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BET protein family plays key role in regulation of normal neuronal development and function

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Regulation of a family of brain proteins known as bromodomain and extra-terminal domain containing transcription regulators (BETs) plays a key role in normal cognition and behavior, according to a study conducted at the Icahn School of Medicine at Mount Sinai and published advanced online on September 21 and in print October 19 in *The Journal of Experimental Medicine*.

The Mount Sinai study focuses on epigenetics, the study of changes in the action of human genes caused by molecules that regulate when, where and to what degree our genetic material is activated, rather than focusing on genetic changes in the DNA code we inherit from our parents.

While scientists have traditionally focused on finding individual genes responsible for Autism Spectrum Disorders (ASD), recent research has found links between epigenetic regulation and ASD in human patients. Such regulation derives, in part, from the function of specialized protein complexes that bind to specific DNA sequences and either encourage or shut down the expression of a given gene.

Mount Sinai researchers found that BETs, a family of epigenetic regulators that bind to many different genes and contribute to the copying of these genes into messenger RNA, the template used by the cell to make proteins, play a key role in the regulation of normal neuronal development and function. The Mount Sinai study was conducted using a new type of pharmacological compound that does not inactivate BET proteins but, rather, prevents them from binding to the genes.

The research team developed a novel, highly specific, brain-permeable inhibitor of BET proteins called I-BET858. The compound was initially tested on in vitro cultured mouse neurons. The researchers found that it affected the function of a particular group of genes with known links to neuron development and synaptic functions. Importantly a significant number of the affected genes have been linked to ASD in humans. Subsequently, the study team evaluated the effect of I-BET858 when injected into mice. They found the compound was able to trigger selective changes in neuronal gene expression in the brain followed by development of an ASD-like syndrome.

"We found that chronic daily administration of I-BET858 in young mice led to the development of behavioral abnormalities consistent with an autism-like syndrome, including reduced sociability and preference for social novelty " says Anne Schaefer, MD, PhD, Assistant Professor in the Department of Neuroscience and Psychiatry at the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai, who led the study.

"One of the most important outcomes of our study is that we found a link between I-BET858-induced ASD and the altered function of a rather limited group of genes," says Dr. Schaefer. "Furthermore, our findings reinforce the idea that ASD could be caused not only by genetic alteration, but by environmental factors that reduce the efficiency of gene transcription into full length RNA during brain development. "

These studies also suggest that pharmacological modeling of ASD in mice provides a valuable tool for the identification of genes that may play a pivotal role in the disease pathology or for the development of novel drugs targeting ASD.

Source:
Mount Sinai Health System