A Conversation with Rick Young

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Rick Young is Professor of Biology at the Whitehead Institute at the Massachusetts Institute of Technology.

Richard Sever: A key component of your work on gene expression and regulation of embryonic stem cells in development is this idea of a super-enhancer. If an enhancer is a region of DNA upstream or downstream of the gene that controls its activity, what's a super-enhancer?

Dr. Young: A super-enhancer is a cluster of enhancers that work together to control the expression of a target gene. We ran into these because we were interested in the transcriptional control of cell identity. We noticed these very large enhancer clusters associated with genes that many investigators knew were important for embryonic stem cell identity. That gave us the clue that they might be functionally interesting and led us to the view that they play special roles in the control of gene expression.

Richard Sever: Is it safe to say that it's a quantitative difference rather than a qualitative difference when you compare them with regular enhancers?

Dr. Young: Part of it's quantitative, but it also looks like they aggregate the transcriptional components downstream of major developmental signaling pathways. If cells need to sense their environment, and they always do, the signaling pathways have components that come right to these super-enhancers, which are then regulating the genes that play prominent roles in that cell's identity.

Richard Sever: So they're higher up the pyramid, so to speak, in the control of cell fates, and super-enhancers are essentially where the combinatorial regulation happens? Is that how you get specificity?

Dr. Young: It seems to be. In every cell type we've looked at, the genes that play the most prominent roles in cell identity seem to have evolved this clustered enhancer structure so that the sequences are there for the dominant transcription factors in the cell type. They seem to recruit some of the signaling transcription factors that are the receivers for signals coming from outside the cell.

Richard Sever: Are they distinct from what we used to call a locus control region (LCR)?

Dr. Young: I think they encompass what we called locus control regions, which are also clusters of enhancers. There are other types of enhancer clusters that have been noticed before. The difference between the locus control regions and the larger group of super-enhancers is that the LCRs classically regulated downstream target genes in different ways, such that during development you might, for example, make the more embryonic form of globin during one stage of erythrocyte development and then the adult globin during a later stage; the different LCRs were capable of differentially regulating those developmentally important genes.

Richard Sever: Beyond the transcription factors that are binding, are there particular proteins that define super-enhancers at the molecular level?

Dr. Young: The thing that characterizes super-enhancers is the unusual density of the transcription apparatuses. A typical enhancer in mammalian cells will usually have a large number of transcription factors. They will recruit various kinds of cofactors like p300-CBP. They'll also recruit chromatin regulators like BRD4 and SWI/SNF apparatuses, but ultimately they recruit the polymerase in the transcription apparatus. Unlike the picture of enhancers we had many years ago, we now understand that they're sites where transcription can occur and where the RNA components can have functions. The super-enhancers seem to have a much higher density of that. We believe that's because, in three-dimensional space, the clusters come together and operate at a point where they're aggregating the transcription apparatuses, and then giving them off to the target gene of interest.

Richard Sever: Are these clusters in *cis* or in *trans*? Do you get loops coming in from elsewhere?

Dr. Young: Super-enhancers are like enhancers in that they can loop some distance to a target gene; they share that feature. The requirement we've seen so far is that they need to be embedded in a larger CTCF-CTCF co-bound

loop to constrain their activity to the single target gene on which that cluster of enhancers is focused.

Richard Sever: One thing that I find fascinating is this idea of the insulator regions that the CTCF binds. Do they, in fact, insulate the effects of the super-enhancer?

Dr. Young: A subset does. Of all the CTCF-bound sites in the genome, ~30%–35% are engaged in forming these loops. It's that set that looks like they're insulating. Although the simple presence of the CTCF protein by itself is not always insulating, loop formation is.

Richard Sever: Cohesin seems to be at those CTCF sites and also at the super-enhancer site. Is this the same cohesin that we more typically would expect to find at mitosis?

Dr. Young: Yes. Cohesin molecules were originally described as being important for sister chromatid cohesion on the metaphase plate during mitosis and during meiosis. They are also recruited by a component at enhancers called NIPBL (nipped-B-like protein) to help maintain the loop that's formed between an enhancer and its target gene. The enhancer promoter loops are stabilized by cohesin molecules that can form a ring around two nucleosome-occupied DNA strands. They also migrate to, and are associated with, CTCF sites. Wherever you find a CTCF-CTCF loop, there's a cohesin molecule co-bound. They're essentially a structural element that fulfills a similar role at mitosis and in interphase. They play both roles.

Richard Sever: Are these structures maintained through mitosis, or does cohesin slide off to somewhere else and then come back to where it was before?

Dr. Young: We know very little about that process. We do know that these fascinating topological domains that Bing Ren, Job Dekker, Edith Heard, and others have described are largely made up of these CTCF cohesin-co-bound loops and nested inside additional loops of that sort are loops of enhancers going to their promoters. Because of the condensation that occurs during mitosis, that structure is lost in these maps of topological domains. They seem to dissolve, and one interpretation is that the DNA is so condensed that you see interactions at very high frequency all along the DNA. When you come out of mitosis into telophase and then into G₁, all of those domains are reestablished. We think the underpinnings of those domains are the CTCF-CTCF loops and the enhancer promoter loops. They're reestablished correctly as you come out of that mitotic state, but the exact controls of that process are not well understood.

Richard Sever: These super-enhancers function in development in the setting of cell identity. Do you see them in normal physiology?

Dr. Young: Yes. There are super-enhancers in every cell type we've examined, and they're associated with the genes that play the most prominent roles in cell identity. Each cell has a different set of genes that play those

dominant roles. Although the structural components, these CTCF-type loops, tend to be maintained, the new super-enhancers and their looping to their target genes are the things that really change dramatically during differentiation.

Richard Sever: There is a dysregulation or dysfunction of super-enhancers in cancer. What's going on there?

Dr. Young: In my view, cancers are just cells evolving very rapidly to adapt to the niche they live in. Whatever mutations occur that give them a growth advantage in that niche are things they'll adopt. Because they're genetically unstable, one of things they do is build super-enhancers to drive oncogenes that are not normally in the parent lineage. Every time we see the development of oncogenic activity, we see evidence of super-enhancer formation in the vicinity of that oncogene.

Richard Sever: Are these de novo super-enhancers you don't see anywhere before or, as often happens in cancer, are they recapitulating something that you see in embryogenesis?

Dr. Young: It's both. Because cancer often resembles something like a dedifferentiated embryonic cell state, you'll often see a gene that's typically involved in early development, such as an early developmental transcription factor that is normally silenced in those cells, will be reactivated and the super-enhancer that drove it in development will be largely the same in cancer. More frequently, we see tumor cells taking advantage of genetic instability by either translocating a super-enhancer that normally is utilized elsewhere to the vicinity of the oncogene, or we'll see insertions or deletions or focal amplifications that create super-enhancers that normal cells never see.

Richard Sever: Is there anything about super-enhancers that make them viable targets for some form of anticancer therapy?

Dr. Young: Working with Jay Bradner and Nathanael Gray, that's exactly what we've found. In many of the most aggressive tumor cells—which tend to have the largest, most aberrant super-enhancers—it looks like the larger you are, the harder you fall. Inhibitors that hit various components of the transcription apparatus can have a disproportionately adverse effect on oncogenic super-enhancers at concentrations of these drugs that have no effect on normal cells. Enhancers are really collections of transcription factors that have very weak interactions with the DNA, and they live there through the many cooperative interactions they have with one another and their cofactors and cohesin and other types of epigenetic regulators. It appears that when you have these collections of weak, synergistic, collaborative interactions, there's a propensity to fall apart under limited duress from transcriptional inhibitors. These inhibitors are small molecules that, at least in the cases we've investigated, are either competitive inhibitors of bromodomain proteins or catalytic inhibitors of the transcriptional kinase CDK7.

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