Unanticipated Success Stories: An Interview with Angelika Amon

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THE Genetics Society of America Medal is awarded to an individual for outstanding contributions to the field of genetics in the past 15 years. Recipients of the GSA Medal are recognized for elegant and highly meaningful contributions to modern genetics. The 2014 recipient, Angelika B. Amon, has uncovered key principles governing the cell cycle and was the first to demonstrate a connection between the physical completion of anaphase and the initiation of mitotic exit. More recently, her research has focused on the consequences of aneuploidy. *GENETICS* spoke with Dr. Amon about her approach to science and what is next on the horizon.

You say your work is driven by curiosity: how does this relate to the applied aspects of your research?

The truth is that most medical breakthroughs have ultimately come from basic research, and I think that we as scientists need to do a better job of telling these success stories. My favorite example is that antibiotics came out of finding a random contaminant on a plate. And remember that we have CRISPR [clustered regularly interspaced short palindromic repeats] tools only because people were studying some bizarro antipathogen mechanism in bacteria. It's a beautiful example of something entirely unanticipated coming out of left field. That's why it's important to maintain funding for a very diverse program of basic research; history tells us you can't predict where the next advance will come from. Right now it seems like funding agencies and the public have an engineering mentality, and they believe that, as long as we think hard enough about a problem, we can solve it. That's an admirable attitude, but in the life sciences it's not always the right path to discovery.

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—A.B.A.

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Aneuploidy is a problem with a lot of medical relevance: why study it in yeast?

For many years, we used to write in the "significance" section of grant applications that the reason that it is important to understand chromosome segregation is because, when it fails, cells become aneuploid and cancerous. But that statement always bothered me. Why should aneuploidy cause cells to proliferate? When you do yeast crosses and by chance get an aneuploid strain, invariably the cells do poorly. And for most chromosomes in multicellular organisms, having an extra copy is lethal.

One explanation is that building an organism is a complicated procedure, so if you change the gene dosage of certain genes, you mess everything up. That's probably true. You could then further argue that, at the cellular level, maybe it doesn't really matter how many chromosomes you have, as long as you have at least one of each. Perhaps extra chromosomes are actually good for an individual cell and allow it to keep proliferating when they should not and this gives you cancer. However, we never thought this was very likely, given that aneuploid yeast often proliferate poorly. So we thought we needed to investigate this conundrum.

So the power of studying a unicellular organism is it's just one cell. You can very agnostically ask: what happens to a cell if you change the chromosome number? Yeast was the right organism for this because we have genetic tricks and selection methods to generate aneuploids that are stable enough to study. Because this allowed us to examine many different types of aneuploidies at the same time, we could

look for broad patterns. We couldn't have done it in any other organism.

Actually, we do all our discovery work in yeast. And when we find something interesting, we move it into the mouse or human cell lines and ask whether we see the same thing. Sometimes the answer is "no," but more often the answer is "yes." It's just harder to discover fundamentally new things in very complex organisms where the repertoire of tools is limited. And I would argue that, under some circumstances, studying yeast cells is a better idea than studying highly transformed human cells in a dish. I guarantee you those cells look nothing like the ones in your body!

Angelika Amon's work over the past 15 years has guided all of us who think about mitotic and meiotic cell division.

—Jim Haber, Brandeis University

What have you found so far with this approach?

The direction of the aneuploidy project was completely unanticipated. At the beginning, we wondered whether there was a systematic way the cell avoids losing or gaining chromosomes. To be honest, I was hoping there would be some kind of cute mechanism that counts chromosomes. That turned out to be completely wrong. Or at least we haven't been able to find anything of this sort. Once we realized that, we had to step back and let the genetics lead the way.

We did a lot of phenotypic characterization and then developed hypotheses to explain the patterns we saw. One of our first productive ideas was that aneuploidy leads to proteotoxic stress. We believe proteotoxic stress is caused mainly by subunit imbalances of protein complexes. If complex subunits are not expressed in the correct ratios, often unassembled subunits need chaperones to maintain their soluble state and eventually need to be degraded if they cannot find a binding partner. This is what overloads the system. Another important idea has been that aneuploidy contributes to genomic instability. Cancer cells don't only lose or gain whole chromosomes, they also have translocations and deletions and point mutations. We know that making and repairing DNA requires a lot of nifty multi-subunit complexes, so our hypothesis was that whole-chromosome abnormalities cause stoichiometric imbalances in these complexes and this leads to defects in their formation and function. This could fuel the evolution of the cancer karyotype.

So we're testing the idea that aneuploidy contributes to cancer because it's a mutator, rather than because it's a promoter of growth and proliferation, and we're doing more and more mouse work to answer those kinds of questions. But we still use yeast to discover new properties of aneuploidy and to look at the cellular effects of changing the dosage of specific genes.

What is on the horizon for your research?

We started a new project on mitochondria a few years ago that I'm really excited about. Mitochondria were once independent entities and now they're part of the cell. One big question is: how did these two organisms start talking to each other? Did one learn English or the other learn French? Or did they resort to a more primitive sign language—metabolites—to talk to each other? The other thing I'm fascinated by is that a large fraction of uncharacterized yeast genes localize to mitochondria. That tells you there's a lot of biology in the mitochondria still to be learned. What I think is even more important is that many of these genes are not at all conserved, not even in fungi. So here are all these very new, very fast-evolving genes and nobody knows what they do! Usually when people hear that a gene is not conserved, they run! "Arrgh! It's something yeast specific!" But in this particular instance I think it's important and suggests mitochondria are still battling it out with the nucleus.

One way to look at it is to say the nucleus and mitochondria are not really symbiotic. If mitochondria don't get anything out of the relationship, they are really just slaves to the nucleus. So the mitochondria are trying to escape the reign of the nucleus and the nucleus is fighting back in an arms race. And if we can understand what all these nonconserved mitochondrial genes are doing, we can begin to find the frictions that still exist between the interests of the nucleus and the mitochondria. I'm totally fascinated by understanding how these different entities interact with each other inside a single cell.

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