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Iris pigment epithelial cell transplantation for degenerative retinal diseases

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Abstract

The transplantation of different types of cells into the eye to treat retinal diseases has advanced in the past 20 years. One of the types of cells used for transplantation is the iris pigment epithelial (IPE) cell, because autologous IPE cells are easily obtained and their properties are similar to those of retinal pigment epithelial (RPE) cells and retinal cells. IPE cells are transplanted as; freshly isolated or cultured cells to replace defective or diseased RPE cells, genetically modified IPE cells for delivering target molecules to the retina or RPE, and retinal progenitor cells. IPE cells have also been transplanted for non-retinal disorders.

The survival of the transplanted cells in the host is an important factor for the success of transplantation. Autologous IPE cells have been found in the transplanted subretinal space and were able to phagocytose rod outer segments even 6 months after transplantation. Allogeneic and xenogenic cells will not remain in the region longer than autologous cells. Allogenic cells transplanted into the subretinal space are rejected in humans. Thus, we have transplanted cultured autologous IPE cells in 56 patients with age-related macular degeneration. The long-term results (more than 2 years with a maximum of 8 years) showed that the visual acuity (VA) was significantly improved over the pre-transplantation VA, although a slight decrease of VA was observed 2 weeks after the transplantation. One patient showed a vasculitis-like lesion.

IPE cells that were transduced with neurotrophic factors by plasmid or viral vectors have also been transplanted in animals. We have transduced several neurotrophic factor genes into IPE cells with a plasmid vector, adeno-associated virus, or adenovirus. Transplantation of these transduced IPE cells into the subretinal space rescued photoreceptor cells from several types of photoreceptor toxicities. In addition, transduction of a gene into the IPE cells suppressed the systemic dissemination of the viral genome. The neuroprotective effects of the IPE cells were different for the different types of neurotrophic factor, and some of the neurotrophic factors may enhance systemic immune reaction after transplantation.

IPE cells have also been used as retinal progenital cells because they originate from the same cell lines that give rise to the neural retina and RPE cells. The transduction of the photoreceptor-related homeobox gene was reported to induce photoreceptor phenotypes in IPE cells. Furthermore, transplantations of IPE cells have been performed to treat central nervous system disorders. In this review, we summarize recent progress on IPE transplantation.

Keywords: IPE; Transplantation; Retinal degenerative diseases; Age-related macular degeneration; Culture autologous IPE

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1. Introduction

The techniques of transplanting different types of cells have advanced in the past 20 years, and the results have suggested that transplantation may be a useful approach to treat some retinal diseases. The retinal pigment epithelial (RPE) cells are probably the most extensively investigated cells in transplantation experiments, and the Royal College of Surgeon's (RCS) rats the most extensively studied animal model of photoreceptor degeneration. The inherited photoreceptor degeneration in RCS rats results from the inability of the RPE cells to phagocytose rod outer segments (ROSs). Morphological and functional studies have shown that when normal RPE cells are transplanted into the subretinal space of RCS rats, the degeneration of the photoreceptors is delayed (Hammer and Yinon, 1991; Jiang and Hamasaki, 1994; Lavail et al., 1992; Li and Turner, 1991; Sheedlo et al., 1995; Whiteley et al., 1996; Yamamoto et al., 1993). Transplantation of RPE cells has also led to successful results in Rpe65$^{(-/-)}$ mice (Gouras et al., 2002), that are not able to isomerize all-*trans*-retinyl esters to 11-*cis*-retinal in the RPE (Redmond et al., 1998). Xenogenic RPE cells on collagen sheets have been transplanted into the subretinal space or anterior chamber (AC) but the transplantation resulted in a decrease in the amplitude of the electroretinogram (ERG) (Bhatt et al., 1994). However, in another study, human RPE xenografts have rescued the photoreceptors of RCS rats from degeneration (Coffey et al., 2002; Wang et al., 2005).

In these studies, the survival of the transplanted cells at the transplanted site was found to be one of the more important factors for the success of the transplantation (Abe et al., 2005). Because of the immunological rejection of the transplanted cells, immunosuppressants, such as cyclosporine, have been used to prevent the rejection of transplanted xenogenic cells (Del Priore et al., 2003; DiLoreto et al., 1996; Lai et al., 2000). However, cyclosporine did not prevent the rejection of allograft RPE cells transplanted from pigmented (brown) to albino rabbits (Crafoord et al., 2000). If the RPE cells from pigment rabbits were activated by IFN-gamma, the transplanted cells showed signs of rejection (Kohen et al., 1997). Fealy et al. (1995) reported that there was evidence of rejection, preservation injury, and mild inflammation with increased amounts of inflammatory cytokines in allograft transplantations.

In our laboratory, transplantation of allogenic rat iris pigment epithelial (IPE) cells into the subretinal space led to the expression of cytokine genes in the transplanted area. The cytokines were similar to those enhanced by the immune system following organ transplantation (Abe et al., 1999a). CD4+ T cells play an important role in immunological reactions against the transplantation of allogenic full-thickness mice retina into the vitreous (Anosova et al., 2001). When we transplanted allogenic RPE cells transduced with enhanced green fluorescein protein (eGFP) into the subretinal space of rats, we detected eGFP-expressing cells even 3 months after the