NEWS

Rett gene function extends beyond neurons, study finds

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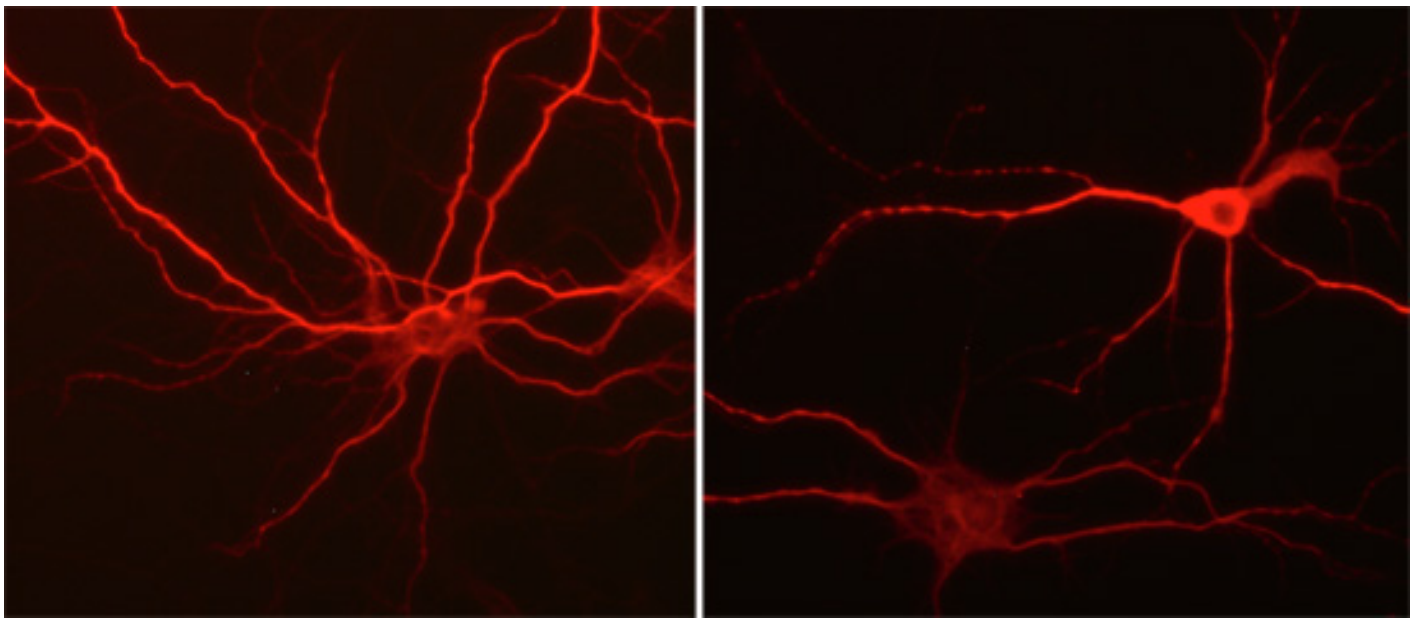

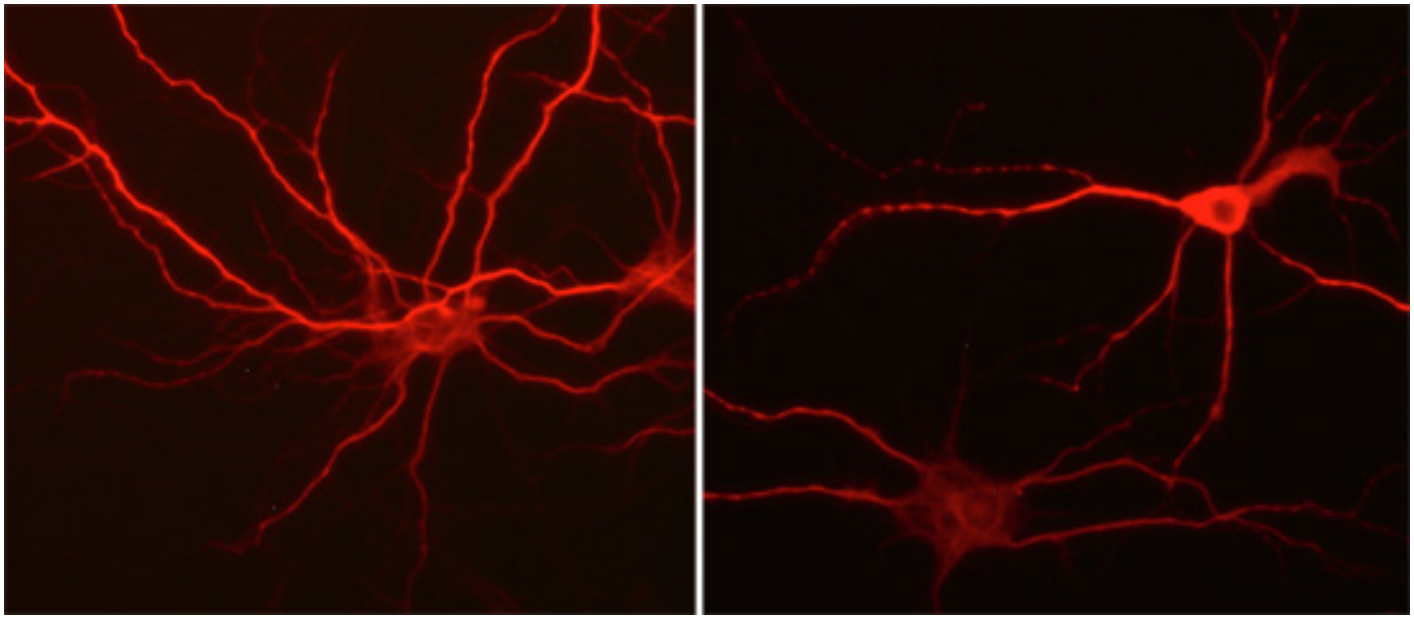

Stunted growth: Microglia lacking MeCP2 release five times more glutamate, resulting in fewer, shorter and thinner dendrites (right) compared with normal (left).

Microglia, brain cells that provide immune protection to neurons, may influence the onset and course of Rett syndrome, according to a study published in the *Journal of Neuroscience*[1].

Cultured microglia cells lacking MeCP2, the protein mutated in people with Rett syndrome, emit too much of the signaling chemical glutamate, disrupting the normal development of neurons, the study shows. Microglia are a subtype of glial cells, or glia, which make up about 90 percent of cells in the nervous system, and are required for the survival and maturation of neurons.

Only a handful of studies so far have implicated glia in Rett. Last year, for instance, two cell-culture studies implicated another type of glia called astrocytes — star-shaped cells that provide nutrients, physical support and chemical balance to the nervous system.

Although differences in experimental conditions make it difficult to directly compare results, it's at least becoming clear that in Rett syndrome, neurons are not the only players involved, researchers say.

"[The new study is the] third paper that has come out in a little over a year that goes against a prevailing wisdom that MeCP2 functions primarily in neurons," notes **Jeffrey Neul**, assistant professor of pediatrics and human and molecular genetics at Baylor College of Medicine, who was

not involved with the work. "Although I think this work is intriguing, we really need some *in vivo* evidence to get to the point of changing how we think."

Rett syndrome is a rare neurodevelopmental disorder caused by the mutated or missing MeCP2 protein. The disorder strikes girls almost exclusively, and causes a progressive deterioration of motor, social and intellectual skills. Children with Rett syndrome often show autism-like behaviors in the syndrome's early stages.

In the new study **Lee-Way Jin** and his team harvested microglia — cells that turn on and multiply in response to immune attacks — from both healthy mouse brains and those missing MeCP2.

The researchers transferred media in which the cells were grown, but not the cells themselves, to dishes containing healthy neurons. Neurons exposed to media from MeCP2-deficient microglia developed stunted dendrites, the slender neuronal branches that receive signals.

In healthy brains, microglia use the neurotransmitter glutamate to activate neurons and other microglia within local brain circuits. In some neurodegenerative disorders, microglia proliferate and release immune molecules that trigger the release of too much glutamate, impairing proper communication and, in effect, paralyzing the circuits.

In this case, compared with healthy cells, microglia lacking MeCP2 release five times more glutamate, the researchers found. When they blocked glutamate synthesis and release from the microglia using several different strategies, they found each time that they could prevent the abnormal growth of the neurons, says Jin, associate professor of pathology at the University of California, Davis.

However, although these microglia release too much glutamate, they don't show signs of immune activation, suggesting that a separate mechanism influences neuronal development in Rett syndrome, Jin says.

Altered growth:

There is already strong support for a distinct **role of neurons** in Rett syndrome. For example, mouse studies have shown that the loss of MeCP2 from neurons decreases the levels of some neurotransmitters, and results in fewer dendrites and Rett-like symptoms[2,3].

In March 2009, researchers at Oregon Health and Science University showed that **neurons cultured on a bed of astrocytes** taken from Rett mice also have fewer and shorter dendrites compared with those cultured on healthy astrocytes[4]. Adding healthy astrocytes to neurons that lack MeCP2 restores the growth of those dendrites.

The following month, Jin's group reported that, compared with neurons grown in the same dish as

healthy glia, those grown with MeCP2-deficient astrocytes have fewer and stunted dendritic branches[5].

Those studies suggest that glia in individuals with Rett syndrome interfere with neuronal growth by somehow altering the brain's chemical milieu.

In the new study, Jin's group showed that neurons cultured in media from Rett astrocytes, but not with the cells themselves, do not show signs of damage. Unlike microglia, Rett astrocytes may require physical contact with neurons to have a detrimental effect, Jin says.

"Our findings imply that astrocytes with MeCP2 missing are not actively producing toxic substance," Jin says. "Rather, they are like a malnourished mother who cannot provide the baby, neurons, with enough milk."

Another group, led by **Nurit Ballas** at Stony Brook University in New York, reached a similar conclusion using different methods. To parse the role of subtypes of glia in Rett syndrome, that group is creating mouse models that lack MeCP2 in each subset of glial cells.

Meanwhile, Jin's team is planning to assess the effects of blocking glutamate release from microglia in a mouse model of Rett syndrome.

"The channel that mediates the release of glutamate into the brain environment – that's unique to glial cells," Jin says. "We believe that it could be an ideal therapeutic target specific to microglia."

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