has formed a highly ordered two-dimensional crystal over a phospholipid bilayer composed of 30% phosphatidylserine/70% phosphatidyl choline that was formed on a mica chip. (B) When an aPL mAb and β_2-glycoprotein I were added to the pre-formed annexin A5 crystal lattice on the bilayer, vacancy defects (small round dark holes) appeared, indicating disruptions in the crystal lattice. (Reprinted from Rand JH, et al. Human monoclonal antiphospholipid antibodies disrupt annexin a5 anticoagulant crystal shield on phospholipid bilayers: evidence from atomic force microscopy and functional assay. Am J Pathol 2003;163:1193–1200, with permission from the American Society for Investigative Pathology.)

initiation by the exposure of the transmembrane protein tissue factor (TF) through the reaction that generates thrombin. This requirement localizes coagulation reactions to sites of vascular injury. TF, in complex with adjacent phospholipids, binds circulating coagulation factor VII, which becomes activated to VIIa. The TF–phospholipids–VIIa complex then binds to, and then cleaves, each of its substrates – the zymogens, factor X, and factor IX – to generate their active enzyme forms, factors Xa and IXa. Each of these enzymes, in turn, cleaves its own substrate – factor II (also known as prothrombin) and factor X, respectively – through the enzyme–cofactor–substrate complexes that require also anionic phospholipids, in particular phosphatidylserine [8], for assembly. These are the factors Xa–Va–II complex (also known as "prothrombinase") that results in the generation of factor IIa (also known as thrombin), and the factors IXa–VIIIa–X complex (also known as "tenase") that augments the formation of factor Xa. The thrombin that is generated then cleaves fibrinogen to form fibrin, has a number of additional complex effects on coagulation proteins and anticoagulant proteins, and also triggers signaling events on platelets and other cells.

Role of Annexin A5 in Placental Trophoblasts and Vascular Endothelium

The role of annexin A5 in pregnancy has been recently reviewed [9]. Annexin A5 is highly expressed by placental trophoblasts, in an apparently constitutive manner