UNH Glycomics Center Helps Identify Sugar Linkage That Could Lead To Better Treatment For Autoimmune Diseases

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DURHAM, N.H. - Researchers at the University of New Hampshire Glycomics Center have helped identify a specific carbohydrate structure that confers anti-inflammatory activity to a glycoprotein antibody that could lead to improved treatment of autoimmune diseases like lupus or rheumatoid arthritis. The study, reported in a recent edition of the journal Science, was led by immunologist Jeffrey Ravetch of Rockefeller University.

The work revolves around immunoglobulin G (IgG), the most abundant antibody in blood plasma. Intravenous immunoglobulin (IVIG) has within it a trace amount of a very active material that is effective in relieving the inflammatory affects of lupus, rheumatoid arthritis, asthma, and other autoimmune disorders. But because of the trace amounts of active material, effective doses of IVIG need to be very high, frequently leading to unwanted side effects.

This study involved rebuilding the human IVIG into a fully active molecule with a slight modification to a carbohydrate residue. These carbohydrate structures are linked to the immunoglobulin and referred to as glycans, and on the tip of this glycan is a specifically linked sialic acid. All the sialic acid on IVIG was converted to the active linkage that confers anti-inflammatory properties.

Understanding and analyzing the exact structure of sialic acid was the contribution of the UNH Glycomics Center, headed by director and research professor Vernon Reinhold. The center has developed tools and protocols using multidimensional mass spectrometry to determine the structure and functional relationships of these carbohydrates. Reinhold notes that while most biopolymers are linear and thus relatively easy to sequence, bush-shaped carbohydrates have proved challenging.

"With sequential mass spectrometry, we systematically untangle this bush," says Reinhold. "We take it down to the trunk then try to put it back together to determine its structure."

Reinhold and Glycomics Center research scientist David Ashline helped Ravetch pinpoint exactly how sialic acid was linked, which let the researchers engineer a synthetic human antibody that mimicked the linkages in IgG, providing an IVIG with enhanced activity for treatment of autoimmune diseases. In the Science paper, the researchers report that when given to arthritic mice, the engineered IgG was about 30 times more effective than IVIG.

"Now that we know what the exact structure is, we can build on it," says Reinhold. "Just as once you know what the motor in a car is, you can modify and make it more effective, and in principle, if you know the antigen, you can build the antibody."

Beyond this work with IgG, the Glycomics Center is demystifying the carbohydrate connections in cancer that contributes to metastatic growth and in avian flu where sialic residues on airway surface tissues serve as doorways for viral entry.

"Carbohydrates are the glue that pulls things together, the cell surface matrix in which cells communicate, and they provide the connections for signal transduction. It's only been within the last decade that we've realized that such structures are critical for all kinds of biological function," says Reinhold. "Now that we can define precise structures, we can begin to understand their function. This structure-functional relationship will have a huge impact on our health in respect to immune regulation."

To read the abstract of the article, from the April 18 issue of Science, go to http://www.sciencemag.org/cgi/content/abstract/sci;320/5874/373.

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