# People & Ideas

## Jody Rosenblatt: To extrude apically or basally, that is the question

Rosenblatt discovered epithelial cell extrusion and studies its regulation and impact.

PHOTO COURTESY OF MICHAEL REDD

**Jody Rosenblatt**

The primary function of epithelia is to serve as a barrier between a tissue and the surrounding environment. To preserve the integrity of the epithelial sheet, therefore, a dying epithelial cell is evicted from the monolayer by a special process called extrusion. But epithelial extrusion has major implications for phenomena beyond epithelial barrier function, as Jody Rosenblatt explained to us when we called her at her lab at the University of Utah's Huntsman Cancer Institute.

Rosenblatt first discovered epithelial extrusion as a postdoc at University College London (1). Now her lab is hard at work dissecting both the mechanisms that guide extrusion (2–4) and its biological significance (5), finding potential connections to cancer and to organismal development.

### A DIFFICULT CHOICE

***Had you worked in a lab at all before entering graduate school?***

Yes. In my sophomore year of college at Berkeley, I was going crazy because I had no idea what I wanted to do, and I felt like I was wasting $4,000 a year on tuition. Now, of course, I'm planning for my two daughters to go to college and it costs ten times as much, so it feels like less of a big deal. [Laughs] But at the time I thought I had better take some time off from school and think about what I wanted to do. I went to Ireland, worked on a goat farm, waitressed, and did things like that for about nine months.

> "I kept getting distracted by all these little wounds in the background."

When I came back, a friend of my family helped me find a job in a lab in Utah to finish out the rest of the year. I worked in Ellie Ehrenfeld's lab here at the University of Utah, and I realized, "Wow. Okay. This is what I'm doing from now on."

***You had several publications even before your PhD…***

That's because I was slow to get going with my graduate degree. When I got out of Berkeley, I tried working in industry for a year. I quickly realized that was not for me, so one day I just quit and decided to go back into academia.

I applied to graduate schools, but I didn't get in to where I wanted to go. I knew I wanted to work on the cell cycle, though, and a friend of mine suggested I approach Dave Morgan, who was just starting his lab studying the cell cycle at the University of California, San Francisco. So I did, and Dave was fantastic.

While I was there, I looked at different homologues of Cdk1. We cloned Cdk2 and got the crystal structure of it, and it was really fun to be working in the cell cycle field because new things were being discovered almost every week.

***You probably had your pick of graduate schools after that…***

Yes, but I wanted to stay in San Francisco because my husband was midway through his PhD program at UCSF. We had met in high school in Utah, and he went to graduate school at UCSF so we could be together while I was at Berkeley.

At the same time, I wanted to switch fields because, although I liked working on cell cycle, it was a very competitive field. I knew that if I was going to have kids I wasn't going to want to work crazy shifts in the lab. Tim Mitchison's lab was really attractive to me because when I was a technician I'd watched all his talks, and somehow his work just clicked with me.

### DISTRACTED DISCOVERY

***You were a postdoc in England when you discovered epithelial extrusion…***

That discovery happened because I couldn't focus very well. [Laughs] I'd joined Paul Martin's lab to study wound healing. But when I looked at my epithelial cultures, I kept getting distracted by all these little wounds in the background, which I hadn't caused. These were extrusions of cells that were dying, but at first I had no idea what I was looking at. I didn't know very much about apoptosis.

Fortunately, Martin Raff knew all about apoptosis, and he was really interested in the extrusion phenomenon. So I ended up working closely with him and with Louise Cramer, a friend of mine who was a postdoc in Tim Mitchison's lab when I was a student. When my postdoctoral fellowship started running out, I applied for some project grants so I could stay on to develop my work. That's why it took awhile before I got around to starting my own lab.

Another thing that contributed to the delay was this other discovery I made showing that actin and myosin help form the mitotic spindle. I'm really glad that I followed up on that, but, on the other hand, it distracted me from focusing on extrusion for a while.

***So when did you return to the States?***

We moved back to Salt Lake City in 2005, which is funny because I grew up here and when I left I really never thought I would end up back here again. But when I was looking for jobs, I realized this wasn't such a bad place. The University of Utah was also very proactive in offering something for both me and my husband. And part of the draw was that he works on zebrafish and there's a huge zebrafish community here.

Text and Interview by Caitlin Sedwick
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I didn't work on zebrafish until we came here, but then I started looking at it and thinking, "This is an amazing epithelium. Why haven't we been using this to study the cell biology of epithelia?" Now my postdoc George Eisenhoffer is putting together a whole toolbox to study the in vivo fate of extruded cells.

## A FATEFUL DECISION

***You first described extrusion toward the apical surface of the epithelial sheet…***

That's because it just pops right to your eye. Cells can also extrude basally, but basal extrusion's a lot more subtle. We were looking at it for a long time before we realized what we were seeing.

We still don't have a very good handle on what causes a cell to basally extrude, but we think that basal extrusion is a default that happens if the right signaling does not happen or if all the mechanisms are not in place. For example, we know that apical extrusion requires a lipid signal, sphingosine-1-phosphate, which goes through a G protein–coupled receptor and seems to get taken up in the surrounding cells. If we block this pathway, we block apical extrusion, but we can still see basal extrusion.

From what we can see, it seems like basal extrusion has major consequences. When cells extrude apically, they soon die because they lose the support of the surrounding cells. But if a cell extrudes basally, then even if it dies it leaves a corpse that has to be cleaned up. And if it doesn't die then it could invade the tissue beneath the epithelium, a scenario that's pretty bad in epithelial cancers. We've made a number of oncogenic mutations, and almost all of them make cells go basally instead of apically. Interestingly, we've also noticed that many pancreatic cancers do not express sphingosine-1-phosphate receptor 2. That might be one reason why these cancers can be so nasty.

> "We think that basal extrusion is a default."

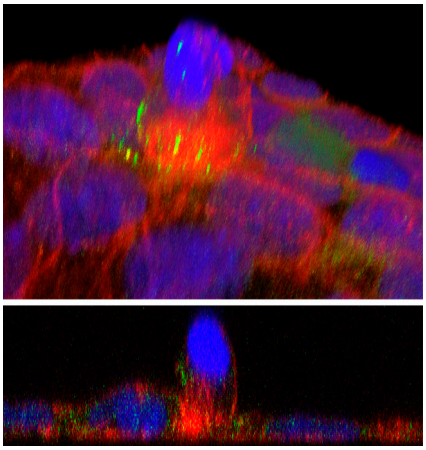
***How do cells get extruded from epithelia?***

We used to say we thought cells are pushed out of the epithelial layer by a contractile actomyosin sphincter ring that forms in the surrounding cells. I still think that's partially true, but now we're seeing many little nuances that are making it seem like that idea is a bit too simplistic. We're looking back at all our old movies and rethinking our model right now.

***You've shown that extrusion is important in controlling crowding…***

Hitting cells with UV kills them and also causes them to extrude from the epithelial sheet, so for a long time this is what we were doing to study extrusion. But then I started wondering how cells normally turn over, so we started looking at how cells die within untreated epithelia. We saw that dying cells do extrude, but many of the extruding cells are still alive and haven't yet started dying. We also found that the regions where this live-cell extrusion was happening were the areas where cells were most crowded. In fact, we showed that, if we plate cells on a stretched silicon matrix and then let the matrix relax so that the cells become more crowded, this triggers extrusion.

That was exciting, but it also made us wonder: If crowding can cause extrusion, can stretching cause division? And the data we have now indicate that it does. It's pretty crazy stuff, but it's great fun. Actually, that feeling is something I try to impress on the kids who visit my lab as part of my outreach efforts. I think it's important to get the public excited about science, especially when the economy's bad. We need to show people that it's important to fund basic science so that we can keep hope alive for the next generation—of children and of scientists.



IMAGES COURTESY OF YAPENG GU

**A cell being apically extruded from an epithelial sheet (top: 3D projection; bottom: XY plane view).**

PHOTO COURTESY OF HUNTSMAN CANCER INSTITUTE

**Rosenblatt enjoys sharing her research passion with the public.**

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