Danica Chen: From early learning to aging research

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Chen studies the cellular and genetic mechanisms that control organismal aging.

Kids growing up in China after the Cultural Revolution were encouraged to excel in science and technology. Although Danica Chen naturally took a liking to science in this environment, she was not the sort of child who knew exactly what she wanted to be from an early age. At the time Chen was applying to university, students in China were supposed to decide on their major before entering college. Following her father's recommendation, Chen intended to study international accounting at Xiamen University but the only slot available for her entire province had already been filled. By chance, Chen's older brother heard that they still had an opening in cell biology and this set her on the path to becoming a biologist. As Chen recalls, "What can I say. My brother, at the mere age of 19, was either a great forecaster or knew more about me than I would have ever admitted at the time."

Genetics and bioengineering courses at Xiamen University sparked Chen's imagination but she was particularly thrilled to be exposed to the world of molecular biology. Looking back, however, Chen is not sure that science would have blossomed into a career for her if she had remained in China. But Chen was again nudged in the direction of becoming a scientist by an unexpected source—Professor Steve, from Texas, who was teaching a class on American culture. Chen was intrigued to hear him talk passionately about customs and practices that seemed incredibly foreign to a girl raised in China at that time by conservative parents who liked rules and restrictions. Chen was hooked by some of the "crazy ideas" Professor Steve was teaching—independence from one's parents and freedom to pursue romantic relationships, in particular. Wanting to learn more, Chen decided to see what the West was all about and left for the United States during a period when Chinese citizens were not free to travel abroad. There was no looking back when Chen first landed in California and she entered the PhD program at the University of California Berkeley. Studying the molecular mechanisms that control HIV transcription with Qiang Zhou provided extensive training in biochemistry and molecular biology. Chen then used these skills to seek a mechanistic understanding of the biology of aging as a postdoc in Leonard Guarente's laboratory at Massachusetts Institute of Technology. She continues to investigate how fasting affects longevity via the activity of sirtuin enzymes and other pathways with her own group, established in the Department of Nutritional Sciences and Toxicology, Berkeley, in 2008.

We contacted Chen to learn more.

What initially drew you to research the aging process?

When I finished my PhD study on HIV transcription in 2003, I was intrigued by the developments happening in the aging field. At the time, molecular biologists had begun to use modern technologies to understand aging. An exciting finding that came out of those studies was that lifespan can be extended by single gene mutations. The idea that we might be able to control the aging process was very exciting to me, and this became one cornerstone of my laboratory.

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A related foundational concept that has been developed in the aging field is healthspan: the number of years one can live a healthy life. As aging is arguably the single biggest risk factor for numerous human diseases, understanding the cellular pathways that control aging holds the promise to identify therapeutic targets for not just one disease but many diseases all at once. In my laboratory, we hope to make contributions to these core principles by learning how we age, how the aging pathways regulate the development of human diseases, and whether we can harness this knowledge for disease treatment and healthspan extension.

Danica Chen. PHOTO COURTESY OF DANICA CHEN.

What is your laboratory currently working on? What is up next for you?

A current focus of my laboratory is understanding how adult stem cells lose their regenerative capacity as we age. There is no doubt that almost every cell type changes with aging, but adult stem cells are particularly relevant in the context of aging because they are responsible for tissue repair and maintenance for the entire lifespan. When I started my laboratory in 2008, I was intrigued by a paper that compared the transcriptional profiling of young and old hematopoietic stem cells and showed that three sirtuins were repressed during aging. We asked the simple question: What do these sirtuins do in hematopoietic stem cells? At the time, I had no idea what these studies would lead us to. However, our biochemical work pointed one way or another to mitochondrial stress as a key factor. We found that SIRT7 regulates the mitochondrial unfolded protein response and links it to stem cell metabolism and proliferation; reduced levels of SIRT7 in aging hematopoietic stem cells hamper their ability to regenerate (1). What has emerged from these studies is the appreciation of a mitochondrial metabolic checkpoint important for hematopoietic stem cell maintenance that becomes dysregulated during aging (1–3). We are now interested in understanding the implications of

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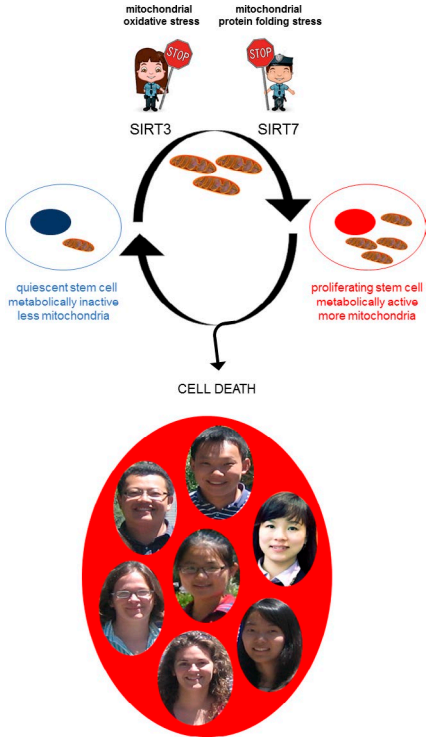

Mitochondrial metabolic checkpoint regulating stem cell quiescence and aging. The cartoon depicts SIRT3 and SIRT7 regulating mitochondrial numbers when stem cells are subject to oxidative or protein folding stress. The students and postdoctoral fellows whose work contributed to the development of this concept of a mitochondrial metabolic checkpoint that regulates stem cell quiescence and aging are shown on the bottom. IMAGE COURTESY OF DANICA CHEN.

dysregulation of this metabolic checkpoint in the development of disease. Another research focus is how we become predisposed to metabolic diseases as we age (4). Finally, because of the wide interest in calorie restriction as a dietary regimen to slow aging, we study how cells sense nutrients and coordinate cellular responses (5, 6).

What kind of approach do you bring to your work?

The approach I take to understand aging is combining biochemistry and mouse genetics. Biochemistry allows us to gain mechanistic insights and mouse genetics enables us to realize the physiological relevance at the organismal level. However, I do not limit the approaches we may take because aging is a complex biological problem, which sometimes requires interdisciplinary approaches.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? What were you unprepared for?

Besides intellectual and academic training, working with my mentors gave me insight into how to structure and manage my laboratory. Of course, there is always on the job learning as well, so over time I was able to combine that with my own experiences to develop a laboratory that fits my management and mentoring style. I treat my students the way I want to be treated. However, my own experience did not fully prepare me to manage a group, as my students are different from me and what I think is best for them may not be perceived the same way by my students. I need to understand every student and their needs at each stage of their development. Another new challenge with transitioning into being a professor is switching from managing one or two projects to overseeing all the projects in a laboratory, and making sure that they have a significant impact. And perhaps the biggest new challenge has been ensuring that the laboratory is well funded in the long run so that my research and mentorship of students can continue. The time commitment and effort required to obtain NIH grants is at an entirely different level than the fellowships I received as a PhD student and a postdoc.

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What has been the biggest challenge in your career so far?

American society has made significant strides in involving women in the work force in general and in science in particular, but there is so much more to be done. When I started my position as a professor, I was struck by how few women even made it to that level in their career, let alone became tenured, full professors. In biology, there are more female than male students at the college level, the graduate school level, and the postdoc level, but that doesn't seem to be translating into a better gender balance of tenured professors. I'd like to find ways to help women and minorities aim high, to create workspaces that are safe, inclusive, and family friendly so that people of all backgrounds can succeed as scientists.

What do you like to with your time outside the laboratory?

San Francisco, where I live, is a city of innovation and creativity. It provides endless opportunities to meet interesting people, explore new places, and try new things—whether it's trying a new flavor of ice cream (anyone ever had bone marrow and roasted cherry?) or taking a walk up one of the city's many secret staircases. My family likes traveling around the world, exploring new restaurants, hiking, and playing tennis together.

What is the best advice you have been given?

The best advice I have been given is: Be confident, but not arrogant.

Any tips for a successful research career?

Success means different things to different people, but for me it means enjoying what you do and enjoying every moment. Since our understanding of life evolves, I find it useful to take time to reflect periodically and make sure one does not get too lost in the present and immediate success without keeping an eye on the ever-evolving big picture.

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Danica Chen and family. PHOTO COURTESY OF DANICA CHEN.