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Research review paper

Peptide-mediated DNA condensation for non-viral gene therapy

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ABSTRACT

The construction of non-viral, virus-like vehicles for gene therapy involves the functionalization of multipartite constructs with nucleic acid-binding, cationic agents. Short basic peptides, alone or as fusion proteins, are appropriate DNA binding and condensing elements, whose incorporation into gene delivery vehicles results in the formation of protein–DNA complexes of appropriate size for cell internalization and intracellular trafficking. We review here the most used cationic peptides for artificial virus construction as well as the recently implemented strategies to control the architecture and biological activities of the resulting nanosized particles.

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Contents

1. Introduction

Gene therapy requires safe and efficient vehicles to transfer and deliver expressible genetic material or silencing nucleic acids to target tissues. The most extensively used delivery tools are viral-based vectors since the properties of the viral cycle permit receptor-mediated recognition and cell internalization, endosomal escape, nuclear transport and DNA integration (Aris and Villaverde 2004). In the last decade, engineered adenoviruses and retroviruses have been largely explored as transfer vehicles with an acceptable degree of success (Edelstein et al., 2007). Nevertheless, the use of viruses as gene delivery systems requires the modification of the viral genome in order to prevent replication and suppress undesirable side effects while keeping the required properties. Reaching a compromise between sufficient efficiency and acceptable safety is an extremely complex issue that has generated intense scientific debates regarding the future development of viral gene therapy (Marshall 2002, 2003; Abbott 2006; Edelstein et al., 2007). In fact, the occurrence of clinically important side effects (ranging from inflammation to death of the patients) has severely delayed the incorporation of new viral vehicles into clinical trials and the whole progress of gene medicine (Edelstein et al., 2007).

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Alternatively, non-viral vehicles, being safer than the viral counterparts are under continuous development and optimization, essentially focused to increase the efficiency of DNA or RNA delivery. Such vehicles, that include polymeric constructs, virus-like particles (VLPs) and protein-only shells (Ferrer-Miralles et al., 2008), can successfully mimic viral properties regarding both size and biological properties (Fig. 1). Therefore, they are usually referred as 'artificial viruses' (Mastrobattista et al., 2006). Artificial viruses have to fulfill some functional requirements such as highly stable transport of DNA, protection against cell nucleases, membrane crossing abilities, high and steady expression of the therapeutic DNA, low systemic and cellular toxicity and low cell complement activation (Plank et al., 1999; Kim et al., 2003). Such properties must be accompanied by the collapse of extended DNA molecule into compact, orderly nanoparticles. DNA condensation has been deeply studied in the context of packaging into viruses and virus-like particles and the revealed concepts can be applied to the functional improvement of artificial viruses. Among the available DNA-condensing tools, cationic peptides are specially appropriate for those vehicles based solely on protein elements (Table 1).

Cationic peptides and other basic polymers are positively charged and interact with the negatively charged phosphate backbone of DNA through electrostatic interactions (Bloomfield 1996). Cationic and basic peptides as well as polymer-based vehicles are known to enhance the condensation of DNA to small particles with variable shapes, namely rods, toroids and spheroids, and finite size conformation (Bloomfield 1997), mainly depending on DNA size (Vijayanathan et al., 2002; Rimann et al., 2008). Moreover, the net positive charge exhibited by cationic-related polyplexes and peptides complexes permit them to interact with cell membranes and internalize into the cell, both *in vivo* and *in vitro* systems (Wadhwa et al., 1997; Wolfert and Seymour 1998; McKenzie et al., 2000a; Tolmachov and Coutelle 2007; Kumar et al., 2007; Henke et al., 2008), overcoming membrane barriers and allowing nuclear gene delivery and expression (He et al., 2000; Martin and Rice 2007). DNA-condensing peptides also prevent DNA from being degraded by cytosolic nucleases (Wolfert and Seymour 1998) and prolong the half-life of the targeted nucleic acid, which is known to be of 50–90 min for naked plasmid DNA (Lechardeur et al., 1999). Nevertheless, the cationic carrier must retain condensation abilities in terms of controlled reversibility, for instance, by adding active groups sensitive to cellular redox-potential gradients to the peptide-based vector (Manickam et al., 2005). In lipid-derived vehicles an irreversible association that prevents DNA from being expressed is often observed (Zabner et al., 1995; Brewer et al., 1999), whereas early dissociation is the result of inadequately condensation (Keller et al., 2003).

2. Poly-L-lysines and polylysine-containing peptides as DNA-binding domains

The most used DNA-condensing cationic peptides in gene delivery systems are poly-L-lysines. Poly-L-lysines (PLL) and related peptides bind the negatively charged backbone of DNA chain, not only promoting

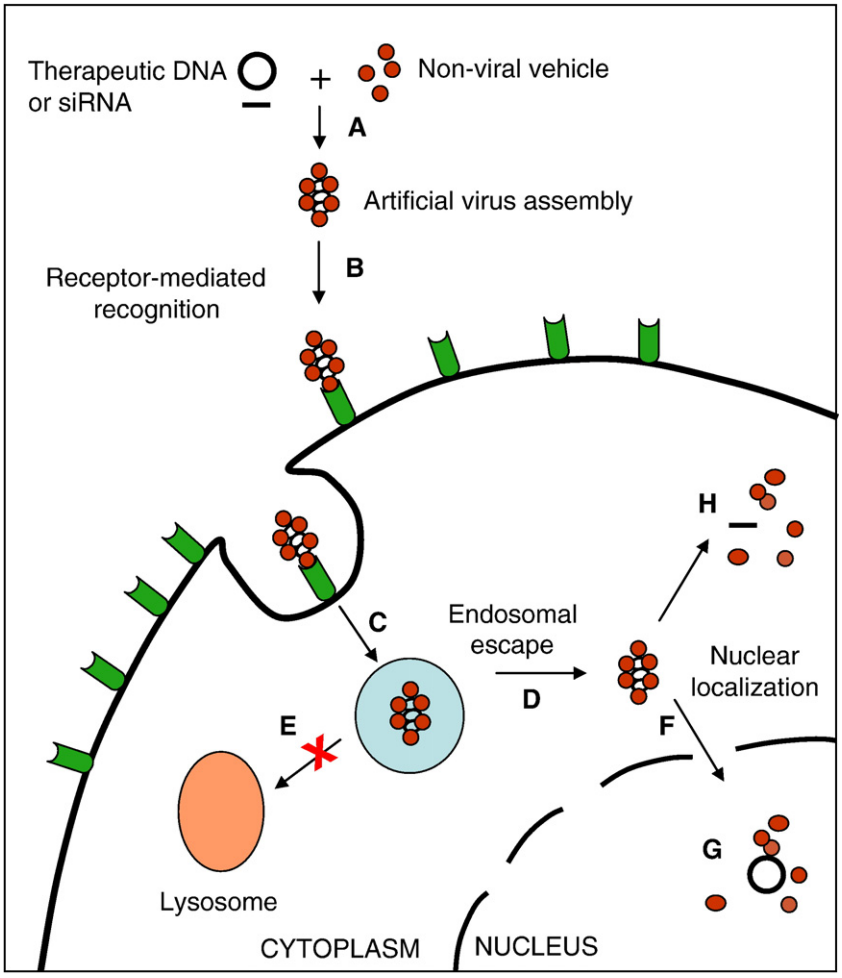

Fig. 1. Targeted cell penetration and trafficking properties of the viral cycle mimicked by an artificial virus. The coating material condenses tightly while binds reversibly the target nucleic acid, usually *in vitro* (A). The final nanocomplex recognizes specific receptors at the cell membrane and is internalized via endocytic pathways (B). Once located within early endosomes (C), the artificial virus escapes from the endosomal route (D) and thus avoids lysosomal targeting (E). Finally, the nanocomplex enters into the cell nucleus (F) and permits transgene expression (G). For the delivery of siRNA, nuclear localization signals are absent and the nucleic acid is released in the cytoplasm (H).

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