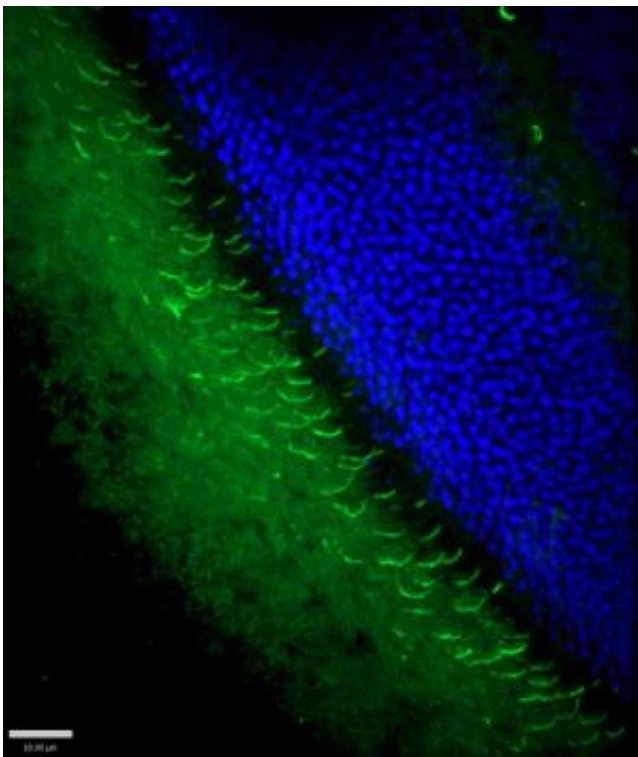


New tool to help define role of mystery appendage in everything from development to obesity

July 4 2013, by Greg Williams



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(Medical Xpress)—A research team has genetically engineered a mouse with glowing primary cilia, the tiny outgrowths seen on the surface of most cells, according to a study published today in BioMed Central's open access journal, *Cilia*. The model will enable researchers to better

study what is now recognized as the "cell's antenna," with key signaling roles in development and tissue function, for the first time in a live mammal.

Studies in recent years had suggested that cilia regulate vital processes including growth, appetite, mood, healing and vision. Defects in cilia have been tied to depression, obesity and cancer, along with [kidney disease](#) and several rare [genetic syndromes](#). Despite these suggestive outlines, the details of how cilia send signals remain largely unknown.

The cilia examined in the study were not the wavy ones that enable single-celled [protozoans](#) to dart around on microscope slides in [biology class](#). Neither were they the kind that sweeps mucus out of airways. They were primary cilia, which occur one per cell and were once thought to be vestiges from our cellular past with no current function.

In the new study, researchers tagged a protein concentrated in cilia with the fluorescent protein GFP, which enabled the first video recordings of cilia at work in the kidneys of live mice.

"There is tremendous interest in being able to closely study cilia in a live mammal, and to study something, you must be able to see it," said Bradley Yoder, Ph.D, professor in the Department of Cell, Developmental and Integrative Biology at the University of Alabama at Birmingham (UAB), and corresponding author on the study. "By tagging the right protein in cilia, we were able to visualize them in their natural environment. This will greatly accelerate research into cilia-driven disorders with serious consequences for development and adult health."

Captured here are primary cilia in kidney tubules knocked over by one-directional, fast-moving, presumably healthy fluid flow.

In a signal that the new mouse model may be useful, researchers made a

discovery the first time they tested it. They were able to observe primary cilia on cells lining kidney tubules as they filtered blood to control levels of water, salt and electrolytes, for example. Going into the study, researchers had believed such cilia stood up unless knocked over by fluid moving through a tubule.

This bending, they thought, might act as a sensor that released chemical signals to regulate the level of urine production, or perhaps the growth rate of nearby cells. Evidence from the new model suggests, instead, that the tubules are usually knocked flat by fluid flow, and that cilia-based sensors might work differently than once thought. Such insights are crucial because related problems lead to the formation of the clogging cysts seen in polycystic kidney disease, a main reason that people need dialysis.

Interestingly, when mice were under anesthesia and had slower blood flow, cilia were no longer continually knocked in one direction by fluid, but instead swung back and forth in a pulse timed with the heartbeat. Future studies will tell if injury, disease or blockage in the kidney, by disrupting flow, change signals sent via primary cilia to further damage tissue.

When moving through kidney tubules is slowed, as may happen with disease, cilia are no longer knocked flat, but instead swing back and forth in time with the heartbeat.

Better model

Many labs, including Yoder's, have studied cilia in the past using organisms like yeast and algae. These simple creatures offer rapid genetic screens and readily visible cilia in living samples, and they have contributed greatly to the understanding of cilia. They share vital signaling pathways with human cells but are far from the same.

A better model is the mouse, which is closer to humans on the evolutionary tree, but no one had been able to visualize primary cilia in a live mammal. Past attempts to affix glowing tags to cilia had required that the cells be static (dead). The problem with that approach is that those cells have features that behave differently.

One reason the UAB team was the first to achieve this [mouse model](#) is the years spent by the team studying proteins unique to primary cilia, a prerequisite to attaching tags to them. They found that the protein somatostatin receptor 3, or SSTR3, was well suited for this role because it occurs in great numbers on cilia, but it is not so central to their function that adding the tag causes problems.

Another key element enabling UAB to design the study was its Hepatorenal Fibrocystic Diseases Core Center, which has for years been looking at the role of [primary cilia](#) in polycystic kidney disease. The genetic engineering behind the new mouse was very expensive and would not have happened without the support provided by the National Institutes of Health.

The research team used standard molecular biology techniques to stitch the genetic code for the SSTR3-GFP fluorescent tag combination into the DNA of a mouse embryo at a special spot called ROSA26. Researchers discovered in 1991 that one can insert any DNA sequence at this spot in the mouse genome, and the desired gene will be expressed in nearly every cell in the mouse as it develops, while leaving the mouse healthy and fertile.

The new mouse will allow for the study of cilia in one organ at a time, as well as at different time points as a fetus develops or as a disease progresses. For example, past studies have shown that cilia on nerve cells in the brain region called the hypothalamus regulate feeding behavior and may have a role in obesity when they malfunction. There are many

types of nerves cells in the hypothalamus, however, and which ones have cilia that contribute to disease is unknown. With the new model, the team anticipates being able to label cilia on each nerve cell type on the way to evaluating their role.

"Beyond kidney disease and obesity, cilia on nerve cells are packed with receptors for serotonin, for instance, suggesting they are part of nerve signaling pathways known to control learning and mood," said Erik Malarkey, Ph.D., a postdoctoral scholar in Yoder's lab and study author. "Cilia also appear to play a role in cell division, suggesting they may have role in cancer when cells reproduce uncontrollably. Cilia help cells to tell the left side of the body from the right as the fetus develops. It goes on and on."

More information: [www.ciliajournal.com/imedia/14 ...le.pdf?random=329621](http://www.ciliajournal.com/imedia/14...le.pdf?random=329621) or www.ciliajournal.com/content/2/1/8

Provided by University of Alabama at Birmingham

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