Tannishtha Reya: Classic pathways, new views on cancer

Reya studies how the balance between self-renewal and commitment is disrupted in cancer.

Hematopoietic stem cells give rise to the myriad specialized cell types of the adult immune system. The environmental and cell-specific cues that guide their differentiation toward distinct cell fates are so complex that there is an entire discipline, developmental immunology, devoted to their study. But proliferation, homeostatic maintenance, and early cell fate decisions of hematopoietic stem cells are regulated by proteins that are no doubt familiar to students of other developmental processes—proteins of the Wnt, Notch, and Hedgehog pathways, for example.

Just what do these pathways contribute to immune cell development, and how might their dysregulation result in diseases such as cancer? These are the types of questions Tannishtha Reya would like to answer. With a background in both developmental immunology (1) and stem cell biology (2), Reya is making big strides with these questions (3–5), as she explained when we reached her at her lab at the University of California, San Diego.

> "My lab is really interested in... how the undifferentiated state is maintained."

FIRST IMPRESSIONS

You're originally from India…

Yes. I spent part of my childhood near the foothills of the Himalayas, close to the city of Darjeeling. When I was 17, I moved to the United States to attend Williams College in Massachusetts. I was interested in going to college in the States because the academic system in India can be rigid, in that you have to commit early on to a specific field of study, whereas colleges and universities in the States are designed to allow you more freedom to discover what really excites you.

I had chosen to go to a liberal arts college specifically so that I could be exposed to both literature and the sciences. I hadn't yet decided what I really wanted to pursue long term. But then I spent the summer at Caltech with Pamela Bjorkman, who was just starting her lab at that point. I had never been in a lab before, and I was probably incredibly unhelpful to them, but she was really patient with me and spent a lot of time teaching me immunology and articulating the unanswered questions in the field. That experience made a really big impression on me, so at the end of the summer I went back to college really excited about biology.

Is that what made you decide to pursue a research career?

Back at Williams, I was able to continue doing research in Dan Lynch's lab. He was a terrific mentor who really encouraged me to pursue a career in the sciences. What excited me most was the feeling of making a new discovery. I decided to go to graduate school to study immunology at the University of Pennsylvania, and, while I was working there, I found that I had a real affinity for development. I was fascinated by the fact that the body develops all this complexity from one cell, and I really wanted to understand that. I decided to study developmental immunology in Simon Carding's lab, where I could address questions about development in the context of the immune system.

Your focus shifted somewhat during your postdoctoral studies…

As a postdoc at the University of California, San Francisco, I wanted to gain a better understanding of how molecular programs underlie developmental decisions. I went to Rudi Grosschedl's lab, where the transcription factor LEF-1 had been identified. For the longest time, people were studying LEF-1 in the context of immune cells, but, just about the time I joined, it was shown to be part of the Wnt signaling pathway. That really changed a lot of things about how the downstream transcriptional elements were viewed, and it also got me more directly interested in signals normally associated with embryonic development. I was working on how LEF-1 and Wnt affect fate decisions in the immune system, but about two years into my postdoc Rudi was recruited away to Germany and I had to find a new home. I moved from UCSF to Stanford, to Irv Weissman's lab.

PHOTO COURTESY OF REMY REYA

Tannishtha Reya

One important thing I learned from Irv was not to be afraid of taking on a big problem or of crossing boundaries into new, unfamiliar territory. In his lab, I learned to work on stem cells. I stepped further back in development and began to ask questions about how stem cell self-renewal is regulated and how it is balanced with fate specification. I found these questions fascinating because stem cell behavior in the immune system basically recapitulates a lot of early development and developmental pathways that are utilized in the organization and morphogenesis of other tissues.

A CAREFUL BALANCE

Your work since then has been a logical extension of that idea…

One of the things my lab is really interested in is how the undifferentiated state is maintained. In the hematopoietic system, stem cells give rise to an incredible variety of differentiated cells. How does a stem cell protect itself from becoming differentiated? This question has defined a lot of our work because it is a critical event in development and is hijacked in cancer.

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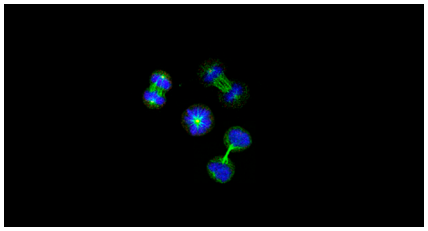

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Hematopoietic stem cells in different stages of division.

At the time we first started working on this, we were trying to piece together how different developmental cues might contribute to the maintenance of the stem cell state. Basically, we found that activation of the Notch pathway is really key for preserving the undifferentiated state. On the other hand, we showed that Wnt signaling promotes stem cell growth and proliferation. Both pathways contribute different elements to the puzzle.

One of the interesting things we've shown is that purified hematopoietic stem cells can divide through asymmetric divisions, wherein one daughter shuts off Notch activity and becomes more differentiated and the other daughter remains immature. Stem cells can also go through symmetric renewal divisions, in which both daughters remain immature, and symmetric commitment divisions, in which both daughters differentiate. We went on from there to show that the balance between asymmetric and symmetric division could be modified by the microenvironment and could be subverted by oncogenes. This was particularly exciting because it could possibly be a core event that underlies cancer progression.

Is this what led you to studying myeloid leukemias?

We originally chose this leukemia because it is a great model for cancer progression as it goes from chronic phase to blast crisis phase. In the chronic phase, the cancer cells are predominantly differentiated. But later, due to the accumulation of additional mutagenic hits, the cancer starts producing mainly undifferentiated cells and becomes very aggressive. The kind of step-wise progression from chronic to blast phase allows us to study how developmental pathways might be dysregulated to recreate a very immature state in the context of a pathological condition.

What are some examples of developmental pathways that are dysregulated in cancer?

We have worked on the Wnt and Hedgehog signaling pathways, using genetics to see if the self-renewal ability of the cancer is dependent on developmental cues. For example, we showed that when you block Hedgehog signaling or when you interfere with regulators of asymmetric division you fundamentally impair the self-renewal capacity of the cancer stem cells that propagate leukemia. Targeting some of these signals allowed us to effectively block the growth of drug-resistant cancers.

> "Oncogenes that are linked to very aggressive cancers shift the balance towards symmetric renewal."

UNRAVELING CANCER

How is asymmetric division involved in aggressive leukemia?

My lab has used imaging in the past to show that certain oncogenes, such as those that give rise to slow-growing differentiated tumors, can promote proliferation or survival but don't appear to alter the balance between asymmetric and symmetric division. But oncogenes that are linked to very aggressive cancers shift the balance towards symmetric renewal divisions. This was really exciting because it said that the unraveling of differentiation that happens as cancers advance might be fundamentally linked to an imbalance in symmetric and asymmetric division.

To test this idea, we looked at the inheritance of Numb, a Notch antagonist that directs committed cell fates. We found that while the cancer is differentiated it has high levels of Numb. Later, when it becomes undifferentiated, it has very low levels. But if you re-express Numb, even in this late phase, you can impair the cancer's growth. That led us to looking for upstream regulators of Numb and identifying Musashi as a new regulator of cancer progression.

What are you doing now at UCSD?

I started my career at Duke, and it was a superb environment for my work. I was recruited to San Diego about a year and a half ago. San Diego of course has great scientific depth and breadth, and it is also attractive because it is well positioned to move basic research forward towards therapy. There is a real need for greater effort in this area, and I hope I am able to contribute to this in a meaningful way.

In terms of basic research, we are currently working to identify other regulators of asymmetric division and trying to understand how they influence cancer progression, both in leukemias and in solid tumors. And finally, one of our long-term goals is to use live imaging to build a four-dimensional, spatial/temporal map of how stem cells grow in vivo and how some of their normal associations with the microenvironment may change during oncogenesis. This is a very challenging undertaking, but I hope it will reward us with a new understanding of how cancers grow within the body.

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Reya and her lab study the regulation of stem cells in development and disease.