PULMONARY

Lee, C., et al. (2012). "Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension." Circulation 126(22): 2601-2611.

BACKGROUND: Hypoxia induces an inflammatory response in the lung manifested by alternative activation of macrophages with elevation of proinflammatory mediators that are critical for the later development of hypoxic pulmonary hypertension. Mesenchymal stromal cell transplantation inhibits lung inflammation, vascular remodeling, and right heart failure and reverses hypoxic pulmonary hypertension in experimental models of disease. In this study, we aimed to investigate the paracrine mechanisms by which mesenchymal stromal cells are protective in hypoxic pulmonary hypertension. METHODS AND RESULTS: We fractionated mouse mesenchymal stromal cell-conditioned media to identify the biologically active component affecting in vivo hypoxic signaling and determined that exosomes, secreted membrane microvesicles, suppressed the hypoxic pulmonary influx of macrophages and the induction of proinflammatory and proproliferative mediators, including monocyte chemoattractant protein-1 and hypoxia-inducible mitogenic factor, in the murine model of hypoxic pulmonary hypertension. Intravenous delivery of mesenchymal stromal cell-derived exosomes (MEX) inhibited vascular remodeling and hypoxic pulmonary hypertension, whereas MEX-depleted media or fibroblast-derived exosomes had no effect. MEX suppressed the hypoxic activation of signal transducer and activator of transcription 3 (STAT3) and the upregulation of the miR-17 superfamily of microRNA clusters, whereas it increased lung levels of miR-204, a key microRNA, the expression of which is decreased in human pulmonary hypertension. MEX produced by human umbilical cord mesenchymal stromal cells inhibited STAT3 signaling in isolated human pulmonary artery endothelial cells, demonstrating a direct effect of MEX on hypoxic vascular cells. CONCLUSION: This study indicates that MEX exert a pleiotropic protective effect on the lung and inhibit pulmonary hypertension through suppression of hyperproliferative pathways, including STAT3-mediated signaling induced by hypoxia.

Zhu, Y. G., et al. (2014). "Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice." Stem Cells 32(1): 116-125.

We previously found that human mesenchymal stem cells (MSC) or its conditioned medium restored lung protein permeability and reduced alveolar inflammation following Escherichia coli endotoxin-induced acute lung injury (ALI) in an ex vivo perfused human lung in part through the secretion of soluble factors such as keratinocyte growth factor (KGF). Recently, MSC were found to release microvesicles (MVs) that were biologically active because of the presence of mRNA or miRNA with reparative properties. MVs are circular fragments of membrane released from the endosomal compartment as exosomes or shed from the surface membranes. These studies were designed to determine if MVs released by human bone marrow derived MSCs would be effective in restoring lung protein permeability and reducing inflammation in E.

coli endotoxin-induced ALI in C57BL/6 mice. The intratracheal instillation of MVs improved several indices of ALI at 48 hours. Compared to endotoxin-injured mice, MVs reduced extravascular lung water by 43% and reduced total protein levels in the bronchoalveolar lavage (BAL) fluid by 35%, demonstrating a reduction in pulmonary edema and lung protein permeability. MVs also reduced the influx of neutrophils and macrophage inflammatory protein-2 levels in the BAL fluid by 73% and 49%, respectively, demonstrating a reduction in inflammation. KGF siRNA-pretreatment of MSC partially eliminated the therapeutic effects of MVs released by MSCs, suggesting that KGF protein expression was important for the underlying mechanism. In summary, human MSC-derived MVs were therapeutically effective following E. coli endotoxin-induced ALI in mice in part through the expression of KGF mRNA in the injured alveolus.

Fujita, Y., et al. (2015). "Extracellular vesicles in lung microenvironment and pathogenesis." Trends Mol Med 21(9): 533-542.

Increasing attention is being paid to the role of extracellular vesicles (EVs) in various lung diseases. EVs are released by a variety of cells, including respiratory cells and immune cells, and they encapsulate various molecules, such as proteins and microRNAs, as modulators of intercellular communication. Cancer cell-derived EVs play crucial roles in promoting tumor progression and modifying their microenvironment. By contrast, noncancerous cell-derived EVs demonstrate protective functions against injury, such as tissue recovery and repair, to maintain physiological homeostasis. Airway cells in contact with harmful substances may alter their EV composition and modify the balanced reciprocal interactions with surrounding mesenchymal cells. We summarize the novel findings of EV function in various lung diseases, primarily chronic obstructive pulmonary disease (COPD) and lung cancer.

Li, L., et al. (2015). "Ischemic preconditioning potentiates the protective effect of mesenchymal stem cells on endotoxin-induced acute lung injury in mice through secretion of exosome." Int J Clin Exp Med 8(3): 3825-3832.

OBJECTIVE: To explore the effect of bone marrow mesenchymal stem cells (MSCs) on endotoxin-induced acute lung injury in mice and verify the role of exosome. METHODS: Exosome was isolated from the culture supernatant of MSC. For ischemic preconditioning, MSCs were subjected to anoxia for 0 min (MSCs group), 30 min (MSCs(IPC-30) group), 60 min (MSCs(IPC-60) group) and 90 min (MSCs(IPC 90) group), and then used to treat endotoxin-injured mice. The exosome from the optimal group was used to treat endotoxin-injured mice. In addition, the exosome from the optimal group was also used to treat the endotoxin-stimulated RAW 264.7 cells for 6 h and 12 h. RESULTS: CD63 positive exosome were acquired through ExoQuick kits. Administration of MSCs, MSCs(IPC-30), MSCs(IPC-60) and MSCs(IPC-90) could reduce the level of white blood cells (WBC) and neutrophils into the bronchoalveolar lavage (BAL) fluid of endotoxin-injured mice, and the

MSCIPC-60 group had the greatest reduction, which reduced WBC by 57% and neutrophils by 55%. Administration of MSCs(IPC-60) exosome could also reduce the level of WBC, neutrophils, MIP-2 and penetration protein into the BAL fluid of endotoxin-injured mice, which had the same effect as MSCs(IPC-60) and showed a dose dependent, compared to MSCs exosome. In addition, MSCs(IPC-60) exosome were used to treat endotoxin-stimulated RAW 264.7 cells, and the level of TNFalpha at 6 h and 12 h was significantly reduced, while the level of IL-10 at 12 h increased. CONCLUSION: Ischemic preconditioning for 60 min can potentiates the protective effect of MSC on endotoxin-induced Acute Lung Injury through the secretion of Exosome.

Simonson, O. E., et al. (2015). "In Vivo Effects of Mesenchymal Stromal Cells in Two Patients With Severe Acute Respiratory Distress Syndrome." Stem Cells Transl Med 4(10): 1199-1213.

UNLABELLED: Mesenchymal stromal cells (MSCs) have been investigated as a treatment for various inflammatory diseases because of their immunomodulatory and reparative properties. However, many basic questions concerning their mechanisms of action after systemic infusion remain unanswered. We performed a detailed analysis of the immunomodulatory properties and proteomic profile of MSCs systemically administered to two patients with severe refractory acute respiratory distress syndrome (ARDS) on a compassionate use basis and attempted to correlate these with in vivo anti-inflammatory actions. Both patients received 2x10(6) cells per kilogram, and each subsequently improved with resolution of respiratory, hemodynamic, and multiorgan failure. In parallel, a decrease was seen in multiple pulmonary and systemic markers of inflammation, including epithelial apoptosis, alveolar-capillary fluid leakage, and proinflammatory cytokines, microRNAs, and chemokines. In vitro studies of the MSCs demonstrated a broad anti-inflammatory capacity, including suppression of T-cell responses and induction of regulatory phenotypes in T cells, monocytes, and neutrophils. Some of these in vitro potency assessments correlated with, and were relevant to, the observed in vivo actions. These experiences highlight both the mechanistic information that can be gained from clinical experience and the value of correlating in vitro potency assessments with clinical effects. The findings also suggest, but do not prove, a beneficial effect of lung protective strategies using adoptively transferred MSCs in ARDS. Appropriate randomized clinical trials are required to further assess any potential clinical efficacy and investigate the effects on in vivo inflammation. SIGNIFICANCE: This article describes the cases of two patients with severe refractory adult respiratory syndrome (ARDS) who failed to improve after both standard life support measures, including mechanical ventilation, and additional measures, including extracorporeal ventilation (i.e., in a heart-lung machine). Unlike acute forms of ARDS (such in the current NIH-sponsored study of mesenchymal stromal cells in ARDS), recovery does not generally occur in such patients.

Zhu, Z., et al. (2015). "MicroRNAs and mesenchymal stem cells: hope for pulmonary hypertension." Rev Bras Cir Cardiovasc 30(3): 380-385.

Pulmonary hypertension is a devastating and refractory disease and there is no cure for this disease. Recently, microRNAs and mesenchymal stem cells emerged as novel methods to treat pulmonary hypertension. More than 20 kinds of microRNAs may participate in the process of pulmonary hypertension. It seems microRNAs or mesenchymal stem cells can ameliorate some symptoms of pulmonary hypertension in animals and even improve heart and lung function during pulmonary hypertension. Nevertheless, the relationship between mesenchymal stem cells, microRNAs and pulmonary hypertension is not clear. And the mechanisms underlying their function still need to be investigated. In this study we review the recent findings in mesenchymal stem cells - and microRNAs-based pulmonary hypertension treatment, focusing on the potential role of microRNAs regulated mesenchymal stem cells in pulmonary hypertension and the role of exosomes between mesenchymal stem cells and pulmonary hypertension.

Aliotta, J. M., et al. (2016). "Exosomes induce and reverse monocrotaline-induced pulmonary hypertension in mice." Cardiovasc Res 110(3): 319-330.

AIMS: Extracellular vesicles (EVs) from mice with monocrotaline (MCT)-induced pulmonary hypertension (PH) induce PH in healthy mice, and the exosomes (EXO) fraction of EVs from mesenchymal stem cells (MSCs) can blunt the development of hypoxic PH. We sought to determine whether the EXO fraction of EVs is responsible for modulating pulmonary vascular responses and whether differences in EXO-miR content explains the differential effects of EXOs from MSCs and mice with MCT-PH. METHODS AND RESULTS: Plasma, lung EVs from MCT-PH, and control mice were divided into EXO (exosome), microvesicle (MV) fractions and injected into healthy mice. EVs from MSCs were divided into EXO, MV fractions and injected into MCT-treated mice. PH was assessed by right ventricle-to-left ventricle + septum (RV/LV + S) ratio and pulmonary arterial wall thickness-to-diameter (WT/D) ratio. miR microarray analyses were also performed on all EXO populations. EXOs but not MVs from MCT-injured mice increased RV/LV + S, WT/D ratios in healthy mice. MSC-EXOs prevented any increase in RV/LV + S, WT/D ratios when given at the time of MCT injection and reversed the increase in these ratios when given after MCT administration. EXOs from MCT-injured mice and patients with idiopathic pulmonary arterial hypertension (IPAH) contained increased levels of miRs-19b,-20a,-20b, and -145, whereas miRs isolated from MSC-EXOs had increased levels of anti-inflammatory, anti-proliferative miRs including miRs-34a,-122,-124, and -127. CONCLUSION: These findings suggest that circulating or MSC-EXOs may modulate pulmonary hypertensive effects based on their miR cargo. The ability of MSC-EXOs to reverse MCT-PH offers a promising potential target for new PAH therapies.

Horie, S. and J. G. Laffey (2016). "Recent insights: mesenchymal stromal/stem cell therapy for acute respiratory distress syndrome."

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Acute respiratory distress syndrome (ARDS) causes respiratory failure, which is associated with severe inflammation and lung damage and has a high mortality and for which there is no therapy. Mesenchymal stromal/stem cells (MSCs) are adult multi-progenitor cells that can modulate the immune response and enhance repair of damaged tissue and thus may provide a therapeutic option for ARDS. MSCs demonstrate efficacy in diverse in vivo models of ARDS, decreasing bacterial pneumonia and ischemia-reperfusion-induced injury while enhancing repair following ventilator-induced lung injury. MSCs reduce the pro-inflammatory response to injury while augmenting the host response to bacterial infection. MSCs appear to exert their effects via multiple mechanisms-some are cell interaction dependent whereas others are paracrine dependent resulting from both soluble secreted products and microvesicles/exosomes derived from the cells. Strategies to further enhance the efficacy of MSCs, such as by overexpressing anti-inflammatory or pro-repair molecules, are also being investigated. Encouragingly, early phase clinical trials of MSCs in patients with ARDS are under way, and experience with these cells in trials for other diseases suggests that the cells are well tolerated. Although considerable translational challenges, such as concerns regarding cell manufacture scale-up and issues regarding cell potency and batch variability, must be overcome, MSCs constitute a highly promising potential therapy for ARDS.

Monsel, A., et al. (2016). "Mesenchymal stem cell derived secretome and extracellular vesicles for acute lung injury and other inflammatory lung diseases." Expert Opin Biol Ther 16(7): 859-871.

INTRODUCTION: Acute respiratory distress syndrome is a major cause of respiratory failure in critically ill patients. Despite extensive research into its pathophysiology, mortality remains high. No effective pharmacotherapy exists. Based largely on numerous preclinical studies, administration of mesenchymal stem or stromal cell (MSC) as a therapeutic for acute lung injury holds great promise, and clinical trials are currently underway. However, concern for the use of stem cells, specifically the risk of iatrogenic tumor formation, remains unresolved. Accumulating evidence now suggest that novel cell-free therapies including MSC-derived conditioned medium and extracellular vesicles released from MSCs might constitute compelling alternatives. AREAS COVERED: The current review summarizes the preclinical studies testing MSC conditioned medium and/or MSC extracellular vesicles as treatment for acute lung injury and other inflammatory lung diseases. EXPERT OPINION: While certain logistical obstacles limit the clinical applications of MSC conditioned medium such as the volume required for treatment, the therapeutic application of MSC extracellular vesicles remains promising, primarily due to ability of extracellular vesicles to maintain the functional phenotype of the parent cell. However, utilization of MSC extracellular vesicles will require large-scale production and standardization concerning identification, characterization and quantification.

Chen, J., et al. (2017). "Extracellular Vesicle MicroRNA Transfer in Lung Diseases." Front Physiol 8: 1028.

MicroRNAs (miRNAs) are single-stranded, small non-coding RNAs that ate involved in the transcriptional and post-transcriptional regulation of gene expression. Recently, miRNAs were demonstrated to be effectively delivered to a target cell or tissue from a host cell via extracellular vesicles (EVs). These EVs can be detected in blood, urine, exhaled breath condensates, bronchoalveolar lavage fluid (BALF), and other fluids. miRNAs are generated by donor cells and then packaged into EVs and delivered with intact functionality. After being delivered to the target cells, they regulate the translation of their target genes and the function of the target cells. Thus, EV transported miRNAs have become a new method for intercellular communication. EV miRNA transfer is well-documented in various pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary hypertension, and acute lung injury (ALI). In this review, we summarize the novel findings of EV miRNA transfer, focusing on the roles of miR-210, miR-200, miR-17, miR-146a, miR-155, and other miRNAs that are transported from primary human bronchial epithelial cells (HBECs), BALF, mesenchymal stem cells, and dendritic cells.

Cruz, F. F. and P. R. M. Rocco (2017). "Stem-cell extracellular vesicles and lung repair." Stem Cell Investig 4: 78.

Four out of the ten leading causes of morbidity and mortality worldwide are lung diseases. Despite advances in comprehending the pathophysiological mechanisms involved in these disorders, for several respiratory diseases, there is still no effective treatment able to stop their natural history or reverse the morphological and functional damage they cause. In this context, recent research has supported a potential role of cell therapy for lung diseases and critical illness. The anti-inflammatory, antifibrotic, and microbicidal effects of stem cells are mainly attributed to their secretome, which contains proteins, lipids, microRNAs, and mRNAs. These are secreted in the conditioned medium and are also present in extracellular vesicles (EVs). This review will provide a detailed discussion of the role of EVs produced by mesenchymal stromal cells in preclinical experimental models of pulmonary disorders and critical illness, as well as in ongoing clinical trials.

Chaubey, S., et al. (2018). "Early gestational mesenchymal stem cell secretome attenuates experimental bronchopulmonary dysplasia in part via exosome-associated factor TSG-6." Stem Cell Res Ther 9(1): 173.

BACKGROUND: Mesenchymal stem cells (MSCs) are promising tools for the treatment of human lung disease and other pathologies relevant to newborn medicine. Recent studies have established MSC exosomes (EXO), as one of the main therapeutic vectors of MSCs in mouse models of multifactorial chronic lung disease of preterm infants, bronchopulmonary dysplasia (BPD). However, the mechanisms underlying

MSC-EXO therapeutic action are not completely understood. Using a neonatal mouse model of human BPD, we evaluated the therapeutic efficiency of early gestational age (GA) human umbilical cord (hUC)-derived MSC EXO fraction and its exosomal factor, tumor necrosis factor alpha-stimulated gene-6 (TSG-6). METHODS: Conditioned media (CM) and EXO fractions were isolated from 25 and 30 weeks GA hUC-MSC cultures grown in serum-free media (SFM) for 24 h. Newborn mice were exposed to hyperoxia (> 95% oxygen) and were given intraperitoneal injections of MSC-CM or MSC-CM EXO fractions at postnatal (PN) day 2 and PN4. They were then returned to room air until PN14 (in a mouse model of severe BPD). The treatment regime was followed with (rh)TSG-6, TSG-6-neutralizing antibody (NAb), TSG-6 (si)RNA-transfected MSC-CM EXO and their appropriate controls. Echocardiography was done at PN14 followed by harvesting of lung, heart and brain for assessment of pathology parameters. RESULTS: Systemic administration of CM or EXO in the neonatal BPD mouse model resulted in robust improvement in lung, cardiac and brain pathology. Hyperoxia-exposed BPD mice exhibited pulmonary inflammation accompanied by alveolar-capillary leakage, increased chord length, and alveolar simplification, which was ameliorated by MSC CM/EXO treatment. Pulmonary hypertension and right ventricular hypertrophy was also corrected. Cell death in brain was decreased and the hypomyelination reversed. Importantly, we detected TSG-6, an immunomodulatory glycoprotein, in EXO. Administration of TSG-6 attenuated BPD and its associated pathologies, in lung, heart and brain. Knockdown of TSG-6 by NAb or by siRNA in EXO abrogated the therapeutic effects of EXO, suggesting TSG-6 as an important therapeutic molecule. CONCLUSIONS: Preterm hUC-derived MSC-CM EXO alleviates hyperoxia-induced BPD and its associated pathologies, in part, via exosomal factor TSG-6. The work indicates early systemic intervention with TSG-6 as a robust option for cell-free therapy, particularly for treating BPD.

Du, Y. M., et al. (2018). "Mesenchymal stem cell exosomes promote immunosuppression of regulatory T cells in asthma." Exp Cell Res 363(1): 114-120.

Mesenchymal stem cells (MSCs) and regulatory T cells (Tregs) are both potent immune-modulators. The aberrant proliferation and function of Tregs plays an important role in the development of asthma. Our previous studies have demonstrated the role of MSCs in promoting proliferation and immune-modulating of Tregs, as well as alleviating airway inflammation of asthmatic mice. In the present study, we isolated exosomes secreted by MSCs and investigated their immunomodulation effect on peripheral blood mononuclear cells (PBMCs) of asthmatic patient. We found that MSC exosomes upregulated IL-10 and TGF-beta1 from PBMCs, thus promoting proliferation and immune-suppression capacity of Tregs. Furthermore, antigen presenting cells (APCs) but not CD4+ T cells-dependent pathway was shown to be possible mechanism involved in MSC exosome-mediated regulation. Our data elucidated the key role of exosomes in immune-modulation of MSCs, and

suggested the therapeutic potential of MSC exosomes for asthma.

Fujita, Y., et al. (2018). "Clinical Application of Mesenchymal Stem Cell-Derived Extracellular Vesicle-Based Therapeutics for Inflammatory Lung Diseases." J Clin Med 7(10).

It is currently thought that extracellular vesicles (EVs), such as exosomes and microvesicles, play an important autocrine/paracrine role in intercellular communication. EVs package proteins, mRNA and microRNA (miRNA), which have the ability to transfer biological information to recipient cells in the lungs. Depending on their origin, EVs fulfil different functions. EVs derived from mesenchymal stem cells (MSCs) have been found to promote therapeutic activities that are comparable to MSCs themselves. Recent animal model-based studies suggest that MSC-derived EVs have significant potential as a novel alternative to whole-cell therapies. Compared to their parent cells, EVs may have a superior safety profile and can be stored without losing function. It has been observed that MSC-derived EVs suppress pro-inflammatory processes and reduce oxidative stress, pulmonary fibrosis and remodeling in a variety of in vivo inflammatory lung disease models by transferring their components. However, there remain significant challenges to translate this therapy to the clinic. From this view point, we will summarize recent studies on EVs produced by MSCs in preclinical experimental models of inflammatory lung diseases. We will also discuss the most relevant issues in bringing MSC-derived EV-based therapeutics to the clinic for the treatment of inflammatory lung diseases.

Horie, S., et al. (2018). "Cell therapy in acute respiratory distress syndrome." J Thorac Dis 10(9): 5607-5620.

Acute respiratory distress syndrome (ARDS) is driven by a severe pro-inflammatory response resulting in lung damage, impaired gas exchange and severe respiratory failure. There is no specific treatment that effectively improves outcome in ARDS. However, in recent years, cell therapy has shown great promise in preclinical ARDS studies. A wide range of cells have been identified as potential candidates for use, among these are mesenchymal stromal cells (MSCs), which are adult multi-lineage cells that can modulate the immune response and enhance repair of damaged tissue. The therapeutic potential of MSC therapy for sepsis and ARDS has been demonstrated in multiple in vivo models. The therapeutic effect of these cells seems to be due to two different mechanisms; direct cellular interaction, and paracrine release of different soluble products such as extracellular vesicles (EVs)/exosomes. Different approaches have also been studied to enhance the therapeutic effect of these cells, such as the over-expression of anti-inflammatory or pro-reparative molecules. Several clinical trials (phase I and II) have already shown safety of MSCs in ARDS and other diseases. However, several translational issues still need to be addressed, such as the large-scale production of cells, and their potentiality and variability, before the therapeutic potential of stem cells therapies can be realized.

Lesage, F. and B. Thebaud (2018). "Nanotherapies for micropreemies: Stem cells and the secretome in bronchopulmonary dysplasia." Semin Perinatol 42(7): 453-458.

Improved survival of extreme preterm infants has made the task of protecting the ever more immature lung from injury more challenging. As a consequence, the incidence of bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, has remained unchanged. The multifactorial disease pathogenesis of BPD - including amongst others inflammation, oxidative stress and excessive lung stretch - adds further complexity to finding effective therapies that would prevent lung injury and promote lung growth. Mesenchymal stromal cells and the discovery of their pleiotropic effects represent an appealing approach for the prevention of BPD. Mesenchymal stromal cells do not engraft but exert their therapeutic benefit through paracrine effects. These paracrine effects seem to be mediated through the release of nanosized extra-cellular vesicles used for cell-cell communication. This review will summarize our current knowledge on these potential nanotherapies for micropreemies.

Willis, G. R., et al. (2018). "Mesenchymal Stromal Cell Exosomes Ameliorate Experimental Bronchopulmonary Dysplasia and Restore Lung Function through Macrophage Immunomodulation." Am J Respir Crit Care Med 197(1): 104-116.

RATIONALE: Mesenchymal stem/stromal cell (MSC) therapies have shown promise in preclinical models of pathologies relevant to newborn medicine, such as bronchopulmonary dysplasia (BPD). We have reported that the therapeutic capacity of MSCs is comprised in their secretome, and demonstrated that the therapeutic vectors are exosomes produced by MSCs (MSC-exos). OBJECTIVES: To assess efficacy of MSC-exo treatment in a preclinical model of BPD and to investigate mechanisms underlying MSC-exo therapeutic action. METHODS: Exosomes were isolated from media conditioned by human MSC cultures. Newborn mice were exposed to hyperoxia (HYRX; 75% O2), treated with exosomes on Postnatal Day (PN) 4 and returned to room air on PN7. Treated animals and appropriate controls were harvested on PN7, -14, or -42 for assessment of pulmonary parameters. MEASUREMENTS AND MAIN RESULTS: HYRX-exposed mice presented with pronounced alveolar simplification, fibrosis, and pulmonary vascular remodeling, which was effectively ameliorated by MSC-exo treatment. Pulmonary function tests and assessment of pulmonary hypertension showed functional improvements after MSC-exo treatment. Lung mRNA sequencing demonstrated that MSC-exo treatment induced pleiotropic effects on gene expression associated with HYRX-induced inflammation and immune responses. MSC-exos modulate the macrophage phenotype fulcrum, suppressing the proinflammatory "M1" state and augmenting an antiinflammatory "M2-like" state, both in vitro and in vivo. CONCLUSIONS: MSC-exo treatment blunts HYRX-associated inflammation and alters the hyperoxic lung transcriptome. This results in alleviation of HYRX-induced BPD, improvement of lung function, decrease in fibrosis and pulmonary vascular remodeling, and

amelioration of pulmonary hypertension. The MSC-exo mechanism of action is associated with modulation of lung macrophage phenotype.

Willis, G. R., et al. (2018). ""Good things come in small packages": application of exosome-based therapeutics in neonatal lung injury." Pediatr Res 83(1-2): 298-307.

Infants born at very low gestational age contribute disproportionately to neonatal morbidity and mortality. Advancements in antenatal steroid therapies and surfactant replacement have favored the survival of infants with ever-more immature lungs. Despite such advances in medical care, cardiopulmonary and neurological impairment prevail in constituting the major adverse outcomes for neonatal intensive care unit survivors. With no single effective therapy for either the prevention or treatment of such neonatal disorders, the need for new tools to treat and reduce risk of further complications associated with extreme preterm birth is urgent. Mesenchymal stem/stromal cell (MSC)-based approaches have shown promise in numerous experimental models of lung injury relevant to neonatology. Recent studies have highlighted that the therapeutic potential of MSCs is harnessed in their secretome, and that the therapeutic vector therein is represented by the exosomes released by MSCs. In this review, we summarize the development and significance of stem cell-based therapies for neonatal diseases, focusing on preclinical models of neonatal lung injury. We emphasize the development of MSC exosome-based therapeutics and comment on the challenges in bringing these promising interventions to clinic.

Porzionato, A., et al. (2019). "Intratracheal administration of clinical-grade mesenchymal stem cell-derived extracellular vesicles reduces lung injury in a rat model of bronchopulmonary dysplasia." Am J Physiol Lung Cell Mol Physiol 316(1): L6-l19.

Mesenchymal stem cells (MSCs) prevent the onset of bronchopulmonary dysplasia (BPD) in animal models, an effect that seems to be mediated by their secreted extracellular vesicles (EVs). The aim of this study was to compare the protective effects of intratracheally (IT) administered MSCs versus MSC-EVs in a hyperoxia-induced rat model of BPD. At birth, rats were distributed as follows: animals raised in ambient air for 2 wk (n = 10), and animals exposed to 60% oxygen for 2 wk and treated with IT-administered physiological solution (n = 10), MSCs (n = 10), or MSC-EVs (n = 10) on postnatal days 3, 7, and 10. The sham-treated hyperoxia-exposed animals showed reductions in total surface area of alveolar air spaces, and total number of alveoli (Nalv), and an increased mean alveolar volume (Valv). EVs prompted a significant increase in Nalv ($P < 0.01$) and a significant decrease in Valv ($P < 0.05$) compared with sham-treated animals, whereas MSCs only significantly improved Nalv ($P < 0.05$). Small pulmonary vessels of the sham-treated hyperoxia-exposed rats also showed an increase in medial thickness, which only EVs succeeded in preventing significantly ($P < 0.05$). In conclusion, both EVs and MSCs reduce hyperoxia-induced damage, with EVs obtaining better

results in terms of alveolarization and lung vascularization parameters. This suggests that IT-administered EVs could be an effective approach to BPD treatment.

Xu, S., et al. (2019). "Concise Review: Therapeutic Potential of the Mesenchymal Stem Cell Derived Secretome and Extracellular Vesicles for Radiation-Induced Lung Injury: Progress and Hypotheses." Stem Cells Transl Med.

Radiation-induced lung injury (RILI) is a common complication in radiotherapy of thoracic tumors and limits the therapeutic dose of radiation that can be given to effectively control tumors. RILI develops through a complex pathological process, resulting in induction and activation of various cytokines, infiltration by inflammatory cells, cytokine-induced activation of fibroblasts, and subsequent tissue remodeling by activated fibroblasts, ultimately leading to impaired lung function and respiratory failure. Increasing evidence shows that mesenchymal stem cells (MSCs) may play a main role in modulating inflammation and immune responses, promoting survival and repair of damaged resident cells and enhancing regeneration of damaged tissue through soluble paracrine factors and therapeutic extracellular vesicles. Therefore, the use of the MSC-derived secretome and exosomes holds promising potential for RILI therapy. Here, we review recent progress on the potential mechanisms of MSC therapy for RILI, with an emphasis on soluble paracrine factors of MSCs. Hypotheses on how MSC derived exosomes or MSC-released exosomal miRNAs could attenuate RILI are also proposed. Problems and translational challenges of the therapies based on the MSC-derived secretome and exosomes are further summarized and underline the need for caution on rapid clinical translation. Stem Cells Translational Medicine 2019.