People & Ideas

Samara Reck-Peterson: Dynein defies expectations

Reck-Peterson studies the mechanism and regulation of dynein's motor activity.

There are 14 different dyneins in the human genome, but 13 of these are found in cilia and flagella. Just one—cytoplasmic dynein 1—handles the bulk of minus end–directed microtubule trafficking for organelles, vesicles, and other cargoes. It is only recently that scientists have started to understand this motor better, and, surprisingly, they have discovered that how it walks can be quite random compared to other cytoskeletal motors.

Samara Reck-Peterson isn't bothered by dynein's unpredictable behavior. After all, she herself took a few detours in her early career but found her scientific home working on molecular motors, first as a graduate student at Yale and then as a postdoc at the University of California, San Francisco (1). Although her own lab at Harvard is only five years old, she has already shown how dynein's behavior (2, 3) and regulation (4, 5) differ from those of other motor proteins. The path to scientific success can take many turns, as Reck-Peterson explained when we spoke to her.

A SIDE STEP

When did you first decide to pursue a career in the sciences?

Well, my general curiosity about the world, which I think is really important for scientists, comes from my parents. But, given my education up until college, it's a little surprising to me that I became a scientist at all. I had a fairly weak education in science and math. My high school, in a small town in Minnesota, didn't have physics or calculus classes, and biology was mostly taxonomy. So, I didn't enter college with a strong science background.

I went to Carleton College, which is also in Minnesota, with the vague idea that, despite my lack of a good education in the sciences up to that point, I did enjoy science and math. One of the courses I enrolled in during my freshman year was a biology course, and it was through that course that I learned about research opportunities in the department. I joined the lab of Susan Singer, a Carleton professor—first as a dishwasher and then working on floral development in tobacco. After I'd spent a few years in Susan's lab, I was pretty sure that I wanted to pursue a career in research.

And then you went to graduate school at Yale?

Not right away, no. At the time, I was interested in continuing to work in plant developmental biology, so I applied to schools based on their programs in that field and ended up at the University of Pennsylvania. There, I took a cell biology course taught by Lew Tilney and became really enamored with molecular mechanisms and mechanistic cell biology. On Lew's suggestion, I attended the physiology course at the Marine Biological Labs, probably the most influential experience in my scientific career. It was at Woods Hole that I met Mark Mooseker—a terrific mentor who would eventually become one of my thesis advisors—and worked on molecular motors for the first time.

> "We both felt that dynein was the next frontier in the motor field."

But about this same time, I was questioning whether grad school was the right path for me. I think I needed some time to sort it out, so I took a temp job as a secretary at an insurance agency in New York City. I realized pretty quickly that I really missed science and decided to return to graduate school. This time, I went to Yale, to work on myosins with Mark Mooseker and Peter Novick.

NEXT STEP

And if you're into motors, Ron Vale's lab must be a great place to do a postdoc…

Ron's great. He's definitely one of my science heroes, and I model the team-based approach my own lab uses on my experience in Ron's lab. I did interview in some nonmotor labs at the time because people were advising me to try something different. But then I met Ron, and we discussed working on dynein. We both felt that dynein was the next frontier in the motor field.

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Samara Reck-Peterson

Little was known about dynein, largely because the sheer size of the protein had prevented it from being easily studied. Whereas for both myosins and kinesins robust recombinant sources of the proteins had been available for a long time, all of the work that had been done so far with dynein was with tissue-purified protein. That can get you quite a long ways, but in terms of really beginning to engineer mutations, remove parts of the motor, add tags, add probes—all of those things weren't possible without having recombinant protein. So, our first goal was to get a robust recombinant source of dynein that we could then use to study the motor more closely. I worked closely with three other postdocs and two graduate students—all of us pooling our skills to complete this ambitious project.

You found that dynein does not work like other motors, such as kinesin…

Some kinesins and myosins can move processively. There are biochemical mechanisms that allow their two motor domains to be coordinated in such a way

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that the motor in the rear lifts up while the one in the front stays tightly bound to its track. And so the assumption was that there'd be some mechanism like that for dynein, allowing it to coordinate which of its two motor domains takes the next step. But both my lab and the Yildiz lab at Berkeley showed that dynein is different. When dynein's motor domains are pretty close together on the microtubule, it is random which of the two motor domains will take the next step. But when the two motor domains are far apart on the microtubule, it's more likely that the trailing one will take the next step. This means dynein can take a wide variety of step sizes, forwards and backwards, and we've even shown it can step to the side.

This all means that dynein is a motor that really meanders along the microtubule, and work from Erika Holzbaur's and Yale Goldman's labs has shown that this might allow dynein to sidestep obstacles, such as microtubule-associated proteins or crossed microtubules. So, we think the fact that dynein is sloppy may be an advantage for cells. About half of my lab continues to work on the mechanism of dynein's motor activity, including studying how dynein's motility is regulated by proteins that directly bind to it.

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Dynein's not the only thing that walks: Reck-Peterson with her dog, Locksley.

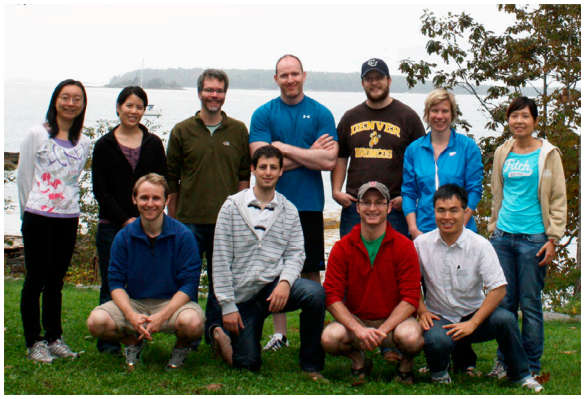
MASTERING THE MOTOR

For example?

Because there is just one dynein that does so many things in the cytoplasm of most eukaryotic cells, we think that its regulation is probably going to be really important for its function. For example, we've been looking at Lis1 and its binding partner Nudel. We showed that Lis1 binds to the dynein motor domain and prevents dynein from letting go of the microtubule, even while the motor domain is undergoing rounds of ATP hydrolysis. We're now trying to figure out how Lis1 accomplishes this.

We've also looked at the role of Lis1 in endosomal transport. For that, we're using *Aspergillus nidulans*, which is a filamentous fungus that uses its microtubules for organelle transport and where it's really easy to engineer the genomic copy of genes. In those experiments, we haven't found any evidence for Lis1 actually moving with dynein and endosomes along microtubules, so our hypothesis is that Lis1 works to keep dynein at the plus end of microtubules so that dynein is more likely to get loaded onto its cargo. We'd like to know how Lis1's activity is regulated.

But that's just one of many things we don't understand about cargo transport. For example, for a lot of cargo, we don't know how the motors bind the cargo or how those interactions are regulated. We just finished a screen in *Aspergillus* looking for mutants with mislocalized or immobile cargo, and we have a bunch of hits that we're excited about. Another thing we don't yet understand is how motors cooperate to move cargo. It turns out that a lot of cargoes have more than one motor—or type of motor—on them, so we're now combining artificial cargoes made out of DNA origami with motor ensembles to explore how this cooperation is achieved.



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The Reck-Peterson Lab on an annual retreat.

So you're happy you ended up in science after all?

Yes! And I'm also really interested in thinking about training the next generation of scientists and what our changing scientific climate will mean for graduate students and postdoctoral fellows. I'd like to see more staff scientist positions created, where people can pursue research without the additional responsibilities of management and teaching.

I'm also currently the Associate Director of the Biological and Biomedical Sciences Graduate Program at Harvard Medical School, and I know that a lot of students choose to pursue careers outside of academia and industry. That's not what I chose to do, but it's something I'm really supportive of because I think the rigorous training that a PhD gives someone can allow people to be transformative in other fields. I don't necessarily think we should be training fewer PhDs; I think it's great for society at large to have scientists out there, particularly in business, law, and government.

> "The fact that dynein is sloppy may be an advantage for cells."

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