Mechanisms of Dynamic IgG Sialylation in Inflammation

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Intravenous immunoglobulin (IVIg) has been in use as an anti-autoimmune therapy in clinical settings for over many years. In 2006, it was discovered that the inhibitor component of IVIg was a relatively small population, approximately 10% of the total IgG, when carried terminal α2,6-linked sialic acids on the conserved Fc N-glycans at asparagine 297 of the heavy chain. In order to understand the role of endogenous IgG sialylation on immune regulation, we created a B cell-specific knockout of the ST6Gal1 sialyltransferase responsible for adding α2,6-linked sialic acids to any glycan outside of the central nervous system by crossing a mouse with a ST6Gal1 gene flanked by LoxP sites with a mouse carrying the CRE recombinase under the power of the B cell-specific CD19 promoter. We then used a combination of liquid chromatography-linked mass spectrometry (LC-MS) and *Sambucus nigra* lectin (SNA) affinity to quantify the sialylation upon IgG in the circulation of the mutant mouse. We found that the sialylation was unchanged on secreted IgG, but that the B cells lacked α2,6-linked sialic acids on the cell surface, indicating that although B cells require ST6Gal1 to sialylate surface molecules, ST6Gal1 in the B cell is dispensable for IgG sialylation. Further studies revealed that the B cell-independent sialylation of IgG occurs in the circulation of the animal, powered by the combination of liver-secreted ST6Gal1 and platelet-released CMP-sialic acid donor. These recently published findings support a model in which an extracellular glycosylation pathway regulates the glycosylation status of circulatory glycoproteins like IgG.