Reply to Mackenzie: A comparison of Neu5Gc and α-gal xenoantigens

We appreciate the thoughtful comments of K. J. Mackenzie (1) regarding our findings, concerning how a red meat-derived glycan can promote inflammation and cancer progression (2). At first glance, there do indeed appear to be very close similarities between the nonhuman sialic acid *N*-glycolylneuraminic acid (Neu5Gc) antigen we are describing and the well-known nonhuman "α-Gal" antigen (Galα1-3Galβ1-3/4GlcNAcβ1-R), which is also present in red meat, and can account for allergic reactions to such foods (3). However, there are also significant differences (see table 1 in ref. 4) that make the metabolic details and outcomes of the respective immune responses dissimilar. Although both glycans are foreign antigens that can be processed in the gut and against which humans have circulating antibodies, the released α-gal would become free galactose, which then cannot be reconverted back into α-gal within human cells (because of the human genetic lack of the appropriate α-galactosyltransferase). Therefore, the antibody response against α-gal should remain targeted only against foreign meat glycoconjugates themselves, resulting in a classic allergic reaction. In contrast, the Neu5Gc remains unchanged, can be taken up by human cells, metabolically incorporated by the endogenous biochemical machinery, and presented on human cell surfaces as if biosynthesized in the very same cell (5). Thus, endogenous glycoconjugate-bound Neu5Gc becomes a true xeno-autoantigen, and the xeno-autoantibody response is directed against human cells that have incorporated this molecule (5). Finally, whereas intratumoral injections of α-gal–containing glycolipids have been tried for conversion of human tumors into autologous vaccines (6), we are not aware of any evidence for direct incorporation of diet-derived intact α-gal glycoconjugates into human tumors in vivo. Given these considerations, α-gal antibodies are more likely to be involved in allergic reactions or associated with rejection of xenografts, and probably not related to the chronic inflammation associated with malignancies. However, further studies are needed to be certain, and also to ask if there are other examples of in vivo conversion of dietary xeno-antigens into xeno-autoantigens, besides Neu5Gc.

Oliver M. T. Pearce[a], Annie N. Samraj[a], Heinz Läubli[a], Nissi M. Varki[a,b], and Ajit Varki[a,c,1]

Departments of [c]Medicine, [b]Pathology, and [a]Cellular and Molecular Medicine, Glycobiology Research and Training Center, University of California, San Diego, La Jolla, CA 92093

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Conflict of interest statement: A.V. and N.M.V. are cofounders of and advisors to SiaMab Therapeutics, Inc., which has licensed University of California, San Diego technologies related to anti-Neu5Gc antibodies in cancer.

[1]To whom correspondence should be addressed. Email: a1varki@ucsd.edu.