Maxence Nachury: A transporting view of the primary cilium

Nachury studies how defective signaling from the cell's antenna causes human disease.

Recent years have seen an explosion of interest in the primary cilium. This long-neglected organelle was widely considered to be an evolutionary dead end before its critical function in cell signaling began to be uncovered. The microtubule-based membrane protrusion is now thought of as a cellular antenna, receiving extracellular signals and transmitting them to the rest of the cell. Defects in cilia function cause a variety of diseases, collectively known as ciliopathies.

Maxence Nachury admits that he hadn't even heard of the primary cilium until a few years ago when he was a postdoc with Peter Jackson at Stanford University and Genentech. Before that, Nachury had studied both nuclear transport and mitotic spindle assembly as a PhD student with Karsten Weis and Rebecca Heald at UC Berkeley (1, 2). But the mysterious primary cilium grabbed Nachury's attention when he realized that mutations in a number of different ciliary proteins caused the pleiotropic human disorder Bardet-Biedl syndrome (BBS). Despite his initial unfamiliarity with the subject, Nachury soon demonstrated that seven of these proteins form a conserved complex called the BBSome that transports membrane proteins to the cilium (3). Nachury then identified an additional BBSome subunit required for both cilia formation and microtubule acetylation (4). Now with his own lab at Stanford University, Nachury recently showed that the BBSome acts as a membrane coat to traffic signaling receptors into the cilium (5).

In a recent interview, Nachury discussed the BBSome's function and the cilium's contribution to human disease.

CILIARY BASE

Where did you grow up?

I grew up in a fairly well-off suburb of Paris. I had a phenomenal biology teacher during high school, who helped me appreciate that what I was learning in physics and chemistry classes also applied to nature. It was the idea of understanding life in terms of basic molecular and physical principles that got me hooked on science.

How did you end up moving to the US?

I studied at the École Normale Supérieure in Paris, and in the summer after my second year, I went to Angus Lamond's lab at the EMBL in Heidelberg. I worked with one of his graduate students—Karsten Weis—on nuclear–cytoplasmic transport, an area that really fascinated me.

Later, as I was finishing my undergraduate degree, Karsten called me out of the blue and asked if I wanted to work for him in his own lab that he was starting at UCSF. Even though I had a PhD position lined up at the Pasteur Institute, it was a great opportunity. So I joined Karsten's lab and began working on nuclear transport again, in particular on the small GTPase Ran.

The lab moved to Berkeley in the middle of my graduate studies and we ended up next door to Rebecca Heald, whose group works on mitotic spindle assembly. Just at that time, a string of papers came out suggesting that Ran was also involved in organizing the mitotic spindle—that it was generated in the vicinity of chromatin to stabilize nearby microtubules. So we collaborated with Rebecca's lab and made some really seminal discoveries. I found that the mechanism by which Ran functions in mitosis is essentially the same as its mechanism in interphase nuclear transport. It was a very exciting time where we went into a wide-open field and simply tested all the ideas that came into our heads.

> "I don't know any other disease where a single mutation causes such diverse symptoms."

Did you intend to continue working on mitosis as a postdoc with Peter Jackson?

Yes. After studying the basic principles of spindle assembly, I wanted to make a slight shift into studying how cells exit mitosis.

Maxence Nachury

It didn't work out too well—I spent two years going nowhere. But it allowed me to slow down and open up to other ideas. I switched to cilia through a series of tenuous molecular links between mitotic exit and an obscure disease called Almström syndrome. I was immediately fascinated by this disease, which has a variety of symptoms including retinal degeneration, obesity, and kidney malformation.

I couldn't figure out anything about the molecular basis of this disease. Then I read that it was similar to another disease called Bardet-Biedl syndrome, which had been linked to dysfunction of the primary cilium. I had never heard of primary cilia before! Few cell biologists were talking about it at the time and those that did thought it was just a remnant of evolutionary history—sort of like a cellular appendix. But now it was linked to human disease, and Kathryn Anderson published a paper showing that primary cilia were essential for Hedgehog signaling. Something clicked in my head, and I decided to work on Bardet-Biedl syndrome with the tools that I had, purifying protein complexes and setting up assays to study the cell biology of proteins mutated in the disease.

TO INDUSTRY AND BACK

By that time you'd moved to Genentech?

Yes, it was right at the time that Peter took

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a job at Genentech to lead a program on cell cycle regulation. He announced to the lab that he wanted everyone to come along. My wife worked for Genentech—she still does—so it was exciting to work closer to her, but I was very nervous about leaving academia. I had always envisioned an academic career for myself, and I just couldn't see academic research being pursued in biotech. But Peter is a very convincing person, and I ended up following him. It turned out that I loved the place: there were almost limitless resources and some fantastic people to collaborate with. There was a great willingness to work together, and a general excitement about the research we were doing. All the things you'd want in an academic department were right there at Genentech.

Were you tempted to stay?

Not really. As postdocs, we had free reign to do all the cool science we wanted. Our only brief was to publish great papers. But starting a lab at Genentech is a different experience—there's more of an obligation to do something that could lead to potential therapies in the medium-term. I couldn't see myself doing that. I just wanted to answer all the incredibly exciting questions ahead of us in primary cilium research.

Let's talk about that research. Why does Bardet-Biedl syndrome have such a wide range of symptoms?

That's what fascinated me the most to start with. How can the loss of a single gene product make you unable to sense odors, make your retina degenerate, make you obese, make you grow extra digits, and make your kidneys fail? I don't know any other disease where a single mutation causes such diverse symptoms.

During my postdoc, I found that most of the proteins mutated in Bardet-Biedl syndrome assemble into a protein complex that we called the BBSome. And just recently we showed that the BBSome forms a membrane coat similar to clathrin that carries membrane receptors to the primary cilium, where they transduce specific signals. So the different signaling pathways regulating body weight, limb morphology, and so on might all be defective because their receptors don't make it to the cilium in the absence of the BBSome.

We think the BBSome forms a membrane coat that clusters receptors in the plasma membrane and transports them through the diffusion barrier that exists at the base of the cilium. An unsolved question is whether the BBSome is strictly a planar coat or whether it forms a vesicle at some point. We're trying to follow single receptors as they move to the cilium, and we hope that will tell us exactly where the BBSome is acting.

> "Cilia loss could facilitate cancer progression."

THE NEXT LEVEL

Bardet-Biedl syndrome isn't the only disease associated with cilia. What are the organelle's links to cancer?

There's nothing definitive yet, but it's appealing to think that signaling cascades would be dysregulated by the absence of cilia. In polycystic kidney disease, which is caused by a loss of cilia function, the kidney cells divide more. That leads to cysts rather than a tumor, but it suggests that cilia loss could facilitate cancer progression.

A postdoc in my lab is working with a mouse model for pancreatic cancer in which you can follow the progression of normal ductal epithelia into full-blown adenocarcinomas. Even at the earliest stages of the most benign lesions, cells have already lost their cilia—before you see any hyperproliferation. So now we're trying to combine the loss of cilia with expression of the K-ras oncogene to test whether losing cilia speeds up the progression toward adenocarcinoma. The organelle itself might be a tumor suppressor—I think that's an area that will become very exciting in the next few years.

What else are you working on?

Ultimately, I want to take things to a structural and biophysical level. We're currently working on the structure of the BBSome using cryo-electron microscopy and x-ray crystallography.

We're also interested in the link between the BBSome and tubulin acetylation. We made the surprising observation a few years ago that when we depleted cells of a specific BBSome subunit called BBIP10, cytoplasmic microtubules were no longer acetylated. Almost everything that's been published says that tubulin acetylation does nothing, but we think that this modification is actually doing something very interesting and important.

What do you like to do outside the lab?

I used to do a lot of mountain climbing. I went to Ecuador and summited a 20,000-foot volcano there. I also climbed a lot in the Sierras in California. It's a great way to disconnect from the lab and get away from your email and everything else. I raced mountain bikes when I was a student and postdoc as well. Now I have a young daughter, so that has definitely cut down on these kinds of things. But I just took her hiking through Big Sur, and she loved it—she liked seeing all the wild animals and birds.

Now I go swimming pretty much every day. I'm not competitive about it—I just do it for fun and to have a little break over lunch.

1. Nachury, M.V., et al. 1998. *Proc. Natl. Acad. Sci. USA.* 95:582–587.
2. Nachury, M.V., et al. 2001. *Cell.* 104:95–106.
3. Nachury, M.V., et al. 2007. *Cell.* 129:1201–1213.
4. Loktev, A.V., et al. 2008. *Dev. Cell.* 15:854–865.
5. Jin, H., et al. 2010. *Cell.* 141:1208–1219.

Nachury atop Mt. Conness in Yosemite.