Getting started: altering promoter choice as a mechanism for cell type differentiation

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In this issue of *Genes & Development*, Lu and colleagues (pp. 663–677) have discovered a key new mechanism of alternative promoter choice that is involved in differentiation of spermatocytes. Promoter choice has strong potential as mechanism for differentiation of many different cell types.

Cell differentiation is both a fascinating and intriguing aspect of the development of multicellular organisms. Regulated gene expression plays a pivotal role in determining the spatial and temporal direction of cellular maturity and diversity (Arney and Fisher 2004). Gene expression during differentiation involves tightly regulated interactions between specific DNA regulatory sequences and protein complexes that can specifically bind to them. Much emphasis has been placed on the role of distal enhancer elements in shaping tissue type-specific transcription at core promoters (Haberle and Stark 2018). For example, certain promoter-proximal elements affect the activities of both enhancers and promoters, which is essential for regulating the specificity of their interactions (Calhoun et al. 2002; Andersson and Sandelin 2020).

However, we are realizing the important role of specific promoter-proximal motifs in directly influencing transcription of genes activated during the differentiation from one cell type to another. For example, protein complexes such as tMAC and dREAM cause either activation or repression of different promoters depending on composition of the complex specific for a particular cell type/stage (Beall et al. 2007; Sadasivam and DeCaprio 2013; Lu and Fuller 2015; Laktionov et al. 2018; Andersson and Sandelin 2020). However, the mechanism by which this choice occurs remained unknown.

Here, Lu et al. (2020) have shown that these complexes can make use of alternate promoters with unique proximal motifs bound by cell type-specific factors to turn off the ongoing transcriptional program and start a new program to transition between two different cell types. This is also a very efficient mechanism for assuring the same level of transcription of the same gene in two totally different cellular environments with variable protein composition. Previously, alternate promoters were reported as means of achieving mRNA heterogeneity in particular tissue types (Landry et al. 2003; Zhang et al. 2007). The present study reveals how the tMAC complex can act similarly to a pioneer factor to initiate transcription by opening cell type-specific promoters by remodeling the nucleosomes present there.

Furthermore, some tMAC components have features found in known pioneer factors such as HNF3 (Cirillo et al. 1998; White-Cooper 2010). Also, there are reports showing dREAM, a similar complex, can recruit other remodeling proteins that in turn can loosen chromatin and thus open chromatin at target loci (Mages et al. 2017). At present, this is a possible mechanistic model that needs to be tested by further biochemical analysis. The presence of other factors that can limit the activity and spread of tMAC complex-induced transcription at multiple promoters indicates the presence of a multilayered fine-tuned regulation essential for such highly dynamic and intricate mechanisms of cell differentiation.

Moreover, tMAC is highly conserved across species, and there are many other protein complexes present that show tissue- or stage-specific binding to chromatin in all phyla (Kent et al. 2004; Creppe et al. 2014; Gregory 2018). Also, the presence of alternate promoters is long known across all organisms to increase tissue transcriptome diversity. There are reports describing several motifs present in promoters that have undefined functions (Smith et al. 2006; Down et al. 2007). Therefore, it is very likely that interplay between chromatin-binding protein complexes and promoter-proximal motifs regulating terminal cell differentiation in different organs will prove to be a highly conserved process in diverse organisms.

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