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Scientists at UCI restore long-term memory to mice

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University of California-Irvine neurobiologists have discovered a protein complex in neurons that is essential to long-term memory formation and is also corrupted in the brains of people with some developmental disabilities such as autism.

This complex is corrupted by the mutation of a specific protein molecule , and replacing that mutated molecule in laboratory mice restores their long-term memory - suggesting a possible gene therapy for humans, the researchers reported.

Protein complexes access genes - portions of DNA - and turn them on and off at the right time to enable neurons in the brain to work properly, said Marcelo Wood, associate professor at UCI's Center for the Neurobiology of Learning and Memory and director of the Interdepartmental Neuroscience Program.

Wood's lab has identified nBAF as the protein complex needed for long-term memory. nBAF is found only in neurons. When nBAF is corrupted by a mutation of its gene-encoding molecule baf53b, it can no longer perform the role of "nucleosome remodeling," the means by which nBAF accesses genes.

When UCI researchers replace mutated baf53b with non-mutated baf53b in laboratory mice, it leads to a functioning, gene-accessing nBAF protein complex and results in the return of their long-term memory, Wood said.

This research furthers the science of epigenetics, which has to do with gene access and gene function without a change to DNA coding. Cognitive impairments in learning and memory and neurodevelopmental disorders once thought to be genetic may be epigenetic.

If you unraveled all of the chromosomes in just one cell and lined them up, there would be 6 feet of DNA, which determines the traits we inherit. DNA resides in the microscopic nucleus of a cell and is packed in chromatin. Chromatin is made of repeating units of nucleosomes, a specific length of DNA wrapped around balls of proteins called histones.

When viewed through a microscope, chromatin looks like beads on a string. DNA must be wrapped around nucleosomes so that it can be compacted about 10,000 times to fit in a cell's nucleus.

Accessing genes in the face of that compaction becomes a physical problem. If genes can't be accessed, they can't get turned on.

The nBAF protein complex, necessary for memory, attaches to chromatin and physically unravels the nucleosomes, allowing for a gene to be turned on and off. That action is called "nucleosome remodeling."

If the nucleosome remodeling mechanism of nBAF fails due to a mutation of baf53b, it can result in severe cognitive and neurodevelopment disorders, Wood said.

Nucleosome remodeling plays a major role in gene function and could also play a role in disorders and diseases such as cancer, obesity, depression and addiction, Wood said.

The emerging field of epigenetics - changes to the expression of genes without any changes in their underlying DNA coding - suggests that the environment and the things we're exposed to can alter our gene function

without changing our genetics.

Molecular biologists who study how normal cells turn cancerous are engrossed in epigenetics and are looking at individualized treatments for cancer patients, Wood said.

Wood, who formerly studied cancer cells, brought his knowledge of epigenetics to the UCI research lab.

"Epigenetics has only recently exploded within the field of neuroscience," Wood said. UCI has one of the first centers for epigenetics research.

Epigenetics is why one twin, in a set of identical twins who share the same DNA, might get autism, cancer or another disorder, while the other one doesn't, Wood said.

Epigenetics links nurture (environment) and nature (genetics).

In contrast to our genome - the DNA we're born with - our epigenome can be altered by environmental factors, such as physical and mental stress, diet, drugs and other things we're exposed to.

This suggests that some of the disease and disorders we get can be prevented.

However, epigenetics is "transgenerational." That means grandma's epigenome, including her disorders and diseases, may bypass her daughter and manifest in her granddaughter, Wood said.

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