People & Ideas

Hyung Don Ryoo: A healthy career in cellular death

Ryoo engages the power of the fly to study apoptosis during development and disease.

In the body, some cells must sacrifice themselves for the greater good. Cell suicide (apoptosis) is essential for sculpting the body during development and for eliminating damaged or potentially dangerous cells that might cause disease.

At his laboratory at New York University, Hyung Don Ryoo uses the fly to study the molecular pathways that control apoptosis. His love for this model organism started during his graduate studies on Hox transcription factor regulation during development (1, 2). His choice to study apoptosis, however, was more of a carefully thought-out career plan. Indeed, in a recent interview with Ryoo, it was clear that his motivation is to be in the best position for making new discoveries, regardless of the field.

Ryoo's apoptosis studies started during his postdoc with Hermann Steller at the Rockefeller University (3, 4), and continue in his own laboratory (5). Though, true to form, Ryoo has recently moved into another field—ER stress (6, 7). What's his ultimate career aim? To start a whole new field of his own, of course.

KNOWING WHAT NOT TO BE

Where did you grow up?

In Seoul, Korea. I spent three years in New York when I was a child, because my father had a job here, but spent most of my youth in Korea.I went to college there, and then did military service.

Tell me about your military service.

It was for two and a half years after college, so I must have been 22 to 24. I was assigned to a military hospital. It was mainly menial work, getting military medical supplies. We also did basic military training.

Korea was a very militaristic society—we had former generals ruling the country until the mid-80s. As a child, one of my favorite movies was *Platoon* by Oliver Stone. But these boyhood fascinations toward the military disappeared during my military service.

Why?

In movies you see John Wayne-like figures, Rambo-like figures—one hero against an entire enemy army. But an individual is weak, and in the military, oftentimes out of fatigue, you get to hate your colleagues more than perhaps the other side.

No military career for you then! Did you consider anything other than science?

I was always pretty sure that I wanted to pursue science. I thought about physics, but my mother was strongly opposed because of a cousin of mine. He broke the all-time grade point average at Caltech in the 70s, and then went on to do his graduate studies at Harvard, studying theoretical particle physics. But after he had obtained his PhD and did a few years of postdoc, he left science because he couldn't get a job. So, I studied biochemistry instead.

> "I do think a lot about whether there will be new opportunities of discovery before taking a new direction."

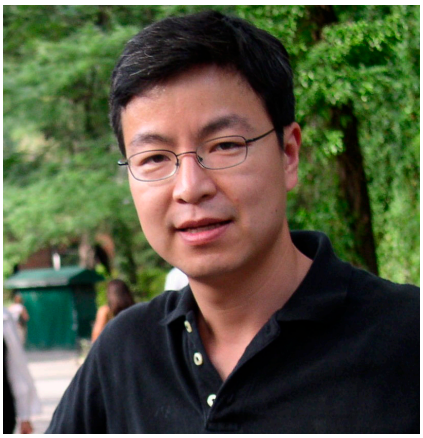
GETTING GOOD TRAINING

You moved to Columbia University in New York for your graduate studies. Why there?

Among the places that I was accepted, Columbia was probably the most reputable. There could've also been some emotional value attached to Columbia because of my childhood years in New York. I remembered visiting the beautiful Columbia campus with my cousin, who was interviewing there for his own graduate studies.

You joined Richard Mann's Laboratory?

Yes. Richard's laboratory was my second rotation. We were supposed to do three rotations, but I asked for special permission.



Hyung Don Ryoo

I went to my graduate adviser, said, "I'm set, I know that this is the lab that I want to work in," and I stayed there.

Back then Richard was a molecular biologist making a transition into developmental biology. He started his fly laboratory just a few years before I arrived there.

Because of his mixed background, Richard's seminars were really fascinating. Lots of biochemistry, molecular biology, three-dimensional crystal structures, and then ultimately in vivo tests using fly genetics. When I saw that, I immediately realized that was the kind of training I wanted—well-rounded and incorporating lots of different disciplines.

What did you study?

Right before I joined the laboratory, Richard had shown that Hox proteins have cofactors—called Exd—and that the two bind together on DNA.

There was a big debate in the field as to whether these were specificity-conferring cofactors. And my thesis work determined that, yes, they are.

CRAFTING A CAREER PATH

How did you pick your postdoc?

I really got to appreciate the power of the fly as a model organism. But the *Drosophila* community was poorly represented outside the field of developmental biology.

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I wanted to find some new directions that would allow me to branch out. In that regard, I thought apoptosis was probably a good place to start, because it's associated with a wide spectrum of processes—developmental apoptosis sculpts the body shape; too much cell death can lead to diseases like neurodegenerative disorders; too little cell death is associated with cancer.

As a young scientist trying to make a career, choosing your postdoc plays a big role in determining your future research. Finding the right postdoctoral laboratory is really challenging because the laboratory should be reputable, you have to get along with the group leader, the topic should be something interesting, but on top of that you have to ask, can I see myself branching out in an independent direction afterwards?

I made the conclusion that Hermann Stellers' laboratory at Rockefeller would provide all of that.

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So you chose apoptosis as a career move as opposed to being passionately interested in the subject?

Well, yes. I do think a lot about whether there will be new opportunities of discovery before taking a new direction. There are scientists who start their seminars by saying they saw gastrulation when they were in high school, and they fell in love instantaneously. I didn't have any such experiences as a young child. Also, I feel that science is a rapidly changing discipline, and if you're at the right place, in the right position, you can run into the most unexpected discoveries. I see that as the source of my excitement. The emphasis would be on trying to find something novel, rather than something that I had fallen in love with many years ago.

When did you decide on your latest direction?

I started thinking about which direction to branch out into after I published my first paper on apoptosis from Hermann's laboratory, in 2002. I realized that many other people were doing similar experiments.

The unfolded protein response field was growing at the time and really reminded me of the apoptosis field in the 90s. Apoptosis lectures used to start out by saying, "If we understand apoptosis well, then we can understand development and cancer and neurodegenerative disease, viral infection, and everything," and you wonder, "What is apoptosis not related to?" In the early 2000s, the unfolded protein response lectures started a similar way. "It's related to virtually every known important problem in the world, and if we understand that well, then we'll bring about world peace."

Whether that's true or not, I thought that bringing in a new model organism, like flies, would generate lots of exciting discoveries—the pioneering work had been done in yeast and mammalian culture cells. Particularly, I thought the flies would be an excellent model to study the connection between ER stress and apoptosis. So in 2002 I started developing some tools to study the unfolded protein response using fruit flies.

Another well-planned career move.

If I'm doing the same thing that everyone else is doing, then I would be dispensable.

In science there's a lot of that, especially in crowded and competitive fields. In fact, if you left, it's likely everyone else would be really happy. So, the goal has to be to come up with questions that other people are not asking, or approaches that other people are not taking. That's how to make important discoveries that have an impact—something that would end up being useful to others. That's the conceptual goal that I've always had.

At what point did you know you wanted to be a group leader?

That was always the aim, since I was an undergrad. If you're a group leader, then you can actually direct your own research, come up with creative ideas, and take the initiative. That's what I wanted.

Is it as good as you thought it would be?

Yes. It's really exciting. I feel like the kind of research that's going on in my laboratory is the best I've ever done. I guess part of it is the freedom; I can do whatever I want. The second thing is, I have people in my laboratory, so I don't have to spend all my time doing mini-preps. I can spend more time discussing ideas.

Now you've made it to group leader, what's next?

I'm still in a learning process here, but of course the most desirable scenario is that I start a new field all by myself and make it very important down the road. But until that happens, the next best scenario is to work in an important field and find a unique approach to studying it.

It's also important to me that my work has some meaning in this world. Since none of my family members, including my wife, are scientists, I should be able to tell them that whatever we're working on is relevant to the general public.

If you're surrounded only by scientists, then I guess you can really excite each other by discussing the fact that the 256th amino acid is behaving a little differently. My father is an elderly banker. Disease, particularly age-related, is something he can relate to. It's important to me that I can talk about my work with him. Otherwise, we'd be talking about the economy all the time.

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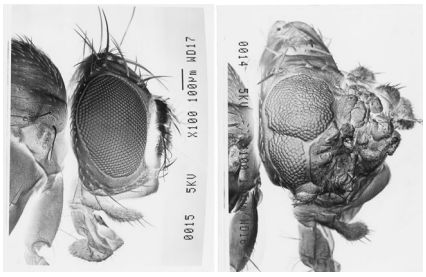

Undead cells in the fly eye (right). The cells initiate but fail to execute apoptosis, and then overgrow. This is one of the many apoptosis anomalies that Ryoo studies.