STEM CELLS TRANSLATIONAL MEDICINE®

PREVIEWS

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

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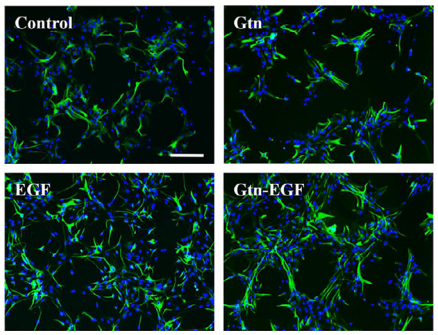
Glial cells make up the bulk of cells within the nervous system and comprise the Schwann cells and oligodendrocytes that mediate myelination, the microglia that mediate local immune defense, and astrocytes - star-shaped cells that represent 25% of total brain volume. Astrocytes play a range of varied roles that include the provision of nutrition, support, and protection to neurons under physiological conditions; however, studies have also indicated a significant role for astrocytes in the development of central nervous system (CNS) pathologies [1] and the regulation of neural stem cell (NSC) behavior through the activity of multiple paracrine acting factors. For example, astrocytes secrete pro-inflammatory cytokines in response to mechanical trauma and ischemia [2], while cerebral ischemia/reperfusion-like stimuli prompt the release of high-mobility group box 1 from astrocytes to induce neural stem/progenitor proliferation and possible brain tissue repair [3]. Overall, these findings suggest that in-depth research into astrocyte biology may foster the development of new means to enhance recovery in the CNS following traumatic injury or neurodegeneration that act synergistically with NSC-based approaches. In our first Featured Article published in *Stem Cells Translational Medicine* this month, Chan et al. report how epidermal growth factor (EGF)-containing hydrogels shift astrocytes into a pro-recovery phenotype; a discovery that may foster the development of enhanced CNS regenerative medicine therapies combining neuron- and astrocyte-based approaches [4]. In a Related Article published in *Stem Cells*, Dai et al. established that neonatal rat astrocytes promoted NSC proliferation to a greater extent than adult rat astrocytes thanks to the overexpression of Tenascin-C (TNC); can these findings facilitate enhanced neuroregeneration in the damaged brain [5]?

Inflammation or tissue damage to organs can trigger a cascade of cellular and molecular responses that promote the development of tissue fibrosis - the excessive accumulation of fibrous connective tissue. Unfortunately, we currently lack adequate treatment strategies for fibrosis, which can cause permanent scarring, organ malfunction, and death. Injury to the microvascular system that occurs during chronic kidney disease correlates with progression to renal fibrosis [6] and loss of function [7] and has hence become a target for therapeutic interventions. The administration of vasoprotective and antifibrotic cytokines or stem/somatic cells that secrete said cytokines have been evaluated as therapeutic options for kidney fibrosis; however, the short half-lives of cytokines and the low survival of cells post-transplantation has hampered the development of these approaches. Radiation therapy can also induce tissue fibrosis as an unwanted side-effect of cancer treatment, with progressive functional and anatomic impairments common outcomes [8]. Treatment strategies include mesenchymal stem cell- (MSC) and endothelial cell-based approaches [9]; however, previous studies have highlighted the regenerative potential of adipose-derived stem cells (ASCs) in wound healing and radiation-induced tissue injuries [10], thereby suggesting them as a possible treatment for radiation-induced fibrosis (RIF). In our second Featured Article published in *Stem Cells Translational Medicine* this month, Imafuku et al. report that the allogeneic transplantation of rat bone-marrow MSC (BMSC) sheets onto the kidney surface of a rat renal ischemia-reperfusion-injury model prevents renal fibrosis via microvascular protection [11]. In a Related Article published in *Stem Cells*, Ejaz et al. established the ability of ASCs to improve limb movement and skin epithelial architecture in a mouse model of RIF and highlighted the essential role of secreted hepatocyte growth factor (HGF) [12].

FEATURED ARTICLES

Shifting Astrocytes into Neuro-Supportive Phenotypes for Enhanced CNS Therapies

While recent regenerative approaches have aimed to repair or reconstitute neurons through the combination of cell- or growth factor-based therapies with biomaterials to enhance bioavailability and delivery [13], we lack a full understanding of how said biomaterials may influence astrocyte responses during CNS regeneration [14]. In the hope of advancing this area of study, researchers from the laboratory of Eng H. Lo (Massachusetts General Hospital, Boston, Massachusetts, USA) evaluated the influence of EGF-containing gelatin (Gtn) hydrogels on astrocytes in culture. Writing in *Stem Cells Translational Medicine* [4], Chan et al. revealed that while EGF and EGF-hydrogels increased the proliferation of primary rat cortical astrocytes to a similar degree, only the EGF-hydrogels displayed the capacity to modulate astrocyte activation by shifting gene expression profiles away from the inhibitory A1-like astrocyte phenotype (expression of Fbln5 and Rt1-S3) toward



the potentially beneficial A2-like phenotype (expression of Clcf1, Tgm1, and Ptgs2). Further analyses employing conditioned media derived from astrocytes cultured on EGF-hydrogels revealed the protection of neurons against injury and the promotion of synaptic plasticity after oxygen-glucose deprivation, thereby providing further evidence that EGF-hydrogels shift astrocytes into neuro-supportive phenotypes. Overall, the authors believe that their findings support future studies to dissect molecular mechanisms and evaluate the potentially beneficial effects of biomaterial-shifted astrocytes in vivo.

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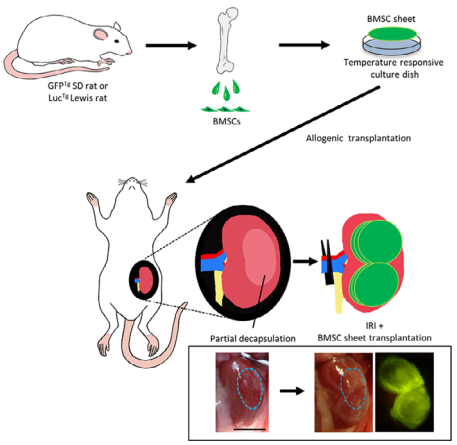
Suppressing Renal Fibrosis Through Microvascular Protection with MSC Sheets

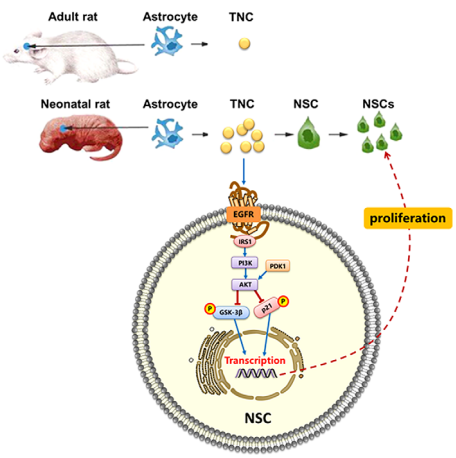


A recent article from the laboratory of Tatsuya Shimizu (Women's Medical University, Tokyo, Japan) reported that the transplantation of transgenic human mesothelial cell sheets onto the kidney surface in a rat renal fibrosis model promoted the long-term survival of transplanted cells and induced robust therapeutic effects [15]. In their follow-up study published in *Stem Cells Translational Medicine*, Imafuku et al. evaluated an allogeneic transplantation approach by assessing the consequences of transplanting rat BMSC sheets onto the kidney surface in a rat renal ischemia-reperfusion injury model [11]. Previous research had highlighted the beneficial effects of BMSC sheet technology, with ischemic cardiac disease as a prime example [16]. In the current study, the transplantation of rat MSC sheets onto the damaged kidney permitted donor-cell survival, the sustained expression of vasoprotective and antifibrotic cytokines, and the associated upregulated expression of the relevant receptors in the kidney when compared with untreated rats or rats receiving BMSCs intravenously. Encouragingly, rat BMSC sheet transplantation also significantly suppressed renal dysfunction, microvascular injury, and suppressed transition into progressive fibrosis via long-term vasoprotection, as evidence by three-dimensional micro-computed tomography-based analysis. Overall, these encouraging findings suggest that BMSC sheets prevented renal fibrosis via microvascular protection and establish this treatment modality as a potential novel therapy for various kidney diseases.

DOI: 10.1002/sctm.19-0113

Related Articles

Young Astrocytes Boost Neural Stem Cell Proliferation via Tenascin-C



While astrocytes obtained from the perinatal rodent brain can strongly influence the function of other cells in the CNS, such as NSCs [17], astrocytes obtained from the adult rodent brain fail to elicit a similar response [18]. Researchers from Nantong University (Nantong, China) suspected that this age-related reduction in astrocyte activity might contribute to the worsened neurologic deficits observed in adults suffering from traumatic brain injury (TBI) when compared with young patients. Their subsequent research published in *Stem Cells* [5] compared the influence of conditioned medium derived from neonatal or adult rat astrocytes on NSCs to explore the influence of paracrine acting factors on NSC function. Dai et al. first confirmed that neonatal rat astrocytes, but not adult rat astrocytes, significantly increased the proliferation of NSCs and then compared protein profiles of conditioned media taken from both astrocyte types by mass spectrometry-based proteomic analysis. The authors discovered the elevated expression of TNC in neonatal astrocytes only, with subsequent in vitro analyses suggesting that this protein binds to the EGF receptor on NSCs to promote proliferation through the PI3K-AKT pathway.

Finally, they confirmed in vivo relevance by confirming the abundant expression of TNC in the cerebral cortex of neonatal rats and by demonstrating how TNC exposure promoted damage repair in a rat TBI model through enhanced NSC proliferation. While this study provides a mechanism behind the age-dependent level of neuroregeneration, these findings also highlight a potential future therapeutic target for injury repair after TBI in TNC.

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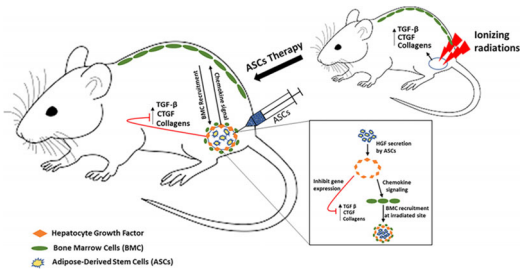
Treating Radiation-Induced Fibrosis with Adipose-Derived Stem Cell Therapy



Cell therapies for RIF have included MSC- and endothelial cell-based approaches [9]; however, recent results have suggested that the application of ASCs or autologous fat tissue may represent a potentially effective means to treat fibrosis [19]. In a recent *Stem Cells* article, researchers led by J. Peter Rubin (University of Pittsburgh, Pennsylvania, USA) sought to confirm the potential of ASCs as a therapy for RIF in vivo and explore the mechanisms controlling the therapeutic effect [12]. Ejaz et al. first studied a mouse model of RIF, which involved a single focused dose of radiation to the mouse hind limb with the loss of limb movement acting as a functional readout for fibrotic development. Encouragingly, a single injection of ASCs 28 days after irradiation improved both skin epithelium architecture (by reducing epithelial thickness and collagen deposition) and limb movement (suggesting a reduction in fibrosis) by day 40 compared with irradiated controls. Using a non-contact transwell coculture system, the authors then discovered that ASCs downregulated fibrosis-related gene expression in irradiated human foreskin fibroblasts and highlighted ASC-secreted HGF as the driving force behind the antifibrotic effects by inducing the downregulation of fibrotic gene expression and the recruitment of bone marrow cells. Overall, the authors provide evidence that ASC administration represents an effective strategy to reduce fibrosis induced by radiation exposure in a mouse model.

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