Ruth Lehmann: Germ cells do things differently

Lehmann studies the developmental program that sets the germ line apart from somatic cells.

In most organisms, germ cells are set aside from somatic cells early in development. How are germ cells programmed for their developmental destiny and for germ line–specific behaviors such as meiosis? These are questions Ruth Lehmann wants to answer.

Working in *Drosophila,* Lehmann has made many seminal discoveries in the field of developmental biology. Early on, her work on maternal effect genes such as *oskar* and *nanos* revealed how these genes, which control posterior development, are subject to complex regulatory mechanisms based on the localization of their mRNAs (1, 2). More recently, she's begun to dissect the unique migration mechanisms that nascent germ cells use to home to the gonads in the developing embryo (3–5). We called her at her lab at New York University's Skirball Institute to discuss how germ cells find their proper developmental path and how she found her way to studying them.

DEVELOPMENTAL PATH

As a child, what did you want to be when you grew up?

My mother, who was a teacher for mentally handicapped children, was interested in literature and the arts; my father, an engineer, was more interested in science. I was interested in both, but, although I liked reading and poetry, it was very clear to me this wouldn't be an easy career track.

I first became interested in biology during high school. I had a biology teacher who was also teaching at the university at the time and who really raised my interest in the subject.

So you studied biology at university?

I went to the University of Tübingen and majored in biology. In German universities, you start right away studying your major, but I was really disappointed about the teaching and the classwork there. So, I did a lot of extracurricular activities, one of which entailed publishing a poetry book every three months. For that, I collaborated with a group of Americans who were working at the university's German department. They knew I was not happy with my courses at Tübingen, and they suggested that I go to America to study. So, I applied for a Fulbright Fellowship to study ecology in the US. I received the fellowship and was sent to Seattle, where I became interested in genetics. I joined the lab of Gerold Schubiger, a fly developmental geneticist. That was a really great experience because Gerold made a real effort to involve everyone in his lab and to take everyone seriously, even undergraduates. It was also a great place to be scientifically, because fly developmental genetics was just starting to explode.

EARLY SPECIFICATION

But you returned to Germany when your fellowship was up?

It wasn't possible to stay in the US or to study developmental genetics in Tübingen. I felt horrible: what was I going to do? Gerold suggested that I attend a meeting of the Society for Developmental Biology. I met several interesting people there, but the most important one was Christiane Nüsslein-Volhard. At that time Janni was a postdoc in Freiburg and was transitioning to take a joint position with Eric Wieschaus at the EMBL in Heidelberg. She was working on how the body plan of the embryo might be established by morphogen gradients. I was sure that this was what I wanted to do, so I got all my courage together, and I went up to her and said, "Could I come and study with you?" But she said, "I'm sorry, we don't have graduate students at EMBL." Whoops!

> "From the first day, I was in the lab all the time."

But then she suggested I contact José Campos-Ortega, at Freiburg, who was working on neurobiology in *Drosophila*. I did, and he agreed that I could come and work in his lab as a diploma student. So I returned to Germany and switched universities from Tübingen to Freiburg. And, from the first day, I was in the lab all the time.

PHOTO COURTESY OF JOHN ABBOTT

Ruth Lehmann

Almost every weekend I would drive up to Heidelberg to visit Janni and Eric when they were doing the zygotic screens that earned them the Nobel Prize to discuss the phenotypes with them. Whenever their screens turned up mutants with defects in nervous system development, they sent them to José for us to analyze. I actually characterized all these mutants and started to do some genetics. I named several genes, such as *mastermind* and *big brain*. *Mastermind* I named after the game Mastermind, which I used to play with my father. He had multiple sclerosis and at that time he was not well, but we enjoyed playing this game together. Now, whenever someone mentions the gene *mastermind*, I always think of my father. It's very nice.

But you did finally get to work with Dr. Nüsslein-Volhard?

Yes. By the time I'd finished my undergraduate studies, including my diploma thesis, she had moved to Tübingen as a group leader, so I joined her lab for my PhD.

Text and Interview by Caitlin Sedwick
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That was where we first started the maternal effect screens, trying to identify genes that need to function in the mother for the normal development of the embryo. I started working on mutants that showed defects in posterior patterning during early development. Toward the end of my PhD, I had identified multiple genes that affected this posterior patterning and the specification of the germ plasm, and I wanted to keep working on them. Fortunately, Janni is a very generous person, and she wasn't terribly interested in this part of the embryo, so she said I could just take the work with me if I wanted.

The year I received my PhD, Janni sent me to a Gordon Conference, which was an amazing experience for me because the climate in Germany at that time was very poor for women scientists. Janni was off the scale—a great intellect and teacher, but even she couldn't get a job. The jobs she applied for kept going to mediocre men. But at that Gordon Conference I realized that in the US there were actually many more women who were really excited about science. One of these women was Barbara Meyer, who must have returned to MIT from the conference and said, "I heard this woman talk," because MIT offered me a faculty position at the Whitehead Institute the following year.

MIGRATION

At the Whitehead Institute, you continued working on these maternal effect genes?

From the whole class of these posterior group genes, I had singled out two genes, *pumilio* and *nanos*, that affected abdominal patterning, and one, *oskar*, that also affected germ cell formation and germ plasm. So the idea then was to clone these genes.

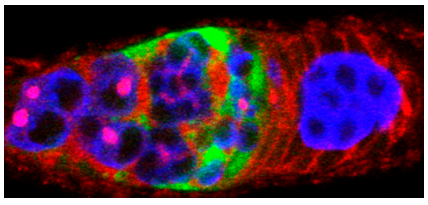

IMAGE COURTESY OF ANDREA ZAMPARINI

The germ line stem cell niche contains germ stem cells (blue), somatic support cells (green), and spectrosomes (red).

I went to the MRC in Cambridge, UK, for one year to learn molecular biology in Mike Wilcox's lab and then started my lab at MIT. When we cloned the three genes, we found they were all novel, which gave us very little information about what they were doing. It took us a long time to figure out how they work. We found that *nanos* and *oskar* RNAs are localized to the posterior pole of the embryo and that their localization controls their translation and their ability to direct posterior patterning and germ cell formation. That work was a real tour de force, putting lots of pieces of data together and testing our ideas about what they meant. I'm still very proud of it.

RNA regulatory mechanisms keep cropping up in your work…

Now we're looking at many different aspects of germ cell biology. There doesn't appear to be any single transcription factor that specifies germ cell identity. Instead, there are many overlapping mechanisms for RNA regulation that are really important. These mechanisms are conserved from flies to worms to mice to humans, and they are all working together to achieve two things: on the one hand, to prevent somatic differentiation and, on the other, to program germ cell–specific behavior. It clearly isn't sufficient to just turn off somatic differentiation; you also have to turn on programs like meiosis. At the moment we're also trying to figure out the transcriptional program in germ cells.

> "When you do forward genetics, you do it for the surprises."

It's clear to us that germ cells do many things differently than somatic cells. For instance, in many organisms the germ cells are set aside somewhere, but they cannot make egg or sperm on their own, so they have to migrate to the developing somatic gonad. When I moved to NYU, we started to look at this systematically by doing forward genetic screens for mutants deficient in germ cell migration, with some quite surprising results. For example, Mark van Doren, then a postdoc in my lab, identified the gene encoding HMG CoA reductase from one such screen. He was at first quite disappointed because it's a housekeeping gene and not a gene that we might expect to be involved in migration. But when you do forward genetics, you do it for the surprises, so he kept working on it. Now we think that HMG CoA reductase is involved in the manufacture of a secreted germ cell attractant. We haven't identified the attractant yet, but we're getting close.

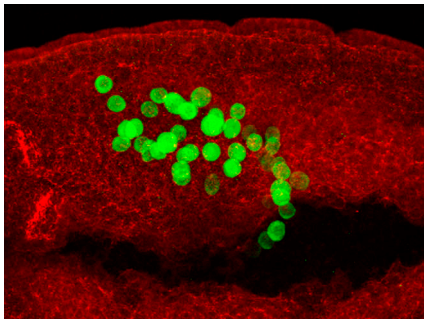

IMAGE COURTESY OF BRIAN RICHARDSON

Germ cells (green) migrating toward the somatic gonad (red).

We've recently become interested in piRNAs. These are small RNAs that are deposited in the germ plasm and are present throughout the germ line life cycle. They're thought to originate from defective transposable elements and to target intact elements for destruction.

Because transposable elements can rearrange the genome, they pose an enormous threat to genome stability. The germ line's goal is to produce successful progeny, so maintenance of the germ line genome is paramount. But it is also important that the next generation is different and has a better chance to survive. piRNAs are one mechanism that helps balance the need to keep the genome intact and yet also allow evolution to carry on.

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