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Virus-inspired nucleic acid delivery system: Linking virus and viral mimicry☆

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ABSTRACT

Targeted delivery of nucleic acids into disease sites of human body has been attempted for decades, but both viral and non-viral vectors are yet to meet our expectations. Safety concerns and low delivery efficiency are the main limitations of viral and non-viral vectors, respectively. The structure of viruses is both ordered and dynamic, and is believed to be the key for effective transfection. Detailed understanding of the physical properties of viruses, their interaction with cellular components, and responses towards cellular environments leading to transfection would inspire the development of safe and effective non-viral vectors. To this goal, this review systematically summarizes distinctive features of viruses that are implied for efficient nucleic acid delivery but not yet fully explored in current non-viral vectors. The assembly and disassembly of viral structures, presentation of viral ligands, and the subcellular targeting of viruses are emphasized. Moreover, we describe the current development of cationic material-based viral mimicry (CVM) and structural viral mimicry (SVM) in these aspects. In light of the discrepancy, we identify future opportunities for rational design of viral mimics for the efficient delivery of DNA and RNA.

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Abbreviations: AAV, adeno-associated virus; AdV, adenovirus; ASFV, African swine fever virus; BLV, bovine leukemia virus; CCMV, Cowpea chlorotic mottle virus; CMV, cytomegalovirus; CP, capsid protein; CPP, cell-penetrating peptides; CVM, cationic material-based viral mimicry; DENV, Dengue virus; EBV, Epstein–Barr virus; ER, endoplasmic reticulum; EV, enteroviruses; FIV, feline immunodeficiency virus; HA-1, hemagglutinin-1; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HS, heparan sulfate; HSV, herpes simplex virus; MLV, murine leukemia viruses; MPyV, murine polyomavirus; NLS, nuclear localization signal; NPC, nuclear pore complex; PBCV-1, large paramecium bursaria chlorella virus 1; PSVM, protein/peptide-based structural viral mimicry; RVG, rabies virus glycoprotein; SA, sialic acid; SINV, Sindbis virus; SIV, Simian immunodeficiency virus; STMV, small satellite tobacco mosaic virus; SVM, structural viral mimicry; SV40, Simian vacuolating virus 40; TBEV, Tick-borne encephalitis virus; TMV, tobacco mosaic virus; VACV, vaccinia virus; Vpr, viral protein R; VSV, vesicular stomatitis virus; WNV, West Nile virus.

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1. Introduction

Since the discovery of gene therapy as a potential strategy to treat genetic diseases, the development of efficient delivery carriers of nucleic acids has been prompted. Gene-based delivery vectors are required to condense and protect nucleic acids (DNA and RNA) in the circulation system, deliver them into disease cells, facilitate their endosomal escape and their cytosolic transport to appropriate subcellular compartments. Viruses, as naturally evolved infectious agents, are efficient vectors with the highest transfection efficiency. Viral vectors have therefore been extensively investigated for gene therapy in recent years [1]; and a number of them have successfully progressed to clinical trials [1–3]. However, due to the size limitation of the payload, inherent immunogenicity and the difficulty of large-scale production [4], the translation from bench to bedside has been hampered. Non-viral vectors provide opportunities to overcome these limitations [5,6].

Numerous materials have been attempted for non-viral delivery, with examples from linear and branched polymers, dendrimers, lipids, to polypeptides and proteins [7–9]. The initial focus on viral mimicry is in the condensation and protection of genetic materials. This goal has been successfully achieved, mostly by nucleic acid condensation with polycations through charge complementarity [7,10]. To enhance cellular entry, and to confer more specific uptake by selected cells (such as tumor cells), the non-viral vectors are modified with various ligands [11,12]. Some of these ligands are derived from viral capsid proteins or envelope proteins, to mimic the first step of cell entry by viruses [13]. Depending on the type of nucleic acid therapy, the target location is in the cytoplasm or the nucleus. Inspiration is drawn from viruses for subcellular navigation. Fusogenic peptides, such as hemagglutinin (HA) from influenza virus, have been used to achieve pH-triggered endosomal escape [14–16]. Nuclear localization signal (NLS), derived from Simian vacuolating virus 40 (SV40), guides the nuclear localization of nanocarriers upon surface modification [17–19]. Even though certain success has been achieved and the gene transfection efficiency has been improved, the level of gene expression is still much lower than viruses and far away from clinical requirement. More understanding of the role of viral ligands and their orchestrated functions in viruses is required to enhance viral mimicking capability. With the expansion of nucleic acid medicine from DNA gene therapy to RNAi (siRNA and miRNA) and genome editing [12,20,21], the requirements of vectors vary due to the nature of cargoes and their intended destinations. This motivates us to examine a variety of viruses to draw insights for delivering different cargoes to different subcellular locations.

Recent advance on atomic level structure characterization techniques accelerates the identification of virus features, such as capsid architecture, capsid assembly and disassembly intermediates [22–24]. These achievements reveal more structure–function correlation about the packing and release of nucleic acids. To deliver gene-based theraputics, nucleic acids must be protected and condensed in the carriers to prevent degradation and allow cell entry. On the other hand, the same nucleic acids must be efficiently released from the carriers for biological function inside the cell in a timely manner. This dilemma remains one of the biggest challenges for the design of non-viral vectors. The viral structures have evolved to address this dilemma in elegant ways, which have not been fully explored in viral mimicry.

Therefore, in this review, we summarize the common features of viruses and highlight how biological functions are conferred by structural properties. We also summarize the current development of virus-inspired mimicry and compare with viruses in parallel, to shed light on the future directions for designing non-viral vectors. An emerging class of synthetic carriers based on bottom-up mimicry of viral architecture is described.

2. Essential features of viruses for efficient nucleic acid delivery

Viruses can be grouped into different categories according to shape, size, host type, genome composition, and morphology. In this review, we emphasize on their capability to deliver cargoes to different destinations, so they are categorized into two main groups: nuclear viruses and cytoplasmic viruses (see some representative viruses in Table 1). As the name suggests, nuclear viruses deliver their cargoes into the nucleus and naturally hijack host cell machinery for gene transcription. Examples include the DNA viruses (e.g. adenovirus (AdV), adeno-associated virus (AAV), Herpes simplex virus (HSV)) and RNA viruses (e.g. retrovirus Murine leukemia viruses (MLV) and lentivirus Human immunodeficiency virus (HIV)), which have been developed as delivery vectors for gene-transcription or silencing-based therapy [25,26]. According to the nature of these viral gene vectors, they can induce gene transfection of different duration [1,27]. For example, AAV, retrovirus and lentivirus can induce long-term gene transfection by integrating their viral genome into the host chromosome; while AdV, which does not have genome integration capability, provides transient transgene expression.

Besides the conventional DNA-based gene therapy, RNA interference has been extensively explored in the therapeutic application, since the discovery of small non-coding RNA (siRNA and miRNA) [28]. SiRNA/miRNA can be produced through an intrinsic biogenesis pathway by nuclear viruses: 1) small hairpin RNA (shRNA) or primary microRNA (pri-miRNA) and precursor microRNA (pre-miRNA) production followed by gene transcription of viral genome in the nucleus; 2) shRNA/pre-

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