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Review

Nanotechnology and vaccine development

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ABSTRACT

Despite the progress of conventional vaccines, improvements are clearly required due to concerns about the weak immunogenicity of these vaccines, intrinsic instability in vivo, toxicity, and the need for multiple administrations. To overcome such problems, nanotechnology platforms have recently been incorporated into vaccine development. Nanocarrier-based delivery systems offer an opportunity to enhance the humoral and cellular immune responses. This advantage is attributable to the nanoscale particle size, which facilitates uptake by phagocytic cells, the gut-associated lymphoid tissue, and the mucosa-associated lymphoid tissue, leading to efficient antigen recognition and presentation. Modifying the surfaces of nanocarriers with a variety of targeting moieties permits the delivery of antigens to specific cell surface receptors, thereby stimulating specific and selective immune responses. In this review, we introduce recent advances in nanocarrier-based vaccine delivery systems, with a focus on the types of carriers, including liposomes, emulsions, polymer-based particles, and carbon-based nanomaterials. We describe the remaining challenges and possible breakthroughs, including the development of needle-free nanotechnologies and a fundamental understanding of the in vivo behavior and stability of the nanocarriers in nanotechnology-based delivery systems.

1. Introduction

The seasonal outbreaks of pantropic infection diseases have elevated the development of effective vaccines to the status of a global healthcare concern. Vaccines have been developed using killed organisms [1], live attenuated organisms [2], or inactivated toxins [3]. Recently, subunit vaccines [4], and DNA vaccines that encode antigenic pathogenic proteins [5] have been examined as new vaccine modalities. Although subunit vaccines and DNA vaccines have the advantages of a high safety profile over traditional vaccine, these vaccines suffer from a relatively lower immunogenicity. The immunogenicity may potentially be improved by modulating the vaccine formulation using nanotechnology.

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The nanotechnologies developed for use in the field of vaccines encompass nanocarriers having a variety of compositions, sizes, and surface properties [6]. Numerous vaccine nanocarriers have been designed and investigated for their utility in the delivery of antigens and adjuvants to immune cells in an effort to promote a protective immune response. Unfortunately, although antigens may be taken up by the immune cells, insufficient adjuvant activity may result in limited immunogenicity. In some approaches, nanocarriers have been designed to co-deliver both an antigen and an adjuvant [7]. Nanocarriers can facilitate the targeting and/or sustained release of antigens or adjuvants to antigen-presenting cells [8,9].

Working mechanisms of nanotechnology-based vaccine formulations support the utility of nanocarriers in the vaccine fields. Particles smaller than 10 μm are readily taken up by phagocytic cells, such as macrophages and dendritic cells (DC). This property has been used to improve the cellular uptake of antigens, thereby increasing the efficiency of antigen recognition and presentation [10]. Solid nanocarriers can protect protein-based antigen vaccines from degradation and facilitate entry into the gut-associated lymphoid tissue and mucosa-associated lymphoid tissues, rendering them appropriate for vaccine delivery via oral or mucosal routes [11]. Surface-modified nanocarriers may assist the targeted delivery of antigens. Immune cells express a variety of surface receptors, including the mannose receptor, scavenger receptor, and toll-like receptors (TLR) [12]. Nanocarriers coated with immune cell-targeting molecules, such as carbohydrates [13], antibodies [14], and peptides [15], may target these overexpressed receptors to improve the efficiency of antigen and adjuvant delivery toward the promotion of specific and selective immune responses in prophylactic vaccines.

This review provides an overview of recent advances in nanocarrier vaccine systems, including liposomes, emulsions, polymer-based nanodelivery systems, and carbon-based nanodelivery systems (Fig. 1). The current status of in vivo applications of nanocarriers is summarized in Table 1.

2. Nanodelivery systems for vaccines

2.1. *Liposomes*

Since the first report that liposomes can act as immunological adjuvants [16], liposome formulations (Fig. 1A) have been extensively studied for use in vaccine delivery systems. As of this publication, at least 8 liposomal vaccines are in clinical trials or have been approved for human use [17]. The physicochemical properties of liposomes, including their size, lipid composition, and structure, may be modulated according to the properties of the vaccine antigen to maximize immunogenicity. Liposomes are composed of biocompatible phospholipid bilayers and are capable of loading and delivering both hydrophilic and hydrophobic molecules. These properties enable the co-delivery of antigen and other molecules, such as adjuvants. The surfaces of liposomes may be easily modified using the appropriate functionally active lipid as a component of the lipid bilayer. Surface-modified liposomes have been designed to target immune cells, co-deliver immunostimulatory agents, and enhance both the humoral and cell-mediated immune responses simultaneously to improve the efficacy of liposomal vaccines.

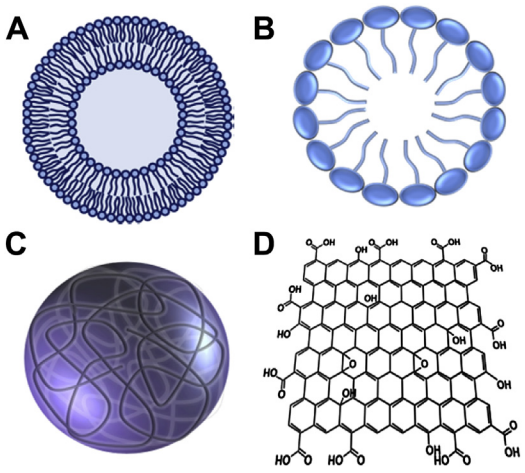

Fig. 1 – Structure of nanocarriers for vaccine antigen delivery. (A) Liposomes, (B) emulsions, (C) polymeric nanoparticles, and (D) graphene oxide nanosheets.

The physicochemical properties of liposomes, such as their size and fluidity, are important for the induction of an immune response. The vesicle sizes of liposomes composed of cationic dimethyldioctadecylammonium (DDA) can affect the cell-mediated immune response, but not the humoral immune response [18]. Liposomes larger than 2 μm in diameter were found to effectively promote interleukin-10 production, whereas liposomes 500 nm in diameter promoted a higher level of interferon-γ production in splenocytes.

Small unilamellar vesicles composed of cationic DDA liposomes were found to produce higher CD8 T cell responses compared to the larger multilamellar vesicles [19]. A recent study reported that rigid DDA lipid-based liposomes produced a Th1-directed immune response against antigens that was 100 times greater than the response produced by fluidic dimethyldioleoylammonium (DODA)-based liposomes [20].

The liposomal delivery of protein antigens via surface adsorption methods may be optimized by tuning the surface antigen and lipid ratio. The protein surface antigen-to-lipid ratio can affect the aggregation behavior of liposomes and can impact general vaccine stability during storage [21]. Surface modifications to antigen-carrying liposomes gearing polyethylene glycol (PEG) groups can reduce liposome aggregation. However, the retention of the liposomes at the injection sites was simultaneously reduced, thereby altering the Th1/Th2 immune response compared to the response produced by unmodified liposomes [22].

The liposomal co-delivery of antigens and an immunostimulatory molecule can enhance the generation of a protective immune response. The entrapment of trehalose 6,6-dibehenate (TDB), an immunostimulatory molecule, within a liposome did not affect the physicochemical properties of neutral distearoyl-sn-glycero-3-phosphocholine (DSPC) or cationic DDA-based liposomes, and significantly increased the production of IFN-γ after immunization [23]. Monophosphoryl lipid A (MPL), a poorly soluble TLR 4 agonist, was added to the bilayers of