Short Communication

Regeneration of Trabecular Meshwork in Primary Open Angle Glaucoma by Stem Cell Therapy

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ABSTRACT

Glaucoma is considered a neurodegenerative disease due to its pathophysiology and is one of the most common causes of vision loss worldwide. The treatment of glaucoma is essentially based on the reduction of IOP, through pharmacological therapies. The iPSCs enabling autologous transplantation and have the advantage of not generating immune-mediated rejection in the host, that iPSC can be induced to differentiate into a cell type that resembles to TM cells, The iPSC-TM. The data demonstrate that intraocular injection of iPSC-TM prevents the IOP elevation, the aqueous humor outflow reduction and results in preservation of Retinal Ganglion Cell (RGC) density in vivo mice models.

Key Words: Trabecular-meshwork; Glaucoma; POAG; IOP

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INTRODUCTION

Glaucoma is considered a neurodegenerative disease due to its pathophysiology and is one of the most common causes of vision loss worldwide. The glaucoma disease causes death of Retinal Ganglion Cells (RGCs), as well as degeneration of the optic nerve head, the optic nerve, and the lateral geniculate nucleus, which leads to a gradual loss of vision. The most common type of glaucoma is the Primary Open Angle Glaucoma (POAG), which accounts for about 90% of all forms of glaucoma. The treatment of glaucoma is essentially based on the reduction of Intra Ocular Pressure (IOP), through pharmacological therapies, or in more severe cases through surgical procedures, which provide an aqueous humor outflow bypass [1].

STEM CELL OVERVIEW

The stem cells can be classified into Embryonic Stem (ES) cells, induced Pluripotent Stem Cells (iPSCs), and adult stem cells. One advantage of iPSCs is that these cells can be derived from readily available cell types of the intended recipient. The iPSCs enabling autologous transplantation and there by iPSCs are cells that have the advantage of not generating immune-mediated rejection in the host. The iPSCs also have the advantage circumventing the ethical and immunological disadvantages associated with ES cells therapy, since the iPSCs are autologous. However, there are safety concerns because the iPSCs may cause oncogenesis [2–5].

Structure, function and embryology of TM

The Trabecular Meshwork (TM) formation involves many genetic networks. Furthermore, the development of this complex tissue involves different molecular signals, among others PITX2, PITX3, PAX6, FOXC1, FOXE3, LMX1B and MAF. These specific gene regulatory networks are involved in tissue developments and include many transcription factors and molecular signals. The PAX6 is the most important eye development regulatory in a different organisms [6-8]. Numerous studies have noted that TM was abnormally formed in PITX2 and FOXC1 mice [9–12]. The LMX1B gene was shown to have an important role into the dysgenesis of the TM [13]. The heterozygous deficiency of BMP4 may cause an absent or hypo plastic TM or Schlemm's canal [14].

Functions and biological features of TM cells

TM cells constitute the proximal portion of the aqueous humor outflow pathway. To assure the effective outflow resistance regulation, the TM tissue has an important function of biological filter self-cleaning, intercepting cellular debris and reducing the Reactive Oxygen Species (ROS). The TM cells have a macrophage-like activity to eliminate the cellular debris derived from the pigmented epithelia. The TM cells integrity is important for the regulation and the maintenance of homeostatic IOP. The TM cells dysfunction may cause an extra resistance that generates an IOP elevation [15].

After dexamethasone treatment the expression of myocilin by TM cells increases. The myocilin expression plays an important role in glucocorticoid-induced ocular hypertension [16-18]. Also the platelet-derived growth factor may increase cells division in TM. Besides, it enhances the phagocytic activity and promotes Extra-Cellular Matrix (ECM) secretion [19]. On the contrary, TM cells growth can be inhibited by the vascular endothelial cell growth factor [20].

TM cells loss and glaucoma

The TM cells decrease with age. This cells reduction is associated with glaucoma. Also the accumulation of ECM is associated with gap junction alteration and leading to TM cells death and IOP elevation. Moreover, the TM cells present damages probably caused by ROS [21,22]. This causes a diminished ability to drain humor aqueous.

Evidence of therapeutic implications for TM stem-cells

In 1982, unusual cells population located just beneath the Schwalbe's line in Rhesus monkeys was discovered by Raviola [23]. Afterwards, an increased TM cell division after Argon Laser Trabeculoplasty (ALT) in the anterior non-filtering portion of the TM [24].

Gonzalez, et al. noted that cultured TM cells can form the free-floating neuro spheres. This function is associated with neural stem cells. When the TM free-floating spheres were incubated, they evolved into cells morphologically indistinguishable from cultured TM cells. This discover,

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indicating the possibility that they might differentiate spontaneously into TM cells [25].

The stem cells therapy can potentially restore the TM function and protect the optic nerve from the damage [26]. Replacing the damaged TM cells with healthy stem cells may restore the micro environment of filtering structures. This could trigger a reparative proliferation of stem cells and a restoration of the physiological aqueous outflow with a IOP reduction.

Du, et al. described the isolation of a stem cells population from human TM. This cells population in culture displaying homogeneous antigenic markers characterized for mesenchymal stem cells and expressing gene products associated with pluripotent stem cells. These cells are capable of differentiating into TM cells with TM markers [27,28].

Zhu, et al. demonstrate that iPSC can be induced to differentiate into a cell type that resembles to TM cells (iPSC-TM), The iPSC-TM responds to glucocorticoids exposure with myocilin secretion. For this purpose mouse iPSC-TM cells were induced from iPSC derived from fibroblasts isolated from transgenic animals. The data demonstrate that intraocular injection of iPSC-TM prevents the IOP elevation, the aqueous humor outflow reduction and results in preservation of RGC density in vivo mice models [29]. Moreover, Abu-Hassan, et al. observed that iPSC-TM cells can restore IOP in a human anterior segment ex vivo model [30].

CONCLUSION

The evidence reveals that there is a stem-like cells population located in the Schwalbe's ring. The increased TM cells division after ALT suggested the repopulation of the TM by stimulating cell division may restore the IOP. Recent progress in stem cell research provides an optimistic prospect on their use in regenerative medicine and tissue engineering.

CONFLICT OF INTEREST

Enzo M. Vingolo, Ayoub Chabib, declares that they have no conflict of interest.

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