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EPIGENETICS

Leaving a lasting mark

Epigenetic modifications may underlie the influence of early life experiences on neuronal development and function, yet the molecular mechanisms involved are poorly understood. Greenberg and colleagues show that in mice, methylation at CA sequences (mCA) in neuronal genes is modified by early postnatal experience, providing a mechanism to fine-tune gene expression in the adult.

Unusually high levels of mCA are found in neurons, which suggests that it is important for neuronal function. To examine the nature of neuronal CA sequence methylation, the authors performed chromatin immunoprecipitation followed by sequencing, using an antibody for DNA methyltransferase 3A (DNMT3A, the enzyme that mediates mCA deposition), on extracts of the developing mouse cortex and hippocampus. They observed a transient recruitment of DNMT3A to the neuronal genome at 2 weeks of age and showed that it preferentially binds to neuronal genes expressed at low but detectable levels. This pattern of DNMT3A recruitment corresponded to stable patterns of mCA deposition observed at 8 weeks of age, and the analysis of mice in which *Dnmt3a* was disrupted in the brain (*Dnmt3a* conditional knockout (cKO) mice) confirmed the importance of DNMT3A in establishing mCA deposition.

> “alterations in activity-dependent gene expression drive… alterations in DNMT3A binding and mCA deposition”

During early postnatal life, neuronal activity associated with sensory experience alters neuronal gene expression. The authors showed that mice in which activity-dependent gene expression was boosted by treatment with kainic acid or through mutation of a transcriptional repressor gene exhibited decreased DNMT3A binding to, and mCA deposition at, activity-regulated genes. *Dnmt3a* cKO mice exhibited no changes in the expression levels of activity-dependent genes, indicating that alterations in activity-dependent gene expression drive (rather than follow) alterations in DNMT3A binding and mCA deposition.

What is the function of activity-regulated mCA deposition? The authors showed that in *Dnmt3a* cKO mice, the loss of mCA at genes normally expressed at low levels modestly increased their expression, suggesting that mCA constrains the transcription of the genes on which the mark is found. The effects of DNA methylation on gene expression are thought to be mediated through the recruitment of a repressive complex that includes methyl-CpG-binding protein 2 (MECP2). Here, the authors showed that MECP2 binding across the neuronal genome was correlated with the pattern of mCA deposition. Mice in which *Mecp2* was disrupted exhibited changes in gene expression that mirrored those of *Dnmt3a* cKO mice, supporting the role of this protein in mCA-driven tuning of gene expression.

This study outlines a mechanism through which early-life influences that drive activity-dependent gene expression can translate into the lasting restraint of the expression of particular genes throughout the lifetime of a neuron. These results may also provide insight into disorders caused by loss of DNMT3A or MECP2 function.

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