Intracellular Vesicle is Critical for Motor Neuron Degeneration

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The wobbler mouse is an intensively investigated animal-model for human motor neuron diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). In the course of positional cloning of the *wobbler* mutation we identified a pointmutation in *Vps54* gene. A transgenic rescue experiment proved *Vps54* to be the *wobbler* gene and thus, critical for motor neuron degeneration (1). The *Vps54* gene encodes a highly conserved vesicle traffic factor. Vps54 protein is a component of the “GARP” (Golgi-associated retrograde Protein) complex, a vesicle tethering factor involved in the retrograde vesicle transport from early and late endosomes to the trans Golgi network. In wobbler mice a single amino acid exchange in the c-terminus of Vps54 leads, besides the signs of neurodegeneration, to enlarged endosomal structures in the degenerating motor neurons, while the null-mutation of Vps54 leads to embryonal lethality around day 11 of the embryonic development. In cells derived from wobbler- and Vps54 knock out embryos we observed a functional impairment of the retrograde vesicle traffic. Furthermore, we observed accumulations of intermediate filaments such as neurofilament and vimentin in wobbler motor neurons, which do not co-localize, but might be caused by the vesicle traffic impairment or might contribute to the transport defects.

(1) Schmitt-John et al., (2005) Nature Genetics, 37, 1213-1215.