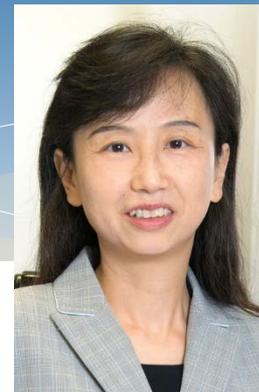


シグナル伝達医学講演会／大学院特別講義

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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