

Therapeutic Interventions in Autosomal Dominant Retinitis Pigmentosa

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Eye is a window to the brain. We visualize and experience our environment through the eye and therefore, visual impairment imposes severe restrictions to our normal life. Retinitis pigmentosa (RP) is a group of genetically heterogeneous retinal degeneration, which is affecting the life of 1 out of 4000 human beings throughout the world [1-3]. The degeneration of rod photoreceptor cells (PR) followed by cone cell degeneration is the characteristic of this disorder. Initially, the loss of rod PR cells causes peripheral vision loss and patient experiences night blindness. This progressive rod cell deterioration eventually ends up with cone cell degenerations that finally lead to the loss of central vision and official blindness. Over 43% of RP is caused by mutations in alleles of genes in rod PR cells and inherited as autosomal dominant RP (adRP). Till to date, more than 100 mutations have been identified in rod-opsin protein in rod PR cells to be responsible for 30-40% of adRP conditions [4]. Among all the mutations, Pro23His (P23H) at the N-terminal domain of rod-opsin protein is responsible for 10% of total adRP disorder. Rod-opsin is a member of G-coupled receptor family proteins. Rod-opsin protein is composed of 348 amino acids with N-terminal (intradiscal domain), C-terminal (cytoplasmic domain) and seven transmembrane domains. The crystal structure of rod-opsin protein was coined by Palczewski, *et al* [5]. The rod-opsin protein after synthesis and post-translational modifications moves towards the outer segment of rod cells, where is complexed with 11-cis-retinal (chromophore) and forms visual pigment [2-4]. This complex is activated by light that initiates isomerization of 11-cis-retinal to all-trans retinal and induce the photo-transduction pathways for vision. In the dominant disorders, one allele remains mutated and the other one is wild type allele of rod opsin genes. Majority of rod-opsin linked mutations in adRP conditions are caused by misfolding of mutant proteins. In case of P23H (at N-terminal domain) disorder, misfolding leads to the accumulation of mutant proteins (encoded by mutated allele) in the endoplasmic reticulum (ER), which creates disturbances in ER homeostasis. This imbalance in ER induces unfolded-protein response (UPR) [6] and overloading of UPR leads to apoptosis of rod PR cells by exhibiting dominant negative effects over the function of wild type (normal) rod opsin protein. Till now, there is no cure available for this disorder. The key obstacle in the development of suitable therapeutics for this severe disease lies in its complex inherited heterogeneity, which includes genetic heterogeneity (different defects in different genes causing same disorder), allelic heterogeneity (different mutations in same gene causing same disorder) and clinical heterogeneity (same mutation shows distinct signs in different patients) [3].

To this end, diagnosis for each mutation in adRP is a difficult process of investigation. Subsequent developments of suitable therapeutics and applications are less practical as targeting each mutation for suitable gene therapy is hard, finding relevant mouse model for each mutation is difficult and huge research costs. Nevertheless, there are some potential therapeutic approaches have been invested with promising results in the developments of practical and effective therapeutics. Neurotrophic factor therapy [7-9], ribozyme therapy [10], suppression and replacement gene therapy [11,12] have highlighted as a potential therapeutic approach in this regard.

Ribozyme therapy showed a slowdown of PR cell degenerations by reducing the production of mutant protein through specifically silencing mutated allele related mRNA [10]. In this process, wild type allele could function normally, however, demands for the developments of huge number of efficient ribozymes. The deliveries of ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) demonstrated promising gene therapy approaches to slowdown PR cell degenerations [7-9]. Suppression and replacement strategies evolved as promising and potential gene therapy approaches in silencing the transcripts of both mutant and normal rod-opsin alleles (non-specifically), while provide silencing resistant rhodopsin gene as replace-

ment element. In summary, developments of gene therapy approaches were mainly focused on the use of adeno-associated virus (AAV) vectors. The strong efficiencies in expressing genes to the retina is a major advantage of AAV mediated gene therapies. However, it also comes with severe disadvantages like size limitation of cargo genes (<~5kb), different immunological responses to Muller cell activation and inflammations in the eye [13]. Due to these drawbacks of AAV mediated approaches, non-viral gene therapy strategies have also been investigated with potential promises due to ease in synthesis, low immunogenicity, easy to handle, low production costs and potent “genomic” protection. Several non-viral gene delivery vehicles were developed in the pipeline of discovery. These were capable in delivering therapeutic genes, which resulted in long-term therapeutic benefits for the retina in different mouse models of human eye conditions with potential safety profiles [14-18]. However, these non-viral methodologies demonstrated less efficiencies in gene therapies and therefore, left a room for further improvements in the progresses and applications of gene therapeutic strategies for adRP disorders. In future, the developments of effective, safe gene delivery tools and earlier diagnosis of adRP may significantly halt this disorder in its initial stage.

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