Mechanisms of neuronal degeneration in ALS

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Neurodegenerative diseases are characterized by the selective loss of specific classes of neurons at relatively late age. Disease-linked genes however are most often expressed ubiquitously from early development onwards. To begin to understand this enigma in the context of motor neuron diseases such as ALS and SMA we have adopted several approaches.
1) We have discovered a motor-neuron specific cell death pathway that is triggered by activation of the Fas receptor or addition of nitric oxide (NO). Embryonic motor neurons purified from transgenic mutant SOD1 mice show greatly increased sensitivity to this cell death pathway. Strikingly, NO up-regulates the endogenous Fas ligand FasL thereby activating Daxx, p38 kinase and neuronal NO synthase. This Fas/NO/FasL feedback loop might contribute to *in vivo* pathology since presymptomatic mutant $SOD1^{G93A}$ transgenic mice display a twofold increase in the number of FasL-positive lumbar motor neurons as compared to wild-type mice.
2) We have shown that motor neuron degeneration in the *pmn* mouse model is caused by an autosomal-recessive mutation in the tubulin-specific chaperone gene Tbce. Tbce is normally expressed in numerous tissues and cell types. The *pmn* mutation decreases Tbce protein stability leading to reduced a- and b-tubulin levels and a progressive loss of microtubules in peripheral nerves. Microtubule loss is most pronounced in distal motor axons, intermediate at proximal levels and absent in ventral roots. Current studies explore the specific role of Tbce for maintenance and function of motor axons.

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