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Mini Review

Signaling Pathways in Retinal Regeneration: A Brief Review

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Abstract

Hundreds of millions of people suffer from retinal degenerative diseases resulting in varying degrees of vision loss. The most common among these diseases are age-related macular degeneration (AMD) and retinitis pigmentosa (RP). In these conditions, the retina gets damaged that lead to loss of vision and/or blindness. Several studies have highlighted deriving the retinal cells in animal models as well as in culture dish using a defined protocol. These studies have documented improved vision in the mouse models. However, the extent of restoring the vision is far from complete. Additional studies will be needed to improve the degree of vision restoration. In this brief review, I will summarize the advancement and molecular networks associated with retinal degeneration and regeneration.

Keywords: *Retina; Retinal degeneration; Age-related Macular Degeneration; Signaling Pathways; Regeneration*

Abbreviations

AMD: Age-related Macular Degeneration; RP: Retinitis Pigmentosa; hiPSCs: Human-induced Pluripotent Stem Cells; ESCs: Embryonic Stem Cells; RPE: Retinal Pigment Epithelium

Retina is one of the complex structures of the eye. The retina consists of multiple different type of cells including, Photoreceptors (rods and cones), Bipolar cell, Retinal ganglion cell, Horizontal cell, Amacrine cell and Retinal pigment epithelium (RPE) [1]. In the conditions of retinal degeneration such as AMD, one or more types of cells are progressively lost leading to blurred vision or blindness [2]. The primary site of AMD impact is the macular region of retina, and is characterized by the presence of drusen, hyperplasia of the RPE, choroidal new vessels [2].

These are irreversible in nature and generally results in damaged retina permanently. Whether it is possible to regenerate the retina completely remains an unanswered problem, however, a significant progress has been made to repair and regenerate the retina in mammals. Studies related to restore the vision by drug or promoting retinal regeneration have advanced tremendously in the past decade or so [3]. Recent study by Berry., *et al.* have shown that injection of genes for a light-sensitive receptor led to improved vision in the completely blind mice [4]. Transplantation of photoreceptors derived from stem cells resulted in improved light responses and with RPE cells could restore vision to some extent [5]. These studies emphasize the need for finding new ways to improve vision in blind people. Methods such as viral mediated expression of microbial opsins or optogenetic tools could be helpful to restore vision in blind mouse model, however, a further improvement in the methodologies or therapeutic interventions or reagents are necessary to prevent the possibilities of irreversible side effects as well as other complication. Similarly, studies from the laboratory of Dr. Reh have shown that it is possible to induce proliferation and transdifferentiation of muller glial cells to generate neurons [6]. Muller glial cells are intrinsic to the retina which normally provide architectural support and have protective and waste-disposal functions [6]. Several studies have indicated

that these glias can be stimulated to give rise to neurons in various vertebral species [6,7]. But these new neurons needed to be integrated into the existing neuronal circuits, and not fully functional photoreceptors. How to generate a highly differentiated and a more mature photoreceptor as well as other cell types remains an unanswered question. The key to harness the neurogenic potential of glia cells and their integration into the existing network is to identify factors such as secreted molecules, signaling pathways and transcriptional networks that are involved in de-differentiation, transdifferentiation, proliferation and neurogenesis are urgently needed.

In contrast to mammals, lower vertebrates such amphibian and zebrafish have the tremendous ability to regenerate multiple tissues including retina following injury [8-10]. Studies suggest that these regenerative organisms have an inherent ability to induce dedifferentiation of the mature cells and help facilitate tissue regeneration following injury [11,12]. In the adult newt, retinal injury results in detachment of RPE cells, proliferate and give rise two rudimentary layers, pro-neural retina and pro-RPE cells [13]. The pro-RPE cells exit cell cycle and mature within 28 days post-injury, while the pro-neural retina cells continue to proliferate and undergo neuronal cell differentiation and reconstruction of the neural network to complete the regeneration steps [13]. These studies suggest that the retina is completely regenerated from the pre-existing RPE cells in the newt. During the regeneration process, the RPE cells undergo de-differentiation/trans-differentiation process after receiving signals via growth factors. This leads to intense proliferation resulting in the formation of multilayered neuroepithelium and eventually forming the neural retina [14]. Similarly, adult zebrafish could also mount retinal regeneration, however, the cell sources of regeneration are different as compared to adult newt [15]. The fish eye grows throughout life and therefore precursors cells are the major source for regeneration of the outer and inner nuclear layers following injury to retina [15]. Regeneration related studies support the notion that tissue injury and the regenerative response are associated with the activation of embryonic regulatory networks [16]. A number of signaling pathways and transcription factors are shown to be involved in this process. In the zebrafish system, sonic hedgehog (Shh) signaling play an important role in reprogramming the Muller glia cells through microRNA dependent mechanism [17]. A recent study by Mizuno., *et al.* have shown that MEK-ERK signaling pathway is the key to activate RPE cells to proliferate and inhibition of this pathway led to impaired regeneration in the newt [18]. The role of Shh, FGF, MEK-ERK signaling pathways are shown to be involved in the regeneration of other tissues in zebrafish and newt [16-18]. These studies suggest an existence of a common regulatory mechanism in the regulation of regenerative process. Transcription factor, Pax6, has been shown to be involved in the process of retinal regeneration following injury in the newt. Genetic loss of Pax6 in the adult newt resulted in absence of retinal regeneration similar to mammalian system [19]. Likewise, expression of SoxC family of transcriptional networks are shown to have critical functions during retinal and optic nerve regeneration [20]. Although significant advancements have been made in the field of regenerative medicine using these model organisms, the networks which coordinate the repair and regeneration of tissues are incompletely defined. Moreover, whether activation such program will boost the retinal regeneration in mammals is urgently needed.

Recent advancement in the field of embryonic stem cell technology and induced-pluripotent stem cells (iPSCs) strategies have provided new hope for the patients with AMD and RP [21,22]. Studies from multiple laboratory have shown that stem cell derived-RPE cells could be successfully used to improve or restore the vision [21]. Several signaling pathways such as BMP4 inhibition along with ERK and retinoic acid have been shown to promote RPE growth in the *in vitro* condition [23]. Similarly, small molecules to activate IGF and FGF signaling has been shown to give rise to photoreceptors following differentiation of hiPSCs [24]. Differentiation protocol of the stem cells into disease-relevant cell types are required to improve the efficiency and their use in clinical settings. Although iPSC technology has revolutionized the field of regenerative medicine, several other outstanding questions such as 1) identification of altered networks as well as genetic mutation by next-generation sequencing; 2) drug screening to inhibit the disease progress *in vitro*; 3) clinically relevant cell types for transplantation therapies, could be explored.

Conclusion

In summary, a significant progress has been made for the treatment of AMD and RP to improve their vision, however, identification of additional networks and pathways will be essential to successfully translate for clinical trials. At the same time, several challenges need

to be addressed including, cell engraftment, survival, method of gene/cell delivery, immunological response prior to implementation for treating patients with AMD or RP. In light of that, several phase I/II clinical trials are underway and found to have promising outcome, therefore, provide great hope for the treatment of these diseases [21,22].

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