Research Abstract

Amyotrophic lateral sclerosis (ALS) is the most frequent form of adult-onset paralytic disorder. Mutations in superoxide dismutase-1 (mSOD1) cause familial ALS, and mSOD1 transgenic rodents capture the hallmarks of this fatal disease, which is characterized by the progressive loss of motor neurons (MNs). Studies in chimeric and conditional mSOD1 mice indicate that non-neuronal cells play an important role in spinal MN degeneration. Consistent with this non-cell-autonomous scenario are our demonstrations that wild-type primary and embryonic stem cell-derived MN (ES-MNs) selectively degenerate when cultured in the presence of mSOD1-expressing astrocytes (Nagai et al., Nat. Neurosci. 2007). We further found that the observed increased death of spinal MNs, in the presence of mSOD1-expressing astrocytes, is related to a toxic activity caused by a soluble factor(s). Worth noting, is the fact that we have preliminary data showing that primary human astrocytes from sporadic ALS patients also selectively kill spinal MNs. Through a combination of candidate-based approaches and unbiased/bioinformatic methodologies, we are searching for the toxic factor(s) present in the medium conditioned with mSOD1 expressing-astrocytes and for the MN molecular death cascade induced by mSOD1 expressing-astrocytes. Furthermore, we have miniaturized our ALS cell-based assay to screen for neuroprotective small molecules using high-throughput screens. The above findings argue for the involvement of non-cell autonomous mechanisms in ALS and that such processes may have to be fully characterized to acquire a better understanding of the neurobiology of this dreadful disease and how to treat it effectively.

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