Researchers demystifying complex cellular communications hubs found in sensory neurons

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It's safe to say that cilia, the hairlike appendages jutting out from the smooth surfaces of most mammalian cells, have long been misunderstood - underestimated, even.

Not to be confused with their whiplike cousins flagella, which propel sperm, one type of cilia has been known to serve as microscopic conveyor belts. (Picture cilia reaching up like concertgoers supporting a crowd-surfer.) But for decades another type of cilia, known as "primary" cilia, was believed to serve little to no purpose. Despite the fact that almost every cell found in vertebrates has at least one primary cilium, the organ was regarded as merely an evolutionary relic - the cellular equivalent to the human appendix.

Of late, however, it has become increasingly clear that primary cilia serve as powerful communication hubs. (After all, they do sort of look like antennae.) Disruptions in the activity of cilia are now understood to lead to a whole class of diseases dubbed ciliopathies, and researchers are hustling to figure out what makes them tick.

One group of scientists in Japan last month marked a milestone in the pursuit to reveal cilia's secrets. In study results that were fast-tracked for publication and deemed a "Paper of the Week" by the Journal of Biological Chemistry, they report that they have identified a long-elusive enzyme necessary for the proper regulation of cilia.

The Hamamatsu University School of Medicine team is optimistic that the discovery may aid in the development of therapies for those with visual and hearing maladies caused by cilia dysfunction.

"Our finding might give insights into the sensory defects associated with problems in cilia function. For example, patients with some syndromes have genetic defects in cilia functions that result in retinal degeneration," explains Mitsutoshi Setou, who oversaw the team's work. "Also, age-dependent visual loss or hearing loss is known to be related to damage of the eye or ear sensory cilia. To enhance or suppress the activity of the newly found enzyme might alleviate the symptoms through the proper regulation of cilia."

With the hopes of one day manipulating cilia's activities on the perimeter of cells and, thus, how those activities affect human health, the team traced cilia's molecular roots into the depths of cells themselves.

If a cilium had a life story, it would begin with a gene. That gene encodes information during a cell's production of tubulin proteins so that they will link up into microtubules, or tiny tubes, and form the interior apparatus of a protruding cilium.

Scientists have known for some time that a group of enzymes can indirectly affect what goes on inside cilia by adding unusually branched chains of amino acids, known as glutamates, onto certain spots of the tubulin proteins that make up the microtubules. Suspecting that the addition of the amino acid chains on the tubulin building blocks might influence how material is transported within cilia, Setou's team took a closer look at how and where the chains of amino acids are added to tubulin proteins and set out to figure out what, ultimately, removed those same chains.

To do so, they analyzed cilia on cells of sensory neurons in a living model organism, the roundworm, and studied purified protein from cultured mouse cells. Ultimately, the enzyme that strips the amino acid chains was elusive no more.

"We found out which enzyme removes part of the glutamate chain, and we now have a better understanding of that lengthening and shortening of amino acids on tubulin that regulates the function of cilia in sensory nerves," he said.

Setou is hopeful the finding will help develop therapies for a group of genetic diseases known as retinitis pigmentosa, which causes degeneration of the eye's retina and, thus, progressive loss of sight.

The human photoreceptor is a sensory neuron composed of two segments that are connected by a cilium responsible for transporting proteins from one end to the other. If that protein movement slows down or stops due to cilium malfunction, the protein accumulates abnormally and induces retinal cell death.

"Retinitis pigmentosa is one of the leading causes of adult vision loss, and yet there is no cure for it," he said. "Recent studies have shown that at least 35 genes are involved. Importantly, some of them are related to cilia formation and maintenance. This important function of cilia could be regulated by the level of polyglutamylation, which is controlled by the level of newly found enzyme."

While Setou's team focused exclusively on cilia found in sensory neurons for their experiments, the findings may prove useful in other types of cilia as well. Defective cilia lining the kidney, for example, can lead to polycystic kidney disease. Mammals rely on cilia lining reproductive organs: If there are too few functional cilia in the Fallopian tubes, which are tasked with moving a fertilized egg into proper position

for growth, the ovum may hunker down too soon, causing a tubal pregnancy. Meanwhile, what are known as chemoreceptor cilia, found on olfactory neurons, detect odor.

More information: The Journal of Biological Chemistry paper can be found here: www.jbc.org/content/early/2010 … C110.128280.full.pdf

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