10th World Congress and Expo on
Immunology, Immunity, Inflammation & Immunotherapies
October 19-20, 2018 | New York, USA

Platelet desialylation in the liver may lead to immunosuppression against platelet-associated antigens

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Background: Platelets are small a nuclear cells in circulation that are generally known to play essential roles in hemostasis and thrombosis. However, over the years, the link between platelets and the immune system and their influence on the immune response are becoming increasingly recognized and studied. We previously demonstrated antibodies targeting GPIbα in autoimmune thrombocytopenia can lead to platelet desialylation and Fc-independent clearance in the liver. However, the subsequent immunological impact of desialylated platelet clearance in the liver versus the spleen has never been explored.

Methods and Results: We found transfusion of sialidase treated (desialylated) BALB/c mouse platelets resulted in decreased antibody generation in both β3-/- and GPIb-/- (iso-response) and C57BL/6J (allo-response) mice, compared with non-treated platelets. The dampened adaptive response was unique to desialylated platelets, as transfusion of desialylated sheep red blood cells did not significantly alter antibody titers. To assess whether desialylated platelets could modulate the immune response and be not only simply less immunogenic, we co-transfused β3-/- mice with desialylated and non-desialylated BALB/c platelets. We found a significant decrease in antibody response in the presence of desialylated platelet antigens, compared to WT platelet antigens alone. Platelet clearance studies revealed desialylated platelets, but not WT platelets are rapidly cleared from the circulation and are targeted almost exclusively to the liver and gut vasculature. Lastly, *in vitro* studies demonstrate splenic macrophages were more adept at up-taking antibody-coated platelets compared to desialylated platelets whereas the inverse was observed with Kupffer cells. Co-cultures of splenocytes and liver cells with desialylated platelets lead to increased Tregs which may play a role in the observed immunosuppression *in vivo*.

Conclusion: The site of platelet clearance significantly impacts the immune response. Increased desialylated platelet clearance in the liver, but not the spleen may have immunosuppressive effects against platelet-specific antigens. These findings may elucidate mechanisms behind the maintenance of peripheral tolerance against platelet antigens as part of normal platelet homeostasis. Additionally, these findings may be exploited as a therapeutic target to decrease the alloantigen response in transfusions or transplants.

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