

Rett protein MeCP2 needed for proper adult neuron function

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The protein MeCP2 is porridge to the finicky neuron. Like Goldilocks, the neuron or brain cell needs the protein in just the right amount. Girls born with dysfunctional MeCP2 (methyl-CpG-binding protein 2) develop Rett syndrome, a neurological disorder. Too much MeCP2 can cause spasticity or developmental delay with autism-like symptoms in boys.

Now, researchers at Baylor College of Medicine and Texas Children's Hospital have found that the neuron needs a steady supply of this [protein](#) for its entire existence. A report on this research appears online in [Science Express](#).

[MeCP2](#) was found in 1999 in the laboratory of Dr. Huda Zoghbi, director of the Jan and Dan Duncan Neurological Research Institute at TCH and professor of neurology, neuroscience, pediatrics and molecular and [human genetics](#) at BCM and a Howard Hughes Medical Institute Investigator. A mutation in MeCP2 results in Rett syndrome, a [neurological disorder](#) that strikes mainly girls. Male fetuses born with the mutation (which results in dysfunctional protein) die before birth, but girls appear normal until they are between 6 and 18 months. Then they begin to regress and their growth slows. They develop abnormal hand motions such as wringing. Their crawling and walking regresses and they eventually lose the ability to speak or communicate. They exhibit some symptoms of autism.

Clearly, MeCP2 is critical to normal mental functioning, but a question

remained. Do neurons need MeCP2 throughout life or would they be protected and work properly if MeCP2 is provided only early in life and then discontinued during adulthood?

To the surprise of Zoghbi and M.D./Ph.D. student Christopher McGraw, the paper's first author, the neurons need the protein throughout life.

"To continue the porridge analogy, taking it away puts you in the same position as someone who never had it," said McGraw.

To demonstrate this, they developed a mouse from which they could eliminate MeCP2 in adulthood.

"We found that they appeared just like the mice born without the protein," said McGraw. The mice developed the Rett-like behaviors, including the limb "clasping" behavior and impaired learning and memory. The mice also died prematurely, 13 weeks after the protein was deleted. Mice born lacking the protein die at about 13 weeks of age as well.

"What this suggests is that the function of this protein is always needed," said McGraw. "Having this protein up to adulthood does not result in the construction of a nervous system that is any more resilient to the loss of MeCP2 than one born without it."

"That was the most surprising to us," said Zoghbi. "The upside of this is if you can add the protein back, you can rescue the neurons, which is indeed what happened when the lab of Dr. Adrian Bird, researcher with the Wellcome Trust Center for Cell Biology, added the gene back in adults in past research," she said. "The new study shows there are no developmental abnormalities. It is all about needing the protein right there to tell the [neurons](#) what to do."

MeCP2 affects the epigenetic program of the cell, changing the expression levels of certain genes without changing the sequence of the DNA itself. Scientists are still trying to determine exactly what it does in the cell, and that may enable physicians to develop a treatment that patients would take throughout their lives.

"If we can figure a way to provide the functions of this protein we have a chance to treat these patients successfully and maintain their health," she said.

Just giving patients MeCP2 would not work because of the need to fine-tune the amount of protein in the cell.

She and colleagues are looking instead for drugs that can serve the same function as MeCP2 or that can alter the pathways through which this gene works.

Dr. Rodney C. Samaco of BCM also participated in this research.

More information: www.sciencemag.org/content/early/recent

Provided by Baylor College of Medicine

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