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NEURODEGENERATIVE DISORDERS

Astrocytes turn nasty

Glia have primarily been considered to provide protection and support for neurons. However, two studies in *Nature Neuroscience* suggest that this is not always the case: astrocytes that express a mutated form of the antioxidant enzyme superoxide dismutase 1 (*SOD1*), found in a subset of patients with familial amyotrophic lateral sclerosis (ALS), selectively induce motor neuron death.

ALS is a late-onset, progressive and fatal motor neuron disease. Previous work on familial ALS implicated both cell-autonomous and non-cell-autonomous effects of mutant *SOD1* in motor neuron

death, but the mechanism(s) of *SOD1*-induced toxicity was poorly understood. Eggan and colleagues set out to establish an *in vitro* model system to investigate this. They co-cultured embryonic stem cell (ESC)-derived motor neurons and glia from mice expressing mutant or wild-type *Sod1*. As expected, the survival of motor neurons expressing mutant *Sod1* was lower than that of neurons differentiated from wild-type mice, indicating that mutant *SOD1* increases the vulnerability of motor neurons to neurodegeneration. However, the survival of mutant motor neurons was further reduced when they were co-cultured with glia that also expressed mutant *Sod1*. Furthermore, mutant glia were able to dramatically reduce the survival of wild-type motor neurons, suggesting that a non-cell-autonomous effect of mutant *SOD1* might contribute to the pathology of ALS.

These results were supported by a separate study in which Przedborski and colleagues examined the effects of astrocytes, the most abundant type of glia, expressing mutated *Sod1*, on primary and ESC-derived motor neurons. Conditioned media derived from the mutated astrocytes triggered motor neuron death through

a BAX-dependent pathway, suggesting that as yet unidentified soluble factors secreted from these glial cells are sufficient to trigger apoptosis. The authors also showed that this finding is specific for motor neurons and astrocytes; astrocytes carrying *SOD1* mutations did not damage other neuronal cell types, and motor neurons were immune to other mutant *Sod1*-expressing cell types.

Despite the fact that only a small proportion of ALS sufferers carry *SOD1* gene mutations, it is feasible that other events or mutations could trigger the release of these toxic factors from astrocytes and cause motor neuron death. Identifying these factors will therefore be key to the development of new therapeutic strategies for ALS and, potentially, other motor neuron diseases.

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ORIGINAL RESEARCH PAPERS Di Giorgio, F. P., Carrasco, M. A., Siao, M. C., Maniatis, T. & Eggan, K. Non-cell autonomous effect of glia on motor neurons in an embryonic stem-cell based ALS model. *Nature Neurosci.* **10**, 608–615 (2007) | Nagai, M. et al. Astrocytes expressing ALS-linked mutated *SOD* release factors selectively toxic to motor neurons. *Nature Neurosci.* **10**, 615–623 (2007)

FURTHER READING Pasinelli, P. & Brown, R. H. Molecular biology of amyotrophic lateral sclerosis: insights from genetics. *Nature Rev. Neurosci.* **7**, 710–723 (2006)