

People & Ideas

Melina Schuh: First comes the egg

Schuh studies the assembly and positioning of the oocyte meiotic spindle.

Envision a typical somatic cell—say, a murine epithelial cell—at metaphase of a mitotic division. Compared side by side with a mouse oocyte undergoing meiosis, these two cells look so radically different under a microscope that one might be forgiven for thinking they come from entirely different organisms. The epithelial cell has a centrally located, oblong spindle apparatus, whereas the oocyte has a barrel-shaped spindle pushed up against one side of the cell. What explains these differences, and how do they affect the business of faithful chromosome segregation in germ cells?

These are the kinds of questions Melina Schuh would like to answer. Schuh has already shown that oocytes use entirely different methods from mitotic cells to assemble (1) and position (2) their spindle apparatus. Spindle positioning, her lab has shown, depends upon a dynamic actin network (2–4) that meiotic oocytes can also exploit for other purposes (5). We called her at her lab at Britain's Medical Research Council Laboratory of Molecular Biology to discuss how these findings have matured in her lab and the plans she's currently hatching.

A GOOD PROJECT

What sorts of things interested you as a child?

When I was a child I did lots of sports like volleyball, swimming, and athletics. I also played different instruments, like flute and piano. I didn't become interested in biology until much later, when I first learned in school how cells are organized internally.

Yet you had your first publication before your PhD...

I grew up in a city called Bad Pyrmont, a spa resort in northern Germany. After I finished high school I wanted to see something new, so I moved to Bavaria to study biochemistry in a city called Bayreuth. For my diploma thesis, which is similar to

a master's, I joined the laboratory of the fly geneticists Christian Lehner and Stefan Heidmann. Christian had recently received the Leibniz Prize for his work on cell cycle regulation in *Drosophila* and had spent some of his award money to purchase a confocal microscope. That's when I fell in love with microscopy.

I was working on a project to understand how the histone variant CENP-A is incorporated into centromeres, and I found that CENP-A was incorporated during anaphase and telophase, which was quite unexpected. I was lucky with that project because pretty much every experiment worked and we had some interesting results. We even had the paper reviewed by *Science*, but ultimately it was rejected because we couldn't show our data were relevant outside *Drosophila* embryos. It was then published in *Current Biology*, and later it turned out the mechanism was conserved in other cell types. That paper remains one of my most highly cited publications.

A NEW MODEL

Why did you select Jan Ellenberg's lab for your PhD studies?

I really enjoyed the quantitative live cell imaging work that I had done during my diploma work, and Jan's lab at EMBL had expertise in studying cell division by quantitative live cell imaging.

It seemed like the perfect fit for my interests. His group was studying the functions of actin in starfish oocytes at the time, and I was thrilled by the idea of studying meiosis. Meiosis is still much more poorly understood than mitosis, especially in mammals. So I convinced Jan to let me establish live cell imaging conditions for mouse oocytes.

Were many other people working with mouse oocytes at that time?

No, this was really a very new field, and I think we were one of the first labs to use confocal microscopy to study mouse oocytes.



Melina Schuh

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"Meiosis is still much more poorly understood than mitosis, especially in mammals."

There were a few studies of meiosis on live mouse oocytes, but they mostly used wide-field microscopy because there were so many challenges to using confocal microscopy with these enormous cells.

It sounds like a rather ambitious project for a graduate student, to establish an entirely new system...

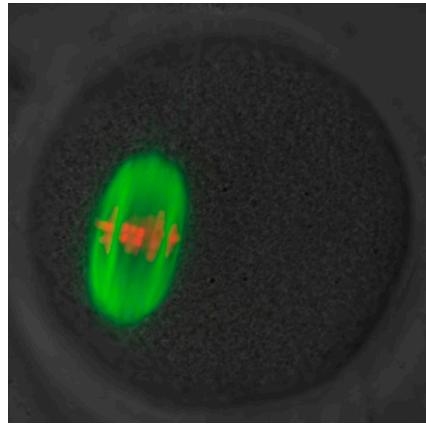
I remember I was interviewed for a fellowship at the beginning of my PhD, and the professor who interviewed me told me, "Gosh, this really sounds like one of those ambitious PhD projects that is going to just waste another student." But I already had some preliminary data showing that it worked in principle. If I hadn't had those data, I probably wouldn't have gotten the fellowship.

I think I was lucky that the work during my diploma thesis had gone so smoothly. I was probably a bit naïve about what science is like and how hard it is to get things to work, but that experience helped me to be courageous and self-confident enough to take on this more challenging project during my PhD.

You first used this system to study spindle assembly in oocytes...

In mitotic cells the spindle is assembled by two centrosomes, but centrosomes are absent in mammalian oocytes, including mouse and human oocytes. So it was not clear how a bipolar spindle assembles in the absence of two centrosomes that can

IMAGE COURTESY OF MELINA SCHUH



The meiotic spindle (green) and chromosomes (red) in a mouse oocyte.

define the spindle poles. We found that numerous microtubule-organizing centers, which lack centrioles, functionally replace the centrosomes in mouse oocytes and self-assemble into a bipolar spindle.

In parallel, I was continuing the work that Jan had started in starfish oocytes on the functions of actin. In particular I wanted to investigate how actin is involved in asymmetrically positioning the oocyte spindle. In mammalian oocytes, the spindle forms quite close to the center of the cell, but then it needs to move to the oocyte surface because the oocyte needs to divide extremely asymmetrically during meiosis. This is only possible if the spindle is asymmetrically positioned.

It had been known for some time that actin was required to position the spindle asymmetrically, but how it was involved in this process was unclear. We found that the oocyte assembles a dynamic cytoplasmic actin network that is required to position the spindle asymmetrically, and we also showed that the spindle poles pull on the actin network in a myosin-dependent manner.

OOCYTES DO IT DIFFERENTLY

You took this project with you directly to your own lab at the MRC LMB...

It happens quite frequently at EMBL that graduate students become group leaders immediately after their PhD, especially if

they've developed a new model system that they want to continue working with. And the LMB was really the ideal place for me to start my own lab. It has a lot of core funding and excellent facilities, so I could have my own confocal microscope, for instance. The LMB also has a tradition of having very small groups, so at the beginning it was just me, a postdoc, and a student. I spent a lot of time working in the lab and setting up projects myself. I enjoyed that a lot, and I think it was a really good way to transition towards the group leader position.

We continue to study the mechanisms involved in asymmetric spindle positioning. We identified, for instance, new actin nucleation factors that are involved in generating the cytoplasmic actin network that helps to position the spindle at the cell surface. We also found that this actin network transports vesicles over long distances, which was very unexpected because long-range transport of vesicles is generally thought to occur along microtubules.

More recently we found that the vesicles are not only passengers on the actin network but they are also involved in modulating the network's properties. For instance, they

drive actin dynamics by recruiting an actin-dependent motor protein, Myosin-Vb, and they also help to control the actin network density by clustering and sequestering actin nucleation factors.

Now we'd like to understand better how the actin network is organized, both on a structural and molecular level. We'd also like to investigate what other functions it might have in addition to transporting the spindle and vesicles to the cell surface.

Why does the oocyte use actin instead of microtubules to position its spindle?

One key difference between the spindle in mitotic cells and meiotic cells is that in mitotic cells the spindle has centrosomes that help to nucleate rather long astral microtubules. But in mammalian oocytes centrosomes are absent, and there aren't these astral arrays of microtubules that can interact with the cortex.

I can only speculate why mammalian oocytes don't have centrosomes, but I think one possibility has to do with the fact that meiotic cells divide twice, without an S phase in between. Normally a cell's centrosome is duplicated in S phase, but in meiosis this doesn't take place. So if an oocyte starts with two centrosomes, then after the first meiotic division it would only have one left. That centrosome could of course split into two centrosomes with only one centriole, and this is in fact what happens in starfish oocytes. But the centrosome with the single centriole that remains after the second meiotic division is degraded shortly after completion of meiosis. The alternative might be to simply get rid of the centrosomes during oocyte development, as happens in mammals. Perhaps this is why the oocyte has devised another way to assemble its spindle and to position it, so that it does not rely on the centrosomes.

Are you also studying the spindle now?

Yes. We're trying to better investigate how the spindle is organized. We want to know whether defects in spindle assembly could contribute to aneuploidy.

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Schuh relishes unexpected challenges, whether they come in the lab or further afield.