People & Ideas

Peter Walter: Investigating how the ER handles secretory proteins

Walter studies how proteins are targeted to the endoplasmic reticulum and how cells deal with ER stress.

Peter Walter views the process of research as an ever-evolving detective story (1). He's spent his long career sleuthing out how proteins reach the ER membrane (2, 3) and how the ER regulates itself in response to the amount of proteins it needs to handle (4–5).

These investigations, says Walter, started in earnest during his graduate and postdoctoral work in the lab of future Nobel laureate Günter Blobel. It was there that Walter first identified the signal recognition particle (SRP) and the SRP receptor (2), which cooperate to guide nascent proteins to the ER translocon (3). His scrutiny of the unfolded protein response (UPR)—the method by which cells sense (4) and cope (5) with backlogs of unfolded proteins—continues to provide important revelations about this process. We called him at his lab at the University of California, San Francisco to discuss how he's identified some of the culprits in these pathways and what new suspects he's chasing down.

> "I get really excited whenever something doesn't make sense."

ROOKIE

You were born in Germany. How did you end up in the United States?

Yes, I grew up in West Berlin. My dad had a little chemist's shop, and I helped out there a little bit and became fascinated with chemistry at a young age. When I was 12, I decided I was going to become a chemist.

I think most of the chemistry that fascinated me as a kid involved things that reacted violently with one another [laughs]. The various explosive reactions were just wonderful to play with. My parents never knew about many of those experiments.

Then, at some point, it became very clear to me that I had to learn some English in order to survive as a researcher. I wasn't very good at languages, and I never got more than a C in my English classes in school. I applied for a Fulbright fellowship to spend a year in the United States but was rejected because my English was not good enough. I was stubborn, though, and I applied for a direct-exchange fellowship. I was assigned to go to Vanderbilt University in Nashville, so in 1976 I went there for a year. It was quite a culture shock. Nashville at that time was a very small town, not particularly cosmopolitan; coming from Berlin, it was quite different.

Where did you go next?

I felt that the curriculum at Vanderbilt was strangely structured, in that it was geared too strongly toward passing exams instead of developing a true understanding of the subject. It was very different from what I loved about higher education in Germany. Rockefeller University, on the other hand, had a very loosely structured curriculum; you could basically design your own classes. And I met fantastic people doing exciting science when I interviewed there. So, it seemed like too good an opportunity to pass up. I had promised my mother that I would only stay for nine months in the United States. She's still asking me when the nine months will be over.

After an initial rejection, I slipped in on the waiting list and went to Rockefeller in 1977 to start my graduate work. They didn't have a rotation system, so we basically just went around, talking to people. I talked to various faculty including Günter Blobel. Günter told me that he didn't have room in his lab, so I went to talk to many others. Then one week, out of the blue, Günter called me back and said I should try out his lab. So I joined his lab, and everything turned out wonderfully.

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Peter Walter

GUMSHOE

It must've been an exciting time to be in the Blobel lab.

Oh, it was absolutely fantastic. The lab was small—I think there were about 15 people. Günter wasn't working at the bench himself anymore, but he was so enthusiastic and engaged with every experiment. The time I spent there was the best time of my life. Everything was working great in the lab, and I loved living in New York. It was just fantastic.

We were trying to identify proteins involved in protein translocation. Günter and Bernhard Dobberstein had postulated in the signal hypothesis that there was a protein machinery taking care of these sorting and translocation events. The alternative hypothesis said that signal sequences are greasy enough that they would just partition spontaneously into the membrane and drag any attached protein along, so that you wouldn't need a special apparatus. We set up chemical assays to monitor protein translocation across membranes. We identified the SRP and, together with Reid Gilmore, the SRP receptor, which between them recognize signal sequences and target ribosomes to the ER membrane.

What did you find most exciting about working on the SRP?

I think what was most exciting was to have

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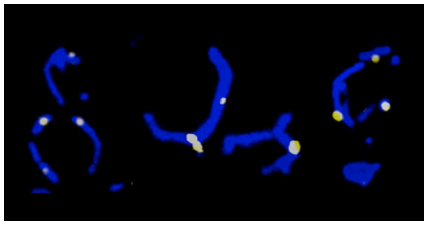

IMAGE COURTESY OF BENOÎT KORNMANN

ER/mitochondrial junction complexes (pale yellow) with the mitochondrial network (blue).

a project where I could just explore and discover components involved in the process. It gave me a flavor of detective work. You're never quite sure who the culprits are.

Another fascinating thing about the process of science is that there is a lot of serendipity involved. If you're paying attention, you can make important observations that can change the landscape completely. This has happened to me a number of times. For example, we had identified the SRP as a protein complex. Only later did we discover that it has an RNA component in it:

I was using a spectrophotometer, as I had done many times previously, but the student who used it before me had left a different filter in the instrument. So, rather than reading the absorption at 280 nanometers, we read it accidentally (or serendipitously) at 260 nm and got this huge peak. I was convinced that the concentration of my sample couldn't have been off so badly, so following up on that, we discovered that there is a nucleic acid contained in the particle. It was really a discovery that was made both by chance and because we followed up on something that didn't make sense.

Now I get really excited whenever something doesn't make sense. It's very aggravating to my students sometimes when they show me a beautiful result and I tell them, "Yeah. So what? We expected that. But what about this lane over here?"

PRINCIPLE INVESTIGATOR

Another major theme in your career has been the unfolded protein response…

By that time I had moved to UCSF, where I still am today. I had two graduate students in my lab, Jeff Cox and Caroline Shamu, who wanted to do some forward genetic screens. (Everyone's lab at UCSF at that time was using genetic approaches in their work, thanks to the persuasive influence of my colleague and mentor, the late Ira Herskowitz.) We wanted to ask a very simple question: how does the transcriptional program in the nucleus become informed about what is going on in the lumen of the endoplasmic reticulum? So, we set up a screen to get at this communication pathway, and the first mutant we isolated was IRE1, a transmembrane kinase sitting in the ER that figures out what's happening on the inside of the ER and then transmits that information across the membrane to the cytosol. Ire1 is one of the major elements that controls the UPR. That discovery started off a whole new field for us.

> "We have an incredible freedom to pursue discoveries."

Because the UPR makes life or death decisions for cells, it has now been implicated in many different diseases. I think one of the most wonderful things for us would be if we could take the process of discovery all the way from yeast and in the end do something that's useful in a clinical setting. So, we are moving more and more toward mammalian systems and trying to establish approaches with which we can manipulate the UPR.

Also, in a new adventure starting once more with a genetic screen, we discovered junction complexes that intimately tether the ER and mitochondria. We think that lipids are transferred between the two organelles at these sites and that, perhaps, the organelles use them to communicate their metabolic state to each other more actively than previously appreciated.

Do you have any advice for those just starting their research careers?

Well, it's a hard job. Usually when we talk to our students, we don't emphasize how difficult it can be. Discovery is unpredictable. Sometimes you have dry spells you have to get through. I think my main advice is never to forget why we got into this in the first place. We have an incredible freedom to pursue discoveries. One really has to enjoy the process and what one's doing every day. If one then pays sufficient attention to detail, one will give serendipity a chance. There remains so much to be discovered, and luck strikes the prepared mind.

What about life outside the lab?

I loved doing experiments as a graduate student and postdoc, but now I seem to spend the whole day in front of a computer. To balance that, I love to do photography and woodworking. I also took some classes in welding, so I make some sculptures. I think for me it's important to balance the theoretical work and the management work with using my own hands and keeping my dexterity.

It's also nice that in woodworking you know right away when you mess up: you then hold this perfectly machined piece of firewood. It's not like science, where it often takes you a few years to figure out whether you barked up the right tree.

1. Walter, P. 2010. *Mol. Biol. Cell.* 21:15–17.
2. Walter, P. 1980. *Proc. Natl. Acad. Sci. USA.* 77:7112–7116.
3. Shan, S.O., R.M. Stroud, and P. Walter. 2004. *PLoS Biol.* 2:e320.
4. Cox, J.S., C.E. Shamu, and P. Walter. 1993. *Cell.* 73:1197–1206.
5. Li, H., et al. 2010. *Proc. Natl. Acad. Sci. USA.* 107:16113–16118.

PHOTO COURTESY OF PETER WALTER

Walter's fountain sculpture entitled "Triffid."