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Potential of glucans as vaccine adjuvants: A review of the α-glucans case

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ABSTRACT

α-Glucans are present in virtually all domains of life, and these glucose chains linked by α-1,4- and α-1,6-linked branches form the most important storage carbohydrates in cells. It is likely for this reason that α-glucans are not generally considered as bioactive molecules as β-glucans are. Nevertheless, it is known that depending on their source, many α-glucans play important roles as modulators of immune response. Recent efforts have attempted to elucidate the mechanisms through which α-glucans exert their immunostimulant effects; however, the main challenge is the accurate identification of the receptors of immune cells involved in their recognition. Here, we review the adjuvant properties reported for some polysaccharides and ultimately focus on α-glucans and how their structural characteristics, such as molecular weight, solubility and derivatization, influence their immunostimulatory properties. As a final point, we discuss the potential and associated challenges of using these polysaccharides as adjuvants, particularly in mucosal vaccination.

Contents

1. Introduction

Vaccine adjuvants are molecules, compounds or macromolecular complexes added to antigens, such as inactivated, subunit, and recombinant proteins, to enhance and modulate their immunogenicity (Garçon, Hem, & Friede, 2012). Because a simple increase in antibody production is not always sufficient to obtain efficient

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candidate vaccines, the emergence of pathogens resistant to antibiotics and the fact that vaccines are currently being developed not only to prevent infectious diseases but also to treat cancers or chronic disorders, we are committed to the rationalized identification, selection, and use of adjuvants (Lee & Nguyen, 2015; O'Hagan & Wack, 2012). A greater understanding of adjuvants' mechanisms of action, experimentation with animal models and human clinical studies have provided evidence and data showing the potential of many adjuvants candidates (Olafsdottir, Lindqvist, & Harandi, 2015; Reed, Orr, & Fox, 2013). Complete information about their names, components, structure, function, safety, and usage in vaccine development can be found in a web-based database (Vaxjo) that was created to analyze, update and select this information and to facilitate rational vaccine design (Sayers, Ulysse, Xiang, & He, 2012). However, the potency of many of these promising candidates has invariably been associated with increased toxicity or even autoimmune disease(s)/disorder(s), which contributes to their exclusion and the dominance of first-generation adjuvants, such as aluminum salts in the form of aluminum oxyhydroxide, hydroxyphosphate, or hydroxide gel (Alhydrogel®), and oil-in-water emulsions, such as MF59, AS03 and AS04 (monophosphoryl lipid A preparation with aluminum salt) (Garçon et al., 2012; Lee & Nguyen, 2015; Pellegrino, Clementi, & Radice, 2015; van der Laan, Gould, & Tanir, 2015). As a consequence, few adjuvants have been approved for human use, and none of them has been approved for mucosal administration (Newsted, Fallahi, Golshani, & Azizi, 2015). Therefore, the main challenge lies in identifying safe adjuvants that enhance vaccine efficacy in infants, the elderly and immunocompromised people, increase the titer of neutralizing antibodies and confer broad and long-term protection with minimum quantities of the antigen and vaccine (Reed et al., 2013). Another important benefit that is also expected to be obtained through the administration of adjuvants are the enhancement of specific immune responses such as cell-mediated immunity and favorable mucosal immunity when administered by this route (Brunner, Jensen-Jarolim, & Pali-Schöll, 2010). This benefit is a very important issue because mucosal vaccines, unlike injected vaccines, can provide protection against pathogens not only at the site of entry but also at the systemic level and thereby simultaneously offer other important advantages, such as lower costs, easier and safer needle-free administration, and higher patient conformity (Rhee, Lee, & Kim, 2012).

Given these considerations and in view of the urgency of developing ideal adjuvants, carbohydrate-based adjuvants are an alternative with increasing importance due to their immunomodulatory properties, low cost, high tolerability and potential for mucosal administration (Petrovsky & Cooper, 2011; Li & Wang, 2015).

In this regard, glucans, which are glucose polymers classified according to their inter-chain linkage as α- or β, have acquired importance in the biomedical and pharmaceutical sectors due to their biological activities, such as anticoagulant, antithrombotic, antioxidant, and anti-inflammatory properties (Kagimura, da Cunha, Barbosa, Dekker, & Malfatti, 2015). β-glucans have been specially recognized for their healing and immunomodulatory characteristics (Zhu, Du, & Xu, 2016), whereas there are sparse reports about the immunostimulatory function of α-glucans and their interaction with the immune system despite their abundance and isolation from natural sources with recognized medicinal properties. This review discusses the immunostimulant properties of polysaccharides, placing particularly emphasis on glucans and their structure-activity relationships. We also provide an overview of the structural and functional properties of α-glucans that could be related to their immunostimulant activities and discuss the α-glucans purified from plants and natural products to provide a different perspective regarding the challenges and potential use of α-glucans as adjuvants, mainly for mucosal vaccination.

2. Generalities of immunostimulatory polysaccharides and their adjuvant mechanisms

Polysaccharides are anabolic products from a wide variety of organisms, including plants, animals and microorganisms, such as fungi and bacteria. These compounds not only have important biological functions in structure and energy storage but also interact with the host immune system, regulating its response, which has resulted in their classification as immunomodulators or biologic response modifiers (Tzianabos, 2000). This important property has permitted their incorporation in prophylactic and therapeutic vaccines based on carbohydrates (glycoconjugate vaccines, synthetic oligosaccharides or modified microbial glycans), because they are epitopes crucial for the activation of Th cells (Anish, Schumann, Pereira, & Seeberger, 2014; Hecht, Stallforth, Silva, Adibekian, & Seeberger, 2009). A better understanding of the mechanisms underlying the recognition of these molecules by the immune system as well as their good safety, high tolerability and efficient stimulation of humoral and cellular acquired immunity have permitted their consideration as promising vaccine adjuvant candidates (Li & Wang, 2015; Petrovsky, 2006).

The majority of these polysaccharides exert their adjuvant activity through the following five mechanisms: (1) specific binding to pathogen-recognition receptors (PRRs), (2) upregulation of antigen presentation and costimulatory molecules, (3) activation of complement pathway, (4) chemotaxis and (5) activation of pro- and anti-inflammatory signals (Awate, Babiuk, & Mutwiri, 2013; Petrovsky & Cooper, 2011). More detailed descriptions exist for fungal β-glucans and chitosan, which can bind Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs) and C-type lectin-like receptors (CLRs) to induce humoral and cellular immune responses (Carroll et al., 2016; Huang et al., 2009; Underhill, 2003; Xia et al., 2015). This ligand-receptor interaction and the stimulation of immune activity depend on the structure of the polysaccharide, particularly the type of monosaccharides and glycosidic bonds in the molecule, and on both the charge and molecular weight (MW) (Zhang, Qi, Guo, Zhou, & Zhang, 2016).

Although polysaccharides that are classified as TLR4 ligands have a broad MW range (from 5 kDa to 2400 kDa), most of the reported ones have weights between 10 and 1000 kDa, which indicates that polysaccharides with molecular weights in this range might exhibit the highest activity. However, the existing data from TLR4-carbohydrate affinity studies are not sufficient to conclude that differences in the binding affinities of these polysaccharides depend only on MW because the monosaccharide composition, the polysaccharide glycosidic bond type and the degree of branching also determine the immunostimulant activity of polysaccharides through TLR4 (Zhang et al., 2016).

Solubility and the presence of contaminants are also important factors that affect the recognition of polysaccharides by antigen-presenting cells (APCs) and, consequently, their activation and cytokine production, which constitute the link between the innate and adaptive immune responses and define the antigen-specific T- and B-cell responses (Wismar, Brix, Lærke, & Frøkiær, 2011). Table 1 summarizes some immunostimulant properties of different non-glucan polysaccharides.

2.1. Zwitterionic polysaccharides (ZPSs): model of immune system activation by polysaccharides

One of the first descriptions of the interaction of polysaccharides with the immune system was the report of bacterial polysaccharides, for which their charge is one of their most important properties. Non-zwitterionic polysaccharides, which have only negatively charged residues or no charge groups, are classic anti-