Implications of xenoglycan sensitivity for increased cancer risk

The excellent study by Samraj et al. (1) shows that dietary intake of the nonhuman sialic acid *N*-glycolylneuraminic acid (Neu5Gc) promotes the production of anti-Neu5Gc antibodies. The resulting “xenosialitis” and associated chronic inflammation was shown to contribute to carcinogenesis.

This article (1) reminded me of another cancer-associated nonhuman glycan stimulating an inflammatory response in the digestive tract of patients. Commins et al. (2) had reported high circulating levels of anti-galactose- α -1,3-galactose (α -gal) antibodies in patients that had been exposed to *Amblyomma americanum* (Lone Star tick) in the states of Tennessee, North Carolina, Arkansas, Virginia, and the southern half of Missouri, which induced allergic reactions in these patients to red meat (beef, pork, and lamb) after exposure. The authors described levels of circulating anti- α -gal IgE, which increased with number of exposures (tick bites).

This allergic reaction was also described in patients receiving chemotherapy using Cetuximab (3). Cetuximab is a chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor,

approved for use in metastatic colorectal cancer and squamous-cell carcinoma of the head and neck. Being produced in mice, Cetuximab was glycosylated with α -gal and was therefore not tolerated by the patients already sensitized to α -gal from their previous tick exposure. According to the manufacturer, severe hypersensitivity reactions to Cetuximab occur in 3% of patients. However, higher rates and clusters of cases have been reported in the same states where *A. americanum* exposure is common, with reports of 22% of patients who were treated with Cetuximab in Tennessee and North Carolina having severe hypersensitivity reactions (3).

With the evidence that Samraj et al. (1) have put forward for chronic inflammation from anti-Neu5Gc antibodies leading to an increased risk of gastrointestinal cancers in mice, it would seem reasonable to assume that high levels of anti- α -gal antibodies may have a similar effect. It may not be entirely unconnected that these patients presensitized to Cetuximab are in the clinic receiving chemotherapy.

It would therefore seem prudent to use the evidence put forward by Samraj et al. (1) as

the basis for further study of the effects of *A. americanum* bites and cancer risk. In the interim period, the states of Tennessee, North Carolina, Arkansas, Virginia, and Missouri should be adopting a more rigorous screening program for digestive tract cancers in patients known to have high circulating levels of anti- α -gal antibodies caused by tick bites.

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1 Samraj AN, et al. (2015) A red meat-derived glycan promotes inflammation and cancer progression. *Proc Natl Acad Sci USA* 112(2):542–547.

2 Commins SP, et al. (2011) The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose- α -1,3-galactose. *J Allergy Clin Immunol* 127(5): 1286–1293, e6.

3 Chung CH, et al. (2008) Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med* 358(11): 1109–1117.

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