Epigenetic culprit in Alzheimer's memory decline

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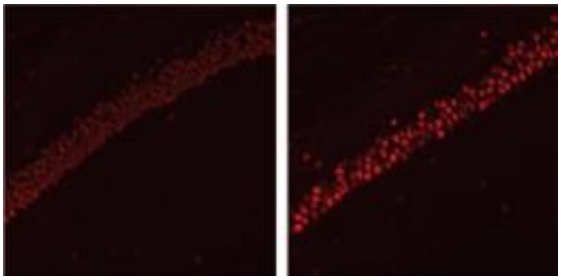

In a mouse model of Alzheimer's disease (right), HDAC2 levels in the hippocampus are higher than in the normal mouse hippocampus (left). Credit: Dr. Li-Huei Tsai, Massachusetts Institute of Technology

In a mouse model of Alzheimer's disease, memory problems stem from an overactive enzyme that shuts off genes related to neuron communication, a new study says.

When researchers genetically blocked the enzyme, called HDAC2, they 'reawakened' some of the neurons and restored the animals' cognitive function. The results, published February 29, 2012, in the journal *Nature*, suggest that drugs that inhibit this particular enzyme would make good treatments for some of the most devastating effects of the incurable neurodegenerative disease.

"It's going to be very important to develop selective chemical inhibitors against HDAC2," says Howard Hughes Medical Institute investigator Li-

Huei Tsai, whose team at the Massachusetts Institute of Technology performed the experiments. "If we could delay the cognitive decline by a certain period of time, even six months or a year, that would be very significant."

In every cell, DNA wraps itself around proteins called histones. Chemical groups such as methyl and acetyl can bind to histones and affect DNA expression. HDAC2 is a histone deacetylase, an enzyme that removes acetyl groups from the histone, effectively turning off nearby genes.

In 2007, Tsai's group reported in *Nature* that this so-called epigenetic change can contribute to cognitive decline. They used a strain of mutant mice developed in her lab called CK-p25, which shows a profound loss of neurons and synapses, the junctions between neurons. The animals also carry the amyloid-beta plaques thought to cause Alzheimer's disease and show impaired learning and memory. When Tsai's team gave the mice drugs that block all HDACs, the animals sprouted more synapses and showed better memory function.

There are 19 known HDACs. In 2009, the researchers found that one of these, HDAC2, can cause a loss of synapses and memory function in normal mice.

The new study pulls from both of these previous findings, investigating HDAC2's affect on CK-p25 mice.

The researchers showed that the mutant animals have an elevated level of HDAC2 in two regions known to be affected in neurodegenerative disease: the hippocampus, important for learning and memory, and part of the temporal lobe called the entorhinal cortex. In these regions, the researchers also found that HDAC2 binds to a host of memory genes and dampens their expression.

Tsai's team then used a technique called RNA interference to silence the expression of HDAC2 in neurons in the hippocampus. Four weeks later, they found a dramatic increase in synaptic density. What's more, when given two different memory tests, the treated animals were indistinguishable from normal controls.

Blocking HDAC2 expression did not change the number of dying neurons. Still, the findings suggest that memory can be improved even in later stages of the disease, Tsai says.

"The neurons that are still alive are essentially zombies: they're not really functioning properly because of the epigenetic blockade," Tsai says. "What we're showing is that, if we can get some of those neurons to wake up, we can get cognitive function to recover to a certain extent."

Using hippocampal neurons grown in culture, Tsai also uncovered a potential mechanism that raises the level of HDAC2 in the first place. She showed that amyloid beta and oxidative stress—both risk factors for Alzheimer's disease—can activate a protein called the glucocorticoid receptor 1. This receptor, in turn, can switch on the runaway expression of HDAC2.

"The striking thing is that amyloid beta has a very, very acute effect in elevating HDAC2 expression, but then the consequences can be very long term," Tsai says. This mechanism could explain why clinical trials of drugs that clear out amyloid beta in people with Alzheimer's haven't worked very well, she says.

Finally, Tsai's team looked at postmortem brain tissue from people who died of Alzheimer's disease. These samples, like those in mice, had elevated levels of HDAC2 in the hippocampus and entorhinal cortex.

The clinical applications of this work are promising, Tsai says, but it's

important not to oversell the findings. "While all the data look very promising in animal models, human studies are a completely different ball game," she says. "We need to do clinical trials to see whether this concept holds up."

More information: Graff J et al. "An epigenetic blockade of cognitive functions in the neurodegenerating brain." Nature, February 29, 2012.

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