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Gene therapy of the central nervous system: General considerations on viral vectors for gene transfer into the brain

Thérapie génique du système nerveux central : considérations générales sur les vecteurs viraux pour le transfert de gène dans le cerveau

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ABSTRACT

The last decade has nourished strong doubts on the beneficial prospects of gene therapy for curing fatal diseases. However, this climate of reservation is currently being transcended by the publication of several successful clinical protocols, restoring confidence in the appropriateness of therapeutic gene transfer. A strong sign of this present enthusiasm for gene therapy by clinicians and industrials is the market approval of the therapeutic viral vector Glybera, the first commercial product in Europe of this class of drug. This new field of medicine is particularly attractive when considering therapies for a number of neurological disorders, most of which are desperately waiting for a satisfactory treatment. The central nervous system is indeed a very compliant organ where gene transfer can be stable and successful if provided through an appropriate strategy. The purpose of this review is to present the characteristics of the most efficient virus-derived vectors used by researchers and clinicians to genetically modify particular cell types or whole regions of the brain. In addition, we discuss major issues regarding side effects, such as genotoxicity and immune response associated to the use of these vectors.

RÉSUMÉ

Suite aux récents succès de divers protocoles thérapeutiques de transfert de gène, notamment appliqués aux pathologies de la rétine, et à la mise sur le marché du Glybera, le premier produit commercial en Europe pour cette classe de médicaments, on observe un regain d'intérêts pour la thérapie génique sur les plans clinique et industriel. Ce nouveau domaine de la médecine expérimentale est particulièrement enthousiasmant si l'on considère que la

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plupart des maladies neurologiques attendent désespérément l'apparition d'un traitement satisfaisant. Le système nerveux central est en effet un organe où le transfert de gène peut être stable et réussi s'il est administré selon une stratégie appropriée. L'objectif de cette revue est de présenter les qualités des vecteurs viraux les plus efficaces utilisés actuellement par les chercheurs et les cliniciens pour modifier génétiquement des cellules neurales ou des régions entières du cerveau. Nous abordons également des questions concernant les effets secondaires, tels que la génotoxicité et la réponse immunitaire associées à l'utilisation de ces vecteurs.

1. Introduction

Gene therapy is a modern field of experimental medicine aiming at modifying the gene pool of cells to halt the disease progression. This specialty, first conceived in the 1960s in the imagination of eminent scientists, such as JBS Haldane [1] has gained practical credibility in the past two decades with the progress of molecular biology and genetics, allowing the enrichment of both our arsenal of tools for gene transfer and our knowledge of the pathogenesis of several obscure diseases. Presently, most efficient tools for gene transfer are vectors derived from viruses, keeping their ability to introduce nucleic acids in the cell but abolishing their replication faculty. In this matter, much progress has been done, putting gene transfer at the gate of current clinical practice [2–4]. This of course has also raised questions about ethical and safety issues regarding the use of virus-derived vectors, the toxicology and pharmacological side effects linked to their use and the possibility for these elements to modify gametes [5]. These topics are being broached at the same time as viral vectors are being developed and have contributed in many ways in their progressive improvement.

Successful gene therapy balances the efficacy of gene transfer on one side and the knowledge of the pathological process on the other. Among all of our organs, of which none resist modern tools for gene transduction, targeting the brain possibly has most awoken our interest due to the complexity of its organization, its role in regulating bodily functions and interactions with the environment but also because it is the place of grave neuropsychiatric affections. The brain is a compact conglomerate of circuits, controlling autonomous activity, storing information and interconnecting sensory structures to effectors through complex neuronal processing of electrical influx. Numerous types of neural cells shape this superstructure of which intimate functions are just being uncovered.

There are four rough families of brain disorders that are candidate to gene therapy treatments, and which have been recently reviewed in detail [6]. These are:

- tumors (glioblastoma);
- inflammatory affections (multiple sclerosis);
- neuronal degeneration (Parkinson's, Huntington's and Alzheimer's diseases);
- neuronal dysfunction (storage diseases, Rett and Down syndromes), among many others.

The suitability of gene therapy for each of these affections is actually being documented in animal models and progressively scaled-up to patients. For all of them, though, the two greatest constraints to restore tissue homeostasis are functional and spatial and require combining appropriately:

- the choice of the transgene;
- the time window of intervention;
- the ability to target the appropriate cell;
- the level and stability of transgene expression.

As regards to the central nervous system (CNS), practical feasibility of gene therapy was acquired in the 1980s and 1990s with several experiments demonstrating the possibility to transfer genes into mammalian brain cells either through direct gene transfer into the parenchyma [7–10] or through *ex vivo* gene transfer [11–13]. Since then, developments of gene therapy for brain diseases have been sporadic, hampered by the extensive media coverage in the scientific community of few clinical trials that have resulted in the occurrence of serious side effects [14], but also by the slow progress in our comprehension of disease pathology and often to the lack of appropriate animal models. Nevertheless, hundreds of approaches have been explored in animals, with disparate results but often raising hopeful medical expectations. This, notably, led to significant clinical achievements in humans that although concerning few patients and despite variable therapeutic efficacies indicated that genetically engineered cells can remain functional for years in human organisms. It is the case for several rare genetic disorders, such as X-linked adrenoleukodystrophy [15] and metachromatic leukodystrophy [16] both treated by hematopoietic stem cells complementation with a functional cDNA replacing the affected gene. Following these recent achievements, and considering the fact that a great amount of neurologic and psychiatric diseases are currently in a therapeutic deadlock, gene therapy appears today as a promising treatment for diverse brain affections. In principle it allows:

- delivery of therapeutic factors directly into the CNS, bypassing the blood-brain barrier;

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