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PEOPLE & IDEAS

Kota Saito: Getting out and about

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Saito studies the mechanisms that control secretion of collagen from the ER.

Having minor heart surgery when he was two years old led Kota Saito's parents and grandmother to discourage him from any form of strenuous physical activity. A tall order for a youngster growing up in a suburb of Tokyo close to the countryside and ocean, so he frequently escaped to play outdoors with friends. But the time spent indoors was put to good use as Saito enjoyed taking apart electronic goods so he could "repair" them. Saito's drive to understand how electronic devices work transformed into curiosity about the cellular machineries that control their basic functions. After working as a researcher in the US and Spain, Saito returned to Japan to start his own research group investigating how the TANGO1 proteins facilitate the export of large cargo, in particular collagen, from the ER.

We contacted Saito to find out more about his scientific journey.

What was your first experience of science?

My father was an engineer in a steel company and he would often talk to me about nature, space, and physics. Most of what he said made little sense to me, but his talks left me yearning to learn more about us and the world we live in. In high school, I joined a chemistry club. We inspected our school's pool water every month using redox titration. I had no idea what I was doing, but it seemed fun. I made up my mind to join the chemistry department at university. At the University of Tokyo, students have two years of lectures and classes before they chose a department for their degree. While I was taking classes, I realized that I was not good at organic chemistry. During this period, I also learned about some of the basic concepts in biology and I still remember being fascinated to find out that triplet codons are universal across all species including bacteria and human! That was my first encounter with modern biology. Instead of choosing pure chemistry, I decided to join the pharmaceutical department that taught both chemistry and biology.

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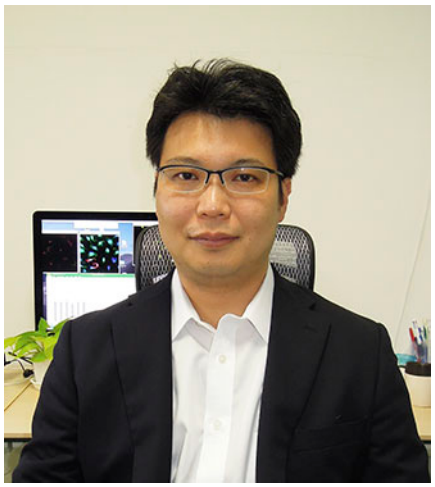
Where and with whom have you studied?

After my undergraduate degree, I joined the laboratory of Toshiaki Katada at the University of Tokyo. Dr. Katada identified the trimeric GTP binding protein Gi as a postdoc in Alfred Gilman's laboratory. He is a first-class biochemist and I worked on the biochemical analysis of small GTPases involved in membrane trafficking. An associate professor of the laboratory, Hiroshi Nishina, sent me to perform genetic screening in medaka fish in Dr. Kondoh's laboratory in Kyoto for a few months. The methodology was quite different from what I had done up until then, but I realized that one needs to master a broad range of expertise to address any specific issue in biology.

I was awarded a fellowship to study outside Japan for two years and joined, as a postdoc, Vivek Malhotra's laboratory at the University of California, San Diego (UCSD). Since I had worked on membrane trafficking, I really wanted to go to the laboratory of an expert in cell biology. At that time, one of the postdocs, Fred Bard, was just in the middle of screening *Drosophila* for new transport components, and this led to the identification of TANGO genes (1). I was one of four postdocs who helped Fred in the molecular analysis of how TANGO genes control protein secretion. Vivek is super friendly, creative, scholarly, fearless, but tough. His laboratory was international and I really enjoyed the challenging atmosphere. I learned that science is not just about pipetting; communication and discussion with colleagues is equally important to maintain a balanced perspective on science and achieving one's goals. After two and a half years at UCSD, Vivek one day announced that he needed a new challenge and decided to move to Barcelona. I was in the middle of the project on TANGO1, and I followed him to Europe. It was a great experience and I enjoyed the change in culture and lifestyle. I feel lucky to have experienced life as a scientist in the US, Europe, and Japan.



Kota Saito. Image courtesy of Kota Saito.

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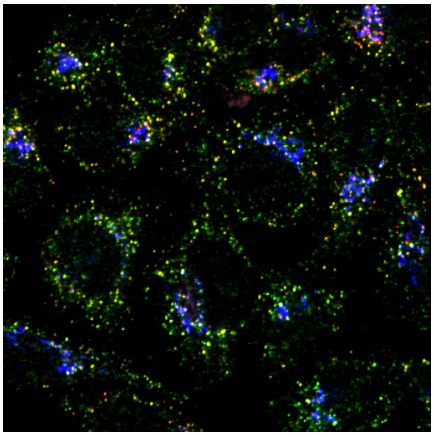

TANGO1 (green) colocalizes with Sec12 (red) at ER exit sites. GM130 stains the Golgi (blue).

During my stay at the Center for Genomic Regulation in Barcelona, we reported the requirement for TANGO1 in collagen export from the ER and basically made the process of collagen secretion amenable to molecular analysis (2). Collagens make up 25% of our dry body weight, which makes them the most abundant secretory cargoes. But they are too bulky to be exported by the standard COPII containers. The identification of TANGO1 as an ER localized protein that interacts with collagen and COPII proteins to facilitate collagen secretion was therefore an important discovery. I am fortunate that Dr. Katada recruited me as an assistant professor at the University of Tokyo and let me continue working on TANGO1.

What are you currently working on and what is up next for you?

After returning to Japan, I discovered that cTAGE5, a homologue of TANGO1 lacking the collagen recognition domain, acts as a coreceptor of TANGO1. Interestingly, cTAGE5 recruits Sec12, an activator of the Sar1 GTPase, to ER exit sites. I found that this localized concentration of Sec12 mediated by cTAGE5 is required for collagen export from the ER by activating the Sar1 GTPase (3). These results suggest that collagen secretion requires higher amounts of activated Sar1 and that the Sar1 GTPase cycle is important for bulky cargo secretion (4).

I recently found that the *TANGO1* gene produces two alternatively spliced isoforms, TANGO1L (original TANGO1) and TANGO1S. TANGO1L assembles into a 900-kD complex together with homomultimeric cTAGE5 and Sec12. TANGO1S, on the other hand, forms a 700-kD complex with cTAGE5 and Sec12. TANGO1L and TANGO1S function in organizing ER exit sites by interacting with Sec16 (5). So, TANGO1 is not just a cargo receptor for collagens, it also organizes the ER exit sites. I am particularly interested in how TANGO1 functions in organizing ER exit sites and how these departure gates are regulated based on the size and quantities of cargo exported. Membrane trafficking is becoming more interesting and challenging with the possibilities of unearthing new ways to transfer cargo between compartments. Overall, Vivek and I are working on different aspects of TANGO1 structure and function. I really appreciate his generosity in letting me continue working on the project after leaving his laboratory.

"Whatever the cost, the goal should always be to solve a problem and to enjoy the journey."

What kind of approach do you bring to your work?

I am willing to use any methodology to help us understand how TANGO1 and its partners function at the ER, but we rely heavily on biochemistry and imaging. We are coming up with new hypotheses about how cells control the export of bulky cargoes and there is no shortage of surprises.

What is the best advice you have been given?

From Vivek: "Think big; follow the data and not the dogma; and one paper, one message." From Dr. Katada: "Any theme is fine, so long as you think scientifically, you will continue to grow as a scientist."

Any tips for a successful research career?

I have recently been recruited as a professor at Akita university. This is exciting and I feel humbled to have come this far. I am not ready to start advising my younger colleagues, but if I am permitted to say something, it would be, "Don't forget the reason you came into science. It is all about solving a problem." It is all about ambition, patience, perseverance, and dedication. My own career path started with a fascination with chemistry and from there to the knowledge that the genetic code is the same across species. But I never knew anything about how cells are assembled into skin and bones. The discovery of TANGO1 has given me a new path to follow and this will likely change again as we learn more about collagens and their export routes. So, be prepared for surprises and don't be afraid of taking on new challenges. In my routine work, I do get frustrated with reviewers and the funding situation, but it is all a learning experience. Whatever the cost, the goal should always be to solve a problem and to enjoy the journey.

1. Bard, F., et al. 2006. *Nature.* https://doi.org/10.1038/nature04377
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3. Saito, K., et al. 2014. *J. Cell Biol.* https://doi.org/10.1083/jcb.201312062
4. Saito, K., et al. 2017. *Front. Cell Dev. Biol.* https://doi.org/10.3389/fcell.2017.00075
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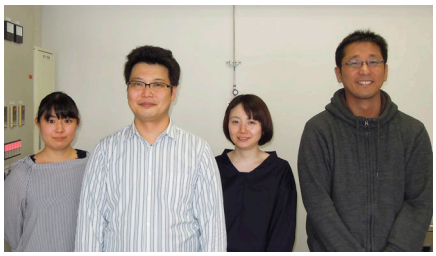

The Saito laboratory at Akita University. From left to right: Miharu Maeda, Kota Saito, Yukie Komatsu, and Takashi Baba. Image courtesy of Kota Saito.