

Dynamic changes in neuronal DNA methylation patterns during brain development

The behavioral and cognitive functions of frontal cortex require the interaction of diverse neurons and glial cells with specific roles arising from their location, connections with other brain cells, as well as each cell's intrinsic, epigenetically defined molecular identity. Dynamic epigenetic changes, including variant histones, histone modifications and DNA methylation, are implicated in brain development, maturation and learning. Among these, DNA methylation is a stable covalent modification that can persist in post-mitotic cells throughout the lifetime and thus confers a capacity for long-term memory of cellular identity. At the same time, the DNA methylation status at each of ~1 billion sites across the genome is potentially an information-rich and flexible epigenetic modification that can be altered by cellular activity. Yet elucidating the role of DNA methylation in brain function has been hampered by the lack of precise knowledge of the genomic distribution of this mark in brain cell types. We will present the genome-wide composition, patterning, cell-specificity and dynamics of DNA methylation at single-base resolution in frontal cortex of humans and mice throughout their lifespan. Extensive methylome reconfiguration occurs during development from fetal to young adult. In this period, coincident with synaptogenesis, highly-conserved non-CG methylation accumulates in neurons, but not glia, to become the dominant form of methylation in the genome. We have uncovered surprisingly complex features of brain cell DNA-methylation at multiple scales, first by identifying intragenic methylation patterns in neurons and glia that distinguish genes with cell-type specific activity. Second, we find >100,000 developmentally dynamic and cell-type specific differentially CG-methylated regions that are enriched at putative regulatory regions of the genome. Finally, whole-genome detection of 5-hydroxymethylcytosine (hmC) at single-base resolution revealed that this mark is present in fetal brain cells at locations that lose CG methylation and become activated during development. CG-demethylation at these hmC-poised loci depends on Tet2 and Tet3 activity. Overall, brain cell DNA methylation has unique features that are precisely conserved, yet dynamic and cell-type specific.