New Marker Found for Sanfilippo Disease

UC San Diego research helps illuminate rare but devastating metabolic disorder

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Sanfilippo disease is a rare disorder caused by the failure of enzymes to break down specific kinds of complex carbohydrates, resulting in their accumulation in cells and often severe physical and neurological problems - and sometimes early death.

In a paper published in the March 4 issue of the *Journal of Biological Chemistry*, researchers at the University of California, San Diego School of Medicine, led by Jeffrey D. Esko, PhD, professor in the Department of Cellular and Molecular Medicine, describe the build-up of a novel secondary metabolite in Sanfilippo disease, a discovery that could improve understanding of the disease's pathology and refine diagnostic techniques.

Sanfilippo is one of a group of genetically inherited metabolic disorders called mucopolysaccharidoses, all of which involve the inability of different lysosomal enzymes to catabolize or break down glycosaminoglycans - complex sugar carbohydrates that help cells build skin, bone, cartilage, tendons and connective tissues.

"It's a very ordered sequence of degradation," said Esko, co-director of the Glycobiology Research and Training Center at UC San Diego. "Interference with any of the steps in the enzymatic process results in an accumulation of metabolites, which causes lyosomal dysfunction. Cells become constipated, leading to internal changes and dysfunction."

For patients with severe mucopolysaccharidosis, the consequences can be catastrophic. As incompletely degraded glycosaminoglycans accumulate in cells and tissues, they cause permanent, progressive damage that affects appearance, physical abilities, organ function and, most profoundly, mental development. Children with the disease can experience severe neuropathology and significant early mortality. It's estimated that 1 in 25,000 children in the United States have one of several forms of the disease. Some mucopolysaccharidoses can be temporarily treated with enzyme replacement therapies, but the body's blood-brain barrier blocks neurological benefit. There is no current cure.

"The three approved drugs on the market mask the genetic defect by supplementing the missing enzymes," said Esko. "They can help resolve storage in many organs, but not the brain because the enzymes do not cross the barrier. And they are very, very expensive."

In the new research, Esko and colleague William C. Lamanna, PhD, studied enzymatic activity in Sanfilippo patient fibroblasts, a type of cell most commonly found in connective tissues. They noted that defective enzymatic activity resulted in the accumulation of not just a glycosaminoglycan called heparan sulfate, but also a secondary metabolite called dermatan sulfate. Sanfilippo cells had levels of dermatan sulfate two- to five-fold higher than normal.

The combined accumulation of heparan sulfate with dermatan sulfate, researchers said, may explain some of the distinct pathological features of Sanfilippo disease. The emergence of dermatan sulfate as an additional

biomarker for Sanfilippo disease could be useful in detection and diagnosis, though Esko said studies using patient tissue biopsies or blood or urine samples remain to be conducted.

"Right now, this discovery probably won't change the current therapy for Sanfilippo" said Lamanna, "but it does improve what we know about how the disease works and how to diagnose it."

The work follows related research published in 2010 in *Molecular Therapy* by Esko, Yitzhak Tor, PhD, UCSD Department of Chemistry and Biochemistry and Moores Cancer Center and colleagues that described a new type of targeting process for delivering modified enzymes to cells.

Co-authors of the *JBC* paper are Roger Lawrence and Stephane Sarrazin, both from the UCSD Department of Cellular and Molecular Medicine, Glycobiology Research and Training Center.

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