

Yasushi Saka: Stirring a melting pot of math and morphogens

Saka uses a combination of mathematical models, yeast, and frogs to investigate the action of morphogens.

"I was lukewarm about a career in science. But once I tasted that excitement, I wanted to taste it again."

in Cambridge, UK—Saka worked on frog morphogens (1, 2) and used mathematical modeling to understand how cells respond to them (3).

Saka strongly believes in the benefits of looking beyond one's field of study for answers. Before his incarnation as a developmental biologist, he was a successful yeast geneticist (4), and recently he's returned to the unicellular organism. Yeast might not be the obvious choice for answering questions about morphogen biology, but Saka believes that it could be very useful for filling in the gaps between frogs and math.

Saka now runs a lab at the Interdisciplinary Research Institute in Lille, France. A fitting home indeed.

EARLY DAYS

How did you get interested in science?

There were no scientists in my immediate

family, so I'd say I'm a bit of an oddball. My science experience was limited during childhood, although my father once bought me a cheap microscope, which I loved.

I looked at things like my hair, or sand, or soil. Once I found something moving in the soil, and in retrospect, I think it was a nematode.

*Aha! A young *C. elegans* researcher!*

Yes, if I may say so.

You went to Kyoto University.

Did you study biology?

Yes, but it was a peculiar system at the time. I don't know what it's like now, but back then, we could pick all sorts of subjects: biology, mathematics, physics, or whatever. Then, gradually, we focused more on one particular subject. In my case, that was biology, because I didn't really understand equations. Mathematics is not my strength.

You stayed on at Kyoto for your Ph.D.?

Yes, I studied the fission yeast cell cycle with Mitsuhiro Yanagida. Actually, I applied to another lab initially—that of Masatoshi Takeichi who was famous for having discovered cadherin. But I miserably failed the selection process, and I had to spend another year as an undergraduate. Since that year was like a holiday for me, I asked around for a lab project and ended up in Dr. Yanagida's lab. I decided to stay there as a graduate student, which turned out to be a very good choice. It was a fascinating period for the cell cycle field.

While analyzing yeast cell cycle mutants, I discovered that a protein called Cut5 was essential for both promoting DNA replication and inhibiting mitosis. The excitement surrounding that discovery was something that made me decide to continue as a scientist. It's like an addictive drug. Before that, I was lukewarm about a career in science. But once I tasted



Yasushi Saka

that excitement, I wanted to taste it again. It doesn't come often, of course.

If things were going so well, why did you decide to leave?

That's a very good question. I think that after five years I was just a bit bored with the cell cycle. And yeast. I wanted to study multicellular organisms.

Also, many other students in the lab were going off and doing postdocs abroad, in the US or Europe. So I thought, "Why not me too?"

GOING MULTICELLULAR

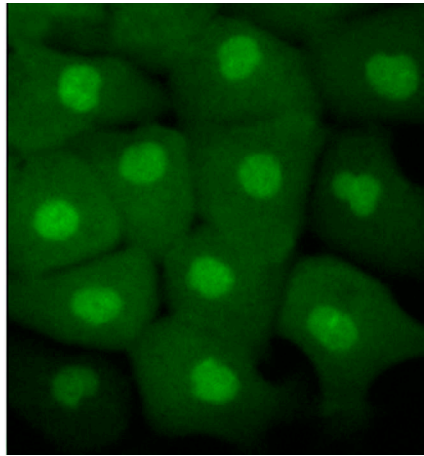
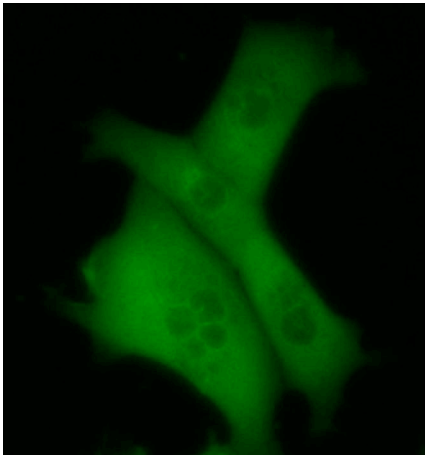
Why did you choose the UK?

My grandparents once lived in the UK a long time ago. My grandfather studied shipbuilding there and my grandma studied English. So I was always quite curious to see what England was like.

I decided to come to London, and I jumped from yeast to *Xenopus*. I started working in Jim Smith's lab on morphogens. I thought that the question of how a single factor activates different genes according to its concentration was a fascinating problem.

You worked with Jim Smith for a long time, what was it like in his lab?

It was a bit too comfortable to leave! It



The morphogen, activin, which Saka studies, prompts a regulatory protein to enter the nucleus and activate target genes (right).

was excellent because I could study anything I wanted—and I always seem to want to do something a bit different from others.

I worked on the *Xenopus* morphogen, activin. We knew that a low concentration of activin induced the transcription factor Xbra, while a high concentration induced the transcription factor goosecoid. And we also knew that Xbra and goosecoid repress each other's expression. I started wondering how they decide which inhibits the other if they are both induced simultaneously—this is at the core of why the concentration-dependent effect works.

It's very hard to understand intuitively. So I translated the relationship between activin, goosecoid, and Xbra into a mathematical model.

And what did it tell you?

By analogy, it's like two boxers fighting in a ring. One is a young newcomer, and the other is an established champion. Meanwhile, the promoter of the match is standing outside of the ring, with a wad of prize money in his hand. The motivation of the boxers for the money is different. You need more money to motivate the champion. But, the young newcomer is hungry for money, whatever the amount may be.

At the end of the match, one of them

will always win. So, if the money is a bit low, then the champion is not so motivated, and the newcomer will win. If the prize money is huge, then both boxers are equally motivated, but the champion's greater experience means he will win.

Xbra is like the hungry newcomer and goosecoid is like the champion. At low doses of activin, Xbra wins the fight, but above a certain threshold of activin, goosecoid will shut down Xbra.

MIXING IT UP

So what are you working on now?

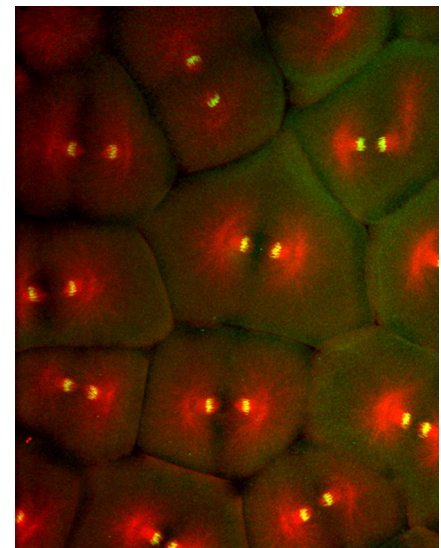
Well, the good thing about the mathematical model is that you can change certain parameters and make predictions about how the behavior of the system changes. However, it's very difficult to test these predictions in vivo. Getting subtle changes in protein levels by doing genetic mutations is often impossible. Another problem in vivo is that the particular system you are interested in is always part of a larger system, so you never know what kind of influence other cellular factors are having.

My plan is to create a completely new, pure model system in yeast. We are engineering synthetic transcription factors that have the same interrelationship as goosecoid and Xbra and that react in the same way to an extracellular mor-

phogen. We are, in effect, creating a very small-scale synthetic gene network. And because we're using yeast, we can manipulate parameters very easily. For example, we can change the binding site sequences for the transcription factors or the stability of these proteins.

We're still doing mathematical modeling, but on other systems in development. And we also still work with *Xenopus*. Being at this institute lets us attack the questions from all angles, and that was my reason for coming here. You can't be an expert in everything, but you can ask questions and collaborate. **JCB**

1. Saka, Y., et al. 2000. *Mech. Dev.* 93:27–39.
2. Saka, Y., et al. 2007. *Development*. 134:4209–4218.
3. Saka, Y., and J.C. Smith. 2007. *BMC Dev. Biol.* 7:47.
4. Saka, Y., and M. Yanagida. 1993. *Cell*. 74:383–393.



Saka studies tissue morphogenesis in the frog. In one of his studies, he followed the different patterns of cell division that arise in different tissues.