シグナル伝達医学講演会／大学院特別講義

Targeting Histone Methylation for Autism Treatment

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Large-scale genetic studies have found that the most prominent autism risk factors are histone-modifying enzymes mediating histone methylation/demethylation. However, the role of histone methylation in the pathophysiology and treatment of autism remains unknown. To address this, we used mouse models of haploinsufficiency of the Shank3 gene (a highly penetrant monogenic autism risk factor), which exhibits prominent autism-like behavioral deficits. We found that histone lysine 9 dimethylation (H3K9me2, linked to gene repression) and its catalyzing enzymes histone methyltransferases EHMT1 and EHMT2 were selectively increased in the prefrontal cortex (PFC) of Shank3-deficient mice and autistic human postmortem brains. Treatment with the EHMT1/2 inhibitor UNC0642 or knockdown of EHMT1/2 in PFC induced a robust rescue of autism-like social deficits in Shank3-deficient mice, and restored NMDAR-mediated synaptic function. Activity-regulated cytoskeleton-associated protein (Arc) was identified as one of the causal factors underlying the rescuing effects of UNC0642 on NMDAR function and social behaviors in Shank3-deficient mice. UNC0642 treatment also restored a large set of genes involved in neural signaling in PFC of Shank3-deficient mice. On the other hand, we found that histone lysine 4 dimethylation (H3K4me2, linked to gene activation) was significantly decreased in the PFC of autistic humans and Shank3-deficient mice. H3K4me2 is demethylated by lysine-specific histone demethylase 1 (LSD1, KDM1A). A brief treatment of Shank3-deficient mice with GSK-LSD1, a highly potent and selective inhibitor of LSD1, led to the robust rescue of core symptoms of autism, including social deficits and repetitive behaviors. Electrophysiological abnormalities in cortical-striatal circuits were also ameliorated by GSK-LSD1 treatment. These results suggest that targeting histone methylation to adjust gene expression and ameliorate synaptic defects could be a potential therapeutic strategy for autism.

References

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