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.

Stuart P. Atkinson

Centro de Investigación Príncipe Felipe, Valencia, Spain
E-mail: satkinson@cipf.es

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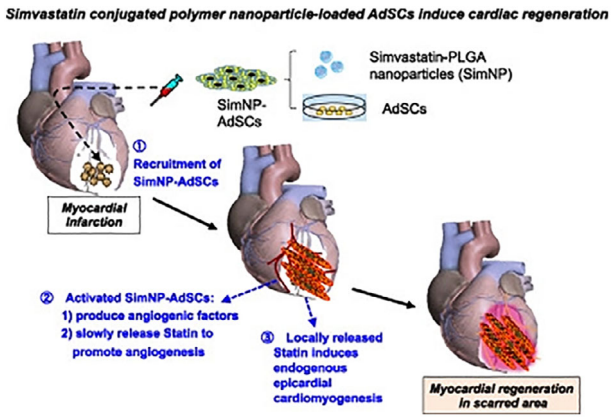
Myocardial infarctions in coronary artery disease patients can prompt ischemic heart damage, involving the loss of cardiomyocytes and subsequent cardiac dysfunction. Unfortunately, the general lack of an endogenous regenerative response in the human heart further compounds this serious condition. Alongside surgical and pharmacological approaches, stem cell therapeutics represent a potentially exciting treatment strategy, and multiple studies have offered evidence that endothelial progenitor cells (EPCs) as well as stem cells derived from the umbilical cord, amnion, and bone marrow, amongst many others, have huge potential in cardiac regenerative medicine. Of these stem cell populations, adipose-derived mesenchymal stem cells (ASCs) exhibit certain advantages when compared with other somatic stem cell types, including their inherent plasticity and the ability to isolate vast amounts of cells through minimally-invasive surgical techniques. Importantly, ASCs also can differentiate into cardiomyocytes [1] and secrete paracrine-acting factors that support cardiac regeneration [2, 3], thereby promoting the development of ASC-based approaches for the treatment of myocardial infarction. However, synergistic combinations of pharmacological and stem cell treatment approaches may provide for enhanced therapeutic outcomes, while the search for additional stem cell types with enhanced therapeutic potential continues. In our first Featured Article this month published in *Stem Cells Translational Medicine*, Yokoyama et al. describe how a single low-dose administration of ASCs loaded with statin-conjugated polymer nanoparticles can induce spontaneous cardiac regeneration in a mouse model of myocardial infarction [4]. In a Related Article published in *Stem Cells*, Nelson et al. used differentiating "recombineered" mouse embryonic stem cells (mESCs) to isolate a cardiac progenitor cell population expressing the ventricle-specific gene *Irx4* that could be used for ventricular repair after myocardial infarction [5].

Ischemic stroke, one of the major causes of death and disability worldwide [6], occurs when the arteries to the brain become narrowed or blocked, causing severely reduced blood flow and the initiation of an inflammatory cascade that leads to brain tissue damage. Currently developed therapies only aim to break down or remove the causative blocking event, usually clots formed in blood vessels, to restore blood flow and inhibit cell death in the brain. The development of neurorestorative stem cell-based therapies hopes to offer an effective treatment option for ischemic stroke sufferers [7], and analyses of preliminary studies of stem cell transplantation to save or replace damaged nerve tissue suggest the safety and potential effectiveness of this approach [8]. While neural stem/progenitor cells (NSCs/NPCs) represent an obvious choice for ischemic stroke treatment, they represent a problematic cell population to isolate in sufficient numbers from human patients and then expand in vitro. For this reason, many studies have used mesenchymal stem cells, due to their pro-regenerative and anti-inflammatory secretory profile or, alternatively, have sought to generate NSCs from pluripotent stem cell sources or isolate them from fetal tissues. In our second Featured Article this month published in *Stem Cells Translational Medicine*, Zhang et al. provide evidence of stable allogeneic neural tissue formation following the transplantation of human (h)NSCs into the brains of chronic stroke patients, with the clinical benefits observed encouraging further studies [9]. In a Related Article published in *Stem Cells*, Garbuzova-Davis et al. evaluated human bone marrow-derived EPCs as a means to repair the blood–brain barrier in ischemic stroke rats, discovering that stem cell-mediated mitochondrial preservation and pinocytotic activity may promote barrier restoration [10].

FEATURED ARTICLES

Treatment with Statin-Loaded ASCs Improves Cardiac Function After Myocardial Infarction

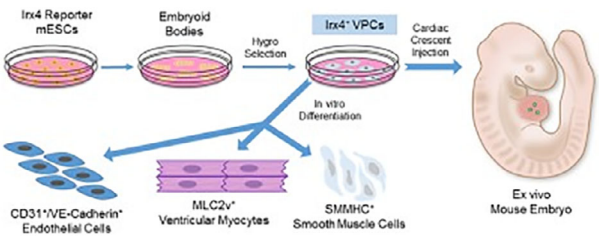
Researchers led by Masaaki Ii (Osaka Medical College, Osaka, Japan) recently reported on the development of a nanoparticle composed of a bioabsorbable PLGA (poly-lactic-co-glycolic acid) polymer conjugated to hydrophobic drugs, the uptake of said drug nanoparticles by a range of cells [11], and an increased therapeutic effect when employing drug nanoparticles to induce neovascularization in model animals [12]. In their new *Stem Cells Translational Medicine* article, the group now explore the potential of ASCs loaded with statin-conjugated PLGA nanoparticles as an enhanced combinatorial therapy for myocardial infarction [4]. Yokoyama et al. discovered that treatment of ASCs with statin-conjugated PLGA nanoparticles prompted an increase in migrational activity and the upregulated expression of various growth factor genes. Encouragingly, the intravenous



administration of only 10,000 statin-conjugated PLGA nanoparticle-loaded ASCs in a mouse model of myocardial infarction improved cardiac function, mainly through the induction of endogenous myocardial regeneration, with an observed improvement in vascularity and increase in the number of pericardium-derived de novo cardiomyocytes. The authors attributed the therapeutic effects in the infarcted myocardium to the sustained release of the statin drug, a family of hydroxymethylglutaryl-coenzyme A reductase inhibitors with pleiotropic effects, rather than the direct contribution of the ASCs to tissue regeneration. Overall, this drug nanoparticle-mediated approach may represent an effective means to treat myocardial infarction with a reduced amount of stem cells, a strategy that will reduce costs and any potential side-effects and increase safety, mainly related to the lower likelihood of pulmonary thromboembolism.

DOI: 10.1002/sctm.18-0244

New Trial Proposes hNSC Transplantation as a Treatment for Stroke-Related Paralysis

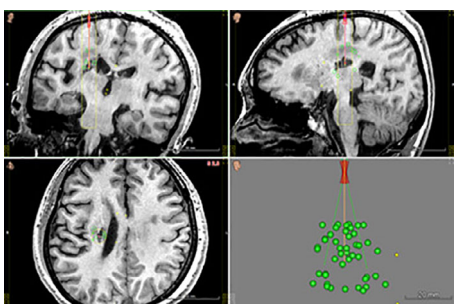


NSI-566, an epigenetically expanded line of primary hNSCs isolated from fetal spinal cord tissue, has been evaluated in clinical trials for the treatment of amyotrophic lateral sclerosis and spinal cord injury. However, the transplantation of these hNSCs has also demonstrated potential in improving motor recovery in rat models of ischemic stroke [13, 14]. In their new *Stem Cells Translational Medicine* article, researchers from the laboratories of Karl K. Johe (Neuralstem Inc., Maryland, USA) and Xu Ruxiang (Army General Hospital of PLA, Beijing, China) investigated the feasibility and safety of transplanting hNSCs to reverse paralysis in nine stroke patients. In their single-site, phase I study, Zhang et al. intracerebrally transplanted three cohorts of three patients with increasing numbers of hNSCs, with immunosuppression therapy maintained for 28 days [9]. Overall, patients tolerated all cell doses well, and after 12 months, patients displayed statistically significant clinical benefits from baseline as measured by three different validated stroke scales. Encouragingly, mean changes remaining stable in six of these patients at 24 months and longitudinal magnetic resonance imaging revealed evidence of allogeneic neural tissue formation from transplanted hNSCs in all nine patients. Overall, the authors believe that their encouraging findings call for larger, randomized, controlled, double-blind studies to prove the beneficial effects of intracerebral transplantation of hNSCs as a treatment for stroke-related paralysis.

DOI: 10.1002/sctm.18-0220

Related Articles

Description of Ventricular Myocardium-Specific Progenitor Cells for Developmental Modeling and Cardiac Repair

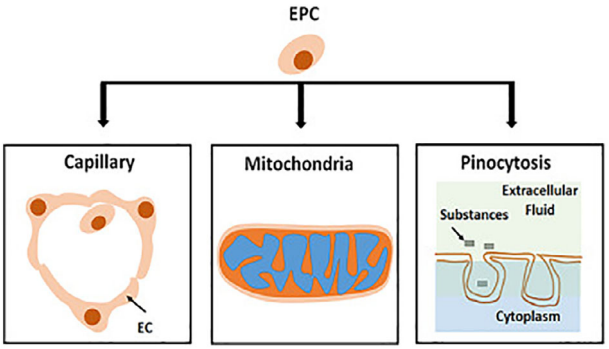


With the aim of identifying proliferative and multipotent cardiac progenitors that contribute to the development and potential repair of both ventricular chambers, researchers from the laboratory of Timothy J. Kamp (University of Wisconsin, Madison, Wisconsin, USA) developed an mESC line expressing a reporter gene under the control of the *Irx4* ventricle-specific gene through a "recombineering" approach [15, 16]. As reported in their *Stem Cells* article, Nelson et al. purified highly proliferative *Irx4*-positive ventricular progenitor cells from early differentiating mESC-derived embryoid bodies. Isolated cells displayed tripotential differentiation capacity, with the ability to generate endothelial cells, smooth muscle cells, and ventricular myocytes in vitro, and expressed cardiac progenitor-associated cell surface markers [5]. Interestingly, the generated cardiomyocytes displayed a ventricular phenotype, as evidenced by expression of the ventricle-specific *Mlc2v* marker gene and their inherent action potential characteristics, as measured through single-cell patch-clamp analysis. Moreover, *Irx4*-positive ventricular progenitor cells gave rise to cardiomyocytes that contributed to the developing ventricular myocardium after injection into the cardiac mesoderm of the early mouse embryo. Through the application of their recombineered mESC reporter line, the authors describe the generation of a novel chamber-restricted, ventricular myocardium-specific progenitor population that will contribute to a deeper understanding

of normal ventricular myocardium development and abnormal development associated with congenital heart disease. Furthermore, *Irx4*-positive progenitors may also foster the development of novel therapeutic approaches for the treatment of congenital heart disorders as well as myocardial infarction.

DOI: 10.1002/stem.2486

Stem Cell Therapy for Blood–Brain Barrier Alterations in Stroke Reveals Novel Mechanisms of Repair



Recent studies from the laboratories of Svitlana Garbuzova-Davis and Cesario V. Borlongan (University of South Florida, Florida, USA) reported blood–brain barrier alterations in areas remote from the initial ischemic insult in a middle cerebral artery occlusion-induced stroke rat model [17, 18]. In their subsequent *Stem Cells* article, the team assessed EPC transplantation as a means to repair said stroke-associated blood–brain barrier alterations due to their vascular phenotype [10]. The authors discovered that the intravenous transplantation of β-galactosidase labeled human bone marrow EPCs 48 hours after the induction of stroke in model rats promoted vascular repair in the bilateral striatum and motor cortex that was characterized by robust cell engraftment within capillaries. Interestingly, electron microscopy-based evaluation of endothelial cells, pericytes, and astrocytes in EPC-treated stroke rats established normal cell and mitochondrial morphology five days after treatment, with no evidence of perivascular edema. However, the authors did note the presence of large numbers of pinocytic vesicles, cell membrane-derived vesicles containing small amounts of extracellular fluid and solute molecules, within engrafted cells, a finding that represents the first description of this phenomenon. Therefore, the authors suggest that preserving mitochondria and augmenting pinocytosis via stem cell transplantation may represent a novel neurorestorative approach for blood–brain barrier repair in stroke patients.

DOI: 10.1002/stem.2578

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