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Mesenchymal Stem Cells as Therapeutic Tools in Ocular Surface Disorder and Lacrimal Gland Regeneration

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Abstract: ***Objectives: Due to the direct exposure to the external environment, ocular surface has the most frequent injury sequences and disease manifestation. The ocular surface has a very significant role in vision. Inflammation is the hallmark, and several cues are yet to be understood to define their etiological significance in the disease progression. However, if this inflammation occurs for a more extended time, it can cause mild to severe levels of dry eye condition, i.e. dry eye disease. DE is a multifactorial disease that occurs due to the deficiency of the aqueous layer of the tear film. The primary purpose of this study is to gain knowledge about the therapeutic role of mesenchymal stem cells and effective cell-based therapy for the regeneration of the lacrimal gland. The different therapeutic techniques of MSCs in different animal/human models and their effects are also discussed in this article. Background: Researchers have been focusing their attention on MSC in recent years because of its unique properties and promising results. MSCs are the residential stem cells in the different parts of the ocular surface. Therefore, any disorder or perturbation in the ocular surface constituents can cause ocular surface disorder (OSD). OSD severely affects eyesight by damaging the epithelial layer of the eye, namely the cornea and conjunctiva. OSD includes Dry eye syndrome (DES), blepharitis, meibomian gland dysfunction (MGD), allergic eye disease (AED).***

Keywords: MSC therapy; Lacrimal Gland; MSC regenerative medicine; MSC ocular surface; Dry Eye; Mesenchymal Stem Cell; Dry Eye Syndrome; MSC in Dry Eye Syndrome

1. Introduction

The ocular surface is the outermost part of the human eye that directly contacts the external environment. The ocular surface includes the outer layer of the cornea, the conjunctiva, the tears, and the margin of the eyelids. Due to the direct exposure to the external environment, this part of the eye has the most frequent injury sequences and ocular disease manifestation. The ocular surface has a very significant role in vision. Inflammation is the hallmark, and several cues are yet to be understood to define their etiological significance in the disease progression. It can cause mild to severe levels of ocular surface inflammatory disorders (OSIDs) or ocular surface disorders (OSDs).

The visual acuity of the ocular surface is maintained by a fragile layer of the tear film. It ensures ocular surface health by acting as a protective barrier from external environmental exposures, keeping the surface moistened, and maintaining ocular epithelial surface homeostasis. The LFU made up of the lacrimal gland, the eye surface (cornea, conjunctiva and meibomian gland), and related sensor and motor neurons, create tear films. (Venable et al., 1940; Kanski et al., 2008; Lang et al., 2014) The LFU are responsible for tear film maintenance, corneal transparency, and image quality projected onto the retina because it is the central regulator of the secretion of the major components of the tear film.

The infiltration caused by the immune cells inhibits the normal function of residential cells/tissue, which leads to the deterioration of the ocular surface. Furthermore, it triggers the immune system, i.e. the lymphocytes, to reach the injury site. β-cells are majorly responsible for the secretion of these lymphocytes/antigens. The persistence of lymphocytes for the more extended period replace the residential cells and change the microenvironment, resulting in loss of regenerative capacity.

Stem cells are the unspecialized cells of the human body that undergo cell differentiation to become a specialized cell type. Due to their self-renewability and multipotency, having the ability to differentiate into many specialized cell types, depending upon the growth factors present, research societies and members have a keen interest. By combining four proteins known as transcription factors, scientists can convert the adult stem cells to induced pluripotent stem cells, which can be differentiated into all cell types. These capabilities of SCs adds new insight into treating chronic disease/ tissue damage/injuries. The pluripotent stem cells are the embryonic stem cells that are the byproduct of in-vitro fertilization.

Mesenchymal stem cells are well-known anti-inflammatory, immunomodulatory and immunosuppressants. Mesenchymal stem/stromal cells (MSC) are the stromal progenitor/multipotent stem cells present in everybody tissue and can differentiate into several cell types. MSC possesses self-renewal, multipotency, immunomodulatory, anti-inflammatory, immunosuppressive, anti-angiogenesis with trophic, homing and paracrine function. (zhou xuntian et al

2020; abderrahim naji et al 2018;). They are suggested to be patient-specific drugs (Matthew B Murphy et al., 2013) for the regeneration and restoration of the injured tissue. MSCs regulate in a site-specific manner and secretes different kinds of secretomes, bioactive factors and signals appropriate to the local microenvironment of the injured tissue. (Vivek singh et al., 2015)

Remarkable efforts are reported towards clinical analysis for the MSCs based therapies in different clinical trials to test the therapeutic effect/advantages of MSC in severe medical conditions. They are using MSC transplantation with or without combining them with other drugs. MSCs are used as the clinical translation of their therapies so far in the treatment of (1) orthopaedics and spine therapies; (2) cardiovascular therapies; (3) wound care and soft tissue repair; (4) neural disorder and spinal cord injury; (5) autoimmune diseases; (Matthew b murphy, 2013) (6) ocular surface disorders; (Padma Priya Sivan et al., 2016) (6) degenerative diseases of the skeletal system; (7) inflammatory diseases of lungs; (8) immune rejection in allogeneic transplantation. (abderrahim naji et al, 2019)

Mesenchymal Stem Cells in Regenerative Medicines

Identification & characterization

According to the criteria suggested by The International Society for Cellular Therapy, MSCs are the plastic adherent cells with cell surface expressions of a cluster of differentiation (CD)73+, CD90+, cd105+, and no expression of CD34, CD45, CD14, CD11b and HLA-DR. (Hasan Mansoor et al., 2019) HLA class I and HLA class II molecules have low to medium expression levels in undifferentiated mesenchymal stem cells; this is to hide/avoid the recognition by immune cells. HLA class I molecules are present in MSCs in detectable levels, and similarly, expression of HLA class II molecules can be induced by the interferon γ (INF-γ). This ability of HLA molecules to hide their expression from the immune system is called stealth ability. (Matthew B Murphy et al., 2013) This is one of the main reasons and advantages of MSC in allogeneic MSC transplantation therapy to be undetectable by the host immune system.

Different surface antigens are present on the surface of MSCs. The identification and characterization of MSCs are by immunophenotype analysis. (Sahar M.M. et al;. 2017; . It is one of the basic tests for MSCs. Fluorescence-activated cell sorting has been done to evaluate the purity of the population of isolated MSCs in culture. (Zhang H,et al; 2012.) One should examine the minimum cell surface markers for MSC confirmation after isolation. The most generally used cell surface markers for MSCs are CD105+, CD90+, and CD73+. CD13+, CD44+, CD106+, CD29+, and CD166+ are additional cell surface markers that confirm MSCs. (Dominici M, et al;. 2006;.) There is a long list of markers that should not be found when examining MSC markers, i.e. negative expression; cell surface markers include CD34-, 45-, CD14-, CD11b-, CD79-, HLA-DR, CD38-, and CD31-.(Lu LL, et al; 2006.)

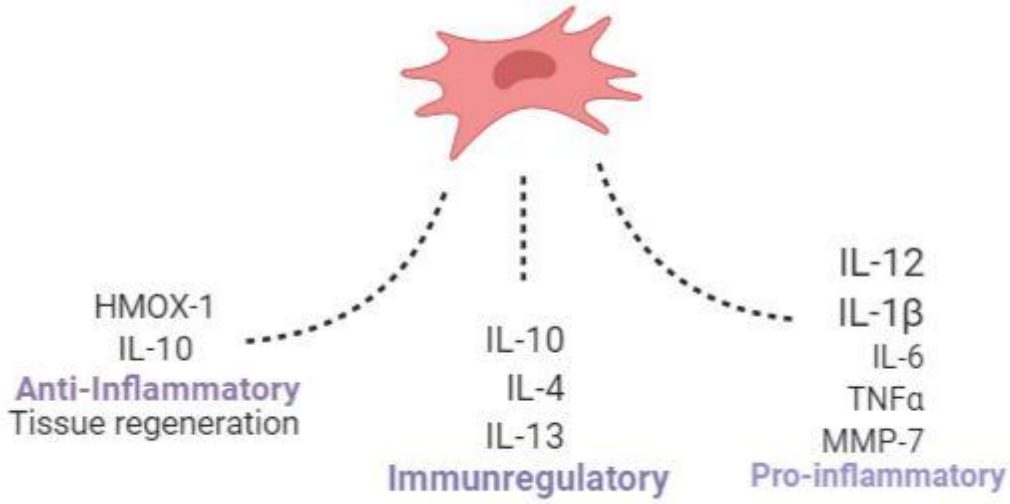
The minimum criteria for identifying and characterizing isolated MSCs: (1) The cells should be plastic adherent. They should adhere to the surface of the culture plate; (2) the cells should express CD105+, CD90+, and CD73+; (3) the cells should have less/lack expression of CD34-, CD45-, CD14-, CD11B- and HLA - DR; (4) can differentiate into osteoblasts, adipocytes and chondrocytes in vitro. (Feng Jung Lv et al, 2014)

Properties

MSCs can promote regeneration and have site-specific action modes, which gives them more power.

MSCs play a very vital therapeutic role in corneal reconstruction and restoration of corneal functions through their unique properties, i.e. immunomodulatory, anti-angiogenic and anti-inflammatory. (Hassan Mansoor et al, 2019) MSCs are used as therapeutic agents due to their immunomodulatory and angiogenesis properties in cell-based therapy of ocular surface diseases. (Harrell CR, et al, 2018;) MSCs can be found in most of the body tissue/organs. They help repair the damaged tissue of the ocular surface (Samaeekia R et al, 2018 Oct 1 ;) and demonstrate powerful cell differentiation capabilities. (Zhang L et al, 2015 Dec 17;)

MSC secretome has been identified as an essential signalling mechanism to affect other cells. MSC-derived EVs and their interaction with target cells are crucial to a complete understanding of MSC-derived EV functionality. (Dolly Mushahary et al, 2018) These secretomes help in the process of tissue wound repair, inflammation, angiogenesis and immune responses (Jasmin S. Nurkovic et al, 2020) during the transplantation of allogeneic MSCs to host ocular surfaces. The MSCs derived exosomes are encapsulated and transfer biomolecules that affect cell and tissue metabolism and involve differentiation, inflammation, angiogenesis, and immunosuppression. (Jasmin S. Nurkovic et al, 2020)



MSCs can be isolated from any source, and every one of them has several different properties. Due to the lack of expression of MHC II proteins, costimulatory molecule B7, and CD40 ligand, MSCs are immune-privileged. The ocular microenvironment, on the other hand, claims to be immune-privileged. MSCs from different tissues have different properties. Succession in clinics by using MSCs. It is crucial to study and examine the multiple sources of MSCs and evolve the most effective and patient-friendly treatment for ocular surface disorders. (Lydia J. Beekan et al, 2020)

Table 1: Therapeutic role of MSCs in various disorders

Treatment	Disease	Title	Number of subjects	Estimated date of completion	Clinicaltrials.gov identifier
Drug: Stem cell IV infusion of stem cells Drug: Plasmalyte A IV infusion	Myocardial Infarction	Ex Vivo Cultured Bone Marrow-Derived Allogeneic MSCs in AMI	20	Aug-12	NCT00883727
Biological: Allogeneic Mesenchymal Stem Cells Single intramuscular administration of the low dose of stem cells Other Name: Stempeucel - CLI Biological: Allogeneic Mesenchymal Stem Cells Single intramuscular administration of an intermediate dose of stem cells Other Name: Stempeucel - CLI	Critical Limb Ischemia Buerger's Disease	A Clinical Trial to Study the Efficacy and Safety of Different Doses of Bone Marrow-Derived Mesenchymal Stem Cells in Patients With Critical Limb Ischemia Due to Buerger's Disease	126	Mar-16	NCT01484574
Biological: Stempeucel(R) Ex vivo cultured adult bone marrow-derived allogeneic mesenchymal stem cells	Critical Limb Ischemia Due to Buerger's Disease	A Clinical Trial to Study the Efficacy and Safety of Stempeucel® in Patients With CLI Due to Buerger's Disease	164	Oct-19	NCT03056742
Biological: Mesenchymal stem cell suspension About 8-10ml of bone marrow would be aspirated under strict aseptic precautions, cell fractionationated with Ficoll sol, centrifuged at 1100rpm for 20-30 mins. The Buffy layer will be centrifuged again at 1100 rpm for another 20-30 mins. The pellet thus formed will be suspended in 5ml of culture medium. The nucleated stem cells thus isolated will be incubated at 37deg.C under 5%CO2 in culture flasks for about 4-6weeks. Those cells adherent to flask removed with 0.05% trypsin-EDTA sol and characterized. The mesenchymal stem cells will be positive for CD90 and CD105 and negative for CD45 and CD34. These will then be expanded to 10×106 for use. Other Name: MSC Biological: PRP Twelve patients will be placed supine with a knee in full extension. Under complete aseptic precautions, 8-10 ml of platelet-rich plasma would be injected by lateral approach with an 18-20 G	Osteoarthritis, Knee	Mesenchymal Stem Cells Enhanced With PRP Versus PRP In OA Knee	24	Jun-14	NCT01985633

needle. Other Name: Platelet gel					
Biological: Ex- vivo cultured adult allogeneic MSCs Single intraarticular dose of allogeneic MSCs suspended in 2ml Plasmalyte followed by 2ml of Hyaluronan Biological: Plasmalyte-A Single intraarticular dose of 2ml Plasmalyte followed by 2ml Hyaluronan	Osteoarthritis of Knee	Allogeneic Mesenchymal Stem Cells in Osteoarthritis	60	Nov-14	NCT01453738
Biological: BOOST cells Four doses of expanded human first-trimester fetal liver-derived mesenchymal stem cells.	Osteogenesis Imperfecta	Boost to Brittle Bones - Stem Cell Transplantation for Treatment of Brittle Bones	15	Dec-21	NCT04623606
Biological: autologous adipose tissue-derived stromal vascular fraction (SVF) the liquid and a solid portion of lipo-aspirate after non-enzymatic processing yields SVF. This isolation process yielded an abundant population of Adipose stromal cells(ASCs), which have multipotent differentiation potential. Immunophenotype is a CD14-, CD29+, CD31-, CD34low/+, CD45-, CD73+ and CD105+ , The SVF represents the 50-70% volume of a lipoaspirate specimen. The SVF hosts a heterogeneous cell population (110x103 cells/ml on average) comprising mainly CD105+ mesenchymal stem cells (MSC, 20%), plus a vast number of CD34+ hematopoietic cells (40%).	Nonunion of Fracture	Adipose Tissue-Derived Stromal Vascular Fraction (SVF) Application in Treatment of Long Bones Nonunion	11	14-Feb-20	NCT04340284
Biological: BQ-A Peptide Extract BQ-A Peptide Extract Biological: Mesenchymal Stem Cells Mesenchymal Stem Cells Device: Transcranial Laser Therapy Transcranial Laser Therapy Device: Median Nerve Stimulator Median Nerve Stimulator	Brain Death	Non-randomized, Open-labeled, Interventional, Single Group, Proof of Concept Study With Multi-modality Approach in Cases of Brain Death Due to Traumatic Brain Injury Having Diffuse Axonal Injury	20	Aug-20	NCT02742857
Biological: Stem cells The mixture of limbus derived corneal epithelial cells, and limbus derived corneal stromal cells in a ratio of 2:1, at a concentration of 50000 cells/uL diluted in fibrin sealant Other: Vehicle 50uL of commercially available fibrin sealant (Baxter, TISEEL)	Corneal Scars and Opacities	Limbus-derived Stem Cells for Prevention of Postoperative Corneal Haze	15	Jun-20	NCT03295292

Mesenchymal Stem Cell in Ocular Surface Disorders

Anatomy, Physiology and Pathological features for Ocular Surface Disorders

The ocular surface is the outpouching part on both sides of the forebrain that directly contact the external environment. It is the outermost layer of the eye, including the tear film. It is constructed and protected by structural and functional modules with highly regulated cross-talk talks. These components include the tear film, cornea, conjunctiva, lacrimal glands, meibomian gland, eyelids and nerves. (Ghasem Yazdanpanah et al, 2019)

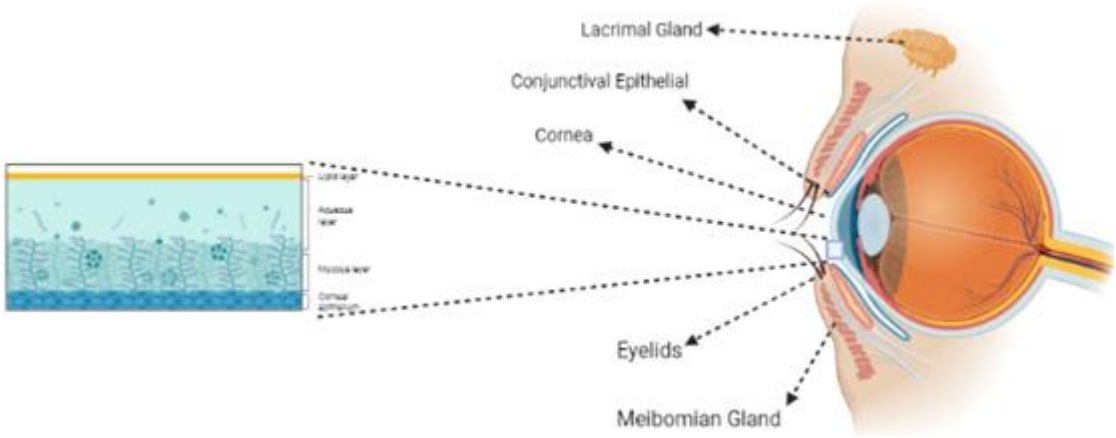


Figure 1: The Ocular Surface

Any damage to the ocular surface represents one of the most common causes of impaired vision or even blindness. Cell therapy is an optional treatment based on the transplantation of stem cells. (Vladimir Holan et al, 2015)

The tear film is the thin fluidic secretion of the associated glands, which comes in direct contact and protects the ocular surface from the external environment, maintains the wet ocular surface, protects the ocular surface epithelium from exposure and physical damage, and maintains epithelial homeostasis. (Tetsuya kawakita, 2018)

The tear film consists of three layers secreted by different glands: (1) The outermost oily layer of tear film acts as a sealant to keep tears from evaporating. It is secreted by the meibomian gland and a small portion of the glands of Zeis. Meibomian secretion occurs 24 hours a day and is aided by blinking. (2) The middle aqueous layer of the tear film is the secretion of the lacrimal gland and accessory tear glands of Krause and Wolfring, (3) The innermost mucin layer is produced by the stratified squamous epithelium of the cornea and conjunctiva. (Vivek Singh et al, 2015, Pflugfelder SC, et al; 2020 Aug; Rouen, et al; March/April 2018)

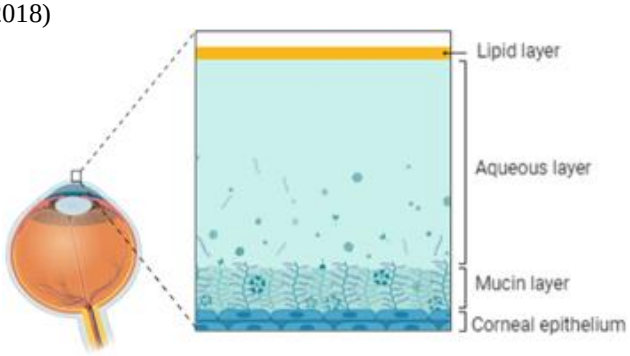


Figure 2: Tear film and its constituents

Perturbation in the stability of tear film results in the damage of the integrity of the ocular surface, which, over a while, leads to Dry Eye Syndrome (DES). There are multiple factors involved which caused DES. Any changes/alterations in the composition of these three layers of tear film can be due to the dysfunction of associated glands.

The TFOS DEWS II global society defines dry eyes as follows:
"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."

Dry eyes can be caused due to the deficiency of the aqueous layer of the tear film. In addition, it may be due to the dysfunction and/or destruction of tear-producing acinar cells of the lacrimal gland.

This lacrimal dysfunction causes hyperosmolarity of the tear film, resulting in a vicious loop of ocular surface inflammation responsible for ocular epithelial damage, leading to corneal ulceration and an eventual decline in visual acuity. (Subha Tiwari et al, 2014)

The current therapy for dry eyes is supportive and palliative. However, patients need to be dependent on them for life and need frequent lubricating or hydrating eye drops. These therapies have their related side effects as well. To overcome the long-term dependence and fear of transplant rejection, one must shift the focus to treatment therapy, which yields promising results, has a low risk of graft rejection, and promotes self-healing and/or regeneration of diseased cells.

Table 1: MSCs as a therapeutic agent and its different sources

Study	Source of MSCs	Disease	Outcome	Reference
Mesenchymal stem cell transplantation alleviates experimental Sjögren's syndrome through the IFN-β/IL-27 signalling axis	MSCs transplatation via tail vein	SS	decreased IL-27 level and increased ratio of Th17/Treg cells	Yao G et al, 2019 Oct 21;
Allogeneic Mesenchymal Stem Cells Transplantation for Primary Sjögren's Syndrome (PSS)	Allogenic MSC (BM-MSCs & UC-MSCs)	SS	treatment with mesenchymal stem cells (MSCs) suppressed autoimmunity and restored salivary gland secretory function in mouse models and SS patients.	Xu J et al, 2012 Oct 11;
Human umbilical cord mesenchymal stem cells alleviate ongoing autoimmune dacryoadenitis in rabbits via polarizing macrophages into an anti-inflammatory phenotype	hUM-MSCs injected via IV	Autoimmune Dacryoadenitis	MSCs attenuated clinical symptoms at all the time points observed via polarizing macrophages into an anti-inflammatory phenotype	Lu X et al, 2020 Feb;
Reduction in the inflammatory markers CD4, IL-1, IL-6 and TNFα in dogs with keratoconjunctivitis sicca treated topically with mesenchymal stem cells	Allogeneic MSCs derived from canine adipose tissue via drop into the eye	Keratoconjunctivitis sicca	MSC treatment promotes a significant decrease in the expression levels of these inflammatory markers CD4, IL-6, IL-1 & TNF-alpha	Sgrignoli et al, 2019
Mesenchymal stem cell transplantation ameliorates Sjögren's syndrome via suppressing IL-12 production by dendritic cells	Fresh umbilical cords of newborn babies and synovial tissues from human knee joints obtained	SS	MSCs ameliorate SS possibly via suppressing IL-12 production in DCs	Shi et al, Nov 8 2018,
Delivery of Bone Marrow-Derived Mesenchymal Stem Cells Improves Tear Production in a Mouse Model of Sjögren's Syndrome	BD-MSCs isolated from C57BL/6-Tg (UBC-GFP) mice were injected intraperitoneally into NOD mice.	SS	BD-MSCs increase tear production in the NOD mouse model of Sjögren's syndrome.	Aluri et al,2017
Mesenchymal stromal cells improve salivary function and reduce lymphocytic infiltrates in mice with Sjögren's-like disease.	BM-MSCs from transgenic GFP mice	SS	MSC-therapy alone reduced inflammation (TNF-α, TGF-β), but the combination of MSC+CFA (complete Freund's adjuvant) reduced inflammation and increased the regenerative potential of SGs (FGF-2, EGF).	Khalili et al, 2012

MSCs as therapeutics in Alkali-injury

Vladimir Holan et al, used an alkali injured rabbit model and treated it with MSCs and/or Limbal Stem Cells (LSCs). The results show that the corneal re-epithelialization occurred after transferring stem cell-seeded nanofiber scaffolds onto the ocular surface. Their group worked on different kinds of stem cells and compared the therapeutic effects of MSCs and tissue-specific LSCs. BM-MSCs have therapeutic effects comparable to tissue-specific LSCs.(Vladimir Holan et al, 2015)

Alejandro Vargas et al, used an alkali burned rabbit model and treated the rabbit with human amniotic membrane-derived mesenchymal stem cells (hAM-MSCs). MSCs have anti-inflammatory and anti-fibrotic effects on animal models that promote corneal chemical burn wound healing after injecting hAM-MSCs intracamerally into the eyes.(Alejado Valenzuela and colleagues, 2018)

MSCs as therapeutic in corneal wound

Golnar Shojaati and colleagues used a female rat and induced a corneal scar with an intraperitoneal injection of ketamine and xylazine. The result shows that the rat treated with extracellular vesicles (EV) of MSCs lacking miRNA develops visible scarring and expresses genes associated with fibrosis and lymphocytic infiltration. Suggests that miRNA has a role in anti-inflammation and regenerative function derived from corneal stromal stem cell (CSSC) EVs. (Golnar Shojjati et al, 2019)

MSCs as a major regulator in Ocular Surface Inflammatory Disorders (OSID):

In-vivo & in-vitro studies

Ravand Samaeekia et al isolated the corneal MSCs (cMSCs) from the human cadaver cornea. They isolate the exosomes from the cMSCs after 72 hours. They investigated the exosome by looking at the expression of CD9, CD63, and CD81. The results show that the corneal mesenchymal stem cells derived exosomes (cMSCs-exosomes) can accelerate corneal epithelial wound healing, proving that the cMSCs-exosomes have a therapeutic effect on ocular surface injuries. The healing effect of cMSCs-exosomes on debridement wounds in mice was observed.(Ravand Samaeekia et al, 2018)

Exosomes derived from mesenchymal stem cells play an essential role in The new research on therapeutic and successful outcomes.MSCs and exosomes both play roles in cancer and tumour growth. They act as drug delivery vehicles, reduce drug resistance, and regulate the immune response. (Zhou Xunian et al, 2020)

Recently clinical trials of MSCs as therapy are currently underway. Clinical studies are registered in the US National

Institute of Health (NIH) database. These trials undertook in very developed and developing countries. Many are still in the early stages, and some are in two or even more advanced stages.

Min Joung Lee and colleagues studied MSCs and discovered that MSCs could repair injured tissue by modulating an overactive immune response in various diseases. The team used a murine model of an inflammation-mediated eye induced through intraorbital injection. The infiltration caused by lymphocytes, especially CD4+, T cells and other inflammatory cytokines, has been reduced after the administration of MSCs to the ocular surface. In addition, after the administration of MSCs, the torn aqueous layer content increased significantly. It demonstrates that MSCs can treat dry eye disease (DED) and reduce inflammation. (Min Joung Lee et al, 2015)

Maura K. W. Bittencourn et al, He and his team investigated the effect of allogeneic MSCs on a dog model of Keratoconjunctivitis Sicca (KCS). Took dogs with mild-moderate and severe KCS and directly transplanted the MSCs into the lacrimal gland. The findings show that a single dose of a small number of MSCs can also be used in KCS dogs. Furthermore, the results were validated after a significant increase in the Schirmer tear test and a significant improvement in the ocular surface.(Maura K. W. Bittencourt et al, 2016)

Different research groups in elegant reviews amazingly summarised the applications of MSCs in ocular surface disorders. Several studies show that MSCs can transdifferentiate into different ocular cell types, such as corneal cell types (corneal epithelial cells, corneal endothelial cells and corneal keratocytes). (Liyun Zhang et al, 2015) MSCs can also help with allergic conjunctivitis, KCS, Lysosomal storage disorder, Ocular GVHD (Anuradha Sahu et al, 2019), and degenerative eye diseases like retinal cell degeneration. (Ben Mead et al, 2014)

Lacrimal Gland Regeneration

Basic Anatomy & Physiology of Lacrimal Gland

The lacrimal gland is situated superotemporally in orbit within the lacrimal fossa of the frontal bone. Grossly, the gland is a pinkish-grey structure composed of small lobules intermixed with connective tissue septations and lacks a valid capsule. (Christopher D. Conrady et al, 2016) the lacrimal gland secretes plenty of proteins like lactoferrin, lipocalin and scglA, which are regulated through the neural system (nerves and their associated neurotransmitter or neuropeptides). Also, a few receptors are present on the lacrimal gland, such as acetylcholine receptors and norepinephrine receptors (Subha Tiwari et al, 2014) and a complex aqueous milieu rich in antibodies, cytotoxic agents, and growth factors on the ocular surface. (Christopher D. Conrady et al, 2016) The secretion of the aqueous tear by acinar cells is critical and necessary for maintaining ocular health and ocular surface stem cells within their niche. Thus, a healthy lacrimal gland helps to protect/prevent the stem cell deficiency of corneal and conjunctival epithelial stem cells. (Tetsuya kawakita, 2018)

The main content of the aqueous tear secreted from the lacrimal gland through acinar cells. More than >80% of the acinar cells produce aqueous tears. The lacrimal gland is the essential component of the lacrimal functional unit (LFU). The LFU constitutes the lacrimal gland ocular surface (cornea, conjunctiva, meibomian gland and other associated glands). (Messmer EM (2015); Subha Tiwari et al, 2014; Yupeng Yao et al, 2017). If any part of the LFU is damaged, it affects ocular health and causes Dry Eye Disease. The most common cause of DED is lacrimal gland dysfunction/destruction. (Yupeng Yao et al, 2017)

The secretion of the lacrimal gland and associated glands forms a fine transparent film over the ocular surface, i.e. a tear film. The tear film improves the optical properties by generating a smooth surface on the corneal epithelium, moistening and nourishing the epithelial cells of the conjunctiva and cornea, removing dust and debris and protecting against pathogens. (Willcox MD, et al; 2017; Jana Dietrich et al, 2019) The main

Dysfunction/Destruction of Lacrimal Gland

Dysfunction and/or destruction of the lacrimal gland can be caused due to inflammation triggered by autoimmune diseases (Ankur Garg et al, 2017), degeneration of lacrimal cell/tissue, and dry eye condition, a multifactorial disease.

Renewing the damaged lacrimal gland or replacing bioengineered implants can potentially provide long-lasting and physiological cures for dry eye disease. (Ankur Garg et al, 2017) Studies in other exocrine tissues such as the salivary gland have demonstrated the transformative potential of regenerative therapies in previously recalcitrant diseases. (Aakalu,et al; (2017).)) A current three-dimensional (3D) tissue engineering technique has been shown to regenerate a secretory gland structure by reproducing reciprocal epithelial-mesenchymal interactions during ontogenesis in vitro and in vivo. A novel direct reprogramming method has suggested a possibility to induce markers in the lacrimal gland developmental process from human pluripotent stem cells. (Hirayama M. et al; 2018 Nov 1;.)iPSC based therapies are often driven by an understanding of the critical factors involved in the development of specialized cells and tissue types. Differentiation along pathways that mimic the normal development of these tissues is undertaken using various methods, including exogenous factors. (Aakalu, et al;(2017).)

Current Treatment Strategies

The current treatment strategies include artificial tears, nonsteroidal or corticosteroid anti-inflammatory agents, immunosuppressive drugs and punctal occlusion. (Xiaoxiao Lu et al, 2017; Beyazyildiz E, et al; 2014)

After the recommendation from the committee on the therapy and management of dry eye, researchers are shifting the focus towards strategies that will increase the production of aqueous tears naturally, maintain the integrity of the ocular surface and minimize or eliminate the existing inflammation. (Subha Tiwari et al, 2014; International Dry Eye Workshop (2007). Stem cells have all these unique

properties to overcome these issues and give a positive output.

Samantha, You and her colleagues isolated the MSCs from the murine lacrimal gland. They have injected IL - 1 to induce inflammation so the lacrimal gland can be injured. They examine the isolated MSCs by expressing nestin-positive cells, ABCG2 and Sca-1. They state that murine lacrimal glands have MSCs that seem to play a pivotal role in tissue wound injury. (Samantha You et al, 2011)

Driss Zoukhri and his team reviewed murine models to study the role of MSCs in lacrimal gland injury and its repair. (Driss Zoukhri, 2010) To investigate the presence of resident progenitor cells and their regenerative potential, Hui Lin et al, induced duct ligation injury in a rabbit model of the lacrimal gland's central excretory duct. The ligation-injured lacrimal glands temporarily decreased in weight and had impaired tear secretion. The aftermath of the injury in this study indicates that lacrimal glands can tissue repair after duct ligation-induced injury, likely involving resident stem/progenitor cells and epithelial-mesenchymal transitions. Lacrimal gland progenitor cells isolated from ligated tissue can differentiate in 3-D culture. These stem cells have the potential to treat severe cases of tear deficiency. Hui Lin et al. (2017)

MScs are site-specific and migrate to the site of injury and damaged tissue. This ability of mesenchymal stem cells is called homing/migration. (Xiaoxiao Lu et al, 2017) the migration of MSCs induced due to the chemokine activation at the injury site. (Chavakis E, et al; 2008;) The axis of stromal cell-derived factor 1α (SDF-1α) and its receptor CXCR4 is an essential biological axis that promotes MSC homing to damaged tissue. (Wang G, et al; 2016;)

Jana Dietrich et al, studied the mouse model of surgically induced dry eye disease through duct ligation. MSC transplantation significantly improved LG regeneration, as the amount of vital acinar structures were significantly increased above the intrinsic regeneration capacity of control.

Additionally, MSC transplantation modulated the immune reaction as macrophage infiltration was delayed and TNFα expression decreased, accompanied by an increased IL-6 expression. (Jana Dietrich et al, 2019)

After treatment, human umbilical cord-derived mesenchymal stem cells (hUC-MSC) promote corneal epithelial growth and function. hUC-MSC downregulated HLA Class I and II expression in IFN-γ-stimulated human telomerase-immortalized corneal epithelial cells. (Siti Mausura Azmi et al, 2020)

2. Conclusion

The tear film is critical to the health of the ocular surface. It is transparent and protects the ocular surface from direct exposure to the external environment. It maintains the standard visual acuity of the ocular surface. In a normal human healthy eye, the ocular surface and associated glands are in charge of tear production, secretion, and regulation. Any perturbation in any of the tear layers may lead to mild to severe dry eye conditions, which causes lymphocyte infiltration at the site of injury. That results in dysfunction and/or destruction of the crucial lacrimal gland and other accessory glands. The 90% content of the tear film is filled by the secretion of acinar cells of the lacrimal gland. Thus, any disturbance to the integrity of the tear film directly leads to an effect on the lacrimal gland. The lacrimal gland secretes aqueous lacrimal fluid and secretes several proteins that nourish the ocular surface and maintain homeostasis.

The infiltration damages the acinar cells and results in less/lack of secretion of aqueous tears. The lacrimal gland has stem cell progenitors and resident stem cells, which turn into the action of regenerating these affected acinar cells to stabilize the equilibrium condition, i.e. the homeostasis condition. The mesenchymal stem cells are site-specific and come into action whenever there is any injury/tissue damage within the human body. When MSCs arrive at the site of action, they release a slew of secrets that aid in reducing inflammation and the regeneration of damaged tissue. In addition, MSCs have trophic and paracrine action, making them more focused and determined on healing the injured tissue.

MSCs' distinct properties distinguish them from other stem cells, making them a more relevant and promising approach to treatment. Clinical trials are also in various stages, with positive results in patients treated with MSCs or derivatives of MSCs at the time of follow-ups.

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