NEONATAL

Gortner, L., et al. (2012). "Regenerative therapies in neonatology: clinical perspectives." Klin Padiatr 224(4): 233-240.

Regenerative therapy based on stem cells is applied as standard therapy in pediatric oncology. Furthermore, they are frequently used to treat immunodeficiency disorders of infants. For severe neonatal diseases, e. g. hypoxic-ischemic encephalopathy in term neonates or bronchopulmonary dysplasia in preterm infants, animal models have been established. According to some first preclinical results stem cell administration appears as a promising tool to improve the clinical outcome in high-risk infants. Provided the benefit of regenerative therapies can further be evaluated in appropriate preclinical neonate models, carefully controlled clinical trials to assess the significance of regenerative therapies, such as autologous stem cell administration, are indicated.

Mitsialis, S. A. and S. Kourembanas (2016). "Stem cell-based therapies for the newborn lung and brain: Possibilities and challenges." Semin Perinatol 40(3): 138-151.

There have been substantial advances in neonatal medical care over the past 2 decades that have resulted in the increased survival of very low birth weight infants, survival that in some centers extends to 22 weeks gestational age. Despite these advances, there continues to be significant morbidity associated with extreme preterm birth that includes both short-term and long-term pulmonary and neurologic consequences. No single therapy has proven to be effective in preventing or treating either developmental lung and brain injuries in preterm infants or the hypoxic-ischemic injury that can be inflicted on the full-term brain as a result of in utero or perinatal complications. Stem cell-based therapies are emerging as a potential paradigm-shifting approach for such complex diseases with multifactorial etiologies, but a great deal of work is still required to understand the role of stem/progenitor cells in normal development and in the repair of injured tissue. This review will summarize the biology of the various stem/progenitor cells, their effects on tissue repair in experimental models of lung and brain injury, the recent advances in our understanding of their mechanism of action, and the challenges that remain to be addressed before their eventual application to clinical care.

Ophelders, D. R., et al. (2016). "Mesenchymal Stromal Cell-Derived Extracellular Vesicles Protect the Fetal Brain After Hypoxia-Ischemia." Stem Cells Transl Med 5(6): 754-763.

UNLABELLED: Preterm neonates are susceptible to perinatal hypoxic-ischemic brain injury, for which no treatment is available. In a preclinical animal model of hypoxic-ischemic brain injury in ovine fetuses, we have demonstrated the neuroprotective potential of systemically administered mesenchymal stromal cells (MSCs). The mechanism of MSC treatment is unclear but suggested to be paracrine, through secretion of extracellular vesicles (EVs). Therefore, we investigated in this study the protective effects of mesenchymal

stromal cell-derived extracellular vesicles (MSC-EVs) in a preclinical model of preterm hypoxic-ischemic brain injury. Ovine fetuses were subjected to global hypoxia-ischemia by transient umbilical cord occlusion, followed by in utero intravenous administration of MSC-EVs. The therapeutic effects of MSC-EV administration were assessed by analysis of electrophysiological parameters and histology of the brain. Systemic administration of MSC-EVs improved brain function by reducing the total number and duration of seizures, and by preserving baroreceptor reflex sensitivity. These functional protections were accompanied by a tendency to prevent hypomyelination. Cerebral inflammation remained unaffected by the MSC-EV treatment. Our data demonstrate that MSC-EV treatment might provide a novel strategy to reduce the neurological sequelae following hypoxic-ischemic injury of the preterm brain. Our study results suggest that a cell-free preparation comprising neuroprotective MSC-EVs could substitute MSCs in the treatment of preterm neonates with hypoxic-ischemic brain injury, thereby circumventing the potential risks of systemic administration of living cells. SIGNIFICANCE: Bone marrow-derived mesenchymal stromal cells (MSCs) show promise in treating hypoxic-ischemic injury of the preterm brain. Study results suggest administration of extracellular vesicles, rather than intact MSCs, is sufficient to exert therapeutic effects and avoids potential concerns associated with administration of living cells. The therapeutic efficacy of systemically administered mesenchymal stromal cell-derived extracellular vesicles (MSC-EVs) on hypoxia-ischemia-induced injury was assessed in the preterm ovine brain. Impaired function and structural injury of the fetal brain was improved following global hypoxia-ischemia. A cell-free preparation of MSC-EVs could substitute for the cellular counterpart in the treatment of preterm neonates with hypoxic-ischemic brain injury. This may open new clinical applications for "off-the-shelf" interventions with MSC-EVs.

Panfoli, I., et al. (2016). "Exosomes from human mesenchymal stem cells conduct aerobic metabolism in term and preterm newborn infants." Faseb j 30(4): 1416-1424.

Exosomes are secreted nanovesicles that are able to transfer RNA and proteins to target cells. The emerging role of mesenchymal stem cell (MSC) exosomes as promoters of aerobic ATP synthesis restoration in damaged cells, prompted us to assess whether they contain an extramitochondrial aerobic respiration capacity. Exosomes were isolated from culture medium of human MSCs from umbilical cord of >/=37-wk-old newborns or between 28- to 30-wk-old newborns (i.e.,term or preterm infants). Characterization of samples was conducted by cytofluorometry. Oxidative phosphorylation capacity was assessed by Western blot analysis, oximetry, and luminometric and fluorometric analyses. MSC exosomes express functional respiratory complexes I, IV, and V, consuming oxygen. ATP synthesis was only detectable in exosomes from term newborns, suggestive of a specific mechanism that is not completed at an early gestational age. Activities are outward facing and comparable to those detected in mitochondria isolated from term

MSCs. MSC exosomes display an unsuspected aerobic respiratory ability independent of whole mitochondria. This may be relevant for their ability to rescue cell bioenergetics. The differential oxidative metabolism of pretermvs.term exosomes sheds new light on the preterm newborn's clinical vulnerability. A reduced ability to repair damaged tissue and an increased capability to cope with anoxic environment for preterm infants can be envisaged.-Panfoli, I., Ravera, S., Podesta, M., Cossu, C., Santucci, L., Bartolucci, M., Bruschi, M., Calzia, D., Sabatini, F., Bruschettini, M., Ramenghi, L. A., Romantsik, O., Marimpietri, D., Pistoia, V., Ghiggeri, G., Frassoni, F., Candiano, G. Exosomes from human mesenchymal stem cells conduct aerobic metabolism in term and preterm newborn infants.

Drommelschmidt, K., et al. (2017). "Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury." Brain Behav Immun 60: 220-232.

OBJECTIVE: Preterm brain injury is a major cause of disability in later life, and may result in motor, cognitive and behavioural impairment for which no treatment is currently available. The aetiology is considered as multifactorial, and one underlying key player is inflammation leading to white and grey matter injury. Extracellular vesicles secreted by mesenchymal stem/stromal cells (MSC-EVs) have shown therapeutic potential in regenerative medicine. Here, we investigated the effects of MSC-EV treatment on brain microstructure and maturation, inflammatory processes and long-time outcome in a rodent model of inflammation-induced brain injury. METHODS: 3-Day-old Wistar rats (P3) were intraperitoneally injected with 0.25mg/kg lipopolysaccharide or saline and treated with two repetitive doses of 1x10(8) cell equivalents of MSC-EVs per kg bodyweight. Cellular degeneration and reactive gliosis at P5 and myelination at P11 were evaluated by immunohistochemistry and western blot. Long-term cognitive and motor function was assessed by behavioural testing. Diffusion tensor imaging at P125 evaluated long-term microstructural white matter alterations. RESULTS: MSC-EV treatment significantly ameliorated inflammation-induced neuronal cellular degeneration reduced microgliosis and prevented reactive astrogliosis. Short-term myelination deficits and long-term microstructural abnormalities of the white matter were restored by MSC-EV administration. Morphological effects of MSC-EV treatment resulted in improved long-lasting cognitive functions INTERPRETATION: MSC-EVs ameliorate inflammation-induced cellular damage in a rat model of preterm brain injury. MSC-EVs may serve as a novel therapeutic option by prevention of neuronal cell death, restoration of white matter microstructure, reduction of gliosis and long-term functional improvement.

Willis, G. R., et al. (2017). "Therapeutic Applications of Extracellular Vesicles: Perspectives from Newborn Medicine." Methods Mol Biol 1660: 409-432.

With the advancements in antenatal steroid therapies and

surfactant replacement, current clinical practices in neonatal intensive care units allow the survival of infants at very low gestational age. Despite these advances, there continues to be significant morbidity associated with extreme preterm birth that includes both short-term and long-term cardiorespiratory impairment. With no effective single therapy in preventing or treating developmental lung injuries, the need for new tools to treat and reduce risk of complications associated with extreme preterm birth is urgent. Stem cell-based therapies, in particular therapies utilizing mesenchymal stem (stromal) cells (MSCs), have shown promise in a number of animal models of lung pathologies relevant to neonatology. Recent studies in this field have consolidated the concept that the therapeutic mechanism of MSC action is paracrine, and this led to wide acceptance of the concept that the delivery of the MSC secretome rather than live cells may provide an alternative therapeutic approach for many complex diseases. Here, we summarize the significance and application of cell-free based therapies in preclinical models of neonatal lung injury. We emphasize the development of extracellular vesicle (EV)-based therapeutics and focus on the challenges that remain to be addressed before their application to clinical practice.

Bruschi, M., et al. (2018). "Metabolic Signature of Microvesicles from Umbilical Cord Mesenchymal Stem Cells of Preterm and Term Infants." Proteomics Clin Appl 12(3): e1700082.

PURPOSE: Microvesicles (MVs), 200-1000 nm bodies budding from the cell plasma membrane, are a promising source of biomarkers. This study aimed at comparing the proteome of MVs collected by ultracentrifugation from cultured Mesenchymal Stem Cells (MSCs) from Human Umbilical Cord of Preterm newborns (<34-weeks gestational age) in comparison to infants at Term (>/=37 weeks). This discovery study was designed to establish the signature of prematurity. EXPERIMENTAL DESIGN: Orbitrap MS, statistical, bioinformatics and biochemical analyses were employed. RESULTS: A total of 3253 proteins were identified, 78.3% matching among Preterm and Term. Principal component dimensional analyses showed that the two proteomes cluster separately. Cytoscape analysis showed that the top gene signatures cluster around inflammation and oxidative metabolism. Both Preterm and Term MVs consumed oxygen, and express ATP synthase and cytochrome oxidase, but only Preterm MVs synthesized ATP. The gene signature of Preterm condition mainly clusters around inflammation and metabolism. CONCLUSION AND CLINICAL RELEVANCE: MVs from MSCs conduct aerobic metabolism similarly to exosomes from the same cells, with interesting differences related to their biogenesis and function. The clinical relevance of the study lays in the perspective to utilize MVs as promising sensor of the inflammatory and metabolic state of the preterm newborn, to help in preventing the complications of prematurity.