People & Ideas

Andy Dillin: Using aging research to probe biology

Dillin uses genetics to probe the pathways that control cellular and organismal longevity.

As time passes, cells accumulate damage to genetic, protein, and lipid components, causing cellular aging and eventually death. Cells have extensive damage-mitigation pathways, but just what these pathways are, and how and when they operate, is still under investigation.

Andy Dillin is fascinated by these questions, but came to studying them in a roundabout way. He got his first taste of research in Ardythe McCracken's lab at the University of Nevada, Reno (1), and developed an addiction to science that only grew during his graduate studies in genetics with Jasper Rine's group at Berkeley (2). He found his true obsession after joining Cynthia Kenyon's lab, where he leveraged the power of *C. elegans* to explore the connection between metabolism and aging (3).

Dillin's own lab at the Salk Research Institute is working to understand how the cellular pathways that affect the rate of aging are triggered and integrated (4, 5). We sat down with him in his office overlooking the Pacific Ocean to chat about young scientists and aging cells.

REVELATION IN RESEARCH

What got you interested in science?

I grew up in Reno, and my high school chemistry teacher there, Mr. Wilcox, is the person who turned me on to science. I was failing every other class, but he took me under his wing and showed me that I could actually be a good student. I guess from then on I always knew I wanted to do science.

> "You can apply simple genetics to a complex trait."

As an undergraduate, I got a job as a technician and research assistant in Ardythe McCraken's lab at the University of Reno, Nevada. When I joined her lab, Ardythe was transitioning from tissue culture to yeast. We were all wrestling with this bizarre phenomenon where we would put an unfolded protein into the endoplasmic reticulum (ER) and it would get degraded in the cytosol. I worked on this as my undergraduate thesis, and figured out some of the mechanism. But it wasn't until after I left that Ardythe and her graduate student, Eric Werner, really figured it out. They, along with Jeff Brodsky at Pittsburgh, are the ones who coined the term ERAD (ER-associated degradation), which of course is widely used now.

Ardythe's a great mentor. She showed me that you can have a balanced lifestyle and do great science. You can be at a small university and make an impact on the bigger world.

So graduate school was a natural next step for you?

Yes. I was in love with Randy Schekman's work, so I applied to and was accepted at Berkeley. I rotated in Randy's lab and was offered a place there, but I had one more rotation to do before I could join. I decided to try out genetics, about which I knew little at the time. I rotated in Jasper Rine's lab and fell in love with the approach. I stayed there for my PhD, studying DNA replication and transcriptional silencing. Jasper's lab co-discovered the eukaryotic replication initiator. It gave us a lot of insights into how DNA replicates, and it was neat to see a whole field open up around it.

Jasper was also an important mentor for me. He taught me how to think critically about scientific results, and how to communicate about them effectively.

DISTRESSING DISCOVERIES

But as a postdoc you made a big jump in your research—into the aging field?

I thought a long time about what I wanted to do as a postdoc but I had a hard time settling on something. I would think about it all day then go home every night, and I'd watch whatever was on the Discovery Channel.

Andy Dillin

I was a total junkie for it; I think that subconsciously I was watching it to figure out what I wanted to do as a postdoc. I got several ideas from this, but for one reason or another most of them didn't pan out. At one point I was thinking about schizophrenia, which is a multigenic trait that would be really hard to study. I thought I might as well study something equally complicated, like aging! So I started looking into that, and found that Cynthia Kenyon's lab had discovered a single gene that could change an animal's life span. Her work showed that you can apply simple genetics to a complex trait—and I knew that was what I wanted to work on.

***In Cynthia's lab, you pioneered the use of RNAi for large-scale screens and conditional gene expression in* C. elegans?**

That screen saved my postdoc. I was so naïve. When I went to Cynthia's lab, the textbooks all said you start aging from the day you're born until the day you die. And I said, "Is that really true?" If that were true, then the genetic pathway that controls aging should be functioning that whole time. But it was possible that instead, there could be critical windows that control aging. I spent an entire year trying to set up an inducible expression system in the worm to test for these windows, but I got

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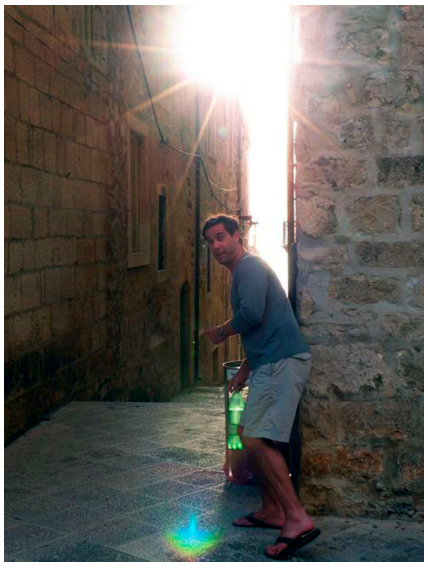
zero positive results. Thank God for Lisa Timmons, who was in Andy Fire's lab. Double-stranded RNA was known to interfere with gene expression, but she'd discovered that you could feed worms bacteria producing this double-stranded RNA. That gave us a means to control the timing of gene inactivation, and later we also figured out how to inactivate the machinery that allows RNAi to work in the first place. Using this system, we found that the worm doesn't start aging from the day it's born until the day it dies. Actually, we found a pathway that only works during a four-day window in the animal's life span, during reproductive adulthood.

As an additional project I set up a genomic screen to identify new genes that affected the aging process. Initially, I was concerned when my screen pulled out many nuclear-encoded mitochondrial genes. Cynthia's and Gary Ruvkun's work with insulin signaling had already pointed to a role for metabolism in aging, and I didn't want to end up competing with them in my own work. But it looked like I was going to be writing a paper on metabolism, after all. The classic metabolic theory of aging says that reactive oxygen species (ROS) cause accumulating damage throughout life. Therefore, if you can reduce metabolism (and ROS production), you should be able to increase lifespan by an amount proportional to the amount of time you decrease metabolism. I decided to take a closer look at this and found that the picture's more complicated. In fact, insulin signaling affects aging throughout reproductive adulthood, but this new mitochondrial pathway is something separate that affects aging only during a small window of development.



Dillin is excited to see what's around the corner for his research.

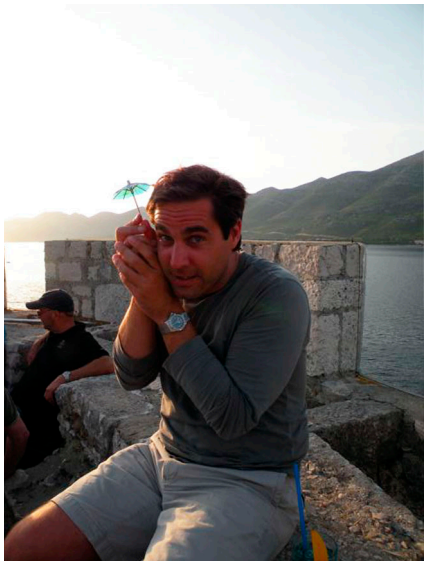
> "We're finding that metabolism is somehow feeding into the fidelity of proteome maintenance."

MANAGED BY METABOLISM

Since arriving at the Salk in 2002, what have you been working on?

Going back to my early fascination with protein folding that I developed in Ardythe's lab, we have turned our attention to how the proteome is protected during aging. We have made some neat discoveries about how toxic proteins are dealt with and followed this body of work into mice and human cells.

The other part of my lab works on the genetic circuitry of aging itself. We can talk of three major pathways that affect aging: the insulin pathway, the mitochondrial pathway, and a separate pathway activated by dietary restriction. We're concentrating on the last two of these. My lab has uncovered the genetic pathway that regulates dietary restriction and we are making equally exciting headway on the mitochondrial pathway. But it has not escaped our attention that all three of these pathways affect metabolism, leading us to ask: what aspects of metabolism promote healthiness? We're finding that metabolism is somehow feeding into the fidelity of proteome maintenance, thereby linking the efforts of all parts of the lab. Our thinking now is that when cells are stressed metabolically—not to the breaking point, but mildly stressed—they say, "If we're going to go to the effort to actually make a protein, we're going to make very sure that it folds properly because we don't have the resources to try again."



Dillin sheltering from UV stress.

This leads to changes in chaperone networks, improved proofreading processes on all levels, and better cell and organismal health. Of course, on a population level such stress is undesirable, because if you're stressed you're not too interested in breeding. But from the individual cell's or organism's standpoint it's a nice thing to live longer and more healthfully.

How do you keep healthy personally?

Well, first I make sure to keep my science addiction well fed at work. Then, I ride my bike to keep fit, although I no longer race like I did when I was at the University of Reno. I also spend a lot of time working on my house; I've renovated every house I've ever lived in. I'm currently building a wine cellar in my home, because I have two partners in the Bay Area, Raul Andino and Judith Frydman, with whom I've been making wine. We make about 700 bottles a year up there, and I'm putting a fermentation facility in my cellar so that I can make wine here, too. It'll be an interesting experiment, to see how differently it turns out from our Bay Area stuff!

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4. Panowski, S.H., et al. 2007. *Nature.* 447:550–555.
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