Novel target for Angelman Syndrome and Autism Spectrum Disorders

Published date: Feb. 1, 2012

Technology description

Summary

MARKETS ADDRESSED:
Angelman syndrome (AS) and Autistic spectrum disorders (ASD): Although it has been known for more than a decade that mutation of Ube3A results in AS, remarkably little is understood about the role of Ube3A in the cognitive impairment underlying AS. This lack of insight has hampered the development of therapeutic strategies for treating AS, and as a result there are currently no effective treatments for this disorder.
This research pinpoints potential therapeutic targets for the development of therapies to treat diseases associated with mutations in Ube3A including AS and ASD. The Greenberg lab demonstrated that disruption of Ube3A activity leads to an increase of Arc and decrease in AMPAR expression at synapses. Drugs that promote AMPAR expression at synapses, such as metabotropic glutamate receptor subtype 5 (mGluR5) antagonists or compounds that inhibit the expression or function or Arc, may reverse symptoms associated with AS and ASD.
Fragile X is a human disorder in which a similar decrease in AMPAR expression at synapses has been demonstrated. This decrease has further been shown to be a result of excessive mGluR5 signaling, resulting in increased Arc translation and excessive AMPAR internalization. Selective mGluR5 antagonists are now entering clinical trials for the treatment of Fragile X, indicating that this type of therapeutic strategy has potential. Angleman Syndrome (AS) is a neuro-genetic disorder characterized by intellectual and developmental delay as well as sleep disturbance, seizure and trembling movements. This debilitating neurological disorder is caused by mutation of the E3 ubiquitin ligase (Ube3A), a gene whose mutation has also recently been associated with autism spectrum disorders (ASD). However, the function of Ube3A in mediating cognitive impairment in individuals with AS and ASDs, as well as its substrates, have been unknown.
To better understand the role of Ube3A in AS and ASD, the Greenberg lab identified a key neural substrate of Ube3A and a mechanism for its regulation of synaptic transmission by conducting the following experiments:
Neural activity induces Ube3A transcription. In the absence of synaptic activation, Ube3A is expressed at low levels. Ube3A transcription is induced upon glutamate release at excitatory synapses.

Ube3A controls synaptic function. The lab showed that reduction of Ube3A expression decreases the plasma membrane expression of AMPA glutamate receptors (AMPAR), due to an increase in AMPAR endocytosis. This also leads to a decrease in synaptic transmission through AMPARs.
Arc is a substrate of Ube3A. The Greenberg lab searched mammalian genomes for proteins that contain a Ube3A binding domain. Their search identified Arc, a protein known to rapidly increase upon glutamate release at excitatory synapses, which regulates the trafficking and expression of AMPARs at synapses. Arc-mediated endocytosis of AMPARs is known to dampen neuronal excitability, and in turn, limit the level of neuronal excitation. The role of Ube3A may therefore be to bind to and regulate Arc-mediated endocytosis to maintain proper synaptic activation.
Ube3A controls synaptic function by ubiquitinating and degrading Arc. They showed that Ube3A controls the level of Arc protein expression by ubiquitinating and thus targeting Arc for degradation. In this way, Ube3A reduces the Arc-mediated internalization of AMPARs.
Ube3A's role in cognitive dysfunction. Finally, the lab demonstrated that mice deficient in Ube3A have elevated levels of Arc in neurons, resulting in excessive internalization of AMPARs at synapses and impaired synaptic transmission. The disregulation of AMPAR expression may contribute to the cognitive dysfunction in AS and possibly other autism spectrum disorders.

Institution

Harvard University

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com