

People & Ideas

Frances Brodsky: So you think you know all about clathrin?

Brodsky studies clathrin's diverse biological functions.

Mention clathrin and what first comes to mind is probably the protein's famous role in designating and constructing endocytic sites at the plasma membrane. But clathrin is a startlingly versatile protein that comes in different forms. Clathrins keep cropping up in new contexts, including actin polymerization, mitosis, and even diabetes.

Frances Brodsky has spent much of her career exploring clathrin's many secrets, spotting them within the thickets of biology like the avian species she finds in her spare time bird watching. Since first encountering clathrins as a postdoc (1), her work on their nature (2, 3) and function (4, 5) has uncovered results that challenge and change our view of these proteins. Her lab is still making surprising new discoveries, as we learned when we spoke with her recently.

A CHANCE ENCOUNTER

You're from the US, but you did your graduate studies in the UK...

During my last year as a Harvard undergraduate, I received a Marshall Scholarship to study in the UK for three years and opted to use the scholarship to fund my DPhil doctoral research. I'd been doing my senior thesis project in Paul Gottlieb's immunology lab at MIT. When I spoke with Paul about where I might go in England, he suggested I consider Walter Bodmer's lab in Oxford. Walter was giving a seminar at Harvard that week, so I went to hear him talk. I was attracted by the combination of immunology and genetics he described.

When I joined Walter's lab, I was involved in making and characterizing some of the first monoclonal antibodies against human HLA proteins. At the time, we knew nothing about HLA except that it was involved in immune function. We didn't even know that it was a peptide-binding protein. Those antibodies we produced were

an important step in facilitating functional and structural analysis of HLA.

Is that where you met your partner Peter Parham?

Peter joined Walter's lab during my second year there. He came to Walter's lab as a postdoc because he had, completely independently, also attended Walter's Harvard seminar. We didn't know each other at Harvard, but when we met in Walter's lab we started working together and then became personally involved. We've been together ever since, though our research has now diverged.

When did you first encounter clathrin?

I'd actually never heard of it until Peter and I returned to Harvard. I was doing a postdoc in Jack Strominger's lab, but Jack didn't have a tissue culture facility in his lab, so I was using a hood in the bottom floor of another building. One of the other people sharing that hood was Tom Kirchhausen, who was working on clathrin assembly in Steve Harrison's lab.

Tommy wanted to make antibodies to clathrin, and he was able to purify milligrams of the protein. I was used to making antibodies against microgram amounts of proteins, so we thought it would be fun to try raising monoclonals to clathrin. I started making the antibodies and characterizing them in collaboration with Tommy and Steve. That's what got me into cell biology—and into clathrin. Then, when Peter and I moved to Stanford together, I continued my postdoc in Peter's lab and brought the clathrin work with me.

DIFFERENT ENVIRONMENTS

For a long time, it wasn't known that there were two different clathrin heavy chains...

That's right. A second form of clathrin was unearthed by the Human Genome Project. By that time, my lab had done a lot of work on the conventional form of clathrin, CHC17,



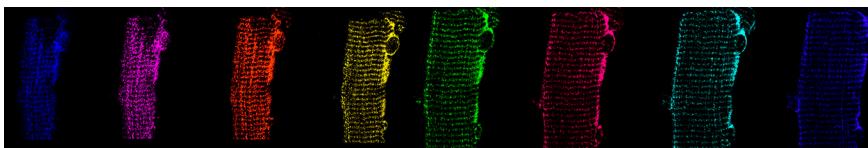
Frances Brodsky

PHOTO COURTESY OF PETER PARHAM

which is the form that generates clathrin-coated pits and is involved in endocytosis. So I was very interested to hear about the second form of clathrin, CHC22. But it took us quite a while to figure out what CHC22 does due to several challenges, one being that this particular form of clathrin is not expressed in mice. It came from a gene duplication that happened when vertebrates emerged, but in the mouse lineage it became a pseudogene.

CHC22 is highly expressed in muscle and, we later found out, in fat. But most of the available models for studying muscle were, of course, mouse models and mouse cell lines. So it took us a few years to find the right human cells in which to study this protein and to figure out its function. It turns out that CHC22 clathrin helps package the GLUT4 glucose transporter, which is the main insulin-responsive glucose transporter in muscle and fat. GLUT4 is normally sequestered inside intracellular vesicles, but, when insulin is released after a meal, GLUT4 is immediately expressed on the cell surface by the fusion of those vesicles with the plasma membrane. And it turns out that CHC22 is involved, not in GLUT4 endocytosis but in packaging GLUT4 into that insulin-sensitive vesicular compartment.

The first lab to make a transgenic mouse to study CHC22 function hadn't found any phenotype because they didn't know to look at glucose levels in the blood. When we found out it was involved in GLUT4



CHC22 clathrin in serial sections of human muscle, visualized by immunofluorescence.

transport, we looked and saw the animals had elevated blood glucose and even some symptoms of insulin resistance. To me, this was incredibly exciting. We started looking at this molecule because we knew so much about the basic biochemistry of the conventional clathrin, and it led us into a very medically relevant problem, human glucose metabolism in type 2 diabetes.

How do mice cope without CHC22?

Mice still traffic GLUT4 to its vesicular compartment; they just use conventional clathrin to do everything from endocytosis to the specialized trafficking steps that, in humans, use CHC22. So, when CHC22 is expressed in mice, this extra protein clogs up the packaging pathway. It causes overpackaging of GLUT4 so that the protein can't be released in response to insulin. I am now wondering if aberrant CHC22 accumulation may cause the GLUT4 release pathway to become jammed up in diabetic humans, too.

Are there lessons to draw from this beyond its importance for diabetes?

I've felt for a long time that, although mice can be approximate models for human pathways and disease, they have limitations because they are missing some of the species-restricted molecules that we have. The mouse models can still tell us a lot, but there can be subtle variation in their pathways that may not translate into humans. Ultimately, one has to test predictions from the animal models in human cells and take into account that the human proteins may work differently.

NEW SIGHTINGS

It turns out that clathrins can have many functions...

Yes, CHC22 has a novel specialization, and what's really fascinating is that we're

now discovering alternative functions for conventional clathrin, too. Steve Royle's lab showed that CHC17 can interact with microtubule-binding proteins, and my lab has shown that it maintains the integrity of centrosomes by being a microtubule cross-linker. Our newest data suggest clathrin may act as a cross-linker for other proteins, as well. But so far, CHC22 does not seem to have these auxiliary functions.

Another difference between CHC17 and CHC22 is that only CHC17 binds to the clathrin light chain subunits, LCa and LCb. Half of my lab is working to understand the light chains' function, focusing initially on their common function, which is binding the HIP protein and organizing actin. But now we're also trying to probe their functional diversity. We've got our first LCa knockout mice, and we're working on the LCb mice.

Of course, the other half of my lab is now focused on projects that have to do with CHC22, finding out how it assembles and disassembles and what regulates it.

Do you have any personal projects you're working on?

Throughout my post-tenure career, I've always had one big project going on besides running my lab. In my first sabbatical period in 1993, I started writing novels—biomedical thrillers. I started writing for fun and also because I wanted a digestible way of describing the scientific community to the general public. I ended up having a contract for three books after publishers picked up the first one. By the time I got to the last book I was rather burned out. [Laughs] Then, when I got together with my good friends and colleagues Sandy Schmid, Mark Marsh, and Thomas Kreis and we started the journal *Traffic*, I didn't have a lot of time for writing fiction. I stepped down from

editorial responsibilities at *Traffic* a few years ago, though I remain on the board. And I'll hopefully go back to writing fiction someday but likely not immediately. I'm starting my third big project now.

What's that?

After 26 years at the University of California, San Francisco, I have just accepted a position as Director of the Division of Biosciences of University College London, to start in 2014. I'm going to miss all my wonderful colleagues at UCSF, but this is an amazing opportunity for me. I'll continue to have a laboratory and interact with new colleagues at UCL—which I'm very excited about, because I still have several big science problems I want to solve. But as head of the division I'll also be in charge of the four main bioscience departments and developing bioscience at UCL. I'm sure it will take some adjustment to become more of an administrator, but there are a lot of creative opportunities there, too, to influence science beyond the laboratory.

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Brodsky bird watching in Colorado.