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Mini Review

Prospective Utilization of Wharton's Jelly-Derived Mesenchymal Stem Cells and Their Conditioned Medium in the Regeneration of Diabetic Corneal Neuropathy

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Abstract

Diabetes Mellitus, a highly prevalent and rapidly increasing metabolic disease, can cause several serious complications including visual damage and blindness caused by ocular nerve damage. Nerve fiber degeneration might occur because of the accumulation of glycation end-products in the Descemet's membrane of the nerve. The severity of corneal nerve diabetic keratopathy can be examined through regeneration of corneal nerves, specifically through GAP-43 and TUB33, which are two markers of nerve regeneration. WJMSCs (Wharton's jelly-derived mesenchymal stem cells) induce its regenerative effects by expressing genes that promote neuronal development, inhibiting proliferation of pro-inflammatory cytokines, suppressing the immune system, and most of all its highly proliferative capacity. WJMSCs are believed to be more superior than other sources of mesenchymal stem cells as the umbilical cord is more easily accessible and stored for further usage. Moreover, WJMSCs possess anti-tumorigenic abilities and does not induce any serious adverse effects. Thus, the prospective of WJMSCs to be utilized as corneal nerve neuropathy in diabetic patients is bright, but further trials are still needed to solidify its efficacy.

Keywords: Diabetic corneal neuropathy; Wharton's jelly-derived mesenchymal stem cells; Neuronal regeneration

Abbreviations: DM: Diabetes Mellitus; MSCs: Mesenchymal Stem Cells; SBN: Sub-Basal Nerve Plexus; Wjmscs: Wharton's Jelly-Derived Mesenchymal Stem Cell; CM: Conditioned Medium

Introduction

Diabetes mellitus (DM) is a highly prevalent and rapidly increasing disease worldwide, affecting 9.3% (463 million) of the global population and is estimated to reach 10.9% (700 million) by 2045 [1]. Aside from being recorded to directly cause 1.5 million

deaths in 2019, DM is also a major source of serious neurovascular complications. One such complication is peripheral neuropathy, which might affect vision or worse, cause blindness [2].

Hyperglycemia in diabetic patients can lead to impaired innervation of the cornea, altered corneal sensitivity, dry eyes, and changes in epithelial basal cells, basement membrane, and the sub-basal nerve plexus (SBN). Reduced corneal sensitivity put the eyes at risk to dryness and infection. Moreover, damaged corneal nerves cause inability to maintain neurotropic peptides, which further exacerbate the complications as it interferes wound healing, causing the patient to be at risk for corneal infections [3]. However, corneal nerve regeneration is currently a challenge that has yet to be tackled by ophthalmologist due to inadequate treatments readily available to stimulate regeneration of corneal nerve and restore normal function of the nerve [4].

In the light of current knowledge, it has been shown that the accumulation of advanced glycation end-products (AGEs) in Descemet's membrane disrupt its composition and leads to nerve fiber degeneration. It is of paramount importance to highlight the severity of diabetic neuropathy through evaluation of corneal nerve regeneration [5]. Research advancements in mesenchymal stem cells (MSCs) and its potential therapeutic efficacy serve as a hope for diabetics in the near future. Furthermore, several studies have shown the ability of Wharton's jelly-derived mesenchymal stem cells (WJMSCs) and their conditioned medium (CM) to differentiate and initiate regeneration of Schwann cells [6]. Thus, the aim of this review is to evaluate and summarize the efficacy of WJMSCs or their CM through recent research and advances in animal trials to evaluate their prospect for future applications in patients with diabetic corneal neuropathy.

Discussion

An overview of Wharton's jelly mesenchymal stem cells

MSCs can be obtained through other sources, such as bone marrow, adipose tissue, periodontal ligament, dental pulp, etc. However, it may be said that WJMSCs currently sits on a superior level compared to other sources of MSC. Studies previously conducted have shown that WJMSCs are more primitive than other adult sources of MSCs, this translates to a higher proliferation rate without being tumorigenic, a greater expansion capability, and a highly potent immunomodulatory capacity [7]. Regarding its potential to regenerate peripheral ocular nerves in diabetic patients, WJMSCs also express genes that promotes neural regeneration and development. Moreover, the CM, which contains its secretome (including nerve growth factor), also takes part in the regeneration, homing, and immunomodulatory capacities of WJMSCs [8].

Currently, MSCs are isolated from WJ through two types of method, which are "enzymatic digestion" and "tissue explant." The former utilizes collagenase, specifically collagenase II at 37°C for 16–20 hours [9]. The latter was developed because some studies suggest that the former might alter the function of the MSCs, thus decreasing their efficacy. It is done by maximizing the ability of MSCs to migrate and adhere to external tissues. The most recent study suggests that 10mm-size tissue explants are the most effective adhering media [10]. After being isolated, the MSCs are centrifuged to extract the precipitate (mesenchymal tissue). We have also previously studied the effect of WJMSCs and their CM in the regeneration of corneal nerve in rats with diabetic keratopathy. The CM we formulated, where the MSCs are cultured, contained 10% in-home platelet lysate, 1% Glutamax-1 (Gibco, Thermo Fischer, USA). 1% Penstrep (Gibco, Thermo Fischer, USA), and 1% amphotericin B (Gibco, Thermo Fischer, USA) in MEM alpha (Gibco, Thermo Fischer, USA). The MSCs can later be harvested and directly used or stored in liquid nitrogen for future use.

The potential of WJMSCs has yet to be fully unraveled, as the studies for corneal nerve regeneration have only been done in animal studies. However, murine models of diabetic keratopathy hold similarities to human corneal structures. In our previous study, the rats are diabetically-induced with streptozotocin through intraperitoneal injection. Diabetic keratopathy in rats is examined through corneal sensibility analysis. After the study, the rats are euthanized using ketamine and xylazine injection.

Effectiveness of WJMSCs and their CM on initiating regeneration

On our recent study, diabetic rats treated with topical WJMSCS eye drops showed regeneration of damaged corneal epithelium and integrity. Moreover, the topical administration of WJMSCs grown in their CM showed increased density of GAP-43 (growth associated protein-43), TUB33 (beta tubulin III), and nerve fibers in the cornea of the rats when evaluated through immunohistochemical staining. This finding indicates significant improvement of corneal growth and reparation. This also validates the ability of MSC's to secrete multiple growth factors and cytokines, as well as extracellular vesicles which support the DNA and miRNA ability to express regenerative genes [11]. Anti-inflammatory abilities of MSCs are shown by Di et al. through pro-inflammatory cytokines tumor necrosis factor-α and interleukin-1β present secreted by MCSs.5 Moreover, the immunomodulatory effects of WJMSCS also include the inhibition of maturation and activation of T cells and dendritic cells and also the activation of natural killer cell cytotoxicity. These immunosuppressive effects give corneal nerves more time for regeneration and growth, as well as minimizing inflammation and damage on the nerve. WJMSCs also express various chemokines which are known to induce angiogenesis to aid the damaged neuronal epithelium [12].

Understanding that the pathophysiology behind diabetic keratopathy involves inflammation and degradation of nerve cells, along with the knowledge on the efficacy of WJMSCs on neuronal development and anti-inflammation, WJMSCs and their CM is a promising alternative to treat diabetic keratopathy. Furthermore, MSCs derived from umbilical cord has also been investigated on other eye diseases. Clinical trials conducted by Kahraman et al.

demonstrated retinal nerve regeneration in patients diagnosed with retinitis pigmentosa. This ultimately translates to statistically significant improvements in the visual field [13]. Numerous clinical trials on WJMSCs to treat diabetes mellitus type 1 and 2 by initiating regeneration are also well on their way.

Safety and applicability

The utilization of MSCs for therapies has met various ethical constraints. However, WJMSCs are highly accessible and applicable as it is easily obtained after birth if informed consent was acquired from donors. The cell collection is also safe and has minimal safety issues. Moreover, the application of therapy for diabetic keratopathy is practical, as it can be applied through topical eye droplets. While stem cell therapies are believed to induce tumor growth, MCSs derived from Wharton's Jelly have the capacity to modulate the microenvironment of tumor sites and possess anti-tumorigenic properties. In addition, research have shown that WJMSCs have the ability to suppress cancer growth and induce apoptosis [5].

Being a novel treatment, safety assessments for WJMSCs must be conducted through monitoring and evaluation. A clinical trial on diabetic patients treated with intravenous WJMSCs to induce insulin regeneration have demonstrated its safety. In the study, no hypersensitivity, hemorrhage, venous/arterial thromboembolic events, proteinuria, or other serious adverse reactions were detected immediately nor during the 36 months follow-up timeframe [14].

Conclusion

Diabetes can cause chronic complications, including corneal neuropathy which can harm visual function. WJMSCs offers a bright hope for its potential of being an effective treatment for diabetic corneal neuropathy. Unfortunately, there has not been a clinical trial on the effectivity of WJMSCs to repair corneal nerves in diabetic patients. However, murine studies have proven WJMSCs to be as adequately effective as bone marrow stem cells to initiate regeneration, showing improvement in GAP-43 and TUB33 on immunohistochemistry analysis. Along with its efficacy, easier accessibility, and high applicability, WJMSCs are believed to have no serious adverse effects after its use. Thus, WJMSC holds a promising future on providing effective treatment for diabetic corneal neuropathy. Nevertheless, further clinical trials are warranted to solidify the efficacy of WJMSC.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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