Published Online: 5 March, 2012 | Supp Info: http://doi.org/10.1083/jcb.1965pi

People & Ideas

Orna Cohen-Fix: Playing with nuclear morphology

Cohen-Fix studies how cells determine and maintain their nuclear morphology.

The eukaryotic nucleus is immediately identifiable even to a new student of cell biology. It's so familiar that many scientists can look right at it and completely lose sight of a rather fundamental question: why is the nucleus round?

This may sound like a funny question, says Orna Cohen-Fix, but it's one she takes quite seriously, because the answer to this question could lend important insights into several processes, including cell cycle regulation, aging, and the genesis of cancer. That's why, after spending the first part of her career studying the metaphase-to-anaphase transition (1, 2), she recently started working to decode the cellular rule book on nuclear morphology (3, 4). She's also turned her talents to another complicated problem: the issue of gender equality in the sciences (5). We called her at her lab at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases to get the inside scoop on what she's uncovered on these topics so far.

LEARNING THE RULES

You're from Israel. What made you choose to come to the United States for your postdoc?

I did my graduate degree in Zvi Livneh's lab at the Weizmann Institute, where I worked on DNA damage and repair in *E. coli*. When I was looking for a postdoc, I knew I wanted to move into a eukaryotic system but to keep working on the biology of DNA and chromosomes. I remember sitting in the library, going through stacks of journals in the hope of getting some ideas of what to do (this was in the days before PubMed), when I came across one of Doug Koshland's papers. Something about it—more the way it was written than the topic—made me feel I had to go work for this guy.

The problem I initially planned to work on in Doug's lab at the Carnegie Institution in Baltimore had to do with sister chromatid cohesion. But when I got there, I found other people already working on that topic. I'm not a very competitive person, so I decided to look for something else.

Pds1 was an enigmatic yeast protein identified in Doug's lab. People didn't know exactly what it did, even though the *pds1* mutant had really amazing phenotypes. Everyone who had worked on it had moved on to work on other stuff, so I picked it up and went with it. In the end, I discovered that, in yeast, Pds1 is a substrate of the anaphase-promoting complex that has to be degraded to allow anaphase to begin.

Was it a difficult transition for you, to come to a new country?

I have a funny story about that. My parents are both Israeli, but I was born in the States while my father, a biologist, was here studying. When I was six, my family returned to Israel. I completely forgot English and had to re-learn it all in school. By the time I came to the States for my postdoc, I hadn't spoken English in years, and I had a terrible vocabulary. Yet because I had spoken it as a child, I had a perfect American accent.

> "There's no escaping the cell cycle."

When you're a foreigner and you speak broken English with a foreign accent, people understand. But when you speak broken English with a perfect accent, they think you're an idiot. [Laughs] It took a whole year before I could pass as a local and people stopped giving me funny looks.

NAME OF THE GAME

Since coming to the NIH, your focus shifted from cell cycle to nuclear morphology…

When I first came to the United States with my husband and two kids, I expected it to be a temporary move. I planned to return to Israel and become a researcher, but, after living here for a few years, we found that we were very comfortable here. My husband and I decided to look for jobs in the States instead, and, of all the places I interviewed, NIH was one of my favorites.

PHOTO COURTESY OF MICHAEL SPENCER, NIH DIVISION OF MEDICAL ARTS

Orna Cohen-Fix

One of the great things about working at the NIH is that NIH researchers don't write grants, so in a way we have a lot more freedom to pursue risky projects than most academic researchers. That's why, about six years after I got to the NIH, I felt able to start shifting my lab from cell cycle to nuclear architecture. I did that because there are so many talented people working on cell cycle, and I felt that my time and resources would be better spent focusing on something less studied.

Now nobody in my lab studies the cell cycle. Except, of course, it turns out that we actually are still studying the cell cycle; we just didn't know it. [Laughs] There's no escaping the cell cycle.

How so?

Several years ago I started wondering why the nucleus looks the way it does. Yeast don't have a nuclear skeleton that we know of, so what is it that determines nuclear shape? Why is the nucleus round? We decided to look for mutants whose nuclei weren't round.

In the literature we found a yeast mutant called *spo7Δ*. Absence of the Spo7 protein results in over-proliferation of the

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ER membrane, which is contiguous with the nuclear membrane. For us, the interesting thing about *spo7* mutants was that, although their DNA looks normal by DAPI staining, they have a flare-like nuclear extension. We showed that these flares are always found at the nuclear envelope adjacent to the nucleolus, which in wild-type yeast cells forms a crescent shape up against the edge of the nucleus. This says that not all areas of the nuclear envelope are equal; for reasons we still don't understand, the extra membrane created by *spo7* mutants accumulates over the nucleolus, causing the nucleolus to change shape, but nowhere else around the nucleus.

What we've found most recently—and this isn't published yet—is that these flares also form in yeast cells that are delayed in mitosis. We think that what's happening is that, when the mitotic checkpoint turns on, it blocks chromosome segregation but not membrane synthesis. Because yeast nuclear membranes remain intact during cell division, the cells end up with all this extra membrane, which they stick over the nucleolus. Why that happens, and how, is something we're working on right now.

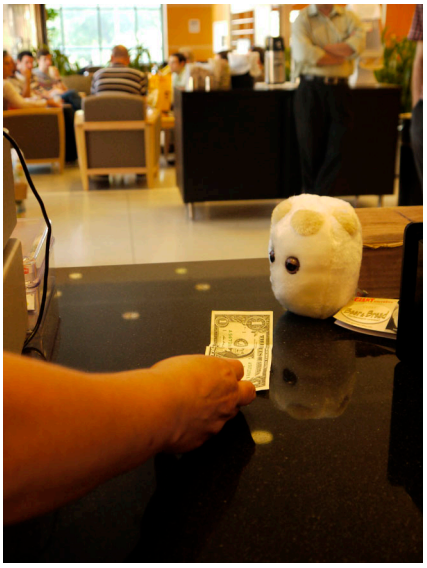

PHOTO COURTESY OF BRANDON LEE

The lab mascot (a toy yeast cell) really needed a coffee break, Cohen-Fix explains. "I take science seriously, but I don't take myself too seriously."

We've also looked in *C. elegans*, where defects in a process analogous to the yeast Spo7 pathway result in impaired nuclear envelope disassembly and reassembly. We think this is due to expansion of the ER membrane that causes a "traffic jam" that prevents the nuclear envelope from being properly absorbed into the ER at mitosis. This has led us to consider additional questions—for example, in higher eukaryotes, when the nuclear membrane reforms after mitosis, how does it "know" to make one round nucleus instead of lots of little micro-nuclei around individual chromosomes?

"Not all areas of the nuclear envelope are equal."

But ultimately one of the most fascinating questions that we're trying to figure out is what determines the nuclear-to-cell volume ratio. It turns out that probably in many systems, but definitely in yeast, there's a constant ratio between nuclear volume and cell volume, and nobody knows how that is determined. No mutants have been found where this is completely abolished—except in cancer cells—so is this ratio important for maintaining normal cell division, or is it simply disrupted as a consequence of transformation?

PLAYING TO WIN

You've also researched why there are so few women in higher-level research careers…

My main motivation for doing that was watching my daughter struggle with being the only girl in the robotics club, even though other girls were also interested in math and science. That led me to wonder what makes women (or girls) stop pursuing their passion. The study we did on postdocs at NIH showed that women in science face many problems that men don't experience. One is that most women who pursue science careers have to split child care duties with a husband who also has a career, whereas many male researchers have wives who either don't work or work part time and so can take on a greater share of that load.

On top of that, we found that women are less confident that they can succeed in a research career in the first place. Whether that's because women are more realistic or because they're more timid than men, we don't know. But if you don't think you'll succeed, you're more likely to quit.

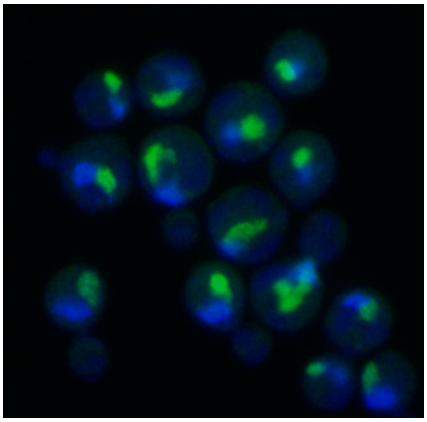

IMAGE COURTESY OF ORNA COHEN-FIX

Flares appear at the nucleoli (green), but not the DNA-containing region (blue), of nuclei in *spo7Δ* mutant yeast cells.

My sense is that women in the US also fear that taking time off during graduate school or a postdoc to bear children creates a perception that you're not serious about your career. As a result, many women wait until late in their postdocs to have kids, making it even harder to start a lab. Something about the science culture needs to change with respect to women having kids.

What can be done to help?

There's no simple answer. One thing we can do is to empower our daughters, and I absolutely think that's important. But I think we also have to work on our sons. My husband was instrumental in my ability to become a scientist, so I think that, if men grew up with the expectation of supporting their wives' aspirations and taking an equal part in child care, it would make it much easier for women to have a career in science.

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