Biochemists Provide New Key for Treating Fabry Disease, a Rare Childhood Disorder

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(PhysOrg.com) -- A research team led by biochemist Scott Garman at the University of Massachusetts Amherst has for the first time determined the mechanism of one of the cell's 'recycling' enzymes, human alpha-galactosidase or alpha-GAL, as it breaks down substances in the lysosome, the cell's recycling center. The work promises to aid treatment of a rare childhood metabolic disorder, Fabry disease. Patients may survive to adulthood but have compromised kidney function or heart disease, for example, due to lipid buildup in blood vessels, tissues and organs.

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In people born with a faulty copy of the GLA gene that codes for the human alpha-galactosidase (α-GAL) enzyme, an oily, waxy lipid known as GB3 builds up to toxic levels that leads to Fabry disease symptoms. The cause is remarkably direct—a defect in a single gene means the body fails to produce one specific protein, which causes metabolic disease. Thus, Garman says, "There is a lot of research interest in this one molecule and how it works." His research team, which includes

graduate students Abigail Guce, Nathaniel Clark and technician Eric Salgado, report in the current issue of the Journal of Biological Chemistry, available online now.

To learn the enzyme's basic function, the UMass Amherst team, with others in Russia and Sweden, used X-ray crystallography, a technique for creating three-dimensional images of the 6,500 atoms in the large protein. Seeing three dimensions is critical because these protein/enzymes can only carry out their metabolic "missions" by changing shape. They're like origami papers: Inactive and uninteresting while flat, but when folded they become biologically active. To follow the action, scientists must see the folded shapes.

Specifically, as Garman explains, "We used some crystallographic, molecular biological and chemical tricks to trap and examine the enzyme at different stages. Others have done crystallography on the alpha-galactosidase enzyme, but not in this way." They first isolated the enzyme-bound substrate. Next they stopped action to view the enzyme in its covalent intermediate form, and finally stopped action again as the enzyme was about to release its product.

These steps proved to be the key to isolating and understanding the enzyme's normal mechanism. "This is the first time anyone has seen how this enzyme binds the sugar molecule during the reaction when it is cutting one galactose from substrate," Garman says.

One active area of research in Fabry disease is using small molecule chaperones to stabilize the large alpha-GAL enzyme in these patients. The current work by Garman and colleagues opens the door to developing new, synthetic chaperones for treating this disease. The researchers found a new binding site on this molecule that had never been seen before. "So if you wanted to design a new drug to stabilize the protein, we've now shown exactly how to do that," he notes.

Overall, Garman summarizes, “Knowing the structure leads to a complete revolution in understanding how the enzyme is defective in different Fabry disease patients: Does the enzyme break due to its folding, its active site chemistry or the lack of enzyme access to the lysosome, for example? This is the key we’ve needed. No one ever saw the way this galactose sugar was bent and folded before. We now have a whole new and different set of shapes we didn’t have before, to test as treatments.”

Also because of these studies, Garman adds, “we now understand the exact mechanism of the human enzyme, and this knowledge also applies to the approximately 1900 other relatives of human alpha-GAL that we find in plants, fungi, yeast and chickens. They all work similarly because it’s a highly conserved protein in nature.”

Enzyme replacement therapy can be helpful in treatment, but is extremely expensive. In addition to providing basic knowledge about alpha-GAL function, this work by Garman and colleagues opens the door for a new treatment for Fabry disease.

More information: www.jbc.org/content/285/6/3625/suppl/DC1

Provided by University of Massachusetts Amherst