People & Ideas

Jiahuai Han: Aflame on inflammation and p38

Han studies the mechanisms of inflammation and immunity, and the many cellular functions of p38.

The mitogen-activated protein kinases (MAPKs) are a class of serine/threonine kinases that frequently act as fulcrums in the cellular response to stressful stimuli. Jiahuai Han discovered the p38 MAPK (1), and he's spent much of his career characterizing members of the p38 family and the many roles they play in cells (2).

Han regards his work on p38 as an important facet of his career, but he says that his real interest is in the cellular response to stress, particularly inflammation (3, 4). His work has touched on many topics related to this subject over the course of his career, and Han has fearlessly pursued the answers to his questions, wherever they lead him. In fact, this pursuit has led him to many different geographical places—from China at the start of his research career, to his pre- and postdoctoral studies in the United States and Belgium (5), a tenured position at The Scripps Research Institute in La Jolla, California, and finally a return to China. We called him at his lab at Xiamen University, Fujian Province, to talk about his many travels.

GROWING ABROAD

Where did you grow up?

In Anhui Province, in the middle of China. I grew up during the Cultural Revolution, and resources were scarce. In middle school and high school, we did not learn much. After high school, I spent a year in the countryside because there weren't any other jobs available, so the government just sent people to the countryside to work on farms. Then I got lucky because they began to reopen the exams for entering university.

> "We study the signaling pathways involved in the immunological response to stress, and inflammation."

Did you know what you wanted to study?

Society was very politically oriented at that time, but the best students were expected to become scientists. So, I took the national exams and entered Peking University in Beijing, which is one of the best universities in China.

Honestly, when I went to college and chose to study biology, I didn't really know anything about biology. I didn't even know what molecular biology was. I gradually became more interested in it the longer I studied, but I didn't have any clear plans for what I wanted to do. Once I reached graduate school, I discovered that the condition of the facilities and the research environment were very poor; they hadn't yet been rebuilt after the Cultural Revolution. I realized that if I wanted to do research, I would have to leave the country for more training.

What did you do next?

In China, I had become interested in cancer, and in trying to find antitumor molecules. Bruce Beutler at UT Southwestern had isolated a protein called tumor necrosis factor (TNF), which I found very interesting, so I wrote to him to see if I could join his lab. I became a visiting student in Bruce's lab, but I completed my PhD in Brussels, Belgium with Georges Huez. Then I went back to UT Southwestern to work with Bruce again, to work on TNF in inflammation. After a while, though, I decided that it was time to move again, so I went to Scripps, where I joined Richard Ulevitch's lab as a senior postdoc.

STATES SOJOURN

How did you first encounter p38?

When I was in Bruce's lab, I studied the induction of TNF by inflammatory molecules like lipopolysaccharide (LPS). I focused on the transcriptional and translational regulation of TNF. When I got to Richard's lab, I wanted to look further upstream, to ask what signaling pathways lead to the stimulation of TNF production. I started looking at the signaling pathway downstream of LPS stimulation, and this is how I first encountered p38. I was specifically looking for novel components of that signaling pathway, and when I got a candidate protein, I went ahead and purified it, and it turned out to be p38.

Jiahuai Han

It was a fortunate discovery for me, because shortly after discovering p38 I got promoted to assistant professor at Scripps. Basically everything has gone pretty smoothly for me since that time. I subsequently cloned p38, other p38 family members, and a few additional components of the pathway. I should mention that other groups also cloned p38 shortly after us and contributed greatly to the study of p38.

Could you have built your career entirely on studying p38?

When I first found p38, all I knew about it was that it was a phosphorylated protein. After I purified and sequenced it, I realized it was a kinase, and that it would probably have a lot of signaling functions

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

outside of this pathway as well. Of course, now we know that p38 is a MAPK, and that it has many different roles in cells. At first, though, I was mainly interested in its role in TNF production, so I spent a lot of time studying that aspect, but gradually I began to shift my focus away from that question, and I started to branch out into studying p38's other roles. I don't know if that was a good thing or not, but I kept coming up with new questions about the kinase. Even today, a large part of my lab is still working on p38.

Is p38's role in inflammation still a major focus of your lab?

Yes, this is still an important part of my lab's research. People often ask me, what is my focus? Sometimes I have to think about it before I can answer them. Basically, we study the signaling pathways involved in the immunological response to stress, and inflammation. But much of our work touches on subjects outside of inflammation, like cell metabolism or death.

HOME AGAIN

What other aspects of p38 function are you working on now?

These days, we mostly work on animal models, looking for the in vivo roles of p38. There are four members of the p38 family, so we have a lot of work to do characterizing the functions of the different isoforms. Sometimes they have really quite different functions; for example, the p38-δ isoform seems to play a role in glucose homeostasis, and is connected with the insulin system.

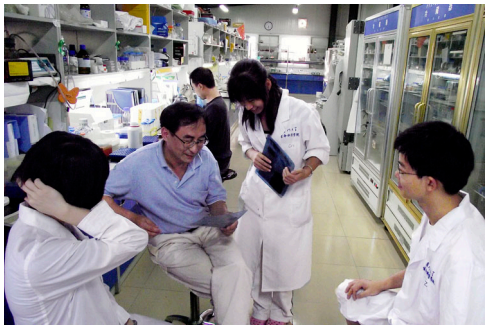
Everyone is hard at work in Han's lab.

Other isoforms, like p38-α and p38-γ, are important for cellular senescence, which is a major mechanism for protecting against tumorigenesis. We are studying p38-α most closely, and we have found that it can modulate the activity of the tumor suppressor p53.

You mentioned that you are also working on cell death…

Actually, that is a very long story; we worked on that one for some time. We started working on it because of our interest in TNF. Certain cells, when treated with TNF, undergo necrotic cell death. The molecular basis of necrosis is poorly defined right now, but the most practical definition for our study is that it is a form of cell death that, unlike apoptosis, does not involve caspases. We wanted to see if we could find a key molecule that is important for necrosis.

We had been working on this problem for a while when I heard about a paper that another group had published, which claimed that TNF-treated NIH-3T3 cells didn't undergo apoptotic cell death, because if you blocked caspases, the cells would still die. I thought this was interesting because, generally speaking and also in our hands, TNF treatment of NIH-3T3 cells causes apoptosis, and does involve caspases. So we got some of these necrotic NIH-3T3 cells, and we compared their gene expression profile to our apoptotic NIH-3T3 cell line. We found very few genes that were different, but the necrotic NIH-3T3 cells expressed a gene called Rip3. At that time, RNAi technology was just becoming available, so we knocked down Rip3 in the necrotic NIH-3T3 cells, and found that now they started to die by apoptosis. Later, we were able to show that the mechanism by which Rip3 causes cell death involves modulating metabolism and reactive oxygen species production.



Han training students in his lab.

That sounds like a lot of different subjects to keep track of!

That is one of the reasons I moved back to China in 2007. Partly I just felt that it was time for a change of scenery, to keep things interesting. But I also wanted to have a big laboratory so that I could follow up on everything we find, and continue to expand on it. I thought it would be easier to have a big laboratory in China—although I still have a partial appointment at Scripps to finish up the work I started while I was there.

The main difference between working in China and working at Scripps is that here, all the work in my lab is done by university students and graduate students. On one hand, that is very nice because their salaries are paid by the university, and the students here work very hard. That means I can have many people working on different projects, and I can get much more done with less money. On the other hand, there are not many postdocs in China; even though the research environment in China is now much stronger than it was, many Chinese students still go abroad for their postdocs. So, I basically have to train everyone up from the beginning. That's OK with me, though, because I think it's fun working with students.

> "I wanted to have a big laboratory so that I could follow up on everything."

1. Han, J., et al. 1994. *Science.* 265:808–811.
2. Sun, P., et al. 2007. *Cell.* 128:295–308.
3. Zhang, D.W., et al. 2009. *Science.* 325:332–336.
4. Kang, Y.J., et al. 2007. *Nat. Immunol.* 8:601–609.
5. Han, J., et al. 1991. *J. Immunol.* 146:1843–1848.