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Protein Trafficking Trouble Links Lowe Syndrome Symptoms in Brain and Kidney

Researchers have provided new insight into how mutations in a single gene can cause mental retardation and kidney dysfunction in boys afflicted with Lowe syndrome. Their studies reveal that the disruption of a protein network that regulates the routing and signaling of cell surface receptors can cause both brain and kidney problems in individuals with the rare genetic condition.

Howard Hughes Medical Institute investigator Pietro De Camilli and his colleagues at the Yale University School of Medicine published their findings online September 3, 2007, in the journal *Developmental Cell*.

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— **Pietro De Camilli**

Lowe syndrome, which affects only boys, was first described in 1952 by Charles Lowe and colleagues at the Massachusetts General Hospital in Boston. The condition causes cataracts, mental retardation, and a kidney problem leading to the abnormal loss of small proteins and some metabolites and ions in the urine. The syndrome is caused by mutations that disrupt the gene encoding an enzyme named after the condition's clinical name, oculocephorenal syndrome of Lowe.

The OCRL enzyme is a phosphatase that removes a phosphate group from inositol phospholipids, molecules in the cell membrane that play an important role in protein traffic and signaling at the cell surface. Researchers knew about the biochemical properties of OCRL, but they did not understand how the loss of its enzymatic function contributed to Lowe syndrome. Although the enzymatic function of OCRL has long been known, there was only a sketchy understanding of the cellular context in which this enzymatic activity operates, said De Camilli.

De Camilli said that the kidney defects associated with Lowe syndrome suggested that kidney cells might be having trouble routing the receptor

proteins on their surfaces that control the exchange of certain small molecules between the urine and the blood. Similarly, failure to properly transport receptor proteins in nerve cells could cause cognitive impairment such as that in patients with Lowe syndrome. But no one had yet uncovered a molecular link between OCRL and cell surface receptors.

Earlier studies suggested that OCRL might assist in the transport of molecules within the Golgi complex, a main hub of membrane traffic within the cell, as well as to the Golgi complex from endosomes, the first intracellular stations to which proteins internalized from the cell surface are directed. Using a tracer molecule to visualize OCRL in human and monkey cells, De Camilli and his colleagues saw that the protein also concentrates at structures on the cell's surface called clathrin coated pits. Receptors concentrate at these sites before they are taken up as part of vesicles that move into the cell. The finding that OCRL participates in this vesicular transport from the cell's surface to the interior of the cell supports the idea that the protein might help regulate cell surface levels and/or the signaling function of receptors, De Camilli said.

The researchers went on to show that OCRL attaches itself to an adaptor protein called APPL1, which is involved in sorting and signaling of cell surface receptors in the peripheral region of the cell. This finding provided a strong hint as to how mutations in OCRL can trigger the symptoms of Lowe syndrome, De Camilli said. APPL1 links OCRL to receptor proteins that are important for both brain and kidney function, he said. In the brain, APPL1 binds to a nerve growth factor receptor called TrkA, as well as to an adaptor protein for that receptor called GIPC. And in the kidney, GIPC binds to another receptor called megalin, which controls the resorption of small proteins and some metabolites in kidney tubules. Thus, said De Camilli, the findings reveal how both brain and kidney function can be compromised when OCRL stops working.

Through structural studies, De Camilli and his colleagues also showed how OCRL's many interactions can be coordinated and how mutations found in patients with Lowe syndrome could compromise OCRL's attachment to APPL1, leading to the disease pathology.

Our next steps will be to provide direct evidence for the functional relevance in the disease of the new properties of OCRL that we have identified, said De Camilli. We hope that these studies will help design therapeutic strategies for the treatment of Lowe syndrome patients. In addition, they will advance fundamental knowledge of the signaling roles of inositol phospholipids in health and disease.