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REVIEW ARTICLE

Stimulatory Effect of β-glucans on Immune Cells

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β-Glucans are naturally occurring polysaccharides that are produced by bacteria, yeast, fungi, and many plants. Although their pharmacological activities, such as immunomodulatory, anti-infective and anti-cancer effects, have been well studied, it is still unclear how β-glucans exert their activities. However, recent studies on the β-glucan receptors shed some light on their mechanism of action. Since β-glucans have large molecular weights, they must bind surface receptors to activate immune cells. In this review, we summarize the immunopharmacological activities and the potential receptors of β-glucans in immune cells.
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CHEMISTRY OF β-GLUCANS

β-Glucans are heterogeneous polysaccharides of glucose polymer, consisting of a backbone of β-(1-3)-linked β-D-glucopyranosyl units with β-(1-6)-linked side chains of varying distribution and length. The activity of β-glucan depends on the molecular structure, size, branching frequency, structural modification, conformation, and solubility. It appears that the most active forms of β-glucans contain β-(1-3)(1-6) linkages (1). The structure of several biologically active β-glucans has been reported. β-Glucan from many mushrooms has a β-(1-3) backbone with shorter β-(1-6) linked branches, while β-glucan from *Alcaligenes faecalis* contains only β-(1-3)-glucosidic linkages (2). Schizophyllan from *Schizophyllum commune* and scleroglucan from *Sclerotium glucanicum* both have a β-(1→3) linked backbone with one β-(1→6)-glucose substitution every three backbone residues (3). Lentinan from *Lentinus edodes* has a β-(1→3) linked backbone and two β-(1→6) side chains every five residues (4). β-Glucan from oat and barley are linear with β-(1-4) linkage with shorter stretches of β-(1-3) (3).

Biologically active β-glucans usually have a large molecular weight. However, it is unclear whether β-glucans having intermediate or small molecular weight have biological activities, although some of them are active *in vivo*. Short β-glucans below 5,000-10,000 Da of molecular weight are generally inactive (5). The optimal branching frequency is suggested as 0.2 (1 in 5 backbone residues) to 0.33. Although unbranched β-glucan curdlan showed proper biological activity, chemical addition of β-(1-6) glucose residues to the curdlan backbone led to an increase in anti-tumor activity (6), as highly branched β-glucan has higher affinity for cognate receptors (7). Furthermore, soluble β-glucans appear to be stronger immunostimulators than insoluble ones. When insoluble scleroglucan is modified by sulfation or carboxymethylation, the anti-tumor activity increases (8).

Further study is still required before we will fully understand the structure-activity relationship in β-glucans. Orally administered β-glucans may be modified to smaller oligosaccharides *in vivo* (3). Thus, the actual β-glucans binding to the immune cell surface receptors *in vivo* may in fact be these smaller ones. However, there is no information on this topic to date. If we can use standardize smaller β-glucans, the biological data might be fruitful.

IMMUNOPHARMACOLOICAL ACTIVITY OF β-GLUCANS

β-Glucans, generally called biological response modifiers, are now recognized as anti-tumor and anti-infective drugs. The most popular β-glucan is lentinan, which is isolated

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from fruiting bodies of *Lentinus edodes* is the most popular β-glucan and is a well-known drug with anti-tumor and anti-infective activities (9). β-Glucan has been shown to protect against infection by bacteria, viruses, and pathogenic microorganisms (10). β-Glucan also prevents cancer promotion and progression and has synergistic anti-tumor effects with monoclonal antibodies and cancer chemotherapeutics (11). β-Glucan promotes antibody-dependent cellular cytotoxicity through a biological pathway involved in carcinogenesis (12). However, lentinan might not directly affect cancer cells or infectious microorganisms. There are no reports on the direct effect of lentinan on these cells. Instead, it is believed that lentinan shows these biological activities through activation of host immune systems.

The effects of β-glucans on immune cells are well established. Traditionally, macrophages and dendritic cells are considered the main target cells of β-glucans, although neutrophils, B cells, T cells, and natural killer cells are also known to be activated by β-glucan. The immunomodulatory activities of β-glucans are usually studied with regard to the activation of macrophages. Lentinan enhances cytotoxic activity and inflammatory cytokines of primary macrophages and RAW264.7 cell lines (13). It can also enhance the phenotypic and functional maturation of dendritic cells with significant IL-12 production (14). Stimulatory effects of lentinan on T cells have also been reported. Lentinan enhances the virus-specific T cell functions induced by DNA vaccine, acts as a vaccine adjuvant (15), and increases T cell functions in tumor-bearing mice (16) and malaria-infected mice (10). In addition, lentinan is reported to enhance T cell functions in cancer patients (17). However, there is no report showing that lentinan directly activates T cells *in vitro*. It has been demonstrated that lentinan indirectly activates T cells via IL-12 and IFN-γ produced by lentinan-activated macrophages and dendritic cells (18). However, lentinan might be an indirect activator of T cells and T cell activation might be observed only under *in vivo* conditions with mixed immune cell subsets. It has been reported that lentinan increases NK cell-mediated killing of Yac-1 cells both *in vitro* and *in vivo* (19). However, this does not necessarily mean that lentinan directly activates NK cells, since total spleen cells were used in this experiment. The only clear fact is that β-glucan directly activates macrophages and dendritic cells, but the effect of β-glucan on other immune cells remains controversial. Further *in vitro* studies with purified immune cell subsets are required to clarify whether β-glucan directly activates these cells.

β-GLUCAN RECEPTORS

Macrophages and dendritic cells have typical cell surface receptors called pattern recognition receptors (PRRs) that detect innately non-self molecules including pathogen-associated molecular patterns (PAMPs) (20). β-Glucans might act as PAMPs and are recognized by PRRs, since β-glucans cannot directly penetrate cell membrane due to their large molecular size (3). The major PRRs for β-glucans might be dectin-1 and the roll-like receptor (TLR). Upon binding with β-glucan, dectin-1 and TLR might inducing signaling cascade and activate immune cells. Other receptors, such as complement receptor 3 (CR3), scavenge receptors (SR), and lactosylceramide (LacCer), might be involved (20).

DECTIN-1

Dectin-1 is a lectin that consists of four components: an extracellular carbohydrate-recognition domain, a short stalk region, a single transmembrane region, and a short 40 amino acid intracellular cytoplasmic tail (21). Dectin-1 consists of 244 amino acids and has six cysteine residues. In particular, two amino acids (Trp221 and His223) located near the fourth cysteine residue appear to be critical for binding of β-glucans (22). Dectin-1 specifically recognizes β-(1-3)(1-6) glucans from fungi, plants, and bacteria (23). However, it is not reactive toward β-(1-4) glucans or α-mannan (24).

Binding of dectin-1 with β-glucans induces several signaling pathways to activate innate immune responses, such as phagocytosis, ROS production, and inflammatory cytokine production (25). The cytoplasmic tail of dectin-1 has an immunoreceptor tyrosine-based activation (ITAM)-like motif (YxxxI/Lx7YxxL) to activate tyrosine kinases (26). Upon ligand binding, tyrosines in the ITAM sequences are phosphorylated by Src family kinases, providing a docking site for Syk (spleen tyrosine kinase) by interacting with the two SH2 (Src homology 2) domains of Syk (26). The spacing between the YxxxL sequences is important to engage both SH2 domains of Syk family kinase, thus contributing to enzyme activation (27). Activated phospholipase C γ (PLCγ) produces inositol trisphosphate and diacylglycerol (DAG) (28). Also, Syk activates the PI3K/Akt pathway, MAPK, NFAT, and NF-κB (29).

TLRs

TLRs are expressed on macrophages, dendritic cells, B cells, T cells and endothelial cells and are type I transmembrane receptors of a novel protein family. At least 13 members of this family exist in human. TLRs can recognize diverse microbes including fungi, bacteria, viruses and protozoa. Several ligands have been shown to bind TLRs: TLR2-zymosan, TLR3-dsRNA, TLR4-LPS, and TLR5-Flagellin, etc. (3). Binding of specific ligands to TLRs induces several signaling pathways, such as My88-mediated signaling and TRIF-mediated signaling. TLR signaling usually results in activation of NF-κB and MAPK signalings (30). There are many β-glucans that can bind to TLRs. For example, zymosan binds to TLR2/4 of macrophages and increases the cytokine production such as TNF-α and IL-12 via NF-κB signaling (31). β-Glucans isolated from plants, such as *Sparassis crispa*, *Phellinus linteus*, *Platycodon grandiflorum*, *Cordyceps millitaris*, and *Angelica gigas* Nakai, induce dendritic cell maturation through binding to TLR4 (32-37). Signalings downstream from TLRs or dectin-1 might cross-talk with each other (38). Zymosan can bind both dectin-1 and TLR2, and both dectin-1/Syk and TLR/Myd88 signalings are required to fully induce the translocation of NF-κB subunits to the nucleus (39).

OTHER RECEPTORS

First identified over 25 years ago, CR3 can recognize carbohydrates (40). CR3 acts as an opsonic receptor for the complement component and as a nonopsonic receptor for a variety of exogenous ligands. CR3 is a heterodimeric transmembrane integrin consisting of CD11b (α_m) and CD18 (β_2) chains. CD11b has two binding sites. One for β-glucan is located within the C terminus, while the other for iC3b (cleaved component 3 fragment of serum complement system) is located within the N-terminus (40). Binding of β-glucan to the C-terminal lectin domain increases adhesion to microbial cells and activates iC3b pathways causing tumor cytotoxicity (41). Ligand binding of CR3 is known to mediate intracellular signaling and induce a variety of cellular responses, including adhesion, cytotoxicity, phagocytosis and migration (41). However, whether CR3 directly binds to β-glucan is still unclear. CR3-deficiency in NK cells reduced cytotoxicity, but CR3-deficient leukocytes are still capable of recognizing and responding to β-glucan (42). The β-glucan of small molecular size binds to CR3 in NK cells and that of large molecular size binds dectin-1 and TLRs in macrophages and dendritic cells.

LacCer (CDw17 and Gal4Glc1Cer) is expressed on neutrophils and endothelial cells. LacCer recognizes a variety of microbes and pathogens, including fungi, such as *Candida albicans*, *Cryptococcus neoformans*, and *Saccharomyces cerevisiae* (43). It consists of a hydrophobic ceramide and a hydrophilic sugar moiety and is identified as a receptor for β-glucan (44). The interaction of β-glucan with LacCer induces a number of cellular responses *in vitro*. In alveolar neutrophils, β-glucan from *Pneumocystis carinii* can induce the production of macrophage inflammatory protein-2 (MIP-2) and TNF-α via NF-κB and PKC signaling. Blocking antibodies to LacCer or CR3 are also reported to inhibit β-glucan binding to and the activation of human neutrophils (45).

SR are expressed on epithelial cells, endothelial cells and myeloid cells and comprise a family of proteins that are structurally diverse and have a range of cellular functions (46). SR were initially described in cultured macrophages in which they mediate cholesterol uptake. Based on their structures, SR can be categorized into class A, B and C. SR-A has a collagen-like domain, which is essential for ligand binding (47). SR recognizes a variety of ligands including LDL (low-density lipoprotein), HDL (high-density lipoprotein), selected polyanionic molecules, and a number of microbes (47). SR has also been implicated in the recognition of β-glucan. Lentinan can bind to SR and activate multiple signals, such as PI3K, Akt kinase, and MAPK (47).

SUMMARY

β-Glucans are potent immunomodulators that have multiple activities such as anti-tumor and anti-infective activities. However, how β-glucan exerts these diverse biological activities is still unknown. The first step mediating β-glucan action might be immunostimulation. In particular, binding of β-glucan to specific receptors in macrophages and dendritic cells can induce the production of various cytokines, indirectly activating other immune cells such as T cells and B cells under *in vivo* conditions. Systemic immunostimulation might be the main route in preventing the growth of cancer cells and infective microorganisms in the host. Several β-glucan receptors in macrophages and dendritic cells, such as dectin-1 and TLRs, might play a key role in the recognition of β-glucans, but the exact signaling pathways downstream from the respective receptors and the cross-talk between

them is unclear to date. If we can understand these issues in greater detail, β-glucans might be widely used in the therapy of cancer and infectious diseases.

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CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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