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β-Glucan – Is the Current Research Relevant?

Abstract

Cancer is a leading cause of death worldwide; responsible for approximately 20% of all deaths in the United States. Most cancers have external causes and, in principle, should be preventable. Evidence suggests that the structure of diet significantly impacts our immune system. Therefore, current research is focusing on changing dietary composition as a method of improving our immune function.

Keywords: β- glucan; Cancer; Immune system; Nutrition

Mini Review

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Introduction

Cancer is a leading cause of death worldwide. Approximately 20% of all deaths in the United States are caused by cancer. It has become clear that most cancers have external causes and, in principle, should be preventable. There is accumulating evidence suggesting that the composition of the diet significantly impacts our immune system. Therefore, changing dietary composition as a tool to improve the immune function is a current research focus.

β-Glucans, present in various forms in foods such as cereals and mushrooms, have been widely used as immunostimulating agents promoting immune responses [1]. β-Glucans belong to a group of natural, physiologically active compounds, generally called biological response modifiers.

Since β-glucan therapy has achieved great success in various preclinical animal models, many efforts have been made to determine their therapeutic efficacy in human patients. Currently, there are over 80 β-glucan clinical trials in various types of therapy. The most attention is focused on cancer. Although data from most of these trials have not been released, a recent trial conducted by Biothera using Imprime PGG plus Erbitux and a chemotherapy drug suggests that the combination of Imprime PGG, Erbitux and Camptosar nearly doubled the overall response rate of second- and third-line metastatic colorectal cancer patients compared with individual components alone.

Additional clinical trials of glucan involve infections, particularly evaluating effects of glucan supplementation of children with chronic respiratory problems[2-3]. In addition to currently running clinical trials, it is important to note that, since 1983, two versions of glucan are already in use as an established drug in Japan [4]. Regardless of the ongoing clinical trials and official drug status in some countries, animal research is still necessary; and there are numerous reasons why we need to continue studying glucans and their biological effects.

We have to remember that the original studies of effects of β-glucan on the immune system focused entirely on mice. Later, additional studies demonstrated that β-glucan possesses a significant immunostimulating activity in a wide variety of species including earthworms, bees, shrimp, fish, chicken, rats, rabbits, guinea pigs, sheep, pigs, cattle, and, of course, humans. These results led to a conclusion that β-glucan represents a unique type of immunostimulating molecule that is actively spanning full evolutionary spectrum [5]. However, despite decades of intensive research, the mechanisms of how β-glucan affected, our defence reactions are still not fully explained [6-8], clearly showing the need for more research.

Discussion

Glucan, as every natural molecule, suffers from some problems slowing down its clinical use. Some problems result from batch-to-batch variability, others from still unknown relation between structure and function [9]. There are literally hundreds of different glucans are currently available, isolated from different sources by different techniques and differing widely in biochemical and physicochemical characteristics. In addition, new glucans appear in the literature almost daily [10]. To make the situation even more difficult, various concentrations and routes of administration (oral, intraperitoneal, intravenous, subcutaneous) have been tested. All this leads to severe confusion, with manufacturers often claiming that their glucan possesses the highest biological activities. The problem of diverse data can be solved only by comparative studies. However, scientific reports directly comparing individual glucans are limited [11-17]. Readers interested in comparisons of glucan in cancer treatment should see the excellent review written by Story et al. [18].

Clearly, more research on glucan and its individual varieties is necessary. As currently very few large companies manufacture glucan, it is often difficult to obtain funding necessary to perform

studies on large animals, pushing the research on glucan back to the mouse model.

Phagocytosis usually represents the first studied effect of glucan, originally described as the nonspecific modulator of macrophages. This activity is considered to be crucial to establishing the glucan quality. So far, there is no glucan at the market which would have significant biological activity without stimulating phagocytic activity. The focus on phagocytosis leads to an important question – does it have any reflection on more complex immune reactions including the cancer treatment? Phagocytosis results in internalization of the prey, but represents only one of the numerous subsequent steps, leading to a burst of metabolic activity and final killing or destruction of the ingested material.

In addition, activated macrophages significantly influence the quality, duration, and magnitude of most inflammatory reactions. Traditionally, macrophages have been described as antigen-presenting phagocytes that secrete proinflammatory and antimicrobial mediators. Classically activated macrophages exhibit a Th1-like phenotype, promoting inflammation, extracellular matrix destruction, and apoptosis, while alternatively activated macrophages display a Th2-like phenotype, promoting extracellular matrix construction, cell proliferation, and angiogenesis [19]. Therefore, evaluating the role of glucan in macrophage activation is crucial for our understanding of glucan action and for our ability to finally reach the holy grail of glucan research – the ability to decide which glucan is the best.

However, these studies should focus on more than one possible effect – it is better to establish that the tested glucan can influence a wider spectrum of immune reactions. Another important marker of glucan action is the effect on superoxide and nitrite production. Superoxide is biologically quite toxic and is deployed by the immune system to kill invading microorganisms. In phagocytes, superoxide is produced in large quantities by the enzyme NADPH oxidase for use in oxygen-dependent killing mechanisms of invading pathogens. The role of redox molecules, such as nitrite oxide, as key mediators of immunity has recently garnered renewed interest and appreciation. To regulate immune responses, these species trigger the eradication of pathogens as well as modulate immunosuppression during tissue-restoration and wound-healing processes [20].

Another important test of glucan action is the production of cytokines. Cytokines are small secreted proteins released by cells and have a specific effect on the interactions and communications between cells. They may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both proinflammatory and anti-inflammatory cytokines. The extremely complex system of cytokines working as bioactive molecules makes the effects of glucans on this network extremely important. On one hand, we do not need long-lasting systemic effects on cytokine production; on the other hand, immunomodulators only rarely skip this part of the defense reactions. Thus, glucans usually stimulate production of several cytokines such as IL-2, IL-10, TGFβ and IFNγ [21], with the only exception being Betafectin [22].

Natural killer (NK) cells make up another important part if the spectrum of immune reaction often used in evaluating of glucan activities. These cells are a type of cytotoxic lymphocyte critical to the innate immune system. The role NK cells play is analogous to that of cytotoxic T cells. NK cells provide rapid responses to viral-infected cells, acting at around 3 days after infection, and respond to tumor formation. Typically, immune cells detect major histocompatibility complex presented on infected cell surfaces, triggering cytokine release, causing lysis or apoptosis. As these cells have both CR3 and Dectin-1 receptors on their membrane, they are highly susceptible to glucan treatment. It is not surprising, therefore, that high quality glucans strongly stimulate NK cell function [23-24].

Recently, glucans have been shown to stimulate not only the cellular branch of immune reactions, but also the antibody formation [25,26].leading to suggestions that they can be part of vaccinations. In farmed animals, such as fish, pigs or chicken, glucan inclusion in vaccine is already being intensively studied [27,28]. An effect on the antibody response is therefore another important part of the glucan evaluation.

Only with successfully establishing significant effects of glucan on small vertebrates/mammals is it possible to step up to additional species of interest, from commercially important animals to human clinical trials.

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Both authors contributed equally.

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