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Fat for Sight

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ABSTRACT

In response to an article by Bandeira F., Goh T., Setiawan M. et al. entitled "Cellular therapy of corneal epithelial defect by Mesenchymal stem cell-derived epithelial progenitors", Stem Cells Research & Therapy, 11:14 (2020), we discussed the use of adipose mesenchymal stem cell-derived epithelial progenitors as a cellular therapy for treating corneal epithelial defects. The commentary will briefly cover the conventional and contemporary strategies used in the treatment process of corneal epithelial defects. The techniques and results presented by the authors in the original article are highlighted.

COMMENTARY

Corneal epithelium is the outermost multilayer part of the cornea which forms a physical and functional barrier against physical insult, infections and inflammations [1]. Replacement of healthy corneal tissue by fibrosis and new vessels formation results in obscuration of vision if it involves the central visual axis [2]. Corneal epithelial cells are self-renewal cells due to the presence of limbal stem cells [3]. Limbal stem cells may be deficient either totally or partly, which leads to limbal stem cells deficiency (LSCD) [4].

The management of epithelial abnormalities in the cornea largely depends on the etiologies [5]. General medical therapies for ocular surface restoration vary from aggressive surface lubrication [6], antibiotics, anti-inflammatory drugs, punctual occlusion, bandage soft contact lens [7], autologous serum therapy [8], tarsorrhapy [9], or others. On the other hand, applied surgical therapies are intended for curative purposes; to reduce inflammation and scarring and to promote cellular re-epithelization [10] such as amniotic membrane grafting, keratolimbal grafts and keratoprosthesis. Other contemporary therapies include cultivated corneal epithelial transplantation or transplantation of artificial cornea.

In response to an article "Cellular therapy of corneal epithelial defect by adipose mesenchymal stem cell-derived epithelial progenitors" by Bandeira et al. [11], there are many issues surrounding the use of mesenchymal stem cells (MSC) for the treatment of severe corneal epithelial defect associated with LSCD. The use of MSC as a cellular or cell-free therapy is a promising technology that opens the avenue for extensive research, both in vitro and in vivo. MSC can be collected from various sources in the body such as cord blood, peripheral blood, dental pulp, and adipose tissues.

This study proposed the use of adipose-derived MSC (ADSC) which is potential for corneal epithelial reconstruction. They constructed an alkali burn-induced (LSCD) model in rats which is fashioned after chemical burns injury; a common traumatic emergency in the eyes [12]. Human ADSC was demonstrated to support limbal stem cells' niche favorably. It was well tolerated when transplanted to the ocular surface. Cellular migration and anti-inflammatory responses were observed with subsequent partial restoration of limbal and corneal epithelial phenotypes [13].

Challenges arise in the appropriate selection of a biological scaffold as a vehicle to transport the MSC into the cornea. This study employed the cultivation of ADSC-derived corneal epithelial progenitors on a thin fibrin gel. Cell growth and differentiation was observed on a tissue-engineered epithelial construct which was then transplanted into the animal model.

Human ADSCs were cultured, isolated and characterized by flow cytometry analysis which showed marked expression of MSC markers (CD73, CD90, CD105 and CD166).

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Adipogenesis, chondrogenesis and osteogenesis proved the tri-lineage multi-potency of the cells. ADSC growth and proliferation was augmented by addition of small molecules inhibiting glycogen synthase kinase 3 (GSK3) and transforming growth factor β (TGF-β) signaling together with all-trans retinoic acid (at RA), with the aim was to upregulate expression of the epithelial phenotype. In this protocol adopted from Setiawan et al. [14], the expression of epithelial related genes like Cytokeratin 5 (CK5) and Cytokeratin 19 (CK19) and epidermal growth factor receptor (EGFR) was demonstrated and ADSC had successfully generated epithelial-like progenitors.

Corneal epithelial culture medium (CNT50) increased the epithelial markers expression like the surface markers ocludin (OCLN) and Zonula Occludens-1 (ZO-1) as demonstrated by immunofluorescence. One of the ways to demonstrate successful epithelial transition process is the downregulation of MSC markers like N-cadherin (CDH2) [11].

Post transplantation period showed reduced corneal epithelial defect as indicated by fluorescein staining and minimal neovascularization in comparison to the control group. Histology showed successful restoration of corneal thickness and reconstruction of corneal epithelium. Corneal epithelial markers were positively detected (CK3, CK12M and CDH1). The study proved that human ADSC-derived progenitors improved corneal epithelial recovery and restoration of the corneal surface.

The results are excellent and promising as previously demonstrated in ADSC; Zipierri et al. in 2017 showed ADSC treatment is effective and showed strong clinical and histological advantages in treating corneal lesions in mice [15]. Agorogiannis et al. in 2011 showed that the topical application of autologous ADSC promoted corneal epithelial healing in patients with persistent sterile corneal epithelial defect [16]. An option for the use of ADSC strategy is by topical or transplantation of tissue-engineered scaffolds. Previously, limbal stem cells have been reconstructed by using induced human bone marrow-derived MCSs on amniotic membrane [4].

Fibrin gel showed good performance as a biological scaffold as demonstrated by biocompatibility analysis, cell attachment and excellent biodegradability rate [17]. Challenges surrounding fibrin gel include weak mechanical properties, shrinkage of the gel and transmission of diseases [18]. Many types of biological scaffolds were used in tissue engineering, like natural and synthetic polymers polyglycolic acid (PGA), polyactide (PLA), poly-lactide-co-glycolide (PLGA), poly-ethylene-glycol (PEG) [19] and polyhydroxyalkanoate (PHA) [20]. The potential treatment agent of ADSC bears further investigations with different types of scaffolds to establish a treatment protocol for corneal epithelial reconstruction. Exploring the possibility of cell-free therapy, by augmenting the MSC secretome or extra cellular vesicles or MSC-derived exosomes are attractive strategies in treating different diseases [21].

CONCLUSION

MCSs are a major potential key player in the treatment of corneal epithelial defect. Adding to the repertoire of existing experimental strategies of corneal epithelial healing, cell therapy using MSC may be a safe way and a convenient method to treat severe corneal epithelial defects with limbal stem cell deficiency. However, prior to the human clinical trials, a standardization process is necessary to optimize for the source of MSC, passage number, suitable dosing, and strategy for cellular induction. In vitro studies to address cell senescence will be useful and donor-to-donor variability should be considered. Longitudinal In vivo studies will be beneficial to reveal any possible side effects in the long run.

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