

Jeremy Nance: Charting gastrulation's gyrations

Nance surveys the cell movements that orchestrate early embryogenesis.

As the son of a chemistry professor and a mom who sent him to bird-watching camp to “get me out of the house,” Jeremy Nance naturally gravitated toward biology. But it wasn't until graduate school at the University of Arizona that Nance discovered his penchant for developmental biology and an admiration for the *C. elegans* nematode, which develops from one cell to 550 in the space of 12 hours.

One of the earliest steps of embryogenesis is gastrulation, in which the embryo reorganizes itself into three cell layers. An unlikely parade performance inspired him to study this process in *C. elegans* as a postdoc with James Priess at the Fred Hutchinson Cancer Research Center in Seattle. In 2004, Nance set up his own group at the Skirball Institute of Biomolecular Medicine at New York University School of Medicine to continue investigating gastrulation's regulation and the cell polarization events that set gastrulation up for success (1).

Since then, Nance's group has identified a RhoGAP called PAC-1 that is responsible for establishing radial cell polarity in the earliest stages of embryogenesis (2). They also discovered two key roles for E-cadherin in early development: an active role in defining the cell-cell contacts that cue up polarity (3) and providing the glue that lets primordial germ cells hitch a ride with endodermal cells during gastrulation (4). His lab also repurposed the cell's ubiquitin-degradation system as a method to rapidly remove target proteins during specific stages of development (5).

Nance spoke with *JCB* about the molecular cues directing gastrulation and how he enjoys nature in the wilds of New York City.

BUDDING INTERESTS

Why have you stuck with *C. elegans* ever since graduate school?

I like the fact that you can focus on individual cells in this whole, developing organism. Early on, there are only 26 cells when the movements of gastrulation happen.

If you've looked at enough embryos, you can identify all the cells. You know all the parts and where they're supposed to be, so that when you start perturbing them, you can understand what's gone wrong.

C. elegans has its own set of developmental problems, too, because it has this invariant embryonic lineage, and so there's not much room for error. Things have to happen the same way every time. It doesn't really tolerate much sloppiness.

How did a parade lead you to your postdoctoral studies?

Near the end of graduate school, I signed up for the Marine Biological Laboratory's (MBL) embryology course. The town of Woods Hole throws a Fourth of July parade, and the MBL participates in it.

The embryology course decided to march like a drill team to emulate gastrulation in different species. It was so nerdy. We had

T-shirts and each of the three different germ layers had different colors. We would get in formation and do a drill and act out sea urchin or *Xenopus* gastrulation.

One of the course coordinators, Scott Fraser, liked to joke that in *C. elegans* gastrulation, the two people who were “endoderm” needed to move a couple of inches to

the side, because the movements are so non-dramatic compared to other organisms.

At first, I took a little offense (I was in yellow for endoderm). But then I thought that this was an amazing opportunity, because only one lab had studied *C. elegans* gastrulation previously, Bill Wood's group at the University of Colorado. It was exactly what I'm interested in: how cells coordinate together to undergo movements that are critically important for development. Very little was known about how gastrulation worked at any kind of molecular level. So I contacted Jim Priess with this idea of looking at gastrulation in worms, because he was an expert in early embryogenesis in *C. elegans*.



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Jeremy Nance

What did you discover in your postdoc?

I really started off just watching those two endodermal cells, because they're the ones that initiate gastrulation by moving into the interior. We showed that they were accumulating nonmuscle myosin and they appeared to be undergoing an apical constriction.

We also noticed that, after the embryo began to cleave, the PAR proteins—which have a role in setting up anterior-posterior polarity in one-cell embryos—reoriented based on contact patterns. At the four-cell stage, one group of PAR proteins moves to the contact-free surface and another group of PAR proteins moves to the contacted surface. You could make new contacts by sticking two embryos together, and the proteins would redistribute.

This was a way for the embryo to dynamically regulate cell polarity as cells were moving past one another during gastrulation. We hypothesized that this redistribution polarized the embryo radially, ensuring that myosin accumulates at the apical, contact-free surface in the endodermal cells.

PARTITIONING CELLS

What were the molecular agents directing polarization?

While we understood that polarity was important for gastrulation, we didn't know how it was being established. In other words,

“Polarity was important for gastrulation, [but] we didn't know how it was being established.”

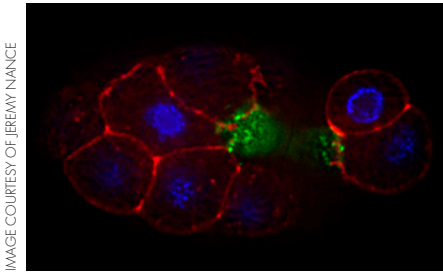


IMAGE COURTESY OF JEREMY NANCE

Endodermal cells (green) begin their internalization in a gastrulating *C. elegans* embryo.

what is the connection between a cell contact and the redistribution of the PAR proteins?

When I started my own lab, we focused on figuring out that connection. We did a genetic screen looking for embryos where the PAR proteins were normal in the one-cell embryo but failed to redistribute based on contact patterns.

We found one really great mutant and named it *pac-1*, which turned out to encode a regulator of Rho GTPase signaling. PAC-1 is recruited to the contact surfaces by cell–cell contact, upstream of the PAR proteins. So this was what was breaking symmetry inside the cell when it perceives that it's touching another cell.

PAC-1 inhibits the Rho GTPase CDC-42, which is a really ancient regulator of cell polarity. It inhibits CDC-42 specifically at the contact sites, leaving CDC-42 active at the contact-free surfaces to recruit the PAR proteins.

What brings PAC-1 to these sites of contact?

We investigated E-cadherin as a candidate because it is at the contact site and it can interact with another cadherin molecule on a neighboring cell. You could imagine how it could mark a contact site and then if a protein interacted with its cytoplasmic tail, it could recruit that protein to those contacts.

There has been an argument about E-cadherin's role in polarization. Is it bringing something to cell contacts to mark them as different from the rest of the cell, or is it simply needed to stick cells together tightly enough for some other signal to operate?

In the worm, it was known that cadherin was not needed for cell adhesion in the early embryo, so we had an opportunity to really separate out those functions.

How did you tease them apart?

The first thing we did was show that PAC-1 indirectly interacts with the tail of E-cadherin. Then, we did a key experiment to really nail this idea that cadherin could function instructively in cell polarization. We took just the C-terminal tail of cadherin, so there's no extracellular domain, and we forced it into the membrane all around the cell, including the contact-free surface. It dragged the PAC-1 protein all the way around the cell. And that had the predicted effect, which was to depolarize the cell.

How do the two primordial germ cells hitch a ride during gastrulation?

The germ cells are fundamentally different from the somatic cells in that they usually have repressed transcription to prevent them from turning on somatic differentiation programs.

Endodermal cells rely on transcription factors to gastrulate, yet here were these cells that couldn't transcribe. So we thought they're probably doing something different to get inside the embryo.

We thought maybe the germ cells were tagging along with the endoderm to become internalized, like a hitchhiker. We did some experiments to keep the endoderm from moving further inside and showed that the germ cells stayed on the surface.

We also noticed that E-cadherin was at really high levels in the two germ cells. When we took away cadherin, those cells detached from the endoderm and remained on the embryo's surface. These cells use some kind of posttranscriptional mechanism—probably through increased translation—to up-regulate cadherin right before gastrulation.

OUT ON A LIMB

What advice do you give grad students?

The beginning of grad school is a great time to take a chance and work on a project that could fall flat on its face or could be really exciting. So I've encouraged most of my students to start off with something pretty exploratory, rather than some A-B-C-D thing that's already laid out for you. This is the time to really go

out on a limb and try something pretty bold. Not crazy, but bold. In many cases, that has turned out to be their thesis.

As an avid birder, is there a bird you'd still like to find?

I would really like to go see the California condors now that they've been released back into the wild. One of my favorite aspects about birding is that it's kind of like development; you can watch things change over time. With every week, things come

and go, and that captivates me. I love to go to Central Park, which is a surprisingly amazing bird-watching spot because it has the only trees around. During migration, you can see 25 species of warblers in a day.

"Birding is...like development; you can watch things change over time."

Do you also garden in the city?

No, but we just bought a house in Connecticut. We did a garden this year and it was so much fun. Heirloom tomatoes were definitely a success. But lettuce? A huge mistake. We have a woodchuck that ate all the lettuce as soon as it came up. It dug under our fence and got into the garden. So there's a rookie mistake. I didn't know that they could dig so well. They're cute, but deceptively so.

1. Nance, J. 2014. *J. Cell Biol.* 206:823–832.
2. Anderson, D.C., et al. 2008. *Science*. 320:1771–1774.
3. Klompstra, D., et al. 2015. *Nat. Cell Biol.* 17:726–735.
4. Chihara, D., and J. Nance. 2012. *Development*. 139:2547–2556.
5. Armenti, S.T., et al. 2014. *Development*. 141:4640–4647.



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Nance birding in a New York City park.