Margaret Gardel: At the interface of physics and biology

Gardel studies the biophysical properties of cells and cellular force generation.

Cell movement and shape are controlled in large part by the actin cytoskeleton. The cytoskeleton is coupled to the cell's environment via focal adhesions, which consist of a multiprotein complex that assembles at the cytoplasmic face of integrins. What prompts focal adhesion assembly and disassembly? And how does the cytoskeleton transmit forces across the cell and focal adhesions to the environment?

To answer these questions, Margaret Gardel melds approaches from her graduate work in soft matter physics (1) with cutting-edge bioscience techniques she picked up as a postdoc with Clare Waterman (2). She has already explored how the cytoskeleton works to produce motive force in individual cells (3, 4) and cell pairs (5). Now she wants to understand how such forces are managed in larger collections of cells, as we learned when we called her at her home in Chicago.

AIMED FOR ORBIT

As a child, what career did you want to have?

I really wanted to be an astronaut. I grew up in a town outside of Boston, Massachusetts, but my family moved to New Mexico when my dad got a job at the National Lab. Science is very big there, and everybody watched the space shuttle *Challenger* take off. That was obviously a big tragedy, but it also inspired me to want to be an astronaut. That was why I pursued an education in science—everything I did was aimed toward going up in space. I even wrote a rather terrible essay for my graduate school applications about how I wanted to be an astronaut.

As things turned out, I never got to go to space because I'm too tall to be an astronaut. The lab I joined as a graduate student actually collaborated with NASA, though. I didn't get to work with the astronauts directly, but some of my colleagues did.

You majored in physics as an undergraduate…

Yes, and my PhD was in physics, too. My graduate lab at Harvard worked on soft matter physics. Soft materials are those that are easily deformable by small stresses. In some cases, even stresses as small as a gravitational field can make these materials collapse. The lab worked on a broad range of things, such as polymers, colloidal materials, and emulsions. We also worked on polymer networks inside cells—that is, the cytoskeleton.

I don't really recall what first interested me about it, but I started studying the polymer physics of the actin cytoskeleton. We'd polymerize actin filaments, crosslink them into networks and bundles, and measure how much they deformed in response to external stresses. That's how I became interested in the mechanics of how cells respond to forces.

COURSE ADJUSTMENT

Did you have much biology background at this time?

No. I had had one really good biology course as an undergraduate at Brown University, and in my graduate lab we collaborated with a lot of great cell biologists. But I didn't get a good feeling for how interesting the cytoskeleton really was until after I graduated, when I went to the physiology course at the Marine Biological Laboratory in Woods Hole. I went there because, toward the end of my graduate work, we were collaborating with Tim Mitchison's lab and one of his students suggested I apply. That was the first year that Ron Vale and Tim were running the course, and they were making a real effort to make cell biology and physiology accessible to people with backgrounds in physics, computer sciences, and mathematics.

"How is the actin cytoskeleton coupled to focal adhesions to allow for efficient force transmission?"

PHOTO COURTESY OF KEVIN SONG

Margaret Gardel

So that changed the path of your career…

I had already accepted an independent postdoc fellowship at MIT. I was trying to decide what I wanted to work on for my postdoc, and I had the idea that I wanted to do something with cell mechanics. During the course at Woods Hole, I met Clare Waterman, who, over the course of five months, convinced me that I should do a postdoc with her in cell biology. It just became more and more exciting to me. Besides, Clare is a person who's hard to say no to.

What sorts of things did you work on with her?

It had been known for a long time that the actin cytoskeleton is dynamic and undergoes large-scale movements across the cell. Later, it was also realized that adherent cells generate large stresses on their extracellular matrix through focal adhesions. So you have a flowing or moving actin network that is able to generate stresses on the extracellular matrix. The question is: How is the actin cytoskeleton coupled to focal adhesions to allow for efficient force transmission?

One idea was that when focal adhesions assemble they act like a clutch to

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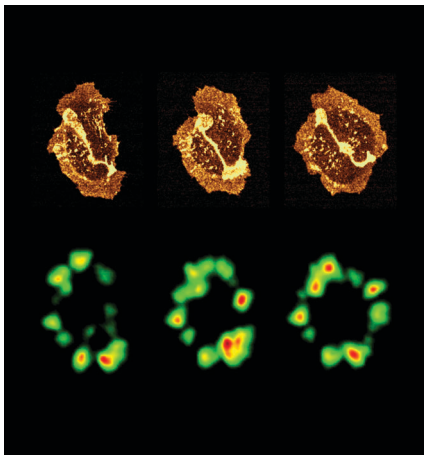

IMAGE COURTESY OF VENKAT MARUTHAMUTHU

An MDCK cell pair expressing GFP–E-cadherin (gold) exerts forces on the ECM (green shades to red with increasing intensity).

stop the actin flow and transfer that force instead to the extracellular matrix. If that's the case, then you would expect that when focal adhesions assemble you'd see the stress on the extracellular matrix increase and actin flow decrease. And that was one of the things we demonstrated during my postdoc.

Another question we looked at was how focal adhesions disassemble. Actin flow is very fast at the leading edge because it's driven by actin polymerization. But it slows considerably, and becomes dependent on myosin II, further back in the lamella. Focal adhesions were thought to be responsive to the amount of tension that's applied to them, so we hypothesized that when actin flow is decreased substantially there may not be enough stress to actually maintain the focal adhesion in an assembled state.

We observed that in focal adhesions that are disassembling there is a direct relationship between actin flow and force. So, as the actin flow decreases, the force exerted by the cell on the extracellular matrix goes down.

NEW AIMS

How important is force to focal adhesion assembly and maintenance?

One of the groundbreaking studies of focal adhesion demonstrated that focal adhesions are dependent on myosin II and the stiffness of the extracellular matrix, so there's a huge amount of work about their force dependencies. But my lab has been finding that there are force-independent effects of myosin II on focal adhesion assembly as well. Myosin II motors generate tension in the actin cytoskeleton that can, for instance, drive retrograde flow. Another important role of myosin II is to cross-link F-actin and change its organization.

We're finding that force per se doesn't seem to be as important for recruiting focal adhesion proteins. It's the ability of myosin II to make very thick actin bundles at the focal adhesion that's important. We think that myosin II is acting as a cross-linker and that by changing the actin architecture it can affect the local density of binding sites for different focal adhesion proteins. I think the jury's still out on the extent to which tension, changes in actin architecture, or changes in flow rate each contribute to recruitment of different proteins.

"Now we're expanding that question to the tissue level."

When I started my own lab, I really wanted to understand how stresses in the actin cytoskeleton control cell adhesion and migration in single cells. Now we're expanding that question to the tissue level. Most of the questions we're working on now deal with epithelial tissues, tumor metastasis, or collective migration that happens during development.

Is it difficult trying to span the fields of biology and physics?

I wanted to try to be in a physics department because that was where my background was, and I wanted to be in a place where there was an expertise in soft condensed matter. The University of Chicago has one of the few physics departments with that expertise. Another benefit of Chicago is that they have this big building where my lab space is housed with the biologists. That was really important to me, in part because of the infrastructure I need to do the kind of work I want to do. Another reason it's important is it makes students less worried about joining my lab. They don't feel like they're going to be isolated.

Of course, there's still some hesitation. Both the biologists and physicists are scared because they'll have to work with things they're not used to thinking about. I try to deal with that by maintaining a culture where it's okay to ask lots of questions and to seek help from different types of people to get the expertise that we need.

Thanks for talking to us even though you're on maternity leave…

Yes, this is my newest project! [Laughs] Starting a lab is, in some ways, like having a child. It's a pretty big endeavor. My partner and I had only been together for a few years when we moved here. It was a new city for both of us, and we had to get settled. I had to deal with all those changes, and I wanted to get my lab to the point where I felt like everyone could take care of themselves for a little bit. For me, this is the right time.

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PHOTO COURTESY OF MARGARET GARDEL AND CLARE WATERMAN

Clare Waterman (left) and Margaret Gardel (right) demonstrating stresses and strains at the Woods Hole Biological Labs.