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Invited Review

Looking into dental pulp stem cells in the therapy of photoreceptors and retinal degenerative disorders

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ABSTRACT

Blindness and vision impairment are caused by irremediable retinal degeneration in affected individuals worldwide. Cell therapy for a retinal replacement can potentially rescue their vision, specifically for those who lost the light sensing photoreceptors in the eye. As such, well-characterized retinal cells are required for the replacement purposes. Stem cell-based therapy in photoreceptor and retinal pigment epithelium transplantation is well received, however, the drawbacks of retinal transplantation is the limited clinical protocols development, insufficient number of transplanted cells for recovery, the selection of potential stem cell sources that can be differentiated into the target cells, and the ability of cells to migrate to the host tissue. Dental pulp stem cells (DPSC) belong to a subset of mesenchymal stem cells, and are recently being studied due to its high capability of differentiating into cells of the neuronal lineage. In this review, we look into the potential uses of DPSC in treating retinal degeneration, and also the current data supporting its application.

1. The Human Eye and its Photosensitive Retina

The eye is a highly complex sensory system in the human body. The inner portion of the eyes are anatomically separated into the anterior and posterior parts. The anterior part consists of the cornea, pupil, iris and lens whereas the posterior part includes the sclera, choroid, retina, macula and optic nerve [1]. Of which, the innermost retina functions as the light-sensing layer for phototransduction (Fig. 1). The retina is a soft transparent tissue derived from the neural ectoderm that develops from the nervous system and the retina, therefore, is considered to be part of the brain [43]. It is composed of nine neural sensory layers that contribute to the visual pathway and a tenth retinal pigment epithelium layer [27]. The first layer is the inner limiting membrane, which acts as a boundary between the retina and vitreous humor. It is formed by both the vitreal and retinal constituents [35]. This occurs when the Muller cell procedures become elaborated and flattened on the vitreal line

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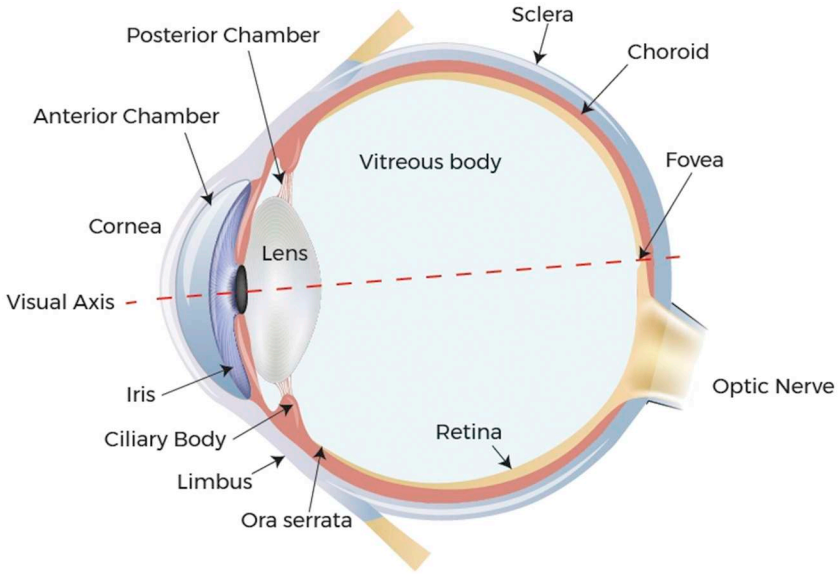

Fig. 1. Anatomy of the human eye.

[29]; the nerve fiber layer, is a combination of ganglionic axons that form the second layer.

The third layer within the retina is the ganglion cell layer, which encompasses numerous cell bodies and have about 1.2 million ganglion cells [2]. Various dendrites stretch out into the inner part of the plexiform layer and create synapses with the inner nuclear layer cells. The outer plexiform layer forms synaptic connections between inner nuclear layer cells and photoreceptor cells (bipolar and horizontal cells). These connections form electrical signals that transmit from one layer to another through specific mechanisms which are essential for initiating the visual process in the retina [29].

The outer nuclear layer (ONL) contains 4–5 million cones and 77–107 million rods. Histologically, the ONL is the thickest layer of the fovea where cones are located. However, the rods are situated outside the foveolar zone of the retina [3]. The external limiting membrane is not a veritable membrane but contains close junctions between photoreceptors and other supporting layers [27].

The last two most important layers, which are the photoreceptor layers and the retinal pigment epithelial layer, contribute highly to visual function (Wolff et al., 1997). All retinal layers are bound together via complex synaptic junctions which are connected to the brain and play a pivotal role in creating images of the external environment and increasing perception capacity. Further discussion will be held on the two most essential cellular components that are related to the retina, namely the photoreceptors and the retinal pigment epithelium.

2. Retinal Degenerative Disorders

Retinal degenerative disorders are a series of multiple retinal diseases that could be acquired such as age-related macular degeneration (AMD), and diabetic retinopathy (DR), or hereditary such as retinitis pigmentosa (RP). All of which affect retinal cells and can lead to vision loss. Retinal degeneration can occur across all ages. Epidemiological studies have shown that RP has a high pathological impact on the pediatric and young adult populations [7], while DR affects middle-aged adults [8], and AMD affects the elderly [9]. The prevalence of eye disease has become the major cause of blindness worldwide, especially in developing countries [10].

Age-related macular degeneration (AMD) is a chronic disorder that manipulates the macula and causes severe neural retinal damage (Fig. 2). The macula is a specialized zone located inside the retina, its function is to provide clearer and finer details of the surrounding. When

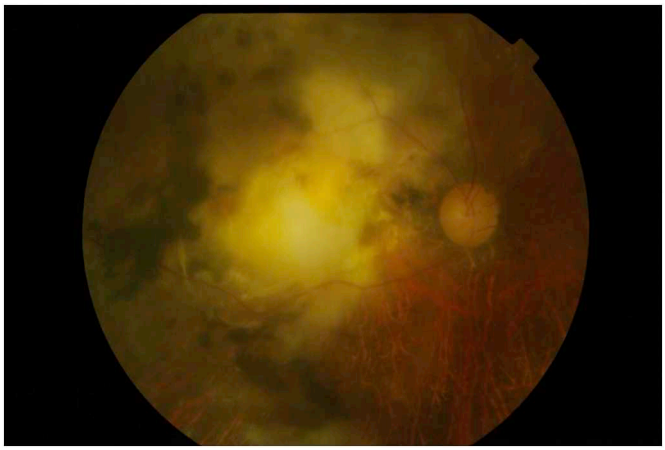

Fig. 2. A patient presenting with wet age-related macular degeneration and formation of disciform scars (right eye).

there is a failure in macular functioning, patients encounter blurry vision with some dark spots in the central part of their vision, which affects their ability to drive, read, and write (Rapantzikos, 2000). Furthermore, the clinical pathology of AMD encompasses the distribution of drusen substances, enlargement of the retinal pigment epithelium layer, choroidal neovascularization (CNV) and geographic atrophy. It has been reported that these changes affect the macular part of the retina which subsequently causes apoptosis of the retinal cells, leading to blindness.

To date, only a few therapies have been successful in treating certain ocular diseases. Yet, other non-treated eye diseases could last forever in the individual and that would cause disruption to the individual him/herself, the family and the community. Retinitis pigmentosa is one of the non-treatable diseases among all ocular disorders as no dynamic treatment has been found [38]. Retinitis Pigmentosa (RP) is a retinal hereditary degenerative disorder that affects retinal cells and causes poor retinal functioning [11] due to retinal photoreceptor apoptosis (Fig. 3). Diverse mutations are found in more than 44 genes exposed in rod photoreceptors [12]. The lack of these genes can cause severe vision impairment. This type of ocular disease has no limitation in affecting people with age-related macular degeneration, and it can affect individuals in any age group [41]. The initial symptoms of RP involve dim light in vision with some black spots in the peripheral part of the

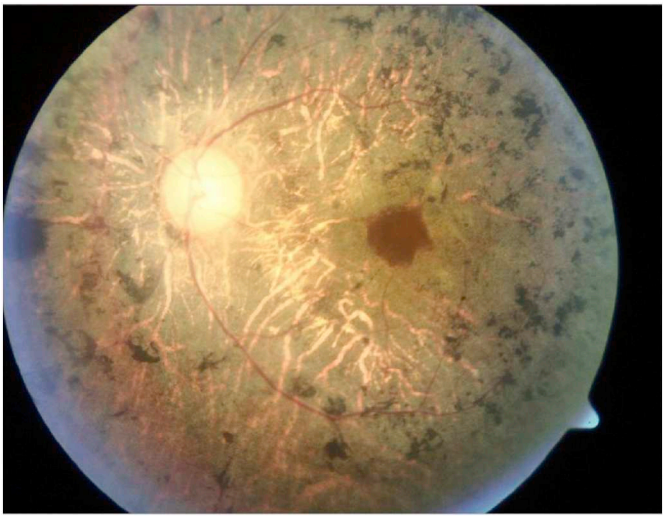

Fig. 3. A patient presenting with a classic case of retinitis pigmentosa (left eye).

eye that might progress during the aging process [38]. Furthermore, other RP symptoms are the severe deterioration of rod photoreceptor cells followed by cone photoreceptor cells. Deterioration, as well as structural abnormalities, also occur in the retinal pigment epithelium layer. Patients with RP undergo gradual tunnel vision and then blindness [22].

3. Stem Cell Therapy

Current strategies for treatment of retinal disorders involve pharmacological, surgical and cell transplantation therapies. The pharmacological strategy is the most prevalent method, but it's not effective for retinal disorders like RP [9]. Surgical intervention has been attempted as an option for ocular treatments [13] by autologous translocation of retinal pigment epithelium. However, the drawbacks of using these methods are attributable to poor renewability and regeneration of retinal neurons [9]. The development of stem cell technology for retinal degeneration treatment has been reported recently [19]. Stem cells are self-renewed through division and can differentiate into other cell types under certain physiological and experimental conditions (Fig. 4) [17]. Stem cells can be derived from early embryonic tissues or from adults [18].

ESCs are specialized cells that are derived from the inner cell mass during the embryonic stage, able to regenerate themselves without any biological assistance and have further potential to differentiate and/or convert themselves into different cell lineages including adult cells that obtained from the three embryonic germ layers [14,20,23]. As a result, ESC carry good therapeutic capacity in the generation of functional neuron [24,26,28], cardiomyocytes [30,31], hepatocytes [33], lung epithelium [34] and pancreatic beta cells [36]. Various studies exhibited the differentiation strategy of ESCs functions into eye cell functions like photoreceptor progenitors, photoreceptor, or retinal pigment epithelium (RPE) in experimental models [37,42]. Based on ERG recording, a recent study displayed that replacement of human ESC-derived in the subretinal area of adult mice type Crx(−/−) stimulated the potential of these cells to be differentiated into photoreceptor cells [44]. Even though the ESC is considered as promising replacement therapy in the retinal, there are still issues in the immune rejection that must have the full attention. Furthermore, the formation of teratoma is shown to be associated with ESC (Thomson et al., 1998; Reubinoff et al., 2000; [14]).

The identification of SCs derived from the bone marrow was suggested as a great cell source for regenerative medicine [46]. This assumes that HSCs extracted from BM are flexible and can differentiate into other SCs types for other organs such as heart, liver, and brain. Regrettably, the SCs flexibility concept was not assured by current studies and lately supporting data representing this in vitro phenomenon could be clarified by cell fusion or heterogeneous populations of SCs in BM [47]. Stem cell remedy has been testified for many neurodegenerative diseases using animal models like Parkinson's disorder spinal cord damage, and multiple sclerosis disease. The therapeutic success relies on the successful replacement of the lost neurons that are not physiologically replaced. In the eye, the retinal neurons loss is a strong hallmark for the presence of ocular disorders such as RP and AMD. In such cases, the loss of photoreceptors is a fundamental event that leads to eventual blindness (MacHalińska et al., 2009).

4. Dental Pulp Stem Cells

Recently, dental pulp tissue found in mesenchymal stem cell populations have been reported to own high proliferative differentiation capabilities. These cells are called dental pulp stem cells (DPSCs) (Fig. 5) [25], human exfoliated deciduous stem cells (SHEDs) [48], periodontal ligament stem cells (PDLSCs) [49], dental follicle progenitor stem cells (DFPCs) [50], and stem cells from apical papilla (SCAPs) [51]. DPSCs and SHEDs located in the cranial neural crest have multipotency and pluripotency characteristic, due to their ability to express mesenchymal and neuroectodermal stem cell markers [25,52]. Sharp and Young were the first researchers who worked on dental tissue engineering and extracted the stem cells from dental tissue [53]. Many studies have shown that dental stem cells have progenitor features and also have the capability to differentiate into odontoblast [54]. In our previous study, we showed that DPSCs which were transplanted into the eye of a retinal degeneration rat model had the capability to differentiate into cells of the retina, and also protect the tissue from acute sodium iodate toxicity [55].

Dental cells sometimes contain undifferentiated cells because the roots of the third molar are incomplete at age 18, and these undifferentiated cells are sitting in the dental germ pulp [15]. Takeda et al. [56], isolated DPSCs from the supernumerary mesiodens and noticed that the cells that derived from the crown stage have more proliferation capacity than the late stage [56]. It has been also testified that the dental cells can differentiate into potential fat, bone, cartilage, and neural cells [32]. For regeneration purposes, DPSCs were previously demonstrated to be effective in treating various diseases such as myocardial infarction, neurotrauma, autoimmune disease, muscular dystrophy and devastated connective tissue [16]. Moreover, the simplicity of their extraction and their ease of availability make them a promising candidate in regenerative medicine.

In vitro model, DPSCs were tested for their neuroprotective effectiveness in treating both Alzheimer's and Parkinson's disease [6]. Initially, they extract the DPSCs from the rat model and coculture it with the neural cells two days before the neurotoxin treatment. The cultured DPSCs have produced neurotrophic factors, for instance, NGF (nerve growth factor), GDNF (Glial cell-derived neurotrophic factor), BDNF (Brain-derived neurotrophic factor), and BMP2. Also, DPSCs showed a protection ability of the primary neurons and enhanced neuron cell viability. Previously, it has been illustrated that the cells from dental pulp are able to catalyze nerve regeneration in the damaged spinal cord for a length of a time [57]. In this experiment, the DPSCs were injected into rats with severely damaged spinal cords. It was revealed that DPSCs promote transected axon regeneration by direct inhibition of axon growth inhibitors and by halting apoptotic neurons, astrocytes, and oligodendrocytes. The DPSCs also converted into mature oligodendrocytes to relocate cells that were lost. It was found that SHEDs and DPSCs expressed numerous neural lineage markers. When compared to BMSCs, DPSC-implanted rats showed improved recovery after the operation, during the acute phase of spinal cord injury. Other than promoting neural differentiation in the host tissue, DPSCs can be induced to form neurons in vitro through cultures spiked with

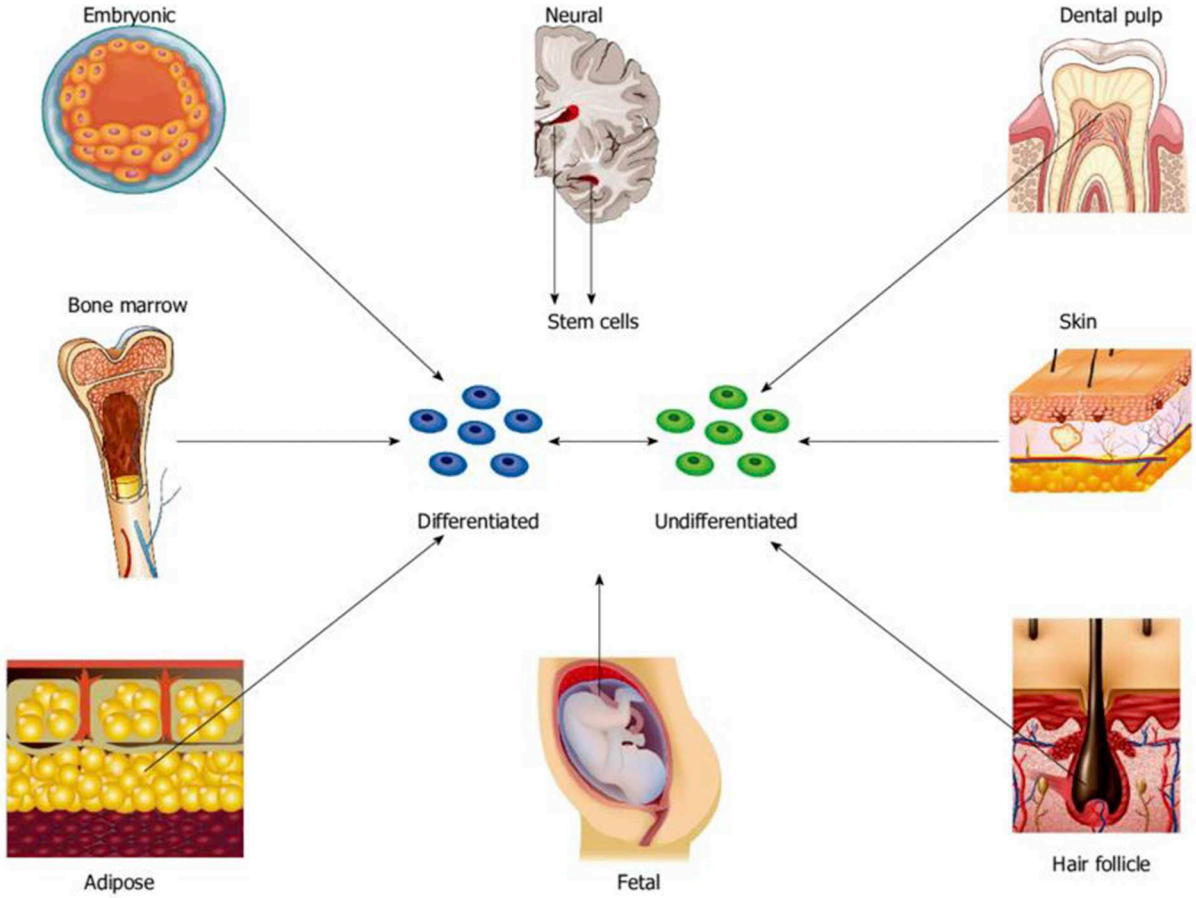

Fig. 4. Harvested stem cells from different sources capable to differentiate into other stem cell sources used as transplanted therapy for regenerative medicine [21].

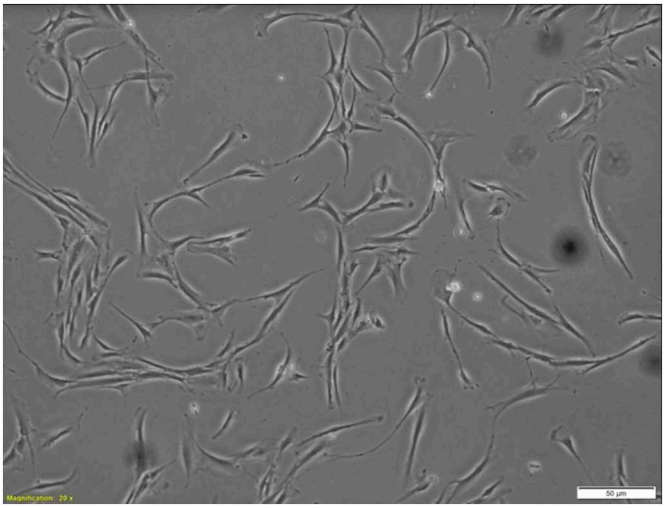

Fig. 5. Cell culture of dental pulp stem cells viewed under a light microscope at 100× total magnification. The scalebar denotes 50 μm.

conventional neurogenic media/supplements. N-2 plus media supplement is one such example that was found to induce differentiation of rat DPSCs into a neural lineage [45]. Other than that, retinoic acid can also be used, which was shown by Bojnordi et al., where human DPSCs were expanded to form neurons by adding the supplement into the induction media [4]. These differentiated neurons were found to express neural markers such as nestin and glial fibrillary acidic protein (GFAP).

de Almeida et al. also supported DPSC-mediated neuroprotection in their study, wherein, they investigated human dental pulp stem cells therapy in a mouse model with severe spinal cord injury [5]. They concluded that the group with human DPSCs showed better preservation of the white matter, high expression of a trophic factor, and better organization of the tissue, with a presence of many myelinated axons by both Schwann cells and oligodendrocytes. Kiraly et al. transplanted DPSCs, which were pre-differentiated and tagged with a dynamic cell dye, vibrant D, into the cerebrospinal fluid of three-day-old Wister rats [40]. It was concluded that DPSC-derived cells incorporated into the host brain and displayed neuronal characteristics for instant expression of neural markers, and sodium/potassium channels.

Dental pulp stem cells have proved to provide relief to patients with Parkinson's disease, which is a neurodegenerative disorder. In a study done by Nosrat et al., researchers have cultured dental pulp stem cells, which produce original neuronal cells and cells that produce useful neurotrophic factors for the treatment of the disease [58]. It has also been proposed that cells isolated from tooth produce neurotrophic support to dying nerve cells and replace dead cells [58]. The protective effect may be attributed to the BDNF and GNF released by the DPSCs, and an also differentiate into dopaminergic neuron-like cells [59].

The comparison between human DPSC and BMSC cells, for better characteristic of neural epithelial stem cell, was done by Karaoz et al. The DPSCs from the third molar were rated for their capacity in proliferation and the expression profiles of gene, phenotypic, ultrastructural, and differentiation characteristics, where HDPSCs were seen to be more metabolically active cells [39]. They expressed cytokeratin (CK 18-19), which is involved in both odontoblast differentiation and dentin repair. Additionally, the immortalized tooth germ cells retained their properties of differentiation. Results of the various studies suggested that the immortalized DPSCs might slow their senescence, and biomaterials coated with DPSCs could also be used for neural stem cell differentiation (Yalvaç et al., 2011).

5. Conclusion

Stem cell therapy is potentially an excellent therapeutic technique in improving the quality of life in individuals with ocular dysfunctions. Various stem cell sources were used in research to treat vision loss. They range from stem cells with embryonic origins, to bone marrow-derived mesenchymal stem cells. However, dental pulp stem cells (DPSCs) have been shown to have superior therapeutic capabilities compared to bone marrow-derived mesenchymal stem cells. Moreover, DPSCs are capable of rescuing retinal ganglion cells from further loss. However, research using this source of stem cells to treat retinal pigment epithelium (RPE) and photoreceptors is still limited. In our study, we used DPSCs to recover the RPE and photoreceptor cells in order to restore vision in our rat model. We surmised that DPSCs have the capability of becoming the choice of stem cells used in stem cell therapy to treat blindness in the future.

Declaration of Competing Interest

All authors declare no competing interests in relation to the publication of this paper.

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