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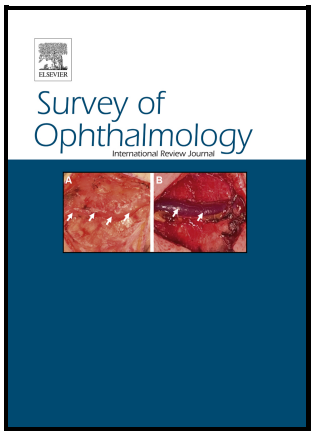

Potential applications of mesenchymal stem cells in ocular surface immune-mediated disordersRunning title: Cornea Immunity and Mesenchymal Stem Cell

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Title: Potential applications of mesenchymal stem cells in ocular surface immune-mediated disorders

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ABSTRACT

We explore the interaction between corneal immunity and mesenchymal stem/stromal cells (MSCs) and their potential in treating corneal and ocular surface disorders. We outline the cornea's immune privilege mechanisms and the immunomodulatory substances involved. In this realm, MSCs are characterized by their immunomodulatory properties and regenerative potential, making them promising for therapeutic application. Therefore, we focus on the role of MSCs in immune-mediated corneal diseases such as dry eye disease, corneal transplantation rejection, limbal stem cell deficiency, and ocular graft-versus-host disease. Preclinical and clinical studies demonstrate MSCs' efficacy in promoting corneal healing and reducing inflammation in these conditions. Overall, we emphasize the potential of MSCs as innovative therapies in

ophthalmology, offering promising solutions for managing various ocular surface pathologies.

I. INTRODUCTION

The cornea, as the outermost layer of the eye, is not only a transparent optical element, but also a vital immunological interface. The intricate network of immune cells within the cornea orchestrates a delicate balance between safeguarding against pathogens and maintaining immune tolerance. Recent studies have unveiled a compelling interplay between corneal immunity and mesenchymal stem/stromal cells (MSCs), highlighting their potential collaborative roles in maintaining ocular surface homeostasis. Herein, we explore the molecular and cellular mechanisms that underlie the interaction between corneal immunity and MSCs, exploring the potential implications and future applications for ocular immune modulation and regenerative medicine. Moreover, we aim to review current evidence regarding the mechanisms by which MSCs contribute to

corneal immune regulation in the context of numerous immune-mediated corneal disorders.

II. CORNEAL IMMUNITY: A BRIEF OVERVIEW

The ocular surface is referred to as immune-privileged because, despite its ability to build a strong immunological defense, it also employs tight immune surveillance systems to prevent undesirable local inflammatory reactions and preserve corneal transparency and visual function[29]. The underlying corneal immune privilege is maintained by various factors, including the morphological and structural properties of the corneal tissue. Key structural components such as the intact epithelial barrier, the absence of blood and lymphatic vessels in the central cornea, and the presence of tight junctions between corneal epithelial cells help to limit the entry and movement of immune cells and pathogens. Additionally, the corneal stroma's organized collagen

matrix and the presence of a basement membrane support corneal transparency and integrity, which are crucial for immune privilege[125]. These structural features-- along with soluble immunomodulatory molecules, resident immune cells, peripheral tolerance to ocular antigens, and neuroimmune cross-talk-- collectively contribute to the maintenance of corneal immune privilege

[29]. The ocular surface and aqueous humor contribute to the cornea's immunological privileged status by preventing the penetration of pathogenic microorganisms, allergens, and toxins. This process is dependent on tear fluid, the glycocalyx that covers the surface of apical cells, intercellular adhesion structures, and the basement membrane of the epithelium[12,98].

Cornea avascularity is a critical anatomical property that ensures immunological privilege. In fact, the lack of afferent vessels prevents infiltration of immune cells to the cornea [142,209].

This privilege of the corneal tissue derives from an interplay between factor that impede neoangiogenesis. such as corneal stem cell functionality [54,70], epithelial basement membrane-derived anti-angiogenic factors (endostatin, neostatins, restin, arresten, canstatin, tumstatin) [1,53], corneal soluble anti-angiogenic factors (sflt-1[4], angiostatin[70], INF-γ[105,210], FasL[149], PD-L1[94]), and neurogenic factors[42,58].

Several immunomodulatory substances play a crucial role in maintaining corneal homeostasis and are constitutively produced by the corneal epithelium [9,29]. For example, PD-L1 induces T cell apoptosis, thereby reducing activated T cell effector responses [51,61,165]. PEDF effectively inhibits the maturation and activation of corneal resident leukocytes [96,171,172]. TSP-1 activates TGFβ-1, which promotes the immunosuppressive phenotype of regulatory T cells (Treg) and inhibits proinflammatory immune responses

[156,196]. Galectin-9 suppresses the CD8+ cell response and enhances Treg function [161,162]. These substances collectively contribute to the intricate immunoregulatory environment of the cornea, crucial for maintaining ocular health and immune balance.

Corneal immunological regulation is also dependent on antigen-presenting cells (APCs), which include stromal CD11b+CD11c- macrophages/monocytes, anterior stromal CD11b+CD11c+ dendritic cells (DCs), and epithelial Langerhans cells [74,76,78,102,161,205]. These cells tend to form a negative gradient from the periphery and limbal regions, where they are more concentrated, to the center of the cornea [76]. Under steady-state conditions, it appears that corneal APCs in the peripheral cornea are MHC class II-positive, but in the central cornea they are regularly MHC class II-negative with a low expression of CD80.

CD86, CD40, which represent co-stimulatory factors [75,76]. These latter cells have decreased antigen presentation capability, increased synthesis of regulatory cytokines, and a proclivity for Treg formation and proliferation; for this reason, they are referred to as tolerogenic APC[56,131]. Nevertheless, inflammation can activate and mobilize APC, which migrate through efferent lymphatic vessel and then activate naïve T cell by secreting T cell-polarizing cytokines and antigenic and co-stimulatory signals, resulting in differentiation into effector Th1, Th2, or Th17 cells [19,28,50,69,103,179] in the draining lymph nodes.

A critical immunoregulatory process that limits and inhibits the proinflammatory effector T-cell response is dependent on Tregs, which are commonly defined as CD4+, CD25+ and Foxp3+ cells[60,154]. Tregs maintain self-antigen tolerance, avoiding autoimmunity, and preventing excessive inflammatory

responses[139,213]. They regulate immune homeostasis through several processes, including cytolysis, release of soluble substances, metabolic competition, and suppression of antigen presentation[194]. Moreover, Tregs play a crucial role in promoting corneal graft survival by suppressing immune responses and preventing graft rejection, highlighting the potential of therapies that enhance graft success through the induction and support of Treg function[6,87]. Subconjunctival injection of Treg cells has been shown to significantly decrease the frequencies of mature antigen-presenting cells in the graft and draining lymph nodes (DLNs), suppress Th1 frequencies in DLNs, and inhibit CD45+ cell infiltration into the graft. Additionally, locally delivered Treg cells significantly reduced the expression of IFN-γ, increased levels of IL-10 and TGF-β in the graft, and promoted long-term allograft survival [163].

Neuro-immune interactions are crucial in preserving corneal immune privilege. Trigeminal nerve's ophthalmic branch extensively innervates the cornea, with neuropeptide-mediated interactions between the neurological and immune systems being essential for ocular surface homeostasis [151]. Neuropeptides modulate immune responses and affect vascular cells, with bidirectional production by immune cells and neurons [22,30,159,176]. Substance P (SP) enhances wound healing, stimulates immune cells, and induces dendritic cell maturation [11,106,135,137]. Calcitonin gene-related peptide (CGRP) reduces pro-inflammatory cytokines and modulates immune cell costimulatory molecules [26,82]. Vasoactive intestinal peptide (VIP) inhibits macrophage and dendritic cell activity, affects T cell differentiation, and promotes regulatory dendritic cells [43,44,95]. α-melanocyte stimulating hormone (α-MSH) reduces inflammation and cytokine release and promotes regulatory T cell development [10,148,199].

As outlined above, immune privilege is critical to the immunological homeostasis of the eye, and this delicate balance between avoiding excessive inflammation while still protecting the eye from external insults is altered in various disorders pertaining the ocular surface. In this setting, MSCs emerge as a promising and innovative immunomodulatory and regenerative therapeutic strategy for a wide spectrum of corneal and ocular surface pathologies. This necessitates a more comprehensive examination of their functions across various clinical subsets [153].

III. MESENCHYMAL STEM CELLS

The terminology “stromal” or “stem” attributed to mesenchymal cells has been used variably in the scientific literature, leading to confusion; however, some researchers argue for a distinction between the two terms[83,136,195]. The terminology “mesenchymal stromal cells” was initially proposed to reflect the heterogeneity

and functional properties of the cells isolated from various tissues. MSCs were considered to possess immunomodulatory and tissue-repair properties without necessarily having the full differentiation potential typically associated with stem cells[195]. They were thought to play a supportive role in tissue repair by secreting various growth factors and cytokines. Mesenchymal stem cells were considered as multipotent cell capable of differentiating in different mesoderm-derived cell types [47]. They were characterized by self-renewal capacity and ability to transform into several cell types in a context-dependent fashion. Specifically, MSCs can differentiate into osteoblasts in the presence of osteogenic stimuli, adipocytes under adipogenic conditions, and chondrocytes when exposed to chondrogenic environments. Additionally, under specific signals, MSCs can give rise to myocytes, neurons, and endothelial cells, demonstrating their versatile potential for tissue regeneration and

repair across various physiological and pathological contexts; [145] however, recent research has suggested that the distinction between the two terms may not be clear-cut. In summary, while mesenchymal stromal and stem cell have been used equally, there is ongoing debate within the scientific community regarding their precise definitions and distinctions. The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy established specific criteria for MSCs identification [48]. These are characterized by their ability to adhere to surfaces made of plastic, to develop clones, to express of specific markers such as CD73, CD90 and CD105, and the absence of hematopoietic and endothelial markers CD45, CD34, CD14, CD11b, CD79α, CD19, HLA-DR [48]. Moreover, MSCs must demonstrate the potential for in vitro differentiation into mesodermal cell lineages [35,191]. MSCs can differentiate in cell of adipose, cartilage, and bone tissues[146]. Moreover, human and murine specific type of

MSC cells can maturate in neuroectodermal or endodermal cells, such as neurons, endothelial cells, and hepatocytes[33,93,122,183].

MSCs are known for their ability to preserve their potent functions, such as self-renewal and multi-lineage differentiation, across different steps of their maturation [104,123]. This includes their transition from early progenitors to intermediate stages like preosteoblasts, preadipocytes, and prechondrocytes, ultimately leading to fully differentiated osteoblasts, adipocytes, and chondrocytes. Throughout these stages, MSCs maintain their capacity to respond to specific signals and differentiate into various cell types, demonstrating their versatility and regenerative potential. Therefore, these cells are considered for their important plasticity features, which make them a promising target of study for tissue repairing and regeneration [23,71,186]. Importantly, these cells have been found in a variety of tissues in the human body,

including bone marrow, adipose tissue, amniotic fluid, placenta, and umbilical cord [17,47,84,111,188,201].

Autologous adult stem cells have been extensively applied in studies due to their immunocompatibility, with minimal ethical concerns [215]. This is an advantage for their application, in contrast with cells derived from neonatal tissues (embryo, cord or placenta) and induced pluripotent stem cells, which have limited use in humans [68]. These limitations include complexity of cellular regulation, promotion of tumor growth, immunogenicity, genetic manipulation, ethical concerns, and difficulties in their preservation [18,187].

Notably, MSCs exhibit a strong tropism towards sites of inflammation or injured tissues, even when administered systemically [86,115,133,169]. This characteristic is essential for their tissue repair function and contribution to immune homeostasis,

which refers to the delicate and finely regulated balance of appropriate immune activation and suppression in tissues and organs, maintained by a complex interplay of various cellular components and chemical factors. MSCs potent immunomodulatory capabilities, mediated by the release of an array of immunoregulatory factors, suppress both the adaptive and innate response [31,86,127,200]. MSCs exhibit extensive immunomodulatory capabilities through both direct cell-cell interactions and the secretion of soluble factors. These cells play a pivotal role in modulating the immune response by inhibiting T cell proliferation and functionality, attenuating NK cell activation, and suppressing the differentiation and activation of APCs [153]. Furthermore, MSCs impede B cell proliferation and differentiation into plasma cells, diminish the antigen-presenting capacity of macrophages, and reduce neutrophil apoptosis, infiltration, and effector functions [62,85]. Additionally, MSCs

induce the differentiation of Tregs, thereby contributing to immune tolerance. (**Figure 1**) These comprehensive immunomodulatory properties underscore the therapeutic potential of MSCs in various immune-mediated disorders, as discussed in details in the following section III.A.

Interestingly, MSCs have been proven to release several factors in their culture media [52]. This so-called "secretome" includes chemokines, cytokines, growth factors, and immunomodulatory proteins. Additionally, MSCs secrete microvesicles and exosomes, which act as packaging systems to deliver these bioactive molecules to target cells, enhancing the therapeutic potential of the secretome [77]. The application of this secretome has been studied in wound healing, cardiac infarction, hepatic diseases, brain ischemia, inflammatory disorders, and ophthalmic diseases [21,67,77,114,120,132,182,202,212]. Given the

multipotentiality of MSCs, we here discuss the potential application of MSCs in regulating immune-mediated processes underlining principal corneal disorders in which ocular surface immune homeostasis is disrupted **(Figure 2).**

Additionally, recent studies have identified a resident population of MSCs within the cornea [63,157]. These corneal MSCs exhibit unique properties that contribute to corneal homeostasis and repair[16]. Notably, corneal MSCs have demonstrated considerable anti-inflammatory and anti-scarring effects. These cells secrete anti-inflammatory cytokines and modulate immune cell activity, reducing inflammation in various corneal disease models[90,168]. Furthermore, corneal MSCs have shown efficacy in minimizing fibrosis and promoting tissue repair, thereby reducing scarring and enhancing corneal clarity[16,158]. Although most current research on corneal MSCs is not directly related to the

specific disease entities we focus on, their potential to mitigate inflammation and fibrosis underscores their importance as a therapeutic option [158]. By including these findings, we aim to present a more comprehensive perspective on potential treatments for corneal diseases (Table 1).

III.A. IMMUNE-MEDIATED CORNEAL DISEASES AND APPLICATION OF MSCs

III.A.1. Dry Eye Disease

Dry eye disease (DED) is a high-prevalence ocular surface disorder characterized by disruption of quantitative and qualitative tear film characteristics, inflammation, and nerve alterations [37,38]. DED is an autoimmune process that may be part of the Sjögren's syndrome or overlap with other systemic autoimmune conditions. Although the pathophysiology of DED is still not entirely clear, it has been proven that inflammation and

the failure of ocular surface immune homeostasis plays a crucial role in disease progression [178]. Protecting and preserving ocular surface homeostasis requires strict regulation of both innate and adaptive immunity in the ocular surface environment [130]. Therefore, DED may result from a disruption of this immunological homoeostasis [13,73,144,177]

Given the regenerative and antiinflammatory potential of MSCs, the therapeutic application of these cells in DED has been explored. Investigators demonstrated that treatment with extracellular vescicle derived from MSCs human umbilical cord (hUC-MSC-sEVs) in a dessicating dry eye murine model proved to be beneficial in maintaining corneal health, by increasing tear production, enhancing goblet cells density, inhibiting apoptosis and reducing CD4+ T cell migration, and reducing proinflammatory cytokines in tear fluid [198]. In a rabbit dry eye

model, injection of hUC-MSC-sEVs induced macrophages to adopt antinflammatory function (M2) and promoted Tregs expansion. This dual effect contributed to reduced inflammation and improved tissue damage [112]. Furthermore, in a murine model DED using benzalkonium chloride, topical application of exosomes of MSCs derived from murine adipose tissue demonstrated anti-inflammatory properties by inhibiting cell apoptosis, reducing proinflammatory cytokine levels such as interleukin-1β, interleukin -6, interleukin -1α, interferon gamma and tumor necrosis factor alpha, and increasing the expression of interleukin-10, an anti-inflammatory cytokine [197]. Moreover, MSC-EVs have been showed to play a potential role in in alleviating the neuropathic physiopathology of DED [5]. In a murine pre-clinical study on Sjögren's syndrome, olfactory ecto-MSCs-derived exosomes effectively slowed down the disease progression and suppressed Th cell responses by expressing high

levels of PD-L1 [150]. In a similar model, injection of MSCs extract effectively preserve salivary and lacrimal glands function, upregulating the expression of various beneficial genes including IL-10a and simultaneously reducing the levels of TGF-β1, MMP2, CASP3, IL-1β and TNF-α.

In a mouse model of DED, topical treatment with extracellular vesicles derived from MSCs reduced disease severity. This treatment also decreased the expression of TNF-α, IL-6, and IL-1β, lowered the frequency of Th17 cells, and inhibited the maturation of DCs [72]. Interestingly, the adoptive transfer of MSCs derived from human umbilical cords improved symptoms and mitigated pathological alterations in the submandibular glands of mice by regulating Tim-3 expression, which was decreased in the cohort of patients with SS. This led to reduced local inflammation, fibrosis, and epithelial-mesenchymal

transition (EMT) [185]. Another study investigating the application of MSCs derived from human umbilical cords in a rabbit model of autoimmune dacryoadenitis found that systemic infusion of these cells effectively reduced chronic inflammation in the lacrimal glands and improved clinical symptoms. Furthermore, the treated animals exhibited significantly lower levels of M1 macrophage activation markers, while their M2 anti-inflammatory phenotype was promoted [118].

In aqueous-insufficient dry eye induced in mice, eGFP-expressing MSC adoptive transfer yielded significant improvements in lacrimal gland (LG) regeneration, modulating the immune response by delaying macrophage infiltration and decreasing TNFα expression, coupled with heightened levels of interleukin-6, and a significant increased regenerative capacity compared to the control groups[46]. Intraperitoneal injection of

MSCs derived from murine bone marrow in Sjögren's syndrome model of dry eye increased tear production and decreased the size of lymphocytic foci in the LGs [3]. In another study, periorbital administration of human bone marrow derived-MSCs led to a reduction of effector T cells infiltration and decreased pro-inflammatory markers such as interleukin-2 and IFN-γ both in intraorbital glands and at the ocular surface [108]. Ultimately, studies have demonstrated that the application of MSC-conditioned media in dry eye therapy could amplify treatment efficacy by attenuating inflammatory and apoptotic mechanisms, while also promoting tear production and stimulating the growth of corneal epithelial cells. This underscores the promise of harnessing the MSC secretome. [21]

III.A.2. Corneal transplantation

Corneal transplantation one of the most performed solid organ transplantation [64] with the highest successful rate [134,180]. Although corneal allografts exhibit elevated rates of survival owing to immune privilege, the predominant reason for graft failure remains the threat of immune rejection. [207,216]. In most uncomplicated cases, this procedure necessitates only topical immunosuppression to ensure graft survival, obviating the necessity for histocompatibility matching in routine keratoplasty[55]. This phenomenon can be attributed to the concept of "immune privilege" [14,124,134,181], which contributes significantly to its high success rate in humans and experimental animals[134,180]. When a corneal transplant involves low-risk conditions, such as non-vascularized and uninflamed host beds, it yields a survival of the graft of more than 90%[147]; however, in cases involving patients who underwent multiple surgery due to previously failed transplantation or in case of vascularized and inflamed host beds,

the success rate diminishes considerably, resulting in more than 50% of grafts failing [39,59].

Given their ability to modulate the immune response, MSCs show promise for use in corneal allograft transplantation. In a model of high-risk corneal transplantation in rats, subconjunctival MSCs derived exosomes subconjunctivally injected significantly prolonged graft survival time, inhibiting infiltration of effector T cells, and reducing levels of IFN-γ and CXCL11, involved in attracting immune cells such as T cells and dendritic cells to sites of inflammation [92]. Similarly, subconjunctival injections of MSCs derived from bone-marrow in rats corneal allograft notably extended the survival of the grafts and ameliorated clinical outcomes, decreasing opacity, edema, neovascularization, Th1 cell and macrophage activation, along with an increase in Tregs function [117]. In an analogous corneal allograft rejection rat model,

injection of MSCs after corneal transplantation significantly extended graft survival and suppress the adaptive-immune response in the allograft [91]. Allogeneic MSCs intravenously injected in rats pre-sensitized to donor antigens extended rejection-free graft survival and significantly promoted Treg differentiation and function in the draining lymph nodes [116]. Additionally, intravenous infusion of human derived MSCs in a murine model of allogeneic corneal transplantation inhibited maturation and migration of CCR7+ antigen presenting cells from the cervical draining lymph nodes to the cornea [79]. In another study, administration of syngeneic MSCs in corneal allograft recipients following surgery reduced antigen presenting cells in both the corneal graft and lymph nodes, leading to increased allograft survival rate [140]. Furthermore, utilizing a rat corneal transplant model, it was demonstrated that treatment with allogeneic bone marrow derived MSCs notably enhanced the

survival duration of corneal allografts, reduced the infiltration of natural killer cells in the corneas and, concurrently, significantly promoted Treg function in the recipients, showing low immunogenicity and potent immunoregulatory function of these cells [189]. Interestingly, intravenous injection of human MSCs suppressed inflammation induced in the early phase following surgery and reduced activation of antigen presenting cells, resulting in prolonged allograft survival [138]. Additionally, TGF-β-1 priming of MSCs cells has been shown to significantly improve corneal graft survival, indicating their superior therapeutic efficacy in modulating immune rejection of corneal allografts [119]. Moreover, the paracrine activity of MSCs holds considerable potential in corneal transplantation by shaping the local environment and regulating the immune response. MSCs secrete numerous factors like platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), hepatocyte growth

factor (HGF), and transforming growth factor beta 1 (TGF-β-1) [20,128,141]. Interestingly, it is notable how these factors, which can promote neovascularization in ischemic conditions such as myocardial infarction [184,204], contribute to suppressing neoangiogenesis and rejection in corneal transplants [57]. These findings emphasize the context-dependent efficacy of MSCs therapy and their capacity to mitigate inflammation and immune activation [2].

III.A.3. Limbal stem cell deficiency

Limbal stem cells (LSCs) possess significant proliferative capabilities, enabling effective regeneration and restoration of the cornea. [107,109,190]. These LSCs are primarily located within specialized regions at the limbus, delineating a niche of stem cell [41]. Within the highly vascularized and innervated limbal microenvironment, LSCs closely interact with a variety of cells

(melanocytes, stromal cells, extracellular matrix) [49,160]. These interactions confer dual roles to the limbus: acting as a barrier between the corneal and conjunctival epithelium, and actively replenishing corneal epithelial cells [36]. Both functions are critical for maintaining ocular surface homeostasis, contributing to corneal integrity and transparency, therefore preserving vision under physiological conditions.

Limbal stem cell deficiency (LSCD) is a complex pathology with a multifaceted origin, resulting in the partial or complete loss of the cornea's regenerative capacity [113]. Pathologies affecting LSCs or their supportive niche can precipitate LSCD, and these conditions may be congenital, traumatic, or acquired (including chemical or thermal ocular injuries, surgical trauma, use of contact lenses, radiation therapy), autoimmune (such as Stevens-Johnson syndrome, mucous membrane pemphigoid, Sjögren's

syndrome, vernal keratoconjunctivitis, graft-versus-host disease), or idiopathic [97]. While LSCD can arise from a broad spectrum of primary and secondary causes, it is most often associated with severe chemical or thermal burns [193]. Stem cell loss in the limbal region, resulting from significant injury, leads to permanent defects in the corneal epithelium and vision impairment due to conjunctivalization of the cornea [164].

Despite the array of surgical treatments, a reliable and effective method for managing severe LSCD, especially in bilateral cases, remains elusive [40]. The use of autologous limbal cell transplantation has gained broad acceptance as a therapeutic strategy for treating unilateral limbal stem cell loss [100]. Nevertheless, in instances of bilateral damage, allogeneic limbal cell transplantation is recommended [45], albeit with a notable risk of rejection and the need for extended systemic

immunosuppressive therapy [32]. Consequently, MSCs have garnered attention as a potential treatment option with reduced or minimal immunogenic potential.

Intrastromal injection of MSCs derived from human bone marrow in a mouse model of corneal epithelial and limbal injury, improved wound healing, reduced neovascularization, and opacity [175]. In a mouse model of chemical injury to the cornea, investigators demonstrated that Pax6 induced bone marrow-derived MSCs can adhere to and regenerate damaged corneas by forming stratified corneal epithelium [66]. Another study demonstrated that EGFP labeled limbal MSCs, when seeded onto decellularized human amniotic membrane and transplanted into rabbits with LSCD, resulted in decreased limbal vascularization, neoangiogenesis, infiltration of inflammatory cells and increased epithelization, despite the low survival of labeled cells in the host

tissue [101]. In an alkali burn rabbit model, researchers demonstrated that subconjunctivally injected bone marrow-derived MSCs led to a significant reduction in the severity of LSCD, evidenced by smaller epithelial cell defects, less fluorescein staining, diminished corneal neovascularization, and a lowered goblet cell density in the cornea [110]. In a murine model of corneal injury, intra injection of induced pluripotent stem cell-derived MSCs or bone marrow-derived MSCs resulted in a significant decrease in corneal opacity and swelling, along with a notable reduction in inflammatory infiltration and a decrease in levels of pro-inflammatory cytokines, including TNF-α, interleukin-1β, and interleukin-6 [208]. Additionally, MSCs derived from human adipose tissue, when transplanted onto the ocular surface of rabbits with partial and total LSCD models, migrated to inflamed tissues and demonstrated safety and efficacy in reducing inflammation, corneal neovascularization, and opacity [65]. In an

alkali-injured rabbit model, bone marrow-derived MSCs and tissue-specific LSCs exhibited similar therapeutic effects, accelerating re-epithelialization, and decreasing neovascularization and local inflammation [81]. Reports indicate that when MSCs are combined with a polysaccharide scaffold, there is an observed multiplicative effect [80]. This is demonstrated by the increased expression of anti-inflammatory cytokines such as TGF-β, and antiangiogenic factors, such as TSP-1 [99]. Additionally, MSCs derived from adipose tissue have been linked to simultaneous decrease in pro-inflammatory cytokines such as TNF-α, chemotactic factors like MIP-1α and MCP-1, and pro-angiogenic factors including VEGF and MMP-2. These findings present promising prospects for a novel therapeutic application of MSCs [27,206]. In an in vivo mouse model of ocular injury, it has been demonstrated that MSCs possess the capability to restore corneal transparency by secreting elevated levels of HGF,

consequently inhibiting activation of myofibroblasts. Intriguingly, this study also revealed that HGF alone could restore corneal transparency, supporting the rationale for utilizing specific factors secreted by MSCs in the treatment of ocular diseases [129]. In humans, a sub-analysis of clinical trials involving patients suffering from LSCD demonstrated that MSCs transplantation induces similar structural changes in the limbal stem cell niche, including the presence of transition zones and palisades of Vogt, comparable to those observed with the cultivated limbal epithelial transplantation (CLET) technique. [143]. A randomized and double-masked study demonstrated that MSCs transplantation was as safe and effective as CLET for patients with total and/or severe LSCD [24].

III.A.4. Ocular graft-versus-host disease

Ocular graft-versus-host disease (oGVHD) represents a major complication associated with allogeneic hematopoietic stem cell transplantation (HSCT), contributing to the elevated risk of non-relapse-related morbidity and mortality following HSCT [170]. Graft-versus-host disease is characterized by a dysregulation of the immune response, particularly involving T cells from the donor that target the recipient's tissues [167,173].

Acute GVHD is an inflammatory condition with an incidence rate ranging from 30% to 50% [211]. It predominantly affects three target organs: the integumentary system, the gastrointestinal epithelium, and the liver and bile ducts, occasionally manifesting in the eyes and oral mucosa[167]. On the other hand, chronic GVHD, with an incidence ranging from 10% to 70%, is the most prevalent persistent complication in allo-HSCT patients[8]. It can impact various organ systems, including

the eyes, skin, oral mucosa, gastrointestinal tract, hepatobiliary system, lungs, genitalia, and joints [89]. oGVHD develops in more than half of patients post allo-HSCT and in the majority of patients with systemic GVHD [88,166]. oGVHD manifests with lacrimal glands, eyelids, and ocular surface involvement, causing inflammation and fibrosis. These alterations yield symptoms such as dry, painful eyes and signs of dry eye, and in severe cases, cicatricial conjunctivitis, potentially leading to significant visual impairment and decreased patient quality of life [152].

Both acute and chronic GVHD are immune-mediated diseases involving various immune cells, including antigen presenting cells, B cells, and T effector cells. T cells (CD4+ and CD8+) play a crucial role in the pathophysiology of GVHD, as both acute and chronic GVHD are driven by donor effector T-cell-mediated immune responses against host antigens, with

regulation by Tregs [15,34]. This T cell response is influenced by differences in host and donor antigen expression, including mismatched human and non-human leukocyte antigens polymorphisms [126].

The primary objective of treating oGVHD focuses is to safeguard the ocular surface, enhance the quantity and quality of the tear film, while also reducing inflammation through topical treatments. In cases where local interventions fail to sufficiently manage inflammation and alleviate symptoms, systemic immunosuppression becomes necessary [25,89]. In this setting of disrupted immune balance, MSCs known for their vast differentiation capabilities and immunosuppressive properties emerge as a promising new treatment option for oGVHD. In a mouse model of GVHD, subconjunctival injection of human MSCs prevented T lymphocyte infiltration, reduced tear

osmolarity and TNF-a expression and inhibited corneal keratinization [121]. Subconjunctival injection of GFP(+)-transduced human bone marrow derived MSCs into a GVHD mouse model showed that these cells migrated and differentiated into corneal tissue with morphological features resembling epithelial, stromal, and endothelial cells [155]. In a prospective clinical trial, topical administration of human umbilical cord MSCs exosomes in patients suffering from refractory oGVHD-associated DED resulted in reduced corneal fluorescein staining, prolonged tear-film breakup time, increased tear secretion, and decreased symptoms [214]. Moreover, intravenous administration of bone marrow-derived MSCs in patients with refractory corneal epitheliopathy secondary to oGVHD demonstrated that this treatment improved corneal fluorescein staining scores, symptoms scores, Schirmer test results, promoted

immunosuppressive Treg function and suppression of pro-inflammatory Th1 cytokines (interleukin-2 and interferon-γ) [203].

IV. LIMITATIONS AND FUTURE DIRECTIONS

While recently published and ongoing clinical trials are designed to elucidate the safety and efficacy of optimal MSCs route of administration to the ocular surface, there remains a critical need to deepen our understanding of the mechanisms underlying their interactions with the ocular environment[174]. Administering MSCs through subconjunctival routes exhibits greater therapeutic effectiveness in treating inflammatory corneal diseases compared to topical or systemic administration[167].

While our review primarily delves into the immunoregulatory functions of MSCs in immune-mediated ocular surface diseases, we recognize the broader implications of MSCs in wound healing and regenerative capacities, especially

pertinent in conditions like limbal stem cell LSCD, ocular surface injuries, DED, and oGVHD. These conditions often predispose patients to significant healing defects such as epithelial defects and ulcers[192], where MSCs have shown promise in promoting tissue repair and regeneration[7]. Therefore, while emphasizing their immunomodulatory roles, it is crucial to acknowledge MSCs' multifaceted potential in addressing the complex challenges of ocular surface diseases through their regenerative properties. Interestingly, ongoing clinical trials (NCT04626583, NCT05705024) are experimenting the application of MSCs in the setting of non-healing corneal diseases. This underscores the importance of optimizing local administration, as it holds the most promise for translational applications. By comprehensively studying how MSCs communicate with their surroundings, we can refine existing protocols and develop innovative strategies

that ensure long-term effectiveness in treating immune-mediated diseases.

We have synthesized current literature on the immunomodulatory properties of MSCs, particularly focusing on their paracrine secretion as a mechanism to modulate the immune environment in immune-mediated diseases. We underscore the profound immunosuppressive capacity of MSCs, which is predominantly mediated through their secretion of soluble factors, but also supported by direct cell-cell interactions. This paracrine activity includes the release of cytokines, growth factors, and extracellular vesicles that collectively dampen inflammatory responses and promote tissue repair. We believe that harnessing the immunomodulatory potential of MSCs holds significant promise for therapeutic interventions in various immune-mediated disorders. This perspective not only

consolidates existing knowledge but also emphasizes the critical role of MSC-derived paracrine signaling in shaping immune responses and mitigating pathological processes in immune-related conditions.

Future research endeavors should be directed towards a comprehensive investigation of paracrine signaling mechanisms to ensure the long-term viability and effectiveness of MSC-based therapies. This deeper insight will not only enhance the scalability and reproducibility of MSC-based therapies but also broaden their application across a spectrum of ocular conditions. Therefore, future research should prioritize investigating the intricate interplay between MSCs and the ocular microenvironment to unlock their full therapeutic potential and facilitate their integration into standard clinical practice.

V. CONCLUSION

We have explored the versatile capabilities of MSCs in treating ocular surface diseases, highlighting their significant role in promoting corneal healing through the regulation of immune responses, positively impacting the clinical outcomes of patients suffering from a range of ocular surface conditions. As the body of research in this area expands, the potential of MSCs in developing new therapeutic approaches in ophthalmology becomes increasingly promising.

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FIGURE CAPTION

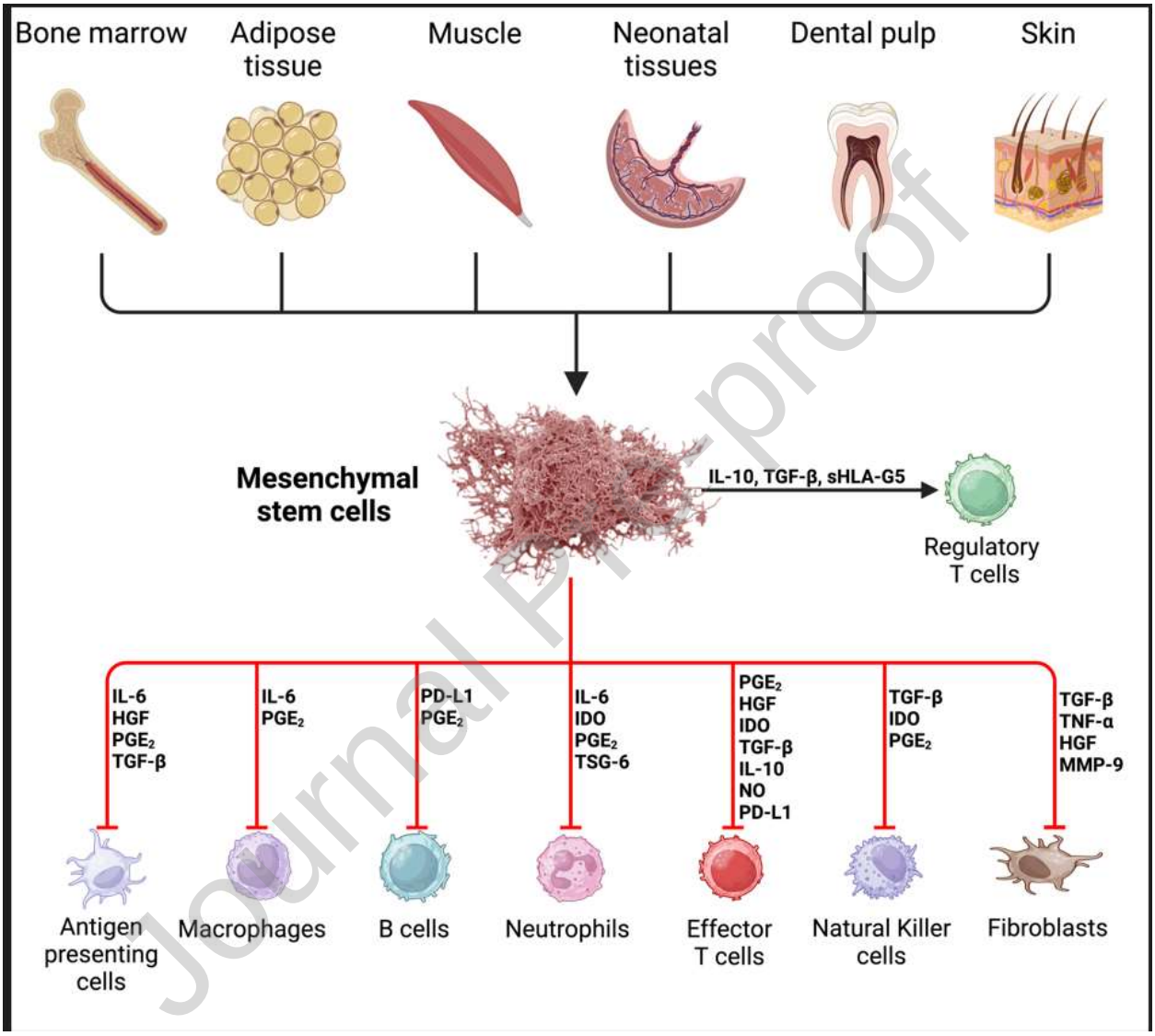

Figure 1: Sources, secreted factors, and immunomodulatory effects of Mesenchymal Stem Cells (MSCs) on various immune cell populations. Interleukin-6 (IL-6), Hepatocyte Growth Factor (HGF), Prostaglandin E2 (PGE2), Transforming Growth Factor Beta (TGF-β), Programmed Death Ligand 1 (PD-L1), Indoleamine 2,3-dioxygenase (IDO), Tumor Necrosis Factor-α-stimulated

Gene 6 (TSG-6), Interleukin-10 (IL-10), Tumor Necrosis Factor Alpha (TNF-α), Matrix Metalloproteinase-9 (MMP-9), and Soluble Human Leukocyte Antigen-G isoform 5 (sHLA-G5).

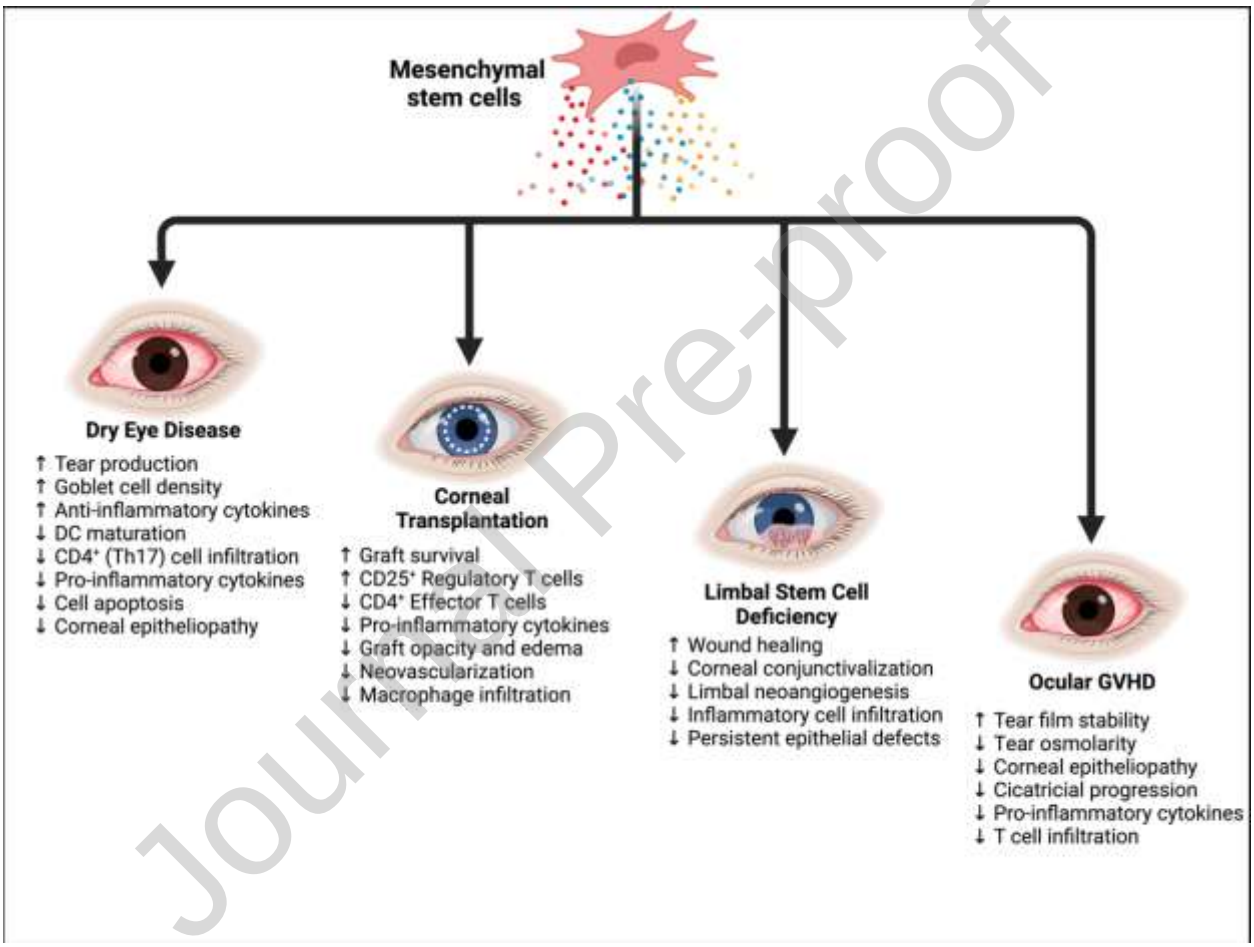

Figure 2: Immunomodulatory effects and outcomes of Mesenchymal Stem Cells (MSCs) application in immune-mediated ocular surface disorders. Dry eye disease manifests as chronic inflammation of the ocular surface, characterized by tear film instability and ocular discomfort. Corneal transplantation highlights the challenges of immune rejection despite advancements in surgical techniques, where MSCs offer potential as adjunctive therapy to enhance graft survival.

Limbal stem cell deficiency underscores the critical need for regenerative strategies to restore corneal epithelial integrity and vision. Ocular Graft-versus-Host Disease illustrates the systemic immune dysregulation affecting the ocular surface post allogeneic hematopoietic stem cell transplantation, where MSCs demonstrate immunomodulatory properties to mitigate inflammation and improve clinical outcomes. Dendritic Cells (DC), T helper 17 cells (Th17), Graft-versus-Host Disease (GVHD).

Table 1. Summary of studies on the application of mesenchymal stem cells (MSCs) in corneal and ocular surface immune-mediated diseases.

AUTHORS	YEAR OF PUBBLICATION	TYPE OF MSCs	TYPE OF STUDY	OUTCOMES
Wang et al. [199]	2023	hUC-MSC-EVs	Mouse model of desiccation-induced DED	hUCMSCs-EVs alleviate DED signs, suppress inflammation, and restore homeostasis of the corneal surface.
Na Li et al. [113]	2022	hUC-MSC-sEVs	Rabbit dry eye model	hUC-MSC-sEVs alleviated autoimmune dacryoadenitis by

				promoting M2 macrophage polarization and Treg generation.
Ke Rui et al. [151]	2022	Olfactory ecto-MSC-Exos	ESS mouse model	OE-MSC-Exos markedly attenuated disease progression and reduced Tfh cell response.
Wang et al. [198]	2021	ADSC-Exos	BAC-induced mouse dry eye model	ADSC-Exos alleviate ocular surface inflammation.
Abughanam et al. [2]	2019	BM-MSCsE	SS-like disease mouse model	MSCsE preserved the function of salivary and lacrimal glands, upregulated the expression of various beneficial genes, downregulated the expression of

				proinflammatory genes, promoted peripheral tolerance and inhibited B cell activity.
Guo et al. [73]	2022	hUC-MSC-EVs	Mouse dry eye model	MSC-EVs reduced severity of DED, downregulated the expression of inflammatory cytokines, the frequency of Th17 cells and inhibited the increase in the number and maturation of DCs.
Sun et al. [186]	2022	hUC-MSCs	ESS mouse model	hUC-MSCs ameliorate SS-like symptoms and pathological changes in the submandibular glands.

Lu et al. [119]	2020	hUC-MSCs	Rabbit model of SS dry eye	Systemic infusion of hUC-MSCs after disease onset efficiently diminished the chronic inflammation in diseased LGs and improved the clinical symptoms.
Dietrich et al. [47]	2019	eGFP-MSC	Aqueous-deficient dry eye mouse model	eGFP-MSC transplantation yielded significant improvements in LG regeneration, delaying macrophage infiltration and decreasing TNFα expression, coupled with an increase in IL-6 expression.

Aluri et al. [4]	2017	BM-MSCs	Mouse model of SS dry eye	Treatment with BD-MSCs increases tear production.
Lee et al. [109]	2015	human BD-MSCs	Murine model of an inflammation-mediated dry eye	Periorbital administration of BD-MSCs led to a reduction in CD4(+) T cell infiltration and decreased levels of inflammatory cytokines in the intraorbital gland and ocular surface.
Jia et al. [93]	2022	BM-MSC-exos	Corneal allograft rejection rat model	Subconjunctival injection of MSC-exos significantly prolonged graft survival time and inhibited the infiltration of CD4+ and CD25+ T cells.

Lu et al. [118]	2019	BM-MSCs	Rat model of corneal allograft rejection	Subconjunctival injection of MSCs was effective in prolonging corneal allograft survival.
Jia et al. [92]	2018	BM-MSCs	Rat model of corneal allograft rejection	Subconjunctival injections of BM-MSCs promoted corneal allograft survival, reduced CD4+ and CD68+ cell infiltration, and enriched Treg population in the allografts.
Lohan et al. [117]	2018	third-party allogeneic MSC	Pre-existing anti-donor immunity corneal transplantation rat model	Allo-MSC extended rejection-free graft survival and significantly increased proportions of CD4+ FoxP3+ regulatory T cells in the graft DLNs.

Lee et al. [80]	2014	human MSCs	Mouse allogeneic corneal transplantation model	IV human MSCs reduced the activation and migration of CCR7(+) APCs in the cornea and DLNs in allogeneic corneal transplantation.
Omoto et al. [141]	2014	BM-MSCs	Murine model of corneal transplantation	Systemically administered BM-MSCs specifically home to the inflamed ocular surface and promote allograft survival by inhibiting APC maturation and induction of alloreactive T cells.
O Treacy et al. [190]	2014	BM-MSCs	Allogeneic rat cornea	Allo- and third-party BM-MSCs treatment prolongs

			transplantation model	corneal allograft survival by suppressing peripheral immune responses and promoting an intragraft immunoregulatory milieu.
Oh et al. [139]	2012	Human MSCs	Mouse model of corneal allotransplantation	Human MSCs improve the survival of corneal allografts without engraftment and primarily by secreting TSG-6.
Soleimani et al. [176]	2023	Human BM-MSCs	Mouse corneal epithelial and limbal injury model	injection of hBM-MSC using both intrastromal and subconjunctival methods improve wound healing and reduce

				neovascularization and opacity.
Pérez et al. [144]	2023	BM-MSCs and limbal epithelial cells	Phase I–II clinical trial.	BM-MSCs transplantation improves the central corneal epithelial phenotype despite only minor changes in the anatomical structures of the limbus.
Gao et al. [67]	2023	Pax6-reprogrammed BM-MSCs	Mouse models of chemical corneal burn.	Pax6-reprogrammed BM-MSCs attached to and replenished the damaged cornea through the formation of stratified corneal epithelium.
Khorolskay et al.	2023	L-MSCs-EGFP	Rabbits with a modeled LSCD.	L-MSCs-EGFP transplantation led

[102]				to reduction of limbal vascularization, neoangiogenesis, epithelialization, and inflammatory infiltration.
Calonge et al. [25]	2019	Allogeneic BM-MSCs transplantation	Randomized, double-masked pilot trial in human.	BM-MSCs transplantation was as safe and effective as CLET.
Li et al. [111]	2018	BM-MSC	Alkali burns rabbit model.	BM-MSCs transplantation group experienced a significant reduction in the severity of LSCD.
Yun et al. [209]	2017	iPSC-MSCs and BM-MSCs	Murine model of corneal injury induced by chemicals and mechanical trauma.	mice treated with iPSC-MSCs or BM-MSCs demonstrated reduction in corneal opacity, inflammatory

				infiltration, pro-inflammatory cytokines
Galindo et al. [66]	2017	hAT-MSCs	Rabbits models of LSCD	hAT-MSCs reduced inflammation and restrained the progression of corneal neovascularization and opacity.
Mittal et al. [130]	2016	BM-MSCs	In vivo mouse model of ocular injury	MSCs have the capacity to restore corneal transparency by secreting high levels of hepatocyte growth factor (HGF).
Ke et al. [100]	2015	BM-MSCs	Alkali burns rat model	Polysaccharide and MSCs are safe and effective treatments for corneal alkali burns

				and that their benefits are additive when used in combination.
Holan et al. [82]	2015	BM-MSCs	Alkali-injured rabbit model	BM-MSCs' therapeutic effect on healing of injured corneal surface is comparable to that of tissue-specific LSCs.
Cejkova et al. [28]	2013	BM-MSCs	Alkali burns rabbit model	BM-MSCs growing on nanofiber scaffolds and transferred effectively suppressed corneal inflammation as well as neovascularization and significantly accelerated corneal healing.

Yao et al. [207]	2012	BM-MSCs	Alkali burns rat model	Subconjunctival injection of BM-MSCs significantly accelerates corneal wound healing, attenuates inflammation and reduces CNV in alkaline-burned corneas.
Zhou et al. [215]	2022	Human UC-MSC-exo	Prospective clinical trial in human	UC-MSC-exo application in GVHD-associated dry eye resulted in reduced fluorescein scores, prolonged tear-film breakup time, increased tear secretion, and lower OSDI scores.
Martínez-Carrasco et al. [122]	2019	Human MSCs	oGVHD mouse model	hMSCs subconjunctival injection is

				effective in reducing corneal inflammation and squamous metaplasia.
Sánchez-Abarca et al. [156]	2015	GFP(+)-transduced human BM-MSCs	oGVHD mouse model	BM-MSCs distribute across the whole mouse cornea after subconjunctival injection and acquire in vivo features characteristic of epithelium, stroma, and endothelium.
Weng et al. [204]	2012	Human BM-MSCs	Clinical trial in human	Intravenous BM-MSCs improved dry eye scores, ocular surface disease index scores, Schirmer test results and increased Tregs.

Adipose-Derived Mesenchymal Stem Cell-Derived Exosomes (ADSC-Exos), Antigen-Presenting Cell (APC), Benzalkonium Chloride (BAC), Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs), Cultivated Limbal Epithelial Transplantation (CLET), Dendritic Cells (DCs), Draining Lymph Nodes (DLNs), Dry Eye Disease (DED), EGFP-Expressing- Mesenchymal Stem Cells (eGFP-MSC), EGFP-Labeled Limbal Mesenchymal Stem Cells (L-MSCs-EGFP), Experimental Sjögrens Syndrome (ESS), Graft Versus Host Disease (GVHD), Human Adipose Tissue-Derived Mesenchymal Stem Cells (hAT-MSCs), Human Umbilical Cord-Derived Mscs (hUC-MSCs), Human Umbilical Cord-Derived MSC-Derived Extracellular Vesicles (hUC-MSC-sEVs), Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells (iPSC-MSCs), Intravenous (IV), Lacrimal Glands (LGs), Limbal Epithelial Stem Cells (LSCs), Limbal Stem Cell Deficiency (LSCD), Mesenchymal Stem Cell-Derived Exosomes (MSC-Exos), Mesenchymal Stromal Cells-Derived Extracellular Vesicles (MSC-EVs), Mesenchymal Stem Cells Extract

Conflicts of interest

The authors have no conflicts of interest to disclose.