Review of: "Association of Platelet Desialylation and Circulating Follicular Helper T Cells in Patients With Thrombocytopenia"

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Thrombocytopenia is a common hematologic finding with variable clinical expression. Identification of the causes of thrombocytopenia is crucial for the appropriate management of these patients. In many cases multiple mechanisms may contribute to the development of thrombocytopenia and may lead to severe life-threatening bleedings. A new and original concept relates to platelet desialylation, a process in which terminal sialic acids are cleaved from glycoconjugates on the platelet surface and leads to accelerate platelet clearance and thrombocytopenia. Indeed, platelet desialylation is relevant for platelet aging *in vivo* where removal of platelet sialic acid may expose β-galactose residues considered as senescence antigens, thus facilitating platelet uptake by the asialoglycoprotein receptors on hepatocytes, and stimulates thrombopoietin production. Over the past decades, platelet desialylation has been shown to be responsible for platelet clearance in many contexts, such as the destruction of chilled platelets, infection-related thrombocytopenia and immune thrombocytopenic purpura (ITP). In this context, the aim of this study was to clarify the roles of platelet desialylation and circulating Follicular Helper T cells (TFHs) in patients with immune thrombocytopenia ITP and non-ITP thrombocytopenia. Authors suggested that desialylation and TFHs may become potential biomarkers for evaluating the disease process (but here, ITP patients discovered at diagnostic) associated with thrombocytopenia.

The study enrolled 190 patients with ITP and 94 patients with non-ITP related thrombocytopenia including case of aplastic anemia (AA) and myelodysplastic syndromes (MDS) and 110 healthy volunteers as controls. It is the first study with a large cohort of ITP.
Platelet desialylation was observed in ITP and non-ITP thrombocytopenia patients (AA and MDS patients). Other thrombocytopenic patients could be used such as constitutive thrombocytopenia (MYH9, Bernard-Soulier, WASP…) to rule out or not the effect of the platelet count. However, these data demonstrated that platelet desialylation could represent a biomarker not only in ITP.

Platelet galactose exposure (or platelet desialylation) was measured by using ECL and RCA lectin. Importantly, statistical representation by the mean +- 2SD or with percentile would be a plus to extract ITP patients showing the higher ECL and/or RCA binding. From a diagnostic point of view, nowadays, reference range of desialylation in the healthy population is a medical need to identify thrombocytopenic diseases link to desialylation and then to allow the possibility of a new medical treatment. For instance, patients with ITP who present with significant platelet desialylation may be identified as

likely non-responders (as present here, but without antibody characterization) to conventional first-line treatments and splenectomy. The pathophysiology of ITP has recently evolved from a model mainly involving Fc receptor clearance of opsonized platelets by spleen macrophages, to a concept where a FcR-independent mechanism could participate to platelet elimination. This new mechanism seems to be mediated by anti-GPIb antibodies, leading to platelet desialylation and hepatic clearance but others found also that anti-GPIIbIIIa could do the same. Do the authors explain and correlate their ITP patients based on: GPIb/GPIIbIIIa or others antibodies with RCA/ECL/platelet count/CXCL13/TFHs? This question is important notably for future therapy. Some ITP patients were treated with a first line therapy in this study. Should authors indicate which therapies have been used? Some patients are already non-responder in the first line therapy, and it is tempting to speculate that they are likely to be multirefractory patients. The use of oseltamivir, an antiviral medication which prevents cleavage of sialic acid residues has demonstrated positive effects on platelet count in those patients but only patients with GPIb antibodies (Revilla et al, DOI: 10.1080/09537104.2018.1513476). The characterization of the antibodies and/or of THFs/CXCL13 expression represent a medical need for those patients, paving the way for a more widespread use of oseltamivir treatment in the future in combination with another drug that has to be determined.

Authors found a positive correlation between elevation of TFHs and desialylation, supporting those cells as critical mediators in synergy to promote platelet desialylation. Future mechanistic studies are needed to understand how TFHs act directly on platelet desialylation: TFHs-platelets contact, neuraminidase activation from sialidases expressed by platelets or from another source?

Authors found the coexistence of platelet apoptosis and desialylation in ITP. However, the link is still missing since the question between the role of platelet desialylation in apoptosis or the role of apoptosis in platelet desialylation is unclear. Future mechanistic studies are of course needed and were out of this current paper.