Angelika Amon: Conquering the divide

Amon studies how cells segregate their chromosomes and what happens when they get it wrong.

Mitosis is a fantastically complex process, but the simple beauty of chromosome segregation can captivate even the untrained eye. When Angelika Amon saw a video of a dividing cell as a schoolgirl in Austria, it set her on a path to a professorship at the Massachusetts Institute of Technology in Cambridge, MA, where she continues to investigate chromosome segregation and the consequences of mitotic errors.

Amon began her research career as a PhD student with Kim Nasmyth at the Institute of Molecular Pathology in Vienna, studying how cyclin levels are controlled over the course of the budding yeast cell cycle (1). After a brief postdoc with Ruth Lehmann at the Whitehead Institute in Cambridge, MA, Amon was offered the chance to start her own lab at the institute as a Whitehead fellow. She returned to studying the yeast cell cycle, identifying some of the key proteins that trigger cyclin degradation and mitotic exit (2, 3). Since joining the MIT faculty, Amon has continued to investigate how one of these proteins—Cdc14—is regulated (4, 5), while also studying how the basic mitotic machinery is adapted for the two sequential divisions of meiosis (6). More recently, Amon has turned her attention to the consequences of aneuploidy—abnormal numbers of chromosomes due to segregation defects—and its potential links to tumorigenesis (7, 8). In a recent interview, we spoke with Amon about her passion for cell division and where her research is heading next.

> "Working in yeast... the rate-limiting step is your brain."

ENTERING THE CELL CYCLE

Where did you grow up?

I grew up in Vienna, Austria. I was always interested in science—I wanted to study dinosaurs when I started school, and then I wanted to be a zoologist for a long time. But when I was in high school, I saw some old chromosome segregation movies—black and white ones from the '50s. I thought it was the coolest thing ever, and I still do. Seeing the sister chromatids split takes your breath away. Most people have the same reaction. I now go to my children's schools to talk about being a scientist, and I always show them that movie. Even the youngest children appreciate that this is something special.

That interest in cell division led to you joining Kim Nasmyth's group for your PhD…

Yes, and he was a fantastic teacher. Kim is probably one of the clearest thinkers of our time. Being in his lab was a remarkable experience, and I had the great privilege of being taught by Kim himself. He was still working in the lab, and my bench was next to his, though that wasn't always easy!

I studied how cyclins are confined to the right stages of the yeast cell cycle. First, I showed that there is some intricate feedback between the different cyclins at the transcriptional level. Then I showed that ubiquitin-mediated cyclin degradation is important for mitotic exit and that this degradation persists through G1 until it's turned off as cells enter the next cell cycle. That had an important practical implication because we could arrest cells at a stage where cyclins were continually degraded and look for mutants that could no longer degrade them. This allowed another postdoc in Kim's lab to identify genes required for cyclin degradation, which led to the identification of the anaphase-promoting complex.

Initially, you took a different direction for your postdoc and joined Ruth Lehmann's lab to work on* Drosophila *germ cell development…

Yes, and I still think she's one of the most wonderful scientists around today. It's just that flies weren't for me. Though I was greatly attracted to the genetics of *Drosophila*, everything had to be done in such a roundabout way at that time. What's so incredible about working in yeast is that the rate-limiting step is your brain. You can do anything you can think of very cleanly and precisely. But after two years, Ruth left for New York, and I got the wonderful opportunity to become a Whitehead fellow and start my own independent research group.

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Angelika Amon

RECYCLING TO CYCLINS

Did you consider doing another postdoc with somebody else instead?

I did think about it. I was unsure about this decision until I realized that it was a great opportunity to see whether I could run a lab on my own. I thought that, if I failed, at least I would have found out earlier that I was no good at it, without wasting four years as a postdoc.

In hindsight, it was truly the best thing that ever happened to me. The Whitehead fellows program is really good for women because it allows you—at a relatively early age—to do science without having to spend 15 hours a day in the lab. You have a technician or maybe a postdoc to do a good fraction of the experiments. I was really lucky to have two gifted and motivated women work with me, so I was able to have my first child at the age of 31. For a scientist, that's young. I really believe this type of fellowship is the best way to promote women in science.

Text and Interview by Ben Short
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As a Whitehead fellow, you returned to working on the budding yeast cell cycle…
The first thing we did was to discover that Cdc20 and Cdh1 activate the anaphase-promoting complex. That was an important discovery for the field. But I realized that the *Xenopus* biochemistry labs were in a much better position than us to figure out the mechanism. So, I made a conscious decision not to pursue this any further.

Instead, we started to investigate how cyclin degradation was triggered during mitotic exit. That was completely unclear at the time. We had developed a number of assays to look at cyclin destruction, and we screened candidates from Lee Hartwell's original Cdc collection. Cdc14 looked the best, and it turned out to be very important for mitotic exit in budding yeast.

We're still very interested in how Cdc14 is regulated. A few years ago, we discovered that a checkpoint that senses whether the spindle is positioned correctly regulates Cdc14 via a GTPase signaling pathway called the mitotic exit network. We still need to understand the details of this spatial control of mitotic exit. But there's a temporal control, too—Cdc14 activation is restricted to anaphase, and we really don't understand at all how that works.

You also work on meiosis. What interests you about this type of cell division?
We're interested in how the basic cell cycle machinery is changed by meiosis-specific factors—how the kinetochore is altered so that sister chromatids co-orient toward the same spindle pole during the first meiotic division, and how sister chromatid cohesion is regulated differently during meiosis. More recently, we've also begun to study how a cell decides to enter meiosis. What triggers the decision to become a germ cell? It's a very poorly understood process.

> "At the organismal level it's clear that aneuploidy is detrimental."

WHEN MITOSIS GOES BAD

A few years ago, you started to work on aneuploidy. How did that come about?
We always write in our grants that we need to understand chromosome segregation because when cells mis-segregate chromosomes, they become aneuploid and this causes cancer. But we don't really know if that's correct. It's true that the vast majority of tumors are aneuploid, but we don't know what aneuploidy does to cells. At the organismal level it's clear that aneuploidy is detrimental. An extra chromosome is frequently lethal or causes severe problems in all species where this has been analyzed. As a yeast geneticist, you'll sometimes get a chromosome mis-segregating during a cross, and that invariably makes the yeast cell sick. But in the context of cancer, aneuploidy is associated with high proliferative potential.

Something doesn't chime there, and we thought that the only way we could understand it was to first determine what the effects of having an extra chromosome are on a normal, untransformed cell. Then we can ask how, if at all, this contributes to cancer.

What effect does aneuploidy have on cells?
It stresses them. It turns out that these extra chromosomes are active in yeast, mice, and humans, and they produce transcripts and proteins. These extra proteins can have specific effects—β-tubulin, for example, is very toxic when it's overexpressed. But our data suggest that there are also more general effects that cause proteotoxic stress. Extra proteins might lead to partially assembled complexes, and cells really don't like that. There are only a limited number of ways for a cell to deal with these extra proteins, using either the proteasome or the chaperone system. So even though, depending on the aneuploid chromosome, the proteins causing the problems are different, they put stress on the same pathways in all cells.

Now the question is: can we identify mutations that suppress these adverse effects? Such mutations might be important during tumor evolution, because they would allow aneuploid cells to grow better. We also want to look for synthetic lethality—perhaps we can find ways to preferentially kill aneuploid cells.

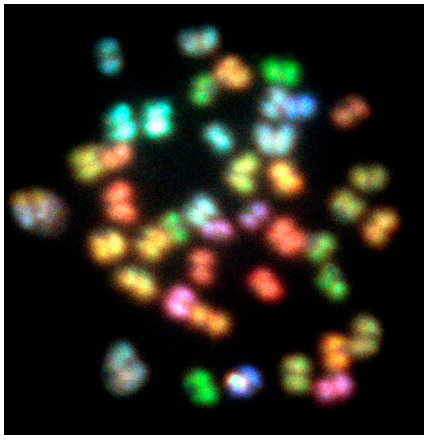
IMAGE COURTESY OF YUN-CHI TANG

A metaphase spread from mouse B cells shows trisomy for chromosomes 5 and 14.

Is mis-segregation just something that cancer cells have to mitigate, or are there actual benefits to aneuploidy?
I think there is a lot of evidence to suggest that even though aneuploidy, per se, is bad for cells, it can be beneficial in specific circumstances. There was a beautiful study from Judith Berman's lab that looked at antifungal resistance in yeast. Duplicating a region of chromosome 5 that encodes ERG11, the target of the antifungal drug, and TAC1, a transcriptional regulator of drug efflux pumps, allowed the yeast to grow better in the presence of the antifungal agent, even though the cells grew poorly under normal growth conditions. So maybe during metastasis, for example, aneuploidy could be beneficial and help cancer cells to conquer a new niche.

There are still lots of things we want to understand in this area, but I'm always looking for new things. I've decided I need to work on how mitochondria talk to the nucleus. I think that's an interesting question. I wish I had 60 people in the lab, and then we could do all these things!

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