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『Epigenetic Regulation of Neurological Disorders: Role of Lysine Acetyltransferases p300/CBP』

Epigenetics is gene function beyond the DNA sequence, operated by DNA modifications, DNA-associated protein modifications, and noncoding RNA. It is reversible and metabolically regulated, thus directly related to habit and lifestyle. Reversible histone acetylation is one of the most investigated epigenetic modifications shown to be involved in diverse physiological as well as pathological phenomena. However, its role in memory and neurological disorders is not fully understood. Several studies have demonstrated that the master Lysine acetyltransferases CBP/p300 catalytic activity could be critical for long-term memory formation. We have shown that specific activation of p300/CBP KAT activity significantly prolongs the long-term memory in mice. We have discovered a small molecule (TTK21) activator of CBP/p300, which, after conjugating to the glucose-derived carbon nanospheres (CSP), crosses the blood-brain barrier and reaches different parts of the brain without apparent toxicity. It induces adult neurogenesis and long-term memory. By administrating this activator to the tauopathy mouse model of Alzheimer's Disease (AD), we could significantly reverse the memory loss in young and older mice. In the course, we identified that the cholesterol biosynthesis pathway is severely deregulated in older AD mice, which could be correlated with available human patient data. Activating p300/CBP KAT activity could normalize cholesterol biosynthesis, reversing cognitive function. Recently, we have found that in Syngap1+/-, a mouse model on intellectual disability (ID) and autism spectrum disorder (ASD), the p300 KAT activity is dramatically reduced in the CA1 region of the hippocampus. Our results demonstrate that the oral administration of CSP-TTK21 in adult Syngap1+/-mice rescued physiological and cognitive/emotional functions, presumably through restoring p300/CBP mediated histone acetylation and adult neurogenesis. The molecular pathways of the amelioration of symptoms are being elucidated.

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