

PEOPLE & IDEAS

Yan Song: How time flies

 Marie Anne O'Donnell 

Song investigates the mechanisms that control stem cell fate in development and disease.

Drosophila melanogaster are the winged insects Yan Song currently studies in her research but she grew up chasing dragonflies, catching grasshoppers, rearing silkworms, and netting butterflies in a small town in East China. Her mother was an accountant and her father an innovative ophthalmologist who designed new devices to help him perform delicate eye surgery. Song says he profoundly influenced her to appreciate both the fun and value of creativity and exploring original ideas, values she brings to her ongoing efforts to understand the temporal-spatial regulation of stem cell fate.

We contacted Song to learn more about her research journey.

What was your first experience of science?

My grandpa was an avid gardener. As a little kid, I often went together with my grandpa to his garden to take care of his plants. I couldn't help but wonder why four o'clock flowers always bloom in the early evening while jasmines always bloom later at night. How could these flowers know when it is the correct time?

My curiosity and love for nature brought me to a top college in China—Peking University—to study cell biology. My first real experience of science was in my junior year when I joined Dr. Jianguo Chen's laboratory. Through microscopes, I found a brand-new world, which is as beautiful and mysterious as my grandpa's garden.

Where and with whom have you studied?

After graduation, my then boyfriend (my college classmate and now husband) and I went to Duke University for our graduate studies. My first laboratory rotation at Duke was with Haifan Lin, who studied germline

stem cell asymmetric division in *Drosophila*. I was immediately intrigued by the fascinating stem cell biology. Although I eventually joined Robin Wharton's laboratory for my PhD studies, I decided to return back to the stem cell world for my postdoctoral training. My husband and I drove all the way from the east coast to sunny California and started our postdoctoral work at Stanford University, where I joined Bingwei Lu's group to study neural stem cell (NSC; so-called neuroblast) asymmetric division in the *Drosophila* larval brain. This turned out to be a great project for me, and I have been working on fly neural stem cells ever since. Bingwei is a wonderful advisor, who gave me a rigorous scientific training, exposure to biochemical approaches, and, at the same time, a lot of freedom to explore my own research interests. After our postdoctoral training, my husband and I decided to return to Beijing and start our own independent groups at Peking University.

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What about stem cell biology most appealed to you?

The long-term goal of my group is to understand how precise and robust decisions of cell fate or cell identity are made in a stem cell lineage and how mistakes in these decision-making events lead to developmental defects or diseases. Although much is known about the molecular mechanisms underlying spatial control of cell fate specification, how the fourth dimension, time, governs cell fate specification remains enigmatic. Therefore, I have been very interested in deciphering the mysteries of the



Yan Song.

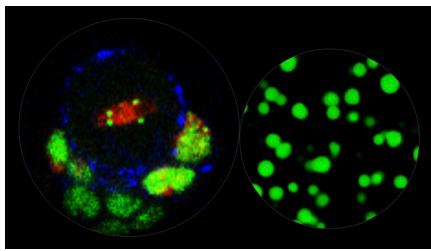
temporal control of cell fate determination: (a) how timely cell fate commitment is achieved (1, 2, 3, 4); (b) how temporal signals are decoded and translated into cell fate decisions; and (c) how temporal and spatial cues are integrated to dictate cell fate or identity (5). In comparison to the spatial control of cell fate specification that has often been studied under static conditions and examined in single time points, understanding temporal control of cell fate determination requires dynamic analysis in a kinetic manner, necessitating technically challenging time-lapse live imaging of stem cell lineages.

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

It is well known that, during mitosis, the gene regulatory machinery, including transcription factors and chromatin remodelers, is largely dislodged by the highly condensed chromosomes. However, recently, we serendipitously discovered that an evolutionarily

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Retention of transcription factor Prospero (green foci) at mitotic chromosomes (red) of fly neural stem cells (blue cortex; left) via liquid-liquid phase separation (right). Image credit: Jingwen Shen and Yan Song.

conserved transcription factor named Prospero (Pros) can be retained on the mitotic chromosomes of fly neural precursors via liquid-liquid phase separation (LLPS) to drive terminal neuronal differentiation (see image; 3). Terminal differentiation is the process by which progenitors or precursor cells exit the cell cycle and differentiate into post-mitotic functional cells. How progenitors/precursors “forget” their self-renewing cell fate and rapidly establish their new terminally differentiated cell fates are largely unknown. Through time-lapse live imaging and molecular genetic, biophysical, and biochemical approaches, we were very surprised to find that, during mitotic exit of neural precursors, mitotically retained Pros recruits and concentrates heterochromatin protein 1 (HPI) into phase-separated condensates and drives heterochromatin compaction. This establishes a transcriptionally repressive chromatin environment that guarantees cell cycle exit and terminal neuronal differentiation. The liquid demixing property not only allows Pros to form phase-separated droplets and manage to hold on to the highly condensed chromosomes but also facilitates Pros to recruit and concentrate HPI protein, driving

heterochromatin condensation. Together, our findings led us to propose an exciting and unexpected model whereby LLPS of a transcription factor ensures its retention at pericentromeric regions of mitotic chromosomes, which in turn drives timely neuronal fate lock-in by promoting heterochromatin condensation. Significantly, these results established a causal relationship between LLPS of a transcription factor and a cascade of biological events in animal development under physiological conditions, highlighting the functional significance of LLPS in vivo. In addition, these totally unexpected findings unveiled the tip of a new iceberg in the transcriptional control of chromatin architecture and guided my group to a new research frontier.

“Time-lapse live imaging of fly larval brain neural stem cells promises to reveal the fundamental principles underlying temporal control of cell fate specification.”

What kind of approach do you bring to your work?

We mainly use time-lapse live imaging of fly larval brain NSCs. Fly NSC lineages are similar to their mammalian counterparts in both functional and molecular criteria, yet with much simpler anatomy and lineage composition. More importantly, these NSCs reside at the surface layer of the semi-transparent larval brains, making them particularly suitable for time-lapse live imaging of NSC lineages in intact brains. Furthermore, these NSCs undergo rapid cell divisions, dividing every 1-2 h. Therefore, time-lapse live imaging of fly larval brain NSCs promises to reveal the fundamental principles underlying temporal control of cell fate specification in stem cell lineages.

What is the best advice you have been given?

Don’t do fashionable science by Max Delbrück, my scientific great grandfather. It is so much more fun making the “fashion” instead of following it.

What do you enjoy doing outside of the laboratory?

I enjoy gardening, just like my grandpa. I grow many plants in my office and at home. The budding sprouts, unfolding leaves, blooming flowers, and their delicate colors, shapes, and patterns always bring me joy and excitement. If I stopped doing science one day, I would probably open up my own floral shop. I also enjoy dancing (Chinese classical dance and folk dance) and Chinese martial arts. To me, body movements are an alternative, or even a better way than words, to express emotions and touch people.

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The Song laboratory in an old Beijing-style restaurant in spring 2018.