People & Ideas

Heike Folsch: Peeling back the layers

Folsch's work sits at the intersection of membrane trafficking and epithelial polarity.

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Heike Folsch

As far back as she can remember, Heike Folsch was always interested in understanding how the world around her functioned. Growing up in Hamburg, Germany, she and her father would plant onions in the garden, and even as a child, she found herself fascinated by the correlation between the compression of the soil and the rate at which the onions emerged from the ground. Despite her family thinking it crazy, Heike was the first in her working-class family to go to high school and university.

Now with her own lab in Northwestern University's Department of Cell and Molecular Biology, Folsch's work has far transcended planting onions in the garden. Building on exciting discoveries from her postdoctoral work, Folsch's research group now utilizes polarized epithelial cells to understand the mechanisms by which cells specifically sort transmembrane proteins between the distinct apical and basolateral domains. Her research has expanded into understanding how these sorting mechanisms work in migrating cells and could be disrupted in the context of cancer. We contacted her to learn more.

Where did you study before starting your own lab?

As an undergraduate at the University of Göttingen I majored in microbiology. My undergraduate research culminated in a diploma thesis in the lab of Dr. Gerhard Gottschalk, where I isolated bacteria that would grow on crude oil. My graduate work brought me to the lab of Dr. Walter Neupert at the University of Munich, where I studied the import of proteins into yeast mitochondria. Back then, large German labs had a C4 professor as a head and several habilitants—super postdocs of sorts—who were in the lab and training to become professors. I worked under the tutelage of Dr. Rosemary Stuart who was a habilitant in the lab at the time. As a postdoc, I studied with Dr. Ira Mellman at Yale University. It is there that I started to work with mammalian cells and became interested in my current research questions.

What was it that first drew your interest to polarized trafficking in epithelial cells?

Initially I was drawn to epithelial cell biology because I wanted to understand a basic question: What is the sorting machinery responsible for basolateral targeting? I was lucky enough to discover AP-1B as a crucial cytosolic adaptor complex (1). AP-1B localizes in recycling endosomes (REs) (2, 3). Since then, my work has indicated that the regulatory proteins that localize to the leading edge of migrating cells to control cell migration also localize in REs to control AP-1B–mediated basolateral sorting. Among those components are Arf6, PIPKIγ-90, and $PI(3,4,5)P_3$ (4, 5). Interestingly we found that AP-1B expression in epithelial cells triggers the accumulation of $PI(3,4,5)P_3$ in REs, and, conversely, $PI(3,4,5)P_3$ is necessary for AP-1B recruitment onto REs (4). Incidentally, Arf6, PIPKIγ-90, and $PI(3,4,5)P_3$ generation are also regulators of cell invasion of metastatic cancer cells. Thus we hope that by understanding how AP-1B controls this network of regulators we may learn how to target and control cancer cells better in the future.

> "Stay true to yourself and to the data you obtain."

What is your lab actively working on?

AP-1B has a close cousin in cells: AP-1A. Both complexes only differ with respect to their medium subunits, μ1B or μ1A. Although μ1A and μ1B are about 80% identical on the amino acid level, they nevertheless lead to the localization of AP-1A and AP-1B to different compartments, with AP-1A at the trans-Golgi network, and AP-1B in REs. In addition, they don't form mixed clathrin-coated vesicles and fulfill largely non-overlapping functions [reviewed in (6)]. Furthermore, I found that AP-1B triggers the recruitment of exocyst complex components onto the REs for incorporation into AP-1B vesicles (2). In recent years, we identified amino acid residues in μ1B that are necessary for membrane recruitment (4). We are currently asking which amino acid residues in μ1B are important for exocyst recruitment. We are creating loss-of-function mutations in μ1B and are aiming to create gain-of-function mutations in μ1A down the road. We are now asking whether it is possible to turn AP-1A functionally into AP-1B by changing only a few amino acid residues.

A second major project in the lab right now is to analyze a putative role for AP-1B in cell migration. We found that expression of Arf6 in LLC-PK1 cells that express HA-tagged versions of μ1B or μ1A triggered the recruitment of AP-1B—but not AP-1A—into lamillipodia of migrating cells (5) (see associated image). We are thus asking if perhaps AP-1B may control cell migration.

What's on the horizon for the lab?

Up next for us is to investigate positive and negative feedback loops in recycling endosomes leading to efficient AP-1B activity and thus basolateral sorting. For example, Arf6 in REs can interact with PIPKIγ-90. Perhaps this interaction is needed for $PI(3,4,5)P_3$ formation from PI(4)P. $PI(3,4,5)P_3$ in REs seems to be necessary to allow the otherwise endocytic

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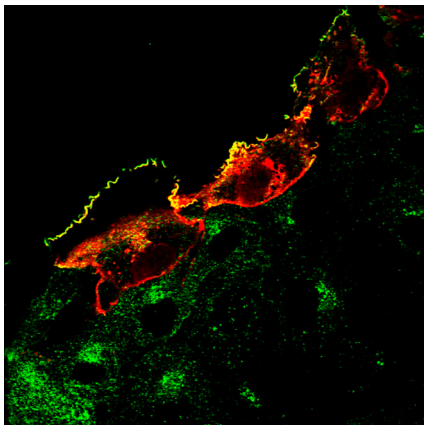

IMAGE COURTESY OF HEIKE FÖLSCH

LLC-PK1::μ1B-HA (AP-1B in green) cells expressing Arf6 (in red).

coadaptor ARH to cooperate with AP-1B in the basolateral sorting of certain cargos (7). Presently, we don't know much about how PI(3,4,5)P_3 is generated and what role AP-1B plays in its accumulation. Moreover, Rab8, and Rab10 may negatively regulate Arf6 and thus AP-1B function [reviewed in (6)]. We are interested in finding out more about possible cross-talk among the small GTPases that localize in REs.

Who were the key influences early in your career?

The scientific teaching in the Neupert lab regarding ethics and thoroughness shaped how I do science to this day. As students we were challenged to never do experiments without good reasoning, so as not to waste too much money and time, and to do vigorous controls. Now I find that more often than not my best discoveries are being made when "control" experiments do not turn out as anticipated.

Dr. Rosemary Stuart was also instrumental in encouraging me to go on to do postdoctoral research. Without her, I would have applied for jobs in industry right after graduate school and would not be an independent scientist today. For me, pursuing an academic career was unimaginable, and I needed her encouragement to reach my full potential as a scientist.

What sorts of obstacles have you faced in your career?

The biggest obstacle in my career so far was probably when I was denied tenure in 2008. The main reason, I guess, was that my colleagues back then doubted my ability to renew NIH funding. However, I successfully renewed my NIH grant shortly after that and moved to Northwestern University Feinberg School of Medicine with the support of my current chairman, Dr. Robert Goldman. Being able to maintain NIH funding, and thus an independent research lab, has been the biggest accomplishment in my career so far, even though I am currently not on a tenure track.

What kind of approach do you bring to your work?

I always tell my students, postdocs, and techs that no matter how brilliant their hypothesis, they have to have an open mind when analyzing their data. Nature may have other ideas, and nature always wins. If necessary, just come up with an improved hypothesis. I don't think there are any circumstances under which it is OK to bend the truth of experimental data just so they would fit a preconceived hypothesis.

> "Nature may have other ideas, and nature always wins."

Have you received any useful advice from your previous mentors?

To quote Ira Mellman, "Why worry? The time and energy you spent worrying could be applied to solving the problem instead."

What hobbies do you have?

I like to read a lot of fiction and nonfiction alike, with no particular genre standing out. I do make it a point to buy German books online after I realized that without this reading, my German became rusty after spending so many years in the US. I enjoy Pilates, yoga, and Zumba workouts and take classes at the gym. Pilates and yoga are excellent mind-body workouts that keep my mind balanced during stressful times, and Zumba classes are just fun, energetic cardio classes.

What do you think you would be if you were not a scientist?

I think I would be either a psychiatrist or a fiction writer. Psychiatry was always an interest of mine, and I find myself curious as to how the human mind works. I also think that, in order to help patients, a psychiatrist has to apply analytical thinking—perhaps not that much different from the analytical thinking a scientist applies to solving a research question. As for being a fiction writer, although I have not written any fiction, I do have a few ideas for novels that I would like to write, all of them exploring complex human experiences.

Any tips for a successful research career?

Follow your passion. You have to enjoy what you are doing. Otherwise, the long hours spent on science are too hard. Stay true to yourself and to the data you obtain; never twist data into a preconceived hypothesis but be open-minded. And lastly, be strong and believe in yourself when you have to overcome obstacles.

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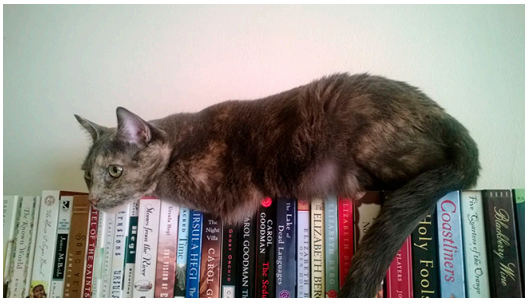

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Folsch chills with cat Callie.