People & Ideas

Inke Näthke: The ABCs of APC

Näthke investigates the many functions of adenomatous polyposis coli protein and its contribution to human disease.

Eighty percent of human colon cancers carry a mutation in adenomatous polyposis coli (APC) protein. APC is an adaptor protein that helps regulate the cytoskeleton and also modulates the behavior of signaling proteins like β-catenin. Inke Näthke is working to understand APC's normal functions in cells, and why APC mutations are so frequently associated with cancers of the gut (1–5).

As a graduate student studying the structure and function of clathrin in Frances Brodsky's lab at UCSF (6), Näthke was focused on biochemistry and her lab mates teased her for working exclusively with purified proteins. But as a postdoc in James Nelson's lab at Stanford, Näthke made the discovery that would shape her career through the lens of a microscope: a striking and unusual interaction between APC and the microtubule cytoskeleton (7).

Her interest piqued by that initial observation, Näthke has uncovered new secrets about APC ever since. We called her at her laboratory at the University of Dundee in Scotland to discuss how APC affects cell biology, tissue architecture, and her career.

CHOICE

Where did you grow up?

In Germany. I stayed there until the end of high school. I had the blessing—or maybe it was a curse—of being pretty good at many different things. I was good at languages. I enjoyed math, chemistry, and music. As a result, I didn't really know what I wanted to do for a career. If I'd gone to college immediately after high school, I'd have had to choose a particular subject to study, but I didn't feel ready to make that choice. Fortunately, my parents were understanding, and when I said I wanted to take some time off before college, they supported me.

I wanted to go to a foreign country, to experience a different way of life, and the easiest way to do that was to become an au pair. So I wrote to newspapers in Ireland, and I looked for jobs in New Zealand. I wasn't really looking to go to the United States, but a friend of my father's helped me find a place with a family in San Jose, California. The family was wonderful. They welcomed me into their home and I fell in love with California. I was supposed to go home after a year but when the time came, I didn't want to leave. By that time, too, I had discovered the college system in the States, which compared to the one in Germany was very open-ended; you didn't have to declare a major right away. I thought that sounded perfect for me.

So you went to college in the States?

It turned out I had to go back to Germany for a year to get some academic prerequisites out of the way, but I finally enrolled at San Jose State University as a premed student. I quickly decided that wasn't for me, partially because I had discovered biochemistry and decided that was fascinating. After college, I was again supposed to go back to Germany. I even had a one-way airplane ticket ready to go, but I called and cancelled it. That felt, even at the time, like one of those major life-altering decisions. If I hadn't stayed, I would not have been in the same environment or met the people who helped me get to where I am today. But I did stay, and I worked for a year as a technician with a small biotech firm in the Bay Area. I hadn't really decided what I wanted to do next, but while I was at that company, I heard about the pharmaceutical chemistry program at UCSF. I decided to enroll as a graduate student there.

> "What interests me is the idea of applying biology to questions related to human disease."

Inke Näthke

SERENDIPITY

What made you decide to pursue a graduate degree?

In the end what really interests me is the idea of applying chemistry and biology to questions related to human disease. I didn't recognize that at the time, but looking back, I see that most of the decisions I've made were guided by that. In fact, I'm currently helping to set up a new cancer center here in Dundee, so I'm able to pursue that interest more directly. But at the time, I just felt that there were many interesting questions out there that I could work on. I wasn't driven by any particular problem.

I did my graduate work with Frances Brodsky, where I worked on clathrin structure and function. That work—and just being at UCSF, where cell biology was really coming into its own—introduced me to a lot of cell biology–related questions. When the time came to decide on a postdoctoral position, I spoke to a number of different people, and in the end I joined James Nelson's lab at Stanford to work on cell adhesion.

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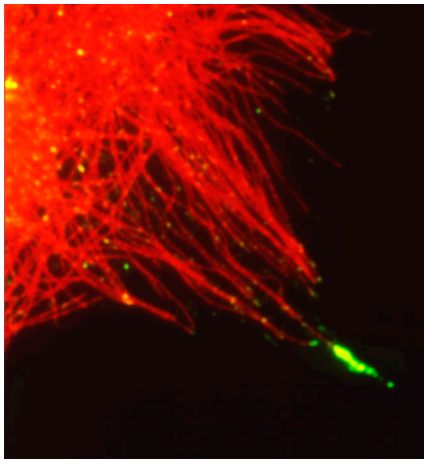


Seeing APC (green) on microtubule (red) ends sparked Näthke's curiosity.

It was during your postdoc that you first encountered APC?

That was serendipity—I just happened to be in the right place at the right time. I had been working with a graduate student in James' lab on the interaction between catenins and cadherins. We'd made some antibodies to catenins, in particular β-catenin, because catenins had just been discovered and there weren't many good antibodies around at the time. One day, Paul Polakis called James looking for antibodies to β-catenin, and we sent him some of ours. In return, Paul gave us some of his antibodies to this protein he'd been working on, APC. APC is a monster of a protein, and Paul had done the early biochemical work on it. He had data suggesting APC might interact with microtubules, so I decided to see if his antibody worked for immunofluorescence. I remember looking in the microscope and seeing that APC was in these little clusters on microtubules, and saying to myself, "What's going on here? This is really different!" I decided I wanted to know more about this protein and its role in cells.

OPPORTUNITY

What about APC captivated you?

Initially I was just intrigued by the really striking localization pattern that it exhibited. But the more I worked on it, the more interested I became. Of course, APC is famous for helping to regulate β-catenin as part of the Wnt signaling pathway, and for the connection that has to cancer. But that's not all there is to APC. It's an adaptor protein, so it has its fingers in a lot of different pies in the cell, but it turns out that it isn't absolutely needed for anything it does. You can knock it out and nothing dramatic happens. Cells that lack APC still move and grow, and although they don't differentiate as well, they can still divide. The fidelity of mitosis is defective, so cells make more mistakes. But these mistakes are tolerated, and the cell can keep growing and proliferating. But without APC, all these processes are slightly off-kilter; all these little errors push the cell just that much closer to having a real problem—to becoming cancerous. All you need is one more nudge in that direction for the real trouble to start.

> "APC has its fingers in a lot of different pies in the cell."

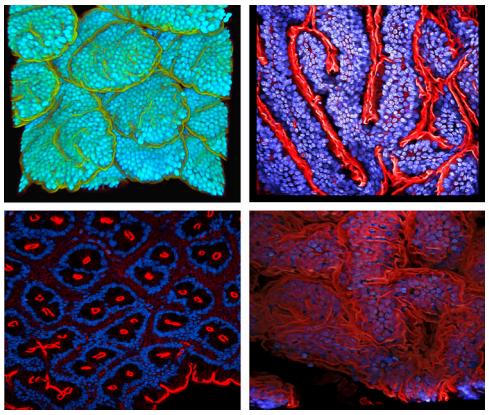
We think this is why you see APC mutations so frequently in colon cancer. The intestine is not a friendly environment; gut epithelial cells only last about five days so they must be continually replaced. As a result, gut tissue is uniquely dependent on adhesion, migration, proliferation, differentiation, and apoptosis—and APC touches on all these processes. APC mutations might permit cells to persist for a longer time in the toxic gut environment and to tolerate small errors, so they have a greater opportunity to accumulate additional genetic hits and become cancerous.

Where are your research interests taking you now?

There are obviously lots of angles from which we could approach working with APC, and that's what I've built my career on. When I first established my lab here at Dundee, we worked on the hardcore cell biology of the protein, looking at its interactions with the cytoskeleton. But over the last several years, we and others have accumulated evidence of new areas where APC plays a role—recently it's even cropped up in DNA repair and in hypoxia. We're now picking apart whether these are direct or indirect links. We're trying lots of new biochemical assays to look at APC's interactions with other proteins, and using fluorescent probes to explore these interactions in cells.

One of our goals is to explore how APC's interactions with its partners are regulated. An increasingly important aspect of our work is to look at whole tissue physiology and whole tissue architecture to see whether the changes we see in cells in Petri dishes translate into changes in gut tissue. We are even starting to explore, using a computer modeling approach, how mutations in APC affect the mechanical properties of gut tissue. It feels like a lot of work and my lab is pretty small, but I have a really talented and dedicated group of people who help shape each step in the work we're doing. I love going to work in the morning.

1. Quyn, A.J., et al. 2010. *Cell Stem Cell.* 6:175–181.
2. Dikovskaya, D., et al. 2010. *J. Cell Sci.* 123:736–746.
3. Li, Z., et al. 2008. *J. Cell Sci.* 121:1916–1925.
4. Dikovskaya, D., et al. 2007. *J. Cell Biol.* 176:183–195.
5. Penman, G.A., et al. 2005. *J. Cell Sci.* 118:4741–4750.
6. Näthke, I.S., et al. 1996. *J. Cell Biol.* 134:165–179.
7. Näthke, I.S., et al. 1992. *Cell.* 68:899–910.



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The elaborate architecture of gut tissue.