Role of Platelet Glycosylation on Platelet Function and Immune Response in Immune Thrombocytopenia Patient

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Glycans (long sugars) are involved in the fine tuning of the immune system and its intricacies. They play a role in immune system activation (causing an immune response) or tolerance (preventing an immune response). Glycans modify proteins required for regulating immune cells (through glycosylation). For example, specific glycans regulate T-cell activation and immunoglobulin functions.

Glycans are recognized by receptors expressed on immune cells. Sialic acids are a different form of sugar usually at the ends of glycoproteins and glycolipids on the cell surface. These acids play important roles in cell communication, in infection and in the survival of pathogens (bacteria, viruses, or other microorganisms that cause illness). When pathogens attempt to escape immune recognition, they express sialic acids on their surface, effectively tricking the host immune system into thinking the pathogen is not an invader, and consequently avoiding immune system activation. Similarly, cancer cells increase their production of these glycans in order to make them invisible to the immune system, preventing their recognition as foreign. This is part of the reason why cancer can be difficult to treat.

Immune thrombocytopenia (ITP) is a bleeding disorder characterized by low platelet counts due to decreased platelet production and increased platelet destruction by autoimmune mechanisms. Our research group previously identified platelet sugar residues and observed that platelets from patients with ITP showed a consistent increase in structures that had a loss of sialic acids. We demonstrated that the loss of sialic acid could be explained by an increase in the activity of platelet's neuraminidase, the enzyme (specialized protein) that mediates the release of sialic acid. In other words, ITP patients have more proteins that cut off the acid which signals to the immune system that our platelets are “ours,” and not a danger to the immune system. Furthermore, this loss of sialic acid from sugars on platelet surfaces contributes to both platelet counts and the platelets’ ability to prevent bleeding in ITP patients.

To determine whether changes in the glycosylation pattern of platelets from patients with ITP trigger the immune system, in this study we looked at 3 groups of patients with ITP and one group of healthy controls.

Group 1	Untreated ITP patients in remission for at least six months after having chronic ITP
Group 2	ITP patients who responded to TPO agents (Promacta/Revolade and Nplate)
Group 3	ITP patients who do not respond to any ITP treatments
Healthy Controls	People without ITP or other illnesses

We found that platelets from patients with untreated and non-responding ITP (groups 1 and 3), had a reduced amount of sialic acid residues. In these patients, increased loss of sialic acid residues on platelets correlated with increased platelet destruction. Moreover, we observed an inverse relationship between the loss of sialic acid and regulatory T cell count, which are responsible for suppressing the immune response by inhibiting the inflammatory response of the immune system and play a critical role in preventing autoimmunity. This observation suggests a relationship between glycan composition on the platelet surface and the immune response. Of note, patients with ITP treated with TPO-RA had a regulatory T cell count similar to that of healthy controls.

The other major component of the “self-tolerance” portion of the immune system, regulatory B cells, are immunosuppressive cells that support immunological tolerance through the production of specific anti-

inflammatory cells and prohibit the production of pro-inflammatory cells. No association was seen between the loss of sialic acid and regulatory B cell count.
In summary, our data suggests that specialized sugar complexes, such as glycoside residues, on the surface of platelets play a role in determining the overall platelet count and function in patients with ITP. Moreover, our results encourage further studies to better characterize the participation of the platelet glycome (all the sugars and their role in platelets) in the pathogenesis of ITP, given that the presence of sialic acid is a good sensor for the discrimination of "self" and "non-self" signals that regulate innate and adaptive immune system responses. This provides a novel explanation for the immune system's detection for whether to destroy platelets in patients with ITP, providing a potential new target for immunotherapies.

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PDSA has designed our research program to specifically focus on patient priorities and funds studies that will make a significant impact on ITP diagnosis, therapies, and quality of life. If you'd like to donate to our research fund, please visit https://www.pdsa.org/pdsa-donation.html.