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Limbal mesenchymal stem cell secretome as potential adjuvant therapy for ocular alkali injury

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Abstract

Chemical injury is one of the main causes of vision loss. Chemical injury is caused by contact with alkaline or acidic substances. Ocular alkali injury which often caused by sodium hydroxide (NaOH) can cause severe corneal damage and blindness. Because of its anti-inflammatory, antiangiogenesis, and immunomodulatory properties, Limbal Mesenchymal Stem Cell Secretome (LMSCS) therapy is currently being developed and researched as a potential treatment for corneal wound healing. Through inflammatory cytokines and growth factors, it can induce and regulate immune responses and tissue repair. It has been reported that limbal niche cells isolated from the limbal stroma produce progenitor cells that may play a role in corneal wound healing. LMSCS are universal so that they can be produced pharmaceutically and can be a promising therapeutic strategy for regenerative medicine. Several studies have shown that MSC not only reduces inflammation and inhibits neovascularization but also reduces corneal opacity in ocular chemical injury

Keywords: Chemical injury, ocular alkali injury, corneal wound healing, limbal mesenchymal stem cell secretome

Introduction

Chemical injury is one of the main causes of vision loss. Chemical injury is caused by contact with alkaline or acidic substances. Its severity is related to concentration, pH, duration of contact, and extent of the wound. Ocular alkali injury often caused by sodium hypochlorite which has a pH between 12 and 14. Ocular alkali injury seems harmless at the onset of injury but it can threaten deeper tissues and has a poorer prognosis because anions (hydroxyl) cause saponification of fats and lipids, which causes tissue softening and increased penetration of cation chemicals. Further damage to the deeper structures of the eye such as the iris, iridocorneal angle, ciliary body and lens, may occur due to the rapid penetration of alkali. Alkali injury damage to the eye is irreversible if it occurs at a pH above 11.5. This requires rapid and intensive management (Mashige, 2016).

Cases of ocular chemical injury are on the rise as a result of the widespread use of chemicals in a variety of fields, industries, and daily tasks. According to a 2019 study conducted by Mishra, alkaline substances caused 70.59 percent of chemical trauma, and men in the age range of 20-40 years who were of productive age had a 73.5 percent higher incidence of chemical trauma. Ammonia, caustic soda/NaOH (paper, textiles, soap), magnesium hydroxide (fireworks), and lime (adhesive, mortar, cement, chalk) are examples of alkaline substances, whereas sulfuric acid (car battery), sulfurous acid (fruit and vegetable preservatives), hydrofluoric acid (rust remover), acetic acid (vinegar), hydrochloric acid (cleaning substance), and chromic (colorant in dye, ink, This can result in severe corneal damage and, in extreme cases, blindness. Eye irrigation, the use of artificial tear drops, antibiotics, cycloplegics, steroids, ascorbic acid, collagenase inhibitors, and surgery are among the treatments available. However, surgery has some drawbacks, including slow epithelial healing, infection,

cataracts, and glaucoma. As a result, an alternative therapy is required to improve the success of current treatments, such as the use of limbal mesenchymal stem cell secretome. Because of its anti-inflammatory, antiangiogenesis, and immunomodulatory properties, LMSCS therapy is being developed and researched as a potential treatment. LMSCS's paracrine process has been shown to promote tissue wound healing and reduce inflammation (Almaliotis et al., 2015; Chen et al., 2020; Mashige et al., 2016).

Pathogenesis of ocular alkali injury

Corneal damage due to alkali injury as a result of adjustments in pH, ulceration, lysis, protein and collagen synthesis defects. Alkaline substances penetrate into the attention quicker than acids and they are lipophilic. Hydroxyl ions can be rapidly deposited on the ocular surface tissue which triggers a saponification reaction in cell membrane fatty acids causing cell disruption. If there is damage to the tissue, it will secrete proteolytic enzymes as an inflammatory response in the early phase. Inflammatory cells will produce enzymes such as matrix metalloproteinases (MMP) that aggravate the destruction of the ocular surface structure. Membrane cell lysis produces chemotactic and inflammatory mediators such as prostaglandins, leukotrienes, and interleukins inflicting an immune reaction (Singh et al., 2013; Mashige, 2016; Mishra et al., 2019).

The next phase will be followed by a cicatricial phase due to the regrowth of healthy tissue around the wound. The destruction of vascular tissue, corneal cells, and conjunctival cells can form ischemic lesions. The presence of cell mutations into fibroblasts and stem cell division results in corneal and conjunctival scarring. The penetration of alkaline substances into the anterior chamber can cause cataracts, damage to the ciliary body, and damage to the trabecular meshwork (Singh et al., 2013; Mashige, 2016; Mishra et al., 2019).

Corneal wound healing

a) Early/Immediate Phase

This phase begins as soon as the chemical compound comes into contact with the surface of the eye. The prognosis was made based on the size of the corneal epithelial defect, the area of the conjunctival epithelial defect, the degree of limbic ischemia, the area and density of the corneal opacity, the increase in intraocular pressure, and the loss of lens transparency (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan). , 2020).

b) Acute Phase

The acute phase occurs in the first seven days after chemical trauma. During this phase, chemical contaminants are eliminated from the tissue with the formation of a defensive layer of the superficial corneal epithelium. The epithelium is a protective layer of enzymes in tears that prevent thinning of the cornea and and development to perforation. The epithelium also modulates stromal regeneration and repair. In the acute phase, residual limbal stem cells undergo epithelial repopulation in the stroma that has lost the epithelial lining. This phase is important due to the fact proteolytic enzymes and enzymes from immune cells can infiltrate the stroma through epithelial defects and cause stromal thinning and perforation in the late phase. (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020).

c) Initial Repair Phase

This phase takes place on days 8-20 which is the transition length of ocular healing. In this phase there is regeneration of the corneal epithelium, chronic inflammatory process, stromal repair and scar tissue formation. This phase is the most likely time for ulceration or thinning of the cornea to occur. Stromal ulceration results in activation of the enzymes collagenase, metalloproteinase and different proteases which are launched from regenerating corneal epithelium and polymorphonuclear leukocytes (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020).

d) Final Repair Phase and Scar Tissue Forming

The final repair phase occurs three weeks after chemical trauma. This phase is characterized by final healing

with a good visual prognosis in grades I and II and a poor visual prognosis in grades III and IV. Late complications of chemical trauma include decreased visual acuity, corneal scarring, dry eye syndrome, xerophthalmia, symblepharon, glaucoma, uveitis, cataracts, adnexa disorders such as lagophthalmos, entropion, ectropion and trichiasis (Singh et al., 2013; Eslani et al. , 2014; Soleimani & Naderan, 2020).

Therapy

Prompt and appropriate management of chemical injury affects the final prognosis. Management of ocular trauma requires treatment for the recovery of epithelial defects, inflammatory responses and complications through modalities that can accelerate epithelialization, reduce inflammation and prevent complications. There are several treatment modalities for ocular chemical trauma, namely non-operative and operative (Singh et al., 2013; Soleimani & Naderan, 2020).

Non-operative therapy includes therapy in the early or immediate phase, management of epithelial defects, control of inflammation and prevention of complications. Therapy in the early or immediate phase is ocular surface irrigation. Epithelial defect management includes artificial tears, epidermal growth factor, retinoid acid (vitamin A), ascorbic acid (vitamin C), hyaluronic acid, tetracycline, autologous serum, platelet rich plasma (PRP), amnion membrane extract. Control of inflammation can be done by giving corticosteroids, topical citrate, NSAIDs. Prevention of complications includes the administration of glaucoma drugs to increase IOP, cycloplegics to prevent synechiae and relieve pain due to ciliary body spasm (Singh et al., 2013; Soleimani & Naderan, 2020).

Chemical ocular trauma operative therapy can be performed at any stage to speed up the healing process and prevent complications. Several operative therapies that can be performed include amniotic membrane transplantation (AMT), tenoplasty, debridement of necrotic tissue, limbal stem-cell transplantation (LSCT), keratoplasty and keratoprosthesis (Singh et al., 2013; Soleimani & Naderan, 2020).

Chemical trauma management can be divided based on the clinical symptom phase as follows (Singh et al., 2013; Soleimani & Naderan, 2020).

a) Early Evaluation and Immediate Therapy

The first step after the patient is exposed to chemicals on the ocular surface is irrigation of isotonic physiological saline solution or Ringer's lactate solution continuously until the ocular surface pH is neutral which is confirmed by periodic examination of pH litmus paper. Another important procedure is cleaning the fornix of chemical particles using a cotton swab or forceps with eyelid eversion. After the pH of the ocular surface is neutral, it is necessary to perform eye examinations, including the fornix area, visual acuity, IOP, and limbal area ischemia (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020).

b) Acute Phase Therapy

The goals of treatment in the healing phase include: (a) reshaping and keeping the corneal epithelium intact, (b) maintaining a balance between collagen synthesis and collagenolysis and (c) reducing scar tissue formation after recovery. Acute phase treatment includes broad-spectrum topical antibiotics, cycloplegics and antiglaucoma. In addition, therapies to accelerate reepithelialization, support ocular surface repair and control inflammation are also given (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020).

Treatment modalities that support re-epithelialization include artificial tears, bandage soft contact lenses and additional drugs. The only artificial tears that can be given are those that do not contain preservatives. Artificial tears and lubricating fluids can help with persistent epitheliopathy, lower the risk of recurrent corneal erosions, and accelerate visual rehabilitation. It is advised to use hydrophilic type bandage soft contact lenses with high oxygen permeability. Bandage soft contact lenses can support epithelial migration, assist basement membrane regeneration and increase epithelial-stromal adhesion. Additional drugs that can be added are retinoid acid and epidermal growth factor because they can increase epithelialization (Singh et al., 2013; Eslani et al., 2014;

Soleimani & Naderan, 2020).

Vitamin C and collagenase inhibitors are two therapeutic modalities that can help to repair the ocular surface and reduce ulceration. Ascorbic acid is a water-soluble vitamin that is required for the formation of collagen. Ascorbic acid administration reduces the occurrence of corneal thinning and ulceration. The use of oral ascorbic acid (2 g/day) and a topical 10% solution in artificial tears was found to be quite effective. Collagenase inhibitors aid in wound healing by inhibiting collagenolytic activity and thus preventing stromal ulceration. Several collagenase inhibitors have been reported to be beneficial, including cysteine, acetylcysteine, sodium EDTA, calcium EDTA, penicillin, and citrate. Corticosteroids are used to control inflammation because they can reduce inflammatory cell infiltration and maintain the stability of neutrophil cytoplasm and neutrophilic lysosomal membranes. (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020).

c) Early Repair Phase Therapy

At this stage it should be able to reach the intact epithelium. If this has not been achieved, then aggressive therapy can be given, namely by giving lubricants, punctal plugs, punctal occlusion with cautery, bandage contact lenses, and tarsoraphy. If the epithelium is not intact, the dose of corticosteroid should be reduced and discontinued on day 14 after trauma. Ascorbic acid and citric acid can be continued, antiglaucoma therapy continued if needed. Antibiotics were still given and evaluation of the sign of symblepharon continued (Singh et al., 2013; Eslani et al., 2014).

d) Late Repair Phase Therapy

Epithelium that has not been intact on day 21 after chemical trauma is at risk for permanent visual impairment. Along with the provision of non-operative therapy, surgical modality is an important therapy in this phase. Conjunctival/tenon advancement, tissue adhesives, penetrating keratoplasty, and amniotic membrane transplantation are all surgical options. (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020).

e) Rehabilitation Phase Therapy

After the eye was in stable condition, limbal stem cell transplantation showed a fairly good response in the rehabilitation of ocular chemical trauma that did not improve with treatment. Limbic stem cells can be donated from a healthy one eye, a sibling or a cadaver. Once the ocular surface is healthy, penetrating keratoplasty or keratoprosthesis can be considered (Singh et al., 2013; Eslani et al., 2014; Soleimani & Naderan, 2020)

Corneal wound healing process

Corneal wound healing is a complex process. Several growth factors, cytokines, and proteases are produced by epithelial cells, stromal keratocytes, inflammatory cells, and lacrimal gland cells during this process (Agrawal and Tsai, 2003).

Corneal epithelial healing

Following epithelial injury, cytokines such as IL-1 and TNF-, bone morphogenic proteins (BMP) 2 and 4, epidermal growth factor (EGF), and platelet derived growth factor are immediately released from the injured epithelium and the epithelial basement membrane (PDGF). The response of keratocytes in the stroma, including IL-1-mediated Fas ligand synthesis, begins after the release of these factors. Fas ligands on keratocytes bind to Fas receptors adjacent to these keratocytes and trigger apoptosis (Eraslan and Toker, 2009). After trauma to the corneal epithelium, the response begins very rapidly within the first 1 hour. IL-1 is a major modulator of various stages involved in corneal wound healing. Both IL-1α and IL-1β mRNA and protein are expressed in the corneal epithelium. IL-1 receptors are also produced by keratocytes and fibroblasts. In healthy corneas, it is not possible to detect IL-1 in keratocytes using immunohistochemistry. Previous studies suggest that IL-1 can be detected in injured corneal keratocytes or myofibroblasts in the absence of trauma or death of the corneal epithelium, it is possible that intact epithelium acts as a barrier and IL-1 present in the tear layer does not enter the anterior stroma (Eraslan et al. and Toker, 2009). The corneal epithelium consists of 5-6 layers of non-keratinized

squamous epithelial cells. The corneal epithelium does not contain goblet cells and is replaced every 4-6 days. In the limbus area, the squamous epithelial layer is thicker (about 10 layers) where the basal epithelial cells in the limbus area play an important role in maintaining the ocular surface epithelium both under normal conditions and in trauma (Wagoner and Kenyon, 2002).

In serious alkali chemical injury, the process of transdifferentiation of the conjunctival epithelium cannot take place completely. This is due to inhibited reepithelialization, neovascularization of the stroma, the appearance of goblet cells between the corneal epithelium, and recurrent epithelial erosions due to an abnormal epithelial basement membrane (Wagoner and Kenyon, 2002).

The initial corneal epithelial healing takes 12 to 48 hours. The released growth factors and cytokines help regulate the new basement membrane, after which the epithelial surface begins to shift and replicate, resulting in an epithelial plug that closes the wound. Epithelial stem cells in the limbus migrate from the periphery to the central cone, as well as from the basal layer to the apex. This cell turnover occurs in a systematic manner. Thoft and Friend's 1983 hypothesis described this mass movement of epithelial cells as X, Y, and Z. X represents basal epithelial proliferation, Y represents centripetal movement of peripheral epithelial cells, and Z represents cell loss due to death and desquamation in this hypothesis. The rate of this re-epithelialization depends on the source of the replacement epithelium. In epithelial defects in the central area, the rate of re-epithelialization ranges from 0.69-1.46 mm2/hour. Large corneal epithelial defects will have a faster re-epithelialization rate than small, centrally located corneal epithelial defects. This could be due to an increase in the rate of mitosis. If there is a large defect in the limbus area and the replacement epithelium only comes from the conjunctiva, the rate of reepithelialization will be prolonged (Wagoner, 1997; Wagoner and Kenyon, 2002).

Apart from the source of epithelial replacement, the rate of reepithelialization depends on the presence or absence of an inflammatory process, damage to the basement membrane epithelium, and degradation of fibronectin in the basement membrane by plasminogen activator. Epithelial migration can be accelerated by reducing the inflammatory process, adequate lubrication, administration of EGF which will increase cell mitosis (Wagoner, 2002).

Mesenchymal stem/stromal cells

Mesenchymal stem/stromal cells (MSCs) are a diverse population of afferent non-hematopoietic fibroblast-like cells defined by the phenotypes CD90+ CD105+ CD73+ CD29+ CD34 CD45. MSCs can repair damaged tissue through direct differentiation or trophic factor secretion. MSCs can be isolated from bone marrow (BM-MSCs), dental pulp (DPSCs), adipose tissue (ADSCs), and umbilical cord blood (UC-MSCs). Through inflammatory cytokines and growth factors, MSCs can modulate immune response and tissue repair (Shukla et al., 2019).

MSCs have now been identified and can be isolated from the stroma and limbus of the cornea. Diverse cell populations with mesenchymal characteristics (e.g., multipotent differentiation, clonal growth, and expression of MSC-specific markers) have been found to support the viability and potency of limbal epithelial stem cells adjacent to the limbal basement membrane. In 2005, these cells were identified as the'side population' on flow cytometry and were dubbed corneal stromal stem cells (CSSCs). These limbal SPMs are thought to be present in the anterior limbus (stroma) of the peripheral cornea as well, and are known as peripheral and limbal corneal stromal cells (PLCSCs). It was reported to meet all of the International Society for Cell Therapy (ISCT) criteria for MSS (plastic adherent, CD105+, CD73+, CD90+, CD45, CD34, CD14, CD11b, CD79, and HLA-DR, differentiated into osteoblasts, adipocytes, and chondroblasts in vitro). The limbal SPM is spindle-shaped and expresses mesenchymal cell markers such as vimentin, N-cadherin, CD 105, and CD 34 (Nakatsu et al, 2014; Shukla et al., 2019; Beeken et al., 2020

Limbal niche cells isolated from the limbal stroma have been shown to generate progenitor cells with MSC-like characteristics, implying a potential role in corneal wound healing. The cells were isolated from the limbal

stroma and dubbed limbus-derived stromal/mesenchymal stem cells (LMSCs) in 2014. LMSCs have the ability to: a) differentiate into a variety of cell types, including keratocytes; b) secrete extracellular matrix (ECM) components such as collagen I, lumican, and keratocan in a regular lamellar pattern; c) repair damaged corneal stromal patterns; d) reduce inflammation and angiogenesis; and e) restore normal corneal transparency. (Shukla et al., 2019).

Mesenchymal stem/stromal cells Secretome

The bioactive factors secreted by MSCs are called MSCs secretome. Secretomes are molecules that are secreted from stem cell culture media into the extracellular space in the form of secretomes, microvesicles, and exosomes. Conditioned media is a term used to describe culture media. Stem cell conditioned media isolation techniques can affect the type and levels of secreted metabolites. Several factors can affect the type and quantity of growth factors produced in the isolation of stem cell conditioned media including the technique of using culture media and supplements, duration of culture (16 hours to 5 days) and culture conditions (normoxia, hypoxia, monolayer culture, or 3 dimensions) (Zhang et al., 2016; Pawitan, 2014; Rangarunlert et al., 2009).

Several cytokines found in MSC secretomes play a role in tissue repair. Growth factors, pro-inflammatory cytokines, anti-inflammatory cytokines, and other cytokines are some of the different types of cytokines. Growth factors contained in LMSCS include vascular endothelial derived growth factor (VEGF), platelet derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I), insulin-like growth factor-II (IGF-II), hepatocyte growth factor (HGF), fibroblast growth factor 2/basic fibroblast growth factor (FGF-2/bFGF), keratinocyte growth factor/fibroblast growth factor 7 (KGF/FGF-7), platelets derived endothelial cell growth factor (PDEGF), heparin binding epidermal growth factor (HEGF), placenta growth factor (PlGF), neural growth factor (NGF) and brain derived neurotrophic factor (BDNF). Various growth factors were found in conditioned media secreted by various stem cells, with the exception of human MSCs, which did not secrete FGF-2, PDGFBB, BMP-2, or SDF-1 but did secrete IGF-1, VEGF, TGF 1, and HGF. Furthermore, different conditions and culture media can result in varying levels of growth factor secretion (Pawitan, 2014). Anti-inflammation cytokines contains in MSC secretome are IL-6, IL-10, IL- 27, IL-17E, IL-13, dan IL-12p70. Pro inflammation cytokines contains in MSC secretome are IL-8, IL- 9, IL-1b. Another kind of cytokines are leptin, angiogenin, granulocyte colony stimulating factor (GCSF), granulocyte macrophage CSF (GM-CSF), macrophage CSF (MCSF), fractalkine, monocyte chemotactic protein (MCP-1), serpin E-1, endostatin/collegen XVIII, UPA, thrombospondins 1 and 2, tissue inhibitor of metalloproteinase-1 (TIMP-1), IGF binding protein (IGFBP), stem cell-derived factor 1 (SDF-1)/CXCL-12, adrenomedullin (ADM), Dickkopf-1 (DKK-1), MCSF receptor (MCSFR) dan PDGF receptor (PDGFR) (Vizoso et al., 2017; Pawitan, 2014; Mansoor et al., 2019).

Several studies on stem cell secretome suggest that the metabolites secreted by stem cells alone without containing the stem cells themselves play a role in the regeneration of damaged tissues or organs. The use of stem cell secretome has advantages over stem cells because it can be mass-produced at a lower cost, can be formed as freeze-dried, and is more stable in shipping and storage. Stem cell secretome do not need to be matched between donor and recipient to avoid rejection because they are universal. So that stem cell secretome can be produced pharmaceutically and can be a promising therapeutic strategy for regenerative medicine. There have been two human clinical trials that have yielded positive results for the use of adipose mesenchymal stem cell conditioned media for hair follicle regeneration and wound healing. MSC not only reduces inflammation and inhibits neovascularization, but it also reduces corneal opacity in ocular chemical injury, according to several studies. As evidenced by the growing number of studies on the use of stem cell secretome for various diseases, the use of stem cell secretome for therapy is currently being developed. Various growth factors and regenerative molecules secreted by stem cells are present in the conditioned media. Various proteomic studies

that show the presence of various growth factors and other cytokines in conditioned media also support the fact that stem cells secrete various growth factors (Pawitan, 2014; Hodgkinson et al., 2016).

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