People & Ideas

Sandra Schmid: Collaring endocytosis

Schmid explores how the dynamin GTPase pinches off endocytic vesicles.

Throughout her career, Sandra Schmid has been at the leading edge of endocytosis research. It was her laboratory that first identified the GTPase dynamin as a central player in endocytosis (1). Since then, she's devoted her research efforts to characterizing this critical cellular process (2) and dynamin's role therein, as the protein that collars and then pinches off forming endocytic vesicles (3, 4).

Schmid did her graduate work in James Rothman's lab at Stanford University (5) and her postdoc with Ira Mellman at Yale (6). For the past 22 years she's headed up her own lab at the Scripps Research Institute in San Diego. There, she's managed the responsibilities of being a lab head, department chair, and mother, while also serving on the editorial boards for several research journals. Schmid also recently completed a master's degree in executive leadership at the University of San Diego and agreed to take on the presidency of the American Society for Cell Biology in 2011. Yet, we managed to collar her for a quick chat about the things that have been keeping her busy.

MAJOR WORKS

Where did you grow up?

I grew up in Vancouver, Canada. My father was a high school science teacher, and he actually wrote the textbooks that were used in grades eight through ten in a couple of Canadian provinces.

Is that what first interested you in science?

My father was definitely an inspiration to me, but another strong influence was my early schooling. I was enrolled in something called a Major Works Class, which was a special class for gifted students from all over the city. There were maybe 25 of us in the class and we stayed together from fourth through seventh grades. We had phenomenal teachers, and they had a really unique approach to education: we didn't do anything according to the textbooks or the regular curriculum. The teacher would just throw it out the window and we'd do it our own way. Our teachers were always challenging us to look outside of textbooks to get our own information, and to think critically about what the different sources of information had to say. I think it was really that class that informed my approach to science.

MAJOR AIMS

How would you characterize your scientific approach?

I'm always questioning whether I really understand how things work. Once you have formulated a hypothesis of how something works, the trick is to design an experiment that's really set up to test that idea. It's important to keep in mind that you can't approach this thinking you already know the answer to your question, or expecting that you know exactly how things should turn out. What's exciting about science isn't what you already know; what you already know goes in a textbook. What's exciting about science is that which you don't yet know.

> "What's exciting about science is that which you don't yet know."

I think that when a student can't produce some expected result, or they can't get the "right" answer, they often feel frustrated or embarrassed. But I have proposed many models throughout my career that have turned out to be wrong, and I'm not embarrassed by that. We propose models based on what we know at the time. Then we try to rigorously test them, and frequently we prove ourselves wrong. I always tell my postdocs, "If you get the result I expect, that's great, but if you get a result that I don't expect, I'm even happier," because that means we've uncovered something new. As scientists, our whole raison d'être is innovation, and yet I've never, in all my training as a scientist, had a discussion about innovation. That's partly why I recently decided to do a master's degree in executive leadership.

Sandra Schmid

How did you complete a master's while also running a lab full-time?

I try very hard to prioritize. For me, doing that master's degree was important. Having a family was also important to me—I have two great kids, one of whom is about to finish college, and one who's just starting. You obviously can't do everything, but if you have a clear idea of what is most important to you, and you're willing to let go of things that aren't so important, then you will be able to get what you want.

Did what you learned in your master's affect your approach to running your lab?

Yes. My lab is now much smaller than it was, and yet it's more productive than ever because I can now help every person be as successful as possible. Each individual needs different levels of assistance from me; no two people are alike. Some need a lot of back-and-forth and guidance

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Text and Interview by Caitlin Sedwick
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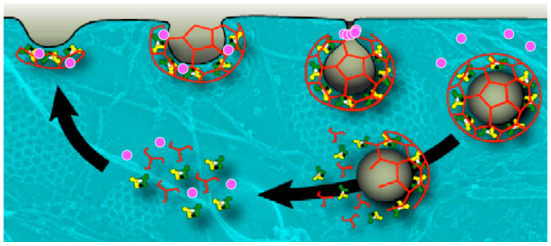

Dynamin (pink) works with coat proteins (red, yellow, green) to determine when it's time to pinch off a budding endocytic vesicle.

in order to thrive, others are highly independent, while most fall somewhere in-between. However, even my most independent fellows need help focusing or coordinating their efforts with others—just like Kobe Bryant still needs a basketball coach! Because I have a smaller lab, I'm able to figure out what works best for everyone, and act accordingly.

In bigger labs, I think there's a tendency for the lab head to try to treat everyone the same, or else to focus their efforts on just one of those types of people: just the successful ones, or just the struggling ones. As department chair, I've seen labs that fall all along that spectrum. I think senior scientists should learn to use a broader range of leadership skills to help young scientists succeed.

You'll be president of ASCB next year—will that help you communicate these ideas?

I'm definitely going to be trying to increase awareness of these issues. ASCB is an organization whose mission is very much aligned with my interests: being an advocate for science, and for the development of young scientists.

MAJOR EMPHASIS

As a young scientist, why did you select endocytosis as the focus of your career?

It was a question that I first came across as an undergraduate. Vesicular trafficking, the process of pinching off a small piece of membrane and fusing it to another place, just fascinated me. I wanted to pick it apart and understand it.

Part of what interests me about it now is the idea that the plasma membrane is not just a barrier; it's how cells communicate with their environment. Accordingly, endocytic processes are not just for transporting proteins from one place to another. They also modulate how cells talk with each other and with their environment. For example, they control everything from the levels of glucose transporters on the cell surface to the levels of activated signaling receptors at the plasma membrane. So, endocytosis needs to be tightly regulated and linked to the vesicle's specific cargo.

What regulates endocytic processes?

I think dynamin is really the master regulator of endocytosis. Dynamin is a giant GTPase that I first encountered when I was just starting my lab here at Scripps. At the time, very little was known about it: biochemical evidence suggested it might be a microtubule motor protein, but genetic studies said it was involved in endocytosis. We set out to test whether dynamin was a motor or an endocytic protein. We made a mutation in the dynamin P loop that prevents it from binding nucleotides. If dynamin was a motor, this mutation would lock it onto microtubules, so we looked for defects in microtubule organization, and found none. Instead, we found defects in endocytosis. But we didn't really begin to understand dynamin's role in endocytosis until later, when we discovered that dynamin self-assembles. When we looked at these assemblies under an electron microscope, we saw that they looked like tiny protein collars. That was our first inkling of how dynamin functions in endocytosis.

> "Dynamin is the brains and brawn of endocytosis."

Now we think that dynamin is the brains and brawn of endocytosis. It plays a role early in vesicle formation to monitor cargo composition, coat assembly, and the mechanics of the early stages of vesicle formation. We think it does this by interacting with vesicular coat proteins that sense vesicle curvature and interact with the vesicles' cargo. When these coat proteins sense that the vesicle is loaded with cargo or that signaling receptors need to be internalized, they activate dynamin's self-assembly into protein collars, which in turn stimulates its GTPase activity. The dynamin collars choke off the neck of a budding vesicle and facilitate its fission from the plasma membrane. We think that dynamin might control an endocytic checkpoint—if certain conditions aren't satisfied, the process of vesicle formation is aborted, and started again from scratch.

Now we're trying to test these ideas. If we're right, then we should be able to observe how protein partners that interact with dynamin affect its assembly and GTPase activities, and how changes to dynamin's basal activity affect the kinetics of vesicle fission. We're using biochemistry, biophysics, and cell biology approaches to these problems, and I also have a collaboration with Gaudenz Danuser at Harvard Medical School using quantitative live cell microscopy to look at vesicle coat dynamics. I'm excited to see what we'll turn up next.

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Schmid flanked by her highest priorities.

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