Study identifies potential new avenue for treating pompe disease

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Researchers at Duke Health have identified a potential new avenue for treating Pompe disease, a rare condition caused by the build-up of glycogen, a storage form of sugar, in cardiac and skeletal muscle, the liver and other tissues, due to deficiency of a particular enzyme.

There are more than 13 diseases like Pompe, which are known as glycogen storage diseases (GSDs), and they cause potentially fatal damage to the liver, heart and skeletal muscles. Pompe disease is treated mainly through enzyme replacement therapy, which helps prevent glycogen accumulation in lysosomes, membrane-enclosed structures found within animal cells. The basic research and clinical translation behind that lifesaving therapy was conducted at Duke.

The current study, co-led by Dr. Priya S. Kishnani, M.D., professor and chief in the Division of Medical Genetics at Duke University School of Medicine, and Baodong Sun, Ph.D., associate professor of pediatrics at Duke, identified a mechanism in mice by which glycogen is transported into lysosomes of liver cells, opening the possibility of new forms of treatment.

"A conceivable alternative way to treat Pompe disease would be to block the transport of glycogen to the lysosomes," Kishnani said. "Thus, understanding how glycogen enters the lysosome is a crucial step in finding new therapeutic targets for Pompe disease."

The study's findings, published recently in the *Journal of Biological Chemistry*, are based on a "double knockout" mouse model in which both acid alpha-glucosidase (GAA), the enzyme that's deficient in Pompe disease, and starch binding domain-containing protein1 (Stbd1), a cellular protein with previously unknown function, were suppressed in mice.

Compared to mice in which only GAA was suppressed, the "double knockout" mice saw a 73 percent reduction in glycogen content in the liver at an age of 3 months old and a 60 percent reduction at 13 months. Yet, glycogen accumulation in skeletal and cardiac muscles was unaffected.

"Glycogen is made outside of lysosomes in animal cells," Sun said. "The results demonstrate that Stbd1 is a major pathway for transporting glycogen to lysosomes in the liver."

"Our findings also suggest that the mechanism of glycogen transport to lysosomes in the liver is distinct from that in muscles," Sun added. "Thus, different treatment approaches can be developed for different target tissues in Pompe disease and other glycogen storage diseases."

More information: Tao Sun et al. Starch Binding Domain-containing Protein 1 Plays a Dominant Role in Glycogen Transport to Lysosomes in Liver, *Journal of Biological Chemistry* (2016). DOI: 10.1074/jbc.C116.741397

Provided by Duke University

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