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Loss of epigenetic regulators causes mental retardation (w/ Video)

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(PhysOrg.com) -- Developing neurons don't just need the right genes to guide them as they grow, they need access to the right genes at the right times. The improper functioning of one specific protein complex that normally suppresses gene activation is responsible for a mental retardation-like syndrome in mice, reports a team of scientists at The Rockefeller University. New findings, published in recent issues of *Neuron* and *Science*, indicate that malfunction of this protein complex causes mental retardation in mice and humans and may even play a role in promoting susceptibility to drug addiction. The research also establishes the complex as a key regulator of neuronal transcriptional identity.

"This research is the result of a close collaboration between our group and that of Alexander Tarakhovsky, which is focused on understanding the role of epigenetic mechanisms in brain function, such as learning and memory," says senior coauthor Paul Greengard, Vincent Astor Professor and head of the Laboratory of Molecular and Cellular Neuroscience. Greengard won the 2000 Nobel Prize in Physiology or Medicine for research into how neurons communicate.

"Our findings may facilitate the identification of mechanisms responsible for long-term storage of environmental information in neurons as well as other cell types," says senior coauthor Tarakhovsky, professor and
head of the Laboratory of Lymphocyte Signaling. "We now have an animal system that not only reproduces the human disease but may also

enable us to understand the underlying mechanisms."

Although genes provide the fixed template that instructs our cells how to grow, increasing evidence suggests that gene activity is governed by a group of proteins known as histones. Histones are subjected to chemical modifications that can permit or prevent genes from becoming active. These modifications are established by specific enzymes that add well-defined chemical residues to the amino acids localized within the tails of the histone proteins. Histone modifications were first identified in the early 1960s by Rockefeller scientist Vincent Allfrey and his colleagues. During the past two decades, research by Rockefeller University's C. David Allis suggested that histone modification could generate a unique epigenetic "code" that regulates the specific recruitment of gene expression activators and repressors to individual genes.

The research program of the Greengard and Tarakhovsky labs focuses on GLP/G9a, an enzyme pair responsible for inducing an epigenetic mark widely known to silence gene expression in mammals, including humans. By attaching two methyl chemical groups to a specific amino acid on a specific histone, GLP/G9a suppresses gene activity. Tarakhovsky and his colleagues, who study GLP/G9a and its role in epigenetic regulation of inflammatory responses, created a strain of mice that enables conditional removal of this complex in various cell types, including neurons in the adult brain.

First author Anne Schaefer, a senior research associate in Greengard's lab, subjected these mice to a battery of behavioral tests and determined that they behave much like humans with a mental retardation syndrome called the 9q34 deletion syndrome, in which the region of chromosome 9 that codes for the GLP genes is missing. The mice lacking GLP/G9a, unlike their normal counterparts, were not afraid of open space, were lethargic (and as a result, obese) and had problems learning to adapt to their environment.

The researchers compared the brains of normal mice and the conditional knockouts and found that there were no structural differences between them. In other words, the behavioral and learning problems associated with the conditional knockouts were not due to any kind of damage to the brain's structure or to the individual neurons.

"This suppressive epigenetic mark completely disappears in these mice, but the neurons themselves do not die and appear normal," says Schaefer. "The mice maintain many of their basal behavioral functions, such as eating and breeding, but they display abnormal behavior in response to various environmental signals."

Schaefer and her colleagues also found that loss of GLP/G9a resulted in increased expression of genes usually found in muscles and the heart. In addition to their analysis of genes that change in the different brain regions, they used a cellular analysis technique developed in labs headed by Rockefeller scientist Nathaniel Heintz and Paul Greengard, called TRAP, which reveals transcriptional profiles by isolating the RNA messages from structurally and functionally defined individual cell populations.

"We found that several nonneuronal genes, normally suppressed by the epigenetic mark, became upregulated in the GLP/G9a conditional knockouts," says Schaefer.

According to Schaefer and her colleagues, it's also possible that genetically predetermined or environmentally induced changes of the epigenetic regulators controlling the methylation mark on histone H3 may be responsible for individual differences in learning and social adaptation.

The Greengard and Tarakhovsky labs have taken these findings a step further in collaboration with Eric Nestler's lab at the Mount Sinai School

of Medicine. In research reported in the the January 8 issue of the journal Science, they found that repeated cocaine administration promotes cocaine preference in mice, revealing a key role for G9a in drug addiction.

Epigenetic regulators are considered the “last frontier” by pharmaceutical companies, Tarakhovsky says, because of their position in the chain of events in cell signaling. “The major excitement of these findings is that there are very few proteins known to have such key regulatory functions and are structurally well defined. That means it should be possible to design drugs that specifically interfere with their activity.”

More information:

• *Neuron* 64, 678-691 (December 10, 2009)
Control of cognition and adaptive behavior by the GLP/G9a epigenetic suppressor complex
Anne Schaefer, Srihari C. Sampath, Adam Intrator, Alice Min, Tracy S. Gertler, D. James Surmeier, Alexander Tarakhovsky and Paul Greengard

• *Science* 327, 213-216 (January 8, 2010)
Essential role of the histone methyltransferase G9a in cocaine-induced plasticity
Ian Maze, Herbert E. Covington III, David M. Dietz, Quincey LaPlant, William Renthal, Scott J. Russo, Max Mechanic, Ezekiell Mouzon, Rachael L. Neve, Stephen J. Haggarty, Yanhua Ren, Srihari C. Sampath, Yasmin L. Hurd, Paul Greengard, Alexander Tarakhovsky, Anne Schaefer and Eric J. Nestler

Provided by Rockefeller University