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Stem cell based therapies for age-related macular degeneration: The promises and the challenges

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in developed countries. AMD is classified as either neovascular (NV-AMD) or non-neovascular (NNV-AMD). Cumulative damage to the retinal pigment epithelium, Bruch's membrane, and choriocapillaris leads to dysfunction and loss of RPE cells. This causes degeneration of the overlying photoreceptors and consequential vision loss in advanced NNV-AMD (Geographic Atrophy). In NV-AMD, abnormal growth of capillaries under the retina and RPE, which leads to hemorrhage and fluid leakage, is the main cause of photoreceptor damage. Although a number of drugs (e.g., anti-VEGF) are in use for NV-AMD, there is currently no treatment for advanced NNV-AMD. However, replacing dead or dysfunctional RPE with healthy RPE has been shown to rescue dying photoreceptors and improve vision in animal models of retinal degeneration and possibly in AMD patients. Differentiation of RPE from human embryonic stem cells (hESC-RPE) and from induced pluripotent stem cells (iPSC-RPE) has created a potentially unlimited source for replacing dead or dying RPE. Such cells have been shown to incorporate into the degenerating retina and result in anatomic and functional improvement. However, major ethical, regulatory, safety, and technical challenges have yet to be overcome before stem cell-based therapies can be used in standard treatments. This review outlines the current knowledge surrounding the application of hESC-

Abbreviations: ACT, Advanced Cell Technology; AMD, age-related macular degeneration; APC, antigen processing cell; ARMS2, age-related macular degeneration susceptibility gene 2; ATP, adenosine triphosphate; AR, acute rejection; BCVA, best corrected visual acuity; BM, Bruch's membrane; BMSC, bone mesenchymal stem cell; BrdU, bromodeoxyuridine; bFGF, basic fibroblast growth factor; CETP, cholesterol ester transfer protein; CIRM, California institute for regenerative medicine; CNV, choroidal neovascularization; DHR, delayed hyperacute rejection; EDTA, ethylenediaminetetraacetic acid; ERG, electroretinography; GA, geographic atrophy; GMP, good manufacturing practices; GWAS, genome wide association study; HAR, hyperacute rejection; HRTA1, high temperature required factor A1; HuCNS-SC, Human Central Nervous System Stem Cell; hESC, human embryonic stem cell; IL, interleukin; IFNγ, interferon gamma; iPSC, induced pluripotent stem cell; iPSC-RPE, induced pluripotent stem cell-derived retinal pigment epithelium; KSR, knock down serum replacement; LipC, lipase C; LPCB, London project to cure blindness; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MLR, mixed lymphocyte reaction; MSC, mesenchymal stem cell; NIC, nicotinamide; NV-AMD, neovascular age-related macular degeneration; NNV-AMD, non-neovascular age-related macular degeneration; OCT, optical coherence tomography; OHT, optokinetic head tracking; PBMC, peripheral blood mononuclear cell; PEDF, pigment epithelium derived factor; RPC, retinal progenitor cell; PR, photoreceptor; RPE, retinal pigment epithelium; SC, stem cell; SOD, standard operating procedure; RCS rat, Royal College of Surgeons' rat; RPC, retinal progenitor cell; TGF, transforming growth factor; Treg, regulatory T lymphocyte; hUTC, human umbilical tissue-derived cells; VEGF, vascular endothelial growth factor.

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RPE and iPSC-RPE in AMD. Following an introduction on the pathogenesis and available treatments of AMD, methods to generate stem cell-derived RPE, immune reaction against such cells, and approaches to deliver desired cells into the eye will be explored along with broader issues of efficacy and safety. Lastly, strategies to improve these stem cell-based treatments will be discussed.

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss and inability to read, drive, and perform daily tasks among people 50 years of age and older around the world. In the United States, AMD affects nearly 2 million Americans (Kahn et al., 1977; Ambati et al., 2003; Bressler, 2004; Friedman et al., 2004; Herm, 2008). This number is expected to grow to 3 million by the year 2020 as the number of elderly individuals increases in the U.S. (Friedman et al., 2004). It is estimated that about one third of individuals aged 75 and older suffer from some form of AMD (Zarbin, 2004). While the disease is particularly prevalent in developed countries, especially in individuals with Caucasian ethnicities, it is becoming a global health concern (Ambati et al., 2003) due to increases in life expectancies worldwide, with the number of people becoming blind or losing substantial eyesight because of AMD predicted to increase steeply (Araujo Filho et al., 2008). Additionally, more attention is now being focused on AMD as expectations for a high quality of life, including functions such as driving and reading, increase in communities around the world.

Early AMD is characterized by the thickening of Bruch's Membrane and deposits under the retinal pigment epithelium layer and by pigmentation changes in the macula. More advanced stages of the disease demonstrate either subretinal neovascularization or atrophy of the retina and RPE. Based on the absence or presence of blood vessel growth progressing from the choroidal side towards the retina, the disease is broadly subdivided into non-neovascular and neovascular AMD. Non-neovascular AMD (NNV-AMD), also known as dry AMD, accounts for the majority of AMD cases (approximately 80%). NNV-AMD is clinically identifiable by the presence of basal laminar deposits and drusen under the RPE layer, as well as by changes in RPE pigmentation, as mentioned above. The presence of drusen, in long term, leads to attenuation of the overlying RPE and photoreceptors. In advanced stages of the disease, the drusen may disappear and well demarcated areas of RPE and photoreceptor loss called geographic atrophy (GA) appear in their place (Fig. 1) (Ambati et al., 2003; Ouyang et al., 2013). On the other hand, a subset of patients with drusen progress to the neovascular form of AMD (NV-AMD) (also known as exudative or wet AMD) where defects in the underlying Bruch's membrane (BM) provide access for abnormal capillaries to grow into sub-RPE and subretinal areas. Vision loss in patients with NV-AMD can be sudden and severe and occurs mainly because of fluid leakage or bleeding from highly-permeable subretinal or sub-RPE vascular networks. This less common, but more visually devastating subtype of AMD, accounts for about 20% of patients with AMD (Kahn et al., 1977), but 90% of AMD patients with severe visual loss.

Despite the increasing burden of AMD on the global health economies (Day et al., 2011), there are limited prevention options and no treatments available for patients with NNV-AMD, although effective, but laborious, treatments exist for patients with NV-AMD. Strong evidence shows that lifestyle and dietary modification can slow the progression of early AMD to advanced forms (Clemons et al., 2005; Age-Related Eye Disease Study Research et al., 2007). On the other hand, for NV-AMD, effective treatments are available using anti-vascular endothelial growth factor (anti-VEGF) (Gragoudas et al., 2004) agents, although this typically requires tedious monthly injections. There is also evidence that the underlying atrophic component of AMD still progresses despite using anti-VEGF therapy (Young et al., 2014). So, while anti-VEGF agents have revolutionized the clinical management of NV-AMD diagnosed early in their disease course, many patients with advanced NV-AMD and almost all patients with advanced NNV-AMD continue to lose vision because no treatment option is currently available for them.

Macular translocation surgery (Machemer and Steinhorst, 1993; de Juan et al., 1998; Fujikado et al., 1998; Pieramici et al., 2000) and RPE transplantation surgery (Algvere et al., 1994; Stanga et al., 2002; van Meurs and Van Den Biesen, 2003) have provided compelling evidence that healthy RPE can support photoreceptor survival and visual function in human patients with choroidal neovascularization (CNV) due to AMD and high myopia (Binder et al., 2007). While technical challenges, including proliferative vitreoretinopathy and torsion, have limited the practicality of these surgeries, the attempts were promising, as demonstrated by decreased visual loss rates and even improvement of vision in some patients (Algvere et al., 1997; Stanga et al., 2001; Fujii et al., 2002). This provided proof-of-principle that replacing dead or dying RPE with healthy RPE can rescue vision in patients with advanced AMD. Limited autologous sources of maculae and healthy RPE sheets for transplantation, and the fact that autologous sheets of peripheral RPE would share genetic risks identical to those of the patient's posterior pole RPE cells, have prevented wide acceptance of autologous transplantation surgeries. The search for other sources of healthy RPE has extended to harvesting RPE from fetal or adult donor eye tissue; however, fetal and adult RPE sources are also limited, and harvesting them confers significant technical and ethical challenges.

The study of differentiation of functional RPE and retinal progenitor cells from human pluripotent stem cells in the early 2000s opened a promising approach to generating a virtually unlimited supply of RPE and photoreceptor cells for replacement therapies (Lund et al., 2006). During the last decade, the stem cell-based cellular therapeutics for retinal degenerative diseases have been mainly focused on (1) replacing RPE to maintain the supportive function of the RPE layer, (2) replacement with retinal progenitor cells (RPCs) to regenerate lost retinal elements, including photoreceptors, or (3) combining RPE and RPC replacement in advanced stages where both RPE and retinal elements are lost. Significant research efforts have focused on finding the ideal methods for efficiently deriving RPE and RPC from embryonic and induced pluripotential stem cells, transplanting these cells into the subretinal space, and preventing immune rejection of the transplanted cells. Multiple excellent reviews have discussed hESC-RPE and iPSC-RPE derivation in depth (Blenkinsop et al., 2012; Carr et al., 2013; John et al., 2013; Melville et al., 2013; Ramsden et al., 2013). The aim of this review is to present an up-to-date summary of hESC-RPE and iPSC-RPE derivation with a focused discussion on the technical and biologic challenges of stem cell-derived RPE and RPC transplantation for the treatment of AMD. We begin with a limited review of RPE cell function and the pathogenesis of AMD and its clinical subtypes. We will not discuss the pathogenesis