People & Ideas

David Bilder: Getting to know epithelia inside and out

Bilder explores epithelial form and function in *Drosophila* using forward genetic screens.

PHOTO COURTESY OF BRYAN ZEITLER

David Bilder

Epithelial tissues are made up of highly specialized cells with distinctive apical and basolateral surfaces. The establishment of this dramatic cell polarity requires specialized procedures and proteins, and its maintenance is a constant challenge for epithelial cells. Understanding these processes is also a challenge for scientists who study them but one that David Bilder has happily taken on.

Leveraging the power of forward genetic screens with the rich experimental possibilities of the *Drosophila* system, Bilder's work has yielded important insights for the field of epithelial biology. As a postdoc in Norbert Perrimon's lab, Bilder uncovered the function of the PDZ domain protein Scribble in localizing apical proteins in epithelial cells (1, 2). And, since founding his own lab, he's mated these techniques with cutting-edge microscopy to make novel observations on epithelial organization (3–5)—and on how the disruption of this organization brings out cancer-like properties in fly tissues (3). We called him in his lab at UC Berkeley to discuss how he became enchanted with science and epithelial biology.

SMITTEN

When were you first bitten by the research bug?

I didn't really catch the science bug until I got to college. Even then, I didn't really know what I wanted to do at first. I kicked around some things—anthropology, cognitive science, and even comparative religion. I think I was very interested in trying to understand things about the mind. But it was really when I had the good fortune to do undergraduate research with Didier Stainier, who was then a graduate student in Walter Gilbert's lab, that I got hooked. I found myself coming into the lab even when I didn't have any experiments to do, because there was always something exciting happening.

What did you do after completing your undergraduate degree?

Despite that great experience, I was still pretty restless in my 20s. Even though I really enjoyed lab work, it was hard to imagine spending my whole life indoors at the bench. So, I was able to get a fellowship to explore ecological research and environmentally sensitive development.

It was great. I spent half the time in Papua New Guinea and the other half in what was then eastern Zaire. It was a wonderful experience and a great adventure, but at the end of the day I felt that there were too many uncontrolled parameters in the work I was doing, and I wasn't certain there would be any long-term impact from it. So, although I really have tremendous respect for people who do this critical ecological and developmental work, I realized it just wasn't for me.

I applied to grad school and got into Stanford, so I came back to the States. It was a big culture and lifestyle shock going from the rainforest to suburban Palo Alto, and I really questioned if I had made the right choice by coming back. But then two things happened: one, I took a genetics class, and I felt like my eyes were opened. I fell in love with how you could use genetics to understand fundamental biological problems. The second thing was that Matt Scott had just recently arrived at Stanford with his really fascinating work on homeobox genes, and I enthusiastically joined Matt's lab.

> "I ignored all the advice that I'd gotten and just went with the science that most excited me."

SHARED INTERESTS

Your graduate work set the foundation for your career…

One important thing I took away from my PhD was the ability to use genetic screens: an unbiased function-based approach that lets us ask the animal what's important for any biological process. But, when I was looking for a postdoc, everyone I talked to said that I shouldn't continue working in *Drosophila* and that I should switch to another organism. I was advised that if I stayed with *Drosophila* I would just be considered a one-trick pony. So, I interviewed in a mouse lab, a worm lab, and an amphibian lab.

Almost as an afterthought, as long as I was in Boston, I went to visit Norbert Perrimon's lab, which of course is one of the premier *Drosophila* genetics labs. I had the idea of applying the genetic mosaic techniques that he'd been using to study patterning to instead study cell biological processes such as cell polarity in a multicellular organism. Basically, I ignored all the advice that I'd gotten and just went with the science that most excited me. That's always a good guide.

How did you choose the problems you then tackled in your own lab?

We really work at the interface of cell and developmental biology. We've had a continuing fascination with cell polarity, but in a larger sense I am interested in a general understanding of epithelial form and function. The reason we study epithelia is that they are really the core tissue of animals.

Text by Caitlin Sedwick
csedwick@gmail.com

In any Metazoan much above the sponge, one of the first things that animal does is make an epithelial sheet to separate the inside from the outside. Across animal phylogeny and in our own bodies, most organs are made up of epithelial tissues. So, in order to understand animal biology, we really need to understand both how cells take on epithelial form and how that form influences the function of the cells and the tissue.

LONG TERM

With regards to epithelial form, you've worked a lot on epithelial polarity…

We've tackled the polarity question in a number of ways, but the primary way is to carry out unbiased forward genetic screens to look for genes that when mutated cause cells to lose their epithelial organization, in particular, their polarity. We've done this, if not to saturation, at least on a very large genome-wide scale, and it's brought us into all sorts of different areas of biology.

For example, at the outset of this project, we expected to get a number of genes involved in exocytosis—polarized delivery to the plasma membrane—because that was a model that had been proposed from mammalian cell culture work. But instead, we actually got a lot of mutants and genes that controlled the other side of the trafficking pathway, the endocytic side. An axiom of doing forward genetic screens is you need to follow your mutants. The animal has told you these genes are required for cell polarity, so now your challenge is to figure out how and why these genes are required.

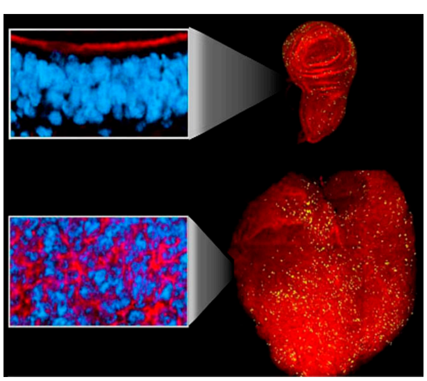

IMAGE COURTESY OF DAVID BILDER

Mutations in fly neoplastic tumor suppressor genes (bottom) cause organs to massively overgrow.

Does polarity affect cell proliferation in the fly?

It does. We found that mutations in the canonical endocytic regulators have the same mutant phenotype—not only in terms of apicobasal polarity but also in the control of cell proliferation and tumor suppression—as some of the proteins I'd worked on as a postdoc: Scribble, Lgl, and Discs Large. Those three genes have been studied for a long time. We know that their loss causes uncontrolled proliferation in the epithelial organs of the developing fly: they're fly tumor suppressors. We also know they encode scaffolding molecules. But although they're required for cell polarity in a number of different species and tissues, how these proteins actually influence the process of polarized trafficking that segregates the apical and basolateral plasma membranes—and also suppresses inappropriate organ growth—has been a mystery. And so, the fact that these scaffold tumor suppressors share phenotypes with canonical endocytic mutants suggests that the former group of proteins may actually control polarity by influencing aspects of the endocytic process. That's something we're actively trying to understand now.

You're now studying a different type of polarity in fly ovaries…

Yes. Epithelial morphogenesis is one of the areas we've been working on since I began my own lab. The follicle epithelium is an adult epithelium that surrounds the egg chamber and arises continuously from a set of somatic stem cells. We became interested in how the follicle epithelium is sculpted, both in terms of the shapes of the individual epithelial cells and the shape of the entire organ.

"Epithelia… are really the core tissue of animals."

As the initially round egg chamber grows, it stops growing isotropically and instead takes on an oval shape. When we began to look at how this actually happened using live imaging, we realized there was this completely unexpected morphogenetic movement where the entire egg chamber, driven by the follicle epithelium, was doing repeated rounds of revolution around its long axis. This rotation is actually required for the elongation of the egg; the model that we've put forward is that this rotation organizes a polarized basement membrane. This membrane wraps itself around the circumferential axis and restrains growth along that axis, leading to the acquisition of an oval egg shape.

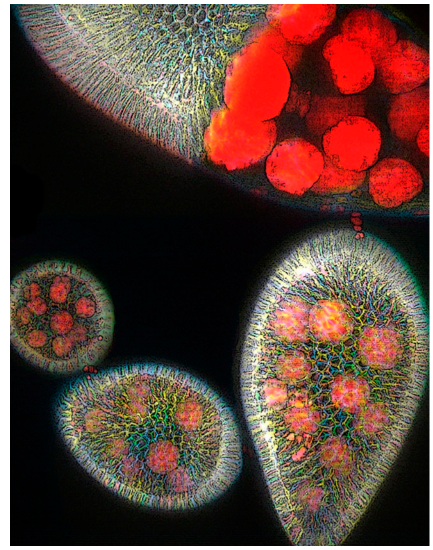

IMAGE COURTESY OF SAORI HAIGO

Overlay of three successive timepoints of rotating *Drosophila* follicles.

Follicle epithelium rotation happens in a planar polarized manner that doesn't depend on any of the familiar and conventional gene products that we know are involved in planar polarity in other fly tissues and in vertebrate tissues. So, it's a planar polarized organization, but it seems to be organized by a very distinct molecular pathway—and that's something we're trying to uncover now. It's going to be really fun!

1. Bilder, D., and N. Perrimon. 2000. *Nature*. 403:676–680.
2. Bilder, D., M. Li, and N. Perrimon. 2000. *Science*. 289:113–116.
3. Lu, H., and D. Bilder. 2005. *Nat. Cell Biol.* 7:1232–1239.
4. Classen, A.K., et al. 2009. *Nat. Genet.* 41:1150–1155.
5. Haigo, S.L., and D. Bilder. 2011. *Science*. 331:1071–1074.