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Molecular genetics and emerging therapies for retinitis pigmentosa: Basic research and clinical perspectives

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ABSTRACT

Retinitis Pigmentosa (RP) is a hereditary retinopathy that affects about 2.5 million people worldwide. It is characterized with progressive loss of rods and cones and causes severe visual dysfunction and eventual blindness in bilateral eyes. In addition to more than 3000 genetic mutations from about 70 genes, a wide genetic overlap with other types of retinal dystrophies has been reported with RP. This diversity of genetic pathophysiology makes treatment extremely challenging. Although therapeutic attempts have been made using various pharmacologic agents (neurotrophic factors, antioxidants, and anti-apoptotic agents), most are not targeted to the fundamental cause of RP, and their clinical efficacy has not been clearly proven. Current therapies for RP in ongoing or completed clinical trials include gene therapy, cell therapy, and retinal prostheses. Gene therapy, a strategy to correct the genetic defects using viral or non-viral vectors, has the potential to achieve definitive treatment by replacing or silencing a causative gene. Among many clinical trials of gene therapy for hereditary retinal diseases, a phase 3 clinical trial of voretigene neparvovec (AAV2-hRPE65v2, Luxturna) recently showed significant efficacy for RPE65-mediated inherited retinal dystrophy including Leber congenital amaurosis and RP. It is about to be approved as the first ocular gene therapy biologic product. Despite current limitations such as limited target genes and indicated patients, modest efficacy, and the invasive administration method, development in gene editing technology and novel gene delivery carriers make gene therapy a promising therapeutic modality for RP and other hereditary retinal dystrophies in the future.

1. Introduction

Retinal cells are interconnected neuronal cells forming the photosensitive tissue that lines the inner surface of the eye. These cells are responsible for the early stages of visual processing. Retinopathies and resultant retinal dysfunction are common causes of blindness (Jo et al., 2010). Hereditary retinopathy or hereditary retinal dystrophy is one of the blinding retinopathies, and it is characterized by slow and progressive degeneration of the retina (Coco et al., 2009). Most cases are due to mutations in a single gene, representing a significant cause of blindness. These mutations occur mainly in the photoreceptor cells (rods and cones) and, to a lesser extent, in the retinal pigment epithelium (RPE) cells (Trapani et al., 2014). The hereditary retinopathies are classified according to the genetic defect (when identified), the type of inheritance (autosomal dominant, autosomal recessive, or X-linked), the type of visual impairment, the rate of disease progression, and changes on the appearance of ocular fundus examination. Inherited retinal dystrophies can also be classified by the affected cells as: 1. rod-dominant abnormality (rod-cone dystrophy [retinitis pigmentosa]), 2. cone-dominant abnormality (cone or cone-rod dystrophy,

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achromatopsia), 3. macular dystrophy (Stargardt disease, Best macular dystrophy, Pattern dystrophy, Sorsby fundus dystrophy, etc.), 4. abnormality of photoreceptors and bipolar cells (X-linked retinoschisis, congenital stationary night blindness), 5. vitreoretinopathies (Wagner syndrome, Stickler syndrome, etc.), 6. hereditary choroidal diseases (choroideremia, central areolar choroidal atrophy, gyrate atrophy of the choroid and retina, etc.). Among the most frequent and severe forms of these retinopathies is retinitis pigmentosa (RP).

Each of these diseases has a different biochemical cause and mechanism. However, in all of them, the final common response is the morphological and functional damage of retinal cells including controlled cell death and tissue remodeling (Cuenca et al., 2014). The therapeutic use of pharmacological agents such as neuroprotective factors seems to be able to prevent further loss of photoreceptors and thereby reduce the rate of disease progression. However, the results of clinical trials of pharmacologic agents are still controversial and further studies are required. Cutting-edge treatments including gene therapy, cell transplantation (stem or retinal cells), and artificial retinal prosthesis have been researched through preclinical and clinical studies and have shown significant progress during the recent decade. Currently, two retinal prosthesis devices are commercially available, and one gene therapy product is about to be approved by FDA for hereditary retinal dystrophies. But there are still many challenges to overcome for these therapeutic devices/vectors, and the treatment of RP is still extremely challenging.

In this article, we review the genetic mechanisms, the current treatment methods focusing on clinical trial results, and future therapeutic strategies of RP. This review may be helpful for both clinicians and researchers to understand the current updated treatment for RP and their drawbacks. It can also provide insight for the development of future treatment technology for RP and hereditary retinal dystrophies.

2. Eye anatomy and physiology

The eye is an extremely specialized organ and has individual structures that work together to capture and process visual information. It can be divided into anterior and posterior segments. The anterior segment is formed by the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens. The posterior part consists of sclera, choroid, Bruch's membrane, RPE, neural retina, and vitreous. The most important cells that suffer from degeneration and atrophy in RP and other hereditary retinal dystrophies are photoreceptors (rods and cones) and retinal pigment epithelial (RPE) cells. (Fig. 1).

Rods and cones are two types of photoreceptors, which are light-sensitive cells. Rods are stimulated by dim light and located in the peripheral retina, while cones are stimulated by bright light and concentrated in the central retina including macula. They are formed by inner and outer segments, cell body, and synaptic terminal (Fig. 1). The outer segment is a photosensitive organelle present at the distal end of each photoreceptor and is in direct contact with the RPE cells (Pearring et al., 2013). It is composed of multiple stacks of discs that are formed by invagination of the plasma membrane. These discs have proteins directly related to the phototransduction cascade such as rhodopsin, transducin, and phosphodiesterases; proteins which bind to calcium, cation channels, and 11-cis-retinal. They must be continuously renewed by the RPE to ensure proper functioning, crucial in the process of vision (van Soest et al., 1999). The RPE consists of a hexagonal monolayer of cells and has several distinct and important functions in addition to the renewal of the outer segments of photoreceptors. Among these functions are: phagocytosis of toxic products, reconstitution, maintenance of the blood-retinal barrier, reduction of phototoxic damage to the retina (Slijkerman et al., 2015), the nutrition of the cones and rods, the fixation of the retina, and the metabolism of retinoids (Koirala et al., 2013). The retinal cells affected by RP and the functional consequences are described in section 3.

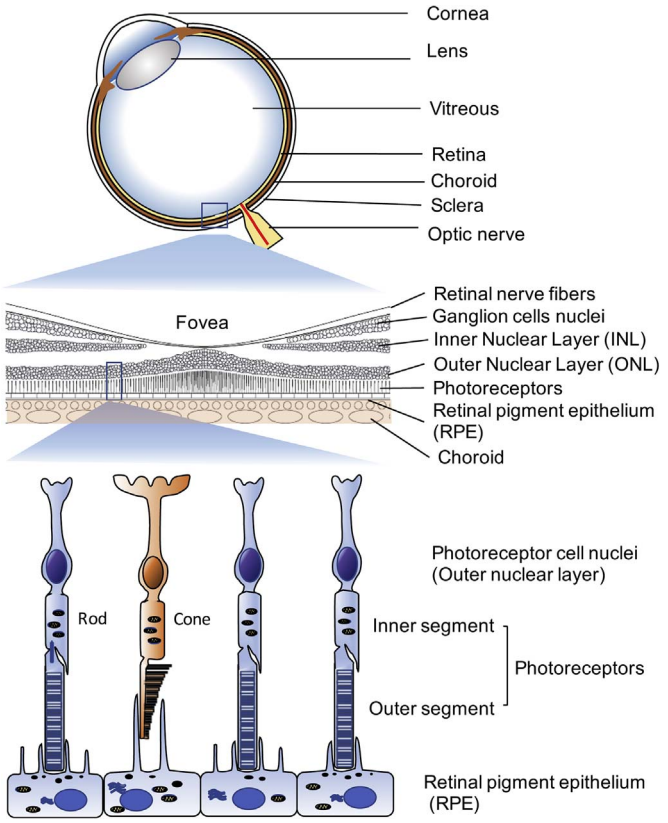

Fig. 1. Schematic representation of the human eyeball and retinal layer structures. The posterior segment of an eyeball consists of retina, choroid, and sclera. Retina is made up of ten layers including three cell nuclei layers. The outer retinal cells -photoreceptors (cones and rods) and retinal pigment epithelial (RPE) cells-are the major target cells of treatment of retinitis pigmentosa and other hereditary retinal dystrophies.

3. Retinitis pigmentosa

3.1. Clinical features of RP

For RP and allied diseases, a unified classification system has yet to be established amongst clinicians, cell biologists, and molecular geneticists. Clinically, RP is a retinal degenerative disease characterized by pigmented deposits called bone spicules, which are a result of a degeneration of the photoreceptors, predominantly in the peripheral retina. The RP is genetically and phenotypically heterogeneous (van Soest et al., 1999) with mutations affecting between 0.025 and 0.04% of the worldwide population. The prevalence has been reported to range from 1 per 750 to 9000 persons (Na et al., 2017). The clinical abnormality is usually restricted to the eye; however, approximately 20–30% of patients also have systemic problems. Mutant proteins that have the retina-specific functions or are mainly expressed in the retina may cause typical RP (nonsyndromic RP), whereas mutations in genes functioning in diverse cell types or tissues result in systemic manifestations (syndromic RP) (Waters and Beales, 2011; Wheway et al., 2014). There are approximately 30 different syndromes related to this form (Hartong et al., 2006). The well-known syndromic forms are Usher syndrome (USH) which also affects the hearing capacity (Trapani et al., 2014) and Bardet-Biedl syndrome that affects the cilia motility function and also leads to obesity, post-axial polydactyly, hypogonadism, and renal dysfunction (Forsythe and Beales, 2013).

In most cases of RP, there is an initial degeneration of the rods with subsequent degeneration of cones (Hamel, 2006). Although RP mainly affects the rods, the degeneration of cones in the advanced stage of RP is due to the co-dependence between rods and cones, and that rods produce factors that increase the survival of cones (Rod-Derived Cone