Checks and Balances: Rpd3 Issues Executive Orders in Developmental Enhancer Regulation

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Stem cells use poised enhancers of developmental regulators to maintain pluripotency and for subsequent activation in differentiating progeny. In this issue of Developmental Cell, Janssens et al. (2017) demonstrate that the erm enhancer is maintained in a poised state in neural stem cells by the histone deacetylase Hdac1/Rpd3.

There are several possible mechanisms that might support the chromatin signature observed at poised enhancers (Figure 1). For example, the complex recruited to these regions of chromatin may lack a co-activator required for p300 enzymatic activity or, alternatively, may contain a direct inhibitor of p300 activity. Additionally, the presence of H3K27me3, installed by the PRC2 complex (Blackledge et al., 2015), might prevent enhancer activation, either through its mutually exclusive relationship with H3K27ac or through H3K27me3-mediated recruitment of the PRC1 complex that might alter local chromatin structure and accessibility. Alternatively, active turnover by deacetylases may keep poised enhancers from premature activation by keeping acetylation levels in check.

Based on their observation that the minimal erm enhancer remained inactive in type II neuroblasts while lacking H3K27me3, Janssens et al. (2017) tested whether the PRC2 complex was required to prevent premature erm expression. In line with their observation of chromatin state, neither loss of Suz12 nor loss of Ezh2, two critical components of the PRC2 complex, resulted in erm enhancer activation in type II neuroblasts. Instead, loss of the histone deacetylase Rpd3 led to premature activation of the erm enhancer, as evidenced by Erm expression in type II neuroblasts and their premature differentiation. These data support a model whereby the poised erm enhancer is kept in this state through constant deacetylation of the regulatory element. The authors went
on to identify Tip60 and HBO1 as histone acetyltransferases required for the differentiation to immature INPs. As these acetyltransferases’ main histone substrates are H2A and H4 (Lee and Workman, 2007), respectively, these observations would invoke a mechanism by which these acetylation events, or perhaps even non-histone acetylation, may play a more prominent role in enhancer activation than H3K27ac.

While the proposed model of deacetylase-mediated regulation is compelling, it is important to note that the data presented here do not rule out other mechanisms that might regulate enhancer activation. Critically, the minimal erm enhancer lacks genomic context that might provide additional means of regulation. Additionally, a direct link between loss of Rpd3 activity, activation of Tip60 and HBO1, and acetylation of the enhancer has not been established. This work would be strengthened by additional mechanistic analysis of the endogenous enhancer at different developmental stages and by extending this analysis to other developmentally regulated enhancers.

In spite of recent advances in our ability to discover genome-wide enhancers based on chromatin signatures and other distinctive features, it has been difficult to directly test the functional impact of the chromatin modification state of enhancers in a developmental context. This study from Janssens et al. (2017) adds significantly to our understanding of the mechanism by which a poised enhancer can be developmentally licensed to activate gene expression and cell fate commitment. Once activated in INPs, Erm restricts developmental potential through a negative feedback loop by repressing the expression of genes that promote type II neuroblast self-renewal. This work paves the way for a host of exciting questions. Specifically, is Rpd3 recruited to the erm enhancer? And if so, by what mechanism? How is Rpd3 function at enhancers delineated from its function at genes? What is the acetylation landscape of this region upon differentiation from type II neuroblasts to INPs? What is the mechanism that prevents Rpd3 activity at the  erm enhancer in INPs? More globally, is this mechanism of deacetylase de-commissioning specific to this enhancer during this developmental transition, or is it a more general mechanism of regulating poised enhancers genome-wide and under many developmental or biological contexts? What is the role of acetylation in enhancer activation, and is it specific to particular histone lysine residues? Further, how are all the regulatory inputs required for developmental cell fate specification integrated through enhancer function and subsequent gene regulation? With the advent of new tools to manipulate genomes, including enhancer elements (Fulco et al., 2016; Sanjana et al., 2016), we look forward to discovering the answers to these questions and more.

In sum, this new study sheds light on a mechanism regulating the “dark matter” of our DNA, and it will certainly inform future investigation of enhancer function.

REFERENCES