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β 1, 3-Glucan in Cancer Treatment

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Abstract: Natural products, useful in preventing and/or treating various diseases, have been sought after throughout the man's history. Despite some problems inherited from the natural source of glucans, there is extensive literature about their activities in animal tumor models. For the past 25 years, Japan has used several forms of mushroom-derived glucans in treating cancer patients. Additionally, close to twenty clinical trials are currently running in several countries, further suggesting the strong possibility of using glucans as an established anti-cancer drug.

Key words: Glucan, cancer, immunity, treatment

INTRODUCTION

β1,3-Glucans derived from a variety of natural sources (such as yeasts, grain, mushroom or seaweed) are well-established immunomodulators (sometimes also called biological response modifiers). Numerous reports demonstrated a wide range of biological activities by individual β1,3-glucans (for review see Schepetkin and Quinn, 2006; Chen and Seviour, 2007; Novak and Vetvicka, 2008; 2009; Rondanelli *et al*., 2009; Ramberg *et al*., 2010; Rahar *et al*., 2011). Over 10, 000 research papers on the isolation, characterization and biological activities of various glucans exist. Some of them originated from the "golden age" of biological experiments, when authors endlessly kept isolating the same material from new sources. The majority, however, represents a serious science.

The basic glucan research can be summarized in several directions. Isolation and chemical analysis fall outside the scope of this review. The remainder is focused on biological effects. The original studies firmly established the effects on infection immunity (mostly via stimulation of the non-specific branch of immune reactions). 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. The protective effect of β-glucans was shown in experimental infection with *Leishmania major*, *Candida albicans*, *Toxoplasma gondii*, *Streptococcus suis*, *Plasmodium berghei*, *Staphylococcus aureus*, *Escherichia coli*, *Mesocestoides corti*, *Trypanosoma cruzi*, *Eimeria vermiformis* and *Eimeria* (Cox *et al*., 2010; for a review see Vetvicka and Novak, 2011). Subsequent experiments returned to the original findings and showed significant support in cancer treatment in both animal and human models (Vetvicka *et al*., 2002; Hong *et al*., 2004; Weitberg, 2008).

Animal data: History of polysaccharides as immunomodulators goes back 70 years when Shear and co-workers described a substance, again from *Serratia marcescens* cultures, that caused necrosis of tumors (Shear *et al*., 1943). Glucan was later tested in numerous animal models, mostly mouse and rat. The original routes of administration were iv. and ip. Injections, but later attention was also focused on oral administration, with similar results (Hanba and Kuroda, 1988). Among individual types of tumors found to be sensitive to the glucan treatment are lung cancer (Abe *et al*., 1985), hepatoma (Abe *et al*., 1984), squamous cell carcinoma (Arika *et al*., 1986), ovarian cancer (Chen *et al*., 1991), sarcoma (Diller *et al*., 1964), prostate cancer (Fullerton *et al*., 2000), bladder cancer, cervical cancer (Nakano *et al*., 1996) and breast cancer (Vetvicka and Yvin, 2004).

The mechanisms of glucan's effect on cancer development are still not fully elucidated. The most pronounced and most known effects of glucans consist of augmentation of phagocytosis and proliferative activities of professional phagocytes, such as granulocytes, monocytes and macrophages. These cells recognize and bind glucan via a number of different receptors such as TLR-2 (toll-like receptor 2), Dectin-1, CR3 (complement receptor 3), lactosylceramide and probably others. Binding of glucan to any of the

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receptors activates macrophages. The activation consists of several interconnected processes including increased chemokinesis, chemotaxis, degranulation, adhesion to the endothelium and migration. In addition, glucan binding also triggers intracellular processes, such as the respiratory burst after phagocytosis of invading cells, increasing activity of hydrolytic and metabolic enzymes and signaling processes leading to activation of other phagocytes and secretion of cytokines and other substances. Persons interested in an excellent review regarding interaction of glucans with macrophages should read (Schepetkin and Quinn, 2006).

The Finding is that glucans bind to the lectin domain of CR3 and prime the receptor for cytotoxic degranulation in response to tumors that bore iC3b and were normally resistant to this form of cellular cytotoxicity was key to the successful treatment of cancer. Most solid tumors generate an immune response that results in the deposition of antibody and iC3b on membrane surfaces. This iC3b on tumors serves as a specific target for CR3-bearing neutrophils, macrophages, eosinophils and NK cells that have been primed with soluble β-glucan (Vetvicka *et al*., 1996). In addition, when tumors lack such iC3b, mouse tumor models it has been demonstrated that monoclonal antibodies to tumor antigens can be administered in combination with β-glucan to restore tumor-bound iC3b and assure tumor-specific targeting. Normal tissues surrounding the tumor cells are spared from leukocyte attack because they lack this targeting iC3b. As a result of these studies, it was only a step away from the current clinical trials using glucans in synergy with commercial anti-tumor molecular antibodies.

Glucan as a drug: In Japan, glucans such as Lentinan derived from the Shiitake mushroom (*Lentinula edodes*) and Polysaccharide K derived from *Coriolus versicolor* are approved for use as immunoadjuvants for cancer therapy and have been used for over 20 years (Mansell *et al*., 1975; Luzio *et al*., 1980; Morikawa *et al*., 1985; Chihara *et al*., 1987). Particular interest is focused on Lentinan which was developed by the Japanese pharmaceutical company Ajinomoto and is now an intravenously administered anti-cancer agent. It is used mainly in patients with advanced/recurrent gastric and colorectal cancers (Taguchi, 1987; Nakano *et al*., 1999), prostate (Tari *et al*., 1994) and breast (Kan *et al*., 1992) carcinoma. Some data obtained on animals suggest the broader possibility of Lentinan action, including acute myeloid leukemia (McCormack *et al*., 2010). The exact mechanisms are not clear and individual studies suggest T cell-dependent stimulation of macrophages, switch to Th2-type cytokine production (Hamuro *et al*., 1999) and activation of NK cells (Amino *et al*., 1983). For more details on Lentinan and its effect sees (Chihara *et al*., 1987).

In contrast to other glucans, Lentinan is usually ineffective when used orally. Recently, a superfine dispersed Lentinan with high oral effectivity was introduced. First studies showed not only safety, but significant effects on advanced prostate cancer (Shimizu *et al*., 2009) and in advanced colorectal cancer (Hazama *et al*., 2009).

Despite the fact that Lentinan is an official drug, Japanese scientist continue with evaluations of new possible venues of lentinan effects. Advanced oral squamous cell carcinoma is a cancer known for a high resistance to chemotherapy. Lentinan used simultaneously with an oral fluoropyrimidine anti-neoplastic agent S-1 strongly suppressed the cancer growth, probably via induction of apoptosis (Harada *et al*., 2010). It seems that, as a drug, Lentinan has a significant future and we can only hope that this anti-cancer drug will eventually show up in Western medicine as well.

Clinical trials: Since cancer is a leading cause of death worldwide, it is not surprising that most efforts currently focus on evaluating of the effects of glucan on cancer treatment. Several studies showed that low molecular weight, yeast-derived β-glucan binds to a lectin domain within the COOH-terminal region of the CD11b subunit of complement receptor 3 (CR3, CD11b/CD18 (Xia *et al*., 1999). Additional studies have indicated that yeast-derived β-glucans prime neutrophils or natural killer cells for cytotoxicity against iC3b-opsonized tumors via complement activation by anti-tumor antibodies (natural or molecular) (Vetvicka *et al*., 1997; Yan *et al*., 1999) Dual ligation of neutrophil CR3 mediated by the I-domain ligand, iC3b and the lectin-like domain ligand by β-glucans, leads to degranulation and cytotoxic responses (Li *et al*., 2006). The conclusion of these studies suggests that glucan-mediated tumor immunotherapy utilizes a novel mechanism by which innate immune effector cells are primed to kill iC3b-opsonized tumor cells.

Additional reports showed that both soluble and particulate glucans induce proinflammatory cytokine secretion thereby stimulating innate immune effector cell activation. These effects appear to be dependent on Toll-Like Receptor 2 (TLR-2), CR-3 and Dectin-1 pathways (Brown *et al*., 2003; Gantner *et al*., 2003; Vetvicka and Yvin, 2004). Our group focused on glucan and CR3 receptors. Subsequent experiments in a variety of murine syngeneic tumors (Yan *et al*., 1999; Hong *et al*., 2003; 2004) as well as in human carcinoma

xenograft models (Cheung and Modak, 2002; Cheung *et al*., 2002; Modak *et al*., 2005; Li *et al*., 2007; Salvador *et al*., 2008) revealed the significant therapeutic efficacy of combined glucan and anti-tumor antibody therapy. This concept was confirmed by experiments showing the presence of natural anti-tumor antibodies in animals and humans and by the necessity of the presence of these antibodies for glucan effects (Yan *et al*., 1999). As control experiments, this therapy completely fails in CR3-KO mice or in antibody-deficient SCID mice. Later experiments showed that even orally administered glucans retain their therapeutic efficacy in cancer (Nanba and Kuroda, 1987; Cheung and Modak, 2002; Hong *et al*., 2004).

Several animal studies showed that orally administered glucan significantly augmented cytotoxicity of tumors, but the effects were stronger when the tumors were opsonized with anti-tumor mAb and iC3b. Prelinical studies confirmed that the combination of daily oral doses of glucan and weekly doses of the anti-tumor antibody 14G2a, caused significant tumor regression of 80% or more compared to treatment with antibodies alone (Hong *et al*., 2004).

With several thousand scientific papers showing significant effects of glucan therapy in numerous animal models, it is not surprising that significant effort exists in determining if these effects are valid in human patients, too. Currently, there are at least 12 glucan clinical trials in cancer therapy, ranging from Phase I to Phase III (for review Yan, 2011). Most of these trials are based on simultaneous treatment with glucan and specific monoclonal antibodies such as Rutiximax, Avastin or Erbitux. Data from most of these trials have not as yet been released, however a trial proprietary glucan-Imprime PGG plus Erbitux and chemodrug-has released its clinical results and showed that the combination of glucan, Erbitux and Camptosar nearly doubled the overall response rate of second- and third-line metastatic colorectal cancer patients compared with treatment with individual drugs (Tamayo *et al*., 2009).

The initial clinical results are both promising and exciting, but without knowing the rest of results, we have to wait for the final judgement on possible use of glucan in cancer therapy.

Glucan as a drug carrier: Lately, glucans found a new role in drug delivery systems either as an actual drug carrier, an adjuvant, or in combination with other materials to form suitable drug delivery systems. Both their immunoadjuvant characteristics and the ability to stabilize drug formulations, facilitate drug delivery and controlled release has been used in drug formulation. The use of pullulan with water soluble polymers in preparation of ingestible films that can contain pharmaceutical, cosmetic, or biologically active agents can serve as an example. Similarly, nanoparticles based on curdlan were evaluated for potential drug delivery to hepatic carcinoma cells using lactobionic acid as a payload drug (Na *et al*., 2000). Another glucan, schizophyllan, has been extensively studied for use in oligonucleotide delivery (Mochizuki and Saturai, 2009). The Ostroff's group is focused on using glucan particles as a novel drug delivery system. First, they prepared hollow, highly porous microparticles. Second, these whole glucan particles were used as an adjuvant (Adjuvax) with excellent results (Ostroff *et al*., 1991). In the next step, this group designed several strategies for encapsulation of biologically active material into these microparticles. The results include DNA delivery, siRNA delivery (Soto and Ostroff, 2008) and protein delivery.

Readers keen to get more details on the role of glucan as a carrier of drugs should see an excellent, up-to-date review (Soto and Ostroff, 2011).

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