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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Original articles: Bernstein, B. E. et al. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. *Cell* **125**, 315–326 (2006); Azuara, V. et al. Chromatin signatures of pluripotent cell lines. *Nat. Cell Biol.* **8**, 532–538 (2006)

Related article: Jenuwein, T. & Allis, C. D. Translating the histone code. *Science* **293**, 1074–1080 (2001)

Epigenetics

The neuronal epigenome is special

When I was a neurobiology PhD student in the 1990s, my colleagues and I obsessed over genes that were "neuron specific", thinking that unique molecular mechanisms must underlie the most interesting functions of our favourite cells. That idea was laid to rest, or so I thought, when the neuron-specific process of synaptic vesicle release was shown to require the same proteins that mediate general vesicle trafficking in all cells. Neurons are just cells, I reluctantly concluded, and their important functions rely on adaptations of common mechanisms.

The methylation of genomic DNA at cytosines is a conserved mechanism that facilitates the expression of cell-type-specific transcriptomes. In most mammalian cells, methylation occurs almost exclusively at CpG dinucleotides. DNA methylation is inherently mutagenic, causing replacement of cytosine by thymine. As a result, CpG dinucleotides are under-represented in mammalian genomes. However, methylation is also pervasive, occurring at ~75% of CpG dinucleotides in somatic cells.

Concepts in epigenetics tend to emerge upwards from data, and the development of methods for genome-wide sequencing of DNA methylation at single-base resolution in the late 2000s propelled a conceptual transformation in this field. One early discovery was that a fraction of DNA methylation occurred at non-CpG sites in pluripotent stem cells, but this modification was thought to be lost after cell differentiation.

Then, in 2013, Lister et al. sequenced the neuronal methylome over the full time-course of brain development in both mouse brains and human brains. They saw, as expected, that CpG methylation was abundant in neurons, and its distribution suggested a conserved function in transcription repression. However, neurons began to accumulate exceptionally high levels of non-CpG methylation after birth. In fact, unprecedentedly, the authors found that adult neurons have as many sites of non-CpG methylation as sites of CpG methylation. Moreover, the postnatal accumulation of non-CpG methylation in the brain is neuron specific, as it was not detected in other brain cell types.

These data were exciting because the rise of non-CpG methylation in neurons coincides with the postnatal period of synapse maturation, suggesting that this distinctive feature of the neuronal epigenome contributes to brain wiring. Taken together with evidence that non-CpG methylation is written and read by the neurodevelopmental-disorder-associated proteins DNMT3A and MECP2, respectively, this paper was foundational for launching studies of how the uniqueness of the neuronal epigenome shapes cognitive development.

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