Fragile X protein loss alters brain pathways responsible for learning and memory

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Geneticists have known for two decades that fragile X syndrome, the most common inherited cause of intellectual disability, is due to the functional loss of fragile X mental retardation protein (FMRP) in the brain. Now they are beginning to understand how FMRP regulates signaling pathways in the brain that are essential for learning and memory in adults.

Researchers at Emory University School of Medicine and the University of New Mexico School of Medicine have described new discoveries about the role of FMRP in the journal PLoS Genetics.

In a mouse model of fragile X syndrome, researchers found that FMRP plays a key role in regulating adult neurogenesis, the process by which new neurons are generated in the adult brain. Adult neurogenesis is considered important for learning and memory.

FMRP is an RNA-binding protein that regulates the translation of genetic information from specific mRNAs into proteins. The researchers found that FMRP regulates the expression of several proteins that are critical for the regulation of adult neural progenitor cells (aNPCs). The dysregulation of these proteins, including CDK4 and GSK3β, interferes with an important signaling pathway in the brain called Wnt. When this pathway is disturbed, aNPCs proliferate and lose the ability to differentiate appropriately. This leads to a reduction in the number of new neurons as well as defective maturation of these neurons.

Neurogenesis occurs throughout life in two areas of the brain: the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus, and the subventricular zone (SVZ) of the lateral ventricles. Research has shown that new neurons generated in the DG are critical for hippocampus-dependent learning and that blocking adult neurogenesis can lead to deficits in learning and memory. Although scientists have shown that adult neurogenesis and learning are altered in conditions such as stress, diabetes, neurological diseases, stroke, and traumatic injury, the link between adult neurogenesis and mental retardation has not been fully explored.

"We discovered that mice lacking the Fmr1 gene have a reduced number of new neurons in the dentate gyrus, and that FMRP-deficient neurons have reduced dendritic complexity and length. Both of these factors could lead to the learning and emotional disabilities associated with fragile X syndrome," says Peng Jin, PhD, assistant professor of human genetics in Emory University School of Medicine and one of the paper's senior authors.

Provided by Emory University

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