Axonal RNA Transport: Roles in Motoneuron Function and Degeneration

Michael Sendtner, Institut für Klin. Neurobiologie, Universität Würzburg, Versbacher Str. 5, 97078 Würzburg, Germany

Human motoneuron diseases are characterized by loss of motor endplates, axonal degeneration and cell death of motoneurons. The identification of responsible gene defects for familial ALS, spinal muscular atrophy (SMA) and spinal muscular atrophy with respiratory distress (SMARD) has pointed to distinct pathophysiological mechanisms responsible for the various forms of the disease. Evidence from mouse models suggests that enhanced vulnerability and sensitivity to proapoptotic stimuli is only responsible for some but not all forms of motoneuron disease (1-3). Reduced levels of the survival motor neuron (SMN) protein, which are responsible for SMA lead to disturbed RNA processing in motoneurons. A prominent phenotype of SMN deficient motoneurons is reduced axon elongation in the absence of defects that result in reduced motoneuron survival (4). In particular, the axonal transport of the mRNA for β-actin is severely reduced. The SMN protein is part of a complex in the cell body that assembles U snRNP particles. These U snRNP particles are central constituents of the spliceosome. In addition, the SMN protein is part of another complex in axons and axon terminals of motoneurons. This complex is distinct from the classical SMN complex, and it includes mRNA transport proteins, in particular the hnRNP-R protein (5). The hnRNP-R protein binds directly to β-actin mRNA, and both cell culture experiments in which hnRNP-R expression is reduced and in vivo studies point to an essential role of SMN/hnRNP-R interaction for axonal translocation of β-actin mRNA.

The consequence is a severe depletion of β-actin-protein in axon terminals, resulting in disturbed axon elongation, reduced growth cone size and functional deficits in neurotransmission that are caused by disturbed integration and clustering of voltage-gated calcium channels in axon terminals (6). The deficit in clustering of voltage-gated calcium channel in growth cones of SMN-deficient motoneurons is accompanied by a significant reduction of spontaneous Ca^{2+} transient frequency. Current research in our lab focuses on the development of imaging techniques to visualize local translation of mRNAs in axon terminals of cultured motoneurons, and to develop techniques that allow biochemical analysis and characterization of mRNA transport complexes in isolated motoneurons. In addition, new mouse models are generated that allow analysis of axon abnormalities and disturbed synaptic function at the neuromuscular endplate in vivo by multiphoton microscopy.

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