People & Ideas

Oliver Rando: Taking chromatin analysis to the genomic scale

Oliver Rando uses microarrays to uncover the chromatin rules of genome usage.

Chromatin is the final filter of many of the cell's signaling pathways, says Oliver Rando. How these signals ultimately unravel the complex structure of chromatin and access particular DNA files is a problem he'd like to solve. His approach is not to look at individual genes and ask how they are regulated, but rather to look at the entire genome, or at least very large chunks of it, using microarrays.

"I'm having a blast right now. I'd like to be having a blast doing science in 20 years, 50 years."

Rando is a pioneer of this genomic scale approach to chromatin analysis and has already published a large number of papers on the subject, despite being only at the beginning of his scientific career. His work includes genome-wide analyses of gene expression changes in yeast that arise from interfering with particular histone modifications—essentially decoding part of the histone code (1). His lab has also worked on high-resolution genomic mapping of aspects of chromatin structure such as histone modifications (2) and histone replacement dynamics (3). He has also mapped nucleosome positioning on a genomic scale (4), a study that was described as a "technical tour de force" (5).

With such a stellar start to his career, it's no surprise that the University of Massachusetts snapped him up. He joined the faculty as an assistant professor in the department of Biochemistry and Molecular Pharmacology just four months ago. Recently he took time out from setting up his new lab to talk about his genome-wide adventures in chromatin structure.

EARLY START

How did you get started in science?

My father's a scientist, so it's an "apple doesn't fall far from the tree" kind of situation. He's at Harvard Medical School as a chemist who works in biology. I sort of grew up seeing science as a happy way to live a life. I enjoyed the way my dad seemed to approach the world, as puzzles and wanting to find out the truth, that sort of stuff. It seemed like an appealing way to have a career.

So you were hooked from a young age?

Yes, actually my first experience in a lab was during high school. I did a summer program called the Research Science Institute, and worked in a lab in Georgetown (Washington, DC). Then, the following summer I worked in my dad's lab. And when I went to university (at Harvard) I did an undergraduate thesis in Tom Maniatis's lab, working on the NFκB transcription factor. I worked in Tom's lab full-time in the summer holidays and whenever I could during the year.

Wow, you really did know early on that science was for you.

Yeah, there's never been a huge question about it.

You did your Ph.D. with Gerald Crabtree at Stanford. What was your project?

Weidong Wang, in the lab, was just beginning to clone subunits of mammalian ATP-dependent chromatin remodeling complexes, and one of the intriguing surprises was that actin-related proteins turned out to be a fairly common component of these complexes. So I was interested in what an actin-related protein would be doing in a nuclear complex; actin wasn't supposed to do anything in the nucleus, according to canon.

How did you go from looking at chromatin-remodeling complexes to looking at chromatin structure on a genome-wide scale?

The reason I got into genomic approaches to chromatin is that I thought, "Well, if there was some direct role for actin polymerization in chromatin structure, it wasn't likely to be shifting a single nucleosome two base pairs to the left." Presumably what would be happening would be large-scale changes in which nucleosomes are positioned or in some other aspect of chromatin structure.

Oliver Rando

I assumed, being at Stanford while all the microarray stuff was going on with Pat Brown and Ron Davis, that there would also be genomic ways to look at chromatin structure. I was surprised to find that there weren't at the time.

So you developed these techniques when you moved to Harvard as a Bauer Fellow. What exactly is a Bauer Fellow?

It's like faculty with training wheels. They're very similar to Whitehead Fellows, although there are differences in detail. But essentially it was a five-year position where we had PI rights and we had funding for ourselves plus two other people. In other words, they would fund you to run a lab of three people.

One of the great things about the program was that there were approximately ten fellows at a time, and they were drawn from a wide range of disciplines. I was the boring molecular biologist, but there were mathematicians and physicists and evolutionary biologists. I collaborated with a number of the other fellows and learned a lot even from the ones I didn't work with. Most extensively, we did a lot of our early chromatin work with Steve Altschuler and Lani Wu, who are mathematicians. Going through the process of learning to talk to someone who speaks such a different scientific language was illuminating, and I think it really forced me to reevaluate some of the hidden assumptions that are built into how I would usually talk about biology.

It was very stimulating working with people from different disciplines. It was a wonderful opportunity, a great position.

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Text and Interview by Ruth Williams
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> "The genome-wide results help to frame the next set of questions about how histone modifications work in the cell."

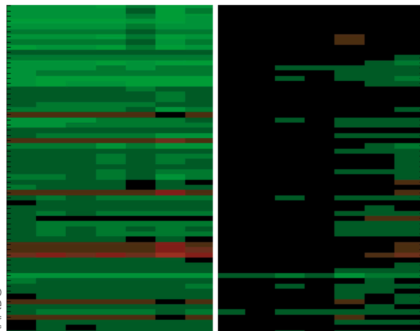
SCALING UP

What is the benefit of studying chromatin questions at a genomic scale?

When you look at a single gene, you wonder whether that gene is unusual in its behavior or whether that's how all genes behave.

A good example of the power of genomic approaches is Audrey Gasch's paper on environmental stress responses. There had been this transcriptional literature for years and years describing how gene A gets turned on when you put hydrogen peroxide on a cell, and gene B gets turned on by heat-shocking cells. This was moving forward piecemeal. Then, Audrey ran yeast through tons of different stresses and found that there was a core group of 800 or so genes that changed expression under virtually all stress situations. It would have required an almost infinite number of single-gene studies to realize that these particular genes behave so coherently, and that this group doesn't just respond to one type of stress, but to all types.

Another example from our own field is histone H3 lysine-4 methylation. If you look genome wide, you find that the more a gene is transcribed, the more trimethylation there is at its 5′ end. So you see this modification all over the place. But when you look at the whole genome's response to not having that mark—if you knock out the gene responsible for lysine-4 methylation—the gene expression defects are not that widespread. In other words, this methylation is happening over all active genes, but only a fraction of genes care about it. Without a genome-wide approach you wouldn't easily have picked up on that. So, the genome-wide results help to frame the next set of questions about how histone modifications work in the cell.



RANDO

Decoding the histone code: microarray data show that mutation of histone H4 K16 (left) almost always switches off genes (green).

You use yeast for these studies. How do you think your work will translate to metazoans?

I feel like yeast is going to end up looking a lot like a subset of metazoan chromatin. In other words, a lot of the things we think we understand about yeast, like the role of K-36 methylation or where K-4 methylation happens, so far turn out to be the same in higher eukaryotes.

The difference is that higher eukaryotes also have these other systems piled on top. So they have additional modifications. They have expansions of the various histone families to form a wide variety of subunits. And so in general I think the basic lessons learned from yeast will apply to metazoans, but then there will be additional layers of complexity.

FUTURE PLANS

You have very recently moved to the University of Massachusetts. How are you finding it?

I really like my colleagues here. There's a strong feeling of excitement about the direction of the place. There's people who work on chromatin, people who work on RNA, people who are interested in transcription and nuclear structure—all things within a stone's throw of what I spend a lot of time thinking about. It's a great fit.

What's next for the Rando lab?

We have an idea for how to look at chromatin's secondary structure, in other words the 30-nm fiber. It's going to be technically challenging, and I don't know if it'll have the kind of signal-to-noise one would need to get anything useful out of it. But we're interested in those questions.

Right now I'm thinking a lot about histone movement, replacement, sliding, etc. Most interesting is the question of what happens to nucleosomes during genomic replication, since the details of their behavior at the replication fork will really help constrain thinking about inheritance of chromatin states. These questions about histone movement are related to our recent work measuring nucleosome exchange rate during G1 arrest, and there is a bunch of interesting mechanistic follow-up to do there as well. One of the things we find is that nucleosomes are exchanging in and out of the promoters of most genes, but the highest exchange rates are found at genes that are regulated by ATP-dependent remodelers. It's possible, then, that either dissociation or reassociation or some part of the turnover process involves ATP-dependent remodelers. So we'd also like to look into that.

We're also planning on extending the histone turnover work to doing studies in the mouse. We'd like to make mice where we can ask what is the turnover rate of a given histone variant in the whole animal and in different tissues.

Lots of fingers in lots of pies. So your childhood passion for science is still going strong?

Yes, I'm having a blast right now. I'd like to be having a blast doing science in 20 years, 50 years. I really enjoy what we're able to think about and look at, and I hope that I manage to structure my life in such a way that I can continue to have fun doing science and thinking about problems well down the road. JCB

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