



Title: Neuroreparative potential of macrophages: new opportunities in regenerative medicine

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Abstract:

Macrophages with anti-inflammatory phenotype (M2) play a critical role in functional recovery after central nervous system injury through the different mechanisms, in particular, clearing dead tissue, down-regulating inflammatory response and promoting neuronal and vascular remodeling. Given this notion, therapeutic approaches targeting M2 polarization or the utilization of these cells/soluble factors has been considered as a novel strategy for stimulating neuroreparative processes. Actually, M2 macrophage-based therapies have demonstrated positive effects in cerebral ischemia, ischemic retinopathy, and chronic neurodegenerative diseases. Since cognitive impairment, anxiety and depression as common complications of cerebrovascular diseases are associated with neuroinflammation and decrease in neurotrophic factors, utilization of M2/their factors may be a perspective approach for the correction of psychoneurological deficit as well. Previously, we have designed a new protocol for the generation of M2-macrophages that produced a wide range of immunoregulatory cytokines and growth factors. The investigation of neurorestorative potential of these cells have shown that M2-derived soluble factors (M2-sf) promoted proliferation and differentiation of neural stem cells in vitro. Intranasal delivery of M2-sf down-regulated pro-inflammatory cytokine levels (IL-1 β , IL-6, TNF- α , IFN- γ) in brain structures (striatum, hippocampus, frontal cortex) and decreased the signs of depression-like behavior in murine depression model. Finally, intranasal therapy with M2-sf in patients with chronic cerebrovascular disease (NCT02957123) is safe and results in reduction of anxiety and depression levels and improvement in cognitive functions.