Doctoral Defense Announcement

Abstract

Chromatin remodeler Chd5 regulates neural cell fate through the interplay with histone demethylase Utx

By

Dong-Woo Hwang

Neural stem/progenitor cells (NSCs) in mammalian brain are multipotent progenitor cells that give rise to major neural lineages such as neuron, oligodendrocyte and astrocyte. Appropriate execution of precise spatiotemporal cell fate decisions of NSCs is regulated by cell type-specific gene expression programs. And yet, the role of chromatin remodeling proteins in cell fate decisions is not well understood. Here I present evidence that chromodomain helicase DNA binding protein 5 (Chd5) facilitates tri-methylation on the lysine residue 27 of histone H3 (H3K27me3), through which the protein orchestrates neural cell-type-specific gene expression programs. In comparison with wild type counterparts, Chd5-deficient NSCs display promiscuous enrichment of a CD24Low neuronal progenitor population, accompanied by changed cellular properties. In addition to alteration of global gene expression, NSC-specific markers are aberrantly expressed. Upon differentiation, Chd5-deficient cells generate more astrocytes at the expense of neurons. Importantly, ectopic expression of Chd5 enhances H3K27me3 levels and induces neurogenesis, effectively rescuing the cell fate defects of Chd5-deficient NSCs. At the chromatin level, Chd5 deficiency leads to a global reduction of H3K27me3 over multiple genomic sites except for the promoters of glia-specific genes. Lastly, Chd5 functionally interacts with the H3K27-specific histone demethylase Utx. These findings underscore the importance of Chd5-mediated regulation of H3K27me3 during differentiation of NSCs and highlight the novel chromatin-based mechanism as a crucial determinant of cell fate decisions in the developing mammalian brain.

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