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Virosomes for antigen and DNA delivery

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Abstract

Specific targeting and delivery as well as the display of antigens on the surface of professional antigen-presenting cells (APCs) are key issues in the design and development of new-generation vaccines aimed at the induction of both humoral and cell-mediated immunity. Prophylactic vaccination against infectious diseases in general aims at the induction of humoral immune responses to prevent infection. This humoral immune response is mediated by antibody-producing B cells. On the other hand, therapeutic immunisation against virally infected cells and tumour cells requires the induction of cytotoxic T lymphocytes (CTLs) that can specifically recognise and lyse infected cells or transformed tumour cells. The induction of Major Histocompatibility Complex (MHC) class I restricted CTL activity is optimally achieved by synthesis of antigens within APCs, for example, after immunisation with live attenuated virus. However, immunisation with live vaccines bears the risk of causing disease. Therefore, alternative vaccine delivery systems, which enable introduction of nonreplicating antigen into the MHC class I presentation pathway, are sought. Furthermore, for the induction of effective humoral and cellular responses, MHC class II restricted activation of T helper cells (Th cells) is required. Among other delivery systems, as described in this theme issue of Advanced Drug Delivery Reviews, virosomes seem ideally suited for delivery of antigens into both MHC pathways. In this review, we will focus on the use of virosomes as carrier vehicles for the intracellular delivery of protein antigens and DNA, and the induction of a cellular immune response against encapsulated protein antigens and proteins expressed by virosome-associated plasmids.

Keywords: Virosomes; Antigen; DNA

Abbreviations: APC, antigen-presenting cells; $C_{12}E_8$, octa(ethyleneglycol)-*n*-dodecyl monoether; CAT, chloramphenicol acetyl transferase; CTLs, cytotoxic T lymphocytes; DCs, dendritic cells; DODAC, dioleoyldimethylammonium; DOTAP, dioleyloxypropyltrimethylammonium methyl sulphate; DTA, diphtheria toxin; F-protein, Sendai fusion protein; HA, influenza hemagglutinin; HAV, hepatitis A virions; HVJ, hemagglutinating virus of Japan; IRIVs, immunopotentiating reconstituted influenza virosomes; ISCOMs, immunostimulating complexes; M1, influenza matrix protein; MHC, Major Histocompatibility Complex; NA, influenza neuraminidase; NP, influenza nucleoprotein; HN-protein, Sendai hemagglutinin-neuraminidase protein; OVA, ovalbumin; PTH-rP, parathyroid hormone-related peptide; PVP-NP, hydrogel nanoparticles of cross-linked polyvinylpyrrolidone; pyrene-PC, pyrene-phosphatidylcholine; Th cells, T helper cells; VSV, vesicular stomatitis virus.

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Contents

1. Background

1.1. The virosomal concept

Binding and fusion of membrane-enveloped viruses with cell surfaces are mediated by so-called spike glycoproteins on the viral membrane. Almeida et al. [1] were the first to report on the generation of lipid vesicles containing viral spike proteins derived from influenza virus. Using preformed liposomes and hemagglutinin (HA) and neuraminidase (NA), purified from influenza virus, they succeeded to generate membrane vesicles with spike proteins protruding from the vesicle surface. Visualisation of these 'liposomes' by electron microscopy revealed that they very much resembled native influenza virus. Consequently, they were named 'virosomes'. In 1987, our group described a new procedure for the generation of influenza virosomes by reconstitution of virus-like particles solely from viral membrane lipids and proteins [2]. These reconstituted viruses/virosomes enabled biochemical and biophysical analysis of the mechanisms involved in, and conditions required for, virus fusion [3–5]. In addition, the unique features of spike proteins have been exploited in the design of delivery vehicles for protein antigens and DNA.

Ever since the first description of influenza virosomes, virus envelopes have been reconstituted from a diversity of viruses as described in Section 3. Yet, in the majority of studies, virosomes have been generated from influenza virus.

1.2. Influenza virus

Influenza virus, a member of the family of Orthomyxoviridae, is the cause of common flu. Based on the internal proteins, the nucleoprotein (NP) and the matrix protein (M1), three subgroups can be distinguished, influenza A, B and C. Of these, influenza A is notorious for its variability. This variability lies in the membrane proteins of the virus, hemagglutinin (HA) and neuraminidase (NA). The major antigenic determinants of the virus, eliciting neutralizing antibodies, reside on these membrane proteins. So far, 15 different types of HA and 9 different types of NA have been identified. Most of the HA and NA variants only exist in animals, mainly birds [6]. Influenza virus is a membrane virus