People & Ideas

Barry Thompson: The delicate choreography in growing epithelia

Thompson is studying how epithelial polarity informs tissue growth and form.

Cells use information about their position and orientation within a tissue to help guide their behavior as tissues are constructed. To learn more about how cells cooperate to build epithelial tissues, we called Barry Thompson at his laboratory at Cancer Research UK's London Research Institute.

Thompson is studying how apical/basal (1) and planar (2) polarity are established and how cells use this information to orient their behavior during tissue development (3). Questions like these have fascinated him since the start of his research career (4, 5). Like a good piece of art or theatre, there are always new layers of meaning to be uncovered.

A NEW ROLE

When did you first fall in love with developmental biology?

I'm originally from Australia. I grew up there and did my undergraduate studies there, and I think a lot of my love of science came from learning about it in school and University. But in Australia at that time there was very little emphasis on developmental biology, so I was quite new to the subject when I moved to Cambridge University for graduate school. It was really thrilling to learn about how organisms develop, and the Laboratory of Molecular Biology in Cambridge was a fantastic place to do that.

I did my graduate degree with Mariann Bienz, an expert on Wingless/Wnt signalling. We were doing genetic screens in *Drosophila*, so I learned about the awesome power of *Drosophila* genetics for gene discovery and for rigorously testing hypotheses. I was also very inspired by other people in the institute, like Peter Lawrence, who wrote the book *The Making of a Fly*. He encouraged me to think about big questions in developmental biology, such as: How is the size and shape of a tissue determined?

You also did your postdoc in a very strong developmental biology lab…

That's right, with Steve Cohen at EMBL in Heidelberg. I wanted to work on questions of tissue growth and form, so I was very excited to join Steve's lab. He had done famous work on how Wingless/Wnt and Dpp/BMP signals act as morphogens to provide positional information and determine patterns of cell fates. Steve's lab then switched to looking for mechanisms that control tissue growth, so when I joined the lab I did some work on a new signaling pathway—the Hippo pathway.

The Hippo pathway controls tissue growth, and mutations in the pathway cause overgrowths—large tumors—because they lead to the activation of the transcription factor Yorkie (YAP/TAZ in mammals). But how Yorkie causes tissue overgrowth wasn't known. Meanwhile, Steve's lab had found a microRNA called *bantam*, which, when overexpressed, also caused large, overgrown tissues. I showed that Yorkie activates *bantam* to promote growth. So the Hippo pathway normally represses Yorkie activity and the expression of *bantam*, and that's one way in which it restricts tissue growth.

> "I wanted to work on questions of tissue growth and form."

I understand that you spent some time in Austria after your postdoc...

Yes. After being in Steve's lab, I went to Barry Dickson's lab in the Institute of Molecular Pathology, in Vienna, to take advantage of the new in vivo RNAi screening facility they had established. I wanted to use the in vivo RNAi system to screen for new regulators of tissue growth and form. Then I took the genes that I'd found and started my lab in London.

SETTING THE STAGE

What drew you to the London Research Institute?

It's one of the best-funded and most exciting institutes in Europe. It has core funding from Cancer Research UK, so we don't have to write grants, which is a huge blessing. Cancer Research UK also provides scholarships for students and fellowships for postdocs. Plus, my colleagues at the LRI are just first-class, really outstanding scientists. I aspire to be able to reach their high level at some point in my career. London also feels like it's at the center of the scientific world.

PHOTO COURTESY OF BARRY THOMPSON

Barry Thompson

London itself is also a very exciting city. Anything you'd like to do, there's always something happening. You have to be the kind of person who has the energy to enjoy a big city, but it's wonderful if you can take advantage of it. Personally, I love going to all the amazing restaurants, pubs, theatres, music festivals, and art galleries. My sister works at the Tate gallery, so I very luckily get to preview the exhibitions.

Are you still following up your Vienna screen?

Definitely. These in vivo RNAi screens are hard work, and it takes time to sort the wheat from the chaff. The first few years we spent a lot of time chasing phenotypes that turned out to be artifacts. We found out the hard way how important it is to confirm

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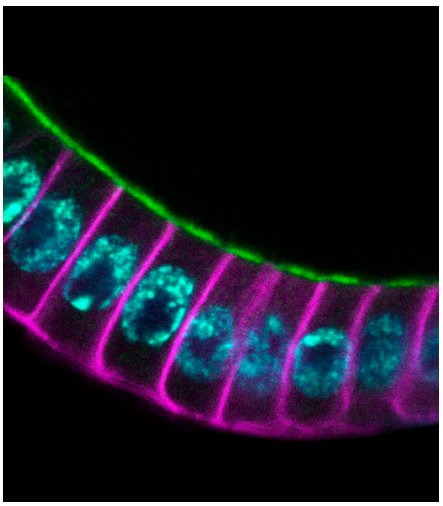

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aPKC (green) is found at the apical surface, whereas Lgl (purple) is confined to the basolateral domain in the fly wing epithelium. Nuclei are shown in blue.

all phenotypes with a second, independent, RNAi line. That was a big lesson for us. Since then we've repeated the entire screen with a second library to make sure that everything we found is real. A lot of the work in my lab now stems from these screens.

We are also using live imaging as a starting point for many projects. One project we're working on is how apical/basal polarity is propagated through the cell cycle. Most studies of the cell cycle have been done in cell culture, so we understand things like how the nucleus replicates and how the cytoplasm is divided. But we don't understand how a polarized cell rounds up and divides while still managing to transmit its polarity to its daughter cells.

We've also been using live imaging to follow how cell divisions are oriented within the plane of the epithelium. It turns out a system of planar cell polarity—the Dachsous-Fat-Dachs system—is important for orienting divisions and thus helping to organize the normal shape of the tissue.

THE MAIN EXHIBIT

Are you still working on Hippo signaling?

Yes, we're very much still working on this—often in collaboration with my colleague Nic Tapon. There's a big mystery about Hippo signaling: we know that the pathway controls growth, but we don't know very well what its normal functions are in tissues. It's a tumor suppressor, so, when you inactivate the pathway, you get tumors. But how is it employed during normal development? That is very unclear.

What we and others have now found is that many components of the Hippo pathway are actually involved in cell polarity, so that signaling to the nucleus may be elicited when cells encounter problems with their polarization. For example, when you have a wound, the polarity of cells surrounding the wound is altered, and those cells respond to that by signaling to the nucleus through the Hippo pathway effector Yorkie. That then induces a proliferative response to close the wound. So there we have one physiological role for this pathway in responding to wounds—but there may be others.

What components of cell polarity pathways tie into Hippo signaling?

We've been working a lot on Crumbs, which is an apical polarity determinant. Crumbs interacts with the Expanded-Merlin-Kibra complex, which we've shown helps to polarize Crumbs to the apical domain as part of a positive feedback loop. So the upstream Hippo pathway components are actually polarity determinants. When you lose Crumbs, Expanded, Merlin, or Kibra (or combinations of them), you get signaling to the nucleus via Yorkie.

> "We're continuing to explore all the interesting hits we find in our screens."

On the planar polarity side of things, the Dachsous-Fat-Dachs system not only orients cell divisions and tissue shape but also signals through the Hippo pathway to regulate tissue growth. So there's this really fascinating connection between both apical/basal and planar cell polarity and signaling to the nucleus through Yorkie.

Where are you going with these projects now?

We're following up our work on Kibra, Expanded, and Merlin and how they regulate apical/basal polarity. We don't fully understand how they manage to stabilize Crumbs and keep it polarized at the apical surface—we know they're essential, but we don't know exactly what their role is. We are also following up our work on planar polarity. We've done genetic screens that have identified new components required for the planar polarization of Dachs and hence for controlling tissue shape. We've also identified other components of the Hippo pathway that regulate Yorkie in the nucleus to control tissue size. Finally, we're continuing to explore all the interesting hits we find in our screens.

Your lab is only five years old. Do you still get to do bench work?

I did quite a lot in the first two years. Now I do less, because I find that group leaders can't really manage a whole project on their own. They keep getting distracted by meetings and things like this. I still enjoy doing technical work, though, to help out my students when they have a lot of dissections or a lot of tedious, repetitive work to do. Students tend to be impressed by the fact that you're willing to roll up your sleeves and actually do some hard work for them.

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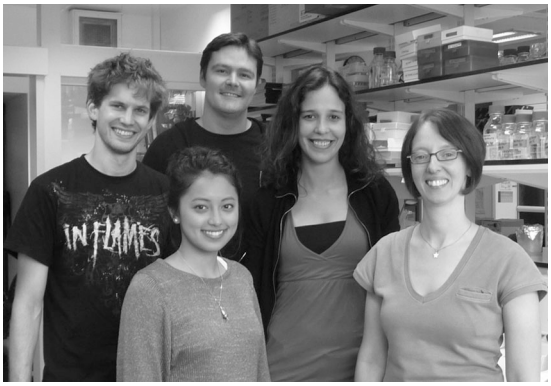

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Thompson's Epithelial Biology Laboratory at the LRI.