

β -Glucan – from Food Supplement to a Licensed Drug

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Background

Natural products, useful in preventing or treating various diseases, have been sought after throughout the history of humankind. Often, these molecules suffer from the same problem - these substances usually represent a complex mixture of ingredients, each of which might contribute to biological activity. These problems, together with difficulties in patenting the isolation, usually leads to lack of interest and natural molecules are left in the area of food supplements.

β -Glucan

However, $\beta(1-3),(1-6)$ -D-glucan (hereafter β -glucan), arguably the most studied natural immunomodulator, offers a different story. The original studies of effects β -glucan has on the immune system focused entirely on mice. Subsequent studies demonstrated that β -glucan possesses a significant immunostimulating activity in a wide variety of species, including earthworms, shrimp, fish, chicken, rats, rabbits, guinea pigs, sheep, pigs, cattle, and, last but not least, humans. Based on these results, it has been concluded that β -glucan represents a type of immunostimulating molecule that is actively spanning full evolutionary spectrum [1]. Some experiments also show that β -glucan can help even in the protection of plants. β -Glucan is therefore not only a biologically active polysaccharide with strong immunomodulating effects, but is also considered to be an evolutionary very old stimulant of a variety of defense immune reactions.

Despite decades of intensive research, the mechanism of how β -glucan affected our defense reactions remained a mystery. Only in the last decade, detailed research by numerous scientific groups has helped to reveal the extraordinary effects that β -glucan exerts on various physiological and pathophysiological processes in of our body. Based on more than 12,000 studies about various types of β -glucan, we can conclude that β -glucans from fungi (both macro- and micromycetes, particularly yeasts) are well-known biologic response modifiers that function as immunostimulants against health problems such as infectious diseases and cancer. Unlike most other natural products, properly purified β -glucan retain their bioactivity in spite of drastic isolation procedures. This allows us to finally characterize how β -glucan works on a cellular and molecular level.

Mechanisms of Action

Biological response modifiers such as β -glucan have usually been classified as non-specific due to our lack of knowledge of specific mechanisms of action and the binding moieties on immune cells. The access to the soluble glucans opened the door to detailed studies of interaction of glucan with cell membrane. The results of these studies, summarized in ref. [2], showed two major receptors (CR3 and Dectin-1) and several minor ones, including Toll receptors and scavenger receptors. In each case, the binding of glucan to the receptor triggers a signaling cascade resulting in cell activation.

Our knowledge of the molecular mechanisms of β -glucan action is still far from clear.

First observations of decrease of NF κ B and NF-IL-6 binding activity was followed up by more detailed study showing that glucan

inhibited LPS-induced NF κ B activation via down regulation of IKK β kinase activity and altered phosphorylation and degradation of I κ B α [3]. Other groups, however, observed activation of NF κ B, which subsequently mediates production of TNF- α . The involvement of Syk kinase was later confirmed on Dectin-1 receptor. The β -glucan binding is followed by phosphorylation of Dectin-1 by tyrosine kinase Src. As a result, Syk is activated and subsequently activates the card9-bcl10-Malt1 complex. Induction of several cytokines follows. In the macrophages, the Syk kinase/CARD9 pathway acquires co-stimulation of MyD88-coupled TLR for the induction of inflammatory cytokines [4]. New studies of β -glucan isolated from *Coriolus versicolor* showed that the effects on phagocytosis of macrophages are related to the Akt and CK2/Ikaros. These findings are not only important for our understanding of signaling events upon binding of β -glucan on cell membrane, but provide an input into recognition of fungal pathogens by the innate immunity as a first line of defense against pathogenic infections.

Conclusion

All these new findings mentioned above open the window for β -glucan to become a licensed drug. In addition to effects in anti-infectious and anti-cancer immunity, novel studies clearly demonstrated significant palliative effects of β -glucan in allergy, arthritis, gastrointestinal tract diseases, stress reduction and reduction of cholesterol levels (for review see [5]). With over 60 clinical trials currently running, the question of whether other countries will follow Japan, where β -glucan is officially used since 1983, is not if, but when.

References

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