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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

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The transplantation/administration of cells differentiated from human pluripotent stem cells (hPSCs), including embryonic stem cells and patient-specific induced pluripotent stem cells (iPSCs), represents a promising therapeutic strategy for a wide range of conditions. However, there exists the possibility that the differentiated progeny of hPSCs may accumulate proliferation-enhancing abnormalities during in vitro culture or that hPSCs may "survive" the differentiation process and contaminate the final cell product, with both these scenarios representing a tumorigenic threat.[1] Proposed solutions to this problem have included the screening and identification of "safe" hPSC clones or the optimized differentiation of hPSCs into the somatic cell type required[2]; however, such "indirect" strategies fail to negate the risk of tumorigenicity. Therefore, we require a combination of pretransplant safety assessments with a means to track, target, and eliminate potentially problematic cells for hPSC-based regenerative therapies to safely advance. How far have we come toward achieving this goal? In our first Featured Article published in Stem Cells Translational Medicine this month, Tanimoto et al exploit the inherent characteristics of human iPSC-derived neural stem/progenitor cells (hiPSC-NS/PCs) to monitor undifferentiated and potentially tumorigenic cells post-transplantation in a noninvasive manner in an attempt to ensure the safe development of this treatment strategy.[3] In a Related Article published in Stem Cells, Ide et al described a novel method for the efficient generation of a diverse selection of tumorigenic cell-targeting lentiviral vectors that can specifically and efficiently eliminate undifferentiated hPSCs both in vitro and in vivo.[4]

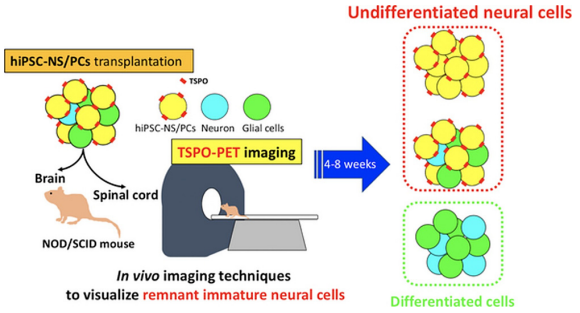
Ongoing neurogenesis in the adult mammalian brain occurs primarily via the activity of NS/PCs residing in the subventricular zone (SVZ) of the lateral ventricles and the dentate gyrus of the hippocampus. Studies have provided evidence for the upregulation of adult neurogenesis in response to various pathological conditions to promote functional recovery of the damaged brain. The potentiation of this limited regenerative response represents a promising means to remedy a variety of conditions that impact the central nervous system, and while the infusion of growth factors can boost the neurogenesis of NS/PCs, prolonged exposure can negatively impact their differentiation.[5] Such unwanted side effects have prompted the exploration of the paracrine-acting proregenerative capacity of mesenchymal stem cells (MSCs) as an alternative.[6,7] Exosomes represent one MSC-derived paracrine-acting factor that may positively influence adult neurogenesis through the transport of proteins, lipids, and nucleic acids.[8] Can we now improve the regenerative potential of MSC exosomes and construct a stem cell-free therapeutic approach to promote functional recovery in the damaged brain? In our second Featured Article published in Stem Cells Translational Medicine this month, Chen et al describe how prostaglandin E2 receptor 4 (EP4) antagonist-induced MSCs secrete exosomes containing a myelin-associated enzyme with the ability to promote neurogenesis in the damaged hippocampi.[9] In a Related Article published in Stem Cells, Cameron et al established that neural stem cells (NSCs) resist apoptosis and ensure ongoing neurogenesis following exposure to concurrent chemotherapy and radiotherapy, thereby suggesting the relative safety of targeting neurogenic brain regions during the treatment of glioblastoma.[10]

FEATURED ARTICLES

Monitoring Tumorigenic Risk In Vivo Following Neural Stem Cell Transplants

In their recent Stem Cells Translational Medicine study,[3] researchers from the laboratories of Masaya Nakamura and Hideyuki Okano (Keio University School of Medicine, Tokyo, Japan) sought to discover a means to noninvasively track the cellular differentiation dynamics of hiPSC-NS/PCs after their transplantation into the human central nervous system as a treatment for neuropathological conditions and neurotrauma. The strategy employed by Tanimoto et al aimed to visualize leftover undifferentiated and therefore potentially tumorigenic neural cells in the brains/spinal cords of immune-deficient (NOD/SCID) mice after hiPSC-NS/PC transplantation with positron emission tomography (PET) using 18 kDa translocator protein (TSPO) radioligands (eg, [^{18}F] FEDAC) as labels,[11] given the fact that the high TSPO expression levels in rodent NS/PCs decrease during neuronal differentiation.[12] Encouragingly, the authors established the ease and effectiveness of this approach in the visualization of residual immature neural cells in vitro and in vivo by evaluating hiPSC-NS/PC lines with different known tumorigenic properties. Furthermore, in vivo PET

analysis revealed the accumulation of radioligands in the administration site of "unsafe" TSPO-expressing and potentially tumorigenic iPSC-NS/PCs and validated this finding by ex vivo autoradiography. Taken as a whole, this fascinating new study highlights PET imaging with TSPO radioligands as an effective means to monitor differentiation and maturation following hiPSC-NS/PC transplantation and thereby ensure the safety of this treatment approach in humans in the future.



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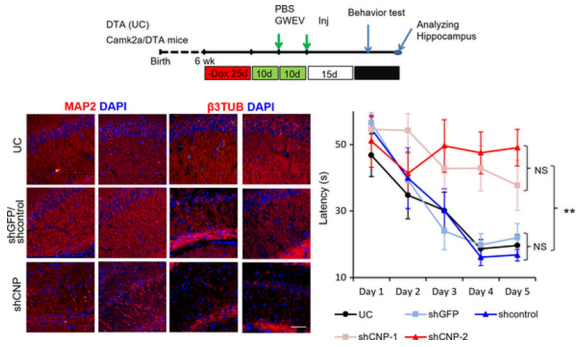
Induced MSC Exosome-Derived Factor Boosts Neurogenesis in Damaged Hippocampi

Previous research from the laboratory of Hua-Jung Li (National Health Research Institutes, Zhunan, Taiwan) demonstrated that EP4 antagonist-induced MSC exosomes possessed a greater ability to rescue cognition and learning deficiencies caused by hippocampal damage.[13] In their new STEM CELLS TRANSLATIONAL MEDICINE article,[9] the team now report on the MSC exosome-derived components that prompt these improved regenerative effects. Chen et al first established that EP4 antagonist-induced MSC exosomes promoted neurosphere formation in vitro and increased neurogenesis and neuritogenesis in damaged hippocampi when compared with basal exosomes. Their subsequent analysis revealed that induced exosomes contained 20-fold higher levels of 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) than basal exosomes and that reducing CNP levels inhibited the ability of induced exosomes to promote neurogenesis and neuritogenesis in damaged hippocampi. Previous studies have reported the enrichment of CNP in myelin and oligodendrocyte and neuron cell bodies and suggested a role for CNP in myelin formation and axonal integrity.[14,15] Encouragingly, CNP-containing induced exosomes partially ameliorated the cognition, learning, and memory deficiencies caused by hippocampal damage when systemically administered in mice, although the loss of exosomal CNP inhibited these regenerative effects. While the authors point to exosomal CNP as a promising means to promote neurogenesis/neuritogenesis in damaged hippocampi without the need to transplant MSCs themselves, they also suggest that their experimental approach may permit the discovery of additional exosomal components with a variety of therapeutic roles.



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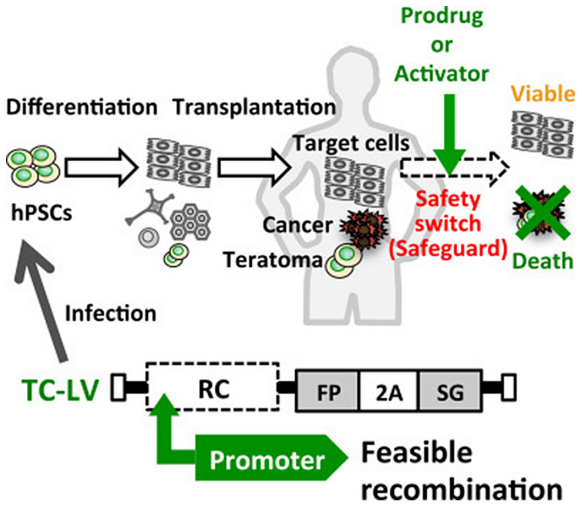
RELATED ARTICLES

Lentiviral Vectors Boost the Safety of Human Pluripotent Stem Cell-Based Therapies

As part of their research toward addressing the tumorigenic risk following the transplantation of hPSCs-derived cells, researchers led by Kenichiro Kosai (Kagoshima University, Japan) have previously described a novel method (adenoviral conditional targeting) for the isolation of target cells to increase the efficacy and safety of hPSC-based regenerative medicine,[16] as well as a novel oncolytic virus-based strategy that specifically and efficiently killed undifferentiated cells to inhibit teratoma formation after hPSC transplantation.[17] In their subsequent STEM CELLS article,[4] Ide et al developed a suicide gene-based approach for the elimination of potentially tumorigenic hPSCs by applying a novel methodology for the efficient generation of tumorigenic cell-targeting lentiviral vectors (TC-LVs) that enables the systematic identification of the best suicide genes and accompanying promoters. The authors exploited a two-plasmid system to rapidly and simultaneously construct TC-LVs with different promoters, and the team soon discovered that TC-LVs expressing the herpes simplex virus thymidine kinase from the



survivin promoter, which is specific for cancer and undifferentiated cells, prompted the conversion of the pro-drug ganciclovir into a cytotoxic form and led to elevated levels of cell elimination in undifferentiated transduced hPSCs. Excitingly, ganciclovir treatment also abolished teratoma formation by TC-LV-infected hPSCs after transplantation into mice without any harmful side effects. The authors hope that the application of this suicide gene therapy will pave the way toward safe clinical applications of hPSC-based regenerative medicine.

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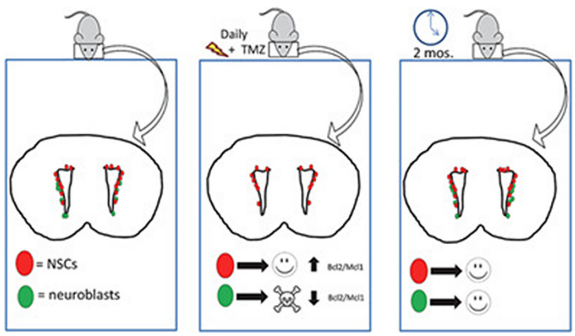
Apoptosis Resistance of Neural Stem Cells Supports Neurogenesis Following Glioblastoma Treatment

The SVZ, located along the walls of the lateral ventricles, represents the largest source of NSCs in the adult brain[18] and, unfortunately, is also one potential site of origin/invasion for aggressive glioblastoma tumors.[19] The standard of care for treatment of glioblastoma involves concurrent temozolomide (an alkylating agent that damages DNA and induces apoptosis) and radiation therapy followed by adjuvant temozolomide chemotherapy; however, the impact of this therapeutic regimen on SVZ-resident NSCs and their neurogenic capacity remained to be fully evaluated. In their recent STEM CELLS article,[10] researchers led by Michael L. Freeman (Vanderbilt University Medical Center, Nashville, Tennessee, USA) discovered that while glioblastoma-targeting chemotherapy and radiotherapy led to the induction of significant levels of apoptosis in neuroblasts in tumor-bearing and non-tumor-bearing preclinical murine models, NSCs themselves displayed high levels of resistance. Interestingly, Cameron et al also established that the high resistance to apoptosis in NSCs did not derive from elevated levels of DNA repair; instead, NSCs expressed higher levels of the Bcl2 and Mcl1 antiapoptotic proteins than neuroblasts, and this characteristic permitted ongoing neurogenesis after exposure of NSCs to the stress of concurrent chemotherapy and radiotherapy. Overall, these encouraging findings suggest that resistance to apoptosis in NSCs would sustain neurogenesis during glioblastoma treatment, thereby providing evidence of the relative safety of this therapeutic strategy.



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