Feng Shao: Getting a sense for the defense

Shao studies pathogenic bacteria and their hosts' innate immune mechanisms.

Multicellular organisms—whether they are plants or people—are under continual assault from microbes. Of course, the first step in mounting a defense is recognizing that an invasion is taking place. Accordingly, pathogenic microbes are highly incentivized to evade detection. But because they live inside or in close proximity to host cells, they inevitably leave evidence of their presence, and host organisms have evolved ways to sense those clues.

Feng Shao's lab at Beijing's National Institute of Biological Sciences is studying the strategies employed by both sides in this ongoing war. Shao is fascinated by the wide variety of methods by which bacteria establish infection and prevent detection by host cells (1, 2), and the equally diverse countermeasures their hosts have developed to stop them (3–5). We recently called him to hear about the new fronts he's exploring, and the novel aspects of biology he's learning about on the way.

TRANSCONTINENTAL CONNECTIONS

Congratulations on your recent election to EMBO.

Thank you. I did not expect it. I guess some of my colleagues in Europe appreciated my work on bacteria and immunity, and wanted to make more connections with me and with the growing research community in China.

You're from China but you trained abroad…

Yes. I grew up in a small town in mid-eastern China. My parents are sales clerks in a department store—a pretty normal family at first glance. But during China's political movement my parents were forced to move from the city to the countryside and do agricultural work. They were not very good at that because they had no background in it, so, when I was born, they could not afford to raise me. They sent me to my grandmother who raised me until the age of 12. Later the policies changed so my parents were able to return to the city. Their financial situation improved, and they got me back.

I think because I lived separate from my parents, I became a very thoughtful, independent child. I was always a good student, and was admitted into a top college—Peking University. I studied chemistry as an undergraduate and then went to the Institute of Biophysics at the Chinese Academy of Sciences to study protein structure for my graduate career. I was supposed to get a PhD there, but then I met my wife. She was a year ahead of me in a master's program and after graduating went to the US to continue her study. So I left early with a master's degree and joined the PhD program at the University of Michigan.

A SUDDEN MOVE

You worked on both human and plant pathogens as a graduate student…

I joined Jack Dixon's lab for my PhD. It's mainly a signal transduction lab, but some people there work on pathogen-related toxins. My first project was on a toxin called YopT, which is injected into host cells by the plague bacterium *Yersinia pestis*. It was known that the toxin can disrupt the cytoskeletal structure of the host cell, and I figured out that it is a protease that cleaves a prenylated cysteine at the tail of the Rho GTPase, causing the GTPase to fall off the cell membrane.

> "I wanted to study bacterial toxins, but with a different approach than I had used in my PhD."

While I was working on YopT, I did a BLAST sequence search and found a homologue of YopT in a plant pathogen, *Pseudomonas syringae*. So then I contacted a plant biologist at Indiana University, Roger Innes, who had been working on this protein, called AvrPphB, for many years. We collaborated to characterize AvrPphB and showed that it cleaves a plant kinase and this cleavage event triggers an immune response in the plant host.

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Feng Shao

The obvious direction would have been to continue studying plant immunity as a postdoc. But that would have been quite a dramatic move, so I wanted to explore it before committing. I went to visit Roger Innes' lab, and also did some experiments in Jianming Li's plant biology lab in Michigan. But after a few months I realized this was probably not the direction I wanted to go because, although it's very interesting from a scientific point of view, plant researchers had little money, particularly in the States. Instead, I remained in Jack's lab to help him in his move to San Diego, then joined Marc Kirschner's lab at Harvard for my postdoc to work on ubiquitination and its role in regulating cellular processes. But I was only there for a little over one year before I came back to China.

Why was that?

My wife had left biomedicine for business school and we were expecting that we would get the green card by the time she finished her MBA, but it just did not come. It was an awful situation. She could not work and we had invested lots of money in business school. Then Johnson & Johnson offered her a job, but when they realized she couldn't work in the States, they offered her a job in China. We wanted to be together and have a family, so I decided to go with her. Also, unbeknownst to me,

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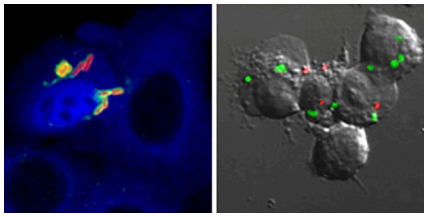

IMAGE COURTESY OF QIUHE LU

Inflammasome activation (red) in mouse macrophages infected with *Salmonella typhimurium* (green).

a professor in Michigan, Kun-Liang Guan, was impressed by my work and had forwarded my CV to Xiaodong Wang, who was setting up a new Western-style research institute, the National Institute of Biological Sciences, in Beijing.

After a simple interview, Xiaodong offered me a job. It was an amazing opportunity. I was in a different position from most junior faculty because I didn't have a specific project. In the US, the NIH funding system is very rigid, very programmed, so many people must continue to work on similar projects to their postdoctoral research in order to get funding. But I was given lots of resources and was free to work on whatever I wanted, so I set up a few different directions.

For some time I continued the ubiquitination project I had started working on in the Kirschner lab, but I stopped after finishing a paper on it. I wanted to study bacterial toxins, but with a different approach than I had used in my PhD. I don't focus on a particular pathogen. Most of the bacteria are not a public health concern because their infections are treatable by antibiotics. But we can learn many interesting new things by studying different bacteria.

We learned that many bacteria employ some kind of posttranslational modifications on critical host proteins to block or disrupt host defense mechanisms. It is becoming an emergent theme in the field that many of these modifications are unique, and different from the kind we normally see in the host cell. For example, some bacteria can perform irreversible "dephosphorylation" of a host kinase, or make methylation modifications on cysteines, or even directly modify host ubiquitin and ubiquitin-like proteins. We have figured out many of these processes.

GOOD ADVICE

You could probably study these indefinitely…

After I published my *Cell* paper in graduate school, I asked Jack for career advice and he said one thing: "Feng, you don't want to repeat yourself." This has strongly influenced me.

After we worked out the mechanism for a couple different toxins I started to feel like I was repeating myself, so I decided to expand my research program to the host side, to work on inflammasome-mediated innate immunity. At that time the concept of the inflammasome was very new. It was proposed to operate as a defense response that recognizes microbial products or dangerous signals in the cytosol, leading to caspase-1 activation, interleukin maturation, and inflammatory cell death.

> "There are probably many mechanisms for sensing pathogen invasion."

All molecules from bacteria are foreign to the host cell, so there are probably many mechanisms for sensing pathogen invasion. For example, we have discovered immune receptors called NAIPs, which can directly recognize bacterial flagellin. Many bacteria use flagella for motility, and flagella share their evolutionary origin with the type III secretion system that injects bacterial toxins into the host. We figured out that some NAIPs recognize flagellin while others recognize the type III secretion system. Upon ligand binding, the NAIPs then mediate the formation of the inflammasome complex to activate caspase-1 and inflammation.

Last year we had two new stories. One is on other inflammatory caspases, where we showed that caspase-4 and -5 in human, and caspase-11 in mouse are receptors for cytosolic lipopolysaccharide from gram-negative bacteria. This is an unusual mechanism because the caspases themselves combine the sensor and execution functions in innate immunity. In the other story, we did a small-scale screen and identified a protein called Pyrin that is activated once a bacterial toxin modifies host RhoGTPase. Therefore Pyrin senses bacterial virulence activity, which is quite different from the NAIPs and caspase-4/5/11 that directly recognize a bacterial product. This type of indirect immune sensing mechanism is prevalent in the plant defense field that I worked on during my PhD. It's amazing that nature uses similar biochemical mechanisms in such different systems to initiate innate immune responses.

You've come full circle…

Right. [*Laughs*] I have a feeling that cytosolic sensing pathways employ diverse modes of recognition. There might be other ways of detecting microbial products or activities in the cytosol that are completely unexpected from our current knowledge. Also, cytokine responses and inflammatory cell death may not be the only downstream events; recognition pathways may activate other cellular defense pathways such as autophagy. We're now exploring these possibilities.

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PHOTO COURTESY OF SHAN LI

The Shao lab on an outing to Heaven Lake, at the top of Baekdu Mountain.