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Use of Stem Cell Extracellular Vesicles as a "Holistic" Approach to CNS Repair

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Neurological diseases and disorders are leading causes of death and disability. These pathologies are associated with high levels of neuroinflammation and irreparable tissue damage. Stem cells have broad therapeutic potential and stem cell therapy has been evaluated for CNS repair. While the exact mechanisms are unknown, it is believed that paracrine factors, such as extracellular vesicles (EVs), mediate many of their functional effects. The potency of EVs is expected to be driven by their biological cargo. Because of their small size, stability, and low immunogenicity, EVs hold high therapeutic potential, especially for CNS pathologies since they can cross the blood-brain-barrier (1). We have isolated high yields of EVs from large batches of induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs). Our EV characterization includes phenotypic (size, tetraspanin expression) and biochemical (protein, cytokine, RNA) (2,3) assays. EV functionality has been assessed in vitro utilizing several cell-based assays using both healthy and damaged cells (3). Our data suggests that stem cell EVs have differential association with various cytokines, proteins, and long non-coding RNAs (4). Furthermore, they appear to exert differential effects on the expression of proteins involved in the innate immune response. We therefore propose a "dual" mode of action, whereas cellular growth initially slows due to activation of innate immune molecules by long non-coding RNAs, followed by initiation of reparative mechanisms via proteins and cytokines that promote repair. Collectively, these results demonstrate the potential of stem cell EVs as a "holistic" approach to reverse or to reduce cellular damage.