# Researchers link gene to increased dendritic spines – a signpost of autism

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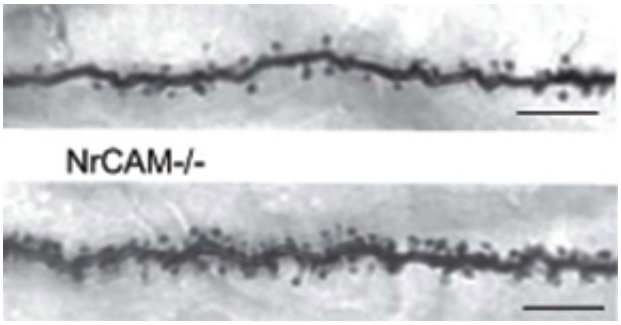


A comparison of a dendrite with the protein NrCAM (top) and a dendrite without the protein (bottom), which has a greater density of spines that neurons use to form synaptic connections.

(Medical Xpress)—Scientists at the UNC School of Medicine have discovered that knocking out the gene NrCAM leads to an increase of dendritic spines on excitatory pyramidal cells in the brains of mammals. Other studies have confirmed that the overabundance of dendritic spines on this type of brain cell allows for too many synaptic connections to form between neurons – a phenomenon strongly linked to autism.

The finding, published in The *Journal of Neuroscience*, adds evidence that NrCAM is a major player in neurological disorders. Previous UNC studies showed that knocking out the NrCAM gene caused mice to exhibit the same sorts of social behaviors associated with autism in humans.

"There are many genes involved in autism, but we're now finding out exactly which ones and how they're involved," said Patricia Maness, PhD, professor of biochemistry and biophysics and senior author of the *Journal of Neuroscience* paper. "Knowing that NrCAM has this effect on dendrites allows us to test potential drugs, not only to observe a change in behaviors linked to autism but to see if we can improve dendritic spine abnormalities, which may underlie autism.

Maness's finding comes on the heels of a report from Columbia University researchers who found an overabundance of the protein MTOR in mice bred to develop a rare form of autism. By using a drug to limit MTOR in mice, the Columbia researchers were able to decrease the number of dendritic spines and thus prune the overabundance of synaptic connections during adolescence. As a result, the social behaviors associated with autism were decreased. However, the drug used to limit MTOR can cause serious side effects, and it is located inside cells, making it a potentially difficult protein to target.

It is too early to tell if NrCAM and MTOR are linked, but Maness is now studying if the decreased amount of the NrCAM protein could trigger activation of MTOR. If so, then NrCAM, which is an accessible membrane-bound protein, might be a preferred therapeutic target for certain autism-related conditions.

In their study, Maness and her colleagues found that the NrCAM protein forms a complex with two other molecules to create a receptor on the membrane of excitatory pyramidal neurons. Maness's team found that this receptor allows dendritic spines to retract, allowing for proper neuron pruning during maturation of the cortex. As a result, excitatory and inhibitory synapses between neurons develop in a balanced ratio necessary for brain circuits to function properly.

Maness, a member of the UNC Neuroscience Center and the Carolina

Institute for Developmental Disabilities, also said that there are likely many other proteins downstream of NrCAM that depend on the protein to maintain the proper amount of dendritic spines. Decreasing NrCAM could allow for an increase in the levels of some of these proteins, thus kick starting the creation of dendritic spines.

"Basic science in autism is converging in really exciting ways," Maness said. "Too many spines and too many excitatory connections that are not pruned between early childhood and adolescence could be one of the chief problems underlying autism. Our goal is to understand the molecular mechanisms involved in pruning and find promising targets for therapeutic agents."

Provided by University of North Carolina at Chapel Hill School of Medicine