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Spotlight on vision

Gene therapy for inherited retinal degenerations

Thérapie génique pour les dégénérescences rétiniennes héréditaires

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ABSTRACT

Gene therapy is quickly becoming a reality applicable in the clinic for inherited retinal diseases. Progress over the past decade has moved proof-of-concept gene therapies from bench to bedside. The remarkable success in safety and efficacy, in the phase I/II clinical trials for the form of the severe childhood-onset blindness, Leber's Congenital Amaurosis (LCA) type II (due to mutations in the *RPE65* gene) generated significant interest and opened up possibilities for a new era of retinal gene therapies. Success in these clinical trials was due to combining the favorable features of both the retina as a target organ and adeno-associated virus (AAV) as a vector. The retina offers several advantages for gene therapy approaches. It is an anatomically defined structure that is readily accessible for therapy and has some degree of immune privilege, making it suitable for application of viral vectors. AAV, on the other hand, is a non-pathogenic helper dependent virus that has little immunogenicity. This viral vector transduces quiescent cells efficiently and thanks to its small size diffuses well in the interneural matrix, making it suitable for applications in neural tissue. Building on this initial clinical success with LCA II, we have now many opportunities to extend this proof-of-concept to other retinal diseases. This article will discuss what are some of the most imminent targets for such therapies and what are the challenges that we face in moving these therapies to the clinic.

Mots clés :
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RÉSUMÉ

La thérapie génique est devenue une réalité applicable en clinique pour des maladies héréditaires de la rétine. Les progrès réalisés au cours de la dernière décennie ont permis de passer du laboratoire à la clinique. Des essais cliniques de phase I/II pour l'amaurose congénitale de Leber (LCA) de type II (due à des mutations dans le gène *RPE65*) ont rencontré un vif succès et ouvert de nouvelles possibilités pour la thérapie génique oculaire. Le succès de ces essais cliniques est principalement dû à la combinaison de deux facteurs. D'abord, l'adéquation remarquable de l'œil comme cible de la thérapie génique. Ensuite, l'utilisation du virus adéno associé (AAV) comme vecteur. La rétine offre plusieurs avantages pour les approches de thérapie génique. Anatomiquement, elle est facilement

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accessible pour la thérapie, et présente un relatif privilège immunitaire facilitant l'application de vecteurs viraux dans cette structure. L'AAV, par ailleurs, est un virus non pathogène qui a peu d'immunogénicité, et qui ne peut se répliquer qu'en s'associant à d'autres virus. L'AAV transduit efficacement les cellules post-mitotiques. Grâce à sa petite taille, il diffuse dans la matrice extracellulaire, ce qui convient pour des applications dans la rétine. À la suite du succès clinique initial pour LCA II, de nombreuses possibilités s'offrent maintenant pour étendre cette preuve de concept à d'autres maladies de la rétine. Cet article décrit les cibles les plus en vue pour la thérapie génique oculaire, ainsi que les défis pour transposer les traitements testés en laboratoire à la clinique.

1. Inherited retinal degenerations that can benefit from gene therapy

Inherited retinal degenerations (IRD) display wide variation in their mode of inheritance, underlying genetic defects, age of onset, and phenotypic severity (https://sph.uth.edu/retnet/disease.htm). Despite growing knowledge on genetics, molecular mechanisms have not been delineated for all retinal diseases, and thus far treatment options are limited. Nevertheless, monogenic inheritance patterns exist and they can be autosomal dominant (i.e. certain forms of retinitis pigmentosa), recessive (LCA type II), X-linked (retinoschisis) or follow a mitochondrial inheritance pattern (i.e. Leber's hereditary optic neuropathy (LHON)). There are nine broad categories of IRD, with many subtypes under each category (Fig. 1).

Here, these inherited retinal diseases are discussed in view of the gene therapeutic approach that can be used to treat them. In view of the mechanisms of disease and genetics, there are a number of strategies where strong proof-of-concept laboratory studies have been obtained. We will place particular emphasis on these strategies.

2. Gene augmentation/replacement

Among monogenic diseases, those caused by recessive null mutations are the ones that are most amenable to gene therapy (Fig. 2). These mutations are mostly localized to the outer retina (photoreceptors and retinal pigment epithelium [RPE]).

Cell type targeting, desired gene expression level and cell-to-cell variation of gene expression are important considerations in identifying disease targets, which can benefit from gene therapy. In most cases, recessive and X-linked mutations cause an absence of protein, or production of functionally null protein, and consequently, the expression of wild-type protein is likely to significantly ameliorate the disease phenotype. LCA 2, choroideremia, Stargardt's disease and retinoschisis are examples of monogenic recessive diseases, where there has been multiple proof-of-concept preclinical or clinical data showing promise [1]. Recessive genotypes where gene replacement would be appropriate include, but are not limited to, *RS1* (XLRS: X-linked retinoschisis), *CNGA3* and *CNGB3* (achromatopsia), *GUCY2D* (LCA1), and *RPE65* (LCA2), *MYO7A* (Usher 1B) and *ABCA4* (Stargardt's), *REP-1* (Choroideremia), and *RPGR* (X-linked Retinits pigmentosa, RP). Of these, LCA2, Usher 1B, Stargardt's disease and choroideremia are already in clinical trials, with a clinical trial on achromatopsia starting soon [2]. As previously mentioned, LCA2 was the first one of these monogenic recessive diseases to come to clinical application [3–5].

2.1. Lessons learned from clinical trials

Several groups have set-up a phase 1 clinical trial for the treatment of LCA2 with four active clinical trials that are ongoing currently (clinical trial numbers: NCT00749957, NCT01496040, NCT00516477, NCT01208389). The data from these clinical trials collectively point to the safety of gene transfer with sustained improvement in retinal

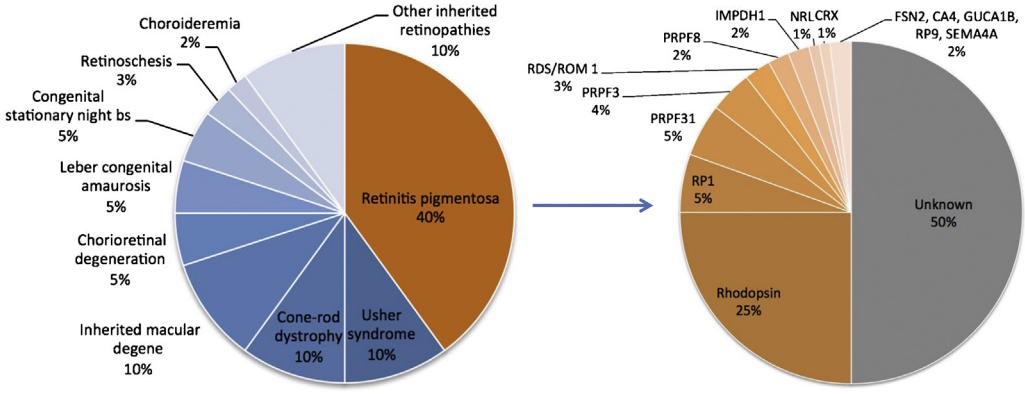

Fig. 1. (Color online) Percentage of broad categories of IRD and sub-categories of retinitis pigmentosa. Adapted from [28].