Anti-cancer Mechanism of Docosahexaenoic Acid in Pancreatic Carcinogenesis: A Mini-review

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Pancreatic cancer is a highly aggressive malignant tumor of the digestive system and radical resection, which is available to very few patients, might be the only possibility for cure. Since therapeutic choices are limited at the advanced stage, prevention is more important for reducing incidence in high-risk individuals with family history of pancreatic cancer. Epidemiological studies have shown that a high consumption of fish oil or ω3-polyunsaturated fatty acids reduces the risk of pancreatic cancers. Dietary fish oil supplementation has shown to suppress pancreatic cancer development in animal models. Previous experimental studies revealed that several hallmarks of cancer involved in the pathogenesis of pancreatic cancer, such as the resistance to apoptosis, hyper-proliferation with abnormal Wnt/β-catenin signaling, expression of pro-angiogenic growth factors, and invasion. Docosahexaenoic acid (DHA) is a ω3-polyunsaturated fatty acid and rich in cold oceanic fish oil. DHA shows anti-cancer activity by inducing oxidative stress and apoptosis, inhibiting Wnt/β-catenin signaling, and decreasing extracellular matrix degradation and expression of pro-angiogenic factors in pancreatic cancer cells. This review will summarize anti-cancer mechanism of DHA in pancreatic carcinogenesis based on the recent studies.

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Key Words: Docosahexaenoic acid, Pancreatic neoplasms, Anti-cancer effect

INTRODUCTION

Pancreatic cancer remains difficult to treat, despite the recent advances in various anti-cancer therapies. Because of difficulties in early diagnosis, most patients with pancreatic cancer receive chemotherapy and/or surgical treatment. Therefore, prevention and early diagnosis are important for reducing incidence of pancreatic cancer.

In recent Japanese cohort study, there was an inverse relationship between the risk of pancreatic cancer and ω3-polyunsaturated fatty acids (PUFAs) consumption. Macášek et al. studied plasma fatty acid composition in patients with pancreatic cancer. They found that longer-term survival of pancreatic cancer patients was connected with higher consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The proportions of EPA and DHA in plasma phospholipid displayed negative trend with tumor staging. He et al. conducted a prospective cohort study for associations of fish types and fish preparation methods with pancreatic cancer risk in Washington State. They found that DHA showed a greater inverse association with pancreatic cancer than EPA. Mohammed et al. determined the impact of ω3-PUFAs on pancreatic intraepithelial neoplasms (PanINs) and their progression to pancreatic ductal adenocarcinoma (PDAC) using ω3-fatty acid desaturase (Fat-1) transgenic mice, which can convert ω6-PUFA to ω3-PUFA endogenously. They found a dramatic reduction in incidence of PDAC in compound Fat-1-p48(Cre/+)-LSL-Kras(G12D/+)+ mice compared to p48(Cre/+)-LSL-Kras(G12D/+)+ mice. In addition, significant reductions of pancreatic ducts with carcinoma and PanIN 3 lesions were observed in the compound transgenic mice. The levels of ω3-PUFAs were much higher in pancreas of compound transgenic mice than in those of p48(Cre/+)-LSL-
lymphoma kinase (ALK)5, PAR2 may also impact signaling by PAR2 controls the expression of TGF-β. et al.22 reported that proteinase-activated receptor 2 (PAR2) is a novel regulator of TGF-β superfamily members that signal through ALK5. Thus, PAR2 could represent a molecular linker between pancreatic cancer development and cancer-related cachexia.

Dysregulation of Wnt/β-catenin signaling is found in many types of cancers, including pancreatic cancer.9,10 During embryonic development and tissue homeostasis, Wnt/β-catenin signaling regulates fundamental processes, such as proliferation, polarity, and fate determination of cells.23 When Wnt signal is absent, the scaffolding protein Axin recruits glycogen synthase kinase-3 (GSK3), casein kinase 1α (CK1α), adenomatous polyposis coli gene product, and β-catenin, forming a destruction complex. CK1α and GSK3 are kinase proteins which phosphorylate serine 45 and threonine 41, serine 33, and serine 37 of β-catenin, respectively.25 This phosphorylated β-catenin serves as a binding site for the E3 ubiquitin ligase, β-transducin repeat-containing protein. Ubiquitination of β-catenin results in proteasome degradation. However, when Wnt binds to frizzled receptors, the axin complex loses its destruction activity, leading to accumulation of β-catenin in cytoplasm. High concentration of β-catenin in cytoplasm eventually causes its nuclear translocation.24 In nucleus, β-catenin acts as a transcription cofactor for genes related to cell proliferation, migration, and matrix metalloproteases secretion.10 Constitutively active Wnt/β-catenin signaling is a feature of pancreatic cancer.9

One of the reasons why survival rate of pancreatic cancer is so low is due to a high risk of local invasion and metastasis in pancreatic cancer. The incidence of lymphatic metastasis in pancreatic cancer is about 65.3% to 89.0%.11 Metastasization begins with invasion of tumor cells into surrounding tissue. Tumor cells release hydrolytic enzymes such as matrix metalloproteases and disintegrate extracellular matrix (ECM), then migrate to blood or lymphatic vessels.25 Rapidly growing cancer cells need more blood vessels in order to meet their metabolic requirements. Thus, tumor growth is dependent on angiogenesis. There are several cytokines and growth factors stimulating or inhibiting angiogenesis. VEGF is one of the most studied angiogenic growth factor. VEGF has been reported to increase vascular permeability, stimulate endothelial cell proliferation and migration, and promote endothelial cell survival.26 In addition, VEGF and its receptor are up-regulated in pancreatic cancer cells.12

EFFECT OF DOCOSAHEXAENOIC ACID ON PANCREATIC CARCINOGENESIS

In 1998, Hawkins et al.27 reported that apoptotic death of
human Mia-PaCa-2 pancreatic cancer cells induced by PUFAs varies with double bond number and involves an oxidative mechanism. They found correlations between the number of fatty acid double bonds and the proportion of apoptotic cells. The extent of PUFAs-induced lipid peroxidation, measured as malondialdehyde, also correlated with the proportion of apoptosis. This is the first study showing the relation of oxidative stress and apoptosis in pancreatic cancer cells. Later, Merendino et al. suggested that a high production which mediates cancer cell invasion. Therefore, DHA induced ROS accumulation and caspase-8-dependent cell death in human pancreatic cancer cells. They also demonstrated that 5% fish oil supplementation reduced the growth of SW1990 and Panc-1. 

Zhang et al. reported that DHA and EPA inhibits proliferation of human Mia-PaCa-2 xenografts in athymic nude mice. We recently summarized that oxidized DHA leads to DNA adduction formation. Oxidative DNA damage triggers cell cycle arrest and apoptosis by p53-dependent and p53-independent pathways in cancer cells. Zhang et al. reported that DHA and EPA inhibits proliferation and induce apoptosis of human SW 1990 pancreatic cancer cells by down-regulating cyclin E expression.

DHA suppressed pancreatic cancer cell growth by inhibiting activation of Wnt/β-catenin signaling. Therefore, DHA inhibited the accumulation of β-catenin in cytoplasm and nucleus, and decreased overall β-catenin protein level in human pancreatic cancer cells. SW1990 and Panc-1. DHA increased the binding of GSK-3β to axin, promoting the phosphorylation and degradation of β-catenin. Activity of the transcription factor, TCF/LEF, which forms a complex with β-catenin in nucleus, was suppressed by DHA in a dose-dependent manner.

DHA inhibited COX-2 expression and prostaglandin E2 production which mediates cancer cell invasion. Therefore, DHA suppression of Wnt/β-catenin signaling, DHA inhibited the accumulation of β-catenin in cytoplasm and nucleus, and decreased overall β-catenin protein level in human pancreatic cancer cells. SW1990 and Panc-1. DHA increased the binding of GSK-3β to axin, promoting the phosphorylation and degradation of β-catenin. Activity of the transcription factor, TCF/LEF, which forms a complex with β-catenin in nucleus, was suppressed by DHA in a dose-dependent manner. 

DHA inhibited COX-2 expression and prostaglandin E2 production which mediates cancer cell invasion. Therefore, DHA was suggested as a potential adjuvant in the treatment of cancer. According to D’Eliseo et al. DHA inhibited invasion of PT45 pancreatic carcinoma cells by down-modulation of granzyme B expression. Granzyme B is a serine protease which is expressed by cytotoxic lymphocytes to induce target cell apoptosis. However, granzyme B is also produced by a variety of normal and neoplastic cells and potentially acts on multiple targets. Granzyme B is considered as a powerful regulator of a wide range of fundamental biological processes. Tumor-expressed granzyme B degrades ECM components and promotes cancer cell invasion. This study is supported by Stroucho et al. who showed that a high ω3-fatty acid diet mitigates murine pancreatic precancer development.

Recent study showed that ω3-PUFAs supplementation reduced circulating pro-angiogenic growth factors, such as PDGF, in the patients with advanced pancreatic cancer. Spencer et al. suggested that DHA and EPA have potent anti-angiogenic effects by inhibiting production of many important angiogenic mediators namely; VEGF, PDGF, platelet-derived endothelial cell growth factor, COX-2, prosta-glandin E2, nitric oxide, NF-kB, matrix metalloproteinases, and β-catenin. They showed that DHA and EPA have therapeutic potential to inhibit tumor angiogenesis in colon, breast, and prostate cancers. However, there has been little research on the effect of DHA on angiogenesis specifically in pancreatic cancer cells. Therefore, it is important to determine whether DHA has an inhibitory effect on angiogenesis in pancreatic cancer cells, which provide insights into the molecular mechanisms by which dietary DHA suppresses the progression of pancreatic cancer.

Swamy et al. found that a synergistic effect was observed on induction of apoptosis (approximately six-fold) and inhibition of cell proliferation (approximately 70%) when pancreatic cancer (BxPC-3) cells were treated with curcumin together with the DHA. A combination of fish oil and curcumin showed a significantly reduced tumor volume in mice. Expression and activity of inducible nitric oxide synthase, COX-2, and 5-LOX are down-regulated, and p21 is upregulated in tumor xenograft fed curcumin combined with fish oil diet when compared to individual diets. Therefore, the combined natural products, such as curcumin and ω3-fatty acids, may provide synergistic pancreatic tumor inhibitory properties.

Previously, we showed that janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway stimulates cell proliferation and malignant transformation and inhibits apoptosis in pancreas. Since DHA reduced STAT3 activation in human liver cancer (HepG2) cells and gastric cancer (AGS) cells, DHA may inhibit JAK/STAT pathway in pancreatic cancer cells. Further study should be performed to determine the effect of DHA on JAK/STAT in pancreatic carcinogenesis. Because the incidence of and mortality from pancreatic cancer is rising, further study of new approaches for prevention of pancreatic cancer using DHA is essential.

**CONCLUSION**

DHA induces apoptosis through ROS accumulation and caspase activation in pancreatic cancer cells. It also down-regulates Wnt/β-catenin signaling that stays activated in...
Figure 1. The preventive effect of docosahexaenoic acid (DHA) against pancreatic cancer development. In pancreatic cancer cells, DHA induces glutathione (GSH) extrusion which increases the levels of reactive oxygen species (ROS) and caspase activation, resulting in ROS-mediated apoptosis. DHA also inhibits activation of Wnt/β-catenin signaling by increasing binding of glycogen synthase kinase-3β (GSK3β) to axin and reducing β-catenin accumulation as well as expression of cyclin E. Thus, DHA suppresses cancer cell proliferation. DHA down-regulates granzyme B, which degrades extracellular matrix (ECM) and promotes cancer cell invasion. DHA also reduces pro-angiogenic factors, such as VEGF and platelet-derived growth factor (PDGF). Therefore, DHA may inhibit resistance to cancer therapies and cancer development, and increase survival rate of pancreatic cancer patients.

pancreatic cancer cells. Moreover, DHA suppresses expression of pro-angiogenic growth factors, such as VEGF and PDGF, preventing cancer cells from getting metabolic requirements and proliferating. Furthermore, granzyme B is down-regulated by DHA. Conclusively, supplementation of DHA-rich foods may prevent the development of pancreatic cancers. Further long-term clinical studies are necessary to determine the preventive effect of DHA against pancreatic cancer development (Fig. 1).

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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