MSC-derived extracellular vesicles for the treatment of ALS

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, characterized by upper and lower motor neurons (MNs) death, with an important contribution of glial cells.
We previously demonstrated that the intravenous administration of mesenchymal stem cells (MSCs), prolonged survival probability and ameliorated pathological features in $SOD1^{G93A}$ ALS mice [**1**]. We postulated that the beneficial effect observed could be mediated by the paracrine activity of extracellular vesicles (EVs) secreted by MSCs [**2**].
The aim of the study was to evaluate the in-vitro effect of MSCs-derived EVs on astrocytes and the efficacy of the EVs in-vivo treatment in symptomatic $SOD1^{G93A}$. In spinal cord astrocytes isolated from symptomatic $SOD1^{G93A}$ mice, 24h in-vitro exposure to MSC-derived EVs significantly reduced the overexpression of glial activation markers (GFAP, vimentin and S100β) and pro-inflammatory factors (TNF-α, IL-1β, IL-6 and CCL2) . In human astrocytes (iAstrocytes) differentiated from inducible neural progenitor cells (iNPCs) derived from ALS patients and healthy donors, the exposure to EVs increased the expression of the Nrf2 anti-oxidant factor and reduced the accumulation of reactive oxygen species. We tested the neurotoxicity of ALS astrocytes on MNs survival, that was significantly reduced after EVs exposure. The transfection with synthetic mimics of miRNAs upregulated in MSCs, reverted the reactive phenotype of $SOD1^{G93A}$ ALS astrocytes and upregulated the Nrf2 antioxidant pathway in iAstrocytes [**3**].
Consequently, we tested the chronic intranasal administration of MSC-derived EVs in $SOD1^{G93A}$ mice starting at 90 days of life (early symptomatic stage). The in-vivo MSC-derived EVs administration significantly slowdown the progression of the disease and increased life span in EV-treated male mice only. Spinal cord MNs survival was significantly preserved at 115 days in male treated mice compared to control.
Our pre-clinical evidence suggests MSCs-derived EVs or even EV-mimicking synthetic particles as a promising pharmacological tool for ALS treatment.

Bibliography

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