

Building multidisciplinary research

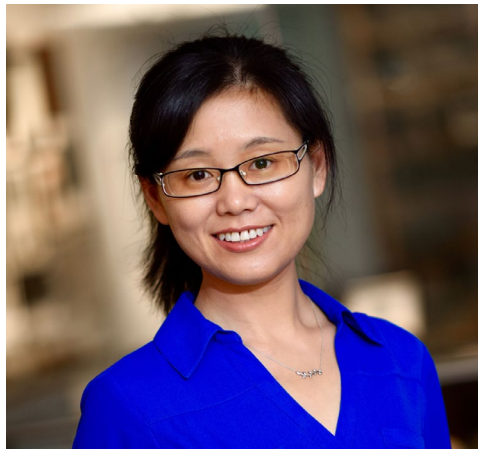
Meng C. Wang*

Department of Molecular and Human Genetics, Huffington Center on Aging, Baylor College of Medicine, Houston, TX 77030

ABSTRACT In his poetry, Walt Whitman sings, “I am large, I contain multitudes.” Most healthy organisms are made up of a multitude of cells and cell types, but none of these cells acts alone. Likewise a cell in homeostasis contains many organelles, but none of these organelles work on their own. How these diverse cells and how these different organelles communicate with each other in time and space are scientific questions that intrigue me. At the same time, like these cooperating cells and organelles, my research is constantly reshaped and transformed by interacting with different people, from my encouraging mentors, energetic trainees, and inspiring colleagues. These personal collaborations motivate and advance my research toward understanding cellular communications that promote metabolic health and organism longevity.

INTERORGANELLAR COMMUNICATION AND INTERDISCIPLINARY COLLABORATION

A eukaryotic cell is a crowded community with many different cellular organelles carrying out specific cellular functions. Among them, lysosomes are well known as scavengers for recycling, mitochondria are famous as the powerhouse for supplying energy, and the nucleus holds the genetic code, a blueprint for all cellular activities. Instead of being solo players, these cellular organelles maintain a harmony to sustain cellular homeostasis and ultimately organism fitness. I trained in the biology of aging with a long-time focus on organism-level regulation. Recently, unexpected findings in my group revealed a lysosome-to-nucleus retrograde lipid signaling pathway and its crucial role in regulating longevity (Folick *et al.*, 2015). This discovery inspired us to dive into subcellular levels and investigate



Meng C. Wang

the signaling role of the lysosome in inter-organellar communications to promote healthy aging. To do this, my group uses multidisciplinary approaches to understand how lysosomes communicate with the nucleus and mitochondria in different cell types, and how this communication is disrupted by metabolic stresses and during the aging process.

Our favorite research system is *Caenorhabditis elegans*, a versatile animal model with whole-body transparency and ease-of-use genetics. For many cellular biologists, “seeing is believing.” Fortunately, these tiny multicellular animals provide an elegant platform for visualizing cellular phenotypes with subcellular resolution at the whole-organism level. For many geneticists, high-throughput screens are particularly intriguing, because they often lead into uncharted territories. With the ease of its genetic manipulation and screening, *C. elegans* also acts as a powerful system for systematic discovery of new mechanisms. These cellular imaging and genetic screening approaches are solid platforms for our research. Equally important, however, to the strengths of this wonderful model system, are the collaborations that we are a part of. We work closely with scientists in the fields of biochemistry (Rudy Zechner, David Moore) and structural and chemical biology (Eric Ortlund, Jin Wang). These collaborations, either short-term (for one experiment) or long-term (for continuous projects), are always stimulating and rewarding. Because we work in very different fields, our collaborators and we often look

DOI:10.1091/mbc.E17-07-0482. *Mol Biol Cell* 28, 2905–2907.

Meng C. Wang is the recipient of the 2017 Early Career Life Scientist Award from the American Society for Cell Biology.

*Address correspondence to: Meng C. Wang (wmeng@bcm.edu).

© 2017 Wang. This article is distributed by The American Society for Cell Biology under license from the author(s). Two months after publication it is available to the public under an Attribution–Noncommercial–Share Alike 3.0 Unported Creative Commons License (<http://creativecommons.org/licenses/by-nc-sa/3.0>).

“ASCB®,” “The American Society for Cell Biology®,” and “Molecular Biology of the Cell®” are registered trademarks of The American Society for Cell Biology.

at the same biological questions from very different angles. The dynamic interactions between our labs frequently trigger new ways of thinking and experimenting, leading to new levels of mechanistic characterization. More importantly, trainees in my group have greatly benefited from these fruitful collaborations. It is a joy to observe them as they learn how to effectively communicate and cooperate with scientists from different scientific backgrounds, and how to integrate distinct disciplinary approaches into their research. I believe that all of these skills are critical components for success in their future careers.

CROSS-SPECIES COMMUNICATION AND SYNERGISTIC COLLABORATION

Like the many organelles in a cell and the many cells in an organism, all organisms live in a broader ecological system, sharing the same environment with other species including microbes. Interspecies communication that orchestrates cellular organelle homeostasis with the outside environment is a new research area in my group. In particular, we are interested in interspecies communication between microbes and their hosts. Not only are there many different types of microbes living together with us, but even within the same group of microbes, their genetic and biochemical profiles are dynamically shaped by environmental factors. Thus, when responding to environmental stimuli, changes in microbes and hosts occur simultaneously and are like the two sides of one coin. So instead of looking at microbial phylogenetic heterogeneity, we focus on how changes in microbial gene expression and subsequent metabolic products impact host metabolism and longevity (Sowa *et al.*, 2015; Han *et al.*, 2017; Lin and Wang, 2017). We have been taking unbiased genome-screening and metabolomic approaches. One interesting finding we got is that specific metabolic products of bacteria can fine-tune mitochondrial dynamics to actively regulate the host's metabolic fitness and longevity (Han *et al.*, 2017; Lin and Wang, 2017). This mode of communication might not be totally surprising, given the close evolutionary association between bacteria and eukaryotic mitochondria, but it is truly exciting to witness how bacterial metabolic products serve as chemical messengers for this cross-species communication and to understand the underlying molecular mechanisms.

When I was looking for an independent faculty position, one piece of advice that I truly valued was to look for synergistic colleagues. Genetically speaking, synergy occurs when the contribution of two mutations to the phenotype exceeds the additive effects of the individual mutation. For a scientific collaboration, synergy occurs when scientists in different fields join their creativity and expertise to raise new questions and open new lines of inquiry. One aspect of science that I find most intriguing is *unpredictability*. This is not only a key feature of research involving unbiased screens -since it is hard to tell where they will lead, but also comes from the dynamic interactions with the scientists surrounding me. I never pictured myself working on bacteria when I started my independent position at Baylor College of Medicine in Houston 7 years ago. Now, a team of graduate students and postdoctoral scientists in my group study the interactions between bacteria and *C. elegans*, and they often comment that when we start to look at bacteria, it feels like we know almost nothing about *C. elegans*. Interestingly, this new area of my research started from by chance having a drink with my bacterial genetics colleagues (Christophe Herman, Jade Wang) at the annual departmental retreat. They inspired and motivated me to take a closer look at how bacterial gene expression and metabolic reprogramming influence the host's physiology, and importantly they provided their synergistic expertise to make these new

inquiries feasible. As time goes by, we are happy to see that our one drink together has become many more drinks, coffee at the coffee corner, and many more lunches. These collaborations have become much more than just scientific endeavors; they have led to strong friendships, where we are able to share our happiness and provide encouragement and support to each other through difficult times. Although science is unpredictable, interaction with them always guarantees fun and new ideas.

SEEING THE INVISIBLE AND BECOMING A FRESHMAN

Claude Bernard highlighted, "Every time that a new technique or instrument comes along, we invariably see scientific progress and questions to which this means of analysis can be applied." Since Robert Hooke's microscope first revealed the cell walls in cork tissue, advances in microscopic techniques have been transforming the ways we study biology, by simply making the invisible visible. Lipid molecules are one of the most important biological components, with broad and vital effects on cell and organism physiology. Unlike proteins, lipid molecules are typically invisible to fluorescence microscopy. Technological innovation in stimulated Raman scattering microscopy has overcome this limitation and has made it possible to visualize lipid molecules in living cells and organisms with diffraction-limited spatial resolution (Freudiger *et al.*, 2008). Using this technique, my group is studying the spatiotemporal dynamics of lipid molecules under different physiological and pathological conditions (Wang *et al.*, 2011; Fu *et al.*, 2014; Yu *et al.*, 2017). On the basis of the fast imaging speed of stimulated Raman scattering microscopy in live animals, we can now also harness its power with functional genomic screens in *C. elegans* to discover lipid regulatory genes and mechanisms (Wang *et al.*, 2011; Yu *et al.*, 2017).

After viewing our stimulated Raman scattering microscopy system, I have had many visitors ask me, "What is your training background?" Jumping out of one's comfort zone and entering new fields as a freshman can be challenging, but at the same time exciting. In 2011, we started to build a stimulated Raman scattering microscopy system in the lab. Investing significant amounts of money, time, and effort on this chemical imaging technique was not an easy decision for me as a newly independent principal investigator, even more so when considering my lack of previous training in optical physics or engineering. Thanks to the generous support of Sunney Xie and Wei Min, we succeeded in operating this imaging system in my lab, and the accessibility to this microscope on a daily basis truly makes a difference to our research. Importantly, this challenging and productive experience has widened our horizons and brought optics and engineering postdoctoral scientists to the lab to work not only on technological development but also on biological questions. For myself, participating at conferences on optics, chemistry, and engineering have been eye-opening experiences to see what tools are available in other fields. I am really looking forward to the future application of these techniques to biological research to transform our ways of investigation.

ACKNOWLEDGMENTS

I am very fortunate to receive the Early Career Life Scientist Award from the American Society for Cell Biology this year, and I cherish this opportunity to share my research experiences. I am forever grateful to two amazing mentors, Dirk Bohmann and Gary Ruvkun, for giving me freedom and support during my career development. I also feel very lucky to work with students and postdoctoral scientists whose excitement, motivation, and creativity brighten every day. I fully appreciate all the support, inspiration, and encouragement

from my fantastic colleagues and collaborators. And finally, a big thank you to all the federal and private foundations that support our work.

REFERENCES

- Folick A, Oakley HD, Yu Y, Armstrong EH, Kumari M, Sanor L, Moore DD, Ortlund EA, Zechner R, Wang MC (2015). Aging. Lysosomal signaling molecules regulate longevity in *Caenorhabditis elegans*. *Science* 347, 83–86.
- Freudiger CW, Min W, Saar BG, Lu S, Holtom GR, He C, Tsai JC, Kang JX, Xie XS (2008). Label-free biomedical imaging with high sensitivity by stimulated Raman scattering microscopy. *Science* 322, 1857–1861.
- Fu D, Yu Y, Folick A, Currie E, Farese RV Jr, Tsai TH, Xie XS, Wang MC (2014). In vivo metabolic fingerprinting of neutral lipids with hyperspectral stimulated Raman scattering microscopy. *J Am Chem Soc* 136, 8820–8828.
- Han B, Sivaramakrishnan P, Lin CJ, Neve IAA, He J, Tay LWR, Sowa JN, Sizovs A, Du G, Wang J, et al. (2017). Microbial genetic composition tunes host longevity. *Cell* 169, 1249–1262.
- Lin CJ, Wang MC (2017). Microbial metabolites regulate host lipid metabolism through NR5A-Hedgehog signalling. *Nat Cell Biol* 19, 550–557.
- Sowa JN, Mutlu AS, Xia F, Wang MC (2015). Olfaction modulates reproductive plasticity through neuroendocrine signaling in *Caenorhabditis elegans*. *Curr Biol* 25, 2284–2289.
- Wang MC, Min W, Freudiger CW, Ruvkun G, Xie XS (2011). RNAi screening for fat regulatory genes with SRS microscopy. *Nat Methods* 8, 135–138.
- Yu Y, Mutlu AS, Liu H, Huang B, Wang MC (2017). High-throughput screens using photo-highlighting discover BMP signaling in mitochondrial lipid oxidation. *Nat Commun*, doi:10.1038/s41467-017-00944-3.