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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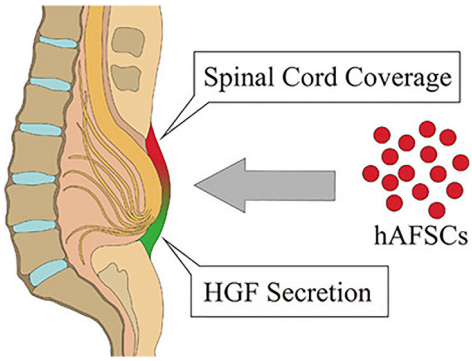
Amniotic fluid, the protective liquid contained by the amniotic sac, serves as a cushion for the growing fetus and aids in the exchange of a range of factors between the mother and fetus. Highly proliferative stem cells (amniotic fluid stem cells, or AFSCs) expressing embryonic and adult stem cell markers can be isolated from the amniotic fluid via routine amniocentesis [1] and in vitro expanded for use in a range of possible therapeutic applications. AFSCs can differentiate into various therapeutically relevant cell types [2], and their ability to successfully and safely engraft in multiple organs has extended their application to the treatment of diseases and disorders of the cardiovascular, gastrointestinal, hematopoietic, musculoskeletal, nervous, respiratory, and urinary systems. Perhaps most excitingly, AFSCs can be isolated, expanded, and modified/engineered for the autologous treatment of a target disease [3]. Furthermore, AFSCs can also be used in prenatal therapeutic approaches through in utero transplantation (IUT); a strategy aimed at treating conditions such as congenital hematological diseases, spina bifida, and other neural tube defects. In our first Featured Article this month published in *Stem Cells Translational Medicine*, Abe et al. establish the potential of human (h)AFSCs for the treatment of fetal myelomeningocele by demonstrating how administration via IUT reduced neural damage and promoted neural regeneration [4]. In a Related Article published in *Stem Cells*, Loukogeorgakis et al. demonstrated how IUT of in vitro-expanded mouse AFSCs resulted in stable multilineage long-term hematopoietic engraftment and, therefore, may represent an appealing approach to the treatment of inherited disorders of hematopoiesis [5].

Blood isolated from the umbilical cord of placental mammals contains a range of stem and progenitor cells, including hematopoietic stem cells, mesenchymal stem cells (UCB-MSCs), endothelial progenitor cells, and a rare population of stem cells known as unrestricted somatic stem cells (USSCs). USSCs are highly proliferative, permitting their long-term in vitro expansion without any loss of stem cell characteristics, and can differentiate into cells of all germ layers (including osteoblasts, chondroblasts, adipocytes, and hematopoietic and neural cells) both in vitro and in vivo [6]. Although they share overlapping cell surface markers with UCB-MSCs, USSCs differ in their broader differentiation profile and unique gene expression profile [7, 8]. Furthermore, USSCs secrete a range of growth factors that promote neuroprotection, axon growth, the homing of neural stem cells to ischemic regions of the brain, and the stimulation of axonal sprouting after spinal cord injury, suggesting their application as a treatment for neurological disorders. Meanwhile, UCB-MSCs display similarities to MSCs derived from other tissues and, hence, may find use in therapies for a wide range of immune or inflammatory disorders such as atopic dermatitis. In our second Featured Article this month published in *Stem Cells Translational Medicine*, Vinukonda et al. report that cord blood-derived USSCs administered in a rabbit model of intraventricular hemorrhage (IVH) decreased microglial infiltration, pro-inflammatory cytokine expression, and apoptotic cell loss, thereby prompting the partial recovery of myelination, preservation of white matter, and recovery of motor function [9]. In a Related Article published in *Stem Cells*, Kim et al. established the efficacy and safety of a single subcutaneous injection of human (h)UCB-MSCs in patients with moderate-to-severe atopic dermatitis [10].

FEATURED ARTICLES

Treating Spinal Disorders In Utero with Amniotic Fluid Stem Cell Therapy

The congenital disability fetal myelomeningocele, a type of spina bifida, occurs due to a failure in neural tube closure, the exposure of the spinal cord to the intrauterine environment [11], and subsequent chemical and mechanical damage in utero if the neural tissue is not protected during pregnancy [12]. Consequences include sensorimotor dysfunction of the lower extremities, skeletal deformities, and bladder and rectal disorders; however, prenatal cell therapy may improve prognosis. Now, researchers led by Daigo Ochiai (Keio University, Tokyo, Japan) report in a recent *Stem Cells Translational Medicine* article on the therapeutic effects and mechanisms behind AFSC-based treatment of fetal myelomeningocele. In a first-of-its-kind study, Abe et al. isolated CD117-positive hAFSCs from consenting 15- to 17-week pregnant women who underwent amniocentesis for prenatal diagnoses and



injected cells into the amniotic cavity of retinoic acid-induced fetal myelomeningocele model rats. Compared with control untreated rats, rats receiving hAFSCs displayed a smaller exposed spinal area, a reduction in neuronal damage, including neurodegeneration and astrogliosis, and an upregulation in hepatocyte growth factor (HGF) expression within the lesion. Indeed, the authors found evidence that HGF-expressing hAFSCs migrated to the lesion, covered the exposed spinal cord, and secreted HGF to suppress neuronal damage, induce neurogenesis, and thereby promote neural regeneration. As fetal myelomeningocele can be diagnosed during the early stages of pregnancy, there exists the possibility of isolating hAFSCs from patients and employing IUT in an autologous treatment approach.

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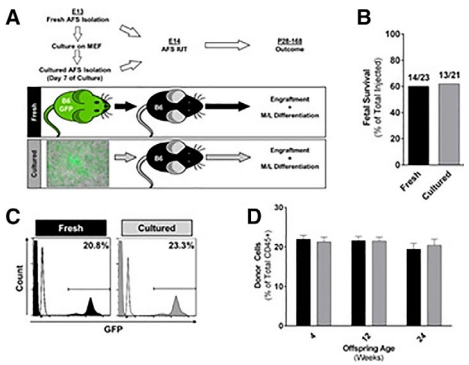
Exploring Human Cord Blood Stem Cell Therapy for Common Preterm Birth Complication

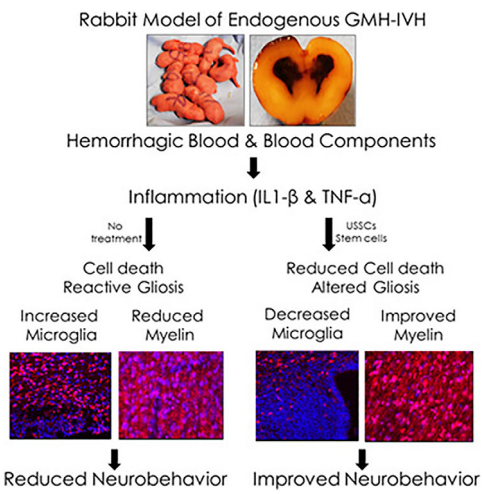


Previous studies from the research team of Govindaiah Vinukonda (New York Medical College, Valhalla, New York, USA) explored engineered human cord blood USSCs as a therapy for recessive dystrophic epidermolysis bullosa, an inherited disease majorly affecting the skin [13–15]. In their new *Stem Cells Translational Medicine* article, Vinukonda et al. sought to extend this approach to the treatment of IVH, a severe complication of preterm birth that leads to hydrocephalus, cerebral palsy, and mental retardation through assessments in a rabbit disease model. In a first-of-its-kind study, the authors administered human USSCs into premature rabbit pups via intravenous or intracerebroventricular injection, with cells later encountered in the injured parenchyma and next to the ventricle wall, respectively. Irrespective of the administration route, USSC injection fostered improvements in IVH symptoms within the central nervous system, which included attenuated microglial infiltration, lower apoptosis, fewer reactive astrocytes with an altered distribution, the reduced expression of crucial inflammatory cytokines, and the partial recovery of myelination and restoration/preservation of white matter structure. The improvements associated with enhanced sensorimotor function, thereby suggesting that a reduction of inflammation in the injured brain by the action of paracrine-acting factors secreted from USSCs may represent a new means to treat the degenerative processes associated with IVH. The authors now hope to undertake longer duration studies and define the optimal dose and frequency of USSC administration to maximize beneficial effects.

DOI: 10.1002/sctm.19-0082

Related Articles

Toward In Utero Amniotic Fluid Stem Cell Therapy for Inherited Hematopoietic Disorders



Previous research from the laboratory of Paolo De Coppi (UCL Great Ormond Street Institute of Child Health, London, UK) provided proof-of principle for the hematopoietic potential of AFSCs [16] and their multilineage hematopoietic engraftment following IUT [17]. However, the loss of hematopoietic potential after in vitro expansion under adherent culture conditions has hindered the development of hAFSCs as a therapy for inherited hematopoietic disorders. In a subsequent *Stem Cells* article, Loukogeorgakis et al. described a means to in-vitro expand mouse AFSCs that engraft well after intravascular administration in an autologous-like murine model of IUT [5]. The study revealed that long-term cultur on a feeder layer of mitotically inactivated mouse embryonic fibroblasts provided AFSCs with favorable proliferation kinetics without the loss of hematopoietic characteristics. Encouragingly, the intravascular administration of a relatively small amount of autologous/congenic freshly-isolated or cultured AFSCs supported higher levels of stable long-term multilineage hematopoietic engraftment after IUT when compared with bone marrow-derived hematopoietic stem cells. Indeed, all animals receiving AFSCs displayed

stable hematopoietic macrochimerism for up to six months, with engraftment in blood and bone marrow exceeding 20%. However, the authors reported the failure of IUT when employing allogenic AFSCs; the resultant adaptive immune response and donor cell rejection may result from a lack of sufficient homing to the host fetal thymus and the subsequent lack of tolerance induction.

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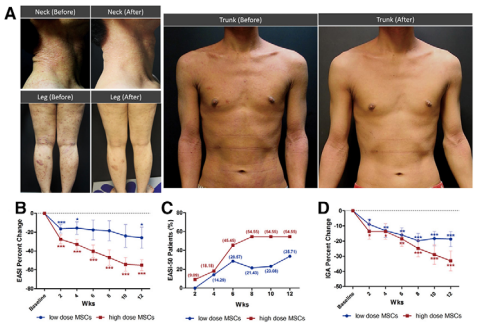
Human Umbilical Cord Blood Stem Cell Trial for Atopic Dermatitis Demonstrates Safety and Suggests Efficacy



Support for MSC administration as an effective therapy for atopic dermatitis, a chronic and relapsing skin disease [18], includes a *Stem Cells* article from the laboratories of Kyung-Sun Kang (Seoul National University) and Tae-Yoon Kim (Catholic University of Korea, Seoul, South Korea). In this article, the authors established the subcutaneous administration of hUCB-MSCs as an efficient means to alleviate atopic dermatitis in an experimental mouse model through the production of multiple soluble factors and the suppression of serum IgE levels and mast cell degranulation [19]. Their subsequent research, also published in *Stem Cells*, assessed the safety and efficacy of hUCB-MSC treatment in moderate-to-severe atopic dermatitis in 34 human patients over twelve weeks. Kim et al. discovered that a single subcutaneous injection of hUCB-MSCs resulted in dose-dependent improvements in atopic dermatitis symptoms; in general, disease scores fell significantly in the cohort treated with the highest doses, while serum IgE levels and eosinophil numbers also fell. Of note, hUCB-MSC administration rapidly ameliorated pruritus, a sensation that causes the desire or reflex to scratch and directly contributes to an improvement in the quality of life of atopic dermatitis patients. Importantly, the trial failed to encounter serious adverse events and all patients continued in the trial due to the lack of any adverse events. Overall, this first-in-class clinical study suggests that hUCB-MSC treatment may represent a safe and effective therapy for patients with moderate-to-severe atopic dermatitis, and planned larger trials will aim to overcome some of the limitations of this trial related to the small number of patients and the lack of a placebo group.

DOI: 10.1002/stem.2401

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