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Cell Replacement in Optic Neuropathy

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Introduction

Glaucoma is a leading cause of blindness worldwide, with an estimated 64 million affected worldwide in 2013 and a projected 111 million by 2040 [1]. Retinal Ganglion Cells (RGCs), which serve as the communicators between the photosensitive retina and the brain, are lost irreversibly in optic neuropathies such as glaucoma. Early in glaucoma, while most RGCs remain viable, neuroprotective agents might slow disease progression modestly [2]. Since axon damage doesn't necessitate an RGC's death immediately, early detection might enable a neuroprotective treatment, and maybe a regenerative one, that encourages axon growth of existing RGC somas. Mitigating vision loss and finding better biomarkers are essential to clinical efforts, but restoring even minimal losses remains a challenge.

RGCs, like other CNS-derived neurons, exhibit minimal, if any, axon regenerative capacities in adult mammals [3], though the understanding of underlying molecular mechanisms is not complete. There is developmental evidence that both intrinsic and extrinsic factors contribute to the observed loss of CNS regenerative capacity[4,5]. Transcription factors necessary for retinal development include Pax6, Math5, and recently Sox4 and Sox11 [6]. In addition to developmental changes, the injury that causes degeneration also contributes to an inhibitory environment that suppresses axon regeneration, such as glial scar formation [5].

RGC Isolation and Culture

To investigate the fundamental questions of basic neuron biology behind axon and RGC regeneration, a protocol for primary RGC isolation from rodents was developed [7]. The immunopanning technique is based on a Thy1 surface marker that is found on RGCs [7]. The technique is robust enough to work on tissue derived from various developmental time points while providing viable RGCs for *in vivo* transplantation. Alternatively, the RGC cell line RGC-5 was widely used for research; however, there are concerns about its origin and nature [8]. To further investigate mechanisms of RGC degeneration and regeneration in animals, the optic nerve crush (ONC) technique is commonly used as an animal model of injury. Upon ONC, axons exhibit degeneration immediately and RGC death follows soon [9]. It is assumed that the basic mechanisms of neurodegeneration are largely the same regardless of the source of injury; however some researchers choose to study ischemic or glaucomatous models of axon degeneration as well [10]. Up to date, many gene therapies such as PTEN [11] and Sox11 [12] showed very promising results for ON regeneration.

RGC Replacement

How can exogenous RGCs be coaxed to integrate into a host retina? *Ex vivo* transplantation studies have demonstrated a capacity for embryonic and postnatal RGCs to integrate to the appropriate retinal layer, while establishing connections [13]. Some success has been reported with the intravitreal injection of RGCs purified by immunopanning [14]. Importantly, these transplanted cells show ability to navigate axons through the optic nerve head and reach normal synaptic targets such as the lateral geniculate nucleus (LGN) as well as the superior colliculus, while maintaining their mature electrophysiological properties [14]. While some success has been shown, there are limitations in cell viability and integration, not to mention the source of cells for future therapies.

Improving RGC Replacement with Stem Cells

Stem cells are versatile, and can be utilized to generate the pool of cells for transplantation and to increase transplanted cell viability of donor RGCs [15]. Co-injection of stem cells along with RGCs is shown to promote cell viability by providing trophic support for the RGCs [15]. Pro-survival support in the form of secreted growth factors can come from neighboring stem cells, but also by simply adding the appropriate molecules provided the correct factors and relative concentrations have been fully worked out.

The precise differentiation of RGCs is not yet perfected, though RGC-like cells have been reported by a few different

protocols [16]. Molecular markers used for identifying RGCs include βIII-Tubulin, RBPMS, and BRN3a/b isoforms [17]. Within differentiating RGC stem cell pools, RGC marker-expressing cells are usually the minority cell type, scattered among other retinal cell types, but heterogeneous populations could be enriched using Thy-1-based techniques, such as MACS, which uses a magnetic Thy-1 detecting particle. Recently, it has been shown that overexpression of SoxC genes promotes RGCs differentiation from human induced Pluripotent Stem Cells (hiPSCs) (Figure 1) [6]. Basic mechanisms of the developmental program of RGCs remain to be discovered that would enable accurate and efficient differentiation from stem cells.

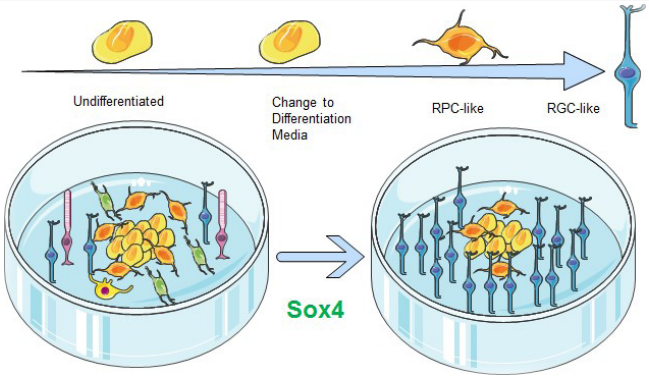

Figure 1: Simplified schematic of differentiation from stem cells. Current methods yield population of mixed cell types, but taking advantage of the SoxC family of genes might lead to a higher percentage of RGCs.

Transplantation of differentiated RGCs might not be optimal for their integration and therefore, different developmental stages of cells could be used, perhaps with supporting cells. Retinal progenitor cells (RPCs) have shown to be effective in replacing degenerated photoreceptors in rats [18] as well as in combination with human mesenchymal stem cells [19]. Similar results might be possible for RGCs, but that remains to be studied (Figure 2).

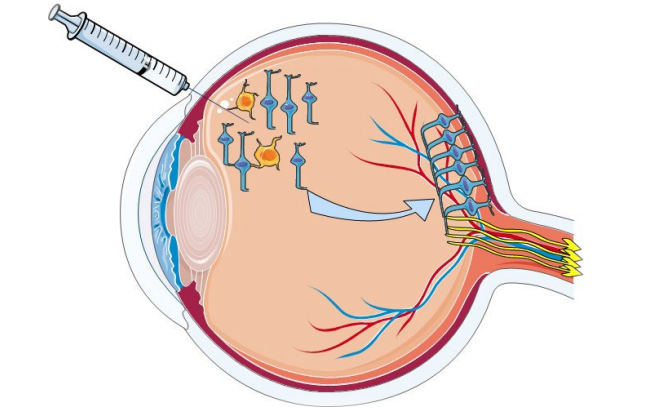

Figure 2: RGC-like cells injected intravitreally integrate into the retina more readily with injection of immature cells. Eventually forming synapses with cortical targets.

While hope for a cell-replacement therapy is high, the aforementioned obstacles remain to be thoroughly examined. Though exciting, we must proceed carefully in order to reap the benefits with clinical endeavors. The basic idea is promising but further study is required to investigate the capacity of RGCs, once transplanted, to reform the complex circuitry necessary to enable vision

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