Astrocytes as cell targets for therapeutic intervention in ALS

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Collective evidence indicates that motor neuron degeneration in Amyotrophic Lateral Sclerosis (ALS) is non-cell-autonomous and requires the interaction with the neighboring astrocytes. Astrocytes can hurt motor neurons by secreting neurotoxic factors, but they can play deleterious roles also by losing functions that are supportive for neurons.

Recently, we reported that stimulation of inositol 1,4,5 triphosphate (IP3)-generating group I metabotropic glutamate receptors in ALS astrocytes triggers abundant and persistent elevations of intracellular Ca2+ concentrations in the absence of spontaneous oscillations. This correlates with mitochondrial disarrangement and cell death in subsets of astrocytes. The interaction of IP3 receptors with the anti-apoptotic protein Bcl-XL was previously described to prevent cell death by generating pro-survival Ca2+ oscillations. In ALS astrocytes, we found that the sole BH4 domain of Bcl-XL, fused to the protein transduction domain of the HIV-1 TAT protein (TAT-BH4), is sufficient to restore sustained Ca2+ oscillations and cell death resistance. Furthermore, chronic treatment of ALS mice with the TAT-BH4 peptide exerts a positive impact on the disease manifestations. Besides, we demonstrated that ALS astrocytes respond to a neuroinflammatory microenvironment with the release of neurotrophic factors, particularly the glial cell line-derived neurotrophic factor (GDNF). This protective response occurs during the late phase of the disease, thereby making it temporally inadequate to counteract the ongoing neurodegenerative process. Nonetheless, one may postulate that the local activation of this mechanism at the proper level and time may be determinant in governing the fate of motor neurons. These observations emphasize the concept that astrocytes can influence the course of ALS and should be considered major cellular targets for therapeutic intervention.