NEWS

Molecular mechanisms: Rett gene boosts protein production

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3 DECEMBER 2013

Small cell: Neurons lacking MeCP2 (bottom), the Rett syndrome gene, are smaller and have fewer branches than controls (top).

The protein mutated in Rett syndrome, **MeCP2**, is normally responsible for boosting the expression of a large number of genes. This finding, published 3 October in *Cell Stem Cell*, may explain why growth factors that promote protein production are able to reverse features of the syndrome in mice[1].

Most cases of Rett syndrome, a rare autism-related disorder, result from one of several mutations in MeCP2. The protein is **thought to be a master regulator** of genes, turning them on or off by **changing DNA structure**.

The new work refined the study of MeCP2's function by making use of TALEN, a **genome-editing tool**. The researchers deleted a portion of the MeCP2 gene in human embryonic stem cells, which they nurtured into forming neurons.

This version of MeCP2 lacks the region that normally binds to DNA, and resembles the mutated protein seen in people with Rett syndrome. Stem cells with this mutation develop into neurons that are smaller and have fewer projections than those from controls.

The neurons also have less RNA — the genetic message that codes for protein — and low levels of

ribosomal RNA, which makes up the machinery that manufactures proteins. In line with this finding, about 60 percent of the genes in these mutant neurons are expressed at significantly lower levels than in controls.

What's more, genes that are normally extremely active are disproportionately represented in the 60 percent. This suggests that MeCP2 usually acts as a general activator of gene expression, the researchers say.

The mutant neurons produce fewer proteins, including those that function in the **mTOR pathway**. Signaling through this pathway regulates cell growth. **BDNF** and **IGF1**, members of this pathway, have been shown to **ameliorate the symptoms** of Rett syndrome in model mice.

BDNF and IGF1 also restore normal protein production and neuron shape to the mutant neurons, the study found.

The researchers also found low levels of the RNA that codes for proteins in the mitochondria — the energy-producing centers of the cell — in the mutant neurons. The mitochondria themselves are also less active than they are in controls. Studies have **linked mitochondrial dysfunction to autism**.

However, another study, published 20 October in *Human Molecular Genetics*, found higher levels of mitochondrial RNA in neurons made from stem cells with mutant MeCP2 than in controls[2].

References:

1: Li Y. *et al. Cell Stem Cell* **13**, 446-458 (2013) **PubMed**

2: Tanaka Y. *et al. Hum. Mol. Genet.* Epub ahead of print (2013) **PubMed**