Special series on thrombocytopenia due to immunization against CD36

More and more we learn that platelets are multifaceted. They are the primary effectors of hemostasis and thrombosis, but also play important roles in inflammation, cancer metastasis, and innate and adaptive immune responses (1,2). Critical to these processes are the many membrane glycoprotein (GP) receptors expressed on the platelet surface, and also the numerous cytokines, growth factors, immunoglobulins and other immunomodulatory proteins released from platelet granules. In addition to their functional roles, some platelet GPs express human platelet alloantigens (HPAs) as single nucleotide variants (SNVs) present in their protein sequences (3). A classic example being the HPA-1a antigen expressed on GP IIIa/cluster of differentiation (CD)61. Antibodies against HPA-1a are the most frequent cause, primarily in White patients, of several immune platelet disorders, including fetal and neonatal alloimmune thrombocytopenia (FNAIT), platelet transfusion refractoriness (PTR), and post-transfusion purpura (PTP). However, in patients of African, Asian, or Middle Eastern descent, the same immune platelet disorders are more frequently caused by antibodies against platelet GPIV/CD36. Two other disorders, thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome have been associated with CD36 autoantibodies in some patients (4,5).

CD36 is a class B scavenger receptor protein expressed on several different cell types, including nucleated erythrocytes, monocytes, macrophages, and platelets in blood. CD36 functions include endocytic uptake of cellular fatty-acids, binding of oxidized LDL cholesterol in atherosclerosis and thrombospondin-1 interactions involved in inflammation (6). Interestingly, a significant percentage of apparently normal individuals of Asian, African, or Middle Eastern origin do not express CD36 on their platelets or monocytes, and are at risk of producing antibodies against this protein when exposed by pregnancy or transfusions (7). Diagnosis and management of immune platelet disorders caused by CD36 antibodies can be challenging. This special series consists of a group of researchers, physicians, and laboratory scientists sharing their knowledge of CD36 structure, function and genetics, as well as clinical and laboratory diagnostics used to detect and identify CD36 antibodies to aid in the diagnosis of several immune platelet disorders.

The series begins with an over-view by May and Sahoo (8) of findings made from the recently solved high resolution X-ray crystal structure of the extracellular domain of CD36 (9). The authors provide a detailed description of amino acids that contribute to the binding sites of CD36 ligands like long chain fatty acids, *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1), and oxidized LDL, and the epitope recognized by many CD36 monoclonal antibodies (amino acids 155–183)—all are elegantly depicted in two color figures showing the extracellular domain of the CD36 molecule.

Next, Xu *et al.* (10) describe the various CD36 gene variants and their associated clinical pathologies. Clinical disorders including thrombocytopenia, malaria, lipid taste perception, obesity, and metabolic syndromes including atherosclerosis and type 2 diabetes mellitus all have associations with CD36. Over 60 different gene variants associated with loss or lack of CD36 expression are described.

Xu and Santoso (11) present a narrative review of methodologies used for detection and identification of platelet antibodies, including CD36 antibodies in patient sera. They compare results obtained for detection of CD36 antibodies using different assays like the MAIPA, MACE, PABA, and PAKLx, and flow cytometry using intact platelets. They stress the importance of having available CD36-negative platelets or CD36 expressing cell-lines to confirm CD36 antibody specificity.

The series concludes with overviews of two major immune platelet disorders, FNAIT and PTR, caused by CD36 antibodies. Xu *et al.* (12) begin with a lengthy survey of the platelet alloantigens and isoantigens most frequently associated with FNAIT in White (HPA-1a, HPA-5), Asian (HPA-4a, CD36), and African (CD36) populations, and the corresponding platelet allo- and iso-antibodies. Sullivan and Perez Botero (13) complete the series by describing the challenges faced in transfusion medicine departments dealing with patients affected by PTR due to antibodies against CD36. Their narrative review nicely covers the clinical aspects of PTR with a focus on the clinical and laboratory findings in cases involving immunization against CD36. A thorough comparison of 13 case reports of PTR is presented, as well as treatment options, including the successful use of CD36 negative donor platelets for transfusion support, an oft over-looked option.

This special series provides an excellent opening introduction to the structure, function, and genetics of CD36 that

prepares readers for an overview of how antibodies formed against CD36 can be detected, as well as their clinical significance in triggering the immune platelet disorders FNAIT and PTR. Overall, readers will find this series educational and an interesting and lucid read.

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Footnote

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