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PEOPLE & IDEAS

Xiaochen Wang: Building up our understanding of breaking down

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Wang studies lysosomal degradation pathways using *C. elegans* as a model system.

Xiaochen Wang has spent almost her entire life in the academic arena. Growing up on the campus of Peking University in Beijing with her parents, she was poised early on to start contemplating important questions and develop an avid curiosity for learning. After earning her undergraduate degree from Shandong University, Wang returned to her home base of Peking as a graduate student. There she became fascinated by the process of cell death in plants, an interest that propelled her across the world to pursue her postdoctoral work. At the University of Colorado, Boulder, Wang investigated the mechanisms that underlie apoptotic cell clearance in *Caenorhabditis elegans*. Now a Head of Lab at the Institute of Biophysics at the Chinese Academy of Science, Wang and her team continue to use the worm to understand how apoptotic cells are degraded by the lysosome and how lysosomal dynamics are controlled.

We contacted Wang to find out more about her scientific journey and ongoing research endeavors.

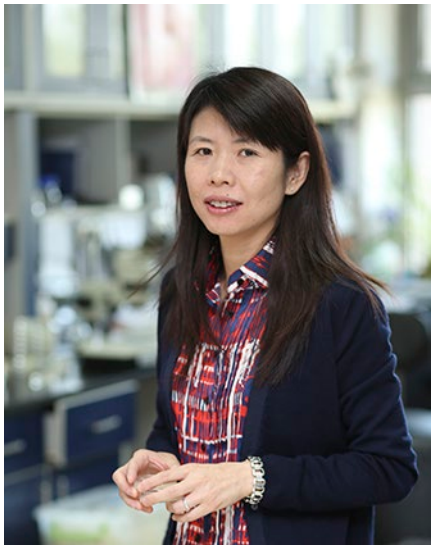
When did your interest in science begin?
My real interest in science began when I was a graduate student in Peking University. It was also my first experience of science. I studied plant biology at that time and was very interested in pathogen–plant interactions, especially plant microbial recognition and the signaling pathways that lead to host defense. Although I did not really work on this topic during my PhD, it indeed interested me and gave me the first taste of doing science.

Where and with whom have you studied?
I was an undergraduate student at the department of microbiology in Shandong University and a graduate student at the College of Life Sciences, Peking University. I studied fungi–plant interactions for my PhD thesis, supervised by Professor Zhangliang Chen, and became very interested in cell death as a defense mechanism in plants. I thus took a postdoc position in Dr. Ding Xue's laboratory at the University of Colorado, Boulder, to study apoptosis and phagocytic removal of apoptotic cells using *C. elegans* as a model.

What drew you to study the lysosome?
Our current research focuses on the lysosome-mediated cellular degradation pathway, aiming to understand how lysosome homeostasis is maintained and regulated at an organismal level. I am interested in lysosomes because they are extremely important for animal physiology and, surprisingly, we understand very little about the mechanisms through which lysosome functions are achieved under physiological conditions or altered under pathological conditions.

> "The attempt to dissect lysosome homeostasis in a multicellular organism is new, and indeed we have plenty of questions to address."

What are you currently working on and what is up next for you?
For the first 5–8 years, my laboratory has focused on the study of lysosome-dependent clearance of apoptotic cells. Using *C. elegans* as a model system, we have identified new genes and have dissected regulatory mechanisms controlling various aspects of apoptotic cell removal including recognition, internalization, and degradation of cell corpses. Among them, TTR-52 and NRF-5 are bridging molecules that mediate recognition of cell corpses (1). Myotubularin phosphatase MTM-1 coordinates with phosphoinositide 3 (PI3) kinases PIKI-1 and VPS-34 to control initiation and completion of cell corpse engulfment (2). Multiple Rab GTPases coordinate to regulate phagosome maturation and lysosomal degradation of apoptotic cells (3). Moreover, we found that nonapoptotic targets, like residual bodies generated during spermatogenesis, are recognized and cleared by the same molecular machinery that removes apoptotic cells. We also demonstrated that the autophagy pathway contributes to cell corpse clearance through the PI3 kinase VPS-34. These findings greatly advanced our understanding of how apoptotic cells are properly removed via the lysosome-dependent degradation pathway, while at the same time aroused our interest in lysosomes.



Xiaochen Wang at her worm laboratory. Image courtesy of the China Young Women in Science Fellowships.

Lysosomes degrade macromolecules derived from endocytosis, phagocytosis, and

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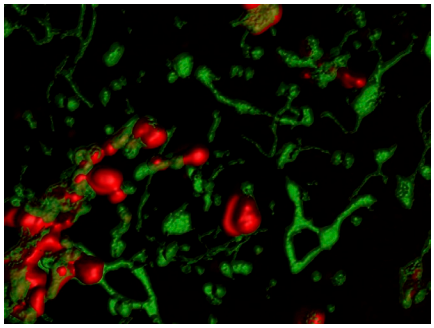

C. elegans lysosomes contain both vesicular and tubular structures labeled by LAAT-1::GFP. The vesicular but not tubular lysosomal structures are strongly stained by LysoTracker red. Image courtesy of Xiaochen Wang.

autophagy, and recycle catabolites to maintain cell homeostasis. They are also involved in other processes such as plasma membrane repair, immune responses, nutrient sensing and signaling, and cell death. Impairment of lysosome function contributes to the pathogenesis of many diseases including lysosomal storage diseases, neurodegenerative disorders, and cancer. However, much less is known about how lysosome functions are achieved and contribute to animal physiology and how lysosome dysfunction leads to pathogenesis of human diseases.

We generated reporters to monitor lysosomes in worms by live imaging. We found that *C. elegans* lysosomes are mobile and exhibit both vesicular and tubular morphology. Interestingly, lysosome morphology and motility appear to change during larval development, throughout the aging process, and under stress conditions, and exhibit cell type specificity. These intriguing observations provide us with a unique opportunity to dissect lysosome homeostasis (e.g., biogenesis, dynamics, activity, and integrity) in a multicellular organism. We want to identify signals and cellular processes that trigger/involve such lysosomal changes, dissect underlying signaling pathways, and reveal regulatory mechanisms and physiological significance. To do this, we developed research tools to monitor and analyze lysosome morphology, dynamics, and activity in *C. elegans* and take genetic approaches to identify genes involved in these processes.

We performed large-scale screens to first isolate mutants with abnormal lysosome morphology and have identified 16 genes so far. These genes are either involved in maintaining lysosome function and integrity or responsible for inducing and regulating formation of tubular lysosomes. Among them, *scav-3* encodes a lysosomal membrane protein homologous to human LIMP-2. We found that SCAV-3 is a key regulator of lysosome integrity. Loss of *scav-3* causes rupture of lysosome membranes and significantly shortens the organism's lifespan. Both phenotypes were suppressed by reinforced expression of LMP-1 or LMP-2 (the *C. elegans* LAMPs), indicating that longevity requires maintenance of lysosome integrity. Remarkably, reduction in insulin/IGF-1 signaling suppresses lysosomal damage and extended the lifespan in *scav-3(lf)* animals. Our data reveal that SCAV-3 is essential for preserving lysosomal membrane stability and that modulation of lysosomal integrity by the insulin/IGF-1 signaling pathway affects longevity (4).

laat-1 and *rnst-2* encode lysosomal amino acid transporter and endoribonuclease, respectively, and loss of their function causes enlargement of lysosomes. We found that LAAT-1 transports lysine and arginine out of lysosomes, while RNST-2 degrades ribosomal RNA delivered by autophagy in lysosomes. We further demonstrate that LAAT-1 and RNST-2 play essential roles in embryonic and larval development by maintaining amino acid and nucleotide homeostasis, respectively (5, 6).

These findings revealed the importance of lysosomes in development and longevity, making us more confident in developing *C. elegans* as a multicellular model to dissect lysosome homeostasis. We will continue to build genetic and cell biological systems to investigate how lysosome biogenesis, integrity, dynamics, and activity are regulated and how lysosomes contribute to cellular functions in the context of development, aging, and stress responses.

"Do not be afraid of taking risks—start from basic and new observations and you will have plenty of work to do."

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

Be focused, persistent, and open-minded. These are the most important things that I learned during my PhD and postdoc training that helped me a lot in my independent research career.

What is the best advice you have been given?

The best advice that I have received is from two great scientists, Xiaodong Wang and Yoshinori Ohsumi, who made key discoveries in the fields of apoptosis and autophagy, respectively. Xiaodong is the director of the National Institute of Biological Sciences, Beijing (NIBS), where I started my independent research. He told me that I should leave the comfortable zone to look for new biology, which should be the goal for people who work on model organisms. The advice that I got from Dr. Yoshinori Ohsumi was actually mediated by *JCB*. I read the People & Ideas article about Dr. Ohsumi in *JCB* in 2012 that described his education, research, and philosophy. I was so inspired by his experience and the advice he gave to scientists: Do not be afraid of taking risks—start from basic and new observations and you will have plenty of work to do. The attempt to dissect lysosome homeostasis in a multicellular organism is new, and indeed we have plenty of questions to address.

What hobbies do you have?

I am a sports fan. I love to play badminton and volleyball. We used to have badminton and volleyball matches at NIBS, which were a lot of fun.

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The Wang Lab won the championship at the NIBS Spring Game. Image courtesy of Xiaochen Wang.