Buzz Baum: The art of cell shape

Baum studies how cell shape affects tissue development, homeostasis, and cancer.

The core genes that regulate cell shape are few in number but highly flexible in application. This is dramatically illustrated in multicellular animals where, by repurposing these few tools, cells from different tissues assume startlingly distinct appearances.

To do this, animal cells must have strong individual preferences for their own shape, says Buzz Baum from University College London. Individual cells battle to maintain their shape by pushing and pulling against their neighbors. In the process they create order as an emergent phenomenon, giving rise to the structure of complex tissues. Through his work, Baum has explored how cells arrive at their preferred shapes (1–4) and how this affects processes such as the development and homeostasis of epithelial sheets (5) and the division of cancer cells (4). We called him at his office to learn more.

THE ART OF SCIENCE

What was your first exposure to science?

I learned basically everything at home by talking with my brothers and my parents over dinner. My father was a pediatrician and my mom is an artist, and they really taught us all to think by chatting with us at the dinner table. I'm the eldest of four boys. Jake and I went into science, and my other two brothers went into art, although my brother Josh does quite science-y art.

My cousin David Baum was also a big influence on me. He's an evolutionary biologist and studied biology at Oxford, where we lived when I was growing up. He used to come around a lot, and he's one of the reasons I went into research. I'm actually collaborating with him now on a project about the evolutionary origin of eukaryotes.

As a child I was obsessed with nature. I loved bird watching and observing nature, drawing what I saw. I always wanted to do either science or art.

You obviously took the science path…

I studied biochemistry at university, which was a terrible choice because we didn't do any evolution or biology. [Laughs] We did mostly organic physical chemistry and didn't get into much biology until the end. For me that was sad, because that was what I loved. On the other hand, at school I found biology very boring because it involved things like counting worms. It was very ecological and very soft. It wasn't until university, when I heard Paul Nurse speak in my third-year biochemistry course, that I realized, "That's science. That's what I'd like to do."

I got my chance in my fourth year when I applied to do my undergraduate degree project in Paul's lab. I was lucky to be one of the people he chose to work with him, and then I applied to stay in his lab for my PhD, where I studied how G1/S phase transcription is coupled to mitotic exit. But I was always envious of the people in Paul's lab who got to work on cell shape because I felt their projects were so much cooler than mine. [Laughs] So for my postdoc I switched to studying cell shape.

> "My core interest has been in trying to think like a cell."

The thing I enjoyed most about my graduate work was how we learned to love yeast as an organism. We were always asking questions like, "What is the cell trying to do? Why?" And ever since I think my core interest has been in trying to think like a cell. Cells are purposeful things. They have preferences and desires. I think everyone in Paul's lab got a good feel for that.

BASIC SHAPES

So you joined Norbert Perrimon's lab specifically to study cell shape…

Yes. Norbert's lab had developed clonal technology that allowed one to study one or two mutant cells in the context of a normal multicellular tissue. David Bilder and I used these tools to apply genetics to cell biological problems in fly tissues. Later, Amy Kiger joined the lab, and we worked together to develop a high-throughput RNAi screening approach to look at genes affecting cell shape in fly cell culture. Then, after I had returned to the UK to start my own lab, Norbert allowed me to come back to finish the screen. For me this was amazing because it was what I had always dreamed of doing: surveying the whole genome for factors that dictate cell shape and size. But very few things came out that weren't already known from yeast. That's because all eukaryotes use the same pathways, with just a few differences. And that was the beginning and the end of my interest in RNAi screening because very quickly it became clear to me that we would soon reach the limit of what simple loss-of-function genetics could tell us about cell shape.

PHOTO COURTESY OF BUZZ BAUM

Buzz Baum

What is your approach to studying cell shape then?

You can't understand how cell shape is generated by just drawing a network with arrows connecting a bunch of genes together. Cell shape is also determined by physical forces and constraints, so these

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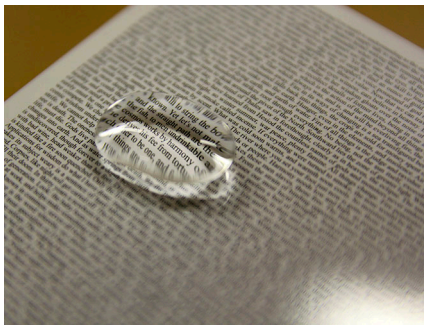
must also be considered. The cool thing about working with animal cells is that they're in a constant dialogue with their environment: with the extracellular matrix (ECM), with their neighbors, or with the dish or microfabricated surface they're growing on. A cell's shape is the result of that dialogue.

Often cells growing on a 2D substrate will adopt a range of different shapes. They're kind of freaking out because they have no constraints. But we noticed that single cells growing on strips of ECM look quite different. They spread the same amount regardless of whether they are growing on fat lines or thin lines, even when this means their height will differ. How far they spread is regulated by microtubules. Their microtubules become aligned as they spread and limit the cell's length. So, although it's a dialogue, under the right conditions one can see that there are limits to the shapes cells will adopt.

So this is some inherent property of the cell…

People often think animal cells can be any shape because they don't have a cell wall and on a 2D substrate things look a bit of a mess. But actually I think cells have very strong opinions about their preferred shape. That's why tissues are homeostatic, because every cell attempts to keep to its preferred shape.



ART BY JOSHUA BAUM; IMAGE COURTESY OF KATHY HINDE

Baum admires his brother's scientific approach to watching nature in this art piece entitled "reading Heraclitus." Watch the video: http://youtu.be/EhyeeTmYp9Q

STRONG PREFERENCES

Can you give examples of how this preferred shape affects tissue homeostasis?

One thing we've found in epithelial sheets is that if cells mistakenly divide asymmetrically—so that one daughter cell with a big apex ends up sitting next to a sister cell with a small apex—both cells will rapidly restore their normal apical area. This suggests they have a preferred area.

But sometimes it's not possible to restore the preferred shape. For example, cells will extrude from a crowded epithelial sheet in a process called delamination. In this case it's very hard to know what's wrong. What does it mean for a cell to feel crowded? Are the cells experiencing mechanical stress and activating a signaling cascade that drives delamination? Or maybe they are simply too long along one axis and this deviation from their preferred shape makes them unhappy, so they wriggle and there's a chance they'll pop out of the epithelial sheet.

> "Cells have very strong opinions about their preferred shape."

Once it's out, the delaminated epithelial cell has no junctions or neighbors. That's not allowed, so the cell dies. But if the cell expresses an oncogene that rescues it from death and enables it to grow and divide, then you're in trouble, because that's the beginning of cancer. I think that's interesting because, in this scenario, the cell did not undergo any kind of epithelial-to-mesenchymal transition to become invasive; it just got pushed out of the epithelial sheet. This also suggests that there may be a direct link between hyperplasia (tissue overgrowth) and metastasis (malignant cancer).

What other connections have you found between cell shape and cancer?

The work we've done recently makes us think that it is really important to look at how cell division differs in cancer and noncancer cells. For a cancer cell, it doesn't matter whether it's on a dish or in suspension; it can ignore its environment and divide wherever. However, cancer cells have problems dividing because they're full of extra chromosomes and centrosomes and have other defects. So to generate the space in which to assemble a spindle to divide they need to be very good at rounding. On the other hand, a normal cell will divide very quickly and efficiently under the right conditions, even when quite flat, but fail to divide as soon as you remove it from those conditions. Instead it arrests and dies.

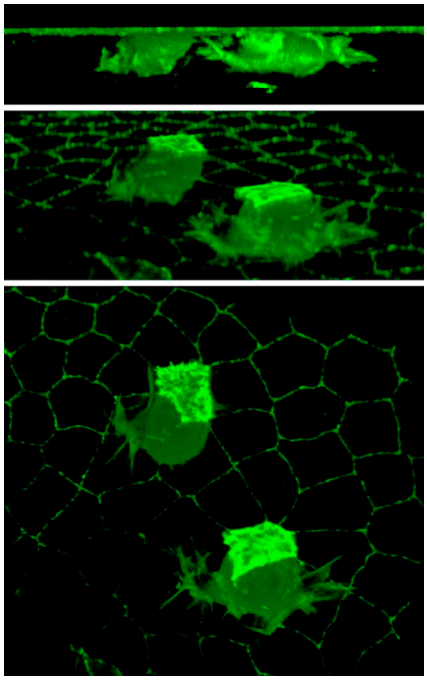


IMAGE COURTESY OF GINGER HUNTER

Single-labeled epithelial cells assume surprising shapes in a developing tissue (the fly notum).

To me, this goes to the heart of what it means to be a cancer cell. It's a profound difference. So we've been asking what enables cancer cells to divide regardless? Working with Matthieu Piel's team we have found that not only are cancer cells better at rounding than normal cells, but they actually need to be round; if you stop them rounding, they fail to divide. By rounding, a cancer cell makes room for itself to divide by pushing other cells out of the way. Cancer cells may need specific molecular machinery that allows them to do this, and someday we hope it will be possible to use that as a therapeutic target.

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