25 β_2-glycoprotein I and Anti–β_2-glycoprotein I Antibodies

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Introduction

In patients with antiphospholipid syndrome (APS), pathogenic antiphospholipid antibodies (aPL) are not directed against phospholipids itself, but against plasma proteins that bind to negatively charged surface, such as β_2-glycoprotein-I (β_2-GPI) [1–3], prothrombin [4–6], annexin V, protein C, protein S, high- and low-molecular-weight kininogens [7], tissue plasminogen activator [8], factor VII [9], factor XII [10], complement component C4, and complement factor H [11]. Among them, autoantibodies against β_2-GPI have been extensively investigated and recognized as the most relevant, because anti–β_2-GPI autoantibodies are not only a marker of APS [12], but also seem to play pathogenic roles in developing thrombosis [12, 13].

Structure and Physiological Function of β_2-GPI

β_2-GPI, also known as apolipoprotein H, is a 50-kDa phospholipid binding protein present in plasma at an approximate concentration of 200 μg/mL. β_2-GPI has 5 homologous short consensus repeats and 4 glycation sites, forming an elongated fishhook-like 3-dimensional structure. Domains of β_2-GPI structurally resemble each other, except that domain V has an extra C-terminal loop and a positively charged lysine cluster. According to the crystal structure of human β_2-GPI, it was proposed that this large positively charged patch interacts with negatively charged phospholipid with a flexible and partially hydrophobic loop inserted into the lipid layer when it binds to the cell surface [14, 15] (Fig. 25.1). β_2-GPI also binds to other negatively charged molecules such as heparin, DNA, oxidized low-density lipoprotein (LDL) [16, 17], and apoptotic bodies [18].

Because negatively charged molecules trigger the intrinsic coagulation pathway, β_2-GPI was proposed to be a natural anticoagulant. β_2-GPI inhibits prothrombinase and tenase activity on platelets or phospholipid vesicles [19], inhibits factor XII activation [20], and modulates ADP-dependent activation of platelets [21]. Recently, β_2-GPI has been shown to bind directly to factor XI and attenuate its activation [22]. On the other hand, β_2-GPI exerts procoagulant activities by reduction of activated protein C [23]. Data from knockout mice suggests that β_2-GPI may

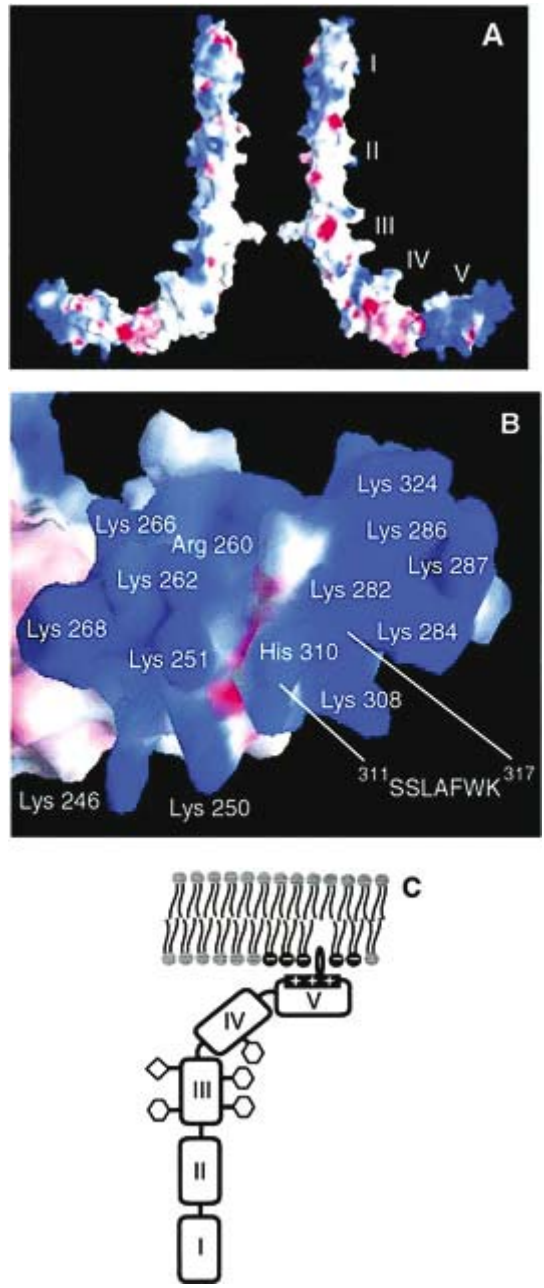

Figure 25.1. Structure of human β_2-GPI and binding model of β_2-GPI and phospholipids. (A) Two views, related by 180° rotation of the electrostatic potential surface of β_2-GPI. (B) Positively charged patch on the aberrant half of domain V. (C) Diagram of the proposed model for binding of β_2-GPI to anionic phospholipids. [Reprinted from Bouma et al. Adhesion mechanism of human beta(2)-glycoprotein I to phospholipids based on its crystal structure. EMBO J 1999;18:5171.]