Terry Lechler: The cytoskeleton is skin deep

If form is function, Terry Lechler thinks scientists should know more about how cells acquire their form. That's one reason he studies the cytoskeleton.

From actin to microtubules, Terry Lechler had a hand in several important cytoskeletal discoveries. As a graduate student, Lechler used an in vitro assay to study cortical actin assembly. He permeabilized yeast cells and used extracts to identify a WASP family protein called Bee1 (1), which was later shown to be an activator of the Arp2/3 complex (2).

Lechler's early work gave him a taste of polarity when he showed that Cdc42 recruits Bee1 and activates myosin to control Arp2/3 locally as budding yeast polarize (3). After taking a break to teach in Nepal, Lechler returned to the study of polarity, this time focusing on mammalian cells in Elaine Fuchs's lab at Rockefeller University in New York City. There, he discovered that polarized skin precursor cells divide asymmetrically, creating one daughter cell that is attached to the basement membrane and one unattached cell that forms additional layers of the skin (4).

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He returned to the cytoskeleton when he noticed that differentiating skin cells reorganize their microtubule networks. This rearrangement, he found, requires a desmosomal protein called desmoplakin (5)—a discovery that gave these cell–cell junctions a new dynamic flavor. Lechler recently started his own lab at Duke University, where he continues to study desmosomes, polarity, and the cytoskeleton.

SKELETAL START

How did you get interested in science?

As a kid, I liked to mix stuff up in the sink. I grew up on a farm, and when we'd butcher the chickens, I'd get some of the internal organs and cut them up.

Coming out of high school, I was really interested in molecular genetics and the ability to clone DNA. Our senior year we got to do independent research projects. So I did a *Drosophila* genetics project.

Why did you choose Dr. Rong Li's lab at Harvard for your graduate work?

There were two reasons. One was the cytoskeleton, which I thought was just amazingly cool and an important system to study. The other was Rong herself. She was a really dynamic person, and in retrospect I couldn't have asked for a better mentor at that stage.

Why did you think the cytoskeleton would be cool to study?

To be honest, at first I thought it was kind of obscure, and that really appealed to me. This was pre-Arp2/3 complex, and at that point there was really nothing known about how actin was nucleated inside the cell. But then it turned out to be about the hottest area in cell biology at the time. It exploded within the next couple of years.

A lot of that was happening around us and in our lab; Marc Kirschner and Tim Mitchison's labs were upstairs. So it was just this incredibly vibrant and exciting time where all these important discoveries were being made.

How were you able to compete so well in that strong field?

I think we had two advantages: we had the genetics; and we could do some of the physiology of the actin assembly that other people couldn't do because we were working in yeast. We could actually look inside the cell at what was happening with gain- and loss-of-function approaches. We had identified most of these molecules from a more physiological standpoint and then went on to find their mechanism.

ASYMMETRY AND KATHMANDU

And why did you choose to do your post-doc in Elaine Fuchs's Lab?

I knew I still really liked the whole area of cytoskeleton morphogenesis, but I also wanted to be exposed to a lot more. The Fuchs lab was the ideal place for me because it did have that cytoskeletal niche, but it also has a broad range of interests in transcription, stem cells, and development. I thought it'd be an ideal place to be exposed to all of that and still have an area of comfort.

Terry Lechler

And she was actually one of the few people who were okay with me taking off for six months to go to Nepal and teach.

Tell me about Nepal.

A group of Nepali doctors wanted to start a medical school in Nepal, but they needed some basic science faculty, so they recruited a bunch of us to come over. In the first six months, there were three graduate students and one post-doc from Harvard. We all knew Cliff Tabin, who was running it; he was the chair of my graduate program.

We did everything you need to do to set up the school. We interviewed the students, set up the library, stuff like that, and then we taught them for the first four months. It was a problem-based learning curriculum, so there were some didactic components, but a lot of it was getting the students to start thinking and interacting and working through problems.

It was fantastic. Everyone should take time off after grad school.

But then it was back to the bench. How was working in the Fuchs lab?

That was a really good experience because I got to completely develop a project from scratch. I began by looking at tissues, which was new for me. I'd worked with yeast and was used to looking at single cells. I think because of that, I looked at the tissue a little bit differently; I looked a lot more at what the cells were

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doing. During that process, I noticed that cells were dividing in different orientations during development and thought that that was a really interesting, important process in the development of the epidermis.

Why did you find this asymmetric division so interesting?

It's one potential way that stem cells could both renew themselves and generate new stem cells, and at the same time contribute transit-amplifying or differentiated cells. It's not necessary that stem cells divide asymmetrically, but it is a really elegant way that they can couple those two characteristics. Asymmetric divisions are also exceptional because they help control epithelial tissue morphogenesis by promoting stratification.

And while developing reagents for that project, I was also able to make observations that opened up additional areas of study. The role of microtubules in differentiated cells and how they reorganized, which was not part of what I was originally doing, was a really happy extension of that.

In some ways, I think I'm more interested in that story. Many people right now are interested in asymmetric cell division, but the role of cytoskeletal reorganization during cell differentiation is an area that's just beginning, and there are a lot of open questions.

Why should more people study it?

It's so fundamental. Form is function. That's clear in differentiated cell types, and yet we have so little idea about how the cytoskeleton reorganizes when cells differentiate, or even what the functions are of most of the cytoskeletal elements in differentiated cells.

UNDER HIS SKIN

How are you taking what you did in the Fuchs's lab and making it your own?

We've become a lot more interested in cytoskeletal remodeling downstream of the desmosome and trying to identify the complement of proteins that are recruited by the desmosome. What's most interesting there is that it looks like there's a group of centrosomal proteins. They're at the centrosome normally, and they're brought to the desmosome when the cells differentiate. We're interested in this family of proteins and how they coordinate the cytoskeleton.

In terms of asymmetric cell division, we are interested in spindle reorientation and in questions like, What are the forces that are acting on the spindle to allow spindle orientation, and how does the spindle anchor to the cell cortex? This is really an open question.

The third area is more of a tissue biology question. In most asymmetric cell division systems, the cells consistently divide asymmetrically. But in the epidermis, cells can divide either symmetrically or asymmetrically. We're interested in how they integrate chemical and mechanical signals across the epidermis to make the decision whether to divide asymmetrically or symmetrically to generate an epidermis that's the right thickness.

Why do you use the skin and intestine to study these questions?

The skin is really the only well-developed system where cells are making this choice between asymmetric and symmetric divisions. Understanding how that decision is made I think is going to be a really interesting area of biology.

> **"I'd worked with yeast and was used to looking at single cells, [so] I looked at the tissue a little bit differently."**

The other big plus is the fact that we can go back and forth between the cultured cells and the in vivo setting to understand both the mechanism and the physiology of the cytoskeletal remodeling.

The intestines are a great extension of that, because they're also an epithelial cell, but they're very different morphologically and functionally. So we can take what we learn in the skin and see whether it's generalizable to other epithelial cell types.

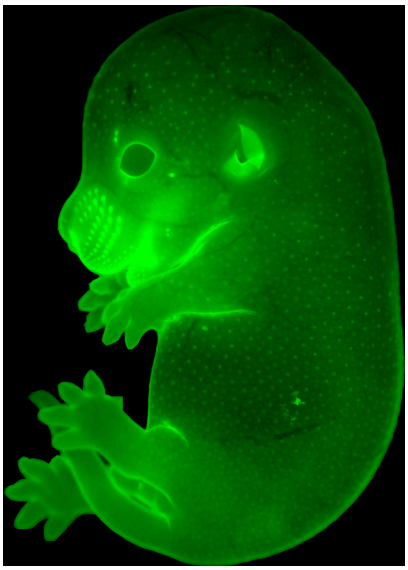
Skin and intestine are highly proliferative tissues. What advantage does that give you?

In terms of the skin, one nice thing is you've got a proliferative department, and you've got a differentiated compartment. So there's also the really interesting question of, How does one transit to the other? What are the morphological consequences of that, and how do those occur?

What made you choose Duke for starting your own lab?

Ultimately, it was pretty much a gut feeling. I knew I fit there. The big draws were the people. It always has to come down to that. You want to surround yourself with people that are going to stimulate you, but also people that you like and want to interact with on a daily basis.

And North Carolina was a really easy adjustment. I adopted a dog, I got my house, I'm kind of set. But I get back to New York for sushi every now and then. JCB



LECHLER

Lechler's fluorescent mice revealed the reorganization of microtubules (green) during the development of the epidermis.

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