Core fucosylation and IgG function in NAIT

Richard H. Aster

In this issue of Blood, Kapur et al show that maternal human platelet-specific antigen 1a (HPA-1a)-specific antibodies causing neonatal alloimmune thrombocytopenia (NAIT) possess oligosaccharides that are deficient in “core fucose” residues and appear to be more effective than fucosylated antibodies in promoting phagocytosis of antibody-coated platelets.

Representative IgG-associated glycans with (left) and without (right) a core fucosyl residue (red triangle). Other saccharides are N-acetylglucosamine (blue), mannose (green), galactose (orange), and sialic acid (purple). "p" designates glycan-bound peptide in tryptic digest subjected to mass spectroscopic analysis. Professional illustration by Alice Y. Chen.
spectrometry analysis to define the composition of IgG-associated glycans. Total IgG from the same individuals was similarly studied. Fourteen distinct glycan species were identified. Slight but significant increases in sialylation and galactosylation were found in the HPA-1a antibodies relative to total IgG. However, the most striking finding was a marked decrease in core fucosylation, which in some cases was as low as 10% of the value for total IgG. This difference persisted even in HPA-1a antibodies obtained several years after delivery. Similar studies of antibodies specific for class I HLA antigens present in 13 nonpregnant individuals who were refractory to platelet transfusions showed that the HLA antibodies did not differ from total IgG in the extent of core fucosylation. However, core fucosylation of an HLA antibody from one of the women sensitized to HPA-1a was significantly lower (43%) than that of total IgG (94%). In studies involving seven of the NAIT sera, it was found that decreased core fucosylation correlated with more effective phagocytosis of antibody-coated platelets by neutrophils. To evaluate the clinical significance of these findings, perinatal status of infants born to the women studied was evaluated retrospectively. A statistically significant correlation was found between decreased core fucosylation of maternal antibody and increased severity of NAIT. However, the data were widely scattered, making it uncertain whether measuring core fucosylation in a particular maternal antibody would be helpful in prenatal management of an infant at risk for NAIT.

The authors leave open the question of whether the anomalous properties of glycans identified in the HPA-1a antibodies reflects the fact that the original antigenic challenge occurred during pregnancy. It seems counterintuitive that this might be the case, because skewing of glycan synthesis to favor production of HPA antibodies lacking a core fucose could be deleterious to a fetus. On the other hand, production of such antibodies against a pathogen acquired during pregnancy could be a protective adaptation. Whatever the explanation, the interesting and provocative findings described by Kapur et al should stimulate further studies to characterize the effects of pregnancy on the properties of IgG glycans and the importance of IgG glycan variation in antibody-mediated human disease.

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REFERENCES

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Comment on Steinberg et al, page 481

“Packaging” of fetal hemoglobin in sickle cell anemia

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In this issue of Blood, Steinberg et al describe the clinical importance of the distribution or “packaging” of fetal hemoglobin (HbF) within erythrocytes of persons with sickle cell anemia.

Ever since Janet Watson’s astute observation in 1948, the “protective” effect of HbF in persons with sickle cell anemia has been appreciated, and during the last several decades, increasing HbF levels by prescribing hydroxyurea has had salutary clinical effects. HbF has been measured by its overall concentration in the blood or by the percentage of erythrocytes containing fetal hemoglobin (F cells). Now, Steinberg et al elegantly characterize a previously unappreciated third means of expressing the
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