Review Article

Gene Delivery: The Non-Viral Vector Advantage

Viney Chawla[1], Shubhini A. Saraf[2], Shailendra K. Saraf*[1]

[1] Faculty of Pharmacy, Northern India Engineering College, Dr. Akhilesh Das Nagar, Lucknow-227105, India.
[2] Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Dr. Akhilesh Das Nagar, Lucknow-227105, India.
* Author for Correspondence
Email: dirpharmniec@gmail.com (Saraf SK)
Phone +91-522-3911052
Fax +91-522-2815187
Email: vchawla_lko@yahoo.com (Chawla V)
Email: shubhini.saraf@gmail.com (Saraf SA)

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Abstract

Gene therapy has opened new vistas for mankind to explore and treat diseases. The delivery of a gene in to the cell has many challenges including extracellular as well as intracellular factors. The delivery of an intact gene without degradation requires specialized carrier systems or vectors. Gene transfer vectors that are safe, efficacious, and tumour-selective are frequently sought after. Vectors can be viral or non-viral. Viral vectors are plagued by issues of random recombination, oncogenic potential, and immunogenicity. Non-viral vectors are becoming popular since they overcome these disadvantages. This review discusses different classes of non-viral vectors with regard to their transfection efficiencies and other related issues.

Keywords: Non-viral vectors, gene therapy, plasmid, DNA, nanoparticles

Introduction

Several types of approaches have been attempted for development of delivery systems for genes. The objective of any gene therapy strategy is to efficiently and safely deliver therapeutic DNA to the cells at the target site. There are various limitations to the delivery of DNA, which include its stability during transit from the site of injection to the target tissue, cellular uptake by endocytosis, the endosomal/lysosomal escape of the DNA, and finally the nuclear import followed by transcription and translation of the protein of interest [1,2]. Gene therapy provides great opportunities for treating diseases from genetic disorders, infections and cancer [3]. The main obstacle for the clinical application of cancer gene therapy is the lack of gene transfer vectors that are safe, efficacious, and tumour-selective. In recent years, targeted gene delivery through cellular receptors, using either viral or non-viral vectors, is emerging as a novel approach to enhance the efficacy of tumour-selective gene delivery [4]. An ideal vector for gene therapy should be inert while in circulation and release its payload in the cell at the target site, resulting in efficient transfection. The vector used should have sufficiently small size and stability, have minimal aggregation in blood, and have the ability to efficiently target cells, disassemble and release the DNA intracellularly, and allow for the DNA to be imported into the nucleus [5]. An ideal non-viral vector and its therapeutic cargo should be stable in the test tube as well as in the body, being biodegradable, nontoxic, and nonimmunogenic [6]. Viral vectors are the most effective because of their evolutionary optimization for this purpose. Viral vectors such as the adenoviruses, retroviruses, adeno-associated viruses, lentivirus, and herpes simplex virus are continuing to be used in many clinical protocols. However, safety issues such as random recombination, oncogenic potential, and immunogenicity have set back the rapid development of viral vectors [7]. Moreover, viral vectors carry small size of DNA. By contrast, non-viral vectors are safe to use but less efficient. In light of safety concerns, non-viral delivery systems have been developed for gene therapy experiments. Non-viral gene delivery vectors may be a key technology in circumventing the immunogenicity inherent in viral-mediated gene transfer. Different research groups have observed that the presence of PEG in non-viral vectors such as cationic lipid emulsions [8] and in liposomes [9] improves their transfection capacity. Liu *et al*. showed that Tween 80 (which has PEG chains in its structure) was the most effective non ionic surfactant to avoid formation of aggregates. Tween 80 may prevent sterically each DNA molecule from binding to more than one particle thus avoiding the formation of aggregates [8]. Besides, it has another important characteristic system for the transfection of these systems *in vivo*. It creates a steric barrier [10] which neutralizes the excess of positive charges of the system and reduces the interaction with blood components, such as serum proteins, which could limit the arrival of gene therapy system to cell surface. Polyplexes (complexes of cationic polymers and plasmid DNA) can have transfection efficiency comparable to adenoviral vectors. Polyplexes are small (diameter <8 nm), have large vector capacity, are stable in nuclease-rich environments, and have relatively high transfectivity for both dividing and nondividing cells [11]. In order to form lipoplexes the positive superficial charge of the system is necessary to electostatically bind the DNA, which has negative charge. When DNA binds with these systems it is condensed, and that condensation increases as the charge ratio (+/-) increases. Condensation is necessary to facilitate the mobility of DNA molecules, which is limited by their large size, and to protect the DNA from agents present inter and intracellularly. Condensation reduces the exposure of DNA to those agents and improves its protection. DNA condensation may limit the transfection efficiency of non-viral systems because the larger the condensation the more difficult the release of DNA from the complexes [12].

Many polymeric cationic systems such as gelatin, polyethylenimine (PEI), solid lipid nanoparticles, polymeric nanoparticles, poly(L-lysines), tetraaminofullerene, poly(L-histidine)-graft poly (L-lysines), DEAE-dextrans, cationic dendrimers, and chitosan have been studied for *in vitro* as well as *in vivo* applications. These carriers carry a variety of plasmids (Table 1). This review discusses different classes of non-viral vectors with regard to their advantages and limitations.