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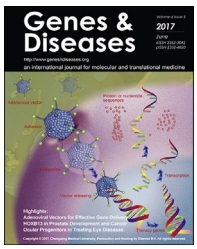

REVIEW ARTICLE

Adenovirus-mediated gene delivery: Potential applications for gene and cell-based therapies in the new era of personalized medicine

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Abstract With rapid advances in understanding molecular pathogenesis of human diseases in the era of genome sciences and systems biology, it is anticipated that increasing numbers of therapeutic genes or targets will become available for targeted therapies. Despite numerous setbacks, efficacious gene and/or cell-based therapies still hold the great promise to revolutionize the clinical management of human diseases. It is wildly recognized that poor gene delivery is the limiting factor for most *in vivo* gene therapies. There has been a long-lasting interest in using viral vectors, especially adenoviral vectors, to deliver therapeutic genes for the past two decades. Among all currently available viral vectors, adenovirus is the most efficient gene delivery system in a broad range of cell and tissue types. The applications of adenoviral vectors in gene delivery have greatly increased in number and efficiency since their initial development. In fact, among over 2000 gene therapy clinical trials approved worldwide since 1989, a significant portion of the trials have utilized adenoviral vectors. This review aims to provide a comprehensive overview on the characteristics of adenoviral vectors, including adenoviral biology, approaches to engineering adenoviral vectors, and their applications in clinical and preclinical studies with an emphasis in the areas of cancer treatment, vaccination and regenerative medicine. Current challenges and future directions regarding the use of adenoviral vectors are also discussed. It is expected that the continued improvements in adenoviral vectors should provide great opportunities for cell and gene therapies to live up to its enormous potential in personalized medicine.

Introduction

By using directed gene transfer to treat human disease, gene therapy may hold the potential to revolutionize medicine — in part because this approach is capable of treating the root cause of a disease, not merely its symptoms.[1] Despite numerous setbacks in the past decades, gene therapy remains as a field that is constantly growing and developing as scientists look for new strategies to treat some of the most difficult health issues. There has been a long-lasting interest in using viral vectors, especially adenoviral vectors, for gene therapy in the past two decades.[1–3] It is well recognized that poor gene delivery is the limiting factor for most *in vivo* gene therapies while the only exceptions are where therapeutic viruses can be injected directly into the target site or where they can be introduced into target cells *ex vivo*.

Adenovirus has received tremendous attention as an effective gene delivery vector and was in fact the first DNA virus to enter rigorous therapeutic development, largely because of its well-defined biology, its genetic stability, its high gene transduction efficiency and its ease of large-scale production.[2–4] Adenovirus (Ad) is a non-enveloped, linear double-stranded DNA virus with 57 identified human Ad serotypes.[2,5] Ad serotypes differ in tropism and are further divided into six subgroups, A—G. Differences in viral capsids delineate tropisms among serotypes. The viral capsid is comprised of capsid proteins, core proteins, and cement proteins. These diverse serotypes can give rise to a vast range of therapeutic candidate viruses. Thus, it is not surprising that adenovirus continues to occupy the center stage in gene therapy arena.[2–4]

Compared with other viral gene delivery systems, adenoviral vectors offer significant advantages.[2] First, adenovirus is the most effective means of delivering genes *in vivo* as most human cells express the primary adenovirus receptor and the secondary integrin receptors. Thus are easily infected with adenovirus vectors and consequently yield high levels of the transgene expression.[2] Second, the development of gutless adenoviral vectors allows us to circumvent anti-adenoviral vector immunity. Third, despite the concern over safety of their use, there has been extensive experience with adenovirus vectors in many different clinical applications, and the safest dosing and routes of administration are now well established.[2] In fact, adenovirus vectors are the most common vector used in clinical trials worldwide and account for >20% of all gene therapy trials (see below). Fourth, adenovirus vectors offer a versatile platform for developing strategies to modify viral capsids in order to enhance therapeutic properties and improve targeting specificity of the virus. Interestingly, some of the inherited shortcomings of adenovirus, such as immunity evoked against the adenovirus capsid and low-level expression of adenovirus genes, may now prove beneficial for the development of anticancer immunotherapies, where inducing immunity against the cancer or directly killing the cancer cell is the goal. Furthermore, the combined immunity against the adenovirus together with the short time of expression is ideal for using the adenovirus as a platform for developing vaccines.[2]

The past two decades have witnessed many advances in the adenovirus vector system, ranging from its deployment as a vector for transgene delivery and supplementation for vaccination to its use as an oncolytic agent. Together with adeno-associated viruses and lenti/retrovirus vectors, the adenovirus now represents one of the three major viral vector categories in the gene therapy "tool box". In this review, we will focus on the basic features of adenovirus, namely by the comparison of adenovirus to other viral and non-viral vectors, the common methods to produce