New Test Spots Early Signs of Inherited Metabolic Disorders

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A team of scientists, led by researchers at the University of California, San Diego School of Medicine and Zacharon Pharmaceuticals, have developed a simple, reliable test for identifying biomarkers for mucopolysaccharidoses (MPS), a group of inherited metabolic disorders that are currently diagnosed in patients only after symptoms have become serious and the damage possibly irreversible.

The findings will be published online January 8 in the journal *Nature Chemical Biology*.

MPS is caused by the absence or malfunctioning of a lysosomal enzyme required to break down and recycle complex sugar molecules called glycosaminoglycans, which are used to build bone, tendons, skin and other tissues. If not degraded and removed, glycosaminoglycans can accumulate in cells and tissues, resulting in progressive, permanent damage affecting appearance, physical abilities, organ function and often mental development in young children. The effects range from mild to severe.

There are 11 known forms of MPS, each involving a different lysosomal enzyme. A number of treatments exist, including enzyme replacement therapy and hematopoietic stem cell transplantation, but efficacy depends upon diagnosing the disease and its specific form as early as possible. That has been problematic, said Jeffrey D. Esko, PhD, professor in the Department of Cellular and Molecular Medicine and co-director of the Glycobiology Research and Training Center at UC San Diego.

"The typical time from seeing first symptoms to diagnosis of MPS is about three years. Since the early signs of disease are common childhood issues like ear infections and learning disorders, the disease is usually not immediately recognized," Esko said.

"A child often has multiple visits with their pediatrician. Eventually they are referred to a metabolic disease specialist, where rare diseases are considered. It takes an expert to identify MPS and its most likely form in each patient. Every subclass of MPS has its own specific diagnostic test, so developing better diagnostics is an essential part of effective treatment. "

In their paper, the scientists describe an innovative method to detect tell-tale carbohydrate structures specific to glycosaminoglycans in the cells, blood and urine of MPS patients. The biomarker assay identifies all known forms of the disease.

Esko is collaborating with Zacharon Pharmaceuticals, a San Diego-based biotechnology company, to develop a commercial diagnostic assay for differentiating forms of MPS from urine and blood samples, a screening test for newborns and a tool for measuring the biochemical response of MPS patients to existing and novel therapies.

"Since the severity of the disease is highly variable among patients, this could provide a tool that a doctor can use to optimize dosing or treatment," said Brett Crawford, Vice President for Research at Zacharon. "Currently, all patients are treated with the same dose of drug."

The biomarker test may also be used to discover new forms of MPS and better characterize existing ones.

DISCLOSURE: Esko co-founded Zacharon Pharmaceuticals in 2004 with Brett E. Crawford and Charles Glass. He is a scientific advisor to the company.

Co-authors include Roger Lawrence and William C. Lamanna, UCSD Department of Cellular and Molecular Medicine, Glycobiology Research and Training Center; Jillian R. Brown, James R. Beitel and Brett E. Crawford, Zacharon Pharmaceuticals; Geert-Jan Boones and Kanar Al-Mafraji, University of Georgia, Athens.

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