24 Lupus Anticoagulants: Mechanistic and Diagnostic Considerations

Jef M. M. C. Arnout and Jos Vermylen

Introduction

Antiphospholipid syndrome (APS) is defined as the association of antiphospholipid antibodies (aPL) with arterial or venous thrombosis, recurrent foetal loss, thrombocytopenia, or neurological disorders [1–3]. The gradual development of the notion APS started in the 1950ss with the recognition of two laboratory curiosities in a subset of patients with systemic lupus erythematosus (SLE). In these patients, rheumatologists frequently found a chronic biological false positive test for syphilis, whereas hematologists described a non-specific coagulation inhibitor manifested by prolongation of the whole blood clotting time and the prothrombin time, without reduction of any specific clotting factor then measurable [1–3]. The non-specific coagulation inhibitor which appeared not to be associated with a bleeding tendency was named the "lupus anticoagulant" by Feinstein and Rapaport [4] and was regarded as a laboratory curiosity until Bowie et al [5] drew the attention to the high prevalence of thrombotic complications in SLE patients with this "anticoagulant." The LA was later also found to be associated with obstetric complications and thrombocytopenia [6].

Only in the 1980s did it became clear that antibodies interacting with anionic phospholipids are responsible for the in vitro LA effect and the chronic biological false positive syphilis serology [7]. This led to the development of better-defined LA tests and the so-called anticardiolipin test in which antibodies binding to solid phase cardiolipin (aCL) are measured [8, 9]. With these improved assays, the majority of SLE patients with a LA also had elevated aCL levels and a statistically significant relation between these 2 types of aPL was observed. It is now well established that persistently present aCL and LA in patients with SLE are associated with thrombosis and pregnancy morbidity [10]. This association is now termed APS [11]. Some patients with similar clinical symptoms and laboratory findings but not suffering from SLE or a closely related autoimmune disease are diagnosed as having a "primary APS" [12]. The availability of a sensitive assay for aCL has been crucial for the further characterization of aPL. Affinity purification of aCL led to the discovery that, in contrast to what the term aPL suggests, aCL do not bind to cardiolipin per se but to β_2-glycoprotein I bound to anionic phospholipid surfaces [13–15].

Antigenic Targets of aPL

Soon after the discovery that β_2-glycoprotein I was involved in the binding of aCL to cardiolipin, it was reported that a subpopulation of aCL possesses LA activity and that certain LAs are directed against prothrombin. It was also reported that aCL bind to β_2-glycoprotein I even in the absence of PL [16]. The affinity of the interaction of these antibodies with fluid phase β_2-glycoprotein I is, however, low. It is now generally accepted that autoimmune aPL have in common that they are directed against proteins with affinity for PL or negatively charged surfaces. The main anti-

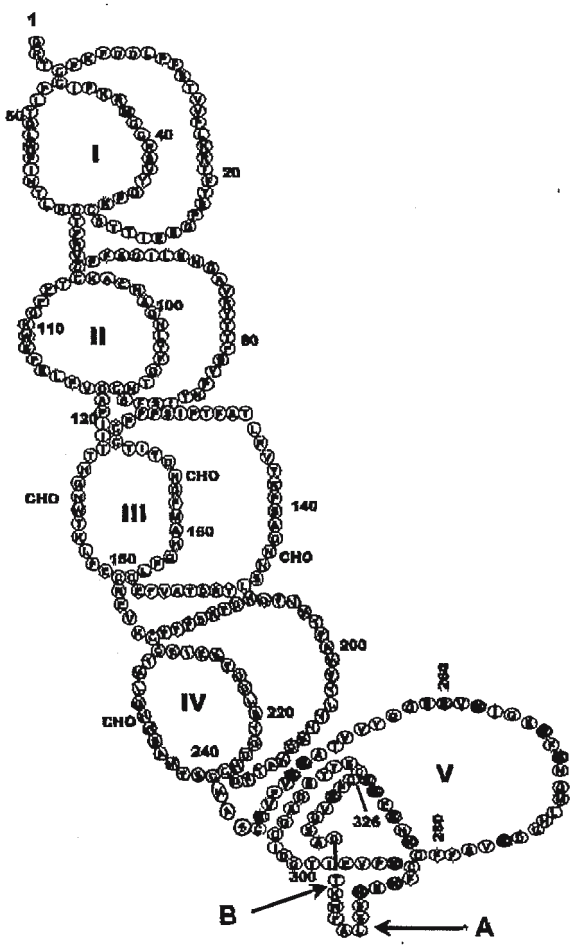

Figure 24.1. Structure of human β_2-glycoprotein I based on amino acid sequence, disulphide mapping, and crystallographic data. The five repeating sushi domains are indicated with roman numbers. CHO denotes N-linked glycosylation sites, 1 denotes amino terminal end, and 326 denotes carboxyterminal end. The hydrophobic flexible loop Ser311–Lys317 is indicated by *arrow A*; the positively charged amino acids interacting with the anionic phospholipid headgroups are marked in grey. *Arrow B* indicates the plasmin sensitive cleavage site at position Lys317–Thr318.