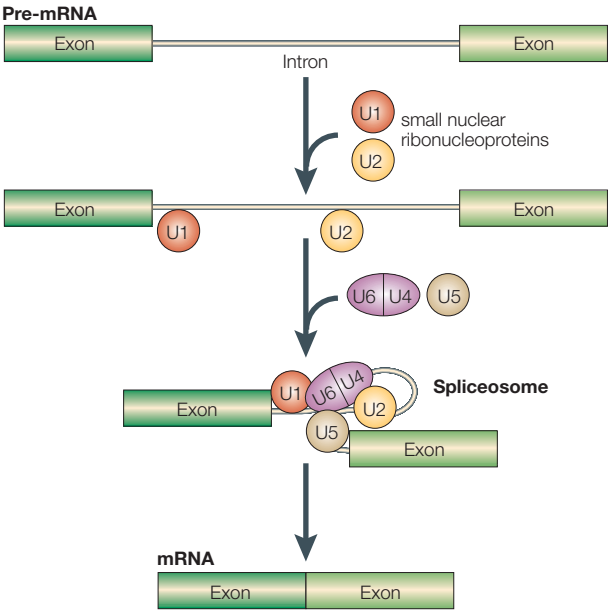
CELL BIOLOGY OF THE NEURON

Splicing up the synapse



There is evidence that splicing — the excision of introns and the joining of exons to form a mature messenger RNA — is important for neuronal physiology, but we know very little about the details of its involvement. Most of our insights come from the study of neurological diseases such as spinal muscular atrophy and, in particular, the so-called paraneoplastic neurological disorders in which aberrant splicing of glycine receptors seems to occur. Now, a (recent) paper in *Current Biology* sheds new light on the relevance of splicing for synaptic transmission, reporting on the characterization of two new splicing-related proteins in *Caenorhabditis elegans*.

Searching for mutant worms with morphological abnormalities in a specific motor neuron, Loria *et al.* identified UNC-75, a protein with three RNA-recognition motifs that belongs to a group of molecules that have been implicated in splicing in other species. Importantly, the authors found that mutations in *unc-75* did not affect neuronal development, but specifically altered the function of cholinergic neurons in a way that resembled what has been found for mutations in synaptic-vesicle proteins.

Although the authors did not find direct evidence for the involvement of UNC-75 in splicing, they found that the protein localized to nuclear speckles, and that this localization was crucial for restoring its function when expressed in a mutant background. Moreover, they found that a human orthologue of UNC-75, which has been shown to participate in splicing *in vitro*, could rescue the abnormal phenotype of the mutant worm.

Loria *et al.* also wondered whether other *C. elegans* proteins with a domain structure similar to that of UNC-75 might also share its functional properties and might even rescue the phenotypic defects of the mutant worms. They found that EXC-7 — the *C. elegans* homologue of the protein Elav, a molecule that is

NEURODEGENERATIVE DISEASES

The C terminus: AD's missing link?

Apolipoprotein E4 (apoE4) is a component of both the amyloid-β (Aβ) plaques and tangles of hyperphosphorylated tau that characterize Alzheimer's disease (AD). The mechanisms by which apoE4, Aβ and tau confer pathogenicity remain to be determined, as does the nature of the interactions between the three proteins. Two new studies in the *Proceedings of the National Academy of Sciences* implicate truncated fragments of apoE4 and tau in AD-like neurodegeneration.

Yadong Huang's group showed previously that the 299-amino-acid apoE can be cleaved *in vitro* by a serine protease to produce carboxy (C)-terminal fragments that interact with tau to form intracellular inclusions. To determine whether the same mechanism operates *in vivo*, the team generated transgenic mice expressing the C-terminal fragment of apoE4(Δ272–299).

Mice that expressed the fragment at high levels died between two and four months of age. Immunolocalization studies revealed that the fragment — which contains the lipid-binding region — was expressed in neurons of the neocortex, cerebellum and spinal cord, as well as in the hippocampus, where degeneration of apoE4(Δ272–299)-positive neurons was evident. Accumulation of excessive amounts of aberrantly phosphorylated tau was a feature of the high-expressers, as was the development of neuronal inclusions containing the apoE4 fragment.

Work by Vincent Cryns and colleagues indicates that proteolytic cleavage of tau might also contribute to AD pathogenesis. Neurofibrillary tangles in AD-affected brain often contain tau that is truncated at its C terminus. On the basis of this data, and the fact that caspases are activated in apoptotic neurons in AD, the authors tested the capacity of this family of cysteine proteases for tau cleavage *in vitro*.

Wild-type tau was cleaved by several caspases at a highly conserved aspartate residue — Asp421 — in its C terminus. The truncated product, which lacks its 20 C-terminal amino acids, assembled more rapidly and extensively into the tau filaments that have the potential to form neurofibrillary tangles. As tangle formation is known to be enhanced by Aβ, the team postulated that caspases might have a role in this process. In rat primary cortical neurons incubated with Aβ, truncated tau was detected after just two hours and cleavage was completely prevented by pretreatment with a caspase inhibitor. It seems that the C terminus is a crucial regulatory domain that is worthy of further experimental attention.

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References and links

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FURTHER READING Herz, J. & Beffert, U. Apolipoprotein E receptors: linking brain development and Alzheimer's disease. *Nature Rev. Neurosci.* **1**, 51–58 (2000)