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Review

Autoantibodies to domain 1 of beta 2 glycoprotein 1: A promising candidate biomarker for risk management in antiphospholipid syndrome

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ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by frequent clotting in arteries and veins and/or miscarriages. Autoantibodies to phospholipids and to beta 2 glycoprotein 1 (β_2GP1) play an important role in the pathogenesis of APS. Antibodies to the domain 1 of β_2GP1 (β_2GP1-D1) have been suggested as a risk marker for thrombosis and to a lesser extent for pregnancy complications in patients suffering from APS. Despite significant interest in anti-β_2GP1-D1 antibodies and a considerable research history, the number of studies is still limited and acceptance of the clinical significance of this biomarker is still evolving. The present review summarizes the current knowledge of anti-β_2GP1-D1 antibodies and provides insights on recent discoveries. Moreover, we present a suggested guideline for future studies to better understand and verify the clinical utility of anti-β_2GP1-D1 antibodies.

Contents

1. Introduction

The creation of domain-specific recombinant beta 2 glycoprotein 1 (β_2GP1) molecules by Iverson et al. in 2002 [1] led to significant effort directed towards understanding the precise significance of autoantibodies to each of the 5 domains of β_2GP1. Domain 1 of beta 2 glycoprotein 1 (β_2GP1-D1) was identified as the primary target of autoantibodies for patients with antiphospholipid syndrome (APS) [2] and considerable research has since focused on the functional and clinical significance of anti-β_2GP1-D1 antibodies. Despite wide interest in the potential diagnostic value of anti-β_2GP1-D1 antibodies, the number of studies is still limited and acceptance of their potential clinical utility is still evolving [3]. The present review article summarizes the current knowledge of anti-β_2GP1-D1 antibodies (Table 1) and suggests a guideline for future studies.

2. Clinical picture of APS

APS, also known as the Hughes syndrome, is an autoimmune disorder which can cause frequent clotting in arteries and veins and/or miscarriages (see Fig. 1a) [4]. The clotting is caused by anti-

Abbreviations: ACR, American College of Rheumatology; A5R, annexin A5 resistance; aPL, anti-phospholipid; APS, anti-phospholipid syndrome; β_2GP1-D1, Beta 2 glycoprotein 1 domain 1; CIA, chemiluminescence assay; CL, cardiolipin; LAC, lupus anticoagulant; LR, likelihood ratio; SARD, systemic autoimmune rheumatic diseases; SLE, systemic lupus erythematosus.

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Table 1
History and milestones of anti-beta 2 Domain 1 antibodies.

Year	Milestones	Reference
1984	Identification of complete amino acid sequence of β_2GP1	[11]
1990	Identification of β_2GP1 as target of autoantibodies in patients with APS	[2]
1999	Generation of human monoclonal antibodies as international standards	[43]
2002	Epitope characterization of β_2GP1 using deletion mutants	[1]
2005	First description of the dual ELISA*	[27]
2005	Inclusion of anti- β_2GP1 antibodies in the classification criteria for APS	[10]
2007	Identification of R39- R43 as the key constitue of the major discontinues β_2GP1 B-cell epitope	[26,28]
2009	International multi-center study using dual ELISA*	[31]
2010	Chemical synthesis of immunoreactive β_2GP1-D1	[33]
2011	Demonstration that anti-β_2GP1-D1 antibodies are associated with multiple APS seropositivity using inhibition studies	[34]

*dual ELISA is based on the measurement of anti-β_2GP1-D1 antibodies using hydrophobic and hydrophilic plates coated with recombinant β_2GP1.

phospholipid (commonly called aPL), anti-β_2GP1 or related autoantibodies which interfere with coagulation, leading to increased clot formation or thrombosis, or with placenta tissues affecting pregnancy [4]. In addition to thrombosis and pregnancy complications (early and late miscarriage, and pre-eclampsia), APS is associated with a variety of clinical symptoms making the syndrome a systemic disease [5]. The syndrome can occur as an isolated pathology (primary APS) or can be accompanied by other autoimmune disorders, appearing as secondary APS (sAPS) mainly in patients suffering from systemic lupus erythematosus (SLE) [4]. Furthermore, recent studies have described patients with clinical evidence of APS without fulfilling the serological criteria for the disease [6,7]. In a few cases, repeated thrombotic events may occur over a short time interval, leading to the progressive damage of several organs. This acute and life-threatening condition is called catastrophic APS [8].

3. Biomarkers in APS

Antibodies to cardiolipin (CL) [9] and to β_2GP1 are a serological hallmark for the diagnosis of APS and are included in the classification criteria of the disease [10]. β_2GP1, (also called apolipoprotein H) is a

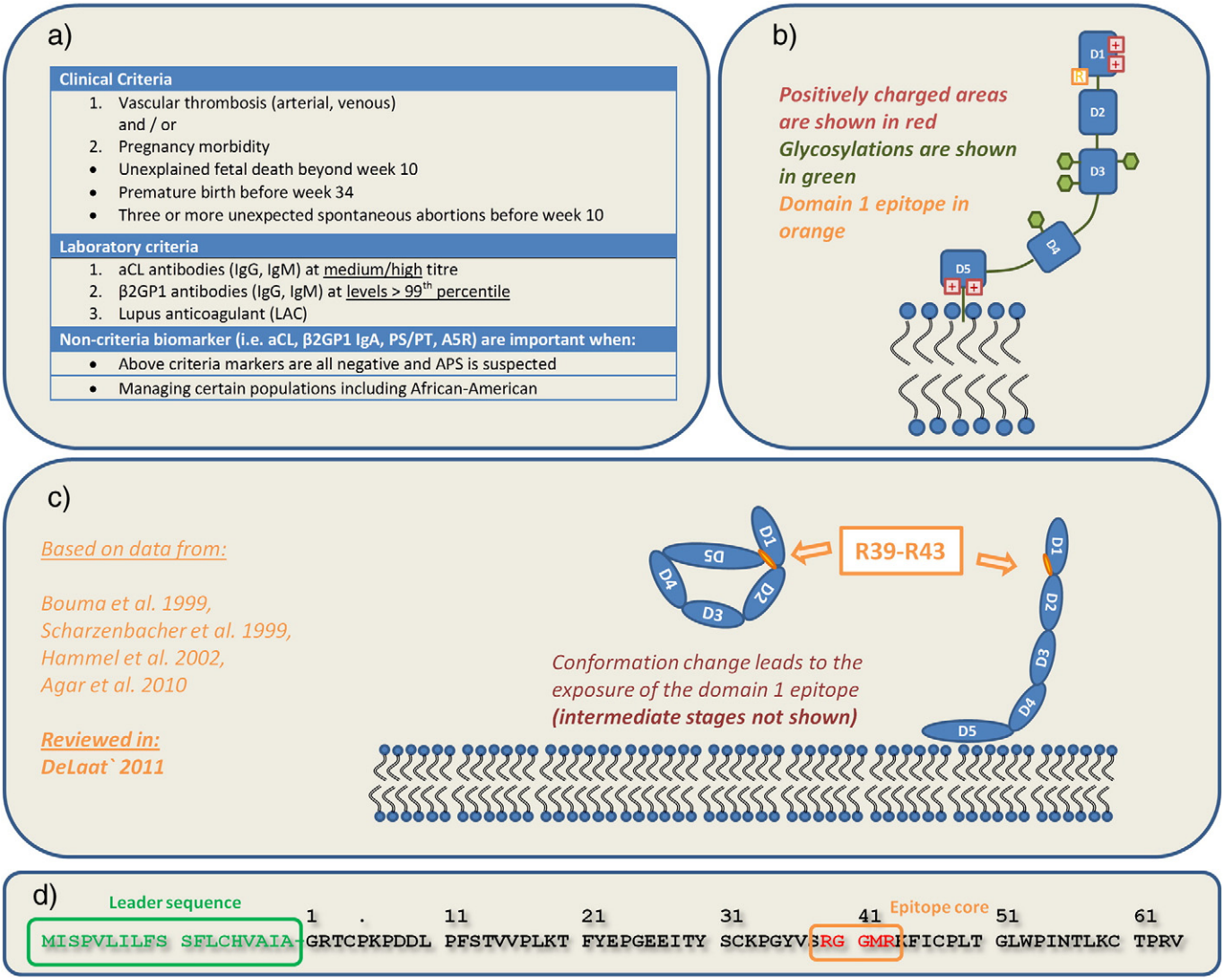

Fig. 1. Clinical, biochemical and immunological background on anti-β_2GP1-D1 antibodies. Disease classification criteria for APS consist of clinical and laboratory criteria and are shown in a). β_2GP1 consists of 5 homologous domains of approximately 60 amino acids each (D1–5; b). The positively charged segment of D5 binds to phospholipids and exposes D1–D4 to the surface. After attaching to the phospholipids, the structure of β_2GP1 opens and the major epitope becomes assessable to autoantibodies c). In d) the amino acid sequence of β_2GP1-D1 is shown. The leader sequence of the protein (green) is found at the N-terminal end of the molecule. Amino acid 39–43 (orange) represent the epitope core of the domain 1 epitope.