Qing Zhong: Scoring a slam dunk on the autophagy court

Qing Zhong uses a classical cell-free biochemistry approach to identify genes involved in autophagy, and to uncover their links to human disease.

Whether he's chasing down a novel disease gene or making rebounds on the basketball court, Qing Zhong loves a spirited competition. He was trained as a physician in China, but soon found that his real passion was in biological research. He decided that his best chance for success in his new profession would come from working in a major laboratory in the United States. He came to San Antonio, Texas to do his graduate work with Wen-Hwa Lee, studying the genetic basis of breast cancer (1–3). He next pursued his postdoctoral studies on apoptosis in Xiaodong Wang's laboratory. While there, he scored big by using classical biochemistry methods of gene discovery to uncover an involvement of the MULE protein (an E3 ubiquitin ligase) in apoptosis (4, 5).

"In science and in sports, I play very hard, and I bring a lot of energy to my work... And I like to win. So I play hard and I play smart, but I play fair."

Zhong is now heading up his own laboratory at Berkeley, where he uses the methods he learned in his postdoc to identify new players in autophagy, a critical pathway for cellular homeostasis. Zhong calls the autophagy pathway "the next apoptosis", because he believes that, like apoptosis, it will turn out to be central to human health and disease. He took a "time-out" to talk to us about his work, before heading out to the basketball court to teach the undergrads a thing or two.

PLAYING TO WIN

What kind of approach do you bring to your work?

I like thinking of myself as a competitor. In science and in sports, I play very hard, and I bring a lot of energy to my work—but while I respect a hard worker, I respect a smart one even more. And I like to win. So I play hard and I play smart, but I play fair.

So you're an athlete.

I like any kind of games, but especially basketball. I still play with undergrads here at Berkeley. I don't play one-on-one with them anymore, but I can be a very good ball player. That's why I put more attention into defense rather than offense right now. These kids can really score, but I help them to get rebounds and blocks. I like to make them think, to coach them to success on the court and in the laboratory.

Are you a fan of professional sports too?

I'm a huge fan of Yao Ming and the Houston Rockets. Yao Ming is definitely my hero. I enjoy watching him play a lot—I have an NBA pass to watch every game of his. He loves to play center, and that's not an easy job, but he's fearless. I play center, so I know what it's like: people will bump you, hit you, and push you. But he can stay calm, and still play tough. That's something I think I admire the most about his style. It's an attribute that I personally want to have.

Did you ever want to be a professional basketball player?

No. In fact, as a child, I wanted to be a physician. I grew up in Beijing, China, in a family where a lot of my relatives were working in medicine. My grandfather is a physician, and he has six brothers and two sisters—and half of them are involved in medicine. Some of them are surgeons, some are in obstetrics and gynecology, and others are practitioners of Chinese traditional medicine. They even have their own clinic, and have all worked at major hospitals in China. So with a background like that, it's no wonder I wanted to be a doctor when I went to college.

Did something happen in college to change your mind?

I went to Peking Union Medical College. It's famous because it's one of the two medical schools in China that were founded by the Rockefeller Foundation, about 100 years ago. It's also famous for having a tough medical program. Most medical schools in China have five- or six-year programs, but this one has an eight-year program.

Qing Zhong

I have to say I wasn't really a great medical student, but I found a new passion at the end of my program, when we had to do eight months of research training. I joined a laboratory studying spermatogenesis and I worked really hard—day and night. I didn't make any scientific breakthroughs as a newcomer, but my professors were very nice and supportive, which really encouraged me.

Did you know you were going to do research from then on?

Actually, I first did a one-year residency in the cancer hospital of the Chinese Academy of Medical Science. But this only confirmed that I wanted to be a scientist rather than a doctor. We saw lots of patients, but there was very little discussion about why a certain drug functioned a certain way. I was curious about things beyond my daily work as a doctor, such as finding new treatments, and understanding the mechanisms behind cancer and the drugs used to treat it. That's why I decided to work in research.

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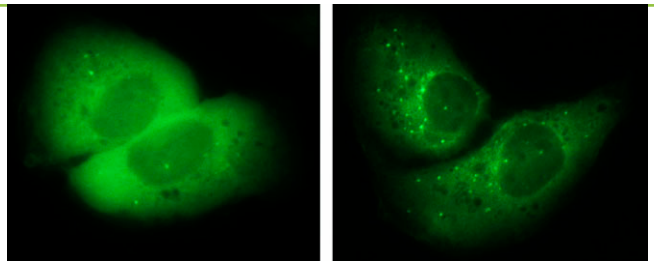

Autophagosomes (punctate staining) form after rapamycin treatment.

EYE ON THE BALL

Which laboratory did you choose for your graduate studies?

I joined Dr. Wen-Hwa Lee's laboratory at the University of Texas Health Center to study for my PhD. He's one of the three scientists who first cloned Retinoblastoma, a tumor suppressor gene that's mutated in a lot of cancers. In Wen-Hwa's laboratory I worked on Breast Cancer Gene 1 (BRCA1), which is mutated in more than half of all familial breast and ovarian cancers. We found that BRCA1 works together with the Rad50/Mre11/Nbs1 protein complex in DNA repair.

What made you switch from breast cancer to apoptosis for your postdoctoral work?

After working on BRCA1 for some time, I decided that instead of just studying one gene, I wanted to master a whole pathway, to ask, "What's the critical step? What are the important genes involved in this pathway?" I wanted to have the tools necessary for discovering novel genes, or novel pathways, so we could figure out how they contribute to human disease. So when I applied to laboratories to do a postdoc, I was specifically looking for one with a strong expertise in biochemistry.

And that's why you selected Dr. Xiaodong Wang's laboratory.

Yes. Xiaodong is famous for his biochemical approach to mapping out the apoptotic pathway. People basically use two approaches to map out novel genes and pathways. One is genetics, and the other is biochemistry. Ten years ago, the human and mouse genome had not been sequenced and mammalian genetic screens were not so easy. If you wanted to do a genetic screen, you would generally use yeast or flies. But, because of my medical background, I've always wanted to study disease processes in mammalian systems. The biochemical system that Xiaodong's laboratory used allowed me to do that.

Xiaodong used a very classical biochemical approach: a cell-free fractionation system. With this approach, which I still use in my laboratory today, you start from the activity you are interested in and work down to identifying the protein responsible for that activity. In Xioadong's laboratory we identified a new E3 ubiquitin ligase for the Bcl2 family member Mcl1. We called this new protein MULE, and ended up cloning the gene that encodes it. It's actually the first ubiquitin ligase to be identified by this method.

GAME PLAN

And you are continuing to use this approach in your new laboratory?

Yes, but now we are looking at autophagy. The autophagy lysosome pathway was first characterized almost 50 years ago, but until recently everyone thought it was a constitutively active housekeeping pathway, so it didn't draw much attention. But now people are realizing that autophagy is a highly regulated process. It responds to stress, it's important for normal development, and it's also involved in a lot of human diseases, such as cancers, autoimmune diseases, and pathogen biology.

I think the autophagy field now is where the apoptosis field was ten years ago. We don't yet know very much about the biochemistry of this pathway, so there is a lot of room to make important new discoveries. The key questions that I want to attack are: how is autophagy induced, and where does its specificity come from? Autophagy can degrade many different targets, from bacterial pathogens to organelles to aggregated proteins—so how are these things specifically targeted for degradation? How does the cell decide what things to degrade, and what to leave alone? Is there some key event regulating this pathway? It's very exciting to be working on these kinds of questions.

What inspires you in your work right now?

I just love thinking about questions like: why do we have cancer? I know that we won't have answers for that question in my lifetime, but I love thinking about it because it is so complex. It's such a puzzle.

When I was in Xiaodong's laboratory, I used to joke with my lab-mates about wanting to win the next Nobel Prize [laughs]. But it's not really about winning a prize. I'm just always thinking about the next big question. I'd like to know what's the key step in autophagy. If we can find out what that is, can we target it with a drug? Can we use the drug to treat a human disease? I would love if I could be involved in something like that. JCB

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2. Zhong, Q., et al. 2002. *Cancer Res.* 62:3966–3970.
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5. Ding, Q., et al. 2007. *Mol. Cell. Biol.* 27:4006–4017.

Zhong sports the team jersey of his basketball idol, Yao Ming, who exhibits the kind of sporting competitiveness that Zhong admires.