NEWS

Scientists find molecular player in Angelman syndrome

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Crowded membrane: In mice lacking UBE3A, neuron junctions collect too many ARC proteins, which eventually leads to impaired cell signaling.

Two independent teams have discovered key molecular steps in the way a single gene disrupts the connections between neurons in individuals with Angelman syndrome, a rare disorder characterized by developmental delays, speech impairment and movement problems.

Because the gene, UBE3A, has also been **linked to autism** and to fragile X syndrome, the findings could help scientists understand and treat a range of neurodevelopmental disorders, researchers say.

"We're prying open a signaling network that may turn out to be quite relevant to autism," says **Michael Greenberg**, lead investigator of one of the new studies.

Angelman syndrome stems from mutations in the maternal copy of UBE3A. The condition unfolds in early development, when the brain uses sensory information from the environment to alter the strength of synapses, the junctions between neurons. During this period, frequently-used synapses are strengthened and unused ones are destroyed, a process dubbed 'synaptic plasticity'.

Because UBE3A belongs to a large class of enzymes — ubiquitin ligases — that target proteins for destruction, researchers had speculated that it helps prune synapses.

But no one knew which proteins UBE3A targets at the synapse. In the first new study, published 5 March in *Cell*[1], Greenberg's team found that the enzyme regulates degradation of a synaptic protein called ARC.

ARC is known to control whether receptors of the neurotransmitter glutamate, called AMPA receptors, are located inside a cell or on the surface of its membrane[2]. AMPA receptors are needed for fast excitatory neurotransmission, and their expression on the cell surface is crucial to bind the excitatory neurotransmitter glutamate.

Greenberg proposes that in Angelman syndrome, mutations in UBE3A lead to an excess of ARC, which, in turn, lowers the number of these receptors on the cell surface. In effect, he says, UBE3A mutations cause learning problems by creating an imbalance of excitatory and inhibitory brain signals.

"This is one of the most — if not the most — informative papers about what UBE3A is actually doing that causes neurological dysfunction," says **Arthur Beaudet**, chair of molecular and human genetics at Baylor College of Medicine, who was not involved in the new work. Beaudet's team discovered in 1997 that UBE3A mutations cause Angelman syndrome[3].

The new findings raise the possibility that drugs that suppress ARC expression could help treat the syndrome, which affects roughly 20,000 people in the U.S. and has no known cure.

"Finding a potential therapeutic target for this severe brain disorder seemed unlikely before now," says Greenberg, chair of neurobiology at Harvard Medical School. "But finding ways to modify ARC levels in neurons seems a plausible idea to explore."

Target proteins:

ARC's pivotal role in synaptic plasticity is further clarified in a mouse study published online 14 March in *Nature Neuroscience*[4]. **Mriganka Sur** and colleagues demonstrated that mice lacking ARC are unable to adapt synaptic connections in the visual cortex to sensory experience.

The visual cortex is normally extremely sensitive to experiences or changes in activity. For example, closing one eye in a normal mouse results in a weakening of the synapses specific to that eye, which results from a decline in the number of AMPA receptors. At the same time, the open eye compensates by increasing its own synaptic strength.

The researchers found that mice lacking ARC are unable to shuttle AMPA receptors from the cell surface to the inside of the cell. "At some level, synaptic dysfunction is the result of the amount or

effectiveness of receptors and their ability to transmit impulses," says Sur, head of brain and cognitive science at Massachusetts Institute of Technology.

Together, these papers provide an unprecedented level of understanding about how UBE3A and ARC can wreak havoc in the brains of people with Angelman syndrome — and perhaps in individuals with autism.

"What is clear now is that both UBE3A and ARC regulate maturation of the neocortex, the brain region where language, motor commands and sensory perception are generated — which may allow us to dissect both the molecular mechanisms and the developmental circuitry involved in autism," says **Michael Ehlers**, professor of neurobiology at Duke University.

UBE3A lies in chromosomal region 15q11, which several autism studies have identified as a hotspot of mutations[5]. Last year, scientists found that individuals with autism also carry DNA **deletions and duplications in UBE3A**[6].

ARC has also previously been implicated in fragile X syndrome. In 2008, researchers showed that ARC expression is disrupted in neurons lacking the fragile X gene FMR1[7]. That study also found that mice lacking both ARC and FMR1 are unable to use experiences to properly mature their synapses.

Unfortunately, the UBE3A enzyme is notoriously difficult to study. The genes that encode ubiquitin ligases, including UBE3A, have numerous subunits, which can swap in and out of the gene and change the properties of the resulting enzyme complex. This makes it difficult for researchers to determine which synaptic proteins the ligase binds to and, ultimately, destroys.

Using a new method to screen UBE3A's potential targets, Greenberg's team found an amino acid sequence to which UBE3A selectively binds. Searching mammalian genomes for this sequence, the team unearthed several other potential target proteins, including ARC.

Subsequent experiments confirmed that the UBE3A enzyme targets ARC for destruction. The researchers also found higher levels of ARC in mice lacking UBE3A compared with controls. Taken together, the evidence suggests that ARC accumulates in the brains of animals that have faulty UBE3A.

Mechanistic breakthroughs:

Confirming that ARC and UBE3A are required to mature synapses through experience represents a breakthrough in the autism field, Ehlers adds. "We are entering a golden era of mechanism-based studies of autism genes," he says.

Last May, for example, Ehlers and colleagues demonstrated that the large scale remodeling of the

visual cortex does not happen in **transgenic mice lacking UBE3A**[8].

In early March, **Michael Stryker** and colleagues at the University of California, San Francisco, discovered that mice lacking the maternally expressed UBE3A gene, which is mutated in Angelman syndrome, are unable to shape synapses based on experience[9].

Greenberg's work details a molecular mechanism that makes sense of all these disparate pieces of data. "Big pieces of this puzzle are falling into place," Ehlers says.

Still, researchers have much to uncover before they can begin to design therapies. For example, several genes associated with autism, such as neurexins and neuroligins, encode synaptic proteins that have no known interaction with UBE3A. Greenberg's lab is tracking the function of other UBE3A targets, but the work is unpublished.

"A major focus of our lab is to think more generally beyond UBE3A to determine how other genes are involved in controlling how experiences help synapses develop," he says.

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