Epigenetics

The double-edged sword of bivalency

The dawn of molecular biology in the twentieth century gave rise to a flurry of excitement in the early 2000s about the role of epigenetics. Next-generation sequencing meant it was now possible to read the DNA sequence of coding and non-coding regions with ease. The first histone modifiers were identified and implicated in gene regulation, and the ‘histone code’ hypothesis was proposed by Jenuwein and Allis to understand chromatin function.

Classical developmental biology had already shown the importance of chromatin modifiers in lineage commitment and tissue diversification from insects to mammals. The evidence collectively pointed to chromatin as a crucial regulatory layer in achieving correct timing and specificity in gene expression. But what really was the histone code and how did it work mechanistically?

Part of the answer came in 2006 from two fundamental papers by the groups of Eric Lander and Amanda Fisher. Using different (now archaic) approaches of chromatin immunoprecipitation (ChIP)–chip and ChIP–quantitative PCR, both groups found that a certain set of genes have both transcriptionally permissive (active) and repressive histone modifications at their highly conserved regulatory regions. These domains were categorized as double-positive for the ‘active’ modification H3K4me3 and the ‘repressive’ chromatin mark H3K27me3, and termed ‘bivalent’. Notably, bivalency was specific to embryonic stem cells and resolved to monovalent active or repressed states upon differentiation. The chromatin of bivalent regions was accessible in stem cells and later became inaccessible if repressed, and remained accessible if active in the differentiated tissue (accessibility was confirmed by studying replication timing in the pre-ATAC-seq era). As bivalency was found mostly at developmental genes, the groups postulated that bivalency keeps developmental genes in a ‘ready-to-go’ state to enable unrestricted and prompt differentiation of pluripotent cells into different lineages upon receiving distinct cues.

Today, 17 years after its inception, the field is still working on understanding the many facets of bivalency. Latest technologies enable the dynamic nature of this double-edged regulation to be captured in detail. Although the concept of bivalency and its claimed specificity for developmental genes has been challenged over the years, it remains supported by and continues to pique the interest of researchers from different backgrounds. A major open question, which also inspires our research, is how differentiation cues are relayed to chromatin to resolve bivalency. Such insights will strengthen or even revise our understanding of bivalency in the great scheme of cellular decisions that underlie developmental timing and trajectories.

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