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Using human induced pluripotent stem cells to treat retinal disease

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ABSTRACT

The eye is an ideal target for exploiting the potential of human induced pluripotent stem cell (hiPSC) technology in order to understand disease pathways and explore novel therapeutic strategies for inherited retinal disease. The aim of this article is to map the pathway from state-of-the art laboratory-based discoveries to realising the translational potential of this emerging technique. We describe the relevance and routes to establishing hiPSCs in selected models of human retinal disease. Additionally, we define pathways for applying hiPSC technology in treating currently incurable, progressive and blinding retinal disease.

Contents

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1. Introduction

Stem cells have the ability to self-renew and the capacity to differentiate into other more specialised cell types. Cell potency describes the general ability of a cell to differentiate into other cells. During human development, one of the first stem cells to arise is the human embryonic stem cell (hESC) which can be found in the inner cell mass of the developing embryo. The embryonic stem cell has the potential to differentiate into cells from the three germ layers: endoderm, mesoderm and neuroectoderm. Consequently the hESC is described as pluripotent. Other stem cells emerge later during development which display a progressively more restricted phenotypic range and can be considered tissue or organ-specific. In adults, endogenous tissue-specific stem cells are multipotent with a more restricted differentiation repertoire normally confined to those cells of the tissue of origin.

James Thomson reported successful isolation and maintenance of hESCs in 1998 (Thomson et al., 1998). HESCs have an infinite proliferation capacity and offered the opportunity to provide a virtually unlimited supply of human cells for clinical translation research. However, ethical concerns regarding the derivation of cells from the inner cell mass of developing blastocysts led to a drive to investigate alternative methods of deriving pluripotent stem cells (Ramalho-Santos, 2011). The methodology that eventually emerged to produce pluripotent stem cells was developed on the background of several breakthroughs in cell biology. Sir John Gurdon first demonstrated the cloning of an adult frog from the transfer of adult intestinal cells into an enucleated *Xenopus laevis* ovum (Gurdon, 1962). This illustrated that adult cell fate was not restricted and that under appropriate conditions differentiated somatic cells could be made pluripotent. Similar nuclear transfer into mammalian cells was more problematic due to the smaller size of mammalian eggs. Although successful mammalian nuclear transfer was later demonstrated using embryonic cells nuclear transfer cloned animals did not develop from differentiated cell nuclei (Cheong et al., 1993; Prather et al., 1989). Wilmut et al. demonstrated that these difficulties could be overcome by nuclear transfer into early embryos. Using this technique an adult sheep was cloned by nuclear transfer from an adult sheep mammary gland cell into a day 9 embryo (Wilmut et al., 1997). This demonstrated that specific factors exogenously expressed by developing embryos can return somatic cells to a pluripotent state. In 2006, Shinya Yamanaka isolated four transcription factors that when expressed exogenously induced the formation of pluripotent cells from somatic cells. This was first confirmed using murine and subsequently human somatic cells (Takahashi et al., 2007; Takahashi and Yamanaka, 2006). The process of generating pluripotent cells from somatic cells was termed "reprogramming" and the resultant cells were called induced pluripotent stem cells (iPSCs). iPSCs shared properties with hESCs including the ability to self-renew and to be differentiated into the three germ layers.

The clinical translation of basic scientific discoveries to treatments has been made a priority of national funding bodies worldwide (McLellan, 2003; MRC, 2013). Ophthalmic research has been at the forefront of the drive for clinical translation. The eye has several properties that are advantageous as an organ suitable for regenerative approaches including relative ease of accessibility, immune privilege and relative isolation from other body systems. HiPSC technology was developed relatively recently on the foundation research in several fields of basic science, the technology is nearing the point of full clinical translation. Recently, hiPSC derived retinal pigment epithelium (hiPSC-RPE) have been approved for use in patient safety trials for the treatment of macular degeneration (Cyranoski, 2013). This article aims to provide a background into the current state of research in this rapidly evolving field with a focus on the cells of the outer retina. We provide a summary for planning hiPSC studies, describing hurdles to clinical translation as well as highlighting future directions of research using hiPSC-derived retinal cells.

2. Basic principles of human somatic cell reprogramming

Complete reprogramming involves the replacement of the tissue specific donor cell transcription factors with those that will induce pluripotency. Additionally, reprogramming requires the epigenetic stabilisation of the new machinery. The original reprogramming strategies have provided valuable insight into the mechanisms involved. A variety of different approaches have now been established to achieve reprogramming since the original procedures described by Yamanaka and Thomson. However, as our knowledge has progressed, the criteria for an ideal protocol have become clearer. The characteristics of an ideal protocol include:

1. Free from Variation
2. Free from Integration
3. Efficient
4. Fast
5. Frugal

2.1. Protocols

In the original reprogramming experiments two sets of transcription factors were identified concurrently but independently by Yamanaka and colleagues in Kyoto, Japan (Takahashi et al., 2007) and Thomson in Madison, Wisconsin, USA (Yu et al., 2007) (Table 1). Both groups used OCT4 and SOX2, but they included variations in other factors. Yamanaka used KLF4 and c-MYC whereas Thomson used NANOG and LIN28. The groups both used retroviral vectors, but whilst Yamanaka and colleagues used the pMXs plasmid back-bone derived from Moloney murine leukaemia virus, Thomson used lentiviral vectors. Lentiviral vectors have the advantage of being able to integrate in non-dividing cells. Lentiviral mediated insertion is still the most frequently used