MedicalXpress

Researchers find cause of metabolic disease -- and possible cure

July 15 2010

An international team of scientists, led by researchers at the University of California, San Diego School of Medicine, has discovered the gene mutation responsible for a condition in which eye and brain development is severely disrupted in affected infants.

They also suggest a potential remedy that would involve a simple, daily dietary supplement.

The condition is one of the congenital disorders of glycosylation or CDG, a group of syndromes in which inborn metabolic errors result in serious, sometimes fatal, malfunctions of different organ systems, especially the nervous system, muscles and intestines. Children and adults with CDG have varying degrees of disability, including cognitive impairment and speech difficulties, poor motor skills, vision problems and stroke-like episodes. CDG is rare, but for most of the disorders, there is no treatment.

Writing in the July 15 online edition of the journal *Cell,* Joseph G. Gleeson, MD, professor of neurosciences and pediatrics at UC San Diego, with Lihadh Al-Gazali, a professor of pediatrics and pathology at United Arab Emirates University, and colleagues discovered that the gene SRD5A3 is responsible for the synthesis of a lipid used by cells as a sugar carrier for protein glycosylation - a complicated, multi-part process in which proteins are modified by the addition of a sugar or sugar chain. Without the added sugars, proteins do not fold or fold incorrectly, resulting in dysfunction and disease.

The UCSD work revealed the molecular basis of an essential, but mysterious, enzymatic reaction in protein glycosylation. "We found the long-sought polyprenol reductase that has been suspected for decades" said Gleeson, a Howard Hughes Medical Institute Investigator who supervised the research. "Using a human genetic approach, we were able to not only find a clue to understand this class of disorder, but also to solve a basic science problem."

After translation, many proteins are modified with the addition of glycans (polysaccharides or oligosaccharides) that are necessary to help them perform their functions. This modification occurs in a specific cell compartment - the membrane of the endoplasmic reticulum - where the glycans are transported by a lipid before transferring onto proteins.

Dolichol is the lipid carrier for glycans used during protein glycosylation; its availability is critical to accomplishing the modification process, but the synthesis or production of dolichol was poorly understood, especially the last step when polyprenol, a natural long-chain alcohol, is reduced to create dolichol.

"Dolichol is used by the cell like a truck to transport glycans to their destination but also as a support to build them" said Vincent Cantagrel, a UC San Diego postdoctoral fellow and study co-author. "A defect in this transportation results in a less efficient process of glycosylation. Some proteins will miss some glycan chains and will not function correctly."

In CDG cases, the conversion from polyprenol to dolichol is blocked by a mutation in the SRD5A3 gene. "The mutation is inherited recessively," said Gleeson. "Both parents must pass along a mutated copy, which is why you don't see it so much in the US. However, in the Middle East, where marriage of cousins is common, these diseases are much more prevalent."

Identifying the blockage, Gleeson said, pointed to a possible treatment.

"The key was identifying the enzyme's role in producing dolichol. This is the basic step that is blocked in our patients, and the disease is the result. Our idea is that if you feed these patients dolichol, that might just treat the condition. It would be similar to giving insulin to diabetics. It's a simple solution, but one nobody had thought of."

Currently, artificially produced dolichol is very expensive, mostly because there hasn't been much demand for it, but the researchers note that the compound is naturally abundant in some plants, such as the gingko or maidenhair tree and spinach. "Ginkgo is already the source of a lot of compounds, so getting dolichol might just mean another step in the extraction process. After that, you could develop a pill that patients could take as a supplement to their diet."

Gleeson and colleagues are now testing their idea with animal models.

While CDG cases are rare, Gleeson and Cantagrel said their discovery about the polyprenol-dolichol block in the glycosylation process has broader ramifications.

Glycosylation is essential to the normal growth and function of all tissues and organs. "If we look at other steps along the glycosylation pathway, it's possible we can find other break points," Gleeson said. "We might be able to treat or cure other forms of CDG or even more common diseases that use this pathway, such as cirrhosis, in which there is deficiency of dolichol."

Provided by University of California - San Diego