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PEOPLE & IDEAS

Yukiko Gotoh: I am fascinated by the beauty of science

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Yukiko Gotoh is a professor in the Department of Pharmaceutical Sciences at the University of Tokyo. Her lab studies the mechanisms that underlie the regulation of neural stem/progenitor cell fate during brain development and homeostasis. They are particularly interested in the underlying genetic and epigenetic mechanisms that control cell fate and neuronal maturation, as well as the relevance of neural stem/progenitor cell dysregulation in neurodevelopmental disorders. We recently spoke to Yukiko about her current work, the joys of teamwork, and her passion for helping other scientists in Japan.

Please tell us a little about yourself and how you first became interested in science.

I was born and raised in Tokyo, Japan. I first became interested in science in junior high school physics class, where I was fascinated by the "beauty" of science. With just a few simple rules (according to Newton), many phenomena in the world can be explained!

Tell us about your career trajectory, and what led you to becoming a group leader.

As a graduate student, postdoctoral fellow, and assistant professor, I participated in the identification of MAP kinase (also known as ERK) and MAP kinase kinase (also known as MEK) in vertebrates. This so-called MAP kinase pathway turned out to be a major intracellular signaling pathway that regulates cell fate in various settings, including cell proliferation and differentiation, and its dysregulation causes diseases such as cancer. The excitement of such a major discovery convinced me that science is a wonderful path that should be pursued.

How did you first become interested in the study of neural cell development?

Through investigation of the MAP kinase pathway, which is context-dependently involved in determining cell fate in various (very different) directions, I became interested in the logic of how cells can correctly and accurately determine their fate during tissue development. I chose brain development and neural stem/progenitor cell fate determination as a model system because I found the brain to be super interesting—the brain is a complex, yet finely organized tissue, highly evolved in humans. So, before starting my own lab at the University of Tokyo, I spent a few years and did my postdoctoral research at two places in the US—first in Jonathan A. Cooper's lab at the Fred Hutchinson Cancer Research Center in Seattle, and then in Michael E. Greenberg's lab at Harvard Medical School in Boston—to extend my studies of cell signaling to brain development and function.

What are you currently working on, and what projects are you most excited about?

I am currently working on mechanisms of cell fate decision, especially focusing on epigenetics and posttranslational modifications. I am most excited about two topics at the moment. The first is related to our previous discovery of the embryonic origin of adult neural stem cells in the subventricular zone (SVZ), which is set aside during development (Furutachi et al., 2015). Our results suggest that the lineage of adult SVZ neural stem cells is distinct from that of embryonic neural stem cells for brain development. We recently identified local and systemic signals that mediate the establishment of this adult SVZ neural stem cell lineage, which is very exciting to me. Second, we previously demonstrated that epigenetic regulation by polycomb group proteins is the key to time-dependent switching of neural stem cell fates during neocortical development. Now, in collaboration with computational scientist Yoshito Hirata, we are establishing a new method to reconstruct the three-dimensional structure of the genome. I hope that this method is applicable to the identification of subnuclear compartments such as polycomb bodies,

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which will help us understand the spatial control of epigenetic machineries and context-dependent regulation of polycomb bodies.

Please tell us about some work in your field that you are currently interested in.

I am interested in "spatial" multi-omics of single cells, including multiplex genome-wide sequential fluorescence in situ hybridization (seqFISH) by Long Cai's lab, multiplex genome architecture mapping by Ana Pombo's lab, in situ genome sequencing by the Boyden/Buenrostro/Chen lab, and multiplex chromatin integration labeling sequencing (ChIL-seq) by Yoshiyuki Okawa's lab. Especially given that many chromatin factors function as condensates (nuclear bodies) by phase separation, this type of method would provide spatial epigenetic information and allow us to understand genomic information more deeply. Furthermore, artificial intelligence–based analysis of such single-cell multi-omics information as a function of space and time during development in the context of the whole organism will reveal new aspects of genomic information and new rules for cell fate determination.

What are some of the qualities that you learned during your graduate studies or postdoc that you maintain and foster in your own lab?

When I get results that do not support my hypothesis, I try to take it as fun (if possible) or an opportunity, not a failure. This is an attitude I learned from my enormous number of failures during my graduate school years. Also, having mentored many students before becoming a principal investigator, I have bitterly learned that everyone is different. I try not to impose my values and ideas on others as much as possible. The advice they need is different for each person.

Do you feel optimistic about the future for women in science?

Honestly saying, I am not very optimistic about the next decade, at least in Japan. I have been deeply involved in diversity, equity, and inclusion (DEI) activities in many places, including the University of Tokyo, and have been repeatedly disappointed and frustrated. For example, our university has worked hard to increase the number of female students and faculty, but the pace of change has been too small. For the past 10 years, the percentage of female students has remained around 20%. One obvious reason for this is the prevailing belief in Japan (especially in rural areas) that women do not need higher education and should support their families at home. At the faculty level in the University of Tokyo, women comprise only 6.5% of full professors in the departments of medicine, engineering, science, agriculture, and pharmaceutical sciences. Strong positive action is needed to change this dire situation. However, as women scientists advance in their careers, I am optimistic about their future!

What is the piece of advice that you find yourself giving out most frequently?

I'm not sure, but perhaps it goes something like this...:

- Doubt dogma.
- Enjoy science, enjoy life.
- When you encounter something unfavorable, try to see it as a pleasure (if possible) or an opportunity, not an obstacle.

What do you most enjoy about your work/role as a group leader? What brings you joy in your role?

The excitement and joy of discovery is so much greater when you work with a team than when you work alone, especially after you have worked hard as a team through a difficult time.

Are there any aspects of lab work that you miss?

I like the feeling of control over the experimental procedures by paying attention to details, improving methods, and getting the positive and negative controls right. Without knowing the details, it is difficult to control the experiment to the level I really want.

While not in the lab, how do you like to spend your time, or alternatively, how would you like to spend your time?

I would like to spend as much time as possible with my family (including my dog) and friends. I would also like to contribute to society in some way or another. Until I retire, I will probably continue to try to solve problems that Japanese researchers face (DEI problems, research funding problems, research assessment problems, etc.) and to encourage young researchers.

Reference

Furutachi, S., et al. 2015. *Nat. Neurosci.* https://doi.org/10.1038/nn.3989