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Sleeping Cells and Maternal Protection: Rethinking Strategies for Healthy Aging

INTERVIEW WITH PROFESSOR ANDREW DILLIN

BY GRACE ZHOU & ARJEN SEN



Dr. Andrew (Andy) Dillin is a Professor of Immunology and Molecular Medicine at UC Berkeley, a Howard Hughes Medical Institute Investigator, and Co-Director of the Robinson Life Science and Business Entrepreneurship (LSBE) program at the Haas School of Business. He earned his B.S. in Biochemistry from the University of Nevada, Reno (1989–1993) and his Ph.D. in Molecular and Cell Biology from UC Berkeley (1993–1998), followed by a postdoctoral fellowship with Dr.

*Cynthia Kenyon at UCSF, where he studied determinants of longevity in *Caenorhabditis elegans*. His research explores why aging organisms lose control over proteome integrity and how this breakdown is communicated across tissues. Using model systems ranging from nematodes and stem cells to mice, his lab manipulates signaling pathways or proteins within a tissue, single cell, or single organelle to study systemic effects on organismal physiology, providing insights into aging-related and neurodegenerative diseases, including Alzheimer's, Huntington's, and Parkinson's, and their implications for human health.*

BSJ: What initially drew you to the study of aging, and how have your experiences at Berkeley shaped your approach to research in this field?

AD: Well, we could spend an hour on that question alone. When I was a graduate student here at Berkeley and I got my PhD in genetics, I got trained deeply in classical genetics by my advisor, Jasper Rine. When I left his lab, I wanted to approach an incredibly complex question that I could begin to unravel through genetics. At that time, my postdoctoral advisor, Cynthia Kenyon, uncovered a single gene that could dramatically influence the lifespan of an animal. This led me to think that something as complex as aging could be impacted by a single gene mutation. That exposure is what sparked my fascination with aging work that I have continued on till this day, 30 years later.

BSJ: In your paper, “Quiescent Cell Re-entry is Limited by Macroautophagy-Induced Lysosomal Damage,” you found that UPR regulators, IRE-1, and XBP-1 are required for the repair and regeneration of damaged lysosomes following prolonged arrest. Given that IRE-1 and XBP-1 typically manage protein folding in the ER, how exactly do they reach out from the ER to specifically fix damaged lysosomes or regenerate new active lysosomes?

AD: A big part of the question we are trying to answer is what is the role of IRE-1 and autophagy in cells being able to come back into a cell cycle? This is a truly important question because, as you know, many of our cells have to be replaced as we age. Therefore, all of our stem cells are sitting there in a quiescent stage. If we want to make new cells, we have to get them back in the cell cycle. Quiescent cells must repair their lysosomes before they can re-enter the cycle.¹

This is fine, as long as you are young, it works perfectly fine. However, as you age, you lose IRE-1 and XBP-1 activity and those factors no longer shine. Even though the factors are here, we are not able to activate them. What we find is that those cells cannot exit the

cell cycle. The quiescent cells are stuck in that area. The question is, well, why can they not? They attempt to, but they just cannot get back into the cell cycle. What happens is that as cells sit for longer periods of time in a non-dividing state, they start to accumulate damage to their lysosomes. That is the major location of autophagy in dealing with cellular damage, but it itself becomes damaged. One way to replenish that is to have the IRE-1/XBP-1 pathway. If we can limit that lysosomal damage then we can have these cells that lack IRE-1, XBP-1, leave the cell cycle.

One way to limit that damage is to reduce autophagy, the cell's ability to recycle its damaged components which is counterintuitive. People often assume that increasing autophagy would clean out cells better, but in this frozen cell state, like our stem cells are in, activating autophagy would be harmful, as it would lead to further lysosomal damage in older cells. This leads to a yin-yang here. You want some autophagy, but as you age, you want to temper that a little. That is what that paper is more or less showing. There are two different ways to protect your lysosomes. Either make more good ones or reduce autophagy so you do not cause damage. This was all the work of Andy Murley, an amazing postdoctoral researcher in my lab, who

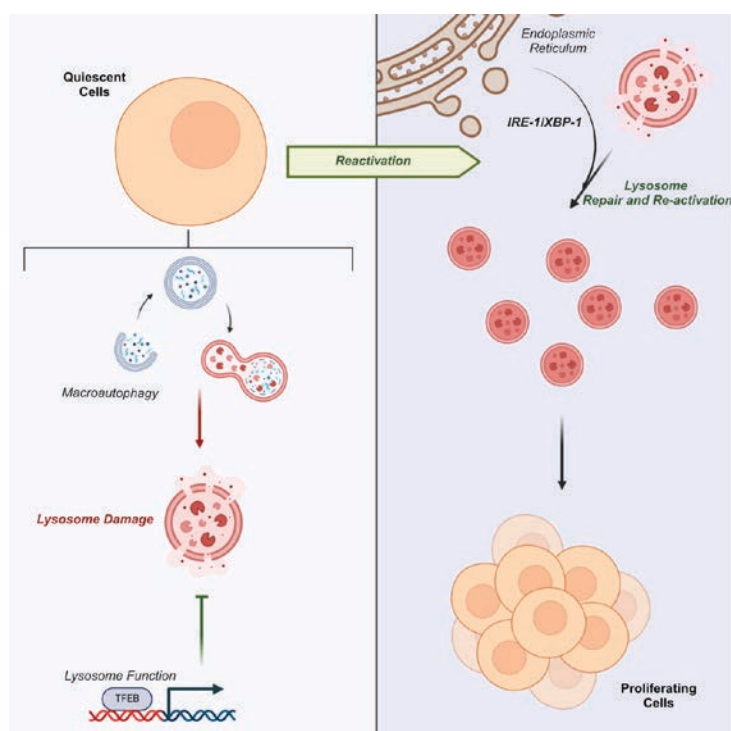


Figure 1: When cells rest in a quiescent state, their recycling centers (lysosomes) can become damaged. Before these cells can divide again, the IRE-1/XBP-1 pathway helps repair lysosomes so they can safely re-enter the cell cycle.

will hopefully be starting his new lab soon as he searches for a faculty position.

BSJ: Your lab's study on quiescent cell re-entry shows that autophagy, usually protective, can drive lysosomal damage and impair reactivation from quiescence, especially in UPR-deficient IRE-1/XBP-1 mutants. Do you think the context, such as quiescent versus proliferating states, dictates whether autophagy is beneficial or harmful?

AD: Absolutely. Being able to divide lets you deal with damage to cells very differently than in a cell that is stuck in a phase of the cell cycle, as quiescent cells are. They have to have different mechanisms to deal with this. I think that in dividing cells, autophagy is perfectly fine. Most of the time, it is also alright in quiescent cells, as

"...people are trying to activate autophagy and they believe this will be really healthy. While I think in these older quiescent cells, it could be really detrimental."

long as they have not been in that state for a long period of time. As we have covered, accumulating damage is fine. However, people are trying to activate autophagy and they believe this will be really healthy. While I think in these older quiescent cells, it could be really detrimental. The longer you are in quiescence, the worse it is. Even if you come out of it, autophagy will play a much more negative role the longer the cell is in quiescence.

BSJ: Considering that autophagy is essential for organisms but it can also be very damaging, how can we balance out the IRE-1/XBP-1 repair with making lysosomes more robust?

AD: Since we only find this phenomenon in quiescent cells, you would have to target autophagy only in the quiescent cells. You would have to do this so that you are not completely knocking down autophagy. It would have to be dose-dependent and cell-type specific. This would be very hard to do and probably not doable. However, we are conducting basic science, and down the road, we may uncover a way to do that.

BSJ: Do you think, from an evolutionary perspective, there is a trade-off between lysosomal damage and autophagy, or could there be a purpose to it? How can we determine whether a lysosome has reached an optimal state both robust and supporting autophagy?

AD: The lysosomal damage is really registering how well you can activate mTOR to come out of the cell. One possibility is that this represents an evolutionary mechanism: if nutrients are insufficient or lysosomes are damaged and mTOR cannot be sufficiently activated, there is no point in exiting quiescence because the cell would likely die. We have data that we cannot activate mTOR at all in these damaged lysosome cells. Evolutionarily, lysosomal integrity may act as a "dial," signaling whether mTOR can be activated.

Lysosomes do many different things. Not only is it a degradation compartment, but it is also a signaling compartment and a cholesterol-trafficking compartment. You have to ask whether the lysosome is optimized for one function or the other and whether enhancing one function compromises the other. This is a very challenging question, which is difficult to answer definitively.

BSJ: What are the implications of this research moving forward in age studies?

AD: Moving forward, one key question is whether the regenerative capacity of older humans is diminished because the stem cells cannot be reactivated. This applies not only to neurogenesis but also to the generation of other new tissues or new

gets incorporated into, if that occurs. Who knows what it is? That is the beauty of it. Genetics is a great tool because it is unbiased—whatever comes out of the screen is what it is. Genetics does not lie.

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BSJ: Your lab’s study also shows that merely perceiving pathogen-derived toxins is sufficient to protect progeny. Do you think this reflects an evolved form of “anticipatory immunity” where parents prime offspring for future threats? How might insights from intergenerational signaling be leveraged to develop strategies that benefit human health?

AD: Many of us study these responses to infection—essentially, “let us turn on this innate immune response to do this”—but all of these approaches require that you become infected. I am wondering why there is not something anticipatory, something that tells us before we get infected. We have done work on sensory systems to see if the perception of pathogens is enough to drive these responses and cause protection. Julian Dishart, a former graduate student in my lab, worked out that the smell of pathogenic bacteria was enough to turn on responses. Now, Cory Pender’s work is showing that the cyanide that the bacteria normally produce while they are growing can be perceived by the worm, which then detoxifies it and turns it into a second messenger. I believe this is an early anticipatory signal and there is likely much more to be discovered.

Now, when we move into humans, is this going to be true as well? How are we going to detect pathogens before an infection occurs and turn on these protective responses? We have been trying to do this in mice with zero success. We are unsure if it is because we do not have the right pathogen or setup for them to smell it, but the idea remains

intriguing. We just have to see if we can uncover something. It would be remarkable if this concept of anticipatory immunity is conserved all the way up to vertebrates.

BSJ: If you were to discover a method of inducing anticipatory immunity in humans, could you imagine this being the future of vaccines?

AD: Think about the future of perfumes! Of course, in this case, you would not want to spray cyanide. However, another graduate student in our lab, Ayane Maruichi, is working with different bacterial pathogens that trigger distinct signaling events, secreting different molecules. Could we figure out what some of those molecules are, and might they actually be used as “perfumes”? Not cyanide or anything toxic, but molecules that, when smelled, could prime a defense mechanism and make the organism resistant to the pathogen. For example, one could imagine a bacterial pathogen molecule that, when detected, primes a defense mechanism and confers resistance to the pathogen. That is one of the things we are thinking about. We also want to understand whether bacteria have evolved strategies to circumvent these responses, such as producing molecules that actually turn off the protective response. It is a very risky project and feels like science fiction, but we will see how it pans out.

BSJ: The study identifies β -cyanoalanine as a metabolic signal mediating protection in immediate progeny. Could parental exposure to pathogen cues also induce protective effects across multiple generations, and what mechanisms might allow such intergenerational information to persist?

AD: We were surprised that β -cyanoalanine only lasts for a single generation. There have been studies of intergenerational effects, but in our experiments under careful observation, the effects only lasted for one generation. This one-generation effect requires chromatin modifications, so there is an epigenetic component involved. It is possible that other responses may persist for multiple generations.

I find this one-generation effect interesting from a biological perspective. If parents encounter a pathogen, their progeny benefit without needing to remain in the same environment. In contrast, a multigenerational effect would imply that animals are committing to live with the pathogen, which does not seem advantageous. Due to this, I like the fact that it is only one generation. I am sure there are some responses out there that may be multi-generational.

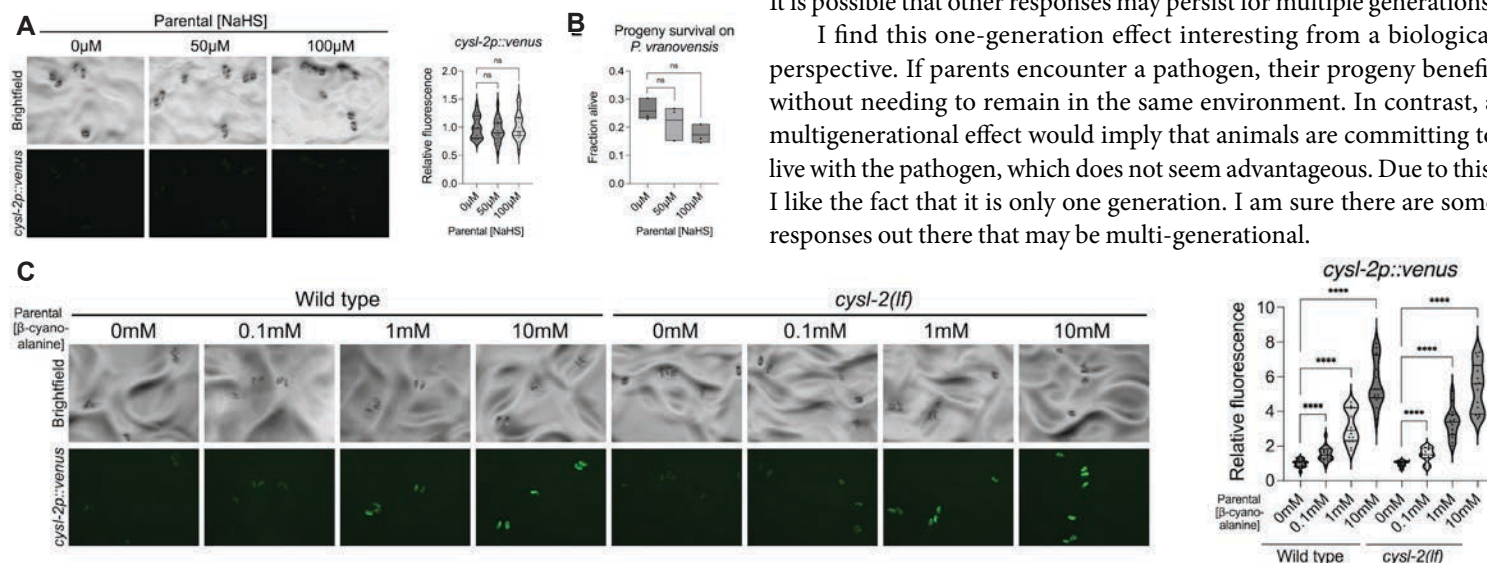


Figure 4: Parental exposure to β -cyanoalanine, but not NaHS, induces *cysl-2* expression and enhances progeny survival. (A) Fluorescence micrographs (left) and quantification (right) of *cysl-2p::venus* expressed embryos from adults exposed to sodium hydrosulfide. (B) Survival of progeny from sodium hydrosulfide-exposed parents on *P. vranovensis*. (C) Fluorescence micrographs (left) and quantification (right) of *cysl-2p::venus* expression in embryos from adults exposed to β -cyanoalanine.

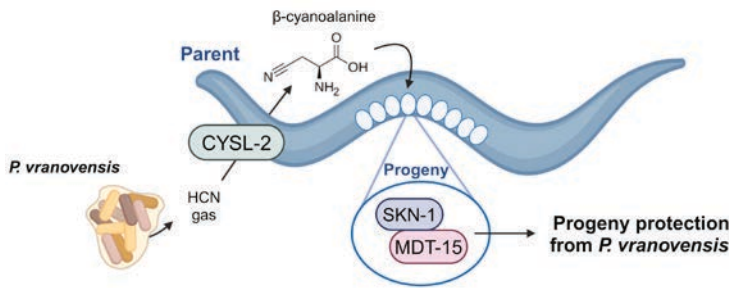


Figure 5: Overview of the mechanism that *C. elegans* undergo to induce protection in progeny. Exposure to cyanide byproduct from *P. vranovensis* induces CYSL-2 expression in parental *C. elegans* and the production of β-cyanoalanine, which activates MDT-15 in progeny, enhancing their survival.

BSJ: Based on your research on cellular stress and organelle function, how do you see the field of aging research evolving over the next decade, and what do you consider the most exciting opportunities or biggest challenges ahead?

AD: Aging research is kind of an anomaly because we really cannot define what aging is. We see it happening to all of us, but we cannot say exactly what it is. In my lab, we often try to study the comorbidities that accompany aging and consider whether the most significant discoveries will come from examining these processes; I believe they will.

Much of the work of my lab is studying infections, and older animals are really ineffective at dealing with infections. Are there better ways for us to treat the elderly who are undergoing infections? Traditional approaches, like antibiotics, are limited, and vaccine responses are often dampened. We need new strategies to help a person deal with infections as they get older. Maybe some of the things we are working on will help turn on these ancient innate systems that we are uncovering.

Another major focus of our work is dealing with muscle regeneration and the ability to retain muscle mass, which dramatically declines with age. Could we find ways to restore muscle mass safely in the elderly? This is important because loss of strength leads to declines in agility and coordination. For example, a fall and hip fracture in someone in their late 70s or early 80s often results in severe complications and is a strong predictor of mortality, with recovery frequently being difficult or incomplete.

I expect that over the next decade, research in aging will have the greatest impact on these issues. We are likely never going to make a drug that makes people or populations live longer, because we all age differently. A pill that works for me may not work for you, and it may be even detrimental for others. Instead, our work focuses on interventions that could improve specific aspects of aging, with infections and muscle mass preservation being two of the most critical areas.

BSJ: Do you think aging research should focus more on prevention or regeneration, or something else?

AD: No, we need to step further back and actually define what aging is. We are so early in it that we have no rules. In molecular biology, A pairs with T, G pairs with C, but we do not have rules like that in aging. We know that certain pathways are absolutely essential, shown through many different organisms, but what do these pathways do? Are they the only ones? We are still so early in

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this research that we cannot have a unifying foundational idea yet, which I believe is our biggest limitation. We may never fully “solve” aging because we might be approaching it from the wrong perspective. Could aging actually be an extension of development? Development in reverse? What we do know is that aging is accompanied by a range of diseases. Therefore, if we can uncover something about these diseases, then that would be meaningful progress.

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