People & Ideas

Laurie Boyer: Stem cell circuitry for commitment

Boyer studies the genetic programs governing lineage commitment in pluripotent stem cells.

PHOTO COURTESY OF KENT DAYTON

Laurie Boyer

Around the time of gastrulation, the stem cells of the early embryo surrender their pluripotency to begin assuming more specialized roles as stem cells for neuronal, skin, and other tissues. Several genetic pathways cooperate to regulate maintenance of the pluripotent state and to govern commitment to distinct differentiation states.

Electrified by this idea, Laurie Boyer has made it her mission to map out the circuitry of these pathways and to explore the mechanics of their operation. Her work has provided important insights into how stem cells manage the transition to more restricted fates (1, 2) and what alterations occur, particularly at the level of chromatin (3), to enable these changes (4, 5). She spoke to us from her laboratory at the Massachusetts Institute of Technology in Cambridge, Massachusetts, explaining these stem cell circuits and how they've run through her life.

EARLY DESIGN

As a child, what profession did you want to pursue?

I'm from a largely blue-collar town in western Massachusetts. When I was growing up, I always thought that my path would be to graduate from high school and then to find a career—what sort of career, I had no idea, although I was always excited by anything in science and biology in school. I wasn't exposed to the idea of a research career in school, though. Looking back, I realize how important it is to expose school-age children, particularly girls, to the career possibilities in science and to what scientists do.

As a child, I had a lot of energy. I had a lot of questions. Even by the age of 10 or 11, I was always out looking for a job to keep myself busy. I knew that I wanted to move forward, but I always felt that my energy was misplaced. I never really had a way of channeling my energy into a direction that I found fulfilling until I discovered research.

When did that happen?

Things started to change during my college years. I went to a small state school, Framingham State University, and studied biology as my major. Biology seemed like a fascinating puzzle to me, and I really enjoyed the lab classes. I assumed at the time that obtaining a biology degree would allow me to find an interesting job in the biotech industry, but the possibility of actually becoming a research scientist seemed daunting and perhaps not within my grasp. When I graduated from college, I took a position as a lab tech, first at Boston University School of Medicine and then at Genzyme. It was at that point that everything changed for me.

CHARGED UP

How so?

My supervisor at Genzyme, Barbara Handelin, was really my first mentor, and she told me, "You really should think about going into academic research."

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Barbara introduced me to David Housman at MIT, with whom she had worked in the past, and I started taking a class that he taught as part of the MIT-Harvard Health Sciences and Technology program. I loved everything about it! One day I got up the nerve to ask him what a career in basic research was like, and, before I knew it, he was driving me over to his lab. It was past 6:00 p.m., but the buzz and the energy there was incredible. It was like somebody flipped the lights on for me. It was one of the most defining moments of my life. So I started volunteering there, working with a postdoc who was trying to pinpoint a melanoma susceptibility locus. I was completely hooked and wanted more.

And you went on to graduate school?

Yes. In graduate school at the University of Massachusetts Medical School, I chose to work with Craig Peterson because he was so engaging and enthusiastic every time he gave a talk about his research. He had been one of the first researchers to identify and isolate a chromatin-remodeling enzyme that could move nucleosomes around to allow transcription factors to occupy DNA sites. I was already interested in how transcription factors regulate gene expression, and this seemed like a different way of thinking about gene regulation, so I found that very exciting.

But your postdoctoral work at MIT's Whitehead Institute was on a different topic…

By the time I joined Rudolf Jaenisch and Richard Young's labs at the Whitehead Institute for my postdoctoral work, I had become fascinated with trying to understand not only the mechanics of chromatin regulation but also how cells control large-scale gene expression programs—for example, during embryonic development. It was already known that there

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were three transcription factors in particular—Oct-4, Sox2, and Nanog—that are critical for establishing or maintaining the pluripotent state. But there was very little known about what the downstream genes controlled by these factors were or how they worked together to maintain pluripotency. I decided that we needed to know all of the binding sites at once in order to figure out the entire circuitry. We had to build our own technology in order to do this, and it was a huge amount of work, but it was worth it because the end result was that we defined the first core regulatory circuitry in stem cells.

After that, I became interested in Polycomb group (PcG) proteins, chromatin-modifying proteins that are important for setting up the developmental plan early in embryonic development. We thought, if we could understand where PcG proteins act in the genome, then we could understand a little bit more about how these factors can influence lineage commitment.

We showed that you can find PcG proteins sitting around the transcription start sites of a large cohort of genes that code for transcription factors with important roles in determining cell fate, including the Hox genes, which are master regulators of body patterning, lineage commitment, and cell specification. Interestingly, we found that, if you get rid of PcG proteins in stem cells, the stem cells don't actually care. They go on as normal—until you ask them to make fate commitment decisions. At that point, they fail to differentiate and cannot commit. This led us to conclude that PcG proteins allow stem cells to execute the proper differentiation programs when signaled to do so.

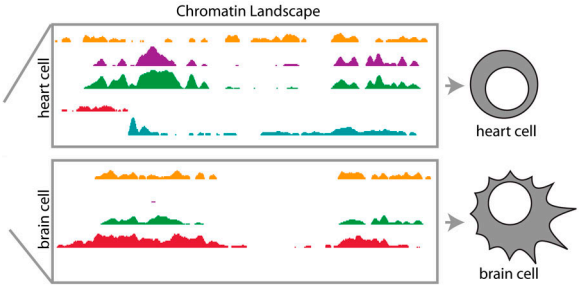

IMAGE COURTESY OF SERA THORNTON

Chromatin modification is important for regulating gene expression during cell fate determination.

COMPLETING THE CIRCUIT

You have continued to work on PcG proteins in your own lab…

Actually, when I started my own group at MIT, I wanted to take a broad approach to study gene regulatory mechanisms. I became interested in thinking more about histone variants. Most people envision that nucleosomes are made up of two copies each of four histones. But really, there are a whole set of histone variants that come in and replace canonical variants and that have different functions. I decided to work on the histone variant H2AZ, which is important for gene activation, because it had been shown that animals lacking H2AZ have a very early developmental phenotype, right around the time of gastrulation. I wondered if H2AZ might play some role in regulating gene expression programs during lineage commitment.

So, we started to look at H2AZ in stem cells and found that it is located not only at genes that are activated but also at PcG target genes. If H2AZ is absent, then stem cells show the same problem as in the absence of PcG: they can't execute lineage commitment programs. We're working right now at understanding how H2AZ and PcG might be connected mechanistically.

But this is just one corner of the broader questions people in my lab are working on: examining how histone modifications, histone variants, and transcription factors all fit together to define developmental programs such as lineage commitment. We've also started studying specific lineage commitment pathways. For example, we're working now to try to define the regulatory circuitry for cardiac commitment. We have recently published our work that describes the founding circuitry that's responsible for cardiomyocyte differentiation.

> "I wanted to take a broad approach to study gene regulatory mechanisms."

So you have a good plan to follow in lab. What about outside the lab?

I don't have a master plan. I follow my instincts and my passion in and out of the lab. I have two kids, and there have been times where I've thought very seriously about whether or not I could pursue a career in science at this level and still be a good parent to my kids. I remember having a discussion with my older son, who was maybe nine years old at the time, when I was transitioning to a faculty position. I had asked him if he'd prefer I stayed home instead. And he just looked at me very perplexed and said, "So, you wouldn't be a scientist anymore? Why would you want to do that? You're so good at it." And you know what? He was so right.

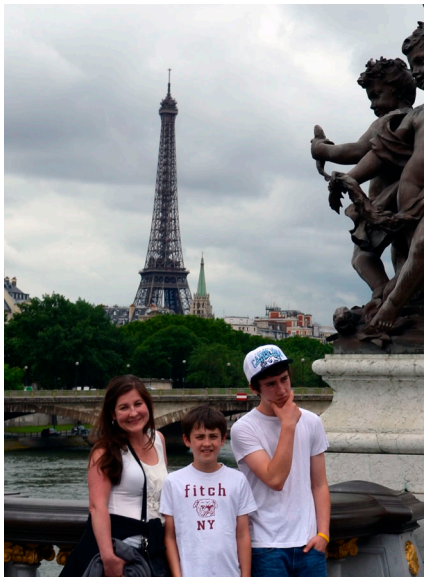

PHOTO COURTESY OF LAURIE BOYER

Boyer and sons make the most of a recent scientific meeting in Paris.

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