

PEOPLE & IDEAS

Tatsushi Igaki: Flying up the research summits

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Igaki explores how cell-cell communication directs tissue and tumor development.

Chasing some strange data he saw in high-performance liquid chromatography of lysates from cells treated with anti-cancer drugs was Tatsushi Igaki's first experience of scientific research as an undergraduate at Okayama University. Igaki describes this as the most exciting year he ever had and says, "Although the work did not get published, I learned one of the most pleasant aspects of science from it; you can go wherever you want just by following your heart." This lesson was cemented by working in industry investigating the mechanisms of neuronal cell death in neurodegenerative disorders. Although this was also an enjoyable time, Igaki became frustrated that he could not devote his time to interesting research questions of his own choosing and tired of the restrictions pharmaceutical companies have to place on publishing and presenting new findings. Thus, Igaki decided to enroll in the Graduate School of Medicine at Osaka University and joined the research group founded by Masayuki Miura, who had identified Caspase-1 and started to use *Drosophila* to understand cell death mechanisms *in vivo*.

Igaki was instantly fascinated by fly genetics as a clear and beautiful way to understand the epistasis of genes or signaling pathways in living animals. During his graduate studies with Miura, he identified the first and sole *Drosophila* orthologue of TNF, "Eiger," named after the impressive mountain he had recently visited. Eiger is now recognized as one of the key molecules that regulate tissue growth, homeostasis, and tumor development in *Drosophila*. "Ask living organisms if you want to know the mechanism," was valuable advice from Miura that Igaki decided to implement for the study of cell-cell communication. To understand how multicellular systems work in animals,

Igaki headed to Yale University for a postdoc with Tian Xu, who had established the FLP/FRT-mediated genetic mosaic technique in *Drosophila* that enables the study of cell-cell communication by "clonal analysis."

In Xu's laboratory, Igaki first worked on the mechanism of tumor growth and metastasis caused by the combination of Ras activation and defective cell polarity. But he came across an interesting phenomenon: clones of oncogenic polarity-deficient cells were actively eliminated from epithelial tissue when surrounded by wild-type cells. Importantly, the polarity-deficient cells could overproliferate and develop into tumors when not surrounded by wild-type cells. These observations suggested the possibility that normal epithelial tissue has an intrinsic tumor suppression mechanism that eliminates potentially oncogenic polarity-deficient cells via cell-cell communication, which is now recognized as "tumor-suppressive cell competition." Intrigued by this phenomenon, Igaki started investigating the underlying mechanism and to his great surprise found that the elimination of oncogenic polarity-deficient cells was mediated by Eiger (1). In 2007, Igaki decided to move back to Japan and set up his own laboratory at Kobe University to continue exploring the process of cell-cell communication and competition.

We contacted Igaki to find out more about his journey.

"Humanity is the most important thing to lead a team."

Where did you grow up?

I was born and grew up in Okayama, in the countryside of Japan. During my childhood, I was always fascinated by nature and went fishing every day right after coming home



Tatsushi Igaki in the fly room of my laboratory. IMAGE COURTESY OF TATSUSHI IGAKI.

from primary school. I worked hard in the evening to make ink rubbings of the fishes I caught; no time was left for homework! I loved catching insects, watching stars, exploring new mountain trails, and spent a lot of time searching for fossils but never found one. When I was around 10 yr old, I transformed a storehouse in the garden of our house into an "experimental room," where I analyzed insects and frogs using miniature bulbs with my friend. However, I went to school in the countryside, so I did not have the chance to learn specialized biology formally until I entered the Okayama University faculty of pharmaceutical sciences in 1989. I was very impressed by biology as an undergraduate and especially fascinated by the beauty of molecular biology. It was the first time I bought extra textbooks for fun and chose those with the most pages because I wanted to learn as much as possible. I realized that thinking about biological science was more fun than anything, and this was the time I became determined to study biology for the rest of my life.

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Members of the Igaki laboratory. IMAGE COURTESY OF TATSUHI IGAKI.

What interested you about your current area of study?

I first became interested in studying cell-cell communication when I identified the *Drosophila* TNF homologue Eiger as a graduate student. When I found the phenomenon of tumor-suppressive cell competition during my postdoc work, I thought, “this is going to be my life’s work,” because the phenomenon could not be explained by any concept so far identified. It was also very fascinating that cell competition could be considered as a cellular “struggle to survive,” the fundamental and universal mechanism that has driven biological evolution.

What are you currently working on?

My laboratory is focusing on understanding the basic principles of cell-cell competition and cooperation that regulate tissue homeostasis, growth, aging, and cancer. We found that oncogenic polarity-deficient cells are physically pushed out from the epithelial layer via a JNK-mediated Slit-Robo2-Ena/VASP pathway that down-regulates the cell-cell adhesion protein E-cadherin, while the surrounding wild-type cells promote elimination of neighboring polarity-deficient cells by activating JNK-dependent engulfment (2, 3). Furthermore, we identified the cell surface ligand-receptor pair, Sas-PTP10D, as a key driver of tumor-suppressive cell competition. When oncogenic polarity-deficient cells emerge in the epithelium, the surrounding normal cells relocalize Sas from the apical to lateral cell surface, while the polarity-deficient cells relocalize the tyrosine phosphatase PTP10D from the apical to lateral cell surface. This leads to trans-activation of Sas-PTP10D signaling in polarity-deficient cells, which causes suppression of EGFR signaling and thereby promotes JNK-dependent elimination of

polarity-deficient cells (4). Importantly, without the surrounding wild-type cells, or Sas-PTP10D signaling, polarity-deficient cells activate both EGFR and JNK signaling pathways that cooperate to cause tumorous overgrowth. Thus, Sas-PTP10D seems to act as a fail-safe mechanism to protect epithelial tissue against neoplastic development. Interestingly, the mammalian homologue of PTP10D, PTPRJ, has been shown to act as a tumor suppressor, suggesting that similar tumor-suppressive cell competition may also prevent human cancers.

We have also been studying the epithelial cell-cell cooperation that drives tumor progression and found that simultaneous Ras activation and mitochondrial dysfunction, frequent alterations in human cancers, trigger the nonautonomous tumor progression of surrounding tissue by up-regulating secreted growth factors (5). Furthermore, we found that Ras-activated cells with mitochondrial dysfunction undergo cellular senescence, indicating that such mutant cells can promote tumor progression of neighboring cells via the senescence-associated secretory phenotype (6). My laboratory moved from Kobe to Kyoto University in 2013 and has continued to work on cell-cell competition and cooperation in a variety of biological contexts. We are now trying to understand the physiological role of tumor-suppressive cell competition and tackling the many different types of cell-cell competition and cooperation that regulate tissue growth, homeostasis, aging, and cancer.

“Cell competition could be considered as a cellular “struggle to survive,” the fundamental and universal mechanism that has driven biological evolution.”

What kind of approach do you bring to your work?

We always take advantage of the power of fly genetics. The most important approach for us is the unbiased genetic screen, which often brings totally unexpected or unpredictable clues that lead into entirely new worlds of exploration. Thus, we are always running more than 10 genetic screens in the laboratory. At the same time, we sometimes reach the unexpected genes or signaling

pathways when we think much more deeply and making time for this is another important approach to achieve great science.

What did you learn during your training that prepared you for being a group leader?

I learned by working with Miura that humanity is the most important thing to lead a team.

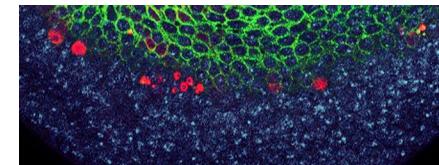
What do you enjoy doing in your spare time?

I love climbing mountains, watching movies, and running full marathons. I run along the beautiful Kamogawa River every morning, which feels great and keeps me motivated in my work every day. I also love taking vacations and my top priority at the beginning of the year is to schedule summer holidays with my wife and defend these desperately no matter what happens.

Any tips for a successful research career?

In science, I feel happiest when I can share and deeply interact with respectful colleagues in the research community throughout the world. So, I want my students to value the human connections they make with other researchers, as this is one of the most important things that enrich and thus make your life successful in science. I also want my students not to underestimate their abilities. I think I have always been happy in science because I believed I can go anywhere just by following my heart.

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3. Vaughan, J., and T. Igaki. 2016. *Dev. Cell.* 39:683–695.
4. Yamamoto, M., et al. 2017. *Nature.* 542:246–250.
5. Ohsawa, S., et al. 2012. *Nature.* 490:547–551.
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Cell competition between ribosomal protein knockdown cells (green) and wild-type cells (blue) induced cell death (red) at the boundaries between these two clones in the *Drosophila* wing disc. IMAGE COURTESY OF NANAMI AKAI.