Non-human sugar in biotech drugs causes inflammation

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Researchers at the University of California, San Diego School of Medicine have discovered that a kind of sugar molecule common to chimpanzees, gorillas and other mammals but not found in humans provokes a strong immune response in some people, likely worsening conditions in which chronic inflammation is a major issue.

This non-human sialic acid sugar is an ingredient in some biotechnology drugs, and may be limiting or undermining their therapeutic effectiveness in some patients, the scientists report in a letter published in the advance online July 25 edition of the journal Nature Biotechnology. However, they also propose a simple modification to the drug-making process that could solve the problem.

The presence of the non-human sialic acid sugar contaminant, called N-glycolyneuraminic acid or Neu5Gc, has long been known but ignored because it was believed healthy human immune systems did not react to it, said Ajit Varki, MD, professor of medicine and cellular and molecular medicine at UC San Diego School of Medicine. "Now we know that to be untrue." "We're all exposed to this non-human sugar," Varki added. "It's part of our diet, and especially abundant in red meat. We all develop antibodies to Neu5Gc, but this immune response varies greatly in people. Meanwhile, Neu5Gc from animal foods can get incorporated into the human body. For most people, this may not be a problem. But for some, the immune response to incorporated Neu5Gc may exacerbate a chronic inflammation process. This isn't the cause of any disease or condition, but we believe it might be akin to adding fuel

to an existing fire."

Every animal cell is cloaked in sugar molecules, which serve as vital contact points for interaction with other cells and their surrounding environment. At the same time, the attached sugars are targets for infectious diseases like influenza, malaria and cholera.

"Sialic acids are required for survival, but they're also used to attack you," said Varki, who is founder and co-director of the Glycobiology Research and Training Center at UC San Diego. "They are crucial for things like brain plasticity and kidney function, but lots of pathogens attach to them, and some even coat themselves with these sugars to avoid detection. In evolutionary terms, if you have sialic acid, you're going to be attacked. But you don't have it, you're going to die."

Perhaps because of this evolutionary pressure, different species can have different kinds of sialic acids. In mammals, there are two major types: Neu5Gc and Neu5Ac, which differ by one oxygen atom. Humans have only the "Ac" version; other mammals also have the "Gc" version. This human-specific change likely happened two or three million years ago, said Varki, who also co-directs the Center for Academic Research Training in Anthropogeny at UCSD. "No one knows why, but this may have been selected by an infectious disease, like malaria"

Although the Ac and Gc versions are very similar in structure, the single oxygen atom difference is recognized by the human immune system, which develops antibodies to the non-human sugar.

And therein lies the problem, said Varki. Antibodies are naturally circulating proteins that identify and neutralize invaders, such as viruses or bacteria. Part of that process involves inflammation, the host's attempt to kill and remove invasive cells or tissues perceived to be harmful. If there is a strong antibody response to diet-incorporated Neu5Gc, the

resulting inflammation could cause harm to the person. This may partially explain associations between certain foods and increased risk of diseases associated with inflammation, such as cancer and heart attacks - diseases that are rare in other primates.

The problem may also be exacerbated by the presence of Neu5Gc in drugs developed through recombinant biotechnology, some of which are actually used to treat inflammatory disorders. Neu5Gc contamination is unavoidable with current methods, said Varki, because many biotherapeutics such as antibodies, clotting factors or hormones are produced using cells, tissues or serum from mammalian sources, which naturally contain the non-human sialic acid.

Varki and colleagues studied several biotherapeutic agents currently in clinical use, and found the non-human sialic acid in almost all of them, although in varying amounts.

They also report that anti-Neu5Gc antibodies from normal humans interacted with a Neu5Gc-containing drug used to treat some forms of cancer, producing immune complexes in vitro. Mice with a human-like defect in Neu5Gc synthesis also generated anti-Neu5Gc antibodies when injected with the drug, and cleared it from the circulation faster.

These problems were not seen with another otherwise similar drug, which happened to be practically free of Neu5Gc.

"It's reasonable to suggest that for some patients who have problems with some drugs, this may be part of the reason why," although a lot more needs to be done to work out the details," Varki said.

Meanwhile, the UCSD scientists have developed a novel yet simple solution: Add the human sialic acid to the drug-making process. The Ac version, said Varki, competes with the Gc version, reducing the chances

of the Gc version making it into the final product.

"In our initial tests, it removes low-level Gc contamination in drugs," said Varki. "It's simple and should only require minor FDA approval for the process adjustment. We think that while we've identified a problem, we've also come up with an answer, at least for some drugs."

Provided by University of California - San Diego