SPINAL CORD INJURY

Huang, J. H., et al. (2017). "Systemic Administration of Exosomes Released from Mesenchymal Stromal Cells Attenuates Apoptosis, Inflammation, and Promotes Angiogenesis after Spinal Cord Injury in Rats." J Neurotrauma 34(24): 3388-3396.

Spinal cord injury (SCI) is one of the most common devastating injuries, which causes permanent disabilities such as paralysis and loss of movement or sensation. The precise pathogenic mechanisms of the disease remain unclear, and, as of yet, there is no effective cure. Mesenchymal stem cells (MSCs) show promise as an effective therapy in the experimental models of SCI. MSCs secrete various factors that can modulate a hostile environment, which is called the paracrine effect. Among these paracrine molecules, exosome is considered to be the most valuable therapeutic factor. Thus, exosomes from MSCs (MSCs-exosomes) can be a potential candidate of therapeutic effects of stem cells. The present study was designed to investigate the effect of whether systemic administration of exosomes generated from MSCs can promote the function recovery on the rat model of SCI in vivo. In the present study, we observed that systemic administration of MSCs-exosomes significantly attenuated lesion size and improved functional recovery post-SCI. Additionally, MSCs-exosomes treatment attenuated cellular apoptosis and inflammation in the injured spinal cord. Expression levels of proapoptotic protein (Bcl-2-associated X protein) and proinflammatory cytokines (tumor necrosis factor alpha and interleukin [IL]-1beta) were significantly decreased after MSCs-exosomes treatment, whereas expression levels of antiapoptotic (B-cell lymphoma 2) and anti-inflammatory (IL-10) proteins were upregulated. Further, administration of MSCs-exosomes significantly promoted angiogenesis. These results show, for the first time, that systemic administration of MSCs-exosomes attenuated cell apoptosis and inflammation, promoted angiogenesis, and promoted functional recovery post-SCI, suggesting that MSCs-exosomes hold promise as a novel therapeutic strategy for treating SCI.

Kim, H. Y., et al. (2018). "Therapeutic Efficacy-Potentiated and Diseased Organ-Targeting Nanovesicles Derived from Mesenchymal Stem Cells for Spinal Cord Injury Treatment." Nano Lett 18(8): 4965-4975.

Human mesenchymal stem cell (hMSC)-derived exosomes have been spotlighted as a promising therapeutic agent for cell-free regenerative medicine. However, poor organ-targeting ability and insufficient therapeutic efficacy of systemically injected hMSC-exosomes were identified as critical limitations for their further applications. Therefore, in this study we fabricated iron oxide nanoparticle (IONP)-incorporated exosome-mimetic nanovesicles (NV-IONP) from IONP-treated hMSCs and evaluated their therapeutic efficacy in a clinically relevant model for spinal cord injury. Compared to exosome-mimetic nanovesicles (NV) prepared from untreated hMSCs, NV-IONP not only contained IONPs which act as a magnet-guided navigation tool but also carried greater amounts of therapeutic growth factors that can be delivered to the target cells. The increased amounts of therapeutic growth factors inside NV-IONP were attributed to IONPs

that are slowly ionized to iron ions which activate the JNK and c-Jun signaling cascades in hMSCs. In vivo systemic injection of NV-IONP with magnetic guidance significantly increased the amount of NV-IONP accumulating in the injured spinal cord. Accumulated NV-IONP enhanced blood vessel formation, attenuated inflammation and apoptosis in the injured spinal cord, and consequently improved spinal cord function. Taken together, these findings highlight the development of therapeutic efficacy-potentiated extracellular nanovesicles and demonstrate their feasibility for repairing injured spinal cord.

Lankford, K. L., et al. (2018). "Intravenously delivered mesenchymal stem cell-derived exosomes target M2-type macrophages in the injured spinal cord." PLoS One 13(1): e0190358.

In a previous report we showed that intravenous infusion of bone marrow-derived mesenchymal stem cells (MSCs) improved functional recovery after contusive spinal cord injury (SCI) in the non-immunosuppressed rat, although the MSCs themselves were not detected at the spinal cord injury (SCI) site [1]. Rather, the MSCs lodged transiently in the lungs for about two days post-infusion. Preliminary studies and a recent report [2] suggest that the effects of intravenous (IV) infusion of MSCs could be mimicked by IV infusion of exosomes isolated from conditioned media of MSC cultures (MSCexos). In this study, we assessed the possible mechanism of MSCexos action on SCI by investigating the tissue distribution and cellular targeting of DiR fluorescent labeled MSCexos at 3 hours and 24 hours after IV infusion in rats with SCI. The IV delivered MSCexos were detected in contused regions of the spinal cord, but not in the noninjured region of the spinal cord, and were also detected in the spleen, which was notably reduced in weight in the SCI rat, compared to control animals. DiR "hotspots" were specifically associated with CD206-expressing M2 macrophages in the spinal cord and this was confirmed by co-localization with anti-CD63 antibodies labeling a tetraspanin characteristically expressed on exosomes. Our findings that MSCexos specifically target M2-type macrophages at the site of SCI, support the idea that extracellular vesicles, released by MSCs, may mediate at least some of the therapeutic effects of IV MSC administration.

Li, D., et al. (2018). "Exosomes Derived From miR-133b-Modified Mesenchymal Stem Cells Promote Recovery After Spinal Cord Injury." Front Neurosci 12: 845.

Dysregulation of microRNAs (miRNAs) has been found in injured spinal cords after spinal cord injury (SCI). Previous studies have shown that miR-133b plays an important role in the differentiation of neurons and the outgrowth of neurites. Recently, exosomes have been used as novel biological vehicles to transfer miRNAs locally or systemically, but little is known about the effect of the delivery of exosome-mediated miRNAs on the treatment of SCI. In the present study, we observed that mesenchymal stem cells, the most common cell types known to produce exosomes, could package miR-133b into secreted exosomes. After SCI, tail vein injection of miR-133b exosomes into

rats significantly improved the recovery of hindlimb function when compared to control groups. Additionally, treatment with miR-133b exosomes reduced the volume of the lesion, preserved neuronal cells, and promoted the regeneration of axons after SCI. We next observed that the expression of RhoA, a direct target of miR-133b, was decreased in the miR-133b exosome group. Moreover, we showed that miR-133b exosomes activated ERK1/2, STAT3, and CREB, which are signaling pathway proteins involved in the survival of neurons and the regeneration of axons. In summary, these findings demonstrated that systemically injecting miR-133b exosomes preserved neurons, promoted the regeneration of axons, and improved the recovery of hindlimb locomotor function following SCI, suggesting that the transfer of exosome-mediated miRNAs represents a novel therapeutic approach for the treatment of SCI.

Liu, W., et al. (2018). "Exosomes Derived from Bone Mesenchymal Stem Cells Repair Traumatic Spinal Cord Injury by Suppressing the Activation of A1 Neurotoxic Reactive Astrocytes." J Neurotrauma.

Mesenchymal stem cell (MSC) transplantation is now considered as an effective treatment strategy for traumatic spinal cord injury (SCI). However, several key issues remain unresolved, including low survival rates, cell dedifferentiation, and tumor formation. Recent studies have demonstrated that the therapeutic effect of transplanted stem cells is primarily paracrine mediated. Exosomes are an important paracrine factor that can be used as a direct therapeutic agent. However, there are few reports on the application of exosomes derived from bone MSCs (BMSCs-Exos) in treating SCI. In this study, we demonstrated that BMSCs-Exos possessed robust proangiogenic properties, attenuated neuronal cells apoptosis, suppressed glial scar formation, attenuated lesion size, suppressed inflammation, promoted axonal regeneration, and eventually improved functional behavioral recovery effects after traumatic SCI. Briefly, lesion size was decreased by nearly 60%, neuronal apoptosis was attenuated by nearly 70%, glial scar formation was reduced by nearly 75%, average blood vessel density was increased by nearly 60%, and axonal regeneration was increased by almost 80% at day 28 after SCI in the BMSC-Exos group compared to the control group. Using a series of in vitro functional assays, we also confirmed that treatment with BSMCs-Exos significantly enhanced human umbilical vein endothelial cell proliferation, migration, and angiogenic tubule formation, attenuated neuronal cells apoptosis, and suppressed nitric oxide release in microglia. Moreover, our study demonstrated that administration of BMSCs-Exos suppressed inflammation efficiently after traumatic SCI and suppressed activation of A1 neurotoxic reactive astrocytes. In conclusion, our study suggested that the application of BMSCs-Exos may be a promising strategy for traumatic SCI.

Sun, G., et al. (2018). "hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation." Mater Sci Eng C Mater Biol Appl 89: 194-204.

The exploration of effective spinal cord injury (SCI) healing still remain a great challenge due to the high morbidity, complex pathology and unclear targets. Human umbilical cord mesenchymal stem cells (hucMSC) play an important role in tissue regeneration. However, transplanting stem cells has a potential risk of teratogenicity. Recent studies have suggested that exosomes secreted by stem cells may contribute to tissue injury repair. We hypothesized that the application of hucMSC derived exosomes may be a potential way for SCI treatment. Our studies showed the hucMSC derived exosomes with a mean particle size of 70nm could effectively trigger the bone marrow derived macrophage (BMDM) polarization from M1 to a M2 phenotype. In vivo studies demonstrated that the hucMSC derived exosomes could improve the functional recovery after SCI through down-regulation of the inflammatory cytokines, such as TNF-alpha, MIP-1alpha, IL-6 and IFN-gamma. Collectively, our findings indicated that hucMSC derived exosomes could facilitate spinal cord injury healing via attenuating the inflammation of the injury region. Our results provided a new perspective and therapeutic strategy for the use of hucMSC derived exosomes in soft tissue repair.

Wang, L., et al. (2018). "Mesenchymal Stem Cell-Derived Exosomes Reduce A1 Astrocytes via Downregulation of Phosphorylated NFkappaB P65 Subunit in Spinal Cord Injury." Cell Physiol Biochem 50(4): 1535-1559.

BACKGROUND/AIMS: Neurotoxic A1 astrocytes are induced by inflammation after spinal cord injury (SCI), and the inflammation-related Nuclear Factor Kappa B (NFkappaB) pathway may be related to A1-astrocyte activation. Mesenchymal stem cell (MSC) transplantation is a promising therapy for SCI, where transplanted MSCs exhibit anti-inflammatory effects by downregulating proinflammatory factors, such as Tumor Necrosis Factor (TNF)-alpha and NFkappaB. MSC-exosomes (MSC-exo) reportedly mimic the beneficial effects of MSCs. Therefore, in this study, we investigated whether MSCs and MSC-exo exert inhibitory effects on A1 astrocytes and are beneficial for recovery after SCI. METHODS: The effects of MSC and MSC-exo on SCIinduced A1 astrocytes, and the potential mechanisms were investigated in vitro and in vivo using immunofluorescence and western blot. In addition, we assessed the histopathology, levels of proinflammatory cytokines and locomotor function to verify the effects of MSC and MSC-exo on SCI rats. RESULTS: MSC or MSC-exo co-culture reduced the proportion of SCIinduced A1 astrocytes. Intravenously-injected MSC or MSC-exo after SCI significantly reduced the proportion of A1 astrocytes, the percentage of p65 positive nuclei in astrocytes, and the percentage of TUNEL-positive cells in the ventral horn. Additionally, we observed decreased lesion area and expression of TNFalpha, Interleukin (IL)-1alpha and IL-1beta, elevated expression of Myelin Basic Protein (MBP), Synaptophysin (Syn) and Neuronal Nuclei (NeuN), and improved Basso, Beattie & Bresnahan (BBB) scores and inclined-plane-test angle. In vitro assay showed that MSC and MSC-exo reduced SCI-induced A1 astrocytes, probably via inhibiting the nuclear translocation of the NFkappaB p65. CONCLUSION: MSC and MSC-exo reduce SCI-induced A1

astrocytes, probably via inhibiting nuclear translocation of NFkappaB p65, and exert antiinflammatory and neuroprotective effects following SCI, with the therapeutic effect of MSCexo comparable with that of MSCs when applied intravenously.

Zhao, L., et al. (2018). "Exosomes derived from bone marrow mesenchymal stem cells overexpressing microRNA-25 protect spinal cords against transient ischemia." J Thorac Cardiovasc Surg.

OBJECTIVE: We investigated the neuroprotection of exosomes derived from bone marrow mesenchymal stem cells overexpressing microRNA-25 on ischemic spinal cords. METHODS: Cultured mesenchymal stem cells were transfected with lentivirus vectors containing pre-microRNA-25 or control vectors. Exosomes were isolated and harvested by centrifugation. Spinal cord ischemia was induced in rats by crossclamping the descending aorta just distal to the left subclavian artery for 15 minutes. Exosomes from mesenchymal stem cells, mesenchymal stem cells transfected with control vector, or pre-microRNA-25 were administered by intrathecal injection before ischemia. Hind-limb motor function was assessed with the motor deficit index. Contents of interleukin-1beta, tumor necrosis factor-alpha, malondialdehyde, and superoxide dismutase activity were measured using commercial kits. Expressions of NADPH oxidase 2, NADPH oxidase 4, and microRNA-25 were detected by Western blot and quantitative reverse transcription polymerase chain reaction. Lumbar spinal cords were harvested for histologic examination. RESULTS: Transfection of pre-microRNA-25 significantly enhanced microRNA-25 levels in mesenchymal stem cells and their exosomes ($P < .001$). All exosome-pretreating groups exhibited lower levels of interleukin-1beta and tumor necrosis factor-alpha ($P < .001$), more intact motor neurons ($P < .001$), and lower motor deficit index scores ($P < .005$) than those of controls. Compared with exosomes, microRNA-25-enriched exosomes markedly enhanced microRNA-25 level ($P < .001$), inhibited NADPH oxidase 4 expression ($P = .012$), but not NADPH oxidase 2 expression, decreased malondialdehyde content ($P = .022$), increased superoxide dismutase activity ($P < .001$) in spinal cords, and had additional neuroprotective effects as evidenced by lower motor deficit index scores ($P < .005$) and more survival neurons ($P = .002$). CONCLUSIONS: The neuroprotection of exosomes from mesenchymal stem cells on ischemic spinal cords can be enhanced by genetic modification of the exosomes to contain elevated microRNA-25.