Mysterious cilium functions as cellular communication hub, study shows

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(PhysOrg.com) -- Nearly all mammalian cells have what's called a primary cilium -- a single, stump-like rod projecting from the smooth contours of the cell's outer membrane. Unlike its more flamboyant cousins, the motile cilia, which beat industriously in packs to clear our airways of mucous or to shuttle a fertilized egg to the uterus, the primary cilium just ... sits there.

Like a bump on a log.

In fact, it looks so useless that, until recently, many scientists considered it to be just a leftover artifact of eons of evolution.

Recently, however, research has shown that defects in the development or function of primary cilia are associated with many human disorders, including polycystic kidney disease, skeletal malformations, neural tube defects as well as obesity. Clearly there's more here than meets the eye. Scientists have since decided that the primary cilium works as a kind of antenna to help the cell respond to outside chemical signals and mechanical forces.

Now researchers at the Stanford University School of Medicine have pinpointed the molecular cause of a rare genetic disease in humans called Bardet-Biedl syndrome, or BBS. People with the disorder suffer from obesity, retinal degeneration, kidney cysts and polydactyly (having extra fingers or toes). And, as you might guess, it all hinges on the primary cilium. Specifically, the researchers have discovered that

genetic mutations associated with the disease affect a protein complex that ferries receptors and other proteins from the cell's membrane to the surface of the primary cilium.

"This provides a very logical explanation for the wide variety of symptoms seen in patients with Bardet-Biedl syndrome," said Maxence Nachury, PhD, assistant professor of molecular and cellular physiology. "The primary cilium used to be thought of as just the appendix of the cell. Now we're finding that it's actually the communication hub where many signaling pathways take place."

The research will be published in the June 25 issue of *Cell*, and will be featured on the journal's cover.

The obesity experienced by Bardet-Biedl syndrome patients is pronounced. They gain massive amounts of weight very early in their lives, and by the time they are 6 months old they weigh more than twice that of the heaviest of their peers. And in mouse models of the disease, these animals are 2.5 times the weight of their littermates.

"We've been able to go within three years from being completely puzzled about what was causing the clinical presentation of the disease to knowing with a very high degree of confidence what the affected molecules are doing inside the cell," said Nachury.

Nachury, who was recently named one of 15 Searle Scholars for 2010, launched his lab at Stanford in late 2007 in order to understand the function of the primary cilium. Earlier that year, as a postdoctoral scholar at Genentech and Stanford, he identified a group of proteins involved in BBS that work together in a group called the "BBSome" as important to the function of the primary cilium. He and his colleagues speculated that the BBSome was somehow involved in moving proteins around on the cell's surface, or membrane.

Cellular membranes are more than just an inanimate skin corralling the contents of the cell and protecting it from outside elements. Instead, they are a dynamic interface with the outside world. Receptor proteins bob and mill about in a sea of membrane molecules called phospholipids, alert for external signals that they then translate to the inner surface of the membrane. Workhorses inside the cell respond to the receptor's signals by activating other proteins or adjusting the expression of key genes in the nucleus.

The situation is much the same in the portion of the membrane that makes up the primary cilium. However, its structure gives it a unique advantage: Because both its membrane and its interior are cordoned off from the rest of the cell, proteins can accumulate in higher concentrations than elsewhere in the cell. These higher concentrations increase the efficiency of the signaling interactions.

Specifically, the surface area of the primary cilium is about 1,000 times less than that of the plasma membrane; protein concentrations inside the cilium are about 100 times greater that of the cytoplasm.

Hua Jin, PhD, a postdoctoral scholar in Nachury's lab, shows in this latest study that the BBSome works by latching on to proteins bobbing in the main plasma membrane and pulling them through the phospholipids to the surface of the primary cilium. It's much like how a tugboat escorts ocean liners into a busy harbor.

"Until now, we knew of essentially no molecules that served this purpose," said Nachury. Once parked on the primary cilium, the proteins can rub shoulders and hobnob with other signaling molecules on the surface and inside the cell. "Now the primary cilium is starting to look less like a mere antenna, and more like the communication hub of the cell."

Research by a variety of groups has pinpointed the primary cilium as the location for important cellular control pathways, such as the hedgehog and retinal-signaling pathways. Nachury and his colleagues are now interested in investigating its role in human obesity.

"It seems from the work of other investigators that the pathways used by the brain to sense fat stores may require the primary cilia," said Nachury. "We're very excited to move into this area and to understand what type of signaling might be regulating body weight."

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