Molecular Therapy
Commentary

Innovative stem cell-based strategies for corneal wound healing: A step forward

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Corneal damage caused by chemical agents is a frequent occupational hazard and is responsible for 11%–22% of ocular traumas.[1] It requires prompt intervention to avoid serious scarring and vision loss. On top of existing medical therapy and surgical treatment, regenerative medicine has provided novel therapeutic possibilities for corneal injuries.[2] However, the corneal epithelium is a heterogeneous tissue structured in five highly organized layers (corneal epithelium, Bowman's layer, corneal stroma, Descemet's membrane, and corneal endothelium) with multiple cell types. Thus, to orchestrate its regeneration, the coordinated action of numerous signaling pathways, a specific microenvironment and special extracellular matrix components are required. Finding strategies for efficient corneal replacement has become essential (Figure 1).

In this issue of *Molecular Therapy*, Yu et al. propose an innovative mRNA-based strategy to enhance the therapeutic utility and efficacy of stem cell therapies for corneal regeneration.[3] The preclinical results show that subconjunctival injection of adipose tissue-derived stem cells (AD-MSCs) modified to release IGF-1, a growth factor capable of promoting corneal nerve regeneration and regulating limbal stem cell fate, achieved multi-dimensional recovery from corneal alkali-burn injury. With respect to both naive AD-MSCs as well as to IGF alone administered as eye drops, cells carrying the IGF-modified RNA showed benefits for the different cell types and structures involved in the corneal repair, i.e., corneal epithelial and limbal cells, lymphatic vessels, and nerves. This work opens a window of possibilities of using RNA technology with a panel of regenerative growth factors or cytokines and stem cell platforms in combinatorial treatment regimen for the resolution of corneal damage. In addition to their role as a platform for curative protein delivery, the use of AD-MSCs themselves was instrumental for promoting regenerative programs and modulating the scarring response, both involved in limiting corneal opacity.[4] Of importance, cell transfection with IGF mRNA did not affect the stem cell characteristics.

Another advance in this field is the possibility of combining stem cells with different types of scaffolds known to possess physical and optical properties to potentiate corneal regeneration.[5] Stem cell-mediated corneal recellularization is yet another promising strategy in this area. Importantly, stem cell transplantation has successfully forged its way into the clinic. In fact, corneal epithelial regenerative therapies using different sources of stem cells, including those of endogenous origins such as limbal stem cells and corneal stromal stem cells, as well as those of exogenous origins, including adipose tissue- and umbilical cord-derived stem cells,

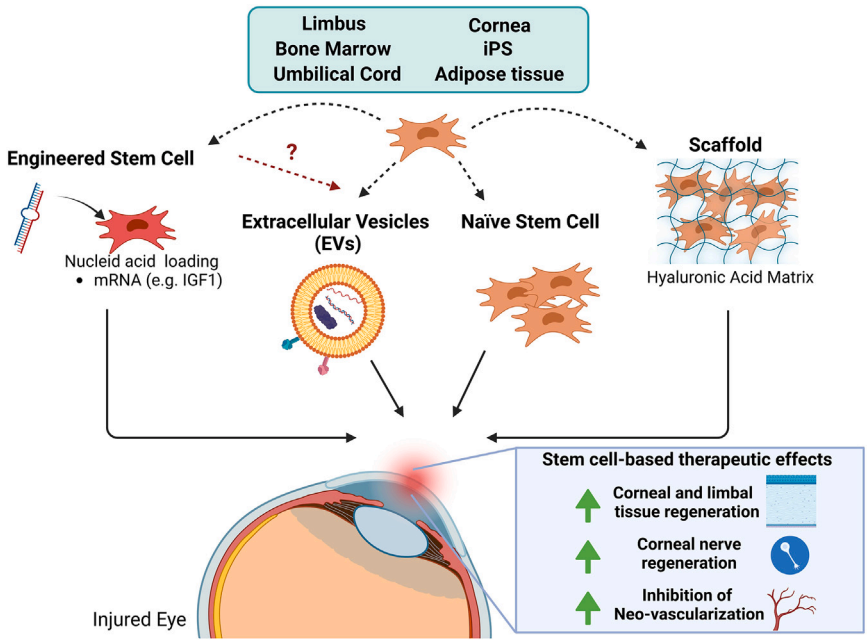

Figure 1. Stem cell-based approaches to corneal regeneration

The scheme summarizes the main stem cell sources (green panel) as a new tool to treat corneal injury. The main stem cell-based strategies may involve cells in a naive state or embedded in scaffolds such as hyaluronic acid matrix or engineered to express curative levels of proteins such as IGF-1. Therapeutic biomolecule-containing EVs released from the stem cells are another new and promising tool for corneal damage resolution. The principal therapeutic effects (green arrow) of stem cells and derived EVs in corneal damage are shown in the legend on the bottom right. iPS, induced pluripotent stem cells; IGF-1, insulin growth factor 1. Created with BioRender.com.

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have been undertaken.[6] Some of these stem cells have been employed in clinical trials for treatment of ocular burn. In particular, *ex vivo*-expanded autologous limbal stem cell (Holoclar) transplantation has been performed in subjects with unilateral or bilateral physical or chemical ocular burns, with the aim of targeting corneal neo-vascularization and epithelial defects (ClinicalTrials.gov: NCT02577861).[7] These limbal stem cells were obtained from areas of undamaged limbus for expansion and culture. The results of this clinical study are not yet available.

The main advantage offered by the proposed approach using combined AD-MSCs and IGF mRNAs is the complete restoration of corneal homeostasis, including corneal nerves and limbus.[8] Notably, MSCs, albeit their efficient endogenous regenerative potential, may suffer from several drawbacks.[8] Although these concerns are mainly related to systemic delivery, such as lung entrapment and possibility of pulmonary vasculature embolism, local delivery of MSCs could be impaired by changes in stem cell properties in response to a hostile tissue microenvironment and rejection despite their reported low immunogenicity. Importantly, several studies have demonstrated that the MSC secretome and source cells have similar healing activities due to the presence of therapeutic paracrine factors and cytokines, mitochondria, and biomolecule-enriched extracellular vesicles (EVs).[9] With regard to the latter, we have recently shown how topically applied bone marrow-derived MSC-EVs could modulate wound repair by acting on apoptosis, inflammation, and angiogenesis in alkali-burned corneas, thus dampening corneal damage[10] and promoting corneal endothelial cell survival.[9] The therapeutic effects of methylcellulose-embedded EVs were attributed to their biomolecular contents, showing the promises of EVs as a cell-free therapy in treating burn injuries.

The stem cell-engineering approaches described by Yu et al. may be further explored to assess their feasibility in loading exogenous mRNAs into EVs secreted by MSCs to enhance their therapeutic potential in the ophthalmic field.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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