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Review

β-glucans as potential immunoadjuvants: A review on the adjuvanticity, structure-activity relationship and receptor recognition properties

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ABSTRACT

β-glucans, a group of polysaccharides exist in many organism species such as mushrooms, yeasts, oats, barley, seaweed, but not mammalians, have a variety of biological activities and applications in drugs and other healthcare products. In recent years, β-glucans have been studied as adjuvants in anti-infection vaccines as well as immunomodulators in anti-cancer immunotherapy. β-glucans can regulate immune responses when administered alone and can connect innate and adaptive immunity to improve immunogenicity of vaccines. When β-glucans act as immunostimulants or adjuvants, a set of receptors have been revealed to recognize β-glucans, including dectin-1, complement receptor 3 (CR3), CD5, lactosylceramide, and so on. Therefore, this review is mainly focused on the application of β-glucans as immune adjuvants, the receptors of β-glucans, as well as their structure and activity relationship which will benefit future research of β-glucans.

Contents

1. Introduction

The term adjuvant was first used to refer to the substances combined with vaccines to improve the intensity and longevity of immune response or to change the type of response, with low toxicity and weak immunogenicity [1,2]. Traditionally, according to the roles that adjuvants play in vaccination, adjuvants were divided into three types, namely, vehicle, storage and immune stimulant [3]. Vehicle adjuvant can take vaccine to specific tissues or to antigen presenting cells (APCs) directly. Storage adjuvant can extend the duration of immune reaction to antigen, whereas

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immune stimulant adjuvant can enhance the sensitivity of immune system to antigen. Nowadays, the definition of adjuvant has been expanded. Adjuvants are not merely used in prophylactic vaccine formulation, but also used in therapeutic formulation and used alone for immunomodulatory purpose. Hence, these adjuvants can be collectively referred to as immunoadjuvants [4]. More recently, extensive research on immunomodulatory activities of these immunoadjuvants demonstrates the relationship and mechanisms between adjuvants and immune system [5,6]. The general mechanism is that immunoadjuvants can be recognized as pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), which present on the surface of immune cells, and then initiate a series of effects such as signaling pathways activation, gene expression, cytokines secretion, cells maturation and differentiation and lead to the activation of adaptive immune response [3]. Thus, substances that have immunomodulatory effects or PRR binding capabilities are studied for their potential use as adjuvants.

Many polysaccharides that can bind to PRRs and stimulate immune system, such as α-glucans (modified dextran), β-glucans (yeast polysaccharides and lentinan), β-fructans (inulin), mannan and chitosan, have the potential to be used as immunoadjuvants [7,8]. Among these polysaccharides, β-glucans are components of fungal cell wall and have lots of immunomodulatory properties [9,10]. β-glucans are β-linked homopolysaccharides composed of D-glucopyranosyl residues and can be extracted from mushrooms, yeasts, oats, barley, seaweed, algae, fungi and bacterial cell walls [11–13]. However, the structures of β-glucans are diverse. For example, β-glucan from microorganism is mainly constituted by β (1 → 3) linked glucose with several (1 → 6) linked branches, while β-glucan from plant is mainly constituted by β (1 → 3) and β (1 → 4) linked glucose without branch. Besides, curdlan, one type of β-glucans from bacteria, is assembled only with a β (1 → 3) glucose molecule without any branches [14]. Based on the β-linked backbones, β-glucans can be recognized and captured mainly by specific receptors, such as dectin-1 on dendritic cells (DCs) and macrophages. Their recognitions initiate signal cascade to promote cytokine production, cell maturation and migration and the sensitivity to antigen, then induce or reinforce Th1 cells biased adaptive immune response so as to exert adjuvant effects [15–17]. Consequently, immunomodulatory activities and receptors of β-glucans are investigated comprehensively and have been developed in anti-infection vaccine as well as anti-tumor therapy.

2. Potential activity of β-glucans as adjuvants

2.1. Immunomodulatory activity

The immunomodulatory activities of β-glucans have been studied for decades [13,18,19], and the investigations have been mainly focused on their effects on cytokines secretion, function changes of immune cells and shift of Th1/Th2 response bias [20] (shown in Table 1). To the effect on cytokine secretion of immunocytes,

Table 1
An overview of β-glucan action as immunomodulators.

Agents	Sources	Subjects and type of experiments	Effects	References
β-glucan-containing products	*Shiitake mushrooms*	Human lymphocytes (*in vitro*)	IL-8, IL-6, IL-1β and TNF-α secretion↑	[21]
β-1,6-glucan	*Agaricus bisporus* or *Agaricus brasiliensis*	THP-1 macrophages (*in vitro*)	TNF-α, IL-1β and COX-2 gene expression↑ (administered alone) Anti-inflammatory activity against LPS stimulation	[22]
Water-insoluble β-1,3-glucan with few branches at C-6 and C-2 positions	*Ganoderma Lucidum*	Raw 264.7 cells (*in vitro*)	Anti-inflammation activity against LPS stimulation	[23]
β-glucan	*Laminara digitata*, *Laminara hyperborea* or *Sacharomyces cerevisiae*	Porcine liver (*in vitro*)	No obvious influence on cytokine secretion when administered alone Resist inflammation induced by LPS	[24]
β-1,3-glucan	*Saccharomyces cerevisiae*	Mouse macrophages and lymphocytes (*in vitro*)	Th2 immune response↑ Th1 immune response↓	[25]
β-(1,3)(1,4)-glucan	Oat	Macrophages (*in vitro*)	Phagocytic activity of macrophages↑	[32]
Microparticulate β-glucan + OVA	*Saccharomyces cerevisiae*	Bone marrow-derived dendritic cells (*in vitro*)	Antigen presentation activity of APC↑	[38]
β-1,3-glucan	Mushroom	B6 mice (*in vivo*)	Th2 immune response↓ Th1 immune response↑	[26]
β-1,6-branched β-(1,3) with an α-(1,3)-linked glucohexaose	Synthetic	BALB/c mice (*in vivo*)	Th2 immune response↑ Anti-inflammatory response↑	[27]
β-1,3-glucan	*Saccharomyces cerevisiae*	Rainbow trout (*in vivo*)	Survival rates after the chellange of *Aeromonas salmonicida*↑	[31]
β-(1,3)(1,4)-glucan	Oat	C57BL/6 mice (*in vivo*)	Disease resistance against *Staphylococcus aureus* and *Eimeria vermiformis* infection↑	[33]
Nano scale β-glucan	Oat	Zebrafish larvae (*in vivo*)	Survival rate after challenge of *Edwardsiella tarda*↑ TNF-α, IL-1β, β-defensin, lysozyme, IL-10 and IL-12 secretion↑	[34]
Particulate β-glucan	Yeast	C57BL/6 mice (*in vivo*)	Clearance of HBV DNA↑ Recruitment of DC, macrophages and effector T cells to liver HBV-specific Th1 immune responses↑	[36]
Particulate β-glucan	Yeast	C57BL/6 mice (*in vivo*)	Conversion of immunosuppressed macrophages into activated type Tumor burden↓	[37]
β-glucan + LPS	*Saccharomyces cerevisiae*	Carp (*in vivo*)	Resistance to *Aeromonas hydrophila*↑	[39]
β-1,3/1,6-glucan	*Saccharomyces cerevisiae*	Dog (*in vivo*)	Serum total IgA↑, IgM↓	[40]

HBV: hepatitis B virus; ↑: increase; ↓: decrease.

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