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β-Glucan in Allergies

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Abstract: Multiple effects of β-glucan are well established. Together with the effects on antibacterial and anticancer immunity, glucan has been shown to stimulate bone marrow cells, lower cholesterol and to protects against stress and some kinds of poisoning. However, despite literally thousands of papers describing biological effects of β-glucan, only limited attention has been focused on the role of β-glucan in allergic reactions. Our review is focused on evaluating the current knowledge of the possible role of β-glucan in allergic reactions. Most of published studies concur that based on the improved Th1/Th2 balance, β-glucan showed a potential for development as an adjunct to the standard treatment of in patients with allergies.

Keywords: Glucan, Allergy, CR3, Cancer

Introduction

Proper history of polysaccharides as immunomodulators goes back to the 40 s of the last century when Shear and Turner (1943) described a polysaccharide substance from *Serratiamarcescens* cultures that caused necrosis of tumors. Generally speaking, immuno-modulatory preparations from bacteria-either extracts from intact cells or isolated products such as Shear's polysaccharide - are *à priori* suspicious and their use can be dangerous. Perhaps due to this fact, focus was given to polysaccharides isolated from "human friendly" organisms, *i.e.*, yeasts and edible mushrooms.

Next step in using of polysaccharides in affecting body response resulted from studies of zymosan. Pillemer *et al*. (1955) demonstrated that the essential activity of zymosan consists in a glucan-rich fraction. In contrast, the mannan-rich fraction-glucomannan protein-showed little activity. Based on these studies, attention soon focused on glucan.

Nicholas DiLuzio and his coworkers from the Tulane University in New Orleans pioneered further medical research of β-glucan. In a series of papers (DiLuzio *et al*., 1970; DiLuzio and Riggi, 1970; DiLuzio, 1983; Williams *et al*., 1980), they demonstrated that glucan administration caused significant phagocytic stimulation of the reticuloendothelial system, enhanced host defense mechanisms and resistance to experimental tumors. Independently, Japanese scientists focused on mushroom-derived β-glucans and their effects on antitumor immunity (Chihara *et al*., 1969; Chihara, 1984). These studies resulted in approval of Lentinan as an official drug.

Despite long-term interest and research, the mechanism of how β-glucan affects our health remained a mystery for a long time. Only in the last decade, extensive research by numerous scientific groups has helped to reveal the extraordinary effects that β-glucan has on our immune system.

Availability of soluble glucans led to the possibility to study the interaction of β-glucans with cell membrane. Experiments done by a research group, led by Gordon Ross, focused on one particular receptor called complement receptor type 3 (CR3 receptor, CD11b/CD18) as a promising target of β-glucan. This group's research has shown that CR3 serves as a major receptor for β-glucans with human or mouse (Czop and Austen, 1985; Patchen and MacVittie, 1982) leukocytes and is responsible for numerous functions of β-glucans. Unlike other non-specific modifiers, β-glucan specifically targets macrophages, neutrophils and NK cells to tumors that are opsonized with antibodies and C3 and therefore β-glucan has the same specificity as the tumor-opsonizing antibodies. Further research has shown soluble β-glucans that bind to CR3 monogamously and prime the receptor for subsequent cytotoxic activation if membrane CR3 are subsequently clustered by contact with the iC3b coating a tumor cell.

For a long time, β-glucans have been studied in infections. Using several experimental models, it has

been well established that β-glucan protects against infection with both bacteria and protozoa and enhances antibiotic efficacy in infections with antibiotic-resistant bacteria. In addition to the effects of β-glucan oriented towards the immune system, β-glucans were also shown to reduce the total and LDL (low-density lipoprotein) cholesterol levels of hypercholesterolemic animals and patients (Tietyen *et al*., 1990; Delaney *et al*., 2003).

β-Glucan was recently found to have an additional use-the regulation of stress. We measured the effects of various types of β-glucan on the levels of stress-induced corticosterone. As experimentally induced stress, we used either restraint or cold. Our results (Vetvicka and Vancikova, 2010) showed that β-glucans successfully helped to keep the stress hormone corticosterone at almost normal levels. In addition, various less-known effects of β-glucan have been reported-significant stimulation of the methotrexate treatment of adjuvant arthritis (Rovensky *et al*., 2011), glucan-collagen matrix that combines β-glucan with collagen was proven to have excellent results in successful treatment of burns in children (Delatte *et al*., 2001) or β-glucan-mediated inhibition of the development of atopic dermatitis (Sugiyama *et al*., 2010).

Basic Information about Allergies

Allergic reactions represent several conditions caused by hyperactivity of the immune system. As one in three people suffers from allergy, the spreading epidemic of allergies and asthma led to increased interest in both research of the mechanisms and of the potential treatment. Allergic reactions include asthma, sinusitis, rhinoconjuctivitis, food allergy, atopic dermatitis, urticarial and anaphylaxis.

Fifty years after demonstration that IgE is capable of transferring sensitivity to allergens (for history of IgE see Stanworth, 1993), we understand that IgE acts as part of protein network which includes FcεRI, CD23 and galectin-3. Additional co-receptor involved in IgE actionis CR3. Generally speaking, allergic diseases are those mediated by expansion of T helper 2 cells together with isotype switching of B lymphocytes to generate IgE antibodies (Georas *et al*., 2005).

Both mast cells and IgE antibodies are concentrated in the mucosal tissue and they are among the first defense molecules encountering invading pathogens. The most classical allergic response is mediated by the IgE-FcεRI complex expressed on the plasma membrane of mast cells and is represented by immediate hypersensitivity with symptoms such as asthma, rhinitis or atopic dermatitis. The crosslinking of these receptors results in mast cell degranulation and chemokine release. The early stages are later changed into late phase, characterized by activation and homing of inflammatory cells and by activation of IgE-sensitized antigen presenting cells (for review see Gould and Sutton, 2008).

Based on 50 years of research, significant progress has been made in understanding of immunological pathways leading to allergies, of chemical mediators and in understanding of environmental agents augmenting allergen sensitization (Eder *et al*., 2006). For a review of possible innovating therapeutics and immunologic and molecular targets, see (Holgate and Polosa, 2008).

Despite the intensive research and significant improvements of our understanding of the immune mechanisms involved in allergic reactions, this mountain of information did not reach any significant new treatment. Studies showing the success of omalizunab in treatment of allergy offer new hope and suggest that allergy as fully immunity-based disease can be cured by immunological means. Particularly promising are monoclonal antibodies directed against cells expressing markers such as IL-5R (interleukin-5 receptor) and CCR4 (C chemokine receptor type 4) (Satoh *et al*., 2006). β-Glucan with well-established multifactorial effects on almost all aspects of immune reactions remains one of the possibilities how to utilize modulation of the immune mechanisms in treatment or even prophylaxis of allergic problems.

Animal Experiments

The role of β-glucan in allergy was, however, rather neglected. One or the reasons might be the fact that the whole situation might be controversial, since glucans are a common structural component in a variety of established allergens. In addition, evaluation of β-glucan levels is currently used for diagnosis of fungal infections. However, nasal inhalation of β-glucan does not induce acute inflammation (Beijer and Rylander, 2005). Lung epithelium forms an important physical barrier that the inhaled allergen encounters. In addition, lung epithelial cells contribute to the developing response by coordinating the activities of other immune cells through the secretion of cytokines (Kato and Schleimer, 2007). Mouse studies have shown that β-glucans are responsible for the induction of IL-6 (interleukin-6) secretion from these cells and that glucans further regulate cytokine/chemokine production of lung epithelial cells (Neveu *et al*., 2011). These effects are, however, more connected with lung response to challenge than with the allergic reaction.

However, some recent studies suggested that β-glucan can also play a role in alleviation of allergic problems (see below). The mechanisms of the role of β-glucan in allergies are, as yet, not fully established. Most hypotheses suggested that β-glucan effects are manifested via decreasing proinflammatory cytokines

(most of all IL-6 and TNF-α), increasing of secretion of IL-10 (interleukin-10) and elevating accession of cellular antioxidants.

In the mouse experimental model, some previous studies have documented anti-inflammatory effects of β-glucans derived from *Aureobasidium pullulans* on formalin- and xylene-induced acute inflammation accompanied by typical signs as severe vasodilation, oedematous changes of skin and infiltration of inflammatory cells (Kim *et al*., 2006; 2007). The authors concluded that β-glucans from this yeast-like fungus have somewhat favourable effects in the reduction of the induced acute inflammatory response.

Another study of the therapeutic effect of β-glucans of *A. pullulans* on the ovalbumin treated allergic reaction in mice found that glucan significantly inhibited the production of IgE antibodies specific to ovalbumin, reduced formation of IL-12 and IFN-γ production by lymphoid cells in the spleen and decreased numbers of CD8- and IFN-γ-positive cell numbers in the small intestine. It suggests that food allergic reaction against ovalbumin could be positively influenced by β-glucan administration support (Kimura *et al*., 2007). Therapeutic effects of β-glucans were confirmed later by Sato *et al*. (2012), who investigated the anti-degranulation effects of β-glucan from *A. pullulansin vitro* by using cultures of rat basophilicleukemia cells and bone marrow-derived mast cells. They also evaluated its effects of orally administered β-glucan *in vivo* on increased vascular permeability induced by stimulating ICR mice with IgE. They concluded that their results confirmed that β-glucans could be a possible compound for the effective therapeutic treatment of allergic diseases.

In this context it should also be mentioned that the effect of *A. Pullulans* β-glucan on the experimental ovalbumin-induced asthma in murine model is considered particularly relevant to the clinical setting (Ku *et al*., 2012). Asthma experimental model is often chosen for study, as this allergic disease has serious health consequences in human population and usually significantly worsens the quality of life. Asthma in man is now accepted as a chronic inflammatory disease characterized by an airway hypo responsiveness to both nonspecific stimuli and also to inhaled allergens of various origin (Takeda *et al*., 2012). Airway lowered responsiveness is caused by accumulation of large numbers of activated eosinophils and mast cells, evoking epithelial damage (Holgate 2008; 2012). Other pathological changes include alveolar hypertrophy, epithelia of bronchi and bronchiole infiltrated by inflammatory cells (Temelkovski *et al*., 1998; Gong *et al*., 2012). Some studies reports that the application of β-glucan had favorable effects in suppressing experimental ovalbumin-induced asthma in mice similar to antioxidants like vitamin A and C (Allen *et al*., 2009) and anti-inflammatory substances of plant origin (Babu *et al*., 2009). The healing effects of β-glucans on the inflammation accompanying asthma could be secondary to the decrease of proinflammatory cytokine (primarily TNF-α and IL-6) and increase of anti-inflammatory and anti-oxidative substances protecting cells from oxidative stress (Senoglu *et al*., 2008).

In further experiments with β-glucan isolated from *Euglena gracilis*, studies also found that an antiallergic activity of β-glucans could be caused by the activation of macrophages by epithelial cells and by the induction of differentiation of precursors of T cells into Th1 cells, which leads to the improvement of relationship of Th1/Th2 cytokines (Bouike *et al*., 2011) and to the downregulation of specific IgG1 and IgE but not IgG2a antibodies and IL-5 responses. In addition, decreased numbers of eosinophils were found. However, the production of IFN- γ increased (Takimoto *et al*., 2008; Hetland *et al*., 2011). Burg *et al*. (2016) reported similar results of orally administeredβ-glucan reducing eosinophil influx and the production of Th2 cytokines (IL-4, IL-5, IL-13) in the lungs of ovalbumin-challenged mice.Additional experiment with rarely used β-glucan isolated from *Euglena gracilis* using macroscopical and histological observations of skin and ear swellingshowed protection effect against atopic dermatitis skin lesions in experimental murine model. The serum concentrations of IgE antibodies, IL-4 and IFN-γ and production of IL-18 and IL-24 within the skin lesions also decreased (Sugiyama *et al*., 2010). This data suggested that oral administration of β-glucan blocked the dermatitis symptoms by suppressing both the Th1 and Th2 responses.

Human Studies

It is predicated that in 2050, up to 4 billion people in the world will suffer from some types of allergy diseases such as asthma, allergic rhinitis, atopic dermatitis orvarious forms of food, drug and insect allergies. Airborne concentrations of common ragweed pollen, a potent allergen, could increase fourfold in Europe by 2050.

Allergic diseases have various manifestations and are always associated with reduced quality of life and decreased work productivity. All allergic patients report that they often have problems with social activities; difficulties with daily activities, sleep disturbances and emotional problems; as well as poorer mental well-being (Leynaert *et al*., 2000; Meltzer, 2001).

It is known that β-glucans represent a group of biologically active polysaccharides with important immunomodulative properties (Novak and Vetvicka, 2009). They appear to be effective at enhancing immune

function and reducing susceptibility to infection and cancer (Murphy *et al*., 2010; Vannucci *et al*., 2013) and might also positively affect many allergies. This was documented by animal experimental and clinical trials and summarized in approximately 15,000 published articles. On the other hand, only a limited number of studies dealing with the therapeutic effect of β-glucans of various origins on the experimentally induced allergyhave been published.

On the basis of *in vitro* and *in vivo* experimental studies documenting the suppressive effects of β-glucans on artificially induced allergic reactions in murine and rat models, the beta-glucans were applied in several clinical trials in patients suffering asthma or other allergic diseases. Whereas it has been suggested that exposure to indoor microbial products or mold can promote the development of asthma (Douwes, 2005), other data show that that β-glucans and other microbial signals may play a protective role against the development of asthma (Heederik and von Mutius, 2012). One of the first studies on the therapeutic use of β-glucans for asthma was a study in which the hot water extract of *Agaricus blazei* was used to treat abronchitic patient with asthma-like symptoms (Miyamoto *et al*., 2002). After oral intake of the extract for two months, the attenuation of bronchitic symptoms was observed. The authors deduced that the amelioration of respiratory symptoms was accompanied with an elevation of a decrease of Th2 dependent IL-10 and increase of the production of IFN-γ by Th1 cells. In other study, after four weeks of application, patients allergic to ragweed demonstrated alleviated symptoms and some patients reported increased physical health, activities and emotional well-being and decreased sleep problems. Approximately 50% of the treated patients reported improved quality of life when compared with the study participants given the placebo. However, the serum levels of IgE remained unchanged (Talbott *et al*., 2013).

Some authors affirm that β-glucan administration can improve, or even prevent, symptoms of allergic rhinitis and upper respiratory tract as well as other allergic symptoms (Wichers, 2009, for review see Jesenak *et al*., 2014a). Similarly, Szabo *et al*. (2000) showed that β-glucans could alleviate the symptoms accompanying allergic conjunctivitis. Jesenak *et al*. (2014b) also demonstrated that in children suffering of recurrent respiratory tract infections the active treatment with β-glucans can contribute to significant depression of eosinophilia and stabilization of IgE serum levels. Kirmaz *et al*. (2005) reached similar results when β-glucan therapy was applied to patients with allergic rhinitis for 12 weeks. They found significant decrease of IL-4 and IL-5 levels and counts of eosinophils in nasal lavage fluid and increase of IL-12, whereas the levels of IFN-γ did not change. None of these monitored parameters changed in the placebo group.

Effect of β-glucans on the production of gel-forming mucins, the glycoproteins MUC_4 and MUC_5B, which are found in the outer layer of airway epithelium having an important role in the defense against pathogenic microorganisms, were studied by Kim *et al*. (2015). Expression of these mucins is influenced by factors including inhaled organic materials (lipopolysaccharides, peptidoglycans etc.) potentially includingβ-glucans, which as most abundant external substances act as imunostimulators of innate immunity (Neveu *et al*., 2011). The authors for the first time proved that β-glucans stimulate expression of these mucins by means of the activation of the TLR4-p38MAPK-NFκB pathway in human airway epithelial cells.

Contrary to the aforementioned animal studies on the therapeutic effect of β-glucans on asthma, there are minimal data on these effects on humans. In the first study dealing with asthmatic children, the particulate β-glucans were applied subcutaneously (Sarinho *et al*., 2009). It was shown that when β-glucans were given weekly for the first four weeks and then every two weeks for the last four weeks, the production of Il-10 increased and asthmatic symptoms were alleviated. The authors deduced that β-glucans could reduce Th2 response. Zhang *et al*. (2016) reported that exposure to fungal antigens elevates Th2 response and promotes severe allergic asthma. The seriousness of asthma after fungal exposure in children is accompanied by increased IL-17 in the serum. This effect can be reconstituted with betaglucan and suppressed by neutralization of IL-17.

A recent study showed that an intranasal treatment with a combination of β-glucan and resveratrol can strongly reduce nasal symptoms in children with pollen-induced allergic rhinitis, which is an IgE-mediated inflammatory reaction consequent to the exposure to allergen. The relatively limited number of patients studied suggests that these data are still of preliminary value (Del Giudice *et al*., 2014).

Can β-Glucan Cause Allergy?

Several environmental studies have related symptoms and disease to the presence and amount of β-glucan, but it is difficult to ascertain if such relations represent causality. The effects studied might also be related to exposure to some other biologically active agent in the environment, which is not measured. Only a few studies on environmental glucan have measured other potential agents such as bacterial endotoxin, which are always present. This is why studies that use the specific agent are of particular importance for the understanding of health risks due to β-glucan exposure.

The exposure to β-glucan takes place through ingestion and inhalation of fungal spores, hyphae and fragments of fungal cells. The limited data available suggest that β-glucan particles are phagocytosed by macrophages and dendritic cells but that the intracellular breakdown is slow due to the absence of appropriate enzymes. The particles are then widely spread in the body and deposited in various organs such as lymph nodes and spleen, where they subsequently degrade. Inhalation experiments on humans using β-glucan are limited to acute exposures with low doses. In one such study, subjects with a previous history or airway reactivity were compared to subjects without symptoms. After inhalation of insoluble β-glucan, the airway responsiveness was evaluated by the methacholine test, with no differences between these two groups. Subjective throat irritation was slightly increased in the group with previous airway symptoms, as compared to saline control exposure. No effects were found on the pulmonary function or airway responsiveness (Rylander, 1996). Animal experiments gave confusing results-some exposure resulted in changes in neutrophil numbers in airways, some found no changes at all (Fogelmark *et al*., 1992; Rylander *et al*., 2008). Intratracheal injection resulted in induction of a more severe pulmonary inflammation (Young *et al*., 2003).

Experiments evaluating the possible effects of yeast β-glucan in allergy development offered unclear results, too. Children living in a home with high mold index had more than twice higher risk to develop asthma. At low levels of β-glucan there was a positive relation between wheezing and exposure, but at higher levels the relationship was inverse. There was no relationship between the allergen sensitization and the exposure to β-glucan (Reponen *et al*., 2011).

Numerous studies never fully answered the question whether β-glucan can cause allergy. There are no doubts that inhaling β-glucan can initiate inflammation of the lungs and decrease immune responses. The possibility that these effects are caused more by additional molecules included in β-glucan was never experimentally rejected. However, β-glucan used orally as a supplement never caused any allergic reaction. Readers seeking comprehensive review on β-glucan exposure should read an excellent review written by (Rylander, 2012).

Conclusion

Studies mentioned in this short review suggest that β-glucan might be a promising candidate to be developed into a new anti-asthmatic agent. However, our report also underlines how little attention has been focused on β-glucan in allergies. With only a limited amount of observations, the exact mechanisms of β-glucan action in allergic diseases are difficult to interpret. However, the published studies concur that based on the improved Th1/Th2 balance, β-glucan showed a potential for development as an adjunct to the standard treatment of in patients with allergies. Clearly, more studies, both animal and human, are necessary before we can reach a full conclusion.

Author's Contributions

Both authors participated fully in all aspect of this manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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