

## Breaking News on Drug Discovery

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# Protein molecule isolated as neurodegenerative drug target

**23/02/2006- Researchers have isolated a protein molecule that may hold the key to learning and memory disorders that have been linked with autism. By isolating this potential drug target, new therapies for diseases in which synapses either fail or proliferate out of control could be produced.**

The master protein shed more light as to the molecular pathway it guides and additionally could help investigators understand the process of learning and memory. More importantly, a host of effective treatments, which are based on these findings, could be a real possibility

Independent research teams from Harvard Medical School and Children's Hospital Boston identified a protein that works in the nucleus of neurons that either pares down or promotes synapses depending on whether or not the neuron is being activated.

The protein, myocyte enhancer factor 2 (MEF2), turns on and off genes that control dendritic remodeling. In addition, one of the teams has identified how MEF2 switches from one program to the other, that is, from dendrite-promoting to dendrite-pruning, and the researchers have identified some of MEF2's targets.

*"Changes in the morphology of synapses could turn out to be very important in a whole host of diseases including neurodegenerative as well as psychiatric disorders,"* said Azad Bonni, HMS associate professor of Pathology who, with colleagues, authored one of the papers.

The protein works by either activating or actively repressing target genes. In working on a group of neurons in the developing rat cerebellum, the researchers found the MEF2 repressor promoted synaptic differentiation.

In a separate study, scientists have found the MEF2 activator inhibited the growth of dendritic spines in the rat hippocampus, an area of the brain associated with memory and learning. Flavell, and also the Bonni team, found the activated, or dendrite whittling, form of MEF2 comes on in response to increased neuronal activity.

That MEF2 activation leads to the inhibition of synapse formation, makes sense in light of what is known about the nervous system.

In memory and learning, as well as development, activity leads to a sculpting, or cutting away, of synapses. What may be more surprising is the way activity causes MEF2 to switch from repressor to activator.

What Bonni and his colleagues found is that molecules modify a particular spot on MEF2, and transform it into a repressor. By removing the modification, known as sumoylation, MEF2 becomes an activator.

Taken together, the findings of the two groups might appear puzzling for they seem to say that MEF2 promotes synapse formation by repressing genes and suppresses synapse formation by activating genes. The puzzle resolves itself when one considers the possibility that the genes being turned on and off act to discourage synapse formation.

In fact, Flavell and his colleagues have identified two of MEF2's targets, arc and SynGAP. The arc

protein appears to play a role in internalising glutamate receptors, which occurs when dendrites are being disassembled.

SynGAP works to turn off the synapse-promoting ras gene. Bonni and his colleagues have identified yet a third target, Nur77. There are bound to be others.

The identification of these targets, and more generally the opening up of the MEF2 pathway, could lead to new therapies for a host of diseases in which synapses either fail to form or run rampant.

Michael Greenberg, HMS Professor of Neurology at Children's Hospital Boston, who led the second team, is currently a member of a consortium that is trying to get at the molecular underpinnings of autism. *"We think the MEF2 pathway may be central,"* he said.

The research appears in two papers in the latest issue of [Science](#) (Feb 17).

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