

Insights: Publications

5-hydroxymethylcytosine is dynamically regulated during forebrain organoid development and aberrantly altered in Alzheimer's disease

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5-hydroxymethylcytosine (5hmC) undergoes dynamic changes during mammalian brain development, and its dysregulation is associated with Alzheimer's disease (AD). The dynamics of 5hmC during early human brain development and how they contribute to AD pathologies remain largely unexplored. We generate 5hmC and transcriptome profiles encompassing several developmental time points of healthy forebrain organoids and organoids derived from several familial AD patients. Stage-specific differentially hydroxymethylated regions demonstrate an acquisition or depletion of 5hmC modifications across developmental stages. Additionally, genes concomitantly increasing or decreasing in 5hmC and gene expression are enriched in neurobiological or early developmental processes, respectively. Importantly, our AD organoids corroborate cellular and molecular phenotypes previously observed in human AD brains. 5hmC is significantly altered in developmentally programmed 5hmC intragenic regions in defined fetal histone marks and enhancers in AD organoids. These data suggest a highly coordinated molecular system that may be dysregulated in these early developing AD organoids.

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