People & Ideas

Suzanne Eaton: The beautiful logic of development

Eaton studies tissue patterning in flies and mammals.

PHOTO COURTESY OF KOSTAS MARGITUDIS, MPICBG

Suzanne Eaton

During development, cells tune their gene expression and determine their position within a growing tissue by referencing the local concentration of certain secreted proteins called morphogens. Morphogens are often present in a concentration gradient across tissues, but, until fairly recently, it wasn't clear how such gradients are established or how morphogens reach their target cells.

Suzanne Eaton has accumulated an important body of research exploring how morphogens direct global tissue patterning (1–3). Recently, she's begun looking at how mechanical interactions with neighboring cells and tissues dictate tissue shape and cellular orientation within tissues (4). And, just as morphogen and mechanical signals converge to drive tissue development, Eaton is also seeing her research flow in new directions (5), as we learned when we called her recently at her lab at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany.

IT IS LOGICAL

Did you have role models, growing up?

My father was always a real inspiration to me. He was an electrical engineer, and he taught for a little while at UC Berkeley after he got his PhD, before being recruited to the research division at IBM. He was interested in everything, and he was a great scientist.

My other role model… it's embarrassing, but I would say that was Mr. Spock from *Star Trek*. I think my favorite thing that Spock ever said was in response to another officer, who said he "felt" something was wrong. The officer said, "It was just an emotional feeling, Mr. Spock. I don't expect you to understand it." And Spock said, "I note it, without understanding it." The lesson I drew from that is that one can take a rational approach to incomprehensible things. If you accept them, then you can think about what they might mean.

> "One can take a rational approach to incomprehensible things."

Besides Spock's words, what have you carried with you into adulthood?

I started playing the piano when I was eight, and I had lessons all through university. I thought of making a career of it, but of course that's a really, really difficult life. But I love playing the piano. My husband plays the flute, so we play together, and sometimes I play with other people, too. My sons also both love music—one plays piano, and the other plays guitar.

Did you take a logical approach to your career?

Actually, early on I was interested in many things and had a hard time deciding between them. In college I took a lot of math, music, literature, and biology. Then, after I graduated, I took a year off to figure out which of those things I was most interested in. I worked as a technician in a hospital by day and as a cocktail waitress at night, and I gave it some thought.

I realized I didn't want to be a cocktail waitress. I worked in a pretty rough bar. [Laughs] After that year, I decided I would apply to graduate school in biology.

METAMORPHOSIS

You joined Kathryn Calame's lab at UCLA…

Yes. I worked on transcriptional control of the immunoglobulin heavy chain genes. By the end of my PhD, I became very interested in how transcriptional control was used to make cells different from each other and got very interested in development. So, for my postdoc, I just leapt to a different field. I started working in *Drosophila* with Tom Kornberg at UCSF, trying to understand how cells separate into different lineage compartments and how organizer regions develop at the boundaries between the lineage compartments.

Then I moved to the EMBL in Heidelberg to do a second postdoc with Kai Simons. There, I was really focused on using *Drosophila* as a system to answer cell biological questions, such as how the actin cytoskeleton contributes to epithelial polarization. I was also interested in lipids and membrane biology. My time in Kai's lab was a turning point for me, because I realized what a powerful thing it is to take two supposedly separate fields—cell biology and developmental biology—and wear both hats at the same time.

At that point, Kai was involved in organizing this new Max Planck Institute in Dresden, and I moved there. This has been fantastic because the institute is really designed to exploit interfaces between groups positioned in development, cell biology, and biophysics. So, we're now trying to think more about tissue mechanics and how they affect the key questions of developmental biology, such as how tissues develop with particular sizes, shapes, and patterns.

Part of that problem concerns how morphogens travel through tissues…

Wingless and Wnts are linked to palmitate, and Hedgehog is linked to both palmitate and cholesterol, which means these morphogens need special mechanisms to be released from cell membranes. I thought this was an interesting cell biological problem: How do these lipidated proteins spread through tissues? Initially, we thought morphogens

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might be incorporated into some kind of extracellular vesicle, such as an exosome. But we showed that Hedgehog is, in fact, incorporated into lipoprotein particles rather than exosomes. We discovered that Hedgehog can associate with lipoproteins just as well as it can with cell membranes, so lipoproteins can help Hedgehog get off of membranes and move over long distances.

But these lipoproteins aren't just vehicles; they actually contain signaling lipids that are important for suppressing signaling by the Hedgehog receptor when Hedgehog isn't there. We think the way that Hedgehog actually signals is by controlling what cells do with the signaling lipids that are in lipoproteins.

There are also other mechanisms that can release Hedgehog from cells. We recently showed, both in mammalian and *Drosophila* systems, that Hedgehog proteins can be released without any lipids on them at all. We found that the two forms of Hedgehog actually synergize with each other in signaling.

How do morphogen gradients form?

We've investigated that question with regard to Wingless and how it spreads through the wing imaginal disc of flies. We found that, when you block endocytosis, Wingless accumulates outside the cells and spreads much, much further. In fact, there's no gradient left. What this tells us is that, to form a gradient, you have to have a source and you have to have a sink. The sink is provided by the tissues through which Wingless is moving, and it's a consequence of cells endocytosing Wingless protein.

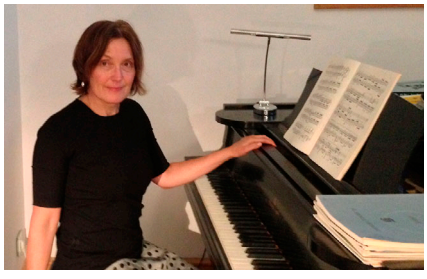

PHOTO COURTESY OF LUKE HYMAN

Eaton's son snapped this image of Suzanne at her piano.

Another thing we noticed was that, when we blocked endocytosis, Wingless accumulated on the apical and basal sides but not the lateral sides of the cell. So endocytosis seemed to be restricted to the apical or the basal surface. Interestingly, there's a glypican called Dally-like that causes Wingless to spread further and to accumulate on the basolateral membrane. We hypothesized that Dally-like allows Wingless to travel along lateral surfaces, where it's immune from internalization.

It's interesting that these glypicans seem to have roles, at least in the imaginal disc, in the spread of Wingless, Hedgehog, and Decapentaplegic, the fly homologue of BMP. In the case of Hedgehog, what we see is that the glypicans are important for the association of lipoproteins with cells.

> "This could be important for signaling at extremely long distances, even between organs."

THE FINAL FRONTIER

Where do the lipoproteins come from?

They come from the systemic circulation; Hedgehog-producing cells are not themselves making lipoproteins. In the fly, lipoproteins come from the fat body and travel through the hemolymph to reach the wing imaginal disc, where Hedgehog-producing disc cells load Hedgehog onto those lipoproteins. We don't know how this works, but it's something we're very interested in understanding.

The fact that disc cells don't make the lipoproteins themselves means that the signaling lipids on lipoproteins also come from the systemic circulation. This opens up the interesting possibility that this is a way in which global lipid metabolism and nutrition can affect local signaling in a developing tissue. We've gotten very interested in lipid metabolism in flies, in identifying these lipids and finding out where they come from.

On the other hand, we also noted that there is a systemically circulating form of Hedgehog in *Drosophila*—and in human and mouse plasma—that is associated with lipoproteins. This could be important for signaling at extremely long distances, even between organs. So one of the areas we're working really hard on in the lab now is understanding what that's for, where it comes from, and where it goes.

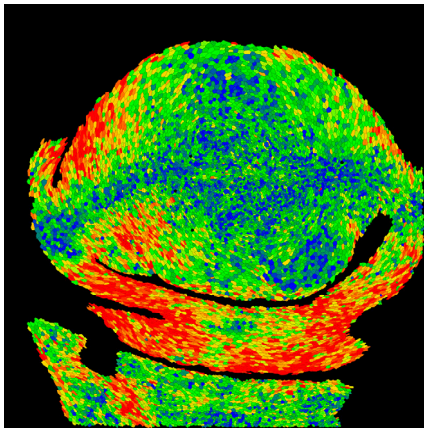

IMAGE COURTESY OF ANDREAS SAGNER

The most elongated cells in a *Drosophila* wing imaginal disc are labeled red, whereas the most isotropic cells are colored blue. The pattern of cell elongation correlates with the major signaling centers at the compartment boundaries of the disc.

You mentioned that you're looking into tissue mechanics, as well…

We have a long-standing collaboration with the group of Frank Jülicher, who's also here in Dresden, trying to develop models for the mechanical properties of cells and epithelia. We'd like to use these models to understand how tissue mechanics control the directions that cells grow—or whether they grow at all—and the direction in which cells rearrange. We now have a really great system to study how stresses in epithelial tissue can orient cell divisions and cell rearrangements and can induce tissue flows that in turn can affect things such as planar cell polarity.

We want to understand the link between the morphogen gradients, the patterns of morphogen signaling, and the local cell mechanical properties that specify these flow and growth patterns. In the end, I'm hoping that all these areas of my lab—morphogen gradient formation, tissue mechanics, and epithelial remodeling—will come together.

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