Sally Horne-Badovinac: Taking a spin around morphogenesis

Horne-Badovinac tracks how coordinated cellular movements mold tissues.

It's hard to tell by the depth of her CV, but Sally Horne-Badovinac took a very unlikely path to become a scientist. She dropped out of her senior year of high school, leaving behind a "horrendously bad" transcript, to live near the beach in Puerto Rico and wait tables.

After five years of exploring, she reentered academics and found her stride when she walked into John Postlethwait's zebrafish laboratory at the University of Oregon in Eugene. Her stint there inspired her to pursue zebrafish gut morphogenesis in graduate school with Didier Stainier at the University of California, San Francisco (1). As a postdoc in David Bilder's group at the University of California, Berkeley, she became fascinated by a remarkable piece of developmental biology—the rotating, elongating egg chambers of the fruit fly ovary.

In 2008, she established her own laboratory at The University of Chicago to dissect this structure's peculiar planar polarity phenomenon in which the layer of epithelial follicle cells that surrounds the germ cells migrates as a sheet (2). Her group has shown that, during this migration, the kinase Misshapen (Msn) decreases integrin levels at the trailing edge of each cell (3), and that the basement membrane (BM) covering the entire egg chamber is secreted in a polarized manner along two axes (4). Last year, her lab found that the epithelial rotation was key to producing the near-perfect alignment of contractile actin bundles in the follicle cells, which are thought to form a "molecular corset" that squeezes the egg chamber from spherical to football shaped (5).

She recently shared with *JCB* why she is captivated by cells that cooperate to rearrange tissues and what makes a good scientific hero.

FRESH STARTS

How did you go from waiting tables to developmental biology graduate student?

I started taking night classes at Oregon Institute of Technology in tiny Klamath Falls. One day, I walked into the dean's office unannounced, told her my story, and asked if I could go to school there. She walked me over to the registrar's office and told them to admit me. So I was admitted into a four-year school without ever having taken the SAT.

I got straight As, and at the end of that year, I transferred to University of Oregon. But I didn't really have any sense of what it was like to be in a laboratory. The first person I went to talk to was John Postlethwait, and at the end of our conversation, he said, "Let's start your training next Friday."

It worked out spectacularly well because zebrafish was really up-and-coming as a model organism and the whole community had been founded in Eugene. That was when I got introduced to developmental biology and I was completely hooked.

> "It's an amazingly good investment for a postdoc to do a genetic screen."

In graduate school, how did you discover what causes the zebrafish gut to loop to the left of midline?

When I got to Didier's lab, I became immediately interested in morphogenesis and how cells work collectively to create the shape of an organ. Originally, I was trying to understand how the lumen forms in the primitive gut tube. I was looking at sections under the microscope when I happened to notice an asymmetric pattern of folds in the adjacent tissue of the lateral plate mesoderm. That pattern immediately suggested what the morphogenesis was going to be to push that gut tube over to the left.

I think that seeing this pattern was my most magical moment in science. I felt like the whole way it was going to work just clicked in my mind. I dragged everyone in the lab to the whiteboard and started drawing, saying, "It works like this!"

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Sally Horne-Badovinac

How did you end up working on* Drosophila *egg chambers?

As a postdoc with David Bilder, I wanted to work on an epithelial morphogenesis process that happens in egg chambers at a later stage than what we currently study. I did a forward genetic screen to try to identify required factors, but it quickly became obvious that those mutations were not coming out of the screen.

In the meantime, I started reading a lot of papers about oogenesis and this unusual planar polarity that occurs at the basal surface of the epithelium. And what *was* coming out of my screen were mutations that made the egg round instead of oblong. I thought this might actually be a much more rich and informative process to study.

Did you screen all 5,000 mutants by eye yourself?

I had a technician working with me full time who helped with all of the genetics, fly-pushing, dissecting the ovaries out of the flies, and mounting of slides. But yeah, every single slide passed under my eyes. I would sometimes sit at the microscope for 6–8 hours at a time and the entire screen took about a year and a half.

But it was worth it. We ended up with a marvelous collection of mutations, which is an ideal way to start a lab because you automatically have built-in projects for all of your first people. So I think it's an amazingly good investment for a postdoc to do a genetic screen.

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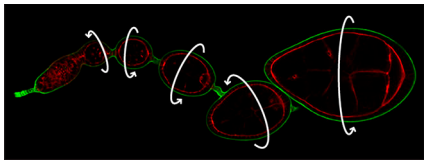
IMAGE COURTESY OF SALLY HORNE-BADOVINAC

Rotation-stage egg chambers labeled for actin (red) and the basement membrane marker collagen IV (green).

SPINNING EGGS

Who discovered that these egg chambers were rotating during their development?

A graduate student in the Bilder lab, Saori Haigo, began doing live imaging and discovered the rotational motion. After Saori's paper was published, someone dug very deep into the literature and found that a researcher at ETH Zurich named D.F. Went had documented this motion in the ovaries of a gall midge in the 1970s with a 16 mm camera.

I never cease being surprised—*Drosophila* oogenesis has been intensively studied for decades and no one knew this was happening. You never look at a female fly the same way if you think about these little egg chambers going around in her ovaries.

Why study egg chambers?

Everything that we're studying is happening on the outer surface of this living, intact, organ-like structure. We can visualize these events with exquisite clarity, both what's happening with the migrating cells and with the extracellular matrix.

What's really useful for us right now is the ability to study collective cell migration and BM dynamics in a way that hasn't really been done before. Collective cell migration happens over and over during development, with cells migrating in cohorts or sheets.

To migrate collectively, they're using the same basic cell migration machinery. But what gets added on top of that is the ability of each cell to influence the migratory behavior of its neighbors. We're interested in how these cells communicate with one another to achieve this efficient group dynamic.

In contrast, you found that Msn acts in a cell-autonomous way within the migrating sheet. Why is that key?

At first, people had speculated that the planar organization of actin bundles at the basal surface could arise through a system where a signal propagates from one cell to the next across the tissue. That could be happening from cell to cell, or from cell to ECM to cell.

Knowing that Msn was a kinase, it seemed reasonable that it might be part of such a signaling system. But instead, we found out it's just a fundamental protein that's required for an individual cell to migrate. We had to start thinking about the system really differently—how does something required in each individual cell to migrate somehow lead to this planar organization of the entire tissue?

It made us realize that it was the migratory behavior of the cells that was probably bringing those actin bundles into alignment across the tissue.

SUPPORTING ACTORS

Why switch gears to look at secretion of BM proteins?

This was a total surprise and why doing forward genetics is so much fun. The first mutated gene we identified in my lab from that round egg screen encoded an enzyme required in the endoplasmic reticulum for the folding of collagen IV—an ingredient in the BM. One of my first graduate students, David Lerner, was fascinated by these cells that had collagen trapped inside.

We eventually realized that all of this BM secretion machinery was not only polarized along the apical-basal axis, but it was also polarized along the planar axis, toward the trailing edge of the migrating cells. We still don't know whether that is a significant finding for the biology. But it was a really striking observation of how localized all of this machinery was, at both the cell and tissue level.

Did that give your developmental biology lab a cell biology twist?

Yes, I've been so influenced by being in a cell biology department. Now I'm taken with this question of how you synthesize these very large matrix proteins, get them through the secretory pathway, and ultimately, how you can use that secretory machinery to modulate BM structure during development. I find these really hardcore protein secretion questions so satisfying. Honestly, I love it and I didn't know that I would!

> "The migratory behavior of the cells was probably bringing those actin bundles into alignment."

You acknowledge your husband, Nick Badovinac, for illustrations in some of your papers—is he an artist?

No, but he has artistic tendencies. He has always been my absolute biggest supporter and he likes being involved in the lab. When I wrote a review on egg chamber morphogenesis, he decided he wanted to teach himself how to use computer drawing packages, and he's been doing illustrations for most of my work ever since. It's great because a simple illustration can often convey the biology much more clearly and can help orient an audience to look at the real data in tissues, too.

Do you have a scientific hero?

My graduate advisor, Didier Stainier, has been and continues to be a wonderful mentor to me. What I really admire about him is that he takes a very rigorous approach to the science that he does *and* he is open to going in new directions.

The number of topics that his lab has made significant contributions to over the years is almost dizzying. He gives his people an amazing amount of freedom to explore their own creativity and I think that's really valuable.

1. Horne-Badovinac, S., M. Rebagliati, and D.Y.R. Stainier. 2003. *Science*. 302:662–665.
2. Cetera, M., and S. Horne-Badovinac. 2015. *Curr. Opin. Genet. Dev.* 32:10–15.
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4. Lerner, D.W., et al. 2013. *Dev. Cell*. 24:159–168.
5. Cetera, M., et al. 2014. *Nat. Commun.* 5:5511.


PHOTO COURTESY OF SALLY HORNE-BADOVINAC

Horne-Badovinac with husband, Nick, adventuring in the Black Rock Desert.