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Mesenchymal stem cells: Potential role in corneal wound repair and transplantation

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Abstract

Corneal diseases are a major cause of blindness in the world. Although great progress has been achieved in the treatment of corneal diseases, wound healing after severe corneal damage and immunosuppressive therapy after corneal transplantation remain problematic. Mesenchymal stem cells (MSCs) derived from bone marrow or other adult tissues can differentiate into various types of mesenchymal lineages, such as osteocytes, adipocytes, and chondrocytes, both *in vivo* and *in vitro*. These cells can further differentiate into specific cell types under specific conditions. MSCs migrate to injury sites and promote wound healing by secreting anti-inflammatory and growth factors. In addition, MSCs interact with innate and acquired immune cells and modulate the immune response through their powerful paracrine function. Over the last decade, MSCs have drawn considerable attention because of their beneficial properties and promising therapeutic prospective. Furthermore, MSCs have been applied to various studies related to wound healing, autoimmune diseases, and organ transplantation. This review discusses the potential functions of MSCs in protecting corneal tissue and their possible mechanisms in corneal wound healing and corneal transplantation.

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Key words: Mesenchymal stem cells; Corneal injury; Wound repair; Immune modulation; Transplantation

Core tip: Mesenchymal stem cell (MSC)-based therapy has been proposed as a possible treatment strategy for tissue wound repair, autoimmune diseases, and solid organ transplantation. MSCs are a promising stem cell population because of their self-renewal, pluripotential capability, immunomodulatory, and anti-inflammatory properties. Recent studies have suggested that application of MSCs may be a new alternative method for wound healing after severe corneal damage and for immune rejection after corneal transplantation. In this review, we discuss the potential functions of MSCs in protecting corneal tissue and their possible mechanisms in corneal wound healing and corneal transplantation.

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INTRODUCTION

Severe corneal injury caused by chemical or thermal burns, mechanical injury, and immune or hereditary disorders results in corneal inflammation, ulceration, neo-vascularization, conjunctivalization, limbal stem cell deficiency (LSCD), and stromal scarring, all of which may lead to blindness. Current therapeutic strategies include anti-inflammatory drug administration, limbal stem cell (LSC) transplantation, and corneal transplantation. However, these treatments have certain clinical limitations. Anti-inflammatory drugs are not sufficient to suppress

angiogenesis, conjunctivalization, and corneal scarring. LSC transplantation has a high risk of immune rejection^[1,2]. Corneal transplantation remains the main and effective method for visual rehabilitation once a disease has affected corneal clarity^[3]. Despite corneal transplantation is the most successful solid organ transplantation, immune rejection is still the major cause of graft failure. Over the last decade, mesenchymal stem cell (MSC) therapy has been proposed and used as a possible treatment strategy for cardiovascular diseases, renal wound repair, diabetes, systemic lupus erythematosus, and solid organ transplantation^[4-7]. MSCs are a promising stem cell population because of their self-renewal, pluripotential capability, low immunogenicity properties, and notable immunomodulatory and anti-inflammatory activities^[8]. Methods for the isolation and proliferation of MSCs are also simple. MSCs are mainly derived from bone marrow tissue. MSCs can also be isolated from niche of other tissues, including corneal limbal stroma. This review summarizes the therapeutic potential of MSCs in corneal wound repair and keratoplasty.

CHARACTERIZATION OF MSCS

Aside from hematopoietic stem cells, bone marrow tissue also contains non-hematopoietic stem cells^[9]. These stem cells, given their multi-lineage differentiation potential and hematopoiesis-supporting function^[10], are called marrow stromal stem cells or MSCs. Friedenstein *et al.*^[11] first described MSCs as spindle shaped cells derived from bone marrow that were able to adhere to plastic and form fibroblast colonies, which were defined colony-forming unit fibroblasts. MSCs derived from the mesodermal germ layer can differentiate into mesenchymal cell lineages (*e.g.*, adipocytes, osteocytes and chondrocytes) and non-mesenchymal cell lineages (*e.g.*, cardiomyocytes, hepatocytes-like cells, neurons, astrocytes, and endothelial cells) both *in vivo* and *in vitro*^[12-15]. MSCs have been isolated from several adult tissues, including the liver, dental pulp, adipose tissue, endometrium, muscle, amniotic fluid, placenta, and umbilical cord blood^[12-14]. MSCs isolated from bone marrow^[16], umbilical cord^[17], and adipose tissue^[18] promote regeneration and corneal wound repair. In addition, MSCs exist in the perivascular niche of several tissues, including the skeletal muscle and pancreas^[19]. These perivascular MSCs, usually pericytes, are regarded as a subset of MSCs that surround the blood vessel wall^[19-21]. However, identifying the authentic MSCs is difficult because of the lack of specific markers for these cells. The International Society for Cellular Therapy (ISCT) has provided the following minimum criteria defining multipotent MSCs: plastic-adherent under standard culture conditions; positive for the expression of CD105, CD73, and CD90 surface markers; negative for the expression of CD11b, CD14, CD19, CD34, CD45, CD79a, and HLA-DR surface markers; and capable of differentiating into osteocytes, adipocytes, and chondrocytes under a specific stimulus *in vitro*^[22]. Studies have demonstrated that human bone marrow-derived MSCs exhibit hetero-

geneity, which is related to proliferation potential and differentiation potency^[23,24]. Heterogeneity also partially effects the inconsistency of therapy in different laboratories^[25,26]. Heterogeneous bone marrow-derived MSCs are involved with mixed MSC subtypes, and their phenotypes remain poorly described.

NICHE OF MSCS IN LIMBAL STROMA

A population of cells isolated from the human corneal limbal stroma express MSC markers, including stem cell protein ATP-binding cassette transporter subtype G-2 (ABCG-2) and ocular development gene *PAX6*, which could not be expressed by adult keratocytes^[27,28]. Human corneal limbal stromal niche cells subjacent to limbal basal epithelial cells^[29] reportedly possess stem cell-like features. Moreover, these cells are similar to bone marrow-derived MSCs in terms of their adherent nature, phenotypic marker expression profile, low immunogenicity, self-renewal capacity, and colony forming efficiency^[30]. Branch *et al.*^[31] confirmed that peripheral and limbal corneal stromal cells are MSCs because they conform to all the ISCT criteria. The limbal stroma is another MSC niche. These cells can support the self-renewal of limbal epithelial progenitor cells^[28] and up-regulate several molecular markers of keratocytes^[27]. They can also differentiate into corneal epithelium^[32], vascular endothelial cells, and pericytes^[33]. Niche stromal cells might provide a specialized microenvironment for the maintenance of LSCs^[30]. In addition, corneal limbal stromal cells possess immune privileged^[34] and immunosuppressive properties. Limbal MSCs can suppress T cell proliferation by constitutively secreting transforming growth factor- β 1 (TGF- β 1)^[35]. However, the immunosuppressive potential of limbal MSCs is considerably weaker than that of bone marrow-derived MSCs. Corneal limbal stroma stem cells, which can differentiate into functional keratocytes, may serve as an excellent candidate for the generation of bio-engineered corneal stroma^[36]. Further studies are required to understand the functions of corneal stromal stem cells in wound healing and corneal tissue regeneration.

FUNCTIONS AND MECHANISMS OF MSCS IN CORNEAL WOUND REPAIR

MSCs contribute to tissue wound repair. Bone MSCs might migrate to the injury sites after tissue damage. The functions of MSCs in corneal wound repair can be attributed to two mechanisms: transdifferentiation and paracrine action.

MSC mobilization and homing

Injury and inflammation induce stem cell mobilization, migration, and colonization^[37]. The mechanisms involved when MSCs home to sites of injury remain unclear. Corneal injury results in the release of specific chemoattractants, which cause bone marrow to mobilize endogenous MSCs into the peripheral blood. Thus, circulating

MSCs increase in number and migrate to the local injured cornea but not the healthy cornea^[16,38]. The chemokine SDF-1 and substance P in the cauterized cornea are involved in regulating the mobilization and recruitment of MSCs to corneal injury sites^[16]. In addition, systemically administered MSCs can migrate toward injured or inflamed tissues because of the presence of chemokines, chemokine receptors, intracellular signals, adhesion molecules, and proteases^[39,40]. Ye *et al.*^[41] showed that systemically transplanted MSCs engraft locally to the cornea with alkali burns. They also suggested that exogenously applied MSCs must be self-renewed, fully activated, and mature in the host bone marrow before reentering the circulation. After systemic intravenous delivery, most cells become trapped in the lungs and other non-target organs, such as the liver, kidney, and spleen^[42]. MSCs have a low frequency in sites with tissue damage. A recent report has shown that systemically administered human MSCs reduced corneal inflammatory damage without engraftment by secreting anti-inflammatory factors in response to injury signals from the cornea^[43]. Alternatively, MSCs may be administered locally to improve the concentration at the injured cornea through subconjunctival administration of MSCs^[44] and through transplantation of MSCs with the amniotic membrane (AM)^[45,46] and a hollow plastic tube onto the cornea^[47].

Differentiation into corneal tissue

LSC transplantation, the currently available treatment for severe corneal epithelium damage, has certain limitations. The renewal and healing of corneal epithelium mainly rely on LSCs. Ocular injury, trauma, congenital diseases, and autoimmune diseases could lead to partial or total deficiency in the number and function of LSCs. These conditions may also contribute to the subsequent development of corneal ulcer, opacity, and corneal neovascularization (CNV), which seriously affect ocular surface function and vision^[48,49]. LSC transplantation is an effective way of treating severe LSC damage. However, this strategy has some limitations. Autologous limbal transplantation is only intended for unilateral lesions and could induce LSCD in the healthy donor eye. Moreover, allograft limbal transplantation has a short supply of donors and has the risk of immune rejection^[2,50].

MSCs have received attention as seed cells for corneal tissue engineering to overcome LSC deficiency and reconstruct ocular surfaces. MSCs can be easily isolated, cultured, and proliferated. They can also retain their pluripotent ability. Gu *et al.*^[51] examined the differentiation ability of MSCs in corneal epithelial cells *in vivo* and *ex vivo*. *In vivo*, rabbit MSCs (Rb-MSCs) were transplanted onto the surface of damaged rabbit corneas using fibrin gels. Results showed that the Rb-MSCs expressed the corneal epithelium specific marker cytokeratin 3 (CK3) and promoted the healing of the injured corneal epithelium. Rb-MSCs were co-cultured *in vitro* with rabbit LSCs (Rb-LSCs) using the Transwell culture system or were cultured in the conditional medium of Rb-LSCs. The

Rb-MSCs rapidly lost their fibroblast morphology, differentiated into cells with a corneal epithelia-like shape, and expressed CK3. Furthermore, the soluble factors secreted by Rb-LSCs were suggested to serve important functions in the differentiation of Rb-MSCs because the two types of cells had no direct contact. In another study, bone MSCs were induced by corneal stromal cells to differentiate into corneal epithelia-like cells and express CK12^[52]. Inducing MSCs in the AM significantly improves the reconstruction of the corneal surface of rats with corneal alkali burn. In a recent *in vitro* experiment, corneal epithelia-like cells were induced from human adipose tissue-derived MSCs by subjecting them to a medium conditioned with corneal epithelial cells^[53]. In addition, MSCs can differentiate into corneal epithelial progenitor cells in Rb-LSC deficiency models^[54]. The expression of limbal epithelial cell markers (*e.g.*, ABCG-2, b1-integrin, and connexin 43) is up-regulated after injecting autologous MSCs under the transplanted AM. The up-regulation of these specific markers indicates the capacity of MSCs to maintain their stem cell-like characteristics or to differentiate into epithelial progenitor cells. However, a previous study showed that MSCs serve functions in wound healing in a rabbit corneal alkali burn model by differentiating not into corneal epithelial cells or limbal progenitor cells but into myofibroblasts, as indicated by the expression of α -smooth muscle actin^[41].

MSCs are promising tissue engineering cells for treating corneal stromal damage and congenital keratocyte dysfunction. Corneal keratocytes are quiescent cells with a flat and dendritic morphology. Keratocytes may become activated by injury, and the syntheses of keratocan and lumican are down-regulated during wound healing^[55]. When cultured in media containing serum *in vitro*, keratocytes change their keratocyte phenotype into activated cells^[56]. In a recent study, human bone marrow-derived MSCs that grow on an AM were cultured in a keratocyte-conditioned medium with cytokines and other growth factors. Results showed that human bone marrow-derived MSCs can directly differentiate into keratocyte-like cells^[45]. The induced MSCs expressed the keratocyte specific markers keratocan, lumican, and aldehyde dehydrogenase 1 family, member A1. They also exhibited a dendritic morphology similar to that of natural keratocytes. Liu *et al.*^[57,58] reported that bone marrow-derived MSCs or umbilical MSCs transplanted into the cornea of keratocyte dysfunction mice significantly increased stromal thickness and improved corneal transparency and host keratocyte functions. These MSCs assumed corneal keratocyte phenotype and expressed the keratocyte-specific markers keratocan and lumican. The results suggest that MSCs can differentiate into keratocyte-like cells and can be influenced by several growth factors and other factors secreted by keratocytes.

MSCs are an ideal candidate for healing damaged corneal endothelium. Corneal endothelial cells mainly provide nutrition to the cornea and maintain corneal transparency by pumping water from the cornea. The cells are

non-renewable after damage and loss. Joyce *et al*^[59] used baseline microarray analysis to show that umbilical cord blood-derived-MSCs (UCB-MSCs) and human corneal endothelial cells (hCECs) have a relative similarity in gene expression. Subsequently, the morphology of MSCs was consistently altered toward a more hCEC-like shape both in tissue culture and in *ex vivo* corneal endothelial wounds when MSCs were grown in a lens epithelial cell-conditioned medium (LECCM). A second microarray analysis showed that UCB-MSCs grown with LECCM had significant changes in the relative expression of genes and differentiated into a more hCEC-like phenotype. These data indicated that UCB-MSCs could be altered toward hCEC-like cells in specific microenvironments and that LECCM influenced the differentiation of UCB-MSCs. However, further research must be conducted to confirm the nature of specific microenvironment.

Paracrine action

MSCs exert therapeutic effects to facilitate tissue wound repair by secreting soluble factors that suppress inflammation and angiogenesis^[60]. Many reports showed that MSCs can improve tissue repair despite exhibiting a small fraction of engraftment in sites of tissue damage^[60]. Ma *et al*^[46] transplanted human MSCs grown and expanded on the AM into chemically burned corneas of rats. After 4 wk, the damaged corneal surface and the vision of the rats were significantly improved. Immunofluorescent analysis showed that epithelial cell markers were not detected in the eyes of rats transplanted with MSCs. However, the expression level of CD45 and interleukin 2 (IL-2) significantly decreased. In addition, matrix metalloproteinase-2 (MMP-2), which is associated with inflammation-related angiogenesis, was not detected in the eyes of the MSC-treated rats^[46]. The subconjunctival injection of MSCs improved the wound healing of corneas with alkali burns. The MSCs remained in the subconjunctival space after 7 d without infiltrating the injured cornea^[44]. These results demonstrate that MSCs exert their therapeutic effects on corneal wound repair by suppressing inflammation and angiogenesis, which serve more important functions than differentiation into corneal epithelial cells. Topically administered MSCs and conditional MSCs medium can obviously attenuate inflammation, reduce CNV, and accelerate corneal wound healing in rats with chemically burned corneas. The soluble factors produced by MSCs are involved in anti-inflammatory and anti-angiogenic effects through paracrine action^[47]. In injured corneas, MSCs transplantation up-regulates the expression levels of the anti-angiogenic factor thrombospondin-1 (TSP-1) and the anti-inflammatory cytokines IL-10, TGF-1, and IL-6 while down-regulates the expression levels of the pro-inflammatory factors IL-2, interferon- γ (IFN- γ), macrophage inflammatory protein-1 α , and vascular endothelial growth factor (VEGF)^[44,47]. Similarly, human MSCs co-cultured with chemically damaged hCECs are associated with changes in the expression level of soluble factors that modulate inflammation and

neovascularization^[61]. Oh *et al*^[62] have recently found that MSCs activated by the signals from injured corneas up-regulate the expression of tumor necrosis factors (TNF)- α -stimulated gene/protein 6 (TSG-6). TSG-6 is an anti-inflammatory protein that can significantly decrease neutrophil infiltration, pro-inflammatory cytokine and chemokine levels in corneas with mechanical injuries, and corneal opacity and neovascularization. In another study, MSCs administered intraperitoneally or intravenously without being engrafted to chemically injured corneas of rats effectively alleviate corneal opacity and inflammation by TSG-6^[43]. MSCs accelerate the neovascularization by secreting VEGF, particularly in ischemic tissues and tumors. By contrast, MSCs are involved in anti-angiogenesis in injured cornea. Such action might be attributed to the high-level of TSP-1, which inhibits VEGF^[47]. The specific mechanism involved remains unclear.

MSCs secrete certain growth factors to facilitate the survival of injured cells and accelerate tissue regeneration in specific microenvironments. Zhang *et al*^[63] cultured MSCs and LSCs that were seeded on a xenogeneic acellular corneal matrix *in vitro*. They observed higher levels of growth factors, including VEGF, epidermal growth factor (EGF), and TGF- β 1, in the MSCs than in the LSCs. The MSCs express beneficial factors for corneal recovery and might permit a potent corneal substitute for healing corneal injury. Aside from up-regulating beneficial factors, MSCs also stimulate the proliferation of LSCs and native corneal cells^[41]. Moreover, MSCs can reduce the severity of LSC loss, suppress inflammation, and improve epithelial regeneration during the acute phase of corneal injury^[16]. The survival and proliferation of rat LECs are markedly promoted and the expression of EGF is up-regulated by co-culturing LECs and rat MSCs or by culturing LECs in a medium pre-conditioned with rat MSCs. The effects of MSCs on LECs might be mediated by paracrine action^[64]. In summary, paracrine mechanisms of MSCs may exert a significant impact in promoting corneal wound repair, which involves the joint participation of different soluble factors that modulate inflammation and angiogenesis as well as improve tissue regeneration. The involved bio-physiological factors and the underlying mechanism in corneal wound healing remain unclear.

MSCS AND CORNEAL TRANSPLANTATION

MSCs, immunity, and solid organ transplantation

Several studies have confirmed that MSCs have potent immune modulatory properties that allow them to exert immunosuppressive effects both *in vivo* and *in vitro*. As immune privileged cells, MSCs reduce the expression of MHC class II and co-stimulatory molecules on the surface of cells (CD80, CD86, and CD40)^[65]. *In vitro*, MSCs influence the innate immune system by suppressing maturation and activation of dendritic cells (DCs) and cytotoxicity of natural killer cells. They also interact with adaptive

immune responses by inhibiting proliferation and cytokine secretion of T cells and maturation of B cells^[7,66]. To effectively influence immunoregulation, the activation of MSCs requires an inflammatory microenvironment and stimulation by pro-inflammatory cytokines, such as IFN- γ and TNF- α , from effector T cells^[67,68]. Several soluble factors produced by MSCs are involved in the immunosuppression of MSCs. These factors include TGF- β , IL-6 and -10, MMP, prostaglandin E2 (PGE2), indoleamine-2, 3-dioxygenase (IDO), human leukocyte antigen-G5 (HLA-G) and nitric oxide (NO)^[69,70]. In addition, MSCs can decrease the expression level of IFN- γ from Th1 cells and increase the expression levels of IL-4 and IL-10 from Th2 cells, thereby promoting immune response of naive CD4⁺ T cells toward the Th2 type response^[71,72]. When co-cultured and placed in contact with naive T cells, human MSCs promote the differentiation and expansion of regulatory T cells (Tregs) in mixed-lymphocyte reactions by secreting PGE2 and TGF- β ^[73]. Tregs, a specialized subset of T cells, retain their capacity to suppress the response of T cells and maintain immune system activation. MSCs were also suggested to maintain tolerance and improve the survival of allografts in solid organ transplantation mainly through the function of Tregs^[74].

Currently, MSCs have been widely used in animal studies that involve solid organ transplantation. However, the *in vivo* effect of MSCs on inhibiting the immune rejection response is controversial. Bartholomew *et al*^[75] first reported that using MSCs can prolong skin graft survival in organ transplantation. In rat and primate models, MSCs can effectively suppress immune rejection; induce immune tolerance; and prolong graft survival in the liver, heart, kidney, pancreas, and other solid organs for transplantation^[76-78]. These results might result from the shifting of the Th1/Th2 cell balance in favor of the latter, thereby increasing the level of Tregs and inhibiting the function of DCs through MSCs. By contrast, other studies suggested that MSCs exert no beneficial effects on organ transplantation. The infusion of donor-derived MSCs accelerated allograft rejection in an immunocompetent rat skin transplantation model^[79]. In addition, Inoue *et al*^[80] reported that MSC therapy with or without cyclosporine A (CsA) is prone to accelerate graft loss in a rat cardiac transplantation model, although donor-derived MSCs inhibit the proliferation of T cells *in vitro*. These results indicate that MSC therapy is not always beneficial and might exacerbate disease under certain circumstances. Interestingly, the combined use of MSCs and mycophenolate mofetil^[81] leads to successfully prolonged graft survival by allowing the IFN- γ stimulation of non-activated MSCs and suppressing the infiltration of antigen presenting cells (APCs) and T cells in the graft of the same model^[82]. The results of this study suggest that the immunomodulation function of MSCs depends on the type of combined immunosuppressive agent. Furthermore, the application of MSCs combined with a subtherapeutic dose of immunomodulator in solid organ transplantation not only potently exerts a synergistic

function in suppressing immune rejection response but also reduces the side effect caused by large doses of immunosuppressive agents alone.

Infusion time is an important factor for MSCs to effectively exert their immunoregulatory effect on organ transplantation^[66,83]. Heart transplants require MSCs to be infused before organ transplantation. An intravenously pre-operative infusion of MSCs can modulate Treg expansion early, and induce immune tolerance before occurrence of inflammation and immune response. By contrast, MSCs infused postoperatively are less effective^[84]. In a mouse kidney transplant model, MSC injection after transplantation failed to prolong graft survival due to complement activation, neutrophil recruitment, and kidney dysfunction. Administering MSCs before kidney transplantation could prevent the deterioration of graft functions^[85]. However, a recent study^[86] that used a rat corneal transplantation model has shown that MSCs prolong corneal allograft survival time only when injected immediately after surgery and that pre-operative infusion exerts no significant effect. The cornea is an immune privileged tissue and is situated in a special immune microenvironment that triggers delayed-type hypersensitivity. Therefore, MSCs injected immediately after the surgery might be more appropriate^[86].

The dose of MSCs is another element that influences their therapeutic effect on solid organ transplantation. During *in vitro* mixed lymphocyte reactions, MSCs could inhibit T lymphocyte proliferation depending on the graded numbers of MSCs^[87]. The best dose and time of MSCs transplantation have yet to be standardized because previous studies used different animal models and infusion methods. In a previous study, patients were intravenously infused with doses of $1.0\text{--}2.0 \times 10^6$ MSC/kg^[88]. Another recent multi-center research has shown that 0.5×10^6 MSC/kg to 9×10^6 MSC/kg is a safe dose range; that is, this range does not elicit adverse side effects^[89]. Results showed that the effects of MSCs are dose-dependent. Therefore, investigating the dose of MSCs is necessary to achieve the best therapeutic results.

MSCs in corneal transplantation *in vivo*

Given their immunomodulatory and anti-inflammatory properties, MSCs are a potential therapeutic tool for corneal allograft transplantation. Corneal allograft has a survival rate that exceeds all other types of solid organ transplantation as a result of immune privilege^[90]. However, corneal graft immune rejection could occur, which remains the leading cause of corneal allograft failure.

Oh *et al*^[91] first examined the immunomodulatory effects of allogeneic recipient-derived MSCs in penetrating keratoplasty in a pig-to-rat model. The topical application of allogeneic rat MSCs caused T cell differentiation in Th2 cells. Subsequently, the balance between Th1 and Th2 cells shifted toward Th2-type. However, the significant increase in Th2-type cytokines induced by MSCs did not effectively prolong the survival of pig corneal xenografts in rats.

Recently, Jia *et al.*^[86] have investigated the immunosuppressive function of MSCs in a rat allogeneic corneal transplant model. In this study, donor MSCs were intravenously injected at different times and were administered with different doses of CsA. They found that the postoperative infusion of MSCs inhibits corneal allograft rejection and prolongs corneal graft survival, whereas pre-operative infusion is ineffective. Moreover, the combined effect of MSCs and CsA highly depends on CsA dose. Combining 2 mg/kg CsA with MSCs is the best regimen for achieving a synergistic effect. Further studies on the possible mechanism of MSCs in allogeneic keratoplasty showed that donor-derived MSCs significantly inhibit allogeneic T cell responses both *in vitro* and *in vivo*, reduce Th1 pro-inflammatory cytokines, and increase Th2 anti-inflammatory cytokine secretion in a rat model. Moreover, MSCs up-regulate the number of Tregs, thereby preventing allograft immune rejection and improving allograft survival.

However, a recent study^[92] has suggested that MSCs function in corneal transplantation through a different mode of action. Pre-transplant systemic infusion of human MSCs inhibits the afferent loop of the immune response primarily by reducing inflammation caused by surgery during the early postoperative period, thereby decreasing the immune rejection responses and prolonging the graft survival time in a mouse model of corneal transplantation. MSCs exert their effects by secreting soluble factors, such as TSG-6, rather than engraftment in the cornea allograft. Suppressing inflammation subsequently decreases the activation of APCs in both the cornea and draining lymph nodes. By contrast, human MSCs with TSG-6 knockdown are not effective in reducing the early inflammatory response or prolonging corneal graft survival. This mechanism might also be involved in reducing the immune rejection responses in other organ transplants.

In summary, the application of MSCs may be a new alternative method for prevention and treatment of immune rejection after corneal transplantation. However, the therapeutic effects of MSCs on corneal allograft immune rejection response in clinical and animal models remain unclear. Further studies on the specific molecular mechanism of MSCs must be conducted to develop a novel therapeutic strategy.

CONCLUSION

MSCs promote the healing of corneal wound through their capability of differentiation and paracrine function. In addition, MSCs inhibit the rejection of corneal transplantation and prolong the survival time of corneal allografts. However, the mechanisms of MSCs in corneal injury and keratoplasty are not clear. The time, manner, dose, route of administration, and terminal differentiation of MSCs *in vivo* require further investigation. It is believed that the microenvironment is crucial in modulating the function of MSCs. Further research on microenvironmental factors must be carried out to improve the

therapeutic effect of MSCs. Moreover, the heterogeneity of MSCs leads to treatment discrepancies. Therefore, investigating the characteristics of MSC subpopulation and improving the culture conditions for MSCs may lead to the improvement and predictability of therapeutic effects. The complex features of MSCs contribute to the complexity of their effects. The functions of MSCs and their tremendous potential effects on corneal and other diseases require further exploration.

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