New therapeutic strategies for motoneuron diseases

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Amyotrophic lateral sclerosis (ALS), the most common form of motoneuron diseases, is a neurodegenerative disorder characterized by progressive weakness and paralysis with fatal evolution within 3-5 years from the diagnosis, since there are no effective treatments to alleviate its course. It is caused by progressive, selective degeneration of motoneurons in motor cortex, brainstem and spinal cord. Several pathological mechanisms have been identified as contributing to the disease, including excitotoxicity, mitochondrial dysfunction, oxidative stress, altered axonal transport, proteasome dysfunction, synaptic deficits, and glial cell contributions. Therefore, it is unlikely that therapies targeting a single mechanism involved in motoneuron death will be effective, whereas multi-targeted treatments targeting on several mechanisms may provide better outcomes.

We have assayed novel therapeutic strategies in the SOD1<sup>G93A</sup> mouse, the most widely used model of ALS. First, the model was characterized in order to develop objective biomarkers to assess the evolution of the disease. We found that electrophysiological tests are highly reliable for the prediction of symptoms onset, rate of progression, and survival of the animals. Then, two potential neuroprotective treatments were studied, one focused on the modulation of sigma-1 receptor, using an agonist drug (PRE-084), and the second administering resveratrol, an antioxidant used successfully in other models of neurodegeneration. The results of both studies showed that administration of each drug delayed the onset of symptoms, improved the progression and prolonged survival. Moreover, in both cases these effects were accompanied by significant preservation of motoneurons in the spinal cord. However, despite the mechanisms of action of each of these compounds is different, their combined administration did not result in higher effects than single treatments. In order to target other distinct etiopathogenic mechanism, we have investigated the neuroinflammatory contribution to ALS. Administration of a selective inhibitor of CSF1 receptor effectively reduced microglial cell proliferation in the spinal cord and the influx of macrophages into the peripheral nerve in SOD1<sup>G93A</sup> mice. These actions were translated in slowed disease progression and delayed death of the mice, thus supporting therapeutic targeting of neuroinflammation in ALS. In ongoing experiments, we are testing novel approaches to promote maintenance of the neuromuscular junction, whose detachment precedes motoneuron death. Thus, by combining treatments that promote neuronal protection, neuroinflammatory modulation and synaptic maintenance, it is expected to obtain synergistic effects to ameliorate the fate of motoneuron diseases.