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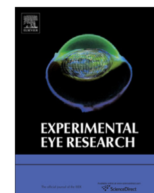

Human embryonic stem cell applications for retinal degenerations

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ABSTRACT

Loss of vision in severe retinal degenerations often is a result of photoreceptor cell or retinal pigment epithelial cell death or dysfunction. Cell replacement therapy has the potential to restore useful vision for these individuals especially after they have lost most or all of their light-sensing cells in the eye. A reliable, well-characterized source of retinal cells will be needed for replacement purposes. Human embryonic stem cells (ES cells) can provide an unlimited source of replacement retinal cells to take over the function of lost cells in the eye. The author's intent for this review is to provide an historical overview of the field of embryonic stem cells with relation to the retina. The review will provide a quick primer on key pathways involved in the development of the neural retina and RPE followed by a discussion of the various protocols out in the literature for generating these cells from non-human and human embryonic stem cells and end with in vivo application of ES cell-derived photoreceptors and RPE cells.

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1. Introduction

The retina is the light-sensing inner-most layer in the eye. The main cells involved in light-perception are the photoreceptor cells lining the back of the neural retina. Additionally, phototransduction requires active participation from the pigment epithelial cells overlying the photoreceptors. Any dysfunction of these two cell-types can lead to varying degrees of visual loss. Inherited and acquired retinal degenerations affect millions of people in the US and abroad. There are no effective therapies for most of these patients. Discovery of human embryonic stem cells in 1998 has revolutionized the way we think about cell-replacement therapy. Embryonic stem cells have the potential to provide an unrestricted source of new cells for patients with any degenerative condition. In the past few years, a number of groups have shown the potential to efficiently guide the cells to various lineages including photoreceptors and retinal pigment epithelial cells. In this review, we will cover some basics on embryonic stem cells and eye development. We will discuss how knowledge of basic development can be used to guide efficient protocols. Embryonic stem cells can in turn allow us to better understand some early human development events which are otherwise difficult to study. In the end, we will show the translational value of embryonic stem cells in eye diseases.

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2. Embryonic stem cells

Embryonic stem cells are undifferentiated cells derived from the inner cell mass of the blastocyst. These cells can self-renew indefinitely under appropriate culture conditions while still maintaining pluripotency i.e. the ability to differentiate into most, if not all, cells in the body. Embryonic stem cells provide an attractive potential towards cell and tissue engineering to generate replacement cells for various degenerative conditions including age-related macular degeneration, diabetes mellitus, cardiovascular disorders, etc. Mouse embryonic stem cells were first isolated by two independent groups in 1981 (Evans and Kaufman, 1981; Martin, 1981). In 1998, James Thomson's group at Wisconsin first derived human embryonic stem cells (Thomson et al., 1998). Since then, a number of labs all around the world have been able to generate new stem cell lines. The current list of NIH approved human embryonic stem cell lines is maintained at the NIH Stem Cell registry (http://grants.nih.gov/stem_cells/registry/current.htm). A number of these lines are also available in GMP-grade from sources including Wicell, City of Hope and Biotime for clinical applications.

ES cells can be maintained in an undifferentiated state using mouse or human fibroblasts or conditioned media from these cells. There has been a recent push towards use of xeno-free chemically defined media. The first such media with good results was the TESR2 media by Stem Cell Technologies. Recently, it has been shown that a minimal chemically defined media using just 8 culture media components can be used to maintain the undifferentiated state of human ES cells (Chen et al., 2011). The key inducers of

pluripotency in the media include very high-levels of TGF-β (or Nodal) and bFGF. Defined xeno-free media have a very important role in GMP manufacture of cells allowing easier approval of cell products at the Food and Drug Administration (FDA). It remains to be seen if this minimal media affects specific protocols or induction efficiencies. Undifferentiated ES cells express a unique set of markers. Human ES cells are characterized by expression of a group of the cell surface markers Tra-1-60 (Tumor-related antigen), Tra-1-81, SSEA-3 (stage-specific embryonic antigen) and SSEA-4 and a number of transcription factors including Oct4, Nanog, and Sox2. These genes have been used now to induce pluripotency in fibroblasts and other peripheral cells in vitro (Okita et al., 2007; Yu et al., 2007). Another cell with similar characteristics are induced pluripotent stem cells (iPS cells). These are cells derived by reprogramming peripheral cells such as fibroblasts and lymphoblasts to a pluripotent state. A companion article in this issue discusses their potential for retinal differentiation and use in disease modeling studies.

The potential of these cells in treatment of various disorders is unlimited. Due to their property of pluripotency, they can be guided to differentiate into any cell or tissue in the body. This will allow us to treat any number of degenerative diseases. This review will focus on retinal applications of human embryonic stem cells.

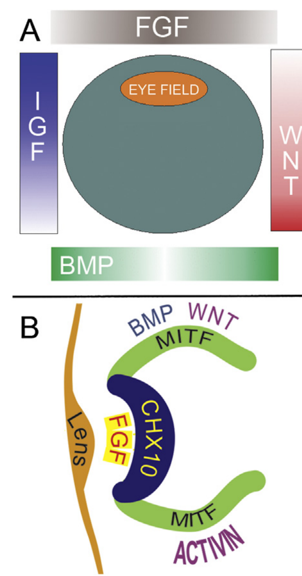

Fig. 1. Morphogens playing a role in eye formation. (A) Early eye-field specification is a result of an interplay between FGF, BMP, Wnt and IGF signaling. (B) Neural retina and RPE fates are induced by secreted morphogens from surrounding microenvironment. FGF from surface ectoderm induces neural retina while WNT, Activin and BMPs from surrounding mesenchyme promote RPE choice.

3. Developmental biology as a guide to retinal specification

In this part of the review, we will summarize the key steps and morphogens involved in eye formation. For a stem cell differentiation protocol, mimicking developmental steps in vitro is bound to generate the purest cultures as has already been shown in multiple protocols (Chen et al., 2012; Laflamme et al., 2007; Shi et al., 2012; Si-Tayeb et al., 2010). Embryonic development proceeds by signals produced by strategically localized organizing centers along the embryo. These signals direct adjacent cell types to differentiate and chose specific lineages. In theory, coordinated use of these morphogens will allow us to specifically generate any tissue in the body from embryonic stem cells. The retina develops as the lateral outpouching from the diencephalic region of the forebrain. Below are described steps in its specification.

The earliest step in this process is the adoption of neuroectodermal identity. This region along the dorsal midline of the embryo forms the neural plate which then undergoes neurulation to form the neural tube. Neural induction is a result of signals from the organizer region in the underlying mesoderm first described in 1938 by Hans Spemann and Hilde Mangold (Spemann, 1938). Numerous studies have shown that the cells of the organizer region secrete BMP antagonists such as noggin, chordin, and follistatin and that these key factors are involved in neural induction (Hemmati-Brivanlou et al., 1994; Lamb et al., 1993; Smith et al., 1993). In the chick model it has been shown that BMP antagonism alone is not sufficient for vertebrate neural induction and that FGF signaling is required as an early step in ectodermal neural induction (Launay et al., 1996).

Anterior specification of the neural ectoderm for head induction is regulated by BMP antagonism in combination with other factors (Fig. 1A). One of key signaling events involved in promoting anterior fates is Wnt inhibition (del Barco Barrantes et al., 2003; Wilson and Houart, 2004). Dickkopf-1 (Dkk1) is a naturally secreted Wnt antagonist from the underlying visceral endoderm involved in anteriorizing the neural ectoderm. Another cell-extrinsic factor found to play a role in head induction is the family of insulin-like growth factors (IGF). Over-expression of insulin-like growth factors in Xenopus embryos has been shown to induce anteriorization of embryos and formation of ectopic eyes (Pera et al., 2001; Richard-Parpaillon et al., 2002). Tyrosine kinase pathways (including FGF and IGF) activate MAP kinase (MAPK) which can phosphorylate the linker region of SMADs (Pera et al., 2003). This inhibits nuclear transport of the SMADs and so inhibits downstream BMP effects, thus promoting neural induction.

In vertebrates, the eyes appear as a bilateral evagination of the diencephalon. The eye-field appears first in the form of the optic pit. The continued evagination results in the optic vesicles which come into close contact with the overlying ectoderm. Interaction between the two tissues induces the formation of the lens and the cornea in the overlying ectoderm. The head of the optic vesicle then undergoes an invagination to form a bi-layered optic cup. The outer layer of the cup gives rise to the retinal pigment epithelium while the inner layer undergoes proliferation to form the multilayered neural retina which consists of the various retinal neuronal cells and the Müller glia. The order of the generation of the retinal neurons is relatively conserved (Sidman, 1961). Ganglion cells are the first to differentiate. This is followed by the cone photoreceptors and the horizontal cells, then the amacrine cells and the final wave of differentiation consists of the rod photoreceptors, the bipolar cells and finally the Müller glia.

The presumptive eye field is specified prior to the development of the optic pits in the diencephalon. This eye field specification in the neural plate is caused by a group of transcription factors expressed in this region called the eye field transcription factors (EFTFs). These include Pax6, Six3, Lhx2 and Rx/Rax. Co-expression of these genes specifies the eye in diencephalon. While we know much about the EFTFs and early eye development, we know relatively little about the extracellular signaling molecules that regulate them. Various groups have looked into the role of Wnt signaling in the initiation and regulation of the eye fields (Rasmussen et al., 2001; Cavodeassi et al., 2005). Ligands and receptors for Wnt signaling, both canonical, ß-catenin-dependent pathway and non-canonical, ß-catenin-independent pathway, are expressed at the site of the prospective eye field. Wnt1 or Wnt8b activate the canonical Wnt-β-catenin pathway and cause a reduction in the eye fields when overexpressed in Xenopus embryos by suppressing Rx and Six3 expression. On the other hand, Wnt11 activates the non-canonical pathway, and results in larger eyes in Xenopus when

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