

The Nutrition Science on Basis of Algae in the Patronage of Neoplastic Processes

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Abstract: In the mechanism of development of the tumor process, a large role is given to the impact on the body of factors causing cell death (apoptosis). Therefore, all technologies aimed at reducing the negative impact are methods of preventing the development of the tumor process. Of great interest in this regard are food compounds with high bioactivity, in particular sulfated polysaccharide brown algae fucoidan. Fucoidan prevents cell death due to antioxidant activity, anti-toxic effects, antibacterial or immunomodulatory effects, normalization of metabolic processes and neuro-endocrine status. In addition, fucoidan has a direct impact on the cancer cell: reduces its survival, improves differentiation and inhibits proliferation, suppresses migration and invasion, or blocks metastasis. This indicates that fucoidan can be used as a functional food product to prevent and treat cancer.

Key words: Cancer, fucoidan, pathogenesis, prevention.

1. Introduction

Cancer is the second cause of death of the population [1], therefore, the development of principles for the prevention and treatment of cancer is an important principle for the preservation and prolongation of human life. The pathogenesis of tumor development involves etiological factors of chemical [2], physical [3] and biological [4] nature, as well as the nature of nutrition [5] and human lifestyle [6]. These factors can affect the genetic apparatus of the cell and activate ways to survive and, in particular, on the way of its transformation. Therefore, the elimination of adverse factors or prevention against their negative manifestation is an important pathogenetic approach in the prevention and treatment of cancer.

Any cell in the human body is formed from the stem, but it goes through several stages of transformation–differentiation. This figuratively can be compared with human development (Fig. 1).

At the stages of growing up, the child is a consumer.

It is necessary to spend material resources. The manufacturer is an adult. The same analogy can be drawn with the development (differentiation) of cells. Only an adult cell performs functions. It may be affected by the negative factors listed above, which can lead to disruption of its activities and death (apoptosis). In the cell there are oncogenes that include the program of survival. It lies in the fact that not fully differentiated cell is easier to survive, but it actively proliferates (multiplies), which leads to the formation of tumors. Therefore, all technologies aimed at reducing the value of apoptosis will be aimed at cancer prevention. The multiplication of cancer cells increases the consumption of food resources, as the cancer cell is a trap of glucose and amino acids or energy and building material. The number of consumers increases and that of producers decreases, which is the main reason for the negative impact of the oncogenesis process. In fact, cancer is our cells that do not want to grow up, and now we have to fight them. However, the technologies used (chemo- and radiotherapy) to combat cancer cells have a negative impact on stem and adult cells, so they have a negative impact.



Fig. 1 Stages of human development.

Developing natural products and dietary supplements has proven to be a promising strategy for the cancer therapy and prevention. Among them, fucoidan, which is isolated from brown seaweed such as *Cladosiphon okamuranus* and *Fucus evanescens* [7], is structurally similar to heparin, with a substantial percentage of L-fucose [8]. Recent studies have shown its various effects on biological activities, in particular anticancer [9, 10] activities. With respect to cancer therapy, fucoidan appears to be highly efficient in treating certain types of cancer, including breast, prostate and lung, as well as leukemia [11-15]. Furthermore, fucoidan can also play a crucial role in inhibiting induced cancer signaling molecules, such as vascular endothelial growth factor (VEGF) [16]. Fucoidan is a non-starchy and sulphated polysaccharide. It is a polymer of α (1 \rightarrow 3) linked fucose pyranose sugar subunits. Fucoidan also has traces of galactose, xylose and glucuronic acid. Two structural features which distinguish fucose from other six-carbon sugars present in mammals are the lack of a hydroxyl group on the carbon at the six-position (C-6) and its L-configuration [17].

Fucoidan exhibits antioxidant [18], immunocorrective [19], anti-toxic [20] activity, which is a prevention against cell death and, accordingly, the development of cancer. Extensive preclinical studies have been conducted in *in vitro* and *in vivo* experiments on fucoidan anticancer activity, which shows the ability of fucoidan to reduce the survival of cancer cells by inhibiting cell growth and cell cycle progression [21]. The first phase of clinical trials—tolerability and

safety [22] was performed and encouraging results were obtained for the second phase of clinical trials [23].

Cancer cell is characterized by rapid growth, which requires increased intake of nutrients and oxygen. Therefore, it was proposed a number of technologies to combat cancer cell by reducing its growth: hypothermia, reduction in the diet of essential nutritional factors (glucose and amino acids), but all these technologies have a negative impact on healthy cells. In many ways, these aspects can be solved by taking fucoidan, as it reduces the nutrition of cancer cells by blocking vascular growth by inhibiting VEGF [24, 25]. Fucoidan inhibits angiogenesis *in vitro* and *in vivo* [26].

Cancer cells are inherently immortal, i.e. there is no apoptosis for them, but under the influence of fucoidan there is a change in the cell membrane, compression of the cancer cell and fragmentation of the nucleus and DNA, so the mechanism of apoptosis is for cleaning up “garbage” [27]. Endoplasmic reticulum (ER) stress cascades play a critical role in fucoidan-induced cell apoptosis. Fucoidan broadly regulates ER stress by attenuating cell survival cascade and activating cell apoptotic cascade in cancer cells [28]. The efficiency of fucoidan in killing cancer cells and preventing metastasis indicates its promising potential as a therapeutic agent in cancer treatment.

Usually apoptosis of the cell is carried out in two ways: (1) violation of the structural integrity of the cell membrane or (2) violation of the energy supply through the destruction of mitochondria. Fucoidan increases

cancer cell apoptosis by means of the second mechanism or it causes mitochondrial destruction by increasing the level of free radicals [29].

Usually apoptosis [30], suppression of angiogenesis [31] and activation of cellular immunity in the form of increased activity of natural killers are considered in the mechanism of fucoidan antitumor activity in studies *in vivo* and *in vitro* [32]. The main mechanism of the anticancer activities of fucoidan is considered to be the regulation of molecules related to apoptosis and cell cycle [33].

Fucoidan increases the activity of natural killers that exhibit anticarcinogenic activity [34]. Antitumor effect of GIV-A (fucoidan) may be correlated with the changing pattern of the Thy1.2-, L3T4- and asialo GM1-positive cells, C3 activation, macrophage activation and depression of the hepatic microsomal drug-metabolizing system.

Metastasis is a leading cause (up to 90%) of cancer-related deaths. Fucoidan inhibits migration and invasion of cancer cells or blocks metastasis [35-40]. This helps to increase the survival of cancer patients. In 20 patients with colorectal cancer for the period (April 2008 to June 2009), the administration of fucoidan at a dose of 4 g/day for 6 months [41] was evaluated together with chemotherapy. On average, the patients were in the clinic for 15 months. The survival rate of 10 patients with fucoidan was higher ($p = 0.314$). Although a small group was under observation, already estimated studies indicate the prospects of using fucoidan as a functional food for cancer patients.

Chemotherapy is toxic and can contribute to the development of muscle atrophy. In this regard, fucoidan had a preventive effect against atrophic effects of chemotherapy [42].

Evaluation of the effect of UPC-fucoidan (90% purity) on the growth, adhesion, invasion and metastasis of cancer Hca-F cells [43] showed inhibition of growth, decreased adhesion (invasion) of cancer cells, which is associated with the effect of fucoidan on signaling pathways, in particular on VEGF expression.

Metastasis of cancer cells is the main cause of death of cancer patients, so preventing invasion and migration of cancer cells is the main way to stop their metastasis.

Fucoidan helps to restore the process of differentiation of cells through exposure to the stage of development [44].

Cancer chemotherapy is a key aspect of cancer therapy. In Japan, oxaliplatin plus 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) ARE is used as chemotherapy drugs. However, they are highly toxic. Diet is one of the ways to reduce toxicity. Clinical studies suggest that fucoidan promotes tumor regression and increases patient survival [45]. Ikeguchi et al. [46] conducted clinical trials on patients with colorectal cancers and found that fucoidan improved the absorption of the chemical and increased the clinical effect. Cisplatin (CDDP) is widely used in cancer chemotherapy.

However, it exhibits cytotoxicity by acting on DNA transcription or replication, leading to a halt in the cell cycle at the G2 stage. CDDP promotes apoptosis through its effects on signaling pathways, including the death of mitogen-activated protein kinases (Mapk) receptor, akt signaling protein, p53 signaling, and mitochondrial pathway activation. Tamoxifen (TAM) is an antagonist of the selective estrogen receptor (ER) and is used in the early stages of breast cancer. The clinical response to TAM is manifested by decreased proliferation and increased apoptosis. The mechanism of apoptosis involves oxidative stress and activation/expression of regulatory proteins such as extracellular signal-regulated kinase and c-Jun N-terminal kinase, transformational growth factor β , kinase protein C, and Bcl-2 protein. Paclitaxel (TAXOL), a natural chemotherapeutic agent isolated from the Pacific yew bark, is widely used in the treatment of breast and ovarian cancer. TAXOL affects the tumor cell cycle and apoptosis. This results in the expression of MAPKs, Raf-1, tyrosine kinase, and regulatory proteins such as Bcl-2, Bcl-xL, and Bad.

These chemotherapy drugs were tested on different types of cancer cells in combination with fucoidan [47]. There was a manifestation of synergism of the effect of fucoidan and chemotherapy in relation to the magnitude of apoptosis of various types of cancer cells.

Breast cancer is widespread in the West and quite low in Asia. This is associated with a wide consumption in the diet of algae. Therefore, it is a very interesting study [48], which evaluated the effect of fucoidan on the menstrual cycle of women and hormone levels. When taking fucoidan at a dose of 0.7 and 1.4 g/day for 4 months, there was a normalization of the menstrual cycle and the level of estradiol and progesterone, an imbalance of which is an important cause of breast and uterine cancer.

The normalizing effect of fucoidan on the hormonal balance of women is an important factor in the prevention of breast cancer. According to Zhang [49], the positive effect of fucoidan is due to the blocking of estrogen receptor and suppression of aromatase activity. Therefore, the authors concluded that the use of fucoidan can be an excellent approach in the prevention of estrogen-dependent pathologies of the breast, endometrium and ovaries.

Recently, in the mechanism of regulation of life processes, much attention has been paid to micro RNA. In particular, their role in the mechanism of cancer development is shown [50]. Micro 29 RNA takes part in the regulation of invasion and migration of cancer cells [51]. Fucoidan increases the expression of micro 29 PHK [52]. With the influence of micro RNA 29 the authors attribute the decline in kolonialapologie cell carcinoma of the liver under the influence of fucoidan.

2. Conclusions

Thus, studies *in vitro* and *in vivo*, as well as observations in humans indicate the prospects for the use of fucoidan in the treatment of cancer patients. Of course, in far-reaching cases, fucoidan can not serve as a panacea, but in a number of observations we found that fucoidan in megadoses (10 g in day) contributed to

the full recovery of patients even with cancer 3-4 stages with metastases, which doctors attributed to the incurable stages. Fucoidan does not belong to drugs, so its structure largely depends on the type of algae, the place of growth and isolation methods, so it should be attributed to nutraceuticals and recommended as a functional food for the prevention and treatment of cancer.

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