MOTOR NEURON DISEASE

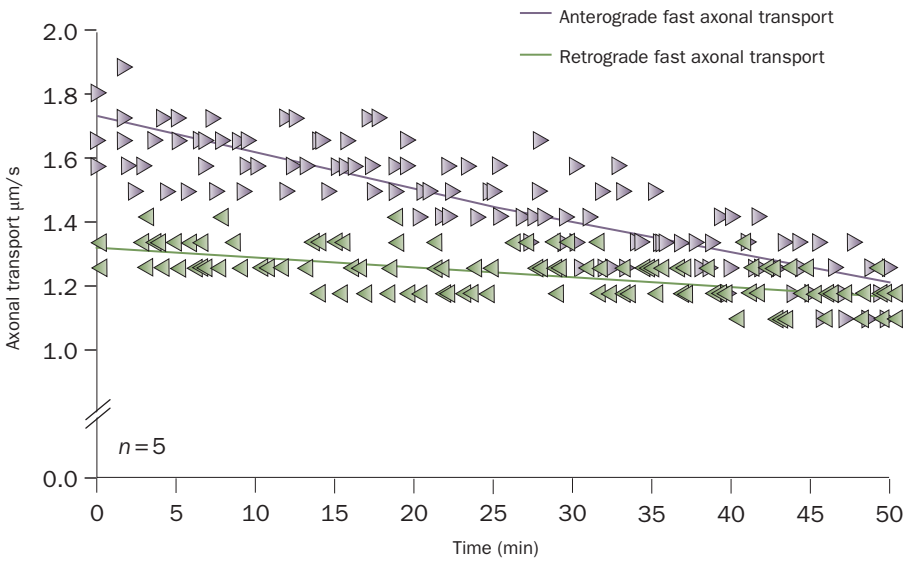
Misfolded wild-type SOD1 may link sporadic and familial ALS

Wild-type copper–zinc superoxide dismutase (SOD1) may cause sporadic amyotrophic lateral sclerosis (ALS) via a conformation and mechanism shared with mutant SOD1—a pathogenic factor in familial ALS—according to newly published research. "The results from our study implicate a misfolded but soluble form of wild-type SOD1 as the toxic species," explains lead author Daryl Bosco.

Mutations in *SOD1*, which underlie ≈20% of familial ALS cases, are believed to induce a conformational change in SOD1 that, in turn, results in a toxic gain of function. In contrast to its involvement in familial ALS, a toxic role for SOD1 in sporadic cases of this disease has remained unclear.

Through a series of *in vitro* experiments, Bosco *et al.* showed that oxidized wild-type SOD1 shared a conformational epitope with a familial ALS-linked form of mutant SOD1. Subsequent vesicle motility assays in squid axoplasm revealed that oxidized SOD1 and another familial ALS-linked SOD1 variant inhibited anterograde fast axonal transport.

The monoclonal antibody (C4F6) employed to detect the conformational epitope *in vitro* was used to analyze spinal cord sections from sporadic ALS cases, with sections from four of the nine cases examined, but no controls, showing C4F6 immunoreactivity.



SOD1 purified from sporadic amyotrophic lateral sclerosis spinal cord sections inhibited anterograde but not retrograde fast axonal transport in isolated squid axoplasm. Permission obtained from Nature Publishing Group © Bosco, D. A. *et al. Nat. Neurosci.* **13**, 1396–1403 (2010).

To determine whether the SOD1 species detected in spinal cord sections affected axonal transport, the researchers purified SOD1 from these preparations and, as before, conducted vesicle motility assays. In agreement with their earlier results, the purified protein from sporadic ALS tissue inhibited anterograde fast axonal transport.

According to the researchers, the study's results indicate that wild-type SOD1 represents a common link between familial and sporadic ALS. "Our immediate goal is to characterize the biochemical nature of the C4F6-positive SOD1 species that are present in sporadic ALS patient samples," says Bosco. "We hope that the immunotherapeutic and RNA-silencing approaches that are currently being developed to target mutant SOD1 ... may potentially be extended to sporadic ALS patients with misfolded wild-type SOD1."

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Original article Bosco, D. A. *et al.* Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS. *Nat. Neurosci.* **13**, 1396–1403 (2010)