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Epigenetic regulation of neuronal fate determination

The role of CHD7

Weijun Feng and Hai-Kun Liu*

Helmholtz Young Investigator Group-Normal and Neoplastic CNS Stem Cells; German Cancer Research Center (DKFZ); DKFZ-ZMBH Alliance; Heidelberg, Germany

Differentiation of stem cells often involves multiple distinct intermediate cell types, which requires a precise control of gene expression in a state-specific manner. Mostly, this process is achieved without the change of DNA sequences that is, by definition, through execution of epigenetic modifications. The combined effects of various epigenetic regulators define and maintain the identity of individual cells. Also, as most epigenetic modifications are reversible, this system also provides cell plasticity, which is essential for stem cell biology.

Adult neurogenesis is a lifelong process of generating functional neural cells from adult neural stem cells (aNSCs). It occurs in 2 discrete areas of the mammalian brain, the subventricular zone of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus.[1] In both regions, aNSCs give rise to transit amplifying cells that divide for several rounds before further differentiating into mature neural cells. The adult neurogenic system has become a very attractive model system for studying neuronal disease-related genes and exploring the intrinsic and extrinsic regulation of adult stem cells.

In a recent study, we have uncovered an essential role of a chromatin remodeler CHD7 (chromodomain helicase DNA binding protein 7) in adult neurogenesis.[2] Using a cell type-specific conditional mutagenesis approach, we showed that in vivo ablation of CHD7 in mouse aNSCs results in a dramatic decrease of newborn neurons in both adult neurogenic regions. The self-renewal capacity of CHD7 mutant aNSCs does not appear to be impaired, but the neuronal differentiation of these cells was largely blocked. Intriguingly, the expression of CHD7 in adult neurogenic niches appears when quiescent NSCs enter the cell cycle, persists in transit amplifying cells and neuroblasts, but is undetectable in mature neurons. Thus, the expression of CHD7 in this time window implicates that it may play a role in neural lineage priming. Indeed, we demonstrated that CHD7 is required for the expression of 2 essential neuronal determination factors, Sox4 and Sox11, in adult neurogenic niches. Overexpression of Sox4 and Sox11 in cultured CHD7 mutant NSCs is capable of largely rescuing the neuronal differentiation defect, suggesting that these 2 factors are the major downstream targets of CHD7 in neurogenesis. Mechanistically, CHD7 activates the expression of Sox4 and Sox11 by keeping their promoters in an open chromatin state, which could well be due to its role in remodeling nucleosomes. At the first sight, it seems to be paradox that immunostaining data show that Sox4 and Sox11 are mainly expressed in neuroblasts but not in NSCs. Importantly, Beckervordersandforth et al. have demonstrated that although not translated, the mRNAs for several neuronal specific transcription factors, including Sox4 and Sox11, are actually expressed in NSCs. These authors interpreted their findings as the neurogenic priming of NSCs.[3] Our data supports this notion and proceeds to show that loss of this priming, i.e., downregulation of *Sox4* and *Sox11* genes upon CHD7 depletion, impairs neuronal differentiation of NSCs.

Importantly, heterozygous mutation of CHD7 leads to CHARGE syndrome in human, which is characterized as choanal atresia, defects of the eye and heart, severe retardation of growth and development, and genital and ear abnormalities.[4] Many CHARGE patients have central nervous system anomalies, like olfaction deficits and mental retardation.[5] Our finding reveals a novel molecular mechanism by which mutation of CHD7 contributes to brain deficits, i.e., the block of neuronal differentiation of CHD7 mutant NSCs. One of the most intriguing observations from our study is that voluntary running led to a complete rescue of hippocampal neurogenesis in the CHD7 mutant, not only the number, but also the dendritic development of newborn neurons. This data suggests a yet-to-be-discovered mechanism that guides CHD7 mutant NSCs to differentiate into neurons; on the other hand, it implicates that exercise may have a potential therapeutic benefit for CHARGE patients.

CHD7 belongs to the trithorax (TrxG) group of chromatin factors. In general, TrxG and its counterpartner polycomb (PcG) group proteins maintain their target genes in the open or closed chromatin states and thereby activate or silence transcription, respectively. Notably, the antagonistic mechanism of TrxG and PcG group proteins holds true in regulating neurogenesis. Two TrxG members of histone modifiers, Jmjd3, an H3K27 demethylase, and Mll1, an H3K4 methyltransferase, have been shown to be required for the neuronal differentiation of NSCs.[6] Our study and a very recent

*Correspondence to: Hai-Kun Liu; Email: l.haikun@dkfz.de
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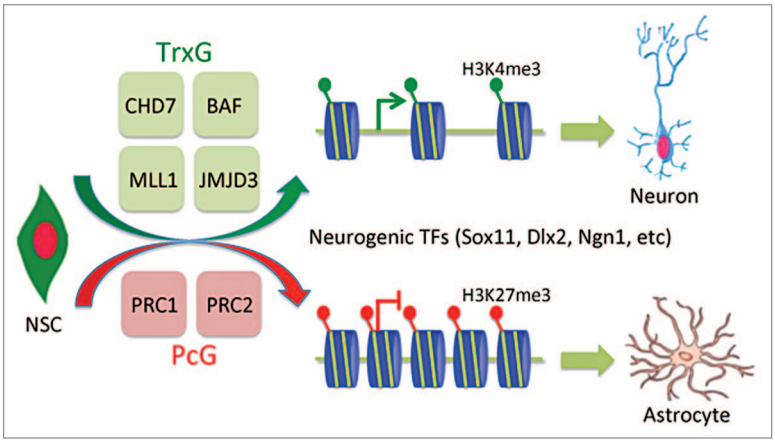

Figure 1. A proposed model of how TrxG and PcG group proteins control neural fate determination of neural progenitors by antagonistically regulating neurogenic transcription factors.

paper demonstrate that 2 TrxG members of the ATP-dependent remodelers, CHD7 and Brg1, promote adult neurogenesis.[7] In contrast, EZH2 and Ring1b, the catalytic subunits of PRC2 (Polycomb repressive complex 2) and PRC1, respectively, are required for the switching from neurogenesis to astrogenesis during embryonic brain development.[8] It appears that TrxG and PcG proteins execute their functions by antagonistically regulating a cross-regulatory network that consists of several essential neurogenic factors, like Dlx2, Sox11, and Neurogenin1 (**Fig. 1**). We anticipate that future work will discover more TrxG and PcG group proteins function in neurogenesis.

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