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Functional Role of a Well Characterized Heteroglycan Isolated from *Pleurotus ostreatus* Mycelia in Driving Immune Stimulation

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Abstract

Polysaccharides or heteroglycan isolated from fungal species have attained wide recognition for their immune modulating functions. However, there exists a significant relationship in the structural and functional activity of this molecule. In this commentary, we focus on a well characterized heteroglycan isolated from the mycelia of *Pleurotus ostreatus* which have been shown to drive immune stimulation in tumor bearing mice. The heteroglycan possessed high molecular weight and was primarily composed of glucose, mannose and fucose in a 3:2:1 ratio with major β-linkages in the repeating chain. The molecule also exhibited triple helical conformation in solutions. These immune driving molecules have a significant impact in decreasing the tumor volume in model mice and they are known to play a significant role in the proliferation and activation of lymphocytes in the tumor bearing mice. The physical traits of the heteroglycan were associated with its immune stimulating ability and such compounds can therefore be utilized as adjuvants in immune based therapies.

Commentary

Fungus such as mushrooms has established their importance as medicines, particularly in oriental countries due to their effect as immunomodulators and anticancer agents. Compounds such as proteins, peptides, lectins, polysaccharides, polysaccharide–peptides and polysaccharide–protein complexes and many of their related compounds have been isolated from mushroom. These mushroom derived compounds possess high potential for immune stimulation or may reduce tumor progression. Among these, polysaccharides, present in fruiting bodies or mycelia have been found to be one of the potent immunologically active compounds due to their structural diversity, and variations in their structural complexity contribute to the functional aspect. These compounds are also recognised as biological response modifiers (BRMs) as they maintain both homeostasis and immune stimulation in an individual. These fungal derived polysaccharides exert their antitumor function either by: 1) preventing oncogenesis by intraperitoneal or oral administration of polysaccharides isolated from medicinal mushrooms (cancer-preventing activity); 2) enhancement of immunity against the bearing tumors (Immuno-enhancing activity); and 3) direct antitumor activity by inducing the apoptosis of tumor cells (Direct tumor inhibition activity) [1]. In many cases, the isolated polysaccharides from medicinal mushrooms have shown anti-tumor function through immune stimulation, although few cases also suggest direct antitumor activity.

Most of the mushroom polysaccharides or glycans possess glycosidic linkages, such as (1-3), (1-6)-β-glucans and (1-3)-α-glucans, while few others are true heteroglycans or glycans linked with proteins or peptides [2–4]. There exists considerable variation in the molecular weight as well as molecular size of these glycans. Immune response to β-glycans has been reported to be associated with physical traits like size, chemical structures such as composition as well as degree of side branching, triple helical conformation, solubility and gel forming ability [5]. Polysaccharides derived from mushrooms such as *Lentinus edodes*, *Schizophyllum commune* and *Grifola frondosa* have now been commercially used as drugs in many countries [6] Among the various mushroom derived polysaccharides studied till date, fungus belonging to the genus *Pleurotus* has gained recognition due to their wide range of biological functions which includes immune-modulation, antioxidative as well as antimicrobial activities [7].

Some of the well-studied species within the genus *Pleurotus* includes *Pleurotus tuber-regium*, *Pleurotus pulmonarius* and *Pleurotus ostreatus*. Extracts derived from the mycelia and sclerotia of *Pleurotus tuber-regium* have shown inhibition of sarcoma 180 and HL-60 cancer in mice models and in vitro cell lines respectively [8]. Another widely studied mushroom called the *Pleurotus pulmonaris* reduced the viability of various colon cancer cell lines [9]. *Pleurotus ostreatus*, also commonly known as oyster mushroom is now gaining importance as a medicinal mushroom due to its high medicinal and prebiotic functions. Glycans isolated from these oyster mushrooms through alkaline and hot water based methods showed growth of prebiotic microbes such as *Bifidobacterium*, *Lactobaccilus* and *Enterococcus* [10]. As the fruiting bodies are seasonal in their growth and have differences owing to temperature variations, the mycelial form of the fungus is now preferred to study biological functions so as to obtain constancy in the results. As the mycelial form is cultured in controlled laboratory conditions, it is expected that less structural variations may be caused by physiological or environmental entities. The polysaccharides or glycans isolated by alkaline-based method from the mycelia of *Pleurotus ostreatus* showed high molecular weight of 2700 kDa and had a structural composition of glucose, mannose and fucose with (1→2), (1→3), (1→4) and (1→6) linkages in the repeating chain of the molecule [11]. A lectin microarray technology has been effectively utilized to study the backbone composition of the polysaccharide molecule. Lectins, which are carbohydrate-binding proteins, interact with the saccharides through chemical bonds such as hydrogen bonds, hydrophobic and van der Waals interactions, and by metal coordination [12]. The molecule also exhibited a triple helical conformation in solutions [11]. On biological testing to immune cells isolated from tumor injected mice, it was observed that cells treated with the heteroglycan isolated from the mycelia of *Pleurotus ostreatus* showed increased lymphocyte proliferation as well as decreased tumor volume in mice models [11]. These findings suggest that characteristics such as (1→3), (1→6) β linkages and triple helical conformations may play a contributing role to the immune stimulating property of the isolated heteroglycan. Molecular weight and size also contribute significantly to the degree of immune response produced by the glycan molecule. It was noted that increase in molecular size of glycan by chemically conjugating with biocompatible molecules such as hyperbranched dendrimers increased their immune modulating functions two-fold times [13]. Physical factors such as size, molecular weight, degree of branching and conformations in solution thus play a significant role in regulating the biological function of glycans. Hence, such biologically potent glycan molecules are nowadays targeted for use as adjuvants along with chemotherapeutic drugs for medicinal benefits.

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