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Review: Mesenchymal stem cells and corneal reconstruction

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Corneal reconstruction is among the most effective methods for curing corneal injury due to various clinical disorders. Mesenchymal stem cells (MSCs) are a type of multipotent cells distributed in various tissues, which can be easily isolated and expanded in vitro. MSCs are self-renewable and have the potential to transdifferentiate into other type of cells under certain conditions. More recently, the modulating angiogenesis, anti-inflammatory, and immunomodulatory properties of MSCs have been confirmed in animal models. The potential roles of MSCs are valuable for corneal reconstruction. Thus, in this review, we summarized the current understanding of the possible roles of MSCs in corneal reconstruction.

The cornea is rich in complexity and functionality. Corneal disorders are commonly initiated from inflammation, trauma, systemic disease, as well as pathological changes from adjacent tissues, which could eventually result in impaired vision, even blindness due to vascularization conjunctivalization, keratinization, corneal scarring, and opacification. In some severe cases, corneal reconstruction is necessary and effective to improve the restoration of corneal transparency.

Corneal reconstruction is a series of techniques for restoring the integrity and transparency of the cornea, and mainly refers to surgical techniques such as cornea transplantation, limbal stem cell (LSC) transplantation and amnion transplantation, and autologous oral mucosal epithelial transplantation. Other techniques involving biologic methods that aim to supply or stimulate the differentiation of LSCs have been widely investigated. Recently, there is mostly evidence from in vivo or in vitro studies for using mesenchymal stem cells (MSCs) in corneal reconstruction. Clinical trials are not available at the moment, and only one case has been reported for MSCs in humans. Accumulated studies on the role of MSCs in corneal reconstruction provided amplified additional evidence that MSCs indeed modify the corneal microenvironment, though the exact mechanisms are still unknown. Related studies on the roles of MSCs in the cornea are reviewed here to summarize the possible mechanisms and shed additional light.

Overview of mesenchymal stem cells: MSCs are a type of multipotent progenitor cells [1]. Although originally identified in the bone marrow [2], MSCs have been found in many other tissues, including the adipose [3], heart [4], Wharton's jelly [5], dental pulp [6], peripheral blood [7], cord blood [8], menstrual blood [9-11], fallopian tube [12], and limbal stroma of the human eye [13]. These cells have self-renewal ability as undifferentiated cells and could differentiate into lineages of mesenchymal tissues, including bone, cartilage, fat, muscle, and marrow stroma [14,15]. Under certain conditions, these cells could transdifferentiate into neurons or cardiac muscle cells [16-19]. Because of the low expression of major histocompatibility class II (MHC II) under unstimulated conditions and the absence of costimulatory molecules such as cluster of differentiation 40 (CD40), cluster of differentiation 40 ligand (CD40L), B71, and B72 on cell surface [20-24], MSCs could escape the monitoring of the immune system and infuse into an allogeneic host without being rejected [20,25].

MSCs can be harvested easily, especially from bone. There are two main ways to administer MSCs, intravenous injection and local administration. The latter is used more frequently for corneal research. MSCs can be administered directly to the cornea [26-31], or by carriers, such as the amniotic membrane [32-35] or fibrin gels [36].

For clinical applications, the regenerative/reparative potential and the immune-suppressive capacity of MSCs are the current areas of research focus. Many clinical studies on MSCs led to positive results, which focused on the effects of MSCs on regenerative medicine [37,38], preventing graft rejection [39,40] and controlling graft versus host disease (GVHD) [41,42].

Transdifferentiation effect of mesenchymal stem cells: MSCs are classified as multipotential progenitor cells. MSCs can transdifferentiate into other kinds of cells, including cardiomyocytes and neuronal cells [16-19]. However, hypotheses still need further evidence to establish that MSCs play a

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role in corneal reconstruction. Recent studies supported that MSCs can differentiate into corneal epithelial cells. Gu demonstrated that MSCs can differentiate into corneal epithelial-like cells in vivo and in vitro. In vivo, rabbit MSCs (Rb-MSCs) were suspended in fibrin gels and transplanted onto the surface of NaOH damaged rabbit corneas. As a result, the damaged corneal surface was restored after the Rb-MSCs were transplanted. Rb-MSCs also participated in the healing process of the NaOH injured corneal epithelium and expressed cytokeratin 3 (CK3), a corneal epithelial-specific marker. In vitro, Rb-MSCs differentiated into cells with a morphological and molecular phenotype of corneal epithelial-like cells that were positive to CK3 [36]. Another in vivo study demonstrated that MSCs have the ability to differentiate into corneal epithelial cells in experimental limbal stem cell deficiency rabbits. The expression of certain stem cell markers, such as adenosine 5'-triphosphate-binding cassette member 2 (ABCG2), β_1-integrin, and connexin 43, in the cornea epithelium after MSCs transplantation indicated that MSCs maintained stem cell characteristics; some MSCs even transdifferentiated into epithelial progenitor cells [33]. The in vivo study on human MSCs (hMSCs) found that hMSCs could survive and migrate into the cornea stroma after being transplanted onto the surface of the alkali-burned rabbit cornea. Not only did the hMSCs differentiate into the corneal epithelium, but also some even migrated into the corneal stroma and differentiated into cells other than epithelia [34]. Another in vivo study found that when MSCs were intrastromal-transplanted into keratocan-null ($Kera^{-/-}$) mice, the cells survived in the cornea without evoking an immune and inflammatory response and expressed keratocan in the host $Kera^{-/-}$ mice. The investigators speculated that these corneal intrastromal-transplanted MSCs may be an effective treatment regimen for corneal diseases involving dysfunction of keratocytes [26]. Similarly, another in vivo study showed that intrastromal-transplanted umbilical MSCs could survive similar to a keratocyte phenotype in the mouse corneal stroma [30]. In an in vitro study, after coculture with corneal stromal cells (CSCs), the induced MSCs expressed positive staining for CK12 with the corneal epithelial cell characteristics confirmed with scanning electron microscopy. In addition, in vivo, the induced MSCs had remarkable effects on treating the corneal alkali burn and reconstructing the corneal surface in a rat limbal stem cell deficiency model [35].

In contrast, some researchers believed that MSCs could not transdifferentiate into corneal epithelial cells in vivo. An in vivo study compared the transplantation of MSCs with LSCs concluded that MSCs and LSCs could assist the reconstruction of the damaged corneal surface in a rat corneal chemical burn model. However, the therapeutic mechanism was not associated with the epithelial differentiation from MSCs because there was no sufficient evidence to support that MSCs could differentiate into corneal epithelial cells [32]. A later in vivo study had the same conclusion in a rat corneal chemical burn model. To a certain extent, the lack of sufficient evidence may be because keratocytes do not have specific markers and share many markers with MSCs [27]. Our in vivo study also found that subconjunctival injected MSCs could not migrate into the injured cornea and transdifferentiate into corneal epithelial cells in a rat corneal alkali burn model [28]. This may be closely related to how the MSCs were administered. Therefore, it is still unclear whether MSCs play a role in corneal reconstruction by the transdifferentiation effect, and the hypothesis requires further investigation.

The anti-inflammatory effect of mesenchymal stem cells: The anti-inflammatory effect is another important function of MSCs. MSCs could ameliorate the inflammation in different damaged tissues, such as dextran sulfate sodium-induced colitis [43], acute kidney injury [44], and lung injury [45]. The anti-inflammatory effect of MSCs on the cornea was demonstrated on a rat corneal chemical burn model. The isolated hMSCs from healthy donors grew and expanded on the amniotic membrane, followed by transplanting the membrane onto rat corneas 7 days after the chemical burns. Four weeks after transplantation, inflammation factors such as cluster of differentiation 45 (CD45), interleukin 2 (IL-2), and matrix metalloproteinase-2 (MMP-2) decreased in the hMSC transplantation model detected with immunofluorescent stain. These findings indicated that the therapeutic effect of the damaged rat cornea treated with hMSCs might be partially due to the inhibition of inflammation [32]. An in vivo study further certified the anti-inflammatory effect of MSCs on the cornea by detecting more inflammatory related factors. In this study, MSCs were applied to the cornea directly without using the amniotic membrane as a carrier. MSCs decreased the expression of IL-2 and interferon-γ (IFN-γ) in the rat cornea after chemical injury. However, increased expression of interleukin-10 (IL-10), transforming growth factor-β1 (TGF-β1), and interleukin-6 (IL-6) was also detected [27]. In our study, we investigated the effects of subconjunctivally injected MSCs in the acute stage of an alkali-burned rat cornea. After MSCs were subconjunctivally injected, the infiltrated $CD68^+$ macrophages in the alkali-burned cornea were significantly decreased. The mRNA expression levels of macrophage inflammatory protein-1 alpha (MIP-1α) and tumor necrosis factor-alpha (TNF-α) were also downregulated. We speculate that MSCs inhibit macrophage infiltration by suppressing the expression of

macrophage chemokine MIP-1α [28,46]. In another in vivo study, the investigators administered hMSCs to the chemically injured rat cornea. The investigators found that hMSCs were effective in reducing corneal opacity and inflammation after either intraperitoneal or intravenous administration following cornea chemical injury. Regarding a specific mechanism, they found chemical injury to corneal epithelial cells could activate hMSCs to secrete TNF-α stimulated gene/protein 6 (TSG-6) in vitro, a multipotent anti-inflammatory protein. In addition, in vivo, the anti-inflammatory effects of hMSCs were largely abrogated by knockdown of TSG-6. Therefore, the authors speculated that systemic administration of hMSCs reduced inflammatory damage to the chemically burned cornea primarily by secreting anti-inflammatory protein TSG-6 in response to injury signals from the damaged cornea [47]. In summary, the anti-inflammatory effects of MSCs on the cornea are undoubtedly apparent. However, the underlying mechanisms require clarification.

Mesenchymal stem cells modulate corneal angiogenesis: Many studies found that MSCs were good activators for angiogenesis, and MSCs could secrete vascular endothelial growth factor (VEGF) in an ischemia or tumor model [48-52]. However, MSCs seemed to have an opposite effect on corneal angiogenesis. Some in vivo studies found that applying MSCs on the cornea could effectively inhibit inflammation-related angiogenesis after chemical injury [27,28,32]. MSCs upregulated the expression of thrombospondin-1 (TSP-1), a powerful antiangiogenic factor. Meanwhile, MMP-2, an inflammation-related proangiogenic factor, was significantly downregulated after MSCs treatment. However, the level of VEGF was similar between the control and MSC-treated cases in an in vivo study of a rat corneal chemical burn model [27]. In our in vivo study, we found that the level of VEGF was downregulated after the MSC subconjunctival injection in the acute stage of rat alkali-burned corneas [28]. In vitro, the coculture of human corneal epithelial cells (hCECs) and hMSCs upregulated the level of VEGF. Furthermore, the hMSCs constitutively expressed MMP-2 and TSP-1. At the same time, hMSCs significantly suppressed the secretion of MMP-9 from hCECs [53]. VEGF, MMP-2, and MMP-9 are proangiogenic factors in the cornea, and TSP-1 is an antiangiogenic factor, which could inhibit VEGF-induced angiogenesis by CD36 activation [54-56]. Therefore, TSP-1 appears to be an antiangiogenic factor, which opposes the proangiogenic effect of VEGF on the cornea in vivo.

Mesenchymal stem cells and solid-organ transplantation: Accumulated several studies proved that MSCs are efficient in reversing ongoing GVHD [41,42,57,58]. Similarly, MSCs could also play a role in host versus graft disease (HVGD) [59-61]. A study on skin transplantation found that applying MSCs could prolong baboon skin graft survival in vivo [60]. In an in vivo study, MSCs were efficient in heart transplantation by prolonging semiallogeneic heart graft survival, rather than a fully MHC-mismatched heart graft in a heart transplant mouse model. This study described a time dependency characteristic of MSCs that the infusion of MSCs was effective in prolonging graft survival when being used before transplantation, and partially effective during transplantation, but inefficient merely one day after transplantation [61].

In the case of corneal transplantation, one of the most common causes of corneal allograft failure is irreversible rejection. In an in vivo study, the immunomodulatory effects of MSCs were investigated with orthotopically transplanted pig corneas in rats. Allogeneic rat MSCs were applied for 2 h topically to the transplanted corneas immediately after operation. Unfortunately, the survival of the corneal grafts was not significantly prolonged, though the IL-6 and IL-10 levels were significantly increased in the rejected grafts after the MSCs were applied. This research proved that topical application of allogeneic rat MSCs does not prolong corneal xenograft survival effectively in a pig-to-rat model [29]. However, in a following in vivo study, the researchers performed orthotopic corneal allotransplantation using C57BL/6 mice (H-2^b) as donors and BALB/c (H-2^d) as recipients. The researchers demonstrated that preoperative intravenous injection of hMSCs decreased early surgically induced inflammation and reduced the activation of antigen-presenting cells (APCs) in the cornea and draining lymph nodes (DLNs). Subsequently, immune rejection was decreased, and allograft survival was prolonged. These results suggested that hMSCs improved the survival of corneal allografts without engraftment and primarily by secreting TSG-6 that acts by aborting early inflammatory responses [62]. Moreover, in another in vivo study of the rat corneal allograft rejection model, which was established by using Wistar rats as donors and Lewis rats as recipients, postoperative intravenous injection of MSCs, rather than preoperative intravenous injection, prolonged graft survival time. The authors also found that injecting MSCs reduced Th1 proinflammatory cytokines and elevated the secretion of IL-4 from T lymphocytes. In addition, Tregs were upregulated by MSC treatment [63]. Therefore, we speculate that suppressing corneal transplantation rejection by injecting MSCs depends on the timing and route of administration.

Mesenchymal stem cells and corneal wound healing: Corneal scarring is the main complication of corneal wound healing. Corneal fibroblasts (activated stromal keratocytes) are thought to be the key underlying mediator of this sight-compromising

response [64]. Fibroblast development is modulated by various cytokines and growth factors [64,65]. Studies were designed to investigate whether factors derived from MSCs could influence corneal healing. The conditional medium from MSCs (MSCs-CM) inhibited the wound healing activities of corneal fibroblasts in vitro. Fibroblast migration and relaxation contraction were significantly inhibited by MSCs-CM. Therefore, certain factors secreted by MSCs appear to have therapeutic value in corneal repair [66].

Intravenously injected MSCs engrafted to the injured cornea and promoted wound healing, by differentiation, proliferation, and synergy with hematopoietic stem cells in an in vivo study of the rabbit alkali burn model. The MSCs homed in on local sites and then differentiated into myofibroblasts due to the local tissue microenvironment [67]. In another in vivo study, corneal injury in mice was induced with thermal cauterization, and then the MSCs were systematically administered. The authors found that the MSCs homed in on the injured cornea and survived there whereas homing toward the normal cornea did not occur. In the setting of corneal injury, MSCs administration elicited significant and rapid corneal epithelial regeneration [68]. Our study showed that subconjunctival injection of MSCs significantly accelerated corneal wound healing in alkali-burned corneas. This may be related to the anti-inflammatory effects of MSCs [28]. Another study showed that hMSCs acted as a source of feeder cells in vitro for cultivating transplantable corneal epithelial cell sheets. In this study, hMSCs expressed keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF), soluble growth factors required for epithelial cell proliferation [69]. Recently, a case report demonstrated, for the first time, a patient with post-traumatic persistent sterile corneal epithelial defect treated with topical application of autologous adipose-derived MSCs. The MSCs were transferred into the bottom of the ulcer using an insulin syringe with a 27-G needle attached. One month later, complete corneal epithelial healing was observed. Nevertheless, the mechanisms were still unclear [31]. An in vitro study tried to determine whether MSCs could be induced to transdifferentiate into hCECs. This was done by evaluating whether MSCs could be injected and home in to a corneal endothelial injury site. In this study, this effect was obtained [70]. This study along with those involving the corneal epithelium showed that MSCs have potential therapeutic value in treating corneal epithelial and endothelial injuries. Their homing capability depended on the administration route.

Conclusion: MSCs have potential therapeutic value in corneal reconstruction since they have anti-inflammatory and modulatory effects on corneal angiogenesis based on results obtained with several animal models. Furthermore, MSCs are useful in suppressing corneal transplantation rejection and facilitating corneal wound healing. Additional animal model research is needed to address questions regarding how to transdifferentiate MSCs into corneal epithelial cells, the most appropriate route and time for applying MSCs for different kinds of corneal reconstruction, the specific mechanisms, and so on. Before MSCs can be tested in a clinical setting, these uncertainties must be resolved, and additional insight gained into how their use elicits such beneficial effects.

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