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REVIEW

Antitumor mechanism of Se-containing polysaccharide, a novel organic selenium compound

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Abstract Recent studies on the inhibition of tumor growth by Se-containing polysaccharide were reviewed. Meanwhile, the possible molecular mechanisms of the inhibition of tumor cell growth through antioxidation, induction of tumor cell apoptosis, blockade of cell cycle, and enhancement of immunity by Se-containing polysaccharide were proposed. In the end, the potential application of Se-containing polysaccharide in the prevention and treatment of tumor was elucidated.

Keywords Se-containing polysaccharide, antitumor, antioxidant, organic selenium, apoptosis

1 Introduction

Se-containing polysaccharide is a bioactive compound synthesized from inorganic selenium and polysaccharide. Natural Se-containing polysaccharides are distributed in many plants and animals growing in high-selenium area, and the selenium randomly embedded in the polymers binds through weak interaction such as hydrogen bond, salt bond, and van der Waals force with the macromolecular polysaccharides (Yang, 2007). The Se-containing polysaccharides are often obtained by artificial synthesis because the natural Se-containing polysaccharides exist rarely in bio-organisms. Biotransformation is a usual pathway. The sodium selenite is added into the medium of fungi, edible mushrooms or algae, then enters the metabolic process of fungi and algae and binds with polysaccharide molecules by chemical linkages. Generally, the sodium selenite binds with the hydroxyl group or aldehyde group of polysaccharides and forms the covalent bond. Se-containing polysaccharide from *Ganoderma lucidum* (SeGLP-1) is pyranopolysaccharide composed of glucose, mannose, xylose, galactose, and rhamnose. In SeGLP-1, the O = Se = O bond forms by substituting selenium for methyl of the methoxy group in rhamnose (Shang et al., 2002). As a new class of organoselenium compounds, Se-containing polysaccharide can inhibit the growth of tumor cells from various cancers, such as lung cancer, breast cancer, ovarian cancer, malignant thymoma, gallbladder carcinoma, esophageal cancer, and bladder cancer. It is generally more effective than both polysaccharide and sodium selenite used separately, in a concentration-dependent manner. Se-containing polysaccharide displays characteristics of scavenging reactive oxygen species (ROS), which makes it helpful to suppress tumors and inhibit carcinogenesis. Recent research results show that Se-containing polysaccharides effectively inhibit the proliferation of cancer cells *via* many pathways. Some researchers suggest that this is related to the anti-oxidation effect of selenium in Se-containing polysaccharide, while others believe that it is attributed to the improved immune function of polysaccharide. Until now, the mechanism of antitumor effect of Se-containing polysaccharide is still uncovered. The general agreement is that compared to inorganic selenium, Se-containing polysaccharide has less side effect and higher bioactivity. Thus, Se-containing polysaccharide is more desirable in practical application (Saito et al., 2003; Serafin et al., 2006).

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2 Inhibition of tumor cell growth by Se-containing polysaccharide through antioxidant activity

Se-containing polysaccharide interferes with cancer cell proliferation by regulation of many biological molecules

such as glutathione peroxidase (GSH-Px), deiodinase (ID), and thioredoxin reductase (TR). GSH-Px, as a Se-containing enzyme, can scavenge free radicals through glutathione and repress the chain reaction of lipid peroxidation, and its activity is affected by the level of intake of selenium (Zhao et al., 2008). Se-containing polysaccharide from *Krestin* (Se-PSK) can effectively increase the anti-oxidant activity by improving the activity of GSH-Px and superoxide dismutase (SOD) and decreasing the content of lipid peroxide, thus preventing or alleviating the injury from lipid peroxidation (Liu et al., 2000; Zhang et al., 2005a). Selenium-containing polysaccharide from *Cardamine UrbanianaO. E. Schlz* (CUS-SeP) significantly inhibited the effect of hydroxyl radical ($-OH$) and superoxide anion with the semi-inhibiting concentration (SC_{50}) of 10.94 mg/mL and 7.65 mg/mL, respectively (Zhao, 2006). The *in vitro* inhibiting rate of CUS-SeP on radical-induced MDA formation in liver homogenate and mitochondria was 33% and 41%, respectively. The GSH-Px activity in whole blood and liver homogenate increased under its action. Selenoastragalan (Se-AMP), an organic selenium compound combining *astragalus membranaceus* polysaccharide (AMP) with trace element selenium might not only promote the tumor inhibitory effects of AMP but also bring antioxidant activity of Se into full play by reducing the contents of lipid peroxide in plasma to exert significant tumor-inhibitory effects in sarcoma bearing mice (Gong, 1996). Liu et al. have proved that Se-containing polysaccharides can elevate both the GSH-Px activity in mouse blood and the content of nitric oxide (NO) both in mouse plasma and the hepatoma cell (H22) culture (Liu et al., 1998). It was speculated that the inhibition of tumor tissue and cell growth by Se-containing polysaccharides was possibly related to the elevation of the activity of GSH-Px and the capability of scavenging free oxygen radicals. As a result, cancer cell proliferation mediated by free radicals is inhibited; meanwhile, the release of NO, which induces cancer cell apoptosis, is stimulated.

Irani et al. suggested that antioxidant activity could induce the apoptosis of cancer cells (Irani et al., 1997). This is possibly the reason why antioxidants have anticancer function. Antioxidants help human body to prevent free radicals from participating in signal transduction and enhance the inhibition of cancer cell proliferation by excessively releasing NO.

Other studies have revealed that selenium and glutathione can, independent of GSH-Px, interact with each other. Glutathione was converted into selenium-oxidized glutathione (GS-Se-SG) through nonenzyme catalytic reaction, where the amount of cellular glutathione decreased, while the consumption of oxygen increased. GS-Se-SG inhibited the generation of cancer protein by repressing the elongation of peptide chain through inactivating the eukaryotic elongation factor II.

3 Apoptosis induced by Se-containing polysaccharide through the regulation of cancer gene expression

Se-containing polysaccharide is a regulatory factor for cancer gene expression. It has the effect of promoting differentiation, repressing division, and inducing programmed death of cancer cells. After the treatment with Se-containing polysaccharide, cancer cells display typical characteristics of apoptosis: shrinkage of cells, compaction of cytoplasmic organelles, karyopyknosis, condensation and margination of nuclear chromatin and cytoplasm vacuolization, dilatation of the endoplasmic reticulum, and the typical DNA ladder fragmentation by conventional agarose gel electrophoresis. The rate of apoptosis is time and dose dependent.

Bcl-2 and Bcl-xL are the most important apoptotic inhibitors exerting their antiapoptotic action in or before the processing of certain caspases turning into their catalytically active forms (Hu et al., 2006). Overexpression of Bcl-2 or Bcl-xL prevents staurosporine-induced cell death of Jurkat T cells and the processing of both caspase-3 and caspase-7 by placing these negative regulators of apoptosis in or upstream of the processing of caspase-3 and-7 (Chinnaiyan et al., 1996). Se-containing polysaccharide can down-regulate the expression of Bcl-2 protein in cancer cells. Along with the increase in the number of apoptotic cells, the expression of *Bcl-2* gene reduced, while that of *Bax* gene enhanced (Zhang et al. 2005a; Wu, 2004).

P53 is a tumor suppressor, a transcription factor normally maintained at low level through interaction with Mdm-2 protein, which can lead to its degradation. Wild type *p53* gene can promote apoptosis and hinder the replication of cancer cells; while mutant *p53* existing in most human tumors loses its ability to initiate apoptosis, and it can be activated by Se-containing polysaccharide (Wu, 2004).

C-myc gene family has always been the research focus. Its gene product can promote the proliferation, immortalization, dedifferentiation, and transformation of cancer cells. Se-containing polysaccharide can induce apoptosis of nonmyelogenous leukemia K562 cells and repress the proliferation of cancer cell by the inhibition of *C-myc* gene expression. The inactivation of *C-myc* leads to the activation of *C-fos*, a cellular proto-oncogene belonging to the immediate early gene family of transcription factors. Zhang et al. proved that one of the important ways to inhibit the proliferation of leukemia cell by selenium compound was the inhibition of *C-myc* expression (Zhang et al., 2005a).

The consequences of these cleavage events are now emerging and suggest that they are responsible for many of the phenotypic changes that occur during apoptosis. In addition, the observation that some caspases can process

other caspases suggests that there is likely to be a stepwise activation of caspases during apoptosis, similar to the clotting or complement cascades (Martin and Green, 1995).

Caspases belong to the most specific protease family composed of cysteine proteases that share a stringent specificity for cleaving their substrates after aspartic acid residues in target proteins (Cohen, 1997; Slee et al., 1999; Fuentes-Prior et al., 2004). In an apoptosis process, caspases function in cell disassembly (effectors) and then initiate the disassembly in response to proapoptotic signals (initiators). Every factor of apoptosis functions finally through the caspase protein system, among which caspase-3 (effectors) is responsible for the cellular changes that occur during apoptosis. In many apoptosis processes, some specific substrates such as ADP-ribose polymerase, DNA-dependent protein kinase, sterol regulatory element binding protein, actin, fodrin, and nuclear lamina protein are hydrolysized after caspase-3 is activated by apoptotic signals. The structural changes in these substrates or interference with specific signal molecules result in the occurrence of cell apoptosis. Se-containing polysaccharide can induce cell apoptosis through the activation of cysteine protease (Chu and Chen, 2006). Se-protein polysaccharide (SPP), obtained from a water extract of Se-rich *Agaricus blazei*, can inhibit the growth of implanted sarcoma 180 and promote lymphocyte transformation and natural killer (NK) cell activity in tumor bearing mice. Also, serum SPP can inhibit the proliferation of K562 cell *in vitro*, causing apoptotic morphological changes and nuclear DNA fragmentation of internucleosomal DNA. Moreover, it can increase caspase-3 activity of K562 cells *in vitro*. This indicates that apoptosis of K562 cells induced by serum SPP is related to the up-regulation of caspase-3 activity (Chen et al., 2007).

Recent studies suggest that the resistance of tumor cells to apoptosis is one of the main reasons for drug resistance. It leads to the universal drug resistance to cytotoxic drugs by inhibiting the activation of caspases in apoptotic signaling pathways. After multidrug-resistant leukemia K562/ADM cells were treated with Se-containing polysaccharides, the proliferation of K562/ADM cells was inhibited. Se-containing polysaccharide-induced apoptosis was indicated by the appearance of typical apoptotic morphological changes, DNA fragmentation (DNA ladder), and the increase in sub-G1 cell population (Wei et al., 2006). Se-containing polysaccharide down-regulates the expression of mdr1 mRNA and its product glycoprotein (P-gp). The positive expression rate and expression intensity of P-gp were decreased by about 20% and 30%, respectively. Meanwhile, the expression of Bcl-2 significantly decreased and the expression level of Fas protein and caspase-3 activity were obviously enhanced in K562/ADM cells. The expression of mdr1/P-gp was inhibited to release P-gp-mediated inhibition of caspase-3 in multidrug-resistant K562/ADM cells. This fact suggests that Se-containing polysaccharide could reverse the inhibitory effects caused by the high expression of mdr1/P-gp in caspase-dependent apoptosis pathways. Caspase-3 was activated as an effector in the signal pathway of apoptosis induced by Se-containing polysaccharide by the regulation of apoptotic factors such as Fas and Bcl-2 in drug-resistant K562/ADM cells (Zhang et al., 2005b)

Wu et al. confirmed that Se-containing polysaccharide showed a significant effect of antitumor and apoptotic induction in human osteosarcoma cells both *in vitro* and *in vivo*. The fact that the regulation of expression of certain apoptosis associated genes such as up-regulation of wild type *p53* and *Fas* and down-regulation of mutant *p53* and *C-myc* triggered by Se-containing polysaccharide indicated that Se-containing polysaccharide could significantly induce the apoptosis of human osteosarcoma cells. The effective constituent of Se-containing polysaccharide is selenium. The inhibition mechanism of invasion and metastasis of human osteosarcoma cell by Se-containing polysaccharide involves its down-regulation of expression of urokinase plasminogen activator (uPA), urokinase plasminogen activator receptor (uPAR), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) mRNA, which interfere with the degradation process of the extracellular matrix of tumor cells and inhibition of tumor angiogenesis (Wu, 2004).

4 Cell cycle arrest induced by Se-containing polysaccharide

The growth of tumor cells can be inhibited by Se-containing polysaccharide through arresting of DNA synthesis in the late S phase of tumor cell cycle. The decrease of cells in both G1 and G0 phases plus M phase, as well as the wrapping of a number of monocytes around a tumor leads to the inhibition of tumor cell growth and large areas of necrosis of tumor tissues (He et al., 1997). 4-seleno-carrageenan can directly exert its cytotoxicity to mouse mastocytoma P815 and human liver cell BeLP7402. The DNA synthesis of tumor cells treated with 4-seleno-carrageenan was inhibited in the S phase of cell cycle; thus, the cells of both G1 and G2 phases plus M phase decreased accordingly, resulting in a decrease in the number of surviving tumor cells (Chen and Lin, 1998; Dai et al., 2001. The RNA and protein syntheses of tumor cells can also be affected under the treatment with high doses of 4-seleno-carrageenan. This indicates that the anticancer activity is related to the selective inhibition of the synthesis of DNA and proteins of tumor cells and disturbance of cell metabolic processes.

Cell division cycle genes (*CDC*-genes) are very important genes that control the transition from G1 to S phase and from G2 to M phase in cell division cycle (Dong et al., 2002, 2004). Se-containing polysaccharide induces the apoptosis of cancer cells by, on one hand, inhibiting the

activity of CDC proteins and, on the other hand, strengthening the reduction of mercapto and the substitution of cysteine residues. In addition, Se-containing polysaccharide has regulatory effects on tumor biomarkers prior to the occurrence of malignancy. The related biomarkers include cyclin A and cyclin D1, CDK inhibitor p21 and p27, and Bcl-2 and Bax, the regulatory protein of cell apoptosis, and mitosis. The expression of cyclin A, cyclin D1, and the mitosis induced protein Bax were up-regulated, and the expression of p21, p27 and the inhibitor protein of mitosis Bcl-2 were down-regulated in tumor cells treated with selenium compounds. All these changes of apoptotic factors resulted in the inhibition of division and the occurrence of apoptosis of cancer cells (Dong et al., 2003; El-Bayoumy and Sinha, 2005).

Dai et al. showed that Se-containing polysaccharide had a biphasic effect in promoting differentiation and inhibiting cancer cell division. It not only regulated the expression of oncogenes for proliferation and division but also inhibited the activity of protein kinase closely related to cell carcinogenesis, thus effectively suppressing protein synthesis and cancer cell growth (Dai et al., 2001).

5 Immunoregulation-mediated inhibition of tumor cell growth by Se-containing polysaccharide

Another important aspect of Se-containing polysaccharide in the prevention and/or kill of tumor is its immunoenhancement effect. The antitumor activity of Se-containing polysaccharide is related to cellular immunity. Se-containing polysaccharide can activate the proliferation of lymphocyte, enhance the expression of cytokine receptor, and stimulate the activity of natural killer (NK) cells and cytotoxic cells, all of which are essential in antitumor immunity. The phase II clinical trial proved that after patients took Kappa-Selenocarrageenan, the percentage of T_4 cells was significantly increased from 28 to 38, and the T_4/T_8 ratio was increased from 0.9 to 1.3 (Xu, 1999; Jiang et al., 1997). Also, the phagocytic rate of macrophages rose obviously, which strengthened the immune ability of those patients who received chemotherapy. Meanwhile, the platelet count was obviously raised, and β2-microglobulins in blood and urine were both kept in normal range, indicating Se-containing polysaccharide protected renal function for those patients who accepted cisplatin treatment. Moreover, treatment with Se-containing polysaccharide did not decrease the efficacy of cisplatin. The enhancement of humoral and cellular immunity by Se-containing polysaccharides mainly displays in three aspects: (1) Se-containing polysaccharide enhances B cell-mediated humoral immunity, which is manifested by the increase in both antibody titer and antibody activity. (2) Se-containing polysaccharide can activate NK cells, killer cells, and macrophages (Mφ) to directly kill or engulf tumor cells. The tumor necrosis factors secreted by NK cells and killer cells are increased, thus accelerating tumor necrosis. The antitumor activity of the selenium-protein polysaccharides (SPP) and the water extracts of selenium-enriched *Agaricus blazei* was tested both *in vitro* and *in vivo*. The results showed that SPP promoted lymphocyte transformation and NK cell activity in tumor-bearing mice. The growth inhibition rate of implanted sarcoma 180 was 37.69% (Chen et al., 2007). (3) Se-containing polysaccharide improves T cell-mediated cellular immunity. One is delayed type hypersensitive T cell (TDH, CD4 +), which can react with antigen and secrete cytokines (such as IL-2). The secreted cytokines then attract and activate macrophages and cells of other types to aggregate at the reaction site, initiating a series of nonspecific immune responses (Zhao et al., 2001). The other is cytotoxic T lymphocyte (TC, CD8 +), which has a specific killing effect on tumor cells. For example, the change in molecular expression level of FasL reflects the antitumor activity of immune cells from one side. After T cell is activated by selenium compounds, not only the expression level of Fas mRNA of the target tumor cells is increased, but also the expression level of FasL mRNA of the effector cell is elevated. The expression level of the genes related to apoptosis increases or that of genes related to cell proliferation decreases. Moreover, the target cell is then impelled to express Fas and related cytokines, leading to its apoptosis (Cui and Shang, 2004).

6 Application prospect of Se-containing polysaccharide in tumor treatment

From recent research, some functions of Se-containing polysaccharides have been gradually clarified. However, its overall functions and biochemical characteristics still remain unknown due to the lack of direct and clear evidence from molecular biologic study. More experiments need to be done in order to understand the structure-activity relation and the action mechanisms of Se-containing polysaccharides.

Se-containing polysaccharide displays double and cooperative activities of both selenium and polysaccharide, possessing complementary advantages of these two compounds. Compared with inorganic selenium compound, Se-containing polysaccharide has the advantages of high bioavailability, less accumulation, and low toxicity. It is regarded as an ideal selenide substance for clinical application. The application prospect of Se-containing polysaccharide in the prevention and therapy of tumor includes (1) acting independently in chemoprevention or integrating with vitamin E, retinoic acid, *etc*. for the combined chemoprevention, antimutation, and anticancer; (2) enhancing the antitumor effect of chemotherapeutic drugs, lowering drug resistance, and toxic side effects as a chemotherapeutic adjunctive drug; (3) improving the

immune function of tumor host as an immunocompetence strengthening agent; (4) improving the activity of tumor killing effector cells in tumor biotherapy as biological response modifier (BRM); and (5) combining with a single Chinese herb or anticancer compounds to increase the anticancer effect of Chinese anticancer drugs.

Se-containing polysaccharide exhibits activities of inhibiting tumor cell growth, activating immune active cells, and improving the immune ability of human body. As an immune response modifier, Kappa-Selenocarrageenan has been tested in phase I and II clinical trials (Xu, 1999). The results show that Se-containing polysaccharide could strengthen the immune function of the patients treated with cisplatin; meanwhile, the efficacy of the chemotherapeutic drugs was retained. Therefore, it is a promising drug for immune regulation and antitumor therapy. We believe that further study on the effectiveness of selenium polysaccharide in clinical tumor prevention, as well as its molecular mechanism will be helpful for the development of drugs and health products.

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