Jodi Nunnari: Keeping an eye on mitochondrial inheritance

Nunnari is using cutting-edge microscopy techniques to explore mutations affecting mitochondrial fusion and fission in living cells and whole organisms.

Jodi Nunnari says she's never been indecisive; once she decides on something, she focuses on it like a laser beam. This intensity has served her well: she set her sights on understanding the biology of mitochondrial inheritance, and her work has helped lay the foundations for the field.

Nunnari at first honed her scientific skills in biochemistry, making heroic efforts to purify adrenergic receptor (1). But as a postdoc in Peter Walter's laboratory studying endoplasmic reticulum membrane biochemistry, Nunnari decided biochemistry couldn't answer all her questions about cell biology. She embarked on a new path, leveraging the newly characterized green fluorescent protein (GFP) and the power of yeast genetics to study mitochondrial fusion and fission (2). Combining these technologies with yeast and mammalian genetics has yielded invaluable insights into how mitochondria pass on their genetic code (3–5).

"If you do what you love and you love what you do, everything will work out."

Her ability to focus is even more useful now, because Nunnari has to divide her time between her family, her laboratory, being an editor for the *Journal of Cell Biology*, chairing her department, running a microscopy facility, and her hobby of horse riding. Thankfully, she was able to set aside a little time to talk with us about how she saw her way through to where she is today.

WEST SIDE TO BENCHSIDE

Where did you grow up?

I grew up on the west side of Cleveland, Ohio, in a working-class neighborhood. My family didn't have a lot of money or any college background.

When you were a kid, did you know what you wanted to be when you grew up?

I really didn't know until I hit my senior year in high school, when I took a chemistry class. My teacher, Ms. Brinza, had a PhD. She was just amazing, and taught chemistry so well that I just fell in love with chemistry.

She had us do an independent study project, and mine was soil analysis. I went all over my neighborhood to get soil samples and analyzed them for the presence of all kinds of chemicals. I basically fell in love with bench work right then and there. And so, rather late in my senior year of high school, I just decided that I wanted to study chemistry.

My decision to go to graduate school for biology was also rather last minute; an independent study project in college introduced me to biology. Up until that point, I had assumed I would go to graduate school in chemistry, but I suddenly decided to veer off into biology. I didn't plan it at all. It just felt right.

The funny thing about my career is that I never thought too far ahead. I just did what I loved, and it took me to where I am today. I tell my students and my postdocs and my undergrads that if you do what you love and you love what you do, everything will work out.

COLD ROOM TO SCOPE ROOM

Your graduate work and early postdoctoral work involved some pretty serious biochemistry.

Yes, I was working on purifying adrenergic receptor. That was a 100,000-fold purification. I lived in the cold room. When I eventually left for my postdoc, my graduate advisor, Lee Limbird, made a tiny replica of the cold room out of Plexiglas so I could take it with me. I still have it.

During my work in Lee's laboratory, I gravitated toward cell biology; I started thinking a lot about membranes and membrane biochemistry. I also decided that I really wanted to live in San Francisco, which narrowed my choices down. I interviewed at several laboratories in the area and ended up joining Peter Walter's laboratory at UCSF.

Jodi Nunnari

But you didn't end up studying the same thing you started out with, in Peter's laboratory.

My first project in Peter's laboratory was on trying to identify the ribosome receptor on the endoplasmic reticulum. It was really hard going; a nightmare. I made some progress at it, but eventually I hit a wall. Sometimes in science, when you hit a wall, you have to respect that; the tools you need may not yet exist, or some crucial piece of information may be missing that keeps you from progressing. I decided that was the case for this project. I was either going to have to really change gears in how I approached the problem, or else rethink what I wanted to do.

I needed to take a step back and really look at what was going on in cell biology, to figure out what I was interested in. So I went into the library and spent about a month reading the cell biology literature, and I discovered mitochondrial biology. I was intrigued by the fact that mitochondria have their own genetic material, and that the transmission of the genome was not random; only maternal mitochondrial DNA is inherited. Then I went and told Peter that I wanted to work on mitochondria. He loved ER, of course, so maybe he wasn't thrilled to hear my decision. But he gave me the space to work on it.

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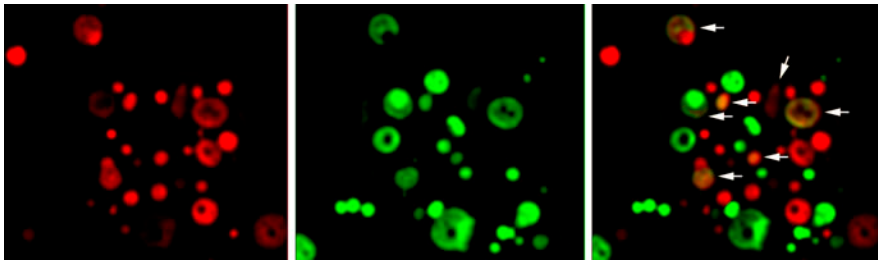

Mitochondria from two different cells (labeled with red and green fluorescent protein, respectively) fuse together (arrows) in an in vitro assay developed in the Nunnari laboratory.

GREEN PROTEIN TO GREEN FIELDS

You jumped into a brand new field.

Yes, and that was before it was cool to study mitochondria, too.

One thing that really propelled all of us at UCSF to do the kind of cell biology I'm doing now was the discovery of green fluorescent protein. Its significance wasn't lost on any of us; we immediately had grand plans for it. I think that we were one of the first groups to express it and target it to an organelle in yeast. In our first paper in this area, we used GFP and some chemistry to show that during mating, mitochondria fuse, but the genome stays segregated; that was the cellular explanation for nonrandom patterns of mitochondrial genome inheritance that Ron Butow had found in the '70s. It's what got me my professorship at UC Davis.

Why did you select UC Davis to open your own laboratory?

Davis felt like a good fit for me when I interviewed there, a natural choice. I like Davis a lot, and not only is it a great school, but there are other perks: my husband, twin daughters, and I live in a lovely house on two and a half acres, which gives both my girls and my two horses plenty of room to run and grow.

Do you ride horses?

Yes. I started riding as a postdoc; I'd take off in the middle of the day to ride at Golden Gate Park. I always wanted to have my own horse, so when I took the job at Davis, I indulged myself: bought my first horse and started riding dressage. I find it's a great de-stressor, though of course dressage isn't totally relaxing since you're riding a test, trying to make points for style and form.

Today you have really embraced fluorescent protein tag technology and the microscopy revolution.

It's amazing what you can do with these technologies today. That's why I run our imaging facility here at UC Davis. I believe very strongly in joint facilities that allow all my colleagues access to this kind of equipment, because on an individual basis these are very expensive pieces of equipment, but they open up so many horizons.

This is especially true when you can combine these technologies with genetics. For example, during our early work on mitochondrial fusion, we knew nothing about any of the machinery of division and fusion, but we certainly could make predictions about what would happen if you messed it up, based on that work. We found all the mitochondrial division mutants by looking at suppressors for mitochondrial fusion; we hopped and skipped our way through dynamics using genetics. GFP and the new microscopy techniques made many of those studies possible.

Nunnari horses around.

What are you working on now in your laboratory at Davis?

We started working in yeast because it's a great system to work out the basic mechanisms of highly conserved processes such as those we study. But we've since expanded into mammalian cells because the mammalian machinery is more complex: in mammalian cells, all the mitochondrial division and fusion machinery has been integrated into other cellular signaling pathways. There is a lot of work to be done exploring how these pathways are regulated in mammalian cells, and we now have the tools we need to ask really interesting questions; for example, we now have enough temporal resolution to actually observe mitochondrial fusion on a coverslip.

"The discovery of green fluorescent protein really propelled me to do the kind of cell biology I'm doing now."

Another fun thing we've started doing is developing a zebrafish model for mitochondrial regulation in a whole organism. What's appealing about zebrafish is the fact that the eggs get fertilized outside the body, and a fully formed fish develops within a couple of days—and you can monitor this entire process through a microscope. So now, we can look at every single organ in a whole animal and see that organs that are right next to each other have vastly different mitochondrial distributions and morphologies. We've become fascinated by why that is and how it comes about. JCB

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