Received: 21 April 2020 | Accepted: 21 April 2020

DOI: 10.1002/sctm.20-0173

PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

STEM CELLS TRANSLATIONAL MEDICINE

Stuart P. Atkinson

Centro de Investigación Príncipe Felipe, Valencia, Spain. Email: satkinson@cipf.es

The enteric nervous system, one of the main divisions of the autonomic nervous system, governs the function of the gastrointestinal tract[1] and operates largely independently of the central nervous system. The dysfunction of the enteric nervous system can impair muscle function within the gastrointestinal tract, leading to the development of dysmotility syndromes[2] and gastroparesis (or delayed gastric emptying)[3] among other neuromuscular disorders. Unfortunately, current standard pharmacological and surgical treatments for conditions such as gastroparesis are palliative only and unsuited for long-term relief in patients; can regenerative medicine offer more efficient therapeutic options? Specifically, can we develop optimized strategies to replace lost or damaged cells or support intrinsic repair and regeneration abilities to promote recovery of neuromuscular function? Possibilities include the transplantation of neural stem/progenitor cells into the gastrointestinal tract as a means to replace lost neurons or the provision of proregenerative conditions via the secretion of paracrine-acting factors by administered mesenchymal stem cells (MSCs). In the first of our Featured Articles this month from *STEM CELLS Translational Medicine*, Dadhich and Bitar employ an ex vivo rat model of gastroparesis to demonstrate how the administration of neural progenitor cells (NPCs) can prompt optimal restoration of functionality when accompanied by specialized gastrointestinal tract interstitial cells.[4] In a Related Article published in *STEM CELLS*, Lin et al discovered that the administration of in vitro preconditioned MSCs represent a promising therapy for gastrointestinal dysfunctions brought on by enteric nervous system injury or neurodegenerative disorders.[5]

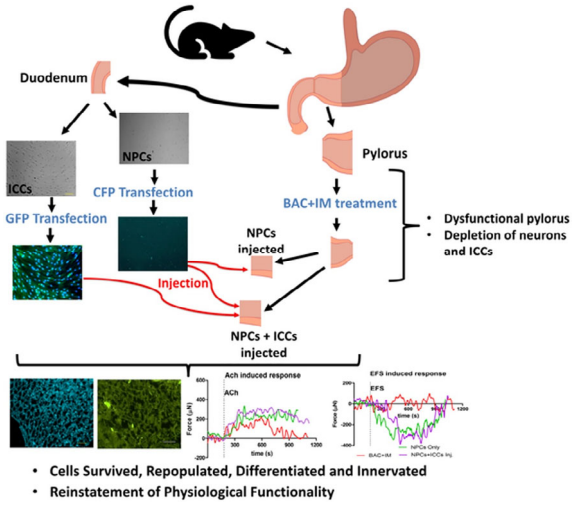
The efficient homing of hematopoietic stem and progenitor cells (HSPCs) to the bone marrow can significantly influence hematopoietic repopulation in patients undergoing hematopoietic stem cell transplantation (HSCT), as studies have established that the majority of HSPCs become trapped or "tethered" in various nonhematopoietic organs.[6] Therefore, targeting migration and homing to the bone marrow may represent an exciting alternative to the in vitro-expansion of rare HSPCs present within umbilical cord blood, as an example, required to generate a therapeutically relevant number of cells.[7] Enhanced migrational and homing abilities may also improve the effectiveness of many MSC therapies/ although these multifunctional cells can exert their influence from afar through paracrine-acting secreted factors, an increase in the proportion of MSCs that target a site of disease/injury will likely enhance therapeutic outcomes.[8] Alternatively, as is the case in tumorigenesis, the targeted inhibition of cell migration has the potential to slow or halt disease progression, inhibit tumor relapse from residual or dormant cancer cells after surgical resection or chemotherapy, and reduce metastasis. In the second of our Featured Articles this month from *STEM CELLS Translational Medicine*, Liu et al report on an innovative strategy to improve HSPC homing and long-term engraftment in mouse bone marrow following HSCT, which has the potential to boost hematopoietic repopulation efficiency in patients.[9] In a Related Article published in *STEM CELLS*, Mamchur et al discovered that the inherent tumor resistance of long-living blind mole-rats derives from the reduced ability of adipose-derived MSCs to migrate and home to the tumor niche, which inhibits vasculogenesis and tumor progression.[10]

FEATURED ARTICLES

Dual Cell Therapy as an Enhanced Treatment for Gastroparesis

Many conventional treatments available for gastroparesis remain inadequate for long-term relief; however, recent research has provided evidence that cell transplantation may represent an effective means to treat gastrointestinal neuromuscular disorders. Indeed, one study highlighted the survival of neural stem cells after transplantation into the mouse pylorus (which connects the stomach to the duodenum),[11] although the ability of said cells to migrate, proliferate, and generate functional neurons remained unknown. Now, a new *STEM CELLS Translational Medicine* article from Prabhash Dadhich and Khalil N. Bitar (Wake Forest Institute for Regenerative Medicine, Winston-Salem, North Carolina) explores the cotransplantation of adult NPCs and interstitial cells of Cajal (ICCs)[12] in an ex vivo gastroparesis model as an optimized therapeutic approach.[4] The authors first ablated neurons and ICCs in the rat pylorus to generate gastroparesis-associated neuromuscular problems and then codelivered ICCs and NPCs into the injured area. Encouragingly, both cell types integrated into the dysfunctional pylorus, promoted recovery of the lost cell populations, and restored neuromuscular functionality, as measured by

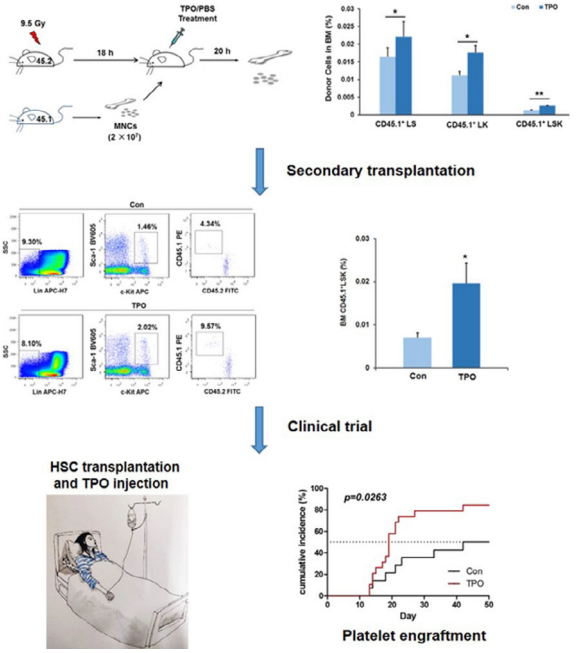
agonist-induced excitatory contraction and neuron-evoked relaxation. Significantly, the coinjection of ICCs with NPCs, evaluated for the first time in this article, significantly improved neuronal differentiation and functional restoration when compared to the administration of NPCs alone. Overall, the authors hope that the simultaneous delivery of ICCs and NPCs will soon represent an efficient cell therapy for the treatment of gastrointestinal neuromuscular disorders such as gastroparesis.



https://doi.org/10.1002/sctm.19-0316

Improving the Homing of Hematopoietic Stem/Progenitor Cells to Boost Therapeutic Outcomes

Researchers led by Hengxiang Wang (Medical Center of Air Forces, PLA), Yanhua Li (Beijing Institute of Radiation Medicine), and Xuetao Pei (Institute of Health Service and Transfusion Medicine, Beijing, China) recently evaluated the potentially beneficial effect of thrombopoietin (or TPO) treatment as a means to improve outcomes following HSCT. Previous research established that thrombopoietin, a glycoprotein hormone, regulates hematopoiesis and HSC self-renewal and quiescence[13] and can also promote HSPC engraftment and hematopoietic recovery in an irradiated mouse model due to increased cell proliferation and survival.[14] In their new *STEM CELLS Translational Medicine* article,[9] Liu et al discovered that a single dose of thrombopoietin after bone marrow transplantation fostered significant improvements in homing of HSPCs to the bone marrow and in short- and long-term engraftment in a mouse model. At the mechanistic level, the authors found evidence that thrombopoietin enhanced HSPC homing by the downregulated expression and secretion of matrix metalloproteinase 9 and the subsequent increase in stromal cell-derived factor 1α chemokine levels within the bone marrow niche. These hugely encouraging results also prompted a clinical trial of thrombopoietin treatment in patients receiving haploidentical bone marrow and peripheral blood transplantation; encouragingly, this strategy improved platelet engraftment outcomes, especially in patients with severe aplastic anemia. Overall, these findings suggest that increased HSPC homing following thrombopoietin treatment may represent a simple and feasible approach to the improvement of clinical outcomes in patients undergoing bone marrow transplants/HSCT.



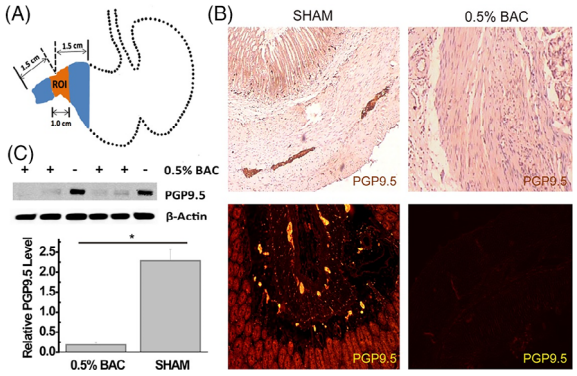
https://doi.org/10.1002/sctm.19-0220

RELATED ARTICLES

Mesenchymal Stem Cells Support Enteric Nerve Regeneration Through Growth Factor Feedback

The administration of MSCs represents a possible therapeutic approach for problems related to the enteric nervous system; however, while studies have described the possible contribution of bone marrow MSCs to 5-HT4 receptor agonist-mediated neurogenesis in a rectal anastomosis model,[15,16] the exact role of MSCs in enteric repair remained unclear.[17] In a recent *STEM CELLS* article, researchers from the laboratories of Xuhang Li (Johns Hopkins, Baltimore, Maryland) and Xiaohua Hou (Tongji Medical College/Union Huazhong University of Science and Technology, Wuhan, China) reported on the potential of bone marrow MSCs to promote neurogenesis in the gastrointestinal tract following in vitro preconditioning with glial cell-derived neurotrophic factor (GDNF) and fetal gut extracts to mimic the growth microenvironment of fetal neurons.[5] Lin et al established that preconditioned MSCs induced de novo regeneration of neurons

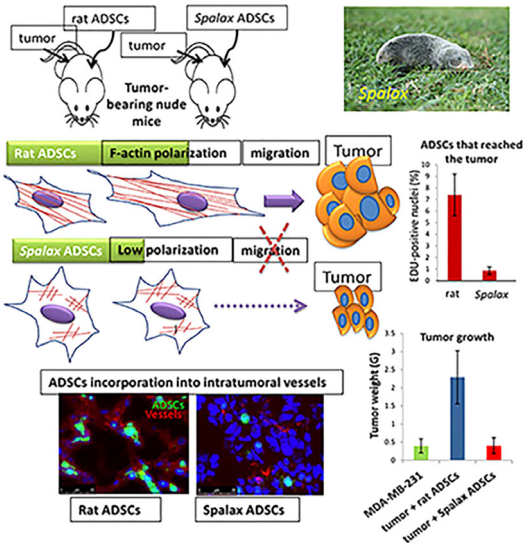
(as determined by PGP 9.5 detection) and enhanced both basal pyloric contractility and electric field stimulation-induced relaxation after subserosal transplantation into an area of rat pylorus denervated by benzalkonium chloride (BAC) treatment. Subsequent analysis established that MSCs survived well and migrated without dedifferentiating; however, nerve regeneration did not involve the transdifferentiation of MSCs, suggesting that paracrine-acting factors secreted from MSCs may represent the true regenerative mechanism. Indeed, given the elevated levels of GDNF observed in both the preconditioned MSCs and the previously denervated pylorus, the authors hypothesized that a GDNF positive-feedback mechanism may regulate neuronal regeneration in this case. Overall, these encouraging findings supported the application of preconditioned MSCs in the treatment of enteric nerve disorders.



https://doi.org/10.1002/stem.2197

Reduced MSC Homing Inhibits Tumor Progression in Blind Mole-Rats

The Middle Eastern subterranean blind mole-rat possesses an unusually long lifespan for an animal with a low body mass; however, its resistance to cancer and tolerance of hypoxia represent more notable characteristics. Previous research from the laboratory of Irena Manov (University of Haifa, Israel) had established the resistance of this mole-rat species to chemical carcinogenesis and that mole-rat fibroblasts possessed the capacity to inhibit the growth of cancer cells.[18] The team's more recent *STEM CELLS* article evaluated the ability of naked mole-rat adipose-derived MSCs (or ADSCs) to migrate toward tumor cells, differentiate into endothelial cell types, and promote intratumoral angiogenesis.[10] Mamchur et al discovered that rat MSCs displayed potent migratory potential in tumor-bearing mice and promoted the formation of dense MSC-derived capillary-like structures; however, naked mole-rat MSCs displayed a lower migratory potential and an associated lower ability to form MSC-derived capillary-like structures. Moving to in vitro assays to decipher any mechanistic insight, the team demonstrated that the inhibition of myosin light chain phosphorylation by blocking Rho-kinase activity prompted an increase in the motility and migration of MSCs. In summary, the authors highlight the lack of MSC migration and homing as a key mechanism mediating the lack of tumor development in naked mole-rats, and they hope that further research into this mechanism may foster the development of novel cancer-preventive strategies in humans.



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