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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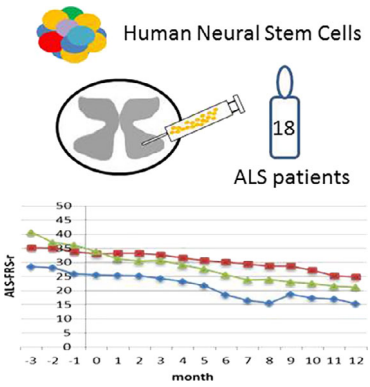
Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is associated with the death of the upper and lower motor neurons that control voluntary muscles, subsequent muscle deterioration, and ultimately death. Currently approved drug treatments offer only modest benefits [1, 2], and so, many have looked to stem cells as novel therapeutic agents for the treatment of ALS and related neurological disorders. The intraspinal transplantation of neural stem/progenitor cells (NSCs/NPCs) as a treatment strategy for ALS aims to reduce local astrogliosis and microgliosis, modulate immune responses, and provide neurotrophic support through the secretion of factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor (GDNF), and vascular endothelial growth factor [3]. While encouraging results have been reported, current research aims in this field include the search for a safe and effective stem cell source, the assessment of cell-engineering approaches that may potentiate therapeutic outcomes, and the appraisal of multiple stem cell administrations to target areas in the spinal cord and the brain. In our first Featured Article published in *Stem Cells Translational Medicine* this month, Mazzini et al. report on a successful phase I trial that assessed the feasibility and safety of transplanting non-immortalized fetal human NSCs into the spinal cord of ALS patients, reporting evidence of therapeutic efficacy [4]. In a Related Article published in *Stem Cells*, Thomsen et al. demonstrated that transplantation of GDNF-expressing NPCs into the motor cortex protected upper and lower motor neurons, delayed disease pathology, and extended survival after transplantation into a rat model of ALS, while also reporting encouraging findings in cynomolgus macaques [5].

The decellularization of organs or tissues leaves behind an extracellular matrix (ECM) scaffold with a unique composition and architecture that can be repopulated by autologous somatic and stem cell populations to generate transplantable graft tissues. Said tissues have the potential to overcome difficulties encountered in allogeneic transplantation approaches, which include immune rejection, pronounced donor shortages, and problems related to organ transport and storage [6]. Current research employing decellularized ECM scaffolds includes the generation of kidney, liver, lung, and heart tissues, but also extends to the generation of corneal, blood vessel, nerve conduit, cartilage, and tendon constructs to name but a few [7]. However, fascinating studies have also used these decellularized scaffolds to ascertain the essential role of the various components of the ECM in the regulation of various types of stem cells [8], including muscle stem cells. In our second Featured Article published in *Stem Cells Translational Medicine* this month, Lu et al. establish that a decellularized allogenic tendon scaffold combined with autologous bone marrow-derived mesenchymal stem cells (MSCs) significantly improves anterior cruciate ligament (ACL) reconstruction in a rabbit model when compared with free tendon allografts [9]. In a Related Article published in *Stem Cells*, Zhang et al. demonstrated how three-dimensional decellularized constructs derived from arsenic-exposed muscles displayed increased fibrogenic conversion and decreased myogenicity after seeding with naïve human muscle stem cells when compared with cells seeded into control constructs in a study that offers insight into the influence of the native myomatrix on stem cell behavior [10].

FEATURED ARTICLES

Long-Term Effects of Intraspinal Neural Stem Cell Injections in ALS Patients

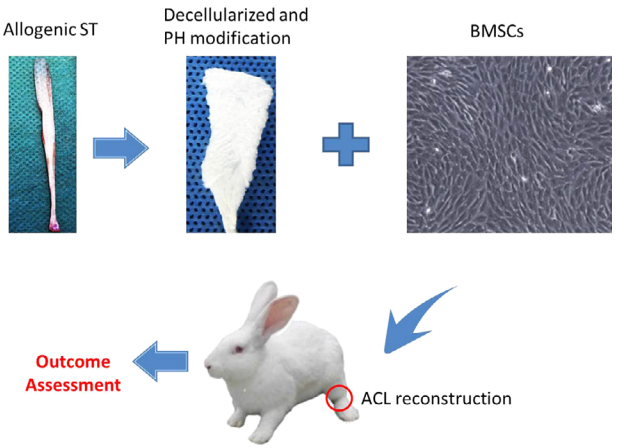
Previous research from the laboratory of Angelo L. Vescovi (Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy) established the capability of hNSCs to integrate into brain tissue and provide therapeutic effects in rodent models of neurological diseases, most probably through the release of growth and immunomodulatory factors [11, 12]. Now, the team returns with a new *Stem Cells Translational Medicine* article that reports the results of a phase I trial that assessed the feasibility and safety of transplanting non-immortalized fetal hNSCs into the spinal cord of ALS patients [4]. The study monitored 18 patients at the clinical, psychological, neuroradiological, and neurophysiological level before and up to 60 months after receiving



microinjections of fetal hNSCs into the gray matter tracts of the lumbar or cervical spinal cord. While patients failed to display severe adverse effects or accelerated disease progression after hNSC transplantation, the authors reported the detection of a transitory decrease in ALS progression that began within the first month after surgery and lasted up to 4 months after transplantation. This trial stands as a first example of the medical transplantation of a standardized cell drug product (fetal NSCs) that can be reproducibly and stably expanded ex vivo with future benefits including enhanced intra- and inter-study reproducibility and homogeneity. To this end, the authors hope to swiftly move to phase II clinical studies employing increased cell dosages and larger cohorts of patients.

DOI: 10.1002/sctm.18-0154

Decellularized Tendon and MSCs Combine for Anterior Cruciate Ligament Reconstruction



The generally poor outcomes observed following the implementation of allografts in ACL reconstructions [13] have been attributed, in part, to immunological rejection; therefore, the application of decellularized allogenic tendon grafts may circumvent these problems. A recent *Stem Cells Translational Medicine* article [9] from the laboratories of Zhenhan Deng (Shenzhen University, Shenzhen) and Jinzhong Zhao (Shanghai Jiao Tong University, Shanghai, China) combined an allogenic decellularized free tendon scaffold with autologous bone-marrow MSCs as additional support for the formation of functional ligament tissues in the hope of improving ACL reconstruction in a rabbit model [14]. Lu et al. injected MSCs within the decellularized tendon scaffold, seeded MSCs on the scaffold surface, and also injected MSCs into the contact point between the bone and ligament before ACL reconstruction. The authors noted the presence of MSCs (labeled with GFP) for up to 12 weeks post-surgery, at which point they discovered that their novel combination significantly improved ACL reconstruction results compared with control tendon allografts, with superior ligamentization, stronger tendon-bone healing, and better bone tunnel wall ossification observed. The authors note certain limitations in their study even given the positive results and they now hope to increase sample size, assess varying MSC doses, and extend the analysis beyond 12 weeks in their future research.

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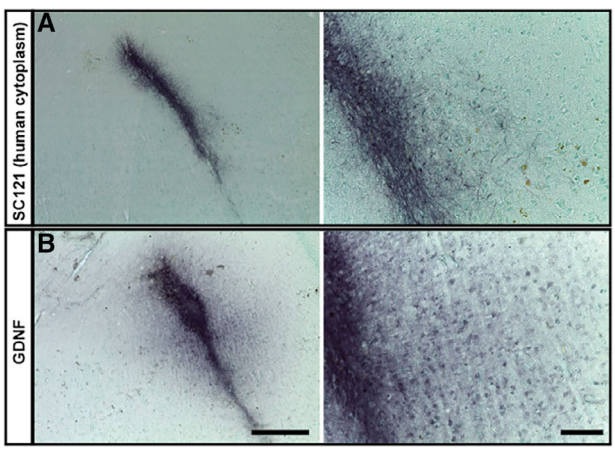
Related Articles

Treating ALS with Motor Cortex Administration of GDNF-expressing NPCs



Previous research from the laboratories of Clive N. Svendsen and Gretchen M. Thomsen (Cedars-Sinai Medical Center, Los Angeles, California, USA) demonstrated that cortical-derived human NPCs engineered to secrete GDNF can survive, differentiate, and release GDNF post-transplantation into the lumbar spinal cord in a rat model of ALS, leading to significantly enhanced motor neuron survival but a failure to reverse paralysis [15, 16]. As a follow-up to this fascinating study, the authors next assessed a role for the transplantation of GDNF-secreting hNPCs into the cortex to protect cortical motor neurons in an ALS rat model. Writing in *Stem Cells*, Thomsen et al. reported that transplanted NPCs migrated, matured into astrocytes, and released GDNF, leading to the protection of both upper and lower motor neurons, delayed disease pathology (paralysis), and the extension of lifespan [5]. Importantly, unmodified hNPCs failed to induce a similar therapeutic effect, highlighting the overriding importance of GDNF secretion. Encouragingly, the team also offered

evidence that engineered hNPCs released GDNF after transplantation into the cortex of cynomolgus macaques, as shown in the adjoining figure, suggesting that this approach may function similarly in a non-human primate. Overall, the authors highlight the possibility that the transplantation of GDNF-expressing hNPCs into the motor cortex and spinal cord may represent an exciting synergistic therapeutic strategy for human ALS patients.

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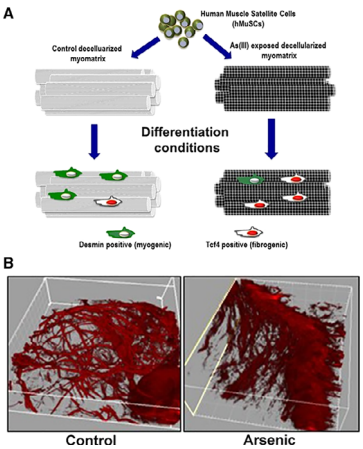
Arsenic-Mediated Matrix Remodeling Impairs Muscle Stem Cell Function in Decellularized Muscle Constructs

Chronic arsenic exposure leads to significant muscle weakness and dysfunction [17], and while most research has concentrated on the effect on muscle stem cells, some studies have indicated that arsenic exposure can disrupt the muscle ECM that forms part of the stem cell niche [18]. To further corroborate a possible link between niche alterations and muscle-related problems, a team led by Fabrisia Ambrosio (University of Pittsburgh, Pennsylvania, USA) assessed the consequences of environmentally relevant levels of arsenic exposure to both mouse muscle tissue and decellularized muscle constructs. Writing in *Stem Cells*, Zhang et al. first reported that arsenic-exposed muscles displayed pathogenic matrix remodeling, defective myofiber regeneration, and diminished post-injury functional recovery [10]. Interestingly, when the authors seeded muscle stem cells on to three-dimensional decellularized muscle scaffolds derived from arsenic-exposed muscles, they observed enhanced fibrogenic conversion and decreased myogenicity (adjoining figure shows experimental design representative second harmonics generation images). Analysis of muscle connective tissue fibroblasts from muscle tissue suggested that arsenic-induced NF-κB expression prompted the elevated expression of matrix remodeling-associated genes, thereby identifying a potential target for future therapeutic interventions. Indeed, the authors confirmed this hypothesis by demonstrating how the inhibition of NF-κB during arsenic exposure to mice preserved normal myofiber structure and functional recovery after injury. Overall, the study of decellularized muscle scaffolds aided the researchers to identify alteration to the muscle ECM as the controlling mechanism behind arsenic-induced muscle stem cell dysfunction and impaired muscle regeneration.



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