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Review

Polysaccharides as vaccine adjuvants

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ABSTRACT

Adjuvant is a substance added to vaccine to improve the immunogenicity of antigens, and it can induce stronger immune responses and reduce the dosage and production cost of vaccine in populations responding poorly to vaccination. Adjuvants in development or in use mainly include aluminum salts, oil emulsions, saponins, immune-stimulating complexes, liposomes, microparticles, nonionic block copolymers, polysaccharides, cytokines and bacterial derivatives. Polysaccharide adjuvants have attracted much attention in the preparation of nano vaccines and nano drugs because natural polysaccharides have the characteristics of intrinsic immunomodulating, biocompatibility, biodegradability, low toxicity and safety. Moreover, it has been proved that a variety of natural polysaccharides possess better immune promoting effects, and they can enhance the effects of humoral, cellular and mucosal immunities. In the present study, we systematically reviewed the recent studies on polysaccharides with vaccine adjuvant activities, including chitosan-based nanoparticles (NPs), glucan, mannose, inulin polysaccharide and Chinese medicinal herb polysaccharide. The application and future perspectives of polysaccharides as adjuvants were also discussed. These findings lay a foundation for the further development of polysaccharide adjuvants. Collectively, more and more polysaccharide adjuvants will be developed and widely used in clinical practice with more in-depth investigations of polysaccharide adjuvants.

Contents

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1. Introduction

As the most effective intervention in modern medicine, vaccination greatly reduces mortality and extends life expectancy [1]. Moreover, vaccination can prevent and control the spread of an infectious disease by generating a sufficient protective immune response [2], and it has changed the lives of millions of people and animals [3]. Over the past several decades, the progress in vaccine development has become the greatest medical achievement of human beings, and vaccines against human papillomavirus (HPV), *Chikungunya* virus (CHIKV), hepatitis C virus (HCV) [4] and influenza (Flu) virus have been exploited, including nanovaccines.

Adjuvant is a substance added to vaccine to improve the immunogenicity of highly purified antigens. Moreover, adjuvants can induce stronger immune responses to antigens and reduce the dosage and production cost of vaccines in populations responding poorly to vaccination. Adjuvants in development or in use mainly include aluminum salts, oil emulsions, saponins, immune-stimulating complexes, liposomes, microparticles, nonionic block copolymers, polysaccharides, cytokines and bacterial derivatives. Among these available adjuvants, aluminum salt is the most widely accepted vaccine adjuvant. However, aluminum salt fails to enhance a cell-mediated type-1 helper T cell (Th1) or cytotoxic T lymphocyte (CTL) response, and aluminum salt is not a good inducer of mucosal immune system [5]. Since aluminum adjuvant cannot stimulate sufficient antigen immunity, thus its accumulation may lead to renal dysfunction and affect brain tissue and bone tissue, resulting in neurological syndrome and dialysis-related dementia [6]. Nowadays, most veterinary vaccines are either inactivated organisms formulated with an oil-based adjuvant or live-attenuated vaccines [7]. However, there are also issues of local injection site reactions for an oil-based emulsion adjuvant [2]. More viscous oil adjuvant is not conducive to injection. Although mineral oil-based adjuvants are generally effective for veterinary vaccines, mineral oils can cause serious side effects, such as local granuloma, abscess or fever [8]. Polysaccharide adjuvant can enhance the immune effect of a vaccine, leading to promoted body-specific immunity and non-specific immunity, cellular immunity, humoral immunity and mucosal immunity. Although not many polysaccharides can be used as vaccine adjuvants, the natural polysaccharides have the characteristics of intrinsic immunomodulating, biocompatibility, biodegradability, low toxicity and safety [9]. Therefore, polysaccharide adjuvants have attracted much attention in the preparation of vaccines, which have become the development trend of vaccine adjuvants, exhibiting a greater potential in the field of vaccine [10].

2. Polysaccharide adjuvant (PA)

In many cases, vaccines only stimulate too weak immunogenicity to prevent infection. Therefore, vaccine adjuvants are required in the preparation of vaccine to boost the immune response. Polysaccharides belong to a class of natural polymers consisting of glycosidically linked carbohydrate monomers [11]. Polysaccharides can activate macrophages, T lymphocytes, B lymphocytes and NK cells, and promote the secretion of immune-related molecules, such as cytokines, antibodies and complement molecules [9,12]. Polysaccharide derivative, monophosphoryl lipid A, has been shown to be virulent and immunologically active adjuvant by binding to toll-like receptor 4 (TLR4) [13]. As vaccine adjuvants, polysaccharides can not only promote antigen-specific immune system, but also enhance the body's natural immune function [10]. Polysaccharide adjuvants mainly include chitosan and its derivatives, including glucan, mannan, inulin and Chinese medicinal herb polysaccharide. Fig. 1 illustrates their structural formula, and Table 1 lists their advantages and disadvantages as adjuvants.

2.1. Chitosan nanoparticles (NPs)

As a biopolymer of cationic polysaccharides derived from the exoskeleton of crustaceans, chitosan has good biological properties *in vivo*, such as low toxicity, good biocompatibility, biodegradability and so on [14,15]. Chitosan is a potential material to boost the effectiveness of vaccines [16]. Chitosan can effectively stimulate humoral and cell-mediated immune responses [17]. Moreover, it

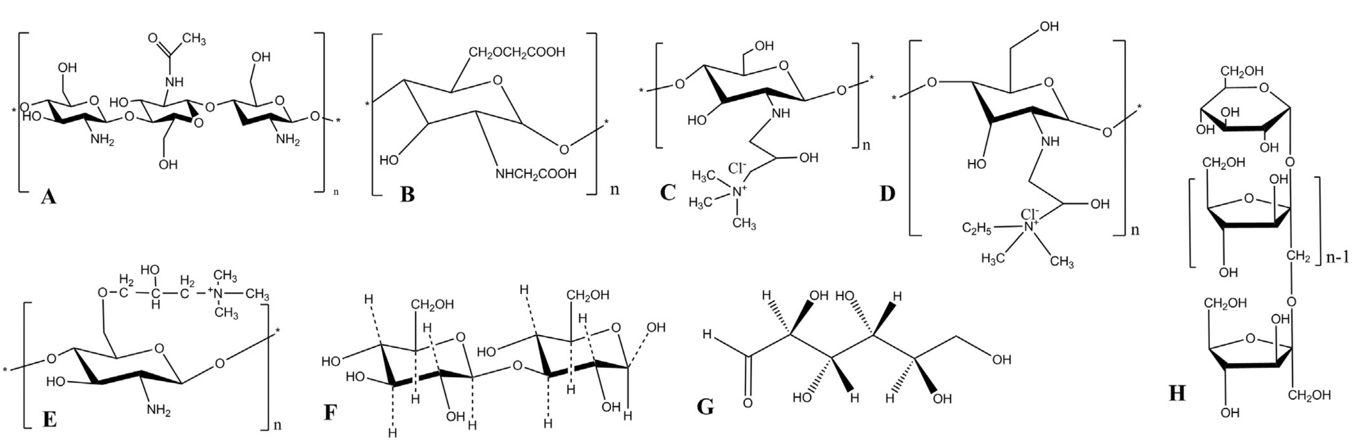

Fig. 1. Structural formula of chitosan, its derivatives and other polysaccharides. A: Chitosan; B: carboxylated chitosan (CMCS); C: *N*-2-hydroxypropyl trimethyl ammonium chloride chitosan (N-2-HACC); D: *N*-2-hydroxypropyl dimethylethyl ammonium chloride chitosan (N-2-HFCC); E: *O*-2′-hydroxypropyl trimethyl ammonium chloride chitosan (O-2′-HACC); F: 1,3-β-glucan; G: mannose; H: inulin polysaccharide.

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