

# Immunomodulatory Aspects and Mechanisms of Action of $\beta$ -Glucans

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## Abstract

$\beta$ -glucans are found in bacterial and fungal cell walls and have been implicated in the initiation of anti-microbial immune response.  $\beta$ -glucans act on Dectin-1, complement receptor (CR3) and TLR-2/6 immune receptors. They trigger a group of immune cells including macrophages, neutrophils, monocytes, natural killer cells and dendritic cells. Most  $\beta$ -glucans enter the proximal small intestine and some are captured by the macrophages. They are internalized and fragmented within the cells, then transported by the macrophages to the marrow and endothelial reticular system. The small  $\beta$ -glucan fragments are eventually released by the macrophages and taken up by other immune cells leading to various immune responses.

**Keywords:** Immunostimulator;  $\beta$ -Glucan; Dendritic Cells; Immunomodulatory; Polysaccharides

## Introduction

Immunostimulators promote activation of immune system cells directly or indirectly [1]. They can increase cell proliferation and cell differentiation. They alter the differentiation of naive CD4<sup>+</sup> Th precursors in Th1 or Th2 cells. They thereby modulate the Th cytokine type production by changing the balance of cell-mediated and humoral immunity as well as the class or subclass of immunoglobulin synthesis [2]. They can activate the complementary complement pathway, resulting in the following immunostimulatory effects: supporting the presentation of the T-cell antigen [3]; stimulation of B-cells by B-cell co-receptors upon direct presentation of the B-cell antigen [4]; helping the function of dendritic cells to preserve B-cell memory and thus enhances the secondary antibody response [5]; generation of other immunostimulators. They are immunostimulators with

- Microbial origin ( $\beta$ -glucans, peptidoglycans, LPS, chitosan, chitin, FCA/ Freund's complete adjuvant, etc.)
- Plant origin ( $\beta$ -glucans, polysaccharides, alginate, etc.)
- Synthetic (isoprinosine, lefamizole, FK 565 (muramylpeptide), MDP / muramyl dipeptide etc.)

## Sources and Structure of $\beta$ -glucan Effects

$\beta$ -glucans are one of the most abundant forms of polysaccharides found inside the cell wall of bacteria and fungus. All  $\beta$ -glucans are glucose polymers linked together by a 1 $\rightarrow$ 3 linear  $\beta$ -glycosidic chain core and they differ from each other by their length and branching structures [6]. Their activity depends on their molecular structure, size, structural modifications, conformation and

solubility. Greater biological activity and immunostimulating effect have those with higher molecular weight and better solubility [7].

The effect of  $\beta$ -glucan has long been proven to protect against bacteria, viruses and pathogenic micro organisms. Recently, a number of studies have demonstrated anti-tumor effect by activating antibody-dependent cellular cytotoxicity [8]. Because of these properties,  $\beta$ -glucans are called modifiers of the biological response. The main targets of  $\beta$ -glucans are macrophages and dendritic cells, although the effect on neutrophils, T- and B-lymphocytes, NK cells is also described [9]. Their immunomodulatory properties are primarily related to the activation of macrophages, their cytotoxic activity and the production of inflammatory cytokines. They also increase the phenotypic and functional maturation of dendritic cells [10]. Their effect on T-lymphocyte activation is indirect, mainly by IL-12 and IFN- $\gamma$ , produced by activated macrophages and dendritic cells. Increased NK-mediated cytotoxicity under  $\beta$ -glucan activity has been demonstrated in vitro and in vivo [11].

### Receptors for B-Glucants

Macrophages and dendritic cells have specific surface receptors called pattern recognition receptors (PRRs) that recognize for eign molecules, including pathogen-associated molecular patterns (PAMPs) [12].  $\beta$ -glucans are recognized by PRRs as PAMPs [12]. The most important receptors in this group are dectin-1 and toll-like receptors (TLRs). By binding to  $\beta$ -glucans, dectin-1 and TLR induce a signal cascade and activate immune cells. Other receptors, such as complement receptor 3 (CR3), scavenge receptors (SR), and lactosylceramide (LacCer), might be involved [13].

### Dectin-1

Dectin-1 is a lectin receptor that specifically recognizes  $\beta$ -glucans of bacterial, fungal and plant origin. Binding of dectin-1 with  $\beta$ -glucans induces several signaling pathways to activate innate immune responses, such as phagocytosis, ROS production, and inflammatory cytokine production [14].

### Toll-Like Receptors

TLRs are transmembrane receptors of a new protein family. They are expressed on macrophages, dendritic cells, endothelial cells, B and T lymphocytes. More than 13 representatives of this family exist in humans. TLRs recognize different micro organisms.

Binding to them leads to the induction of intra cellular signaling pathways [15].

In experimental studies,  $\beta$ -glucans have been shown to activate TLR2 / 4 on macrophages and to increase cytokine production of TNF- $\alpha$  and IL-12 by NF- $\kappa$ B [16]. Moreover, signals from TLRs and the receptor are interacting and potentiating each other.

### Mechanism of Action

Most  $\beta$ -glucans enter the proximal part of the small intestine and are captured by the macrophages, where they are internalized and fragmented. They are transported from them to the bonemarrow and the reticulo-endothelial system. Small fragments are detached from macrophages and taken up by the circulating granulocytes, monocytes and dendritic cells. The immune response then be elicited [17]. Most  $\beta$ -glucans are believed to activate both non-specific and specific immune responses as most immunostimulators. An essential feature of their action, however, is the lack of polarization of the immune response to Th-1 or Th-2. Recent studies in experimental models show an increase in regulatory T lymphocytes (T-reg) under the action of  $\beta$ -glucans. This important circumstance expands the possibilities for their application without potential risks of auto immunity. Clinical trials are needed to confirm the pungent results of experimental research so far.

### Conclusion

$\beta$ -glucans are a promising group of immunostimulators whose long-known empirically proven properties are confirmed in modern experimental studies. Future clinical studies will expand our knowledge of their role as therapeutics in the immune protection of the human body.

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