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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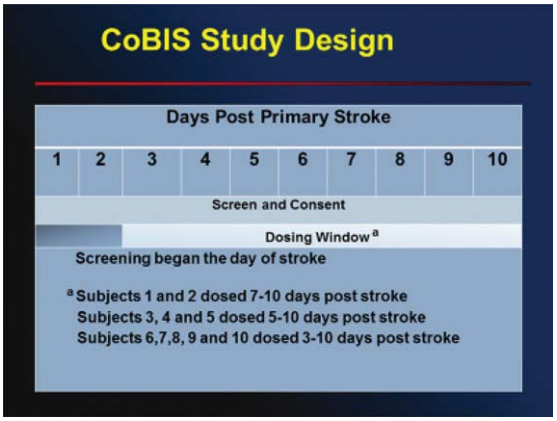
Current statistics suggest that someone in the U.S. suffers a stroke every 40 seconds and, given that prevalence increases with advancing age in both males and females [1], stroke will likely remain as a major cause of death and long-term disability in the coming future. Cell-based therapies aim to improve recovery following ischemic stroke, caused by a lack of blood flow to the brain, via the modulation of the immune system, the secretion of neurogenic and angiogenic factors, and the reduction of infarct volume. Umbilical cord blood (UCB) represents a safe, readily-available, cryopreserved, banked, and immunologically tolerant stem cell-rich product that does not require the invasive collection of autologous cells via bone marrow harvesting or peripheral stem cell collection from already fragile patients [2]. Does UCB also represent a relevant cell source for stroke treatment? This month's first Featured Article from Laskowitz et al. reports the positive results of their phase I safety study of the intravenous (i.v.) infusion of allogeneic UCB as a means to improve functional outcomes in patients with ischemic stroke. In a Related Article, Yang et al. describe how the i.v. infusion of human multipotent adult progenitor cells (MAPCs) immunomodulates splenic responses to generate a more favorable environment for endogenous brain repair after stroke.

Similar to UCB, the application of human placental-derived stem cells (HPDSCs) has emerged as an exciting therapeutic option for a range of indications. The HPDSC population consists of a combination of hematopoietic stem cells, megakaryocytic precursors, and nonhematopoietic stem cells depleted of red blood cells, nonviable cells, and tissue debris [3]. Of note, HPDSCs have been safely employed in combination with allogeneic UCBs in patients suffering from a wide range of diseases/disorders. As animal studies have established the success of enriched hematopoietic progenitor cell therapy for recessive dystrophic epidermolysis bullosa (RDEB), an inherited skin blistering disease [4], HPDSC therapy may, therefore, represent an exciting new therapeutic strategy for this disease. This month's second Featured Article from Liao et al. explores the potential for HPDSC therapy as a safer, more effective regenerative approach for skin blistering in a mouse model of RDEB. In a Related Article, Kim et al. investigate the therapeutic efficacy of activated human UCB-derived mesenchymal stem cells (hUCB-MSCs) for the treatment of murine atopic dermatitis (AD), discovering a requirement for MSC-derived PGE2 and transforming growth factor beta-1 (TGF-β1).

FEATURED ARTICLES

Phase I Success for Allogeneic Umbilical Cord Blood Infusion for Ischemic Stroke



While stroke represents a major cause of death and long-term disability, we currently lack effective treatment options targeting neuroprotection and promoting recovery. To further explore cell-based therapies for ischemic stroke, the laboratory of Ellen R. Bennett (Duke University, Durham, NC, USA) conducted a Phase I open-label trial to assess the safety and feasibility of a single i.v. infusion of nonhuman leukocyte antigen-matched, unrelated allogeneic hUCB in adult ischemic stroke patients. When compared with bone marrow-derived cells, UCB cells display improved immunotolerance and availability for infusion and may bolster recovery by downregulating inflammation and promoting neuroprotection and plasticity. Encouragingly, Laskowitz et al. report that patients tolerated UCB therapy, did not suffer from any serious adverse events noted, and all participants exhibited improvements in functional outcome by 3 months postinfusion [5]. The authors hope that these results, reported in *STEM CELLS Translational Medicine*, will support a randomized, placebo-controlled phase II study.

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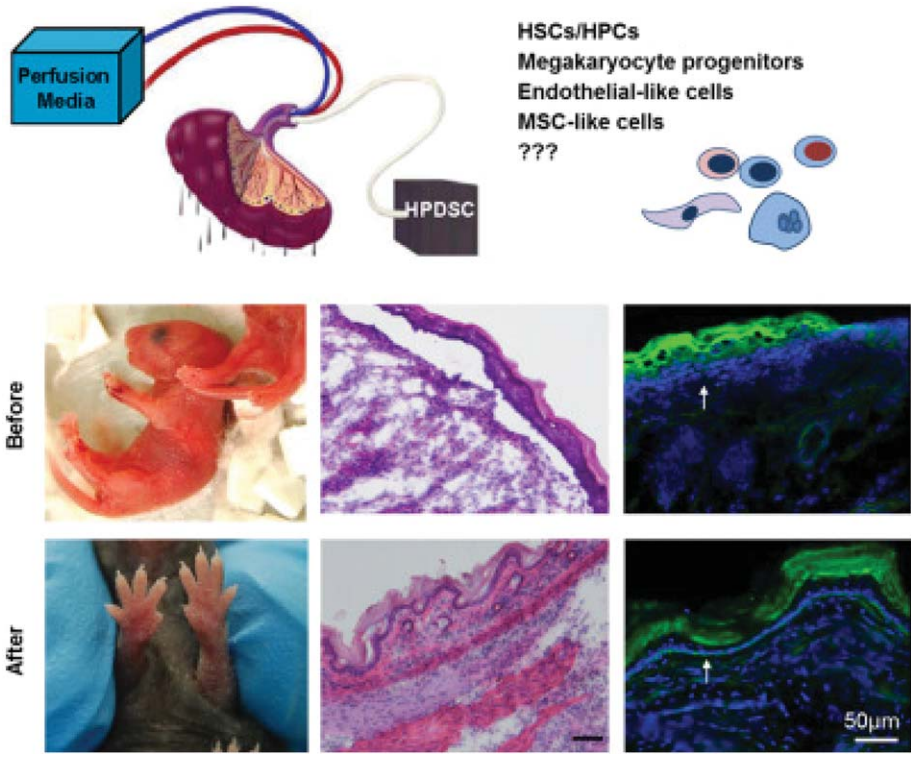
Animal Study Highlights Placental-Derived Stem Cell Therapy for Inherited Skin Disease

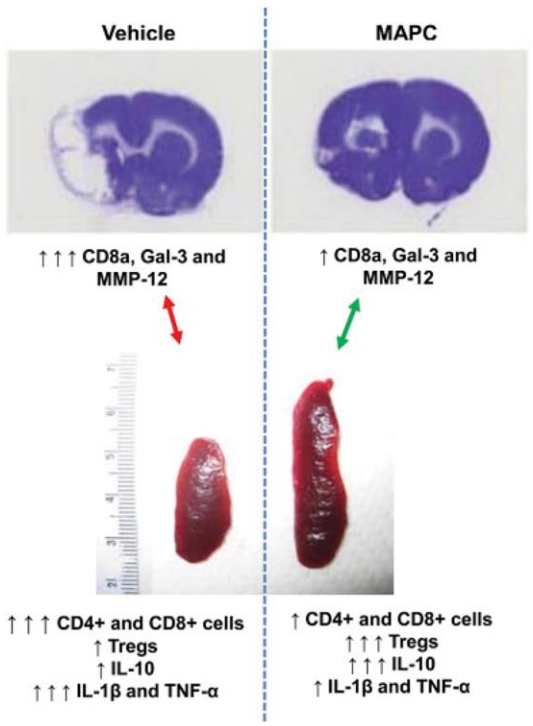


Mutations in the *COL7A1* gene, which encodes type VII collagen (C7), lead to the disruption of the dermal-epidermal junction and the development of the inherited skin blistering disease RDEB. The associated high risk of developing aggressive cutaneous squamous cell carcinomas and a lack of effective RDEB treatments (other than supportive and palliative care) have motivated the search for new cell-based therapeutic approaches. A recent *STEM CELLS Translational Medicine* study from the laboratory of Mitchell S. Cairo (New York Medical College, Valhalla, NY, USA) evaluated HPDSC therapy in an RDEB mouse model, discovering that HPDSCs migrated to the skin and the gastrointestinal tract, deposited C7 protein, and improved dermal-epidermal adherence [6]. Liao et al. note the reported safety of HPDSC therapy in human patients with malignant and nonmalignant diseases and, therefore, hope that their findings will facilitate future clinical investigations.

DOI: 10.1002/sctm.17-0182

Related Articles

Stem Cell Modulation of Systemic Immune Responses Enhances Recovery from Stroke



While stem cells may enhance recovery from stroke in animal models by boosting endogenous repair mechanisms, i.v. injected stem cells can also influence the systemic immune response in the periphery to inhibit or diminish secondary central nervous system damage. To explore this strategy, researchers from the laboratory of Sean I. Savitz (McGovern Medical School at UT-Health, Houston, TX, USA) investigated human MAPC treatment in a male rat model of ischemic stroke [7]. Reporting in *STEM CELLS*, Yang et al. demonstrate that MAPC therapy enhances stroke recovery in rats with intact spleens by modulating spleen-derived immune responses but displayed no effects in rats without spleens. Further analysis discovered that MAPCs modulated the expression of immune-related genes and reduced pro-inflammatory signaling from the spleen, thereby promoting a pro-regenerative environment for the brain to recover from stroke.

DOI: 10.1002/stem.2600

Umbilical Cord Blood Stem Cells Alleviate Inflammatory Skin Disorder via PGE2 and TGF-β1

A recent report from the laboratories of Kyung-Sun Kang and Kwang-Won Seo (Seoul National University, South Korea) sought to harness the immunomodulatory and anti-inflammatory power of MSCs to treat a common allergic skin disorder. In their study [8], Kim et al. investigated the potential for hUCB-MSCs in the treatment of AD, a disease caused in part by mast cell (MC) degranulation, the subsequent release of inflammatory mediators, and the recruitment of lymphocytes/eosinophils into the dermis. Interestingly, this *STEM CELLS* study demonstrated that subcutaneous local administration (but not i.v. administration) of nucleotide-binding oligomerization domain 2 (NOD2)-activated hUCB-MSCs suppressed the infiltration and degranulation of MCs via NOD2-mediated prostaglandin E2 (PGE2) production and IL-4-mediated TGF-β1 production. The authors hope that their results will provide for the development of improved stem cell therapies for allergic skin diseases.

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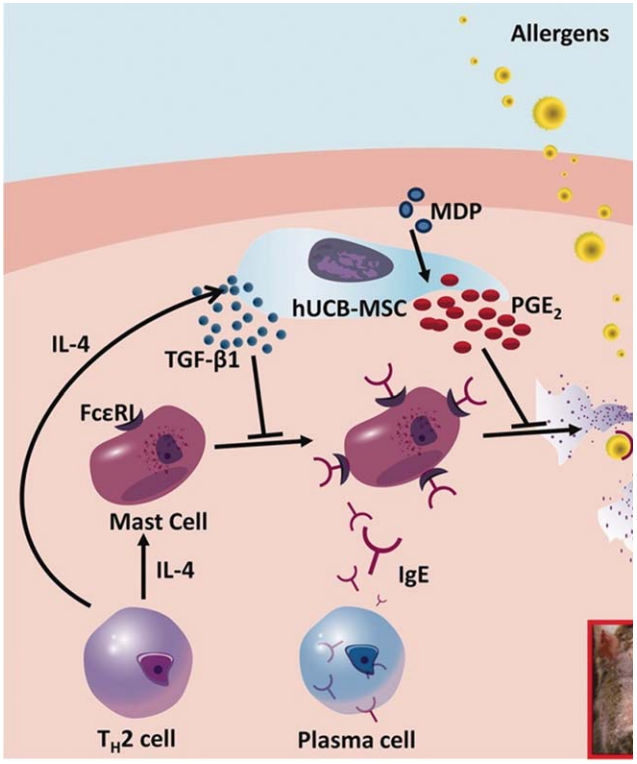

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