A cancer marker and treatment in one? Researchers finds promise in non-human sialic acid antibodies

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Researchers at the University of California, San Diego School of Medicine say antibodies to a non-human sugar molecule commonly found in people may be useful as a future biomarker for predicting cancer risk, for diagnosing cancer cases early and, in sufficient concentration, used as a treatment for suppressing tumor growth.

The work was led by Richard Schwab, MD, assistant clinical professor of medicine, and Ajit Varki, MD, professor of medicine and cellular and molecular medicine, with other faculty at the UCSD Moores Cancer Center and the UCSD Glycobiology Research and Training Center. Collaborators include researchers from the groups of Xi Chen at UC Davis, Inder Verma at the Salk Institute and scientists from Sialix, Inc., a biotechnology company based in Vista, CA.

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Every animal cell is cloaked in complex molecules called sialic acids that serve as vital contact points for interaction with other cells and the surrounding environment. Humans produce a particular kind of sialic acid called N-acetylneuraminic acid (Neu5Ac), but can also carry another non-human type called N-glycolylneuraminic acid or Neu5Gc, which is obtained through the diet, notably by the consumption of red meat. The molecular structures of these sialic acids differ by just a single

oxygen atom, but this difference is enough to prompt the human immune system to produce a complex anti-Neu5Gc response.

In previous research, Varki and colleagues described how low-dose anti-Neu5Gc antibodies can lead to chronic inflammation, an immunological response associated with cancer development and growth. In the new work, using a novel sialoglycan-microarray, the team discovered that patients with carcinomas have elevated levels of antibodies to one specific Neu5Gc-containing sugar chain. This unusual antigen arises from dietary Neu5Gc incorporation into the cancer marker Sialyl-Tn. It is the first example of a biomarker in the form of human "xeno-autoantibodies" to a dietary molecule.

Following up on this discovery, the scientists also found that purified human anti-Neu5Gc antibodies have immunotherapeutic potential: they specifically kill Neu5Gc-expressing mouse or human tumors when applied at higher concentrations. These findings point to a dual response of anti-Neu5Gc antibodies that can either stimulate tumor growth at a low dose (serving as a biomarker of disease) or suppress tumor growth at a high dose.

"Precisely how therapeutic antibodies work in patients remains unclear, even in therapies already approved by the Food and Drug Administration," said Schwab. "It is likely a combination of signaling immune cells to kill cancer cells and antibodies directly killing cells by recruiting other proteins in the body. Understanding how lower levels of antibodies stimulate cancer growth while strong responses can kill cancer cells will be critical to moving this approach safely into cancer treatment."

Schwab noted that many questions and much research remains to be done. Long-term studies are required to learn whether levels of anti-Neu5Gc antibodies are a reliable indicator of future cancer risk, if this

risk can be reduced, and if they can be used for early detection of cancers. Developing these antibodies as cancer treatments will require further study of how exactly the antibodies act against Neu5Gc-expressing tumors.

Nonetheless, Schwab expressed optimism about the significance and future of the work.

"This is the first evidence that anti-Neu5Gc antibodies may be useful for the early detection of cancer, identifying cancer risk, or for treatment," he said. "The biggest problem with advancing this work is that sugars are inherently difficult to study, but more people are beginning to pay attention – including the National Cancer Institute, which organized a specific multi-institute glycomics program that funded our project. A blood test that could detect cancer early or identify a modifiable risk for cancer would be a tremendous breakthrough in cancer care."

Provided by University of California - San Diego