NEWS

Molecular mechanisms: Autism mutants cause cell stress

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19 JULY 2011

Binding glue: Mutations in proteins that stabilize neurons at their junctions are associated with autism.

Some autism-associated mutations activate a stress response that could lead to symptoms of the disorder, according to a study published 3 June in *Cell Death and Disease*[1].

In particular, two proteins, neuroligin 3 (**NLGN3**) and the synaptic cell adhesion molecule 1 (**CADM1**) have autism-associated mutations that cause them to misfold and accumulate in neurons. Both proteins are involved in organizing and strengthening connections between neurons.

These and several other proteins that function at synapses, the junctions between neurons, have been **implicated in autism**.

Mouse models of NLGN3 suggest that an autism-associated mutation in the gene, called R451C, enhances **inhibitory signals** in the brain, but loss of the gene does not. This suggests that mutants in synaptic proteins could have gain-of-function effects, meaning that they may activate a process that could be harmful to the cell.

In the new study, researchers investigated this theory by looking at two autism-associated

mutations in CADM1 — H246N and Y251S, as well as the R451C mutation in NLGN3.

The two mutations in CADMI result in amino acid changes that are likely to disrupt protein folding, the study found. Expressing the mutant proteins in neurons leads to an accumulation of CADM1 in the endoplasmic reticulum, a transitional processing center of the cell.

When there is a protein backlog in this organelle, the cell activates a stress response. This leads to the expression of several proteins, including C/EBP-homologous protein, or CHOP, which also regulates connections between neurons at the synapse.

Expressing either of the two CADM1 mutations or the R451C mutation of NLGN3 in neurons leads to elevated CHOP expression, the study found.

Elevated CHOP can lower the levels of gamma-aminobutyric acid (GABA) receptors — proteins expressed on the surface of neurons that inhibit signals in the brain. Mutations in GABA receptors and the chemical message to which they bind have been associated with both autism and the related **Rett syndrome**.

References:

1. Jujita E. *et al. Cell Death Dis.* **1**, e47 (2011) **PubMed**