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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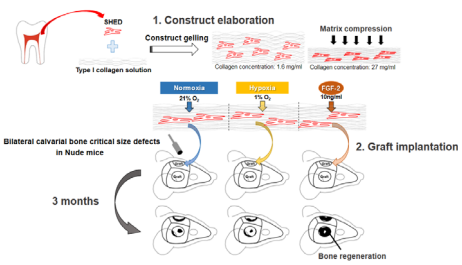
Dental pulp stem cells (DPSCs) are a mesenchymal stem cell-like population that derive from the neural crest and can be easily isolated in large numbers from discarded or extracted deciduous ("baby") teeth [1]. They represent a potentially useful cell type for tissue engineering purposes thanks to their extended potential for proliferation without apparent loss of function, their multipotential differentiation capacity, and the release of paracrine acting pro-regenerative factors [2]. Their applications in the regenerative arena include dental pulp regeneration, tooth reconstruction, bone tissue engineering, and angiogenic, vasculogenic, endocrine, and neurologic cell therapy. With regard to bone tissue engineering, the strong osteogenic properties of DPSCs [3] have encouraged their application in bone regeneration/repair, while their neurogenic potential has prompted their use as a means to understand neurogenetic disorders without resorting to the generation of induced pluripotent stem cells (iPSCs) [4]. However, we still require novel strategies to derive the full regenerative potential from cells as plentiful and potentially utile as DPSCs. In our first Featured Article from *Stem Cells Translational Medicine*, Novais et al. report that growth factor-priming of DPSCs enhances craniofacial bone regeneration following transplantation into model mice within a dense collagen hydrogel scaffold [5]. In a Related Article from *Stem Cells*, Dunaway et al. used comparisons of whole-genome DNA methylation profiles to identify DPSCs as a more appropriate model than human pluripotent stem cells (hPSCs) for the study of the methylation abnormalities associated with an imprinted neurodevelopment disorder [6].

Müller glia represent the major glial component of the vertebrate retina and support retinal homeostasis and integrity by various mechanisms, including controlling the uptake of neurotransmitters, removal of debris, and mechanical support. While Müller glia in zebrafish can mount a regenerative response to injury via a reprogramming event that endows cells with retinal stem cell characteristics that permit the regeneration of the entire adult retina [7, 8], studies have failed to observe a similar response in humans. However, studies have established that a population of Müller glia isolated from the adult human retina exhibits stem cell characteristics and, additionally, that the transplantation of their differentiated progeny can partially restore visual function in rodent and feline glaucoma models [9, 10] and improve rod function in a rat retinitis pigmentosa model [11]. To move retinal regenerative therapies forward, we must identify a suitable source for Müller glia; can we derive these highly useful cells from hPSCs? In our second Featured Article from *Stem Cells Translational Medicine*, Eastlake et al. establish that the intravitreal transplantation of iPSC-derived Müller glia into an experimental rat model of glaucoma partially restores visual function, thereby suggesting their potential application in human retinal therapies [12]. In a Related Article from *Stem Cells*, Xu et al. demonstrated how a sphere-induced cell rejuvenation and reprogramming protocol returned lost function to human and swine Müller glia, which may extend their application in basic research and therapeutic approaches [13].

FEATURED ARTICLES

Priming Dental Pulp Stem Cells Boosts Bone Defect Repair



Autologous bone grafting represents the current gold standard for the treatment of large bone defects; however, this approach suffers from significant limitations that have prompted the search for novel stem-cell-based therapies [14]. In a previous article published in *Stem Cells Translational Medicine* [15], researchers led by Caroline Gorin (Paris Descartes University, France) reported that priming DPSCs derived from human exfoliated deciduous teeth with FGF2 (basic fibroblast growth factor, or bFGF) and/or hypoxia induced the expression of stemness-related markers and enhanced angiogenesis following subcutaneous transplantation of tissue-engineered constructs in immunodeficient mice. The team now returns with a new *Stem Cells Translational Medicine* article [5], in which they explore the potential of primed DPSCs to contribute to bone formation in the context of craniofacial bone repair. Novais et al. discovered that, although priming with hypoxia

and FGF2 boosted the proliferation and osteogenic differentiation of DPSC, FGF2 supported a more robust response. Indeed, following the transplantation of DPSCs within a dense collagen hydrogel scaffold into critical size calvarial defects in an immunodeficient mouse model, FGF2 primed DPSCs mediated faster craniofacial bone formation when compared with control unprimed or hypoxia primed DPSCs, which both produced smaller amounts of new bone. Overall, the authors propose the application of FGF2 primed DPSCs as a potentially exciting new tissue engineering strategy for the repair of craniofacial bone defects.

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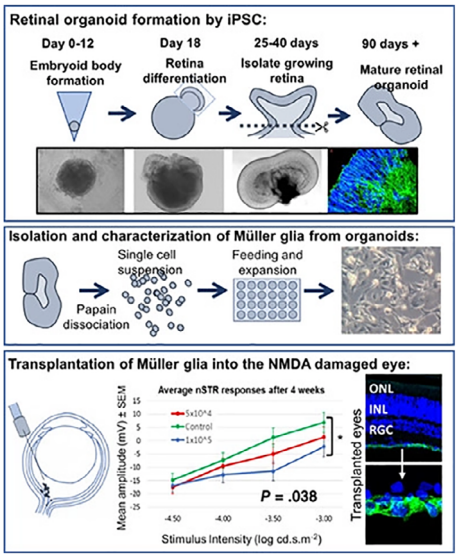
Battling Vision Loss with Müller Glia from iPSC-Derived Retinal Organoids

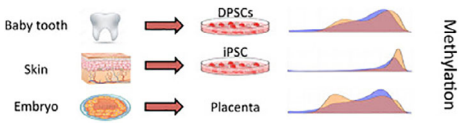


The generation of hPSC-derived retinal organoids that exhibit the characteristics of a whole laminated neural retina may permit the isolation of considerable numbers of Müller glia for therapeutic applications, including the treatment of glaucoma-associated vision loss. Researchers from the laboratories of G. Astrid Limb and Karen Eastlake (UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK) previously discovered that the transplantation of retinal ganglion cells differentiated from a human Müller glia cell line in a rat model of glaucoma-like damage provided encouraging therapeutic outcomes [9, 10]. Now, the team returns with a new *Stem Cells Translational Medicine* **article** in which they report on the therapeutic outcomes of the transplantation of Müller glia isolated from human (h)iPSC-derived retinal organoids [12]. Eastlake and colleagues first confirmed the identity and purity of Müller glia isolated from hiPSC-derived retinal organoids via gene/protein analysis of well-known Müller glia markers. Encouragingly, the intravitreal transplantation of these Müller glia into a glaucoma rat model partially restored visual function, as judged by an improvement in electroretinogram-based readings and immunohistochemical analysis of the transplanted retina. As the study failed to observe significant retinal integration of transplanted cells, the authors hypothesize that the production and secretion of neurotrophic factors by iPSC-derived Müller glia most probably supports the improvements observed. Do Müller glia isolated from hiPSC-derived retinal organoids represent the future of retinal degeneration treatment?

DOI: 10.1002/sctm.18-0263

Related Articles

Dental Pulp Stem Cells Aid Neurodevelopmental Disorder Research



Investigations into disease development often employ hPSC models; however, the lack of concordance between the DNA methylation patterns of these cells and preimplantation embryonic tissues has hampered research into epigenetic alterations associated with human disease. A recent *Stem Cells* article from the laboratory of Janine LaSalle (University of California, Davis, USA) reported on the characterization of DPSCs via genome-wide epigenetic approaches in the hope that these cells may display appropriate early developmental epigenetic patterns before differentiation into disease-specific cell types, such as neurons [6]. Dunaway et al. used whole-genome bisulfite sequencing of DNA methylation to compare DPSCs with cells often used in human genetic studies. Excitingly, the team discovered that the DNA methylation profile of DPSCs more closely resembled that of cells present within the early embryo than the profile observed in hPSCs. Subsequent comparisons of the methylation profiles of DPSCs in children with Dup15q syndrome (an imprinted neurodevelopment/autism spectrum disorder [16]) and control DPSCs suggested the overall suitability of DPSCs in modeling epigenetic differences associated with disease, as evidenced by the detection of Dup15q hypermethylation at the imprinting control region, hypomethylation at the non-coding RNA SNORD116 locus [17], and novel differentially-methylated regions covering several candidate autism-related genes. Overall, the authors of this study propose DPSCs as an easy to acquire and utile cell type for use in epigenomic and functional studies of human neurodevelopmental disorders.

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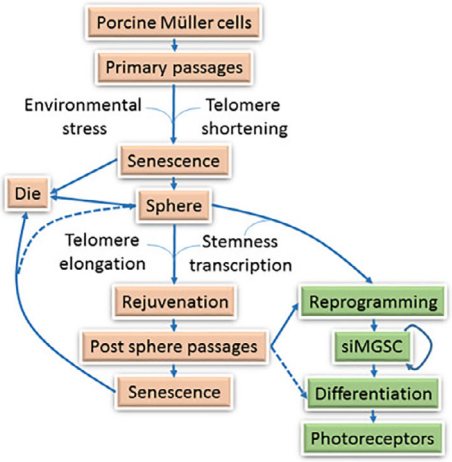
Sphere-Induced Rejuvenation Boosts the Therapeutic Potential of Müller Glia



Müller glia, like other mature somatic mammalian cells, suffer restrictions to their proliferative potential due to telomere attrition that can significantly inhibit their therapeutic potential [7]. Researchers from the laboratories of Yongqing Liu (University of Louisville, Kentucky, USA) and Fangtian Dong (Peking Union Medical College Hospital, Beijing, China) previously described the development of a sphere-induced rejuvenation protocol with the ability to immortalize and stably reprogram fibroblasts to multipotency [18]. The team returned with a *Stem Cells* article that used the same rejuvenation protocol to revive and reprogram culture-expanded Müller glia into an immortalized cell line with stem-like cell properties [13]. Xu et al. began by demonstrating that telomere attrition occurred in both swine and human Müller glia over time, prompting the accumulation of senescent cells. However, cell-contact mediated signaling during sphere culture in suspension rejuvenated Müller glia through the elongation of shortened telomeres thanks to the activation of the alternative lengthening of telomeres pathway or telomerase activation through the upregulation of telomerase reverse transcriptase expression. Furthermore, sphere culture also induced the expression of endogenous stemness factors that permitted both rejuvenation and dedifferentiation of Müller glia. Overall, the authors believe that their sphere-induced cell rejuvenation and reprogramming protocol could represent a valuable tool for the development of effective and efficient regenerative medicine approaches.

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