Primary Cilia Formation Provides Insight into Genetic Diseases

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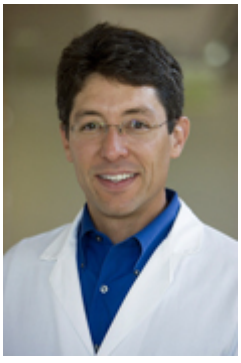
Identification of protein targets and genes may be key to possible drug therapies for ciliopathies

A team of scientists at the University of California, San Diego School of Medicine have identified a network of genes that initiate and manage cilia formation. Although scientists have known about cilia for decades, only recently have they discovered their role in disease. This new discovery, which may lead to new therapies for ciliopathies, will appear in the April 15 edition of *Nature*.

Primary cilia are small, hair-like appendages attached to the surface of human cells. They act like antennae, sensing and evaluating extracellular signals to coordinate the development and stability of a wide variety of organs. Ciliopathies are a newly emerging group of genetic diseases caused by defects in the function or structure of cellular primary cilia. These diseases present symptoms such as mental retardation, retinal blindness, obesity, polycystic kidney disease, liver fibrosis, ataxia and some forms of cancer.

The scientists, led by Joe Gleeson, MD,



Joe Gleeson, MD

professor of neurosciences and pediatrics at UC San Diego and a Howard Hughes Medical Institute Investigator, and Joon Kim, a UC San Diego postdoctoral fellow, utilized a high-throughput, cell-based screen to evaluate the impact of more than 8,000 genes and their relation

to cilia function and development.

"Utilizing high-throughput screening, we were able view a wider array of the genes implicated in ciliopathies and enact systematic approaches, which enabled us to gain deeper insight into the molecular mechanisms of cilia formation," said Gleeson.

Additional investigation revealed that the endocytic recycling pathway, which absorbs and processes plasma membrane, also plays a key role in primary cilia formation. The scientists also identified protein groups that are key modulators between cilia and the endocytic recycling pathway. These findings suggest that there are specific protein targets for the development of ciliopathy therapy, according to Gleeson.

When cytochalasin D, a small molecule which permeates cells and inhibits cytoskeleton polymerization, was applied to one of the identified proteins, it repaired cilium formation in cells carrying mutations.

"While the use of cytochalasin D is not a viable solution in patients because of its toxicity, we now know that pharmacological solutions for ciliopathy exist," said Kim. The research team intends to continue searching for "cleaner" small molecules, which can be utilized for ciliopathy treatment.

Additional contributors to the study include Ji Eun Lee of UC San Diego, School of Medicine, Department of Neurosciences; Keiichiro Ono, KiYoung Lee, and Trey Ideker of UC San Diego School of Medicine and Bioengineering; Susanne Heynen, Eigo Suyama, and Pedro Aza-Blanc of Sanford-Burnham Institute for Medical Research.

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