STEM CELLS TRANSLATIONAL MEDICINE®

PREVIEWS

A Preview of Selected Articles

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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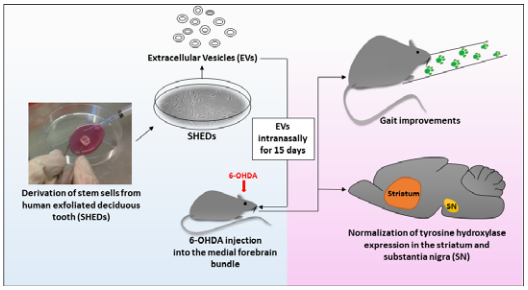
The term extracellular vesicles (EVs) describes 30–1,000 nm-sized lipid bilayer-delimited particles containing multiple proteins, RNAs, lipids, and metabolites that have been identified in various biological fluids [1, 2]. Evidence suggests that most, if not all, cells actively shed EVs for purposes including intercellular communication; however, recent studies have also highlighted their potential therapeutic value. The proposed therapeutic application of EVs stems both from the wish to avoid problems related to transplanting cells themselves, including the massive loss of transplanted cells, risk of malignant transformation, and immune rejection, and the simple, stable, and controllable nature of EVs that encourages large scale clinical manufacture [3]. Additionally, studies have established the therapeutic relevance of stem cell-EVs, with, for example, mesenchymal stem cell (MSC)-EVs able to pass through the mouse blood–brain barrier following intranasal administration to prevent abnormal neurogenesis and memory dysfunction [4] and neuroinflammation and cognitive impairments [5] in mouse models of brain disorders or following brain damage, respectively. Studies such as these provide evidence that stem cell-EV therapy may represent a potentially safe and efficient cell-free approach to the treatment of a wide range of conditions. In our First Featured Article from *Stem Cells Translational Medicine*, Narbute et al. report that the intranasal administration of EVs from stem cells derived from the dental pulp of human exfoliated deciduous teeth (SHEDs) can suppress disease symptoms in a rat model of Parkinson's disease [6]. In a Related Article from *Stem Cells*, Schoefinius et al. establish that mouse bone marrow-derived MSC-EVs can target hematopoietic, long-term repopulating stem cells to rescue them from radiation-induced damage associated with the conditioning of patients before hematopoietic stem cell transplantation [7].

The corneal epithelium protects the eye, plays an essential role in preserving corneal clarity, and undergoes a highly coordinated stem cell-mediated regeneration process in response to severe injury or disease. However, this endogenous response does not suffice when faced with certain pathologic, highly inflammatory conditions that put the entire ocular surface at risk for permanent scarring and visual loss. The loss of or damage to the resident corneal epithelial stem/progenitor cells [8, 9] can significantly contribute to these outcomes. The management of corneal wounds consists mainly of supportive measures, including sutured lid closure or amniotic membrane grafting [10], although stem cell-based treatments are currently under assessment. A deeper understanding of the mechanisms that control corneal epithelial stem/progenitor cells under normal and pathogenic conditions may also shed light on the mechanisms underlying corneal physiology and contribute to the development of novel therapeutic strategies to restore vision. In our second Featured Article from *Stem Cells Translational Medicine*, Fernandes-Cunha et al. demonstrate how the reconstitution of the lyophilized MSC secretome within a viscoelastic gel can enhance corneal epithelial wound healing and mitigate the development of stromal scarring and neovascularization after corneal damage [11]. In a Related Article from *Stem Cells*, Bhattacharya et al. report that SOX2 regulates and interacts with P63 to control the corneal epithelial stem/progenitor cell state and that downregulation of SOX2/P63 by miR-450b induces cell differentiation, findings that may provide new targets for novel therapeutic approaches [12].

FEATURED ARTICLES

Stem Cell-Derived Extracellular Vesicles: A New Treatment Approach for Parkinson's Disease Treatment?

Human exfoliated deciduous teeth stem cells, or SHEDs, originate from the peripheral nerve-associated glia and exhibit neurogenic properties [13]. Previous in vitro studies from the laboratory of Augustas Pivoriūnas (State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania) described how SHED-EVs suppressed the apoptosis of 6-hydroxydopamine (6-OHDA) treated human dopaminergic neurons [14], thereby suggesting SHED-EVS as a potential ameliorative approach for Parkinson's disease. In their recent *Stem Cells Translational Medicine* article, Narbute et al. examined the therapeutic effects of intranasally administered SHED-EVs in a rat model of



Parkinson's disease obtained by the unilateral injection of 6-OHDA into the medial forebrain bundle [6]. This method generates a severe but not full lesion to nigrostriatal structures to permit the assessment of SHED-EVs as a means to slow disease progression. The authors discovered significant improvements in all measured gait parameters in rats treated with SHED-EVs when compared with control untreated rats, which all displayed significant gait impairments. These improvements correlated to normalized nigrostriatal levels of tyrosine hydroxylase, a crucial part of the dopamine synthesis machinery. The authors propose that SHED-EVs exert neuroprotective actions by simultaneously targeting dopaminergic neurons and modulating astroglial/microglial responses to injury in the nigrostriatal pathways and believe that their proof of concept study will foster the development of novel minimally-invasive stem cell-EV-based therapies to delay disease progression and mitigate Parkinson's disease-related disability.

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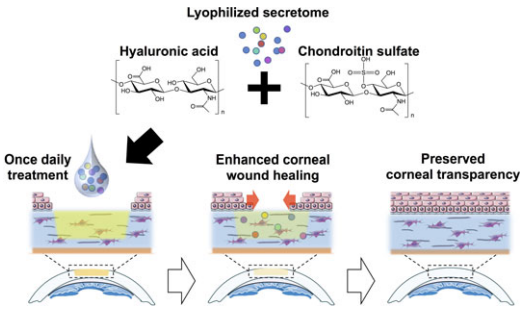
Corneal Epithelial Wound Healing with Mesenchymal Stem Cell Secretome-Laden Hydrogels

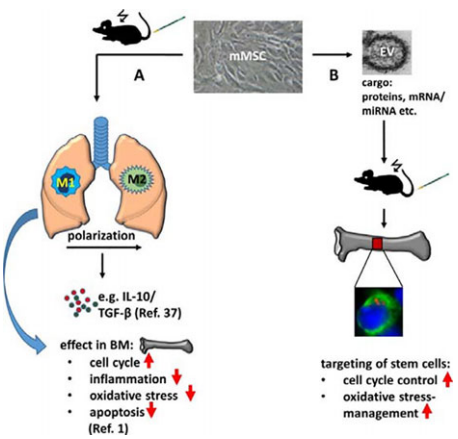


The suboptimal nature of currently used supportive measures for patients suffering from severe ocular surface injuries has led to the exploration of alternative pro-regenerative treatment options. These alternatives include the application of MSCs or MSC-secreted factors (the secretome), known to boast anti-scarring, anti-inflammatory, and anti-angiogenic properties, in corneal wound healing [15]. In their recent *Stem Cells Translational Medicine* article, researchers from the laboratories of David Myung (Stanford University, California, USA) and Ali R. Djalilian (University of Illinois at Chicago, USA) explored the in vitro and in vivo delivery of the lyophilized MSC secretome as part of a hyaluronic acid/chondroitin sulfate viscoelastic gel to cultured primary human corneal epithelial cells and mechanical/alkaline corneal burn wound rat models, respectively [11]. Encouragingly, Fernandes-Cunha et al. discovered that application of the secretome-laden hydrogel enhanced corneal epithelial cell proliferation and wound healing both in vitro and in vivo and reduced scar formation, neovascularization, and hemorrhage in vivo when compared with control. Interestingly, detailed analyses suggested that the upregulation and activation of the CD44 receptor on corneal epithelial cells by hyaluronic acid partly mediated the therapeutic effects of the MSC secretome. Given the overall attractiveness of this strategy, evidenced by the overall stability, storability, consistency, and cell-free nature of the lyophilized MSC secretome and the fact that the viscoelastic gel used is a biocompatible FDA-approved hydrogel with a known beneficial influence on corneal wound healing, the authors anticipate that their approach will soon be developed into an efficient and reproducible therapy for severe corneal injuries.

DOI: 10.1002/sctm.18-0178

Related Articles

Mesenchymal Stem Cell Extracellular Vesicles: The Key to Radiation-Induced Damage Rescue



The lethal levels of total body irradiation associated with the conditioning required for hematopoietic stem cell transplantation or radiation leakage incidents can trigger the suppression of the bone marrow system and lead to high levels of morbidity and mortality. Previous research from the laboratory of Claudia Lange (University Medical Center Hamburg-Eppendorf, Germany) suggested that paracrine effects supported the long-term survival of lethally irradiated recipients after mouse bone marrow MSC treatment [16]. Now, in a new *Stem Cells* article, Schoefinius et al. attribute the radioprotective effect of MSCs to secreted EVs [7]. Specifically, a homogenous ultracentrifuged population of MSC-EVs that excluded apoptotic bodies and other larger particles boosted in vitro long-term survival but not short-term reconstitution of lethally irradiated mice by rescuing hematopoietic stem cells but not progenitor cells. Further in vivo analysis revealed that systemically infused MSC-EVs reached the irradiated mouse bone marrow in 2 hours, where they targeted and rescued long-term repopulating Sca-1 positive and c-kit low-positive hematopoietic stem cells from

radiation damage to boost long-term survival. Of note, MSC-EVs did not require additional hematopoietic support for their positive therapeutic impact. While the authors highlight the need to understand the cargo that mediates the radioprotective effect, they expect that MSC-EVs will represent a successful treatment approach for patients suffering from radiation-induced damage and even for alleviating myelosuppression due to chemotherapy and toxic drug reaction.

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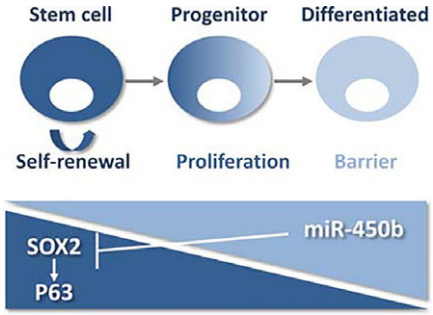
Delineating the Essential Regulators of Corneal Epithelial Stem Cells



A deeper understanding of the regulatory mechanisms that control corneal epithelial stem/progenitor cell function may provide insight into disease development and the construction of novel efficient therapeutic approaches. Studies have reported that mutations in the SOX2 [17] and P63 [18] transcription factor genes correlate with congenital eye pathologies that involve corneal abnormalities, so suggesting to researchers from the laboratory of Ruby Shalom-Feuerstein (Technion - Israel Institute of Technology, Haifa, Israel) of their general importance to corneal epithelial stem/progenitor cell function. In their recent *Stem Cells* article**,** Bhattacharya et al. demonstrated SOX2 and P63 co-expression in stem/progenitor cells of the murine cornea and in human corneal epithelial stem/progenitor cells in vitro [12]. The team subsequently discovered that SOX2 regulates and interacts with P63 to induce heightened expression levels of P63, and while knockdown of SOX2 attenuated cell proliferation and long-term colony-forming potential and induced robust cell differentiation, the forced expression of P63 reversed the effects of SOX2 knockdown. Finally, the authors uncovered the miR-450b microRNA as a direct repressor of SOX2 and therefore a mediator of P63 downregulation and cell differentiation. In summary, the authors offer convincing evidence of the essential nature of SOX2 as a "guardian" of the corneal epithelial stem/progenitor cell state and suggest that further analysis of the interaction between SOX2 and P63 will foster the development of novel therapeutic approaches for corneal pathologies.

DOI: 10.1002/stem.2959

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