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PEOPLE & IDEAS

Hongyuan Yang: Tracking lipids, one droplet at a time

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Hongyuan Yang investigates lipid trafficking and lipid droplet biogenesis.

Hongyuan Yang grew up in a small city east of Beijing, China. From his childhood, Hongyuan recalls that "food was not abundant, so I was hungry at times, but education was free and good." Driven by his curiosity for science, after completing his undergraduate studies at Peking University Health Science Center, China, he enrolled at Columbia University, NY, for his doctoral training. Under the guidance of his advisor, Dr. Stephen Sturley, Hongyuan studied lipids in budding yeast. The laboratory's research department fostered a strong interest in lipids and atherosclerosis, and after earning his PhD, Hongyuan obtained a faculty position at the National University of Singapore (NUS) in 1999. In 2007, he moved to the University of New South Wales (UNSW) in Sydney, Australia, to continue his scientific journey exploring lipids. We contacted Hongyuan to learn more about his career and interests.

What interested you about lipids?

My five-year doctoral study focused entirely on the enzymes Sterol O-Acyltransferases (SOAT, also known as ACAT, Acyl-CoA Cholesterol Acyltransferases), which catalyze the formation of sterol esters from sterols/cholesterol and fatty acyl CoAs (1). SOATs, integral membrane proteins of the ER, are potential therapeutic targets for heart disease and Alzheimer's disease. Since then, I have been fascinated by two things related to SOAT: first, what happens upstream of SOAT, i.e., how exogenous cholesterol reaches SOAT/ER; and second, what happens downstream of SOAT, i.e., how its product—cholesterol esters—is stored in cells in the form of lipid droplets (LDs).

These are fundamental questions in cell biology. While reading on how cholesterol arrives at the ER for esterification by SOAT/ACAT in the late 1990s, I realized that the trafficking of most lipids was poorly characterized with little molecular insight. Significant progress has been made in the last 20 years, but the lack of tools that track the movement of lipids has hampered our understanding of the selectivity, efficacy, and kinetics of lipid trafficking. Few cell biologists cared about LDs ∼20 years ago, even though LDs are prominent cellular structures in many disease conditions. Each LD comprises a hydrophobic core of storage lipids (triglycerides and sterol esters) wrapped by a monolayer of phospholipids. Largely considered inert lipid granules, LDs originate from the ER and are relatively simple cellular structures as compared with other organelles (see image). Now, we know that LDs are not that simple: their biogenesis is tightly regulated, they actively interact with other organelles, and they regulate many aspects of cellular function as well as disease progression. Astonishingly, we still have little understanding of how LDs originate from the ER. I am very much intrigued by the complexity of these two seemingly simple cellular processes, i.e., lipid trafficking and LD biogenesis.

What are some of the scientific questions currently of interest in your laboratory?

We are currently focusing on how LDs originate from the ER. The first significant paper from my own laboratory was the discovery of seipin as a key regulator of LD formation (2). Results from many groups have demonstrated that seipin can organize the formation of LDs; however, the exact molecular function of seipin remains mysterious. Our data suggest that seipin may directly impact the level and/or distribution of lipids such as phosphatidic acid near sites of LD biogenesis, and the effect of seipin deficiency on LD formation is secondary to changes in local lipids. We are now working hard to test this hypothesis. Moreover, data from my laboratory and others indicated that nonbilayer lipids may have a greater impact on the biogenesis of LDs than that of other ER-derived structures, such as COPII vesicles. This may result from the

Hongyuan Robert Yang. Photo courtesy of UNSW.

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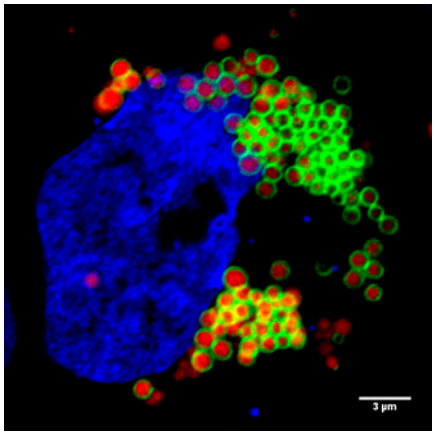
monolayer nature of the LD surface. We hope to dissect the dynamic changes of lipids at ER domains where LDs are born. More broadly, the ER is a fascinating organelle to me. The simple division of ER into sheets and tubules does not reflect the dynamic nature of this organelle. Dissecting the composition and organization of lipids and proteins of the ER would help answer key questions relating to LD biogenesis, and it is therefore one of our future directions.

Another major focus is to understand how cholesterol and phosphatidylserine are moved between organelles. We have been working on how low-density lipoprotein (LDL)–derived cholesterol (LDL-C) reaches the ER for two decades. The release of LDL-C from lysosomes requires the Niemann Pick C1&2 proteins, whose malfunction causes lysosomal cholesterol accumulation and a lethal genetic disorder affecting young children. The Ara Parseghian Medical Research Foundation has led the way in supporting research into cholesterol trafficking, and I take this opportunity to thank their generous support. Once released from lysosomes, LDL-C is believed to reach the plasma membrane first and then the ER. We identified ORP2 as a possible carrier of LDL-C to the plasma membrane using a $PI(4,5)P_2$ gradient (3). There must be other carriers and/or pathways because ORP2 deficiency only causes a minor accumulation of cholesterol in lysosomes. Another interesting question is what prevents LDL-C from reaching the ER directly from lysosomes, given the close contact between lysosomes and the ER. We reported that ORP5 may bring LDL-C directly to the ER (4). However, it was later found that ORP5 binds and transfers phosphatidylserine, not cholesterol. Thus, our observed link between ORP5 and cholesterol is through some indirect yet unknown mechanism. We have been perplexed by these observations for many years, but a recent study demonstrated that phosphatidylserine is required for the trafficking of LDL-C, establishing a close link between cholesterol and phosphatidylserine (5). We are now trying to understand how the trafficking and distribution of cholesterol, phosphatidylserine, and $PI(4,5)P_2$ are interconnected. For a long time, I felt that it was impossible to figure out the molecular details governing the cellular trafficking of lipids due to redundant pathways and a lack of tools to track lipids. Recent progress in this field has given me hope.



Lipid droplets in a HeLa cell are shown in red (BODIPY), with their surface in green. DAPI (blue) labels DNA. Image courtesy of Hongyuan Yang.

What kind of approach do you bring to your work?

Besides honesty and open-mindedness, we emphasize rigor and comprehensiveness. We often make our initial discoveries in cell-based screens. This approach has many advantages, but it also gives rise to artifacts and cell-line specific observations. We aim to complement our initial findings with biochemical and structural analyses in vitro as well as animal studies in vivo. To further establish the reproducibility of our data, I often ask my close friends and collaborators to independently repeat the key findings of a study before submission. It generally takes a long time for us to complete a study, but I believe the effort will pay off in the long run.

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

During my PhD at Columbia, I was most impressed with the general attitude of my mentors toward research. No matter how much they have achieved, they take every new experiment and every poster presentation seriously.

As I did not have postdoctoral training, I was somewhat unprepared at the beginning of my independent career. One difficult challenge was knowing when to finish a paper and project. We often kept working and working. I have now gotten a lot better.

You've done research on three continents throughout your career. Can you tell us about some of these transitions?

During the last year of my doctoral studies at Columbia, I was offered a lecturer position by the Department of Biochemistry at NUS. It was a very hard decision to leave the United States, but I was excited by the prospect of starting my own laboratory at a top institution. Life at NUS was very good overall, despite some struggles. I had to make ~700 slides for teaching during the first year and my start-up fund was 10,000 Singapore dollars (~6,000 USD). But the graduate students were fully supported by the university, and most of them are hard working and talented. The crucial screen that led to the discovery of seipin as a key regulator of LD formation was performed at NUS (2). I enjoyed my time at NUS, where I was promoted and tenured. However, my family and I could not get used to the heat and humidity. We looked for a place with better climate, and it happened that my current employer, UNSW, had an opening in 2006. Moving continents with two kids was very disruptive, and I had zero publications in 2007. Our work on seipin was delayed and almost got scooped. I was also very worried about funding in Australia since I hardly knew anyone and the funding system. It turned out that the Australian community was very supportive of our research from day one. I have also been very fortunate to receive generous support from the Ara Parseghian Medical Research Foundation, based in the United States, after my move to Sydney.

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

While I am mostly recognized for discovering seipin's role in lipid droplet formation, I am prouder of the work we have done on lipid trafficking and the oxysterol binding proteins. We struggled mightily for the first 15 years. At one point in 2015, I seriously considered abandoning this line of research. But we persisted and discovered their roles in regulating plasma membrane $PI(4,5)P_2$ and cholesterol, as well as in lipid droplet formation (3, 6).

Hongyuan's "metabolism team" after a basketball game. Photo courtesy of Hongyuan Yang.

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

The biggest challenge has to do with the subject of my research topic: the fundamental cell biology of lipids. The sorting, distribution, and storage of cellular lipids are clearly very important topics in biology, but they are sometimes too fundamental to explain to funding agencies and new students. These days, lipid research is not as "sexy" as other topics. But there are so many unanswered questions in lipidology. I strongly believe that lipid research is going to be the next "big thing" as new techniques such as cryoEM now allow us to appreciate lipids and membrane proteins with unprecedented clarity.

Who were your key influences early in your career?

Besides mentors and teachers at Columbia, I really enjoyed reading and studying the works by Drs. Mike Brown and Joseph Goldstein, Ta-Yuan Chang, and Scott Emr. While they were not my teachers, their work inspired and impacted many young scientists, including me.

What is the best advice you have been given?

I have been given many pieces of great advice during my career. The best one in my view is "Less is more." I was once told, "You would be better off with a lab of six than twelve." Initially, I did not get it because I thought that a bigger group would allow me to explore more directions and be more productive. The reality is that, as a little-known junior researcher, few experienced people would join my laboratory. Funding is also a major limiting factor. Supervising a large number of students is fulfilling, but it also takes away some of my own time to think critically about the projects. I have largely kept my group under six, and this allows me to better supervise and guide the trainees. People say, "Once your team has more than 15 members, you become a manager instead of a scientist." My own experience corroborates that statement because I struggled quite a bit when my group reached 12 at one point.

What hobbies do you have?

I am heavily into sports, especially basketball and tennis. I follow the NBA closely, and Jeremy Lin is my hero. I still play basketball at least twice a week. I am the captain of a basketball team comprised of scientists working on metabolism (see image). We play real, refereed basketball games against local teams during conferences. As I am getting older, I have also picked up tennis. I watch coaching videos on YouTube but still need a lot of work on my forehand. Through sports, I learned teamwork and the spirit of fighting to the last second. If I were not a scientist, I would probably run a sports-related business.

What has been your biggest accomplishment outside of the laboratory?

I got married and had children relatively early. Both of my kids are now in college and they appear to be decent human beings. I have been extremely lucky because my wife did most of the heavy lifting in looking after the kids. It was still a struggle for me to balance work and parental duties during the early days of my independent career. I am very proud and happy with where we are as a family right now.

Any tips for a successful research career?

Everyone is unique. Knowing your strengths and especially your weaknesses can be crucial to your success. My undergraduate training was in medicine and health management, and my PhD work focused on genetics and cell biology, so my understanding of physical chemistry is rather inadequate. I am also very bad at developing new methods. To alleviate these deficiencies, I constantly monitor new methods in my field and I purposefully look for collaborators with strong chemistry backgrounds. I have benefited immensely from such efforts.

References

1. Yang, H., et al. 1996. *Science.* https://doi.org/10.1126/science.272.5266.1353
2. Fei, W., et al. 2008. *J. Cell Biol.* https://doi.org/10.1083/jcb.200711136
3. Wang, H., et al. 2019. *Mol. Cell.* https://doi.org/10.1016/j.molcel.2018.11.014
4. Du, X., et al. 2011. *J. Cell Biol.* https://doi.org/10.1083/jcb.201004142
5. Trinh, M.N., et al. 2020. *Proc. Natl. Acad. Sci. USA.* https://doi.org/10.1073/pnas.2010682117
6. Du, X., et al. 2020. *J. Cell Biol.* https://doi.org/10.1083/jcb.201905162