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Major review

Stem cell therapy for glaucoma: Science or snake oil?

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ABSTRACT

In recent years there has been substantial progress in developing stem cell treatments for glaucoma. As a downstream approach that targets the underlying susceptibility of retinal ganglion and trabecular meshwork cells, stem cell therapy has the potential to both replace lost, and protect damaged, cells by secreting neurotrophic factors. A variety of sources, including embryonic cells, adult cells derived from the central nervous system, and induced pluripotent stem cells show promise as therapeutic approaches. Even though safety concerns and ethical controversies have limited clinical implementation, some institutions have already commercialized stem cell therapy and are using direct-to-consumer advertising to attract patients with glaucoma. We review the progress of stem cell therapy and its current commercial availability.

1. Introduction

Glaucoma is a chronic neurodegenerative disorder of the optic nerve that results in optic nerve cupping and visual loss. Pathological hallmarks include the degeneration of retinal ganglion cells (RGCs) and malfunction of the trabecular meshwork (TM). Current clinical management focuses on reducing intraocular pressure, but this often fails to prevent disease progression.[72] Many are now focusing research efforts on the development of downstream therapies that target the underlying susceptibility of RGCs and TM cells to degeneration.[22] Since Tansley first used immature tissue for retinal replacement,[124] others have investigated the possibility of replacing RGCs, photoreceptors, retinal pigment epithelium, and TM cells with stem cells.[13,43,81,132] Although disagreements persist regarding the appropriate use and safety of this technology, some institutions have already commercialized stem cell therapy for glaucoma. Therefore, both physicians and patients must know the potential benefits and risks of these new technologies at their current stage of development. We review the progress in stem cell therapy for glaucoma and discuss its current commercial availability.

2. Stem cell therapy for optic nerve degeneration

The irreversible nature of RGC loss in glaucoma has spurred interest in techniques to protect existing cells and regenerate new cells. Stem cells could become the ideal source for

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cell-based therapies in glaucoma because of their capacity for self-renewal and their potential to differentiate into many types of adult cells. Although cells that fulfill all these criteria are not yet available, current studies have identified cells that possess components of these advantages. Figure 1 presented by Dahlmann-Noor et al displays sources of stem and progenitor cells for retinal cell replacement. Figure 2 shows the stem cell derivations as described in this section.

2.1. *Potential stem cell resources*

2.1.1. *Embryonic stem cells*

2.1.1.1. *Stem cells derived from blastocysts*. Embryonic stem (ES) cells, derived from the inner cell mass of blastocyst-stage embryos,[110,64] as well as the closely related embryonic germ cells derived from the primordial germ cells in fetal tissues, were the first cell types identified as possible sources of stem cell therapy.[83] Both cell types are pluripotent and demonstrate germline transmission in experimentally produced chimeras. Most investigations on ocular disease have used ES cells derived from animals such as rats and monkeys.[87,109,138] For example, Meyer et al found that implanted mouse ES cells could incorporate into the different layers of the retina. These ES cells expressed calretinin, a ganglion cell marker, and enhanced the survival of host retinal neurons. These findings suggest that ES cells might be able to delay the progression of optic nerve degeneration in glaucoma.[87]

Investigators have also investigated human ES cell lines, with promising results. Human ES cells are stable, have a remarkable proliferative capacity, and can form the derivatives of three embryonic germ layers even after prolonged culture. Hambright et al demonstrated that retinal progenitor cells derived from U.S. National Institutes of Health–maintained human ES cells can integrate into the RGC layer of mice, stirring interest in their potential to provide long-term neuroprotection in glaucoma.[49]

2.1.1.2. *Retinal stem cells derived from the fetal retina*. Retinal stem and progenitor cells isolated from the dissociated embryonic or neonatal retina[2] are another potential source of regenerative tissue. This cell-based strategy is attractive in that its homogeneity theoretically may reduce the risk of rejection. A single fetal eye can also yield a considerable number of stem cells.

Researchers have studied transplantation using fetal retinal tissues, including the entire retinal sheet, in animals including rats, rabbits, monkeys, and pigs. Several groups have reported that these grafts can successfully differentiate into photoreceptors.[31,76,78,113] Other researchers have demonstrated spontaneous ganglion cell activity after transplantation of neural fetal tissue in a mouse with retinal degeneration, a result that may be due to partial functional integration between the graft and host retinae.[103,104] Other studies of humans with retinitis pigmentosa have, however, demonstrated no apparent visual improvement after transplantation, a result that may the result of failure to achieve long-term survival and also the use of a highly inefficient transplantation method.[105,15]

As with ES cells, transplanted fetal retina stem cells may also have rescue effects on damaged host cells.[42] A recent study demonstrated that embryonic retinal cells from mid- to late-developmental stages transplanted into chicken eyes could effectively promote the survival of colchicine-damaged RGCs.[120] This finding led the authors to propose that this type of cell has the potential to not only replace the degenerating retina, but also to provide neuroprotection for the surviving RGCs. Further investigation will be needed to determine the particular stage of development at which these cells will work as expected.

2.1.2. *Adult tissue-derived stem cells*

2.1.2.1. *Retinal stem cells derived from the ciliary epithelium*. Traditionally, the adult mammalian eye has been assumed devoid of retinal stem cells and incapable of substantial neural regeneration.[135] Later, Amato et al discovered that in some vertebrates stem cells located in the peripheral margin of the neural retina enable the formation of new retinal neurons throughout life.[7] This area, known as the ciliary marginal

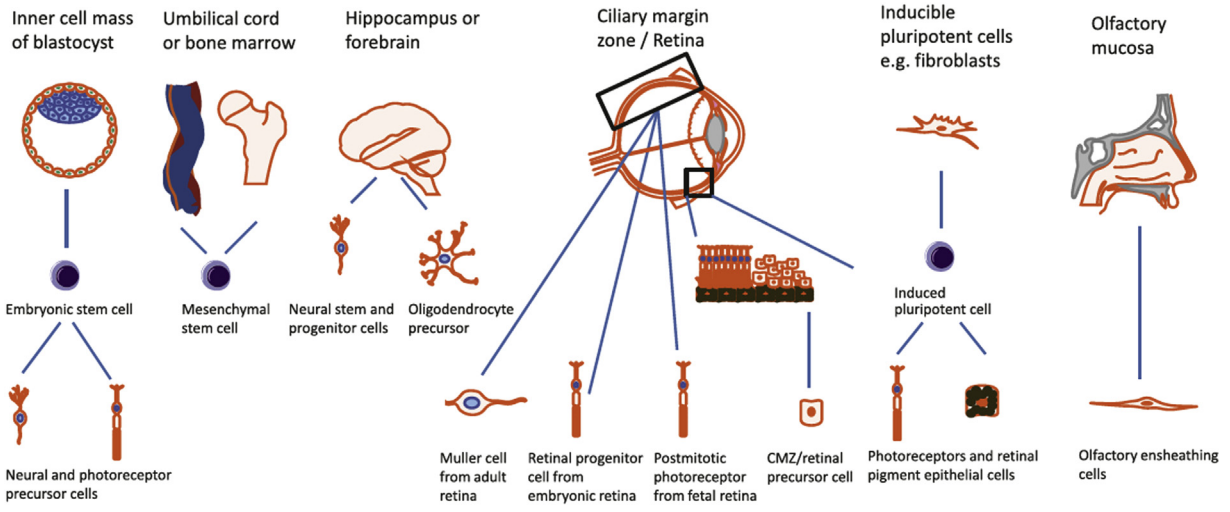

Fig. 1 – Sources of stem and progenitor cells for retinal cell replacement. (Reprinted from Dahlmann-Noor et al[27] with permission of Elsevier).