31. VIRAL GENE DELIVERY

Summary. Somatic gene therapy aims at increasing the expression of deficient or protective factors, or at the suppression of deleterious factors. This goal will probably be achieved best by the use of viral vectors. Currently, vectors are being optimised with respect to transduction properties, levels of transgene expression, and reduction of toxicity and immunogenicity. While a multitude of gene transfer approaches have been completed in experimental models, gene therapy is now slowly moving into the clinic, and promising results can be hoped for in several cases. Caution is required, however, not to overstrain hope in this emerging therapeutic modality, and drawbacks in gene therapy studies outside the nervous system warrant meticulous caution for safety concerns.

1. INTRODUCTION

For many neurological diseases still no satisfactory treatments are available. Molecular genetics has in the past decade helped to identify causative genes and mutations for a number of familial neurological diseases, and progress in our understanding of pathogenic events led to the hope that it may soon be possible to specifically and causally interfere with such mechanisms. Here, we will introduce the concept and basic science of gene therapy approaches, illustrate some examples of experimental and clinical gene therapy studies, and discuss future perspectives of this emanating treatment modality that may help ameliorate the course of neurological disorders, and change the lives of affected patients.

2. WHAT IS GENE THERAPY?

2.1. The concept of gene therapy

Classical pharmacotherapy usually aims at relief of disease symptoms (e.g., pain, impairment of movement, altered muscle tone) rather than targeting of underlying (causative) molecular genetic alterations. Typically, drugs have short half lives, necessitating administration on a regular scheme, often several times daily. In addition, pharmacotherapy for CNS conditions is inevitably administered systemically, and hence prone to cause systemic side effects.

Gene therapy was originally envisaged as a concept to overcome many of the restrictions and side effects of classical pharmacological therapies. The original concept involved the replacement of gene products (enzymes) deficient in autosomal recessive inborn errors of metabolism. Thereby, following somatic gene transfer,
these enzymes will be produced by the very cell population that express them under physiological conditions. Gene delivery would be a single event, followed by long-term – ideally, permanent – gene expression and, hence, definite phenotypic compensation. If this was feasible, gene therapy would be much more effective than classical pharmacotherapy and protein delivery – (facilitated) administration of recombinant proteins. While this concept still holds, current experience shows that gene therapy is still an ambitious goal. On the other hand, with ongoing research on the molecular biology and pathophysiology of nervous system diseases, and progress in gene transfer techniques, possible applications of gene delivery to the nervous system are getting even broader. At the same time, scenarios emerge where gene transfer or – with view to future clinical application – gene therapy can become an important therapeutic modality in diseases as diverse as metabolic diseases, acute neuronal demise in stroke, brain trauma and spinal cord injury, chronic neurodegenerative conditions such as Alzheimer’s and Parkinson’s disease, and brain tumours, and many of these concepts are now aimed at more or less symptomatic relief rather than causative cure. Therapeutic strategies for neuronal rescue usually follow one of three basic principles: to replace missing enzyme or protein functions in recessive diseases; to provide general trophic support to neurons at risk in acute or chronic neurodegeneration, or to decrease the extent of protein dysfunction in dominant negative gain of function mutations.

The basic principle of gene therapy, however remained the same: to deliver genetic blueprints of desired factors specifically and effectively to target tissues or target cells or, especially in the CNS, to target regions, and express the proteins of interest. Still, due to specificity of the approach only minor – if any – side effects, and no systemic drawbacks should be encountered.

2.2. Gene transfer: principles and basic science

In gene therapy, it is not the remedy (i.e. protein or active compound) itself that is administered, but rather the nucleic acid (i.e., DNA or, less frequently, mRNA) that is delivered to target cells. Therefore, the cellular “biomachinery” is utilized to produce beneficial factors, for an extended period of time. In many instances, gene transfer will be additive, i.e., genes for factors that are deficient, or that would be favourable, are introduced by means of gene transfer, and an additional function is introduced. However, the contrary is also conceivable: to eliminate by ablative gene transfer gene products that may be deleterious, e.g., in dominant gain of function mutations, or to abolish genes associated with tumour growth (such as constitutively active oncogenes or growth factor receptors, such as ErbB2, for example). The latter can be achieved by dominant negative approaches, by antisense oligonucleotides, antisense RNA, catalytic ribozymes, RNA “decoy” and small inhibitory RNA (Xia et al., 2002), and will not be discussed to much detail in this chapter.

Among the factors that can be added are genes for deficient enzymes in metabolic diseases. Here, it is important to note that many such diseases are inherited in an autosomal recessive manner indicating that expression of even a minor amount of the respective protein may suffice to maintain a normal phenotype.