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β_2-Glycoprotein I – A Protein in Search of Function

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1. Introduction

β2-glycoprotein I is a lipid-binding 50-kDa glycoprotein that circulates in plasma at a concentration of approximately 4 μM (200 μg/ml). The amino acid sequence of human β2-glycoprotein I was completely determined (1), the cDNAs have been isolated (2, 3) and the crystal structure has been solved (4). β2-glycoprotein I is a member of the so-called "complement control protein" (CCP) superfamily, whose members are identified by the presence of one or more of a motif containing a characteristic disulfide bond pattern (5). These motifs are called CCP or sushi domains. CCP repeats are units of approximately 60 amino acids with a relatively invariant arrangement of 2 disulfide bonds and a number of other highly conserved residues. Other members of the CCP superfamily include at least 12 complement proteins, the B subunit of blood clotting factor XIII, haptoglobin, the interleukin 2 receptor and selectins. β2-glycoprotein I is made up entirely of five CCP repeats. CCP5 diverges from the norm for CCPs, including CCPs 1-4 in that it has a relatively unique pattern of 3 disulfide bridges (6), and contains a positively-charged sequence, CKNKEKKC (residues 281-288), that mediates its binding site for anionic phospholipid (7). The crystal structure of β2-glycoprotein I showed the four CCP domains 1-4 are arranged like a beads on a sting and CCP5 folds back giving fishhook-like conformation. The CCP5 contains a central spiral structure with positively charged motif CKNKEKKC close to a hydrophobic patch (LAFW). B2-glycoprotein I anchors to the anionic phospholipid membrane surface via CCP5 with its hydrophobic loop adjacent to the positively charged lysine rich region in CCP5. Subsequently, β2-glycoprotein I penetrates the membrane interfacial headgroup region. This binding restricts the mobility of the lipid side chains and aggregates the vesicles without inducing fusion (8-10). In addition to anionic phospholipids, β2-glycoprotein I binds to sulfatide (11), heparin (12), complement C3 (13), annexin A2 (14), platelet glycoprotein Ib (15), megalin (16), apolipoprotein receptor 2' (17) von Willebrand factor (18, 19) and possibly many others ligands. The solution structure of β2-glycoprotein I was studied by small angle X-ray scattering (20), the experimentally derived curves fitted poorly to the simulated scattering curves calculated from the crystallographic coordinates of human b2GPI, suggesting different conformation in solution. Recent studies with negative staining electron microscopic studies showed β2-glycoprotein I can exist in two different

conformations – a circular conformation due to the interaction of CCP1 with CCP5 and an open elongated conformation consistent with the fishhook-like structure seen in the crystallographic studies (21). In closed conformation β2-glycoprotein I bind less well to anionic phospholipids or to complement C3 (13). Binding to anionic phospholipids, and possibly other ligands stabilizes the elongated conformation (22). Circulating plasma β2-glycoprotein I contains free thiols and these moieties are proposed to interaction with platelets and endothelium, protecting these cells from oxidative stress (18). Oxidized form β2-glycoprotein I is increased in patients with thrombosis (23). Oxidized β2-glycoprotein I induces human dentritic cell maturation and promotes a T helper type I response (24). These studies imply the antibody response to β2-glycoprotein I are due post translational modifications due to oxidative stress.

β2-glycoprotein I was designated as apolipoprotein H initially as it could be isolated from very low density lipoprotein fractions and had high affinity for triglyceride-rich particles (25). However, recent studies do not suggest an interaction between β2-glycoprotein I with either high or low density lipoproteins (26).

Despite the extensive physicochemical characterization, the physiological role of β2-glycoprotein I remains uncertain. Based on several *in vitro* studies, a wide range of functions have been attributed such as regulation of coagulation (27), modulation of complement activity and clearance of apoptotic cells from the circulation (28). In this review, we will summarize newer data on the possible physiological role of β2-glycoprotein I.

2. Modulation of hemostasis

Since β2-glycoprotein I is the target of the majority of antiphospholipid antibodies associated with thrombosis, an anticoagulant function for β2-glycoprotein I was anticipated. Anionic phospholipid surfaces play an essential role in normal hemostasis by providing a site for the assembly of enzyme-cofactor complexes involved in virtually every step of the enzymatic cascade that results in the generation of fibrin, which polymerizes to form an insoluble fibrin clot. In normal cells, anionic phospholipids such as phosphatidylserine are present only in the inner leaflet of the membrane bilayer. Platelets externalize anionic phospholipid when stimulated by agonists. Binding of β2-glycoprotein I to anionic phospholipid vesicles (29) and platelets (30, 31) is accompanied by inhibition of phospholipid-dependent coagulation tests (27, 32), suggesting a likely physiological role of β2-glycoprotein I in the regulation of coagulation, particularly on activated platelets and possibly on other cell surfaces. In addition, β2-glycoprotein I inhibits the contact activation of the intrinsic coagulation pathway (15, 33). β2-glycoprotein I binds to factor XI with an affinity equivalent to that of high molecular weight kininogen. The binding inhibits the activation to factor XI by thrombin and FXIIa. This was suggested to be a mechanism, by which β2-glycoprotein I may modulate thrombin generation. β2-glycoprotein I also binds to heparin – a fact used in its isolation (12, 29). Heparin binding site had been localized to the positively charged CCP5 (12). Heparin also promotes plasmin cleavage of β2-glycoprotein I at Lys317-Thr318 bond (34). Plasmin-cleaved β2-glycoprotein I has markedly decreased affinity for anionic phospholipid. This form of cleaved β2-glycoprotein I is seen in patients treated with streptokinase and in patients with disseminated intravascular coagulation (35), showing this cleavage reaction can occur in vivo during accelerated fibrinolysis.

Several procoagulant effect of β2-glycoprotein I have also been described. β2-glycoprotein I binds to thrombin and protects it from inactivation by heparin cofactor II/heparin complex (36). Furthermore, Mori et al (37) showed β2-glycoprotein inhibited activated protein C inactivation of factor Va – an effect diminished by the addition of phospholipids. At similar concentration, β2-glycoprotein I inhibited weakly factor Va- and phospholipid-dependent prothrombinase activity. The depletion of beta β2-glycoprotein I from plasma led to only a slight shortening of the diluted Russell's viper venom-dependent clotting time, but to a strong and significant potentiation of the anticoagulant activity of APC. These results suggest that under certain physiological conditions β2-glycoprotein I may have procoagulant function.

In contrast to these hemostatic activities demonstrated in vivo, neither the β2-glycoprotein I-deficient mice (generated by homologous recombination) nor β2-glycoprotein I-deficient individuals exhibit any bleeding manifestations (38-40). On the contrary, β2-glycoprotein I-deficient mice have diminished rate of thrombin generation compared with normal or even with heterozygous mice. No significant differences in clotting time were observed in plasma from these three genotypes when measured by dRVVT, dKCT, aPTT, and protein C pathway assays (41). Hereditary deficiency of β2-glycoprotein I was reported since 1968 (42), and its potential association with risk of thrombosis had been examined. Bansci *et al.* (43) have described two brothers with total deficiency of β2-glycoprotein I, one of whom had experienced recurrent unexplained thrombosis by age 36. However, six other heterozygous individuals (ages 9-73) from this family and the proband's brother with homozygous deficiency were free of thrombosis. Takeuchi et al (39) described two asymptomatic individuals with complete deficiency of β2-glycoprotein I. The routine coagulation assays were normal. A slight shortening of the DRVVT was observed in these individuals, which interestingly were not corrected by exogenous addition of β2-glycoprotein I.

Thrombosis is a complex multigene phenotype (44). Because of the large number of genes that influence this phenotype teasing out the role of β2-glycoprotein I in in this prothrombotic phenotype will be difficult. It is also possible that the thrombosis seen with antiphospholipid antibodies is not related to any of interaction identified above.

3. β2-glycoprotein I as an opsonin

The term opsonins is used to refer molecules that target a cell for phagocytosis. A number of observations suggest β2-glycoprotein I can be an opsonin for clearance of anionic phospholipid vesicles containing surfaces from the circulation. In normal cells, anionic phospholipids such as phosphatidylserine are present only in the inner leaflet of membrane bilayer. There is transbilayer movement of phosphatidylserine during apoptosis and phosphatidylserine exposed can be a tag for their clearance by macrophages (45-47). In artificial membranes, the phosphatidylserine content has to be at least 5-10% before a significant binding of β2-glycoprotein I could be observed (48). Nevertheless, the binding of β2-glycoprotein I to phosphatidylserine containing surfaces such as apoptotic cells and platelet microvesicles have been shown (49, 50). In addition to the anionic phospholipids, β2-glycoprotein I is also shown to bind the Ro/SSA, a 60 kDa a nuclear antigen and target of autoantibodies in primary Sjogren syndrome (19). Ro/SSA translocates to cell surface during apoptosis and can serve as additional binding site. The complex of anionic

phospholipid and ß2-glycoprotein I are taken into a receptor-mediated pathway by macrophages and possibly endothelial cells also. The phagocytic receptors mediating the uptake have been shown to be toll-like receptor 4 in macrophages (51) and lipoprotein receptor related family members (49). In endothelial cells toll-like receptor 2 and 4 (52, 53), annexin A2 (14), and apolipoprotein E receptor 2 (54) have been implicated. Deficiencies of factors, implicated in the removal of apoptotic cells such as lactadherin and Gas6 receptors, are associated with systemic lupus erythematosus and autoimmunity (55). However, no immunological dysfunction is reported in β2-glycoprotein I deficiency.

β2-glycoprotein I may also have a role in the clearance of exogenous liposomes. Liposomes have been used extensively as vehicles for drug delivery and following in vivo infusions, liposomes are preferentially taken up by the mononuclear phagocytic cells of the reticuloendothelial system (56). In 1982, Wurm et al (57) showed that infusion of ß2-glycoprotein I in rats results in an accelerated clearance of triglyceride-rich vesicles from the circulation. The clearance of liposomes by the phagocytic cells, is markedly affected lipid composition of the liposomes and anionic phospholipid containing are cleared very rapidly from blood (56). By analyzing the proteins that associate with the liposomes in blood, Chonn et al. have identified β2-glycoprotein I as a major protein associated with rapidly cleared liposomes and noted that pretreating the mice with anti-β2-glycoprotein I antibodies markedly increased the circulating half-life of the liposomes (58). It is interesting to note that in 1982, Wurm et al (57) showed that infusion of ß2-glycoprotein I in rats results in an accelerated clearance of triglyceride-rich vesicles from the circulation.

The complement system is involved in the clearance of dead cells and debris from the circulation and recently a role for β2-glycoprotein I its regulation has been identified (13). The elongated and open conformation of β2-glycoprotein I binds to C3 and induces a conformational changes so that the regulator factor H binds. As factor H promotes factor I-induced the cleavage of C3, β2-glycoprotein I acts as special cofactor for factor H and factor I. The enhanced the degradation of C3 limits further complement amplification. Deficiencies of complement factor H and I are associated atypical hemolytic uremic syndrome and no such association has been described for β2-glycoprotein I.

4. A role in gestation

Because of the association with fetal loss and anti-β2-glycoprotein I antibodies, a role in gestation has been proposed. Infusion of cyanine labeled β2-glycoprotein I in mice show preferential localization on the endothelium of uterine vessels and at the implantation sites in pregnant mice (59), suggesting a role in early gestation. However, the β2-glycoprotein I null mice were fertile and carried viable fetuses to term and there were no thrombosis in placental vessels (60). Nevertheless, there was an 18% reduction in the number of viable implantation sites and reduced fetal weight and fetal:placental weight ratio in late gestation in β2-glycoprotein I null mice.

5. β2-glycoprotein I and angiogenesis

β2-glycoprotein I is enzymatically cleaved by plasmin at the peptide bond between Lys317-Thr318 to form a cleaved form β2-glycoprotein I (61, 62). This form is seen in the circulation in patients with increased fibrinolysis. The cleaved form of β2-glycoprotein I binds to

plasminogen and inhibits plasmin generation. In addition to modulating fibrinolysis, a role in angiogenesis had been proposed for the cleaved form of β2-glycoprotein I. The cleaved form of β2-glycoprotein I inhibits endothelial cell proliferation in vitro, inhibits neovascularization into subcutaneously implanted angiogenic matrices and the growth of orthotopic prostate cancer in C57BL/6 mice (63, 64). The cleaved β2-glycoprotein I strongly reduced HUVEC growth and proliferation as evidenced by the MTT and BrdU assay and delayed cell cycle progression arresting endothelial cells in the S-and G2/M-phase (65). However, the cleaved form of β2-glycoprotein I can also be promote angiogenes is as it binds angiostatin 4.5 (plasminogen kringle 1-5) and attenuates its antiangiogenic property (66). The murine β in vivo apparently displayed only mild anti-angiogenic properties. β2-glycoprotein I deficient mice developed larger tumors with more vessels than β2-glycoprotein I replete mice but no survival benefit is conferred to tumor bearing animals regardless of β2GPI status raising questions about the its pathophysiological role in tumorigenesis(66).

6. Conclusion

Since its discovery in the sixties and following the recognition that it is the antigenic target for antiphospholipid antibodies in nineties, several structural and functional studies have been described. However, there is no convincing pathogenetic mechanism or theoretical framework for the hypercoagulable state associated with antibodies to this protein. Many hypotheses have been proposed based on in vitro findings and most of them revolve on the anionic phospholipid binding properties of β2-glycoprotein I. At least two patients are described with antiphospholipid syndrome who had mutations in β2-glycoprotein I rendering it in capable of binding phospholipids (67, 68), questioning its phospholipid binding in pathogenesis. These findings underscore the importance finding its physiological function to elucidate the mechanism of thrombosis seen with antibody to this molecule.

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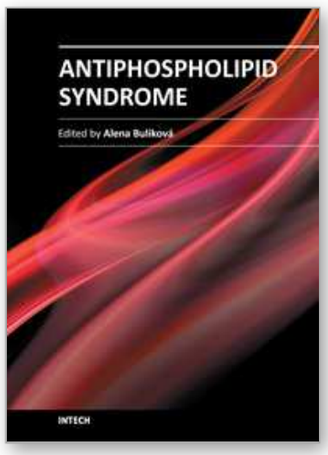

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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. Form that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities . This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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