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Particulate formulations for the delivery of poly(I:C) as vaccine adjuvant ☆

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ABSTRACT

Current research and development of antigens for vaccination often center on purified recombinant proteins, viral subunits, synthetic oligopeptides or oligosaccharides, most of them suffering from being poorly immunogenic and subject to degradation. Hence, they call for efficient delivery systems and potent immunostimulants, jointly denoted as adjuvants. Particulate delivery systems like emulsions, liposomes, nanoparticles and microspheres may provide protection from degradation and facilitate the co-formulation of both the antigen and the immunostimulant. Synthetic double-stranded (ds) RNA, such as polyriboinosinic acid–polyribocytidylic acid, poly(I:C), is a mimic of viral dsRNA and, as such, a promising immunostimulant candidate for vaccines directed against intracellular pathogens. Poly(I:C) signaling is primarily dependent on Toll-like receptor 3 (TLR3), and on melanoma differentiation-associated gene—5 (MDA-5), and strongly drives cell-mediated immunity and a potent type I interferon response. However, stability and toxicity issues so far prevented the clinical application of dsRNAs as they undergo rapid enzymatic degradation and bear the potential to trigger undue immune stimulation as well as autoimmune disorders. This review addresses these concerns and suggests strategies to improve the safety and efficacy of immunostimulatory dsRNA formulations. The focus is on technological means required to lower the necessary dosage of poly(I:C), to target surface-modified microspheres passively or actively to antigen-presenting cells (APCs), to control their interaction with non-professional phagocytes and to modulate the resulting cytokine secretion profile.

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Abbreviations: AIM 2, absent-in-melanoma 2; APC, antigen-presenting cell; BMDC, bone marrow-derived DC; CLR, C-type lectin receptor; CTAB, cetytrimethylammonium bromide; CTL, cytotoxic T lymphocyte; DAI, DNA-dependent activator of IFN-regulatory factor; DAMP, danger-associated molecular pattern; DC, dendritic cell; DDA, dimethyldioctadecylammonium; DEAE, diethylaminoethyl; ds, double-stranded; GM-CSF, granulocyte macrophage colony-stimulating factor; HFF, human foreskin fibroblast; iDCs, immature DCs; IFN, interferon; IL, interleukin; IP 10, IFN-γ-inducible protein 10 (CXCL10); IRF 3, IFN-regulatory factor 3; LCs, Langerhans cells; LPS, lipopolysaccharide; MDA-5, melanoma differentiation-associated gene—5; mDC, mature DC; MHC, major histocompatibility complex; mincle, macrophage-inducible C type lectin; MoDC, monocyte-derived dendritic cell; M720, Montanide ISA 720; NAP 1, neutrophil activating peptide 1; NLR, NOD-like receptor; ODN, oligodeoxynucleotide; OVA, ovalbumin; PAMP, pathogen-associated molecular pattern; pDC, plasmacytoid dendritic cell; PEI, polyethyleneimine; PK3, pH-sensitive polyketal copolymer; PLGA, poly(lactic-co-glycolic acid); PLL, poly(L-lysine); PLL-g-PEG, Poly(L-lysine)-*graft*-poly(ethylene glycol); PEG, poly(ethylene glycol); poly(A:U), polyriboadenylic–polyribouridylic acid; poly(IC·LC), poly(I:C) stabilized with poly(L-lysine) and carboxymethylcellulose; poly(I:C12U), Ampligen; poly(I:C), polyriboinosinic acid–polyribocytidylic acid; PRR, pathogen recognition receptor; PS, polystyrene; RIG I, retinoic acid-inducible gene-I; RLRs, retinoic acid-inducible gene-I-like receptors; SLN, solid-lipid nanoparticle; TCR, T cell receptor; TDB, trehalose 6,6′-dibehenate; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-alpha.

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1. Introduction and background

In contrast to traditional vaccines, consisting of live attenuated or killed pathogens, current development of vaccines is often based on highly purified recombinant proteins, synthetic oligopeptides, synthetic oligosaccharides, or viral subunits. This approach improves manufacturing reproducibility and lowers the risks of adverse reactions. Nevertheless, such subunit vaccines are often prone to degradation and intrinsically poorly immunogenic. This calls for improved delivery systems and potent immunostimulants, two issues which are typical for current adjuvant research.

In general, an adjuvant may be defined as an additive or vehicle that improves the adaptive immune response or stimulates the innate immune system in such a way that the desired effectors or mediators are efficiently induced. Current trends in vaccine adjuvants were recently reviewed [1]. Adjuvants can be classified into three types based on their mode of action [2]: Type A adjuvants are mostly derived from pathogens and act via specific immunostimulatory mechanisms on antigen-presenting cells (APCs) by providing a danger signal (Fig. 1). In case of dendritic cells (DCs), such type A adjuvants induce maturation and thus enhance both antigen presentation, i.e. signal 1, and associated costimulation, i.e. signal 2 (for more details see Section 2.1). Ideally, by choosing the right danger signal, DCs may be programmed to induce a tailored immune response to the pathogen against which the vaccination is directed. In contrast, type B adjuvants solely enhance the presentation of the antigen, i.e. signal 1. Typical type B adjuvants comprise antigen delivery systems like mineral salts, oil-in-water (o/w) and water-in-oil (w/o) emulsions, liposomes, nanoparticles and microspheres (or microparticles), as recently reviewed by [3] (Fig. 1). They are thought to promote or prolong antigen presentation via the formation of a depot, protect from hydrolytic or enzymatic degradation, facilitate antigen delivery directly to the lymph nodes, or enhance APC targeting. Furthermore, some type B adjuvants induce a strong cytotoxic T lymphocyte (CTL) response by triggering cross-presentation of the antigen [3]. A major drawback of type B adjuvants is their lack of immunostimulation, which may result in the development of tolerance [2]. In contrast, type C adjuvants directly provide signal 2 and do not require APC activation. Prominent examples are soluble factors like type I interferon (IFN) [4], tumor necrosis factor (TNF)-α, [5], or a CD28-specific monoclonal antibody mimicking CD80 or CD86 binding [6] (Fig. 1).

The combination of an immunostimulant (type A) with an adequate antigen delivery system (type B) is a promising strategy to protect both partners from degradation on the one hand, and deliver them directly to the target cells, e.g. APCs, on the other. In fact, several combined adjuvant formulations are currently evaluated in preclinical and clinical studies [7]. Furthermore, the combination of type A and B adjuvants is often synergistic: It has been proposed that the presentation of a phagocytosed antigen is more efficient when co-formulated with a danger signal [8,9]. In general, the combination of adjuvants represents a recent trend in adjuvant research [10].

Double-stranded (ds) RNA is a virus-associated danger signal. Several synthetic dsRNAs, like PIKA, Ampligen, also denoted as poly(I:C12U), or polyriboinosinic acid–polyribocytidylic acid, commonly denoted as poly(I:C) (Table 1), efficiently mimic viral dsRNA. This makes them potential type A adjuvant candidates for vaccination against viral infections. Such dsRNAs are known ligands to the Toll-like receptor (TLR) 3, which is located in the membrane of the endosomal compartments of most APCs. A general overview on the mechanisms of nucleic acid sensing by APCs as well as bystander cells through TLRs was recently reported [11]. Particulate type B adjuvants are ideal for the endosomal delivery of dsRNAs, especially in the context of APCs as professional phagocytes. However, several type A adjuvants, such as poly(I:C) and other nucleic acid-based TLR ligands, have been linked to over-stimulation of the immune system and even autoimmunity [12]. Such adverse effects need to be brought under control before their clinical applicability can be fully appraised.

In this review, we outline potential variables that may influence the immunostimulatory profile of a combination of particulate delivery systems (type B) and a prototype TLR3-ligand (type A), as well as the receptor expression pattern on target and bystander cells. We focus on the immunological benefits and adverse effects of poly(I:C), and how the latter may be controlled by properly designing and optimizing the delivery system.

2. Dendritic cells as a privileged target for vaccines

During the last two decades, dendritic cells (DCs) became increasingly recognized as target cells for vaccination according to their role as the most potent antigen presenting cells (APCs) of the innate immune system. Yet, the human DC population is very heterogeneous. At least four major subsets can be distinguished by different paths of development: (i) the interstitial DCs that are found in the stroma of most tissues, (ii) the resident DC subtypes that populate the draining lymph nodes, thymus and spleen, (iii) the Langerhans cells (LCs) that represent a specialized DC contingent in the skin, and (iv) the plasmacytoid DCs (pDCs) that are detected in the peripheral blood at very low levels (<1%) as well as in lymphoid tissue [13,14]. A scheme for the different pathways to pathogen-specific response after pathogen entry into epidermis is given in Fig. 2. In a different approach, DCs were classified according to their surface expression of typical lineage markers into myeloid ($CD8^-$) and lymphoid ($CD8^+$) DCs, with pDCs belonging to the lymphoid lineage [15–17]. Because of the very low frequency of DCs in human blood, protocols have been designed to generate monocyte-derived dendritic cells (MoDCs) in vitro [18]. A cytokine cocktail of interleukin (IL)-4 and granulocyte macrophage colony-stimulating factor (GM-CSF) induces the differentiation of human peripheral monocytes, isolated from blood, into MoDCs [18]. Although it has yet to be determined to which in vivo occurring DC subtype the in vitro-generated MoDCs correspond, they represent a commonly accepted in vitro model to study the effect of immunomodulating agents. Notably, all DC subsets are capable of antigen presentation but substantially differ in surface phenotype, localization,

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