Valerie Horsley: Getting under the skin

Valerie Horsley investigates the regulation and differentiation of stem cells in mammalian skin.

Epidermal stem cells in mammalian skin can develop primarily along three alternative paths, differentiating into hair follicles, sebaceous glands, or the interfollicular epidermis. How the stem cells are guided into these different fates by signaling molecules and transcription factors is a question that first grabbed Valerie Horsley's interest as a postdoc in Elaine Fuchs' laboratory at the Rockefeller University. Now an assistant professor at Yale University, she's continuing to use a powerful combination of mouse genetics and cell biology to study how the skin is developed and maintained.

Before her time at Rockefeller, Horsley attended Furman University as an undergraduate, and studied for her PhD with Grace Pavlath at Emory University in Atlanta. In Pavlath's laboratory, she worked on signaling pathways and transcription factors regulating skeletal muscle development (1–3). As a postdoc, she switched her attention to skin, looking at the functions of two transcription factors in particular: NFATc1, which controls the exit of epidermal stem cells from their niche to grow new hair follicles (4), and Blimp1, which regulates the differentiation of specific precursor cells into the sebaceous gland (5).

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We caught up with Horsley to ask her about these precursor stages of her career and her recent differentiation into an independent group leader at Yale.

AN EARLY START

What do you think you'd be if you weren't a scientist?

I kind of always knew I was going to be a scientist. I wanted to be a doctor when I was a kid, but that's because it was the only thing I knew you could do as a career that's science-y. When I was in college, I realized that I didn't really want to take care of sick people. I was more interested in how the body works—that's why research really suited me better than medicine.

What gave you this idea at such a young age?

I think it's mostly just my personality. But when I was 12, I had a biology teacher who told stories and made it really interesting. We did experiments, and it was a lot of fun. That really inspired me. From then on, I knew I wanted to be a scientist.

What kind of experiments did you do?

We put plants in black boxes with different colored light and tried to see which ones they could grow in. That's the only one I remember. When I was in ninth grade I went to the Fernbank Science Center in Atlanta, which has a science program. High school students attend one- or two-week classes in physics, ornithology—all these different science classes over the course of three months. We did a few experiments there. I thought cloning was cool after going to this program, so I remember trying to clone plants for a science fair project! When you're a kid, you need to come up with ideas for doing experiments and I think our education system could be better at stimulating those ideas.

When did you get your first proper taste of being in a laboratory?

When I went to grad school, really. Furman is a very small undergraduate college, so there's not a large research enterprise. When I got to Emory, I didn't know what research was really like. My first year there was a great learning experience, I learned a ton.

TRANSCRIPTION AND TISSUES

What made you choose Grace Pavlath's laboratory?

I'm interested in how the body works and she was one of the only faculty members at Emory who was really working on tissue function. She had a lot of interesting cell and developmental biology projects in the laboratory, working on skeletal muscle. I looked at how NFATc2, which is a transcription factor, controls muscle development. I identified an intermediate stage of muscle development, in which multinucleated myotubes grow larger by recruiting additional nuclei. NFATc2 controls that step.

BRADLEY HODGES

Valerie Horsley with her daughter, Avery.

I found that a secreted factor, IL-4, is released from these initial myotubes and gives that "come fuse with me" signal. I also did some work on prostaglandins and how they control this stage of myogenesis as well. That was my first love: I still love that project!

So why did you change fields for your postdoc?

A few of my favorite faculty at Emory told me, "Don't change, stay in muscle development," but I really thought it would broaden me to go to a different tissue. Bone development was initially what I wanted to do, but I also wanted to go to a large laboratory and work with someone that was famous. Skin development seemed like it had a lot of tools to study developmental questions, so I came to Rockefeller.

Text and Interview by Ben Short
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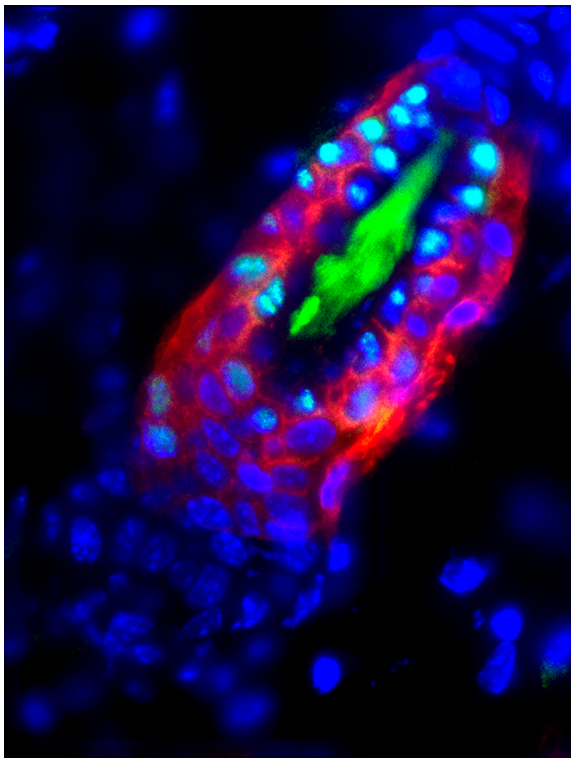
What did you work on during your postdoc?

I looked at a transcription factor called Blimp1. I found that it was expressed in a progenitor population for the sebaceous gland, which is the gland that produces the oil for the skin. When I deleted Blimp1 from the epidermis of mice, they developed oily skin. We really know almost nothing about this gland, so now I want to study how it forms. Clinically, it's important for acne, and there are some human tumors that form from it. I hope that by understanding what Blimp1 does, we can start to understand how these clinical diseases arise.

I also worked on a transcription factor called NFATc1—from the same family that I worked on in graduate school. It's expressed in the hair follicle stem cell compartment, and I found that it controls the proliferation of those cells and therefore controls hair growth. It basically puts the brakes on proliferation and allows the stem cells at the hair follicle to grow slowly. Then, as the cells exit the stem cell niche, they turn off their NFATc1 expression and start to proliferate, and that allows them to form a new hair follicle.



Epidermal stem cells reside in the bulge region of the hair follicle (red), where the transcription factor NFATc1 (green) keeps them from proliferating too quickly.

BECOMING INDEPENDENT

Why did you choose Yale as the place to start your own laboratory?

It's a very good developmental biology department in terms of research, but it also has a strong teaching element and I've always enjoyed that. As I said, when I was 12 a teacher inspired me to be a scientist, so I think you can really stimulate people this way. That's why I went to graduate school actually: to teach at a school like Furman. It was only as I went along that I found I really enjoyed research as well.

Your husband has also just begun his own group at Yale. Any advice on dealing with the "two-body" problem?

You have to be as broad as possible in your applications, and hope that multiple options will work out for the two of you. It's hard when you're in the middle of the job search because you have two independent careers; you're trying to fit them into one place, and there really aren't a lot of mechanisms that universities have come up with to try to help. But in the end, if they really want you, they'll make it work, and we had a number of places that made us good offers. To have a choice was amazing—I never thought that would happen. But it was very stressful.

What's the funding situation like for you as you begin your independent career?

I'm not worried about funding right now. Science is hard enough without worrying about money! I just have to do the best work I can and plan ahead. I have a good startup package, and a transitional award from the NIH: the K99/R00 Pathway to Independence series. Connecticut also has stem cell grant opportunities that I'm applying for at the moment.

"Science is hard enough without worrying about money! I just have to do the best work I can."

You were a finalist in the New York Academy of Science Blavatnik Awards. It must be nice to get recognition this early in your career.

Yeah, this was great! Besides fellowships, I don't know of another way that postdocs are rewarded for what they've done—usually the credit goes to the head of laboratory. So it's a real honor to have this award.

What's up next for you in terms of projects?

I want to understand how the sebaceous gland develops, and how NFATc1 is regulated in the stem cell compartment of the hair follicle. But I'd also like to use some of the tools that have been developed in the skin—such as specific keratin promoters—to understand other epithelia in our body. There's a lot of epithelia that express the same keratins as skin, so we can use these genetic tools to study those tissues as well. I want to understand how transcription factors regulate the development of the mammary gland and the thymic epithelium. These are the type of questions I like to ask: how does a tissue form and then maintain itself? What happens in disease states? That's the overarching theme for what I've done since graduate school, and what I want to do now in my own laboratory. JCB

1. Horsley, V., et al. 2001. *J. Cell Biol.* 153:329–338.
2. Horsley, V., and G. Pavlath. 2003. *J. Cell Biol.* 161:111–118.
3. Horsley, V., et al. 2003. *Cell.* 113:483–494.
4. Horsley, V., et al. 2008. *Cell.* 132:299–310.
5. Horsley, V., et al. 2006. *Cell.* 126:597–609.