

## **Disruption of Molecular Motors as a Primary Cause of Motor Neuron Degeneration in Amyotrophic Lateral Sclerosis**

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects 1 in 1000 people in the United States and is characterized by a progressive loss of motor neurons<sup>1</sup>. The median age of onset is 55 and only 10% of patients survive ten years after symptom onset. There is currently one FDA-approved drug for the treatment of ALS; however, the drug only extends life expectancy by two to three months<sup>2</sup>. Approximately 20% of cases of familial ALS (fALS) are linked to mutations in the ubiquitous enzyme Cu<sup>2+</sup>/Zn<sup>2+</sup> superoxide dismutase (SOD1)<sup>1</sup>. Interestingly, the neurotoxicity of these mutations is not due to a loss of function of the enzyme, but rather to a poorly understood toxic gain of function. SOD1 aggregates are found in the spinal cords of ALS patients and SOD1 transgenic mice with an ALS-like phenotype<sup>3</sup>, but the mechanisms behind aggregate formation and toxicity are not yet known. Many groups have focused on SOD1 as a potential drug target, but the question arises, *if SOD1 is expressed in all cells, why do SOD1 mutations only perturb motor neurons?* Evidence suggests that the unique shape of motor neurons renders them susceptible to SOD1 toxicity<sup>3-7</sup>. The long processes of motor neurons present unique challenges for intracellular transport machinery, leading to the hypothesis: **Disruption of axonal transport is the primary cause of motor neuron degeneration in ALS.**

There is an emerging trend in the field to investigate the components of axonal transport in ALS models, both *in vitro* and *in vivo*. Tateno et al. examined the interaction of misfolded SOD1 with kinesin-associated protein 3 (KAP3) and its impact on the anterograde transport of choline acetyl transferase (ChAT)<sup>5</sup>. They developed a novel *in vitro* model of fALS using NG108-15 cells expressing mutant SOD1. This cell model allowed the authors to study acetylcholine (ACh) release at the nerve terminal. The presence of mutant SOD1 appeared to significantly decrease the amount of ACh released<sup>5</sup>. In other studies, the Hayward group found dynein in SOD1 containing high molecular weight (HMW) complexes<sup>6</sup>. They suggested that a decrease in dynein function leads to a decrease in retrograde transport of important neurotrophic factors to the cell body<sup>3,6</sup>. Consistent with this idea, these investigators showed that overexpression of dynein subunit p50, which causes a transport defect in wild type cells, increases viability of cells expressing mutant SOD1<sup>6</sup>. Finally, Perlson et al. investigated changes in retrograde signaling mediated by the dynein complex<sup>7</sup>. Retrograde transport of several survival promoting molecules, such as NGF, BDNF and Erk5, was found to be significantly decreased in a fALS cell model. In addition, transport of several stress/death promoting factors, such as JNK and activated caspase-8, was greatly increased. These transport alterations may promote the rapid neurodegeneration seen in ALS, but inhibition of stress signaling can increase cell survival<sup>7</sup>.

Together, these data point to regulation of axonal transport as an important drug target for the treatment of ALS. Further studies on reversing transport defects observed in ALS may lead to the discovery of more effective ALS treatments.

## References

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