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PhD Exit Seminar

NEURAL STEM CELL DERIVED EXTRACELLULAR VESICLES AS AN ANTI-INFLAMMATORY STROKE THERAPEUTIC

Extracellular vesicles (EVs), nanosized (30-1000nm) vesicles, have garnered attention recently as a novel type of intercellular communication. These vesicles, which contain proteins, mRNA, miRNA, and lipids, can invoke downstream changes in recipient cells [1]. The conveyance of this biological material and downstream effects on recipient cells has potential applications in regenerative medicine. Specifically, EVs from multiple cell types have been shown to decrease activation of microglia, resident immune cells of the central nervous system (CNS). Therefore, EVs have exciting therapeutic potential, carrying the anti-inflammatory efficacy of their parent cells, while surmounting some of the current limitations of whole cell therapies, including rejection risk, inaccessibility to site of interest, and lack of engraftment. One such exciting type of EVs are neural stem cell (NSC) EVs. Here, the efficacy of NSC EVs is assessed in a large animal (porcine) middle cerebral artery occlusion (MCAO) model of stroke. While midline shift, or the deviation of the septum pellucidum of the brain from the midline, was predictive of control animal recovery 12 weeks after stroke, this correlation was ablated in NSC EV-treated animals. Furthermore, NSC EV treatment of stroked animals revealed significant differences in gait, behavior, survival, recovery speed, and brain herniation compared to control animals. To further investigate potential mechanisms of action of NSC EVs, a novel label-free imaging system, spatial light interference microscopy (SLIM), was utilized. SLIM revealed label-free EVs not only induce downstream responses in various recipient cells distinguishable from labeled EVs, but also attenuate characteristic responsive increases in dry mass seen in microglia following cytokine or endotoxin activation. To assess the effects of NSC EVs on microglia and other neural cells *in vivo*, morphological analysis was applied to stained histology slices of stroked, non-stroked, and NSC EV-treated stroked animals 4 weeks after MCAO. While stroked non-treated animals had significant deviations in microglia positive area, morphology, and perimeter, NSC EV-treated stroked animals did not. Together, these studies elucidate the efficacy of NSC EVs to promote survival and recovery in large animal models of stroke, as well anti-inflammatory mechanisms of EVs through their interactions with microglia *in vitro* and *in vivo*. *INDEX WORDS*: Neural Stem Cells, Extracellular Vesicles, Middle Cerebral Artery Occlusion Model, Anti-Inflammatory

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