Rong Li: Tipping the balance in cell biology

Li takes multiple approaches to understand how signaling pathways really work.

It's common in cell biology to see regulatory pathways depicted as a hierarchical sequence of events. But according to Rong Li, this is an incomplete representation of how pathways really work. Instead, she says, pathways are often composed of interwoven feedback loops that amplify tiny stochastic imbalances into explosive change.

Li's early training was in yeast genetics, first as an undergraduate in Dieter Söll's lab at Yale and then as a graduate student with Andrew Murray at UCSF (1). At that point, she had a more linear view of signaling pathways. But after her first forays into cytoskeletal biology as a postdoc with David Drubin (2), her views of pathway mechanics—especially those involved in her favorite topic, the breaking of cellular symmetry—have been constantly evolving (3–5). We called her at her lab at the Stowers Institute for Medical Research in Kansas City, Missouri, to discuss how these evolving ideas have shaped her career.

ADJUSTING

What was it like for you to come to the United States from China for college?

I was wide-eyed, though I didn't really have culture shock because I was expecting everything to be strange. My English was very bad in the beginning, but I picked up conversational English fairly quickly. In classes it was a little more difficult because of all the vocabulary and terminology, but I had been to a good high school in China, so I was familiar with some of the material already. That helped.

> "When cells reach a certain internal biochemical state, they can polarize spontaneously."

Did you consider returning to China after you finished your schooling?

At the time, China didn't have a very advanced research community, so I didn't really consider going back. Also, I really liked America; here I had so many opportunities that just weren't available to me when I was growing up in China. So I embraced American culture from the very beginning. By now, I've gotten to live in many different areas of this country and to see the subtle differences between these regions, and there are things to love about all of them.

How has being an immigrant affected your experiences in the US?

Earlier this year I was giving seminars at many different places, and it's funny that, everywhere I went, people would ask me if I was a "Tiger mom." That's because a book recently came out describing how a Chinese-American woman raised her kids: they had very limited playtime and studied very hard so they would succeed in life. It fits the stereotype that says Asian kids do nothing but study. But, in fact, my upbringing was nothing like that, and I don't parent my kids that way. Of course I want my kids to be good students, but it's more important that they're happy and have time to explore life and use their imagination.

As a graduate student you studied mitosis. Why switch to the cytoskeleton for your postdoc?

I'd had success as a graduate student, but I think at the time it was expected that students should do their postdoc in a different area of expertise than their graduate work in order to broaden their abilities. I had done a lot of genetics as an undergrad and in Andrew Murray's lab as a PhD student, so I really wanted to learn another skill set.

David Drubin's lab has a great deal of expertise in actin biochemistry, and I expected that I could use that expertise to ask some detailed mechanistic questions but also combine it with genetics to test my findings in in vivo settings. So I joined David's lab, and I learned a lot. But I had not even published my first paper in the actin field before Marc Kirschner recruited me for a faculty position at Harvard.

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Rong Li

What was it like setting up your first lab?

I was very young and inexperienced. No one in the actin field knew who the heck I was, why I had the position I did, or why I deserved a grant—which I think was fair—but it made my start as an independent PI quite difficult. I didn't get my first grant until I had published three papers from my own lab, so I had quite a lot of funding failures early on. However, Marc was very patient and helpful. With a supportive chair like him, I was able to keep grinding away, and eventually I was able to make it.

EVOLVING

Since those first papers in your lab, you've been studying the Cdc42 pathway…

Yes, but my thinking about how this pathway works has evolved a lot since I first started working on it. I was trained as a geneticist, and as a geneticist you tend to think about processes as linear pathways. You think in terms of who's upstream of whom, and genetics is very powerful in ordering gene functions within those pathways.

So I started out thinking about cell polarity as a hierarchical chain of command: extracellular cues or asymmetric signals instruct a set of proteins, including Cdc42, which then instruct the cytoskeleton to generate polarity. But what made me realize that that might not be the case was when we observed that simply expressing

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a lot of activated Cdc42 will cause a G1 yeast cell (which is normally nonpolarized) to polarize on its own, randomly. Cdc42 clusters in a random spot along the cell cortex and causes the cell to break cytoskeletal symmetry. That tells me you don't actually need an extracellular cue; when cells reach a certain internal biochemical state, they can polarize spontaneously.

Another interesting observation we made is that if we prevent actin polymerization in cells overexpressing activated Cdc42, then the Cdc42 cannot polarize anymore. That was surprising because actin was supposed to be downstream of Cdc42, but this suggested that they're actually interdependent. So it becomes a chicken or egg question: Which one comes first? That's what led us to consider a model where it's really a feedback loop operating between these two things that breaks the symmetry in both of them.

So external cues just impose directionality on the process?

Right, at least in the case of budding yeast. So basically what we're seeing is that these feedback loops become a sort of vicious cycle. Even a small perturbation in the existing balance, such as a tiny asymmetry that occurs due to random fluctuations, can be quickly amplified by this positive feedback mechanism to generate another state, one that is polarized. If that's an intrinsic ability of the cell, then you can imagine that many kinds of external or internal cues, such as a chemical gradient or a bud scar, that bias this machinery a little bit can engage the feedback loop leading to polarization in a particular direction.

> "A system's behavior cannot be explained by the properties of one or a few genes."

FINE-TUNING

How do you observe these processes?

It's hard to rely on traditional genetic analyses to study these kinds of problems where there isn't a clear causal or linear relationship between the components of the system. When I was at Harvard I felt that mathematical modeling and quantitative analysis would be very useful, because certain types of mathematical models can predict this kind of behavior. Then you can use genetics to test the predictions that are made by those models.

We've also come to realize that a system's behavior cannot be explained by the properties of one gene or a few genes. Instead, it's the interplay between many components that describes how the whole system works. Making it more challenging is the fact that the activities of these proteins and the interactions between them are very dynamic, far different from the static structures often depicted in cartoon drawings. So since I arrived here at the Stowers Institute, we've been taking a systems-level approach to see if we can find patterns in the dynamics and function of all the proteins involved in building cell polarity, in the hopes that it will help us understand this great, complicated system. To do that, we've had to develop the capability to measure protein concentrations and the dynamics of protein interactions in live cells. One of the first things we did was to develop some microscopy-based approaches such as fluorescence correlation spectroscopy to make these measurements feasible in live cells.

Another thing that is going to motivate a lot of our work for quite some time has to do with the evolutionary dynamics of cells. I think it's intriguing that cells can evolve and that they can do so on very rapid time scales that we can observe in the lab. For example, if cells are challenged by certain perturbations, they can very quickly come up with workarounds or alternative strategies. I would like to understand how this ability to evolve is linked to the complexity of the cellular systems.

How else have you changed your approach since you moved to the Stowers Institute?

It was a little scary moving here because I had to start my lab again from scratch with all new people. But the good side of it was that I was able to reinvent myself here. I had learned a lot from my mistakes running my first lab at Harvard, but I found that, once you get a lab started, it's hard to change certain habits. So when I started my new lab, I took a very proactive approach to figure out what I did or didn't do right and try to do a better job.

For example, maybe because I'm not a "Tiger mom," I used to wait for people to come to me when they had problems. But then I realized there are certain people who, even when they need help, don't come to talk to me. So one very simple thing I did after coming here is I set up regular meetings with everyone in the lab. That allows me to give them my input frequently and also stay actively engaged in their projects.

I've also changed some things about my life outside of the lab. One thing that we're really cherishing is that we have a little family farm not too far from Kansas City. We raise chickens, ducks, and geese there, and it's a great place for my family to play and to refresh our minds. That's something I would never have had the chance to do had we not come here.

1. Li, R., and A.W. Murray. 1991. *Cell*. 66:519–531.
2. Li, R., Y. Zheng, and D.G. Drubin. 1995. *J. Cell Biol*. 128:599–615.
3. Li, R. 1997. *J. Cell Biol*. 136:649–658.
4. Wedlich-Soldner, R., et al. 2003. *Science*. 299:1231–1235.
5. Pavelka, N., et al. 2010. *Nature*. 468:321–325.

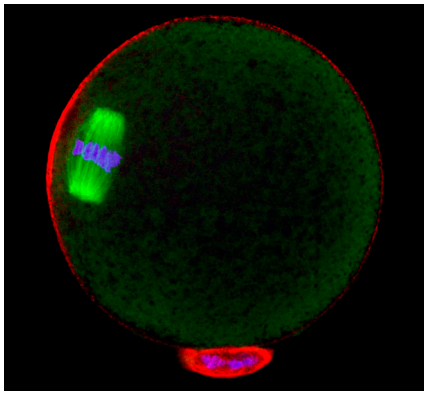

IMAGE COURTESY OF KEXI YI

A polarized oocyte with a cortical actin cap (red) and asymmetrically positioned spindle (green), poised to undergo a second asymmetric meiotic cell division.