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Molecular Actions of Marine Bioactive Compound Fucoidan

Xue-lian WANG[a] and Yan ZHAO[b,*]

Department of Bioengineering, Harbin Institute of Technology, Weihai, Shandong, P.R. China, 264209

[a]15137383165@163.com

[b]zhaoyan@hitwh.edu.cn

*Corresponding author

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Abstract. Fucoidan is a complex sulfated polysaccharide mainly found in brown seaweed. It has been used in a wide range of applications across different industries such as food additives, dietary supplements and pharmaceuticals. Studies have shown that fucoidan has numerous biological activities including anti-cancer, anti-inflammation, anti-coagulation and neuroprotection; however, the exact mechanisms are not clear. This paper discusses the molecular actions of fucoidan that contribute to its biological activities.

Introduction

Seaweedsare marine macroalgae that are distributed widely in East Asia and consumed as a marine vegetable. The seaweed industry has an annual global value of 5.5-6 billion US dollars, among it the food industry accounts for 5 billion US dollars of market share, and the rest comes from industries of fertilizers, animal feed, cosmetics and pharmaceuticals[1].Various bioactive substances have been extracted from the seaweeds including fucoidan, which is a complex sulfated polysaccharide[2]. Studies have shown that fucoidan has numerous biological activities including anti-cancer, anti-inflammation, anti-coagulation and neuroprotection[3-9]. However, the molecular mechanisms of fucoidan are not clear. This paper discusses the molecular actions of fucoidan that contribute to its biological activities.

Antioxidant Activity of Fucoidan

It has been reported that fucoidan treatment can reduce the levels of reactive oxygen free radicals such as superoxide anion and hydroxyl radicals and the levels of nitric oxide (NO) and peroxynitrite anion (ONOO-)[3,10]. In animalmodel, it has been shown that fucoidan pretreatment significantly reduces the content of malondialdehyde (MDA), whichis a marker of lipid peroxidation and oxidative stress[11]. Fucoidan can also significantly enhance the activity of superoxide dismutase(SOD) and glutathione peroxidase(GSH-Px) which are enzymes important for antioxidant system[9]. The evidence indicates that fucoidan is an excellent natural antioxidantand it may have a good potential for preventing or treating free radical-mediated diseases[12]. It has been suggested that the antioxidant activity of fucoidan is closely related to its contents of fucose and sulfate. The increase of sulfate content correlates with the physiological activity of fucoidan[13]. And the ratio of sulfate content to fucose is an effective indicator for evaluating the antioxidant activity of fucoidan[14].

Activation of Nuclear Factor Erythroid-2-Related Factor 2 (Nrf2) Signaling Pathway by Fucoidan

Nrf2 is an important regulator of antioxidant responses and an important cellular protective mechanism against oxidative or electrophilic stress[15]. Under normal circumstances, Nrf2 is kept in the cytoplasm by the actin-associated kelch-like ECH-associated protein1 (Keap1) protein[16]. When the cells suffer oxidative stress or phase II enzyme induction, Nrf2 is dissociated from the Keap1 protein, phosphorylated and translocated to the nucleus[17]. Nrf2 activates the expression of genes such as heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1), which participate in the elimination of reactive oxidants and detoxification of electrophilic agents, eventually leading to the attenuation of oxidative and electrophilic stress[18]. In HaCaT cells, it was shown that fucoidan attenuated oxidative stress by up-regulation of the expression of HO-1 and SOD-1 via activating Nrf2 signaling pathways[19]. It was also found that fucoidan inhibited ischemic-reperfusion injury induced by oxygen-glucose deprivation followed by reperfusion in mouse neuroblastoma N2a cells via increasing the nuclear translocation of Nrf2 and the expression of Nrf2 downstream target genes such as HO-1[20]. In addition, activation of Nrf2 has been shown to be involved in the reduction of the volume of cerebral infarction in rats after cerebral ischemia-reperfusion injury[21].

Activation of Caspase 3 and Caspase 9 by Fucoidan

Caspases are a family of cysteine proteases that have a large number of intracellular substrates. They play essential roles in programmed cell death and inflammatory responses[22]. Caspase 9 is an initiator caspase, once caspase 9 is activated, it can directly cleave and activate caspase-3, which is a hallmark of late apoptosis[23]. In MDA-MB-231 breast cancer cells, it has been shown that fucoidan induces apoptosis via the activation of caspase 9 and caspase 3[24]. In human colon cancer cells, fucoidan-mediated apoptosis is also associated with the activation of caspase family [25,26].

Activation of Akt by Fucoidan

Phosphatidylinositol 3 kinase (PI3K)-Akt signaling pathway plays important roles in cell proliferation, differentiation and apoptosis[27]. In PC12 cells, fucoidan pretreatment enhanced Akt phosphorylation, protecting the neurocytes against H2O2-induced apoptosis[28]. Activation of Akt signaling pathway by fucoidan was suggested to be important in its protection of mesenchymal stem cells against oxidative stress and enhancement of vascular regeneration in a murine hindlimb ischemia model[29]. In a hypertensive rat model, it was indicated that the activation of PI3K-Akt signaling by fucoidan treatment prevented vascular dysfunction[30]. In addition, activation of Akt signaling by fucoidan has been shown to be involved in the inhibition of the growth of human colon cancer cells and the migration of human urinary cancer cells [31,32].

Inhibition of Extracellular Regulated Protein Kinases (ERK) and c-Jun N-terminal kinase (JNK) by Fucoidan

Mitogen-activated protein kinases (MAPKs), which include p38, ERK and JNK signal pathways, are important transmitters for signaling from the cell surface to the nucleus.

They participate in regulating a wide range of cellular events including cell growth, differentiation, stress and apoptosis[33,34]. It has been shown that fucoidan pretreatment inhibits the activation of ERK and JNK signaling pathways induced by ethanol while suppressing the oxidative damages[35]. In human alveolar bone marrow-derived mesenchymal stem cells, fucoidan induced osteoblast differentiation through inhibiting the phosphorylation and activation of ERK and JNK[36]. In the human skin fibroblast cell line, it was shown that fucoidan treatment inhibited the production of matrix metalloproteinase induced by ultraviolet (UV) B irradiation. It was indicated that the action of fucoidan was contributed by its inhibition on the activation of ERK [37].

Conclusions

In summary, a complicated array of molecular mechanisms may contribute to the biological activities of fucoidan. A better understanding of the absorption and metabolism of fucoidan*in vivo* may further clarifying the molecular actions of fucoidan.

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