Rahman, M. J., et al. (2014). "Exosomes released by islet-derived mesenchymal stem cells trigger autoimmune responses in NOD mice." Diabetes 63(3): 1008-1020.

Exosomes (EXOs) are secreted, nano-sized membrane vesicles that contain potent immunostimulatory materials. We have recently demonstrated that insulinoma-released EXOs can stimulate the autoimmune responses in nonobese diabetic (NOD) mice, a spontaneous disease model for type 1 diabetes. To investigate whether primary islet cells can produce EXOs, we isolated cells from the islet of Langerhans of NOD mice and cultured them in vitro. Interestingly, cultured islets release fibroblast-like, fast-replicating cells that express mesenchymal stem cell (MSC) markers, including CD105 and stem-cell antigen-1. These islet MSC-like cells release highly immunostimulatory EXOs that could activate autoreactive B and T cells endogenously primed in NOD mice. Serum EXO levels and EXO-induced interferon-gamma production were positively correlated with disease progression at the early prediabetic stage. Consistent with these observations, immunohistological analysis of pancreata showed that CD105(+) cells are restricted to the peri-islet area in normal islets but penetrate into the beta-cell area as lymphocyte infiltration occurs. Immunization with EXOs promoted expansion of transferred diabetogenic T cells and accelerated the effector T cell-mediated destruction of islets. Thus, EXOs could be the autoantigen carrier with potent adjuvant activities and may function as the autoimmune trigger in NOD mice.

Oh, K., et al. (2015). "In Vivo Differentiation of Therapeutic Insulin-Producing Cells from Bone Marrow Cells via Extracellular Vesicle-Mimetic Nanovesicles." ACS Nano 9(12): 11718-11727.

The current diabetes mellitus pandemic constitutes an important global health problem. Reductions in the mass and function of beta-cells contribute to most of the pathophysiology underlying diabetes. Thus, physiological control of blood glucose levels can be adequately restored by replacing functioning beta-cell mass. Sources of functional islets for transplantation are limited, resulting in great interest in the development of alternate sources, and recent progress regarding cell fate change via utilization of extracellular vesicles, also known as exosomes and microvesicles, is notable. Thus, this study investigated the therapeutic capacity of extracellular vesicle-mimetic nanovesicles (NVs) derived from a murine pancreatic beta-cell line. To differentiate insulin-producing cells effectively, a three-dimensional in vivo microenvironment was constructed in which extracellular vesicle-mimetic NVs were applied to subcutaneous Matrigel platforms containing bone marrow (BM) cells in diabetic immunocompromised mice. Long-term control of glucose levels was achieved over 60 days, and differentiation of donor BM cells into insulin-producing cells in the subcutaneous Matrigel platforms, which were composed of islet-like cell clusters with extensive capillary networks, was confirmed along with the expression of key pancreatic beta-cell markers. The resectioning of the subcutaneous Matrigel

platforms caused a rebound in blood glucose levels and confirmed the source of functioning beta-cells. Thus, efficient differentiation of therapeutic insulin-producing cells was attained in vivo through the use of extracellular vesicle-mimetic NVs, which maintained physiological glucose levels.

Heiler, S., et al. (2016). "Pancreatic cancer stem cell markers and exosomes - the incentive push." World J Gastroenterol 22(26): 5971-6007.

Pancreatic cancer (PaCa) has the highest death rate and incidence is increasing. Poor prognosis is due to late diagnosis and early metastatic spread, which is ascribed to a minor population of so called cancer stem cells (CSC) within the mass of the primary tumor. CSC are defined by biological features, which they share with adult stem cells like longevity, rare cell division, the capacity for self renewal, differentiation, drug resistance and the requirement for a niche. CSC can also be identified by sets of markers, which for pancreatic CSC (Pa-CSC) include CD44v6, c-Met, Tspan8, alpha6beta4, CXCR4, CD133, EpCAM and claudin7. The functional relevance of CSC markers is still disputed. We hypothesize that Pa-CSC markers play a decisive role in tumor progression. This is fostered by the location in glycolipid-enriched membrane domains, which function as signaling platform and support connectivity of the individual Pa-CSC markers. Outside-in signaling supports apoptosis resistance, stem cell gene expression and tumor suppressor gene repression as well as miRNA transcription and silencing. Pa-CSC markers also contribute to motility and invasiveness. By ligand binding host cells are triggered towards creating a milieu supporting Pa-CSC maintenance. Furthermore, CSC markers contribute to the generation, loading and delivery of exosomes, whereby CSC gain the capacity for a cell-cell contact independent crosstalk with the host and neighboring non-CSC. This allows Pa-CSC exosomes (TEX) to reprogram neighboring non-CSC towards epithelial mesenchymal transition and to stimulate host cells towards preparing a niche for metastasizing tumor cells. Finally, TEX communicate with the matrix to support tumor cell motility, invasion and homing. We will discuss the possibility that CSC markers are the initial trigger for these processes and what is the special contribution of CSC-TEX.

Nong, K., et al. (2016). "Hepatoprotective effect of exosomes from human-induced pluripotent stem cell-derived mesenchymal stromal cells against hepatic ischemia-reperfusion injury in rats." Cytotherapy 18(12): 1548-1559.

BACKGROUND: This study aimed to evaluate the effect of exosomes produced by human-induced pluripotent stem cell-derived mesenchymal stromal cells (hiPSC-MSCs-Exo) on hepatic ischemia-reperfusion (I/R) injury. METHODS: Exosomes were isolated and concentrated from conditioned medium using ultracentrifugation and ultrafiltration. hiPSC-MSCs-Exo were injected systemically via the inferior vena cava in a rat model of 70% warm hepatic I/R injury, and

the therapeutic effect was evaluated. The serum levels of transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) were measured using an automatic analyzer. The expression of inflammatory factors was measured using enzyme-linked immunosorbent assay (ELISA). Histological changes indicated changes in pathology and inflammatory infiltration in liver tissue. Apoptosis of hepatic cells in liver tissue was measured using terminal-deoxynucleoitidyl transferase mediated nick end labeling (TUNEL) staining along with apoptotic markers. RESULTS: hiPSCs were efficiently induced into hiPSC-MSCs with typical MSC characteristics. hiPSC-MSCs-Exo had diameters ranging from 50 to 60 nm and expressed exosomal markers (CD9, CD63 and CD81). Hepatocyte necrosis and sinusoidal congestion were markedly suppressed with a lower Suzuki score after hiPSC-MSCs-Exo administration. The levels of the hepatocyte injury markers AST and ALT were significantly lower in the treated group than in the control group. Inflammatory markers, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and high mobility group box 1 (HMGB1), were significantly reduced after administration of hiPSC-MSCs-Exo, which suggests that the exosomes have a role in suppressing the inflammatory response. Additionally, in liver tissues from the experimental group, the levels of apoptotic markers, such as caspase-3 and bax, were significantly lower and the levels of oxidative markers, such as glutathione (GSH), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), were significantly higher than in the control group. These data point to an anti-apoptotic, anti-oxidative stress response role for hiPSC-MSCs-Exo. CONCLUSIONS: Our results demonstrated that hiPSC-MSCs-Exo alleviate hepatic I/R injury, possibly via suppression of inflammatory responses, attenuation of the oxidative stress response and inhibition of apoptosis.

Wen, D., et al. (2016). "Mesenchymal stem cell and derived exosome as small RNA carrier and Immunomodulator to improve islet transplantation." J Control Release 238: 166-175.

Human bone marrow mesenchymal stem cells (hBMSCs) and their exosomes can suppress immune reaction and deliver small RNAs. Thus, they may improve islet transplantation by delivering small RNAs for promoting islet function and inhibiting immune rejection. Here, we proposed an hBMSC and its exosome-based therapy to overcome immune rejection and poor islet function, both of which hinder the success of islet transplantation. We found overexpressed siFas and anti-miR-375 in plasmid encoding shFas and anti-miR-375 transfected hBMSC-derived exosomes, which silenced Fas and miR-375 of human islets and improved their viability and function against inflammatory cytokines. This plasmid transfected hBMSCs downregulated Fas and miR-375 of human islets in a humanized NOD scid gamma (NSG) mouse model, whose immune reaction was inhibited by injecting hBMSC and peripheral blood mononuclear cell (PBMC) co-cultured exosomes. These exosomes suppressed immune reaction by inhibiting PBMC proliferation and enhancing regulatory T cell (Treg) function. Collectively, our studies

elucidated the mechanisms of RNA delivery from hBMSCs to human islets and the immunosuppressive effect of hBMSC and peripheral blood mononuclear cell co-cultured exosomes for improving islet transplantation.

Lu, D., et al. (2018). "Microgravity-induced hepatogenic differentiation of rBMSCs on board the SJ-10 satellite." Faseb j: fj201802075R.

Bone marrow-derived mesenchymal stem cells (BMSCs) are able to differentiate into functional hepatocytelike cells, which are expected to serve as a potential cell source in regenerative medicine, tissue engineering, and clinical treatment of liver injury. Little is known about whether and how space microgravity is able to direct the hepatogenic differentiation of BMSCs in the actual space microenvironment. In this study, we examined the effects of space microgravity on BMSC hepatogenic differentiation on board the SJ-10 Recoverable Scientific Satellite. Rat BMSCs were cultured and induced in hepatogenic induction medium for 3 and 10 d in custom-made space cell culture hardware. Cell growth was monitored periodically in orbit, and the fixed cells and collected supernatants were retrieved back to the Earth for further analyses. Data indicated that space microgravity improves the differentiating capability of the cells by up-regulating hepatocyte-specific albumin and cytokeratin 18. The resulting cells tended to be maturated, with an in-orbit period of up to 10 d. In space, mechanosensitive molecules of beta1-integrin, beta-actin, alpha-tubulin, and Ras homolog gene family member A presented enhanced expression, whereas those of cell-surface glycoprotein CD44, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, vinculin, cell division control protein 42 homolog, and Rho-associated coiled-coil kinase yielded reduced expression. Also observed in space were the depolymerization of actin filaments and the accumulation of microtubules and vimentin through the altered expression and location of focal adhesion complexes, Rho guanosine 5'-triphosphatases, as well as the enhanced exosome-mediated mRNA transfer. This work furthers the understanding of the underlying mechanisms of space microgravity in directing hepatogenic differentiation of BMSCs.-Lu, D., Sun, S., Zhang, F., Luo, C., Zheng, L., Wu, Y., Li, N., Zhang, C., Wang, C., Chen, Q., Long, M. Microgravity-induced hepatogenic differentiation of rBMSCs on board the SJ-10 satellite.

Nie, W., et al. (2018). "Human mesenchymal-stem-cells-derived exosomes are important in enhancing porcine islet resistance to hypoxia." Xenotransplantation 25(5): e12405.

BACKGROUND: Hypoxia-induced damage is one of the key factors associated with islet graft dysfunction. Mesenchymal stem cells (MSCs) could be used to enhance the therapeutic effect of islet transplantation due to their paracrine potential such as exosomes. In this study, we investigated whether exosomes from human umbilical cord-derived MSC-conditioned medium (hu-MSC-CM) could increase the survival and function of neonatal porcine islet cell clusters (NICCs)

exposed to hypoxia. METHODS: Neonatal porcine islet cell clusters were cultured with hu-MSC-CM, with or without exosomes, and native medium RPMI-1640 (Control) under hypoxic conditions (1% O2 ). The effects of exosomes on NICCs viability and function in vitro were examined by FACS, the Loops system, and the Extracellular Flux assay, respectively. RESULTS: Compared with NICCs cultured in RPMI-1640 medium and hu-MSC-CM without exosomes, the survival ratio, viability, and function increased in NICCs cultured in hu-MSC-CM with exosomes. CONCLUSIONS: This study found that hu-MSC-CM could protect NICCs from hypoxia-induced dysfunction, and exosomes played an important role in hypoxic resistance, suggesting a potential strategy to improve islet transplantation outcomes.

Xue, R., et al. (2018). "A Rising Star in Pancreatic Diseases: Pancreatic Stellate Cells." Front Physiol 9: 754.

Pancreatic stellate cell (PSC) is a type of pluripotent cell located between pancreatic lobules and the surrounding area of acinars. When activated, PSC can be transformed into myofibroblast-like cell. A number of evidences suggest that activated PSC is the main source of the accumulation of extracellular matrix (ECM) protein under the pathological conditions, which lead to pancreatic fibrosis in chronic pancreatitis and pancreatic cancer. Recent studies have found that PSC also plays an important role in the endocrine cell function, islet fibrosis and diabetes. In order to provide new strategies for the treatment of pancreatic diseases, this paper systematically summarizes the recent researches about the biological behaviors of PSC, including its stem/progenitor cell characteristics, secreted exosomes, cellular senescence, epithelial mesenchymal transformation (EMT), energy metabolism and direct mechanical reprogramming.