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Structural Changes in β₂-Glycoprotein I and the Antiphospholipid Syndrome

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1. Introduction

1.1 History of β₂-glycoprotein I

β₂-Glycoprotein I (β₂GPI) was described in literature for the first time in 1961 (Schultze et al., 1961) and seven years later the first β₂GPI deficient, seemingly healthy individual was identified (Haupt et al., 1968). β₂GPI's alternative name, apolipoprotein H, suggests a function in lipid metabolism, but this was based on a single publication that dates from 1979 in which it was shown that β₂GPI was distributed over different human lipoproteins (Polz & Kostner, 1979). Since 1983, the names β₂GPI and apolipoprotein H were used side by side for the same protein (Lee et al., 1983), and the official designation for the β₂GPI gene has become APOH. From 1990 on, the interest in this protein has increased significantly when β₂GPI was identified as the most important antigen in the antiphospholipid syndrome, which is amongst others characterized by the presence of antibodies directed to β₂GPI (McNeil et al., 1990; Galli et al., 1990). In 2010, a second three-dimensional conformation of β₂GPI was identified (Ağar et al., 2010) besides the known fishhook-like conformation that was suggested by the crystal structure of the protein (Bouma et al., 1999; Schwarzenbacher et al., 1999). In this chapter we will focus on this novel conformation of β₂GPI and discuss the consequences of the transition between the two conformations for β₂GPI on past but also on present findings.

1.2 Biochemistry of β₂-glycoprotein I

β₂GPI is a 43 kDa protein and consists of 326 amino acid residues (Lozier et al., 1984). β₂GPI is synthesized in the liver and it circulates in blood at variable levels (Rioche et al., 1974). β₂GPI is an anionic phospholipid binding glycoprotein composed of five homologous complement control protein repeats, CCP-I to CCP-V (Bouma et al., 1990; Schwarzenbacher et al., 1990). These CCPs are generally found in proteins from the complement system and mediate binding of complement factors to viruses and bacteria (Breier et al., 1970; Pangburn & Rawal, 2002). The first four domains contain approx. 60 amino acids each, whereas the fifth domain has a 6 residue insertion and an additional 19 amino acid C-terminal extension. The extra amino acids are responsible for the formation of a large positive charged patch within the fifth domain of β₂GPI (Hunt et al., 1993) that forms the binding site for anionic

phospholipids (Figure 1).The crystal structure of β$_2$GPI has been solved in 1999 by two groups (Bouma et al., 1990; Schwarzenbacher et al., 1990), and revealed a structure that resembles a J-shaped fishhook. The phospholipid binding site is located at the bottom side of CCP-V and consists of two major parts, a large positive patch of 14 charged amino acid residues and a flexible hydrophobic loop. This flexible loop has the potential to insert into membranes (Planque et al., 1999).

### 1.3 β$_2$-Glycoprotein I and the antiphospholipid syndrome

The antiphospholipid syndrome (APS) is an auto-immune disease defined by the presence of antiphospholipid antibodies in blood of patients in combination with thrombotic complications in arteries or veins as well as pregnancy-related complications (Miyakis et al., 2006). In APS patients, the most common venous event is deep vein thrombosis and the most common arterial event is stroke. In pregnant women with APS early and late miscarriages can occur (Eswaran & Rosen, 1985). Next to miscarriages also placental infarctions, early deliveries and stillbirth have been reported (Lockshin et al., 1985; Branch et al., 1989; Birdsall et al., 1992). Antiphospholipid antibodies often occur transiently after infectious diseases, but there is a general consensus that these transient auto-antibodies are not related to an increased thrombotic risk (Miyakis et al., 2006). The syndrome occurs more in women than in men, and is most common in young to middle-aged adults but can also occur in children and the elderly. Among patients with systemic lupus erythematodes or lupus, the prevalence of antiphospholipid antibodies ranges from 12 to 30% for anticardiolipin antibodies, and 20 to 35% for lupus anticoagulant antibodies (Gezer et al., 2003). It is now generally accepted that the relevant auto-antibodies are not directed against phospholipids, but towards proteins bound to these phospholipids (Galli et al., 1990; McNeil et al., 1990; Bevers & Galli, 1990). β$_2$GPI has a relative low affinity towards these negatively charged phospholipids but its affinity increased more than 100-fold in the presence of auto-antibodies. Anti-β$_2$GPI antibodies were found to be the most prominent auto-antibodies in APS (de Groot & Meijers, 2011). Recently, three independent groups have shown the importance of antibodies against β$_2$GPI (Pierangelli et al., 1999; Jankowski et al., 2003; Arad et al., 2011) Mice that were challenged by injection of antiphospholipid antibodies had increased thrombus formation and foetal resorption (García et al., 1997; Ikematsu et al., 1998). Despite the wealth of data on the role of β$_2$GPI in the pathophysiology of APS, there were no convincing indications that help our understanding of the function of β$_2$GPI in normal physiology.

2. Conformations of β$_2$-glycoprotein I

### 2.1 β$_2$GPI exists in two conformations

There is overwhelming evidence that antibodies against β$_2$GPI can induce thrombosis in animal models (Blank et al., 1991; Pierangelli et al., 1999; Jankowski et al., 2003, Arad et al. 2011), but it was unclear which metabolic pathway was disturbed by the auto-antibodies. Nevertheless, the β$_2$GPI protein itself must hold an important functional clue that could lead us to both its function and its role in the antiphospholipid syndrome. Since patients with antiphospholipid antibodies do not have circulating antibody-antigen complexes despite the presence of large amounts of β$_2$GPI and antibodies in the circulation, the epitope

for the auto-antibodies on β₂GPI must be cryptic. As a consequence, the conformation of β₂GPI in plasma must be different from the one coated on an ELISA tray in tests for the detection of antibodies. The crystal structure of β₂GPI revealed a fishhook-like shape of the molecule (Bouma et al., 1990; Schwarzenbacher et al., 1990) (Figure 1). Part of the epitope that is recognized by auto-antibodies is located in the first domain of β₂GPI (Iverson et al., 1998; de Laat et al., 2006). The crystal structure indicated that these amino acids are expressed on the surface of domain I of β₂GPI and should thus be accessible for auto-antibodies. But the lack of binding of antibodies to β₂GPI in solution fits better with a circular structure of β₂GPI, a structure that was originally suggested by Koike et al. (1998). Electron microscopy (EM) studies showed that when antibodies were bound to β₂GPI, the protein indeed showed a fishhook-like shape, but native β₂GPI in the absence of antibodies showed a closed 'circular' shape (Figure 2) in which domains I and V interact with each other (Agar et al., 2010).
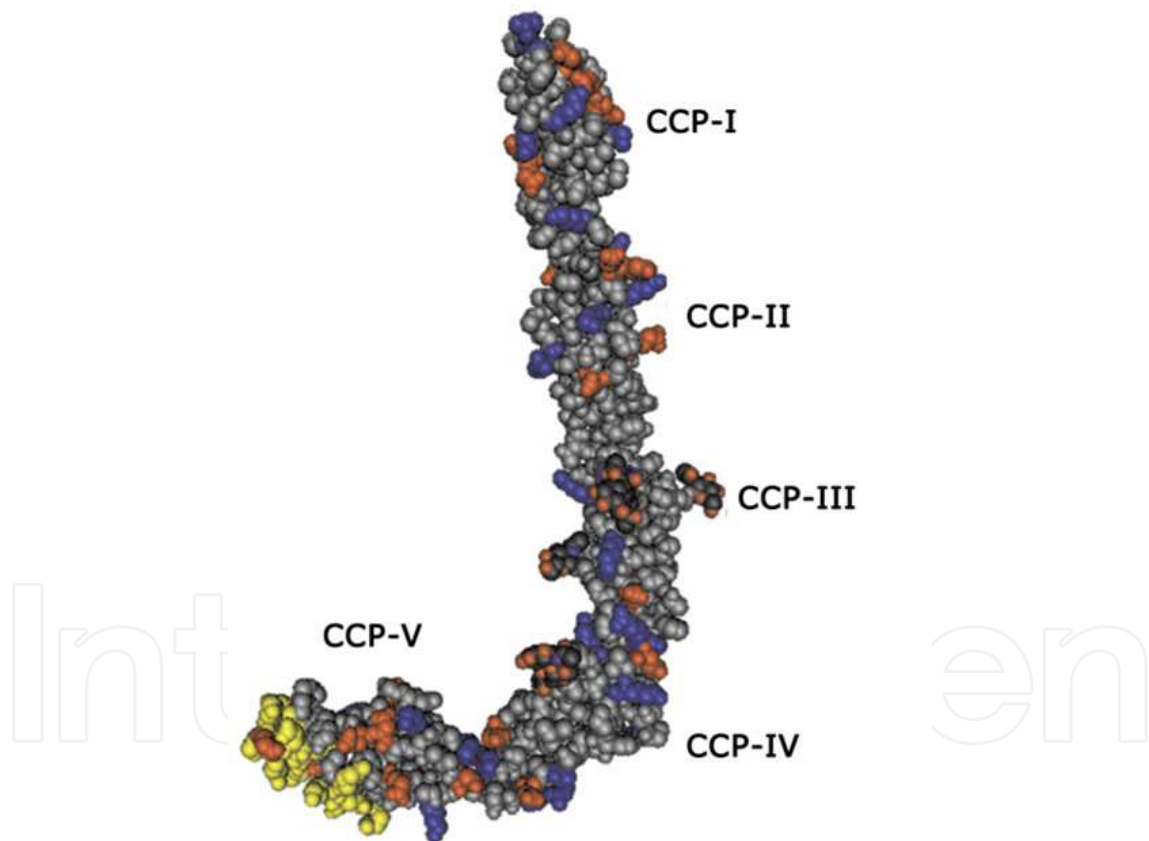
In blue the negatively charged amino acids are depicted and in red the positively charged amino acids. In yellow the large positive charged patch is shown within the fifth domain of β₂GP that forms the binding site for anionic phospholipids. Picture was made using Cn3D version 4.1, produced by the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

Fig. 1. Crystal structure of β₂GPI with the five CCP domains (CCP-I to CCP-V).
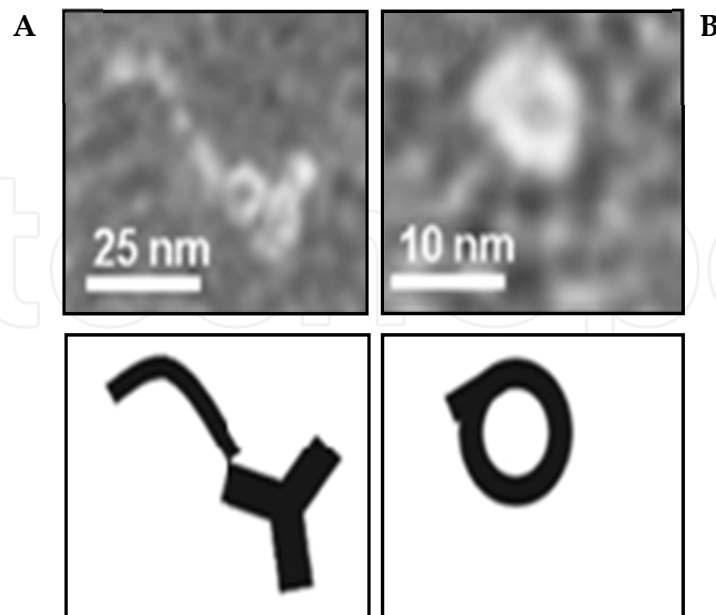
(A) Purified plasma β$_2$GPI in the presence of antibodies directed against domain I of β$_2$GPI shows on magnification an open fishhook-like shape of β$_2$GPI. (B) Magnification of purified plasma β$_2$GPI shows a circular conformation of the protein. This figure was modified from work originally published in *Blood.* C. Agar, G.M.A. van Os, M. Mörgelin, R.R. Sprenger, J.A. Marquart, R.T. Urbanus, R.H.W.M. Derksen, J.C.M. Meijers, P.G. de Groot. β$_2$-Glycoprotein I can exist in 2 conformations: implications for our understanding of the antiphospholipid syndrome. *Blood* 2010;116(8):1336-1343. © the American Society of Hematology.

Fig. 2. Electron microscopy analysis of β$_2$GPI.

By changing pH and salt concentrations, it was possible to convert β$_2$GPI from the native closed conformation into the open conformation and back (Agar et al., 2010). Analysis of EM pictures showed that more than 99% of plasma β$_2$GPI was in a closed conformation. These observations suggested that plasma β$_2$GPI circulates in a circular (closed) conformation, whereas after interaction with antibodies β$_2$GPI undergoes a major conformational change into a fishhook-like (open) structure.

2.1.1 Effect of the conformation of β$_2$GPI on coagulation

β$_2$GPI is present in high concentrations in plasma, and depletion of β$_2$GPI from normal plasma does not influence the results of coagulation assays (Oosting et al., 1992; Willems et al., 1996). When antibodies toward β$_2$GPI were added to plasma, clotting times prolonged in a β$_2$GPI-dependent way. This effect of anti–β$_2$GPI antibodies is known as lupus anticoagulant (LA) activity. A LA could also be seen with open β$_2$GPI (Agar et al., 2010). When closed native β$_2$GPI was added to normal plasma or β$_2$GPI-depleted plasma, no effect on an activated partial thromboplastin time (aPTT)-based clotting assay was observed.

When open β_2GPI was added to plasma or β_2GPI-depleted plasma, the aPTT prolonged. Addition of antibody and open β_2GPI together to normal plasma gave an additional anticoagulant effect on top of the effect of open β_2GPI alone (Agar et al., 2010). The presence of β_2GPI in a certain conformation is dependent on the presence of anionic surfaces but also on the method of purification of β_2GPI. As was described by Agar et al (2010), the conformation of β_2GPI is dependent on the pH and salt concentration used during the purification of native β_2GPI. The structure of β_2GPI needs confirmation before doing experiments with purified β_2GPI.

Schousboe (1985) was the first who described β_2GPI as a plasma inhibitor of the contact activation of the intrinsic blood coagulation pathway. With the current knowledge of the two conformations (Agar et al., 2010), these studies were most likely performed with the open conformation of β_2GPI, the only conformation that gives a prolongation in an aPTT. Furthermore, it was suggested that β_2GPI inhibited coagulation by inhibition of activation of coagulation factor XII (Henry et al., 1988) and coagulation factor XI (Shi et al., 2004). It is likely, that also these observations were obtained with the open 'activated' conformation of β_2GPI. The purification method that all these groups used included the use of perchloric acid, and these harsh conditions may have induced a conformational change of closed native β_2GPI into the open activated conformation of β_2GPI. It is highly recommended that the conformation of β_2GPI is confirmed in coagulation tests or by electron microscopy. It is expected that in the near future specific immunological assays will become available to determine the specific conformational state of β_2GPI.

2.2 Functional consequence of the conformations of β₂GPI

Lipopolysaccharide (LPS), a major constituent of the outer membrane of Gram-negative bacteria, plays a role in activating the hosts' immune response by binding to white blood cells (van der Poll & Opal, 2008). Analysis of electron microscopy pictures of β_2GPI incubated with LPS, showed that LPS was bound to domain V of β_2GPI and thereby induced a conformational change to the open conformation of β_2GPI (Figure 3) and showed the same fishhook-like shape when β_2GPI was bound to anionic surfaces or antibodies (Agar et al., 2011a).

A functional consequence of β_2GPI binding to LPS was investigated in an *in vitro* cellular model of LPS-induced tissue factor (TF) expression. Native plasma-purified β_2GPI dose-dependently inhibited LPS induced TF expression both in monocytes and endothelial cells (Agar et al., 2011a). Furthermore, in an *ex vivo* whole blood assay β_2GPI inhibited LPS induced interleukin-6 expression, an inflammatory marker in innate immunity. Furthermore, an *in vivo* relevance was found of the interaction between β_2GPI and LPS in plasma samples of 23 healthy volunteers intravenously challenged with LPS (de Kruif et al., 2007). A reduction of 25% of baseline values was observed of β_2GPI immediately after LPS injection, suggesting an *in vivo* interaction between β_2GPI and LPS.

Also, a highly significant, negative association was found between plasma levels of β_2GPI and plasma levels of inflammatory markers TNFα, IL-6 and-IL-8 after the LPS challenge. In agreement to this, there was a highly significant inverse relation between the baseline β_2GPI levels and the observed temperature rise upon LPS challenge (Agar et al., 2011a). Subsequently, a significant difference in β_2GPI levels was observed between non-sepsis
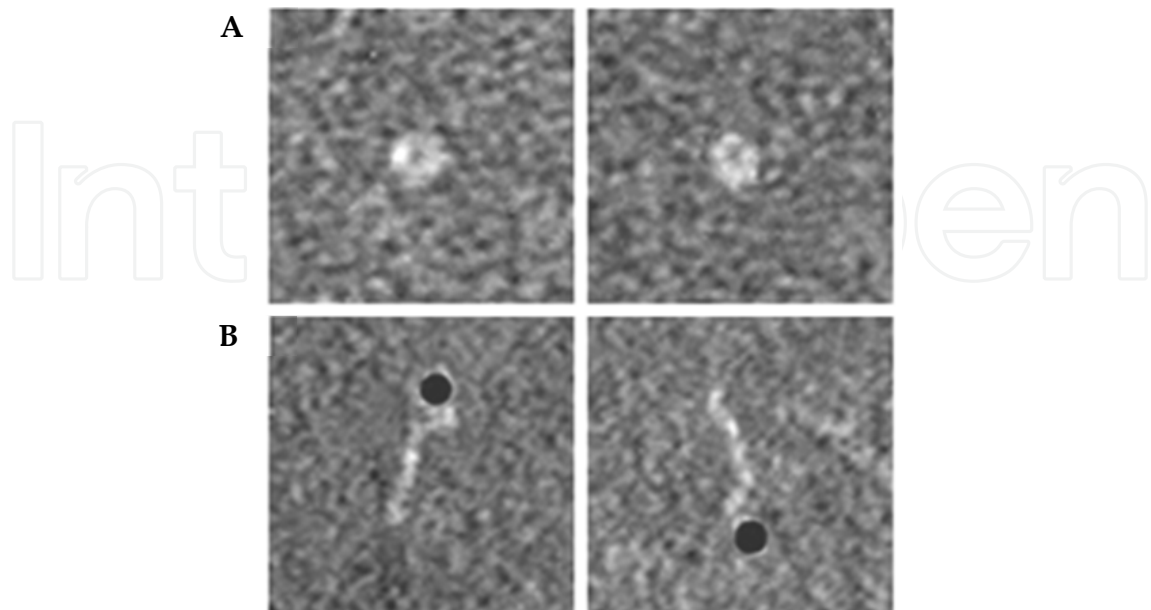
(A) Magnifications of purified plasma β₂GPI show a circular conformation. (B) Purified plasma β₂GPI in the presence of gold-labeled (black dots) LPS shows on magnification an open fishhook-like shape of β₂GPI. This figure was modified from work originally published in *Blood.* C. Agar, P.G. de Groot, M. Mörgelin, S.D.D.C. Monk, G. van Os, J.H.M. Levels, B. de Laat, R.T. Urbanus, H. Herwald, T. van der Poll, J.C.M. Meijers. β₂-Glycoprotein I: a novel component of innate immunity. *Blood* 2011;117(25):6939-6947. © the American Society of Hematology

Fig. 3. Electron microscopy analysis of β₂GPI and LPS.

and sepsis patients in the intensive care unit. β₂GPI levels returned to normal after recovery, again suggesting an *in vivo* interaction between β₂GPI and LPS. The reduction in β₂GPI levels after LPS challenge coincided with an uptake of β₂GPI by monocytes. When β₂GPI binds to LPS, it changes conformation after which the LPS-β₂GPI complex is taken up by monocytes. Interestingly, the binding of this complex could be dose-dependently inhibited by receptor associated protein, indicating that binding of β₂GPI is mediated via a receptor of the LRP-family (Lutters et al., 2003; Pennings et al., 2006; Urbanus et al., 2008).

The ability of native β₂GPI to inactivate LPS *in vivo* might offer opportunities to use β₂GPI for the treatment of sepsis. β₂GPI binds to LPS via domain V of β₂GPI. It seems logical to use domain V of β₂GPI, and not the whole molecule for sepsis treatment. The use of the whole protein could induce the formation of auto-antibodies against the cryptic epitope located in domain I, which could lead to the development of APS (McNeil et al., 1990). The use of only domain V could potentially avoid the development of the pathological auto-antibodies against β₂GPI.

2.2.1 Evolutionary conservation of the LPS binding site in β₂GPI

A survey of the genome sequences of 40 vertebrates and of the fruit fly and roundworm, revealed a 14% amino acid homology with β₂GPI from the fruit fly *Drosophila melanogaster* and a 17% homology with the roundworm *Caenorhabditis elegans*, the most primitive organisms in which β₂GPI could be identified (Agar et al., 2011b). It was found that the majority of mammals showed 75% or higher homology for the complete human β₂GPI amino acid sequence. Remarkably, all mammals except the platypus, showed 100% homology for all 22 cysteine residues present in β₂GPI, which serve an important structural role in protein folding and stability.

Surface plasmon resonance experiments revealed that the peptide AFWKTDA comprising a hydrophobic loop within a large positively charged patch in CCP-V of β₂GPI, was able to compete for binding of β₂GPI to the LPS. This amino acid sequence within domain V was completely conserved in all mammals (Agar et al., 2011b). The same amino acid sequences also attenuated the inhibition by β₂GPI in a cellular model of LPS-induced tissue factor expression. This indicated that the AFWKTDA amino acid sequence found in the genome of all mammals is the LPS binding region within CCP-V of β₂GPI. From this it can be concluded that the LPS scavenging function is not only present in humans but evolutionary conserved throughout all mammals. This certainly emphasizes an important role for β₂GPI in biology, explains its high concentration in blood, its conformational change and suggests a general role in scavenging of unwanted toxic substances and cells.

2.3 β₂GPI as an overall scavenger

Analysis of the structure and function of β₂-GPI has induced a turn into our understanding of the antiphospholipid syndrome. For the last two decades the protein β₂GPI has been linked mainly to the regulation of coagulation, but recent developments (Agar et al., 2011a,b; Gropp et al., 2011) has broadened the focus on β₂GPI from coagulation to innate immunity. For many years the characterization of the antibodies was the line of approach to understand the pathophysiology of the syndrome, unfortunately with little success.

During the last years, more and more evidence has become available that β₂GPI is a more general scavenger in our circulation. Maiti et al (2008) showed a β₂GPI-dependent phosphatidylserine (PS) expressing apoptotic cell uptake by macrophages. Binding of β₂GPI to these cells caused recognition and uptake of the β₂GPI-apoptotic cell complex by the LRP receptor on macrophages. The receptor for binding to apoptotic cells was determined to be the Ro 60 receptor (Reed et al., 2008, 2009). Furthermore, another study suggested that the binding of β₂GPI to PS-expressing procoagulant platelet microparticles might promote their clearance by phagocytosis (Abdel-Monem et al., 2010).

Blood contains microparticles (MPs) derived from a variety of cell types, including platelets, monocytes, and endothelial cells. MPs are formed from membrane blebs that are released from the cell surface by proteolytic cleavage of the cytoskeleton (Owens & Mackman, 2011). MPs may be procoagulant because they provide a membrane surface for the assembly of components of the coagulation protease cascade. Importantly,

procoagulant activity is increased by the presence of anionic phospholipids, particularly phosphatidylserine (PS), and the procoagulant protein tissue factor (TF), which is the major cellular activator of the clotting cascade (Owens & Mackman, 2011). Since microparticles are considered to be important in coagulation, the efficient recognition and removal of these particles is critical for the maintenance of homeostasis and resolution of inflammation.

It has been shown that autoantibodies to β_2GPI inhibit this uptake of microparticles and bound TF to induce a procoagulant state (Abdel-Monem et al., 2010). The role of TF was studied in a renal injury mouse model that shared many features with thrombotic microvascular disease (Seshan et al,. 2009). Both complement-dependent and complement-independent mechanisms were found to be responsible for endothelial activation and microvascular disease induced by antiphospholipid antibodies obtained from APS patients. The presence of antibodies against β_2GPI showed a disturbed uptake of microparticles leading to increased TF in the circulation, which on its turn caused renal injury. It was also shown that mice expressing low levels of TF were protected against this injury induced by the presence of the antiphospholipid antibodies (Seshan et al., 2009).

3. Conclusions and future perspective

In conclusion, over the last few years a wealth of interesting data has become available that increased our knowledge on β_2GPI. The discovery of the native state of β_2GPI as a circular protein explained the important paradox that antibodies and protein could circulate separately in blood. Also, other previously ascribed functions were probably functions of the protein induced by the harsh method of purification after which only the open, activated, conformation of the protein was obtained. Furthermore, the potential of antibodies, anionic phospholipids, LPS and probably even more agents to switch the conformation of β_2GPI from a circular to an open activated conformation has given a clue to its role as scavenger, since the open conformation can bind to and subsequently be taken up by cells such as monocytes and macrophages. A role of β_2GPI as overall scavenger in coagulation and innate immunity, two complex processes that are highly intertwined, may provide clues to one of the remaining questions in APS research, namely how binding of antiphospholipid antibodies to β_2GPI result in thrombosis. An interesting option is that β_2GPI disturbs the uptake of microparticles resulting in a procoagulant state due to increased levels of TF and anionic phospholipids in the circulation. If the formation and presence of antibodies against β_2GPI also disturbs the scavenging function of β_2GPI still needs to be proven.

By identifying agents that can switch the conformation of β_2GPI, other areas of biology can be identified where β_2GPI might play a role. With the evolutionary conservation that was observed for the protein, its role in biology must be significant. It goes beyond saying that the appreciation of the different conformations and the ability to switch conformation has provided an important basis for research in this area.

4. Acknowledgments

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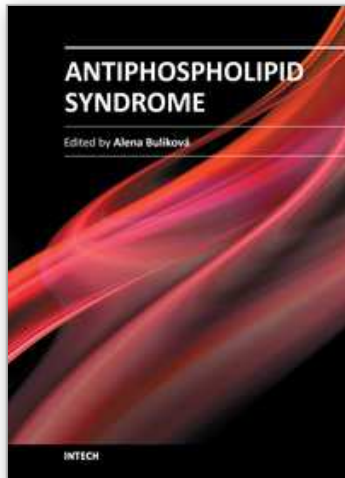
Antiphospholipid Syndrome

Edited by Dr. Alena Bulikova

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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