People & Ideas

Sean Morrison: A root and branch approach to stem cells

Morrison compares different stem cells to understand the mechanisms that regulate regeneration, cancer, and aging.

Throughout life, stem cells maintain themselves by dividing to produce one or two daughter stem cells with an identical developmental potential. Although this self-renewal process is fundamental to all types of stem cells, the precise mechanism varies between different tissues and stages of development. Sean Morrison examines the self-renewal of different types of stem cells to understand how the process declines with age and how it is hijacked by cancer cells to drive tumorigenesis.

After a brief stint running a biotech company in his native Canada, Morrison's interest in stem cells began as a graduate student with Irv Weissman at Stanford University, where he developed new techniques to purify and characterize hematopoietic stem cells (1). He then adapted these techniques to the nervous system and neural crest stem cells as a postdoc with David Anderson at Caltech (2). In his own lab at the University of Michigan, Morrison goes back and forth between the blood and nervous systems, identifying new regulators of stem cell self-renewal and studying how their actions change during development and aging (3, 4). Morrison's lab also investigates the self-renewal of cancer stem cells that are proposed to drive tumor growth (5), while demonstrating that not all cancers follow this model of tumorigenesis (6). Morrison has challenged other commonly held assumptions too, such as the immortal strand hypothesis that daughter stem cells always inherit older copies of chromosomes (7).

In a recent interview, Morrison discussed what his work has taught him about cancer and aging, and the importance of explaining stem cell research to the general public.

FROM THE ROOTS UP

Where did you grow up and what were your earliest experiences of science?

I'm from Nova Scotia in Canada. I did a lot of sports and a lot of science fair projects growing up. My senior year high school project won national awards. It was on fungi called Mycorrhizae that colonize plant roots and enhance their ability to take up nutrients from the soil. The fungus is used agriculturally, but it was very expensive and difficult to grow. My lab partner and I thought we could grow the fungus more effectively using hydroponics and we ended up starting a company. The university where I did my undergraduate work, Dalhousie, gave us lab space, and we'd work on it full-time over the summer and part-time during the academic year.

I'd run back and forth between the lab and classes, and pretty soon I wasn't going to class anymore. I quit school after my sophomore year and ran the company full-time for a few years. We had a successful field trial but the stock market crashed, and all the money for biotech dried up, just as I was trying to arrange another round of financing. I shut the company down, finished my undergraduate work, and then went on to Stanford. So I went to graduate school because I failed in biotech!

When did your interest in stem cells begin?

After my experience in agricultural biotech, I wanted to do medical research because everything seemed better funded and more competitive. When I joined Irv Weissman's lab, it became clear that stem cell research was an exciting area that was going to be really big. I developed techniques to purify hematopoietic stem cells and distinguish them from other blood cell progenitors, which made it possible to characterize their properties more precisely.

Why did you switch to neural stem cells for your postdoc with David Anderson?

I wanted to do something different for my postdoc, while carrying over aspects of my graduate work. Neural stem cells had recently been discovered, but it was early days in terms of understanding their biology. Everything was based on retrospective analyses of cultured neural cells. If we saw multi-lineage colonies, we'd know that a stem cell had been there, but by that point, its properties had completely changed, so it was impossible to understand what these cells were actually doing in vivo. So I took the approaches I'd used in my PhD and adapted them to the nervous system—identifying markers for neural crest stem cells, purifying them by flow cytometry, and then studying the properties of uncultured cells that could be transplanted from animal to animal. That helped us understand their role in the peripheral nervous system.

Sean Morrison

DIFFERENT STEMS

Did you always plan to go back and forth between the blood and nervous systems in your own lab?

People were just starting to think that regulatory mechanisms might be conserved between stem cells in different tissues. My lab was one of the first to carefully compare different stem cells. Some mechanisms are extraordinarily conserved but there are others that differ between stem cells in different tissues. Identifying both types of mechanisms is really important to understanding the cells' biology.

You also compare stem cells across time—how does stem cell regulation change over an organism's lifespan?

It's only in the past five years or so that we've begun to understand that stem cell self-renewal mechanisms change throughout life: embryonic stem cells self-renew differently from fetal somatic stem cells, which, in turn, have different self-renewal

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mechanisms compared to adult stem cells in the same tissue.

The mechanisms continue to change as adult cells age. One reason the regenerative capacity of tissues declines as you get older is that self-renewal programs change. Stem cells in many tissues upregulate tumor suppressors to shut themselves down as they age.

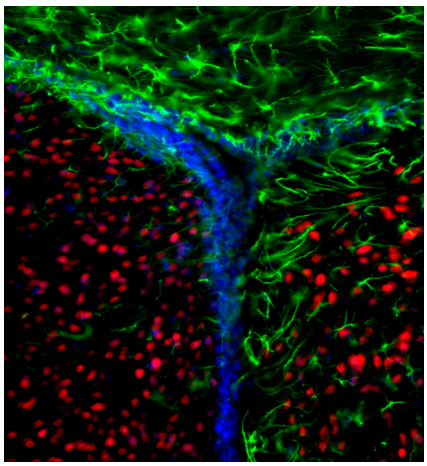
What are the links between stem cell self-renewal and cancer?

Cancer is a disease of dysregulated self-renewal where the cancer cells hijack normal stem cell self-renewal programs. When we identify new self-renewal mechanisms, they invariably turn out to be involved in cancer in some way, giving us new insight into cancer cell proliferation. I think the age-dependent changes in stem cell self-renewal programs explain the different spectrums of mutations you see in childhood versus adult cancers. The cancer cells have to hijack a different self-renewal program during childhood compared to during adulthood, so they need different mutations to do it.

Whether tumors are then driven by cancer stem cells is controversial. Where do you stand on the subject?

We come down in the middle of this debate, which is an uncomfortable place to be because everyone disagrees with you! We think that some cancers really do follow the cancer stem cell model in which a small sub-population of tumorigenic cells proliferate extensively and give rise to non-tumorigenic cells that form the bulk of the cancer and have a limited capacity to divide. But there are lots of other cancers where we think tumorigenic capacity is a common attribute of the cells. Single melanoma cells routinely form tumors when we inject them into mice, and we've not been able to find any markers that distinguish tumorigenic from non-tumorigenic cells. So we have to figure out which cancers follow the model and which don't. In some cancers, such as brain tumors, it might even differ from patient to patient.

It's critical from a therapeutic point of view because if it's only a rare sub-population of cancer cells driving tumor growth—if it's a needle in a haystack—then you've got to find those needles and target them directly. But if every cell is bad, there's no point trying to target rare cells because that won't cure the disease.



Neural stem cells reside in the subventricular zone, stained here for neurons (red), glia (green), and DNA (blue).

It seems you like testing key assumptions like the cancer stem cell model …

Science involves figuring out the truth. Sometimes that means discovering new mechanisms that nobody's ever thought of before. But sometimes it means testing existing mechanisms that haven't been adequately tested.

In the stem cell and cancer fields, there are lots of ideas that are intuitively attractive to people—and are therefore widely discussed as if they're true—but which are based on very little direct evidence. Those ideas really affect the way fields develop because they're the prism through which people view their own data. So we try to test them. Sometimes we find that they're correct, like when we tested the cancer stem cell model for acute myeloid leukemias, but sometimes we find those ideas aren't consistent with the data—the ideas might be completely wrong or just oversimplified.

"I went to graduate school because I failed in biotech!"

BRANCHING OUT

What is your lab working on now?

We're doing a lot of experiments related to cancer. Although we can't find markers that distinguish tumorigenic from non-tumorigenic melanoma cells, we still see lots of markers that differ between cells from the same patient. Where does this heterogeneity come from? We're trying to understand that, and I think it will provide new insights into cancer biology.

You're also involved in public policy. Why is that important to you?

If we don't explain why research is important and what it means, we will get bad laws for bad reasons. You'd be surprised at how few congresspersons really understand the issues they vote on. We have a responsibility to explain these things to the public so that we have appropriate and effective legislation.

When I became the director of the University of Michigan Center for Stem Cell Biology, I asked the University to support efforts to change state laws that restricted embryonic stem cell research. We weren't able to do it through the legislature, so we went directly to the people of Michigan with a ballot initiative and eventually prevailed. I spent an enormous amount of time during that election talking about stem cells, and it was an educational experience to see how the sausage gets made.

What would you be if you weren't in academia?

I definitely wouldn't be a politician. I don't like any field where people just make up facts to support their positions. I was shocked at the extent to which that happened in the campaign to protect stem cell research in the Michigan state constitution: opponents were unrestrained in inventing things that they thought could frighten the public into not supporting stem cell research.

If I weren't in academia, I think I would be in biotech. I really enjoyed starting my company as an undergraduate. Since I joined the University of Michigan, I helped found one company and I consult for a few others—I enjoy it very much.

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