Effect of MLL modified H3K4me3 on aluminum induced cognitive impairment—Both population and animal epigenetic studies

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Objective: Epigenetic modifications play critical roles in cognitive function. Brain-derived neurotrophic factor (BDNF) is involved in synaptic plasticity and may be modified by tri-methyl histone H3 lysine residues 4 points (H3K4me3), which may be modified by mixed-lineage leukemia protein (MLL), a zinc finger-rich enzyme, thus affecting cognition. This study aims to explore mechanism of this epigenetic modification. Methods: 1. 235 male Al-exposed workers were recruited. An occupational epidemiological investigation questionnaire and cognitive tests were performed. The contents of H3K4me3 in lymphocyte and BDNF in plasma were determined by enzyme-linked immunosorbent assay. 2. 24 healthy SD male rats were randomly divided into four groups by weight. The rats drank water containing different doses of aluminum chloride (AlCl3) (0, 2, 12, and 72mg/kg Al3+) for 120d. The neurobehavior of animals was tested, and expression of H3K4me2 and MLL was detected with western blot. Results: 1. With the increasing of blood aluminum level, the cognitive function of Al-exposed workers decreased. The expression levels of H3K4me3 decreased, and BDNF decreased. Multiple correlation analysis showed that Blood aluminum concentration was negatively correlated to H3K4me3, BDNF, and cognitive function, respectively. 2. With the Al dose increasing, the neurobehavior of animals decreased, the expression of MLL and H3K4me3 decreased too. Conclusion: Aluminum inhibits MLL by replacing zinc, then the activity of MLL decreases, the methylation of H3K4 increases, the expression of H3K4me3 decreases, then BDNF decreases.

Reference

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