Title: **Exosomal OTULIN from M2 Macrophages Promotes Recovery of Spinal Cord Injury via Regulating WNT Pathway-Mediated Vascular Regeneration**

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Abstract:
Vascularization following spinal cord injury (SCI) provides trophic support for rebuilding up and maintaining the homeostasis of neuronal networks, and the promotion of angiogenesis is beneficial for functional recovery after SCI. M2 macrophages have been reported to exhibit powerful pro-angiogenic function during tissue repair. Exosomes are important paracrine mediators of their parent cells and play critical roles in tissue regeneration. However, the role of M2 macrophage-derived exosomes (M2-Exos) in SCI is still largely unknown. In the present study, we determined that M2- Exos could augment the angiogenic activities of spinal cord microvascular endothelial cells (SCMECs) in vitro. Hydrogel-mediated sustained release of M2-Exos significantly promoted vascular regeneration and functional recovery in mice after SCI. Furthermore, proteomics analysis showed that ubiquitin thioesterase otulin (OTULIN) protein was highly enriched in M2-Exos. Functional assays demonstrated that OTULIN protein was required for the M2-Exos-induced pro-angiogenic effects in SCMECs, as well as positive effects on vascular regeneration, cell proliferation and functional recovery in the mouse model of SCI. Mechanically, OTULIN from M2-Exos could activate the Wnt/β-catenin signaling by increasing the protein level of β-catenin via inhibiting its ubiquitination, and trigger the expression of angiogenesis-related genes that are reported to be the downstream targets of Wnt/β-catenin signaling. Inhibition of the Wnt/β-catenin signaling by ICG101 in SCMECs markedly attenuated the proangiogenic activities of M2-Exos. Our findings indicate that M2-Exos positively modulate vascular regeneration and neurological functional recovery after SCI by activating Wnt/β-catenin signaling through the transfer of OTULIN protein.