The Emerging Field of Nutritional Tumorigenesis: The Role of Omega-3 Fatty Acids

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Abstract

The field of nutritional tumorigenesis, particularly in relation to dietary fats, has emerged as one of the most important research areas in cancer investigation. The role of omega-3 fatty acids as those found in fish oil has been of special interest because of its tumor growth inhibitory potential. This article will discuss major concerns related to the use of omega-3 fatty acids in cancer therapy.

Key words

Nutritional tumorigenesis, omega-3, cancer.

The field of nutritional tumorigenesis has a potential for producing an enormous impact in many areas of cancer research; in relation to nutritionally relevant fatty acids such as linoleic acid and eicosapentaenoic acid, it has been recently reported an apparent regulatory function of these fatty acids on gene expression in vitro.[1]

The proposed mechanisms by which diets high in omega-3 PUFAs inhibit mammary gland tumorigenesis are numerous and varied. The omega-3 fatty acid-eicosanoid metabolism relationship has been the most intensely examined mechanism. Although in a particular cell line used in the studies reported herein (MDA-MB231), cell growth has been reported to be more dependent on leukotrienes than on prostaglandins.[2] Nevertheless, in BHK-21 transformed cells, when inhibitors of cyclooxygenase (indomethacin) or lipoxygenase (nordihydroguaiacetic acid) were added along with the fish oil, there was no diminution in the inhibitor actions of the oil,[3] suggesting that the involvement of prostaglandins or leukotrienes may be negligible in this process. At variance we have proposed the hypothesis that dietary fish oil inhibits mammary gland tumorigenesis, at least in part, by the generation and/or accumulation of secondary products of lipid peroxidation in the tumor tissue, a concept we have first described in recent publications.[4-6]

These secondary products of lipid peroxidation (e.g., 4-hydroxynonenal), besides affecting a whole array of cellular biochemical and physiological functions,[4] have been recently reported to suppress the expression of specific genes involved in the metabolic cascade leading to cell proliferation.[7] Furthermore, fish oils have also been reported to decrease oncogene expression when compared to corn oil.[8] This concept of modulating gene expression by dietary fatty acids and/or their oxidative products, is without doubt, the next logical step in nutritional tumorigenesis research. This will clarify the specific molecular mechanism(s) of action hindered in this phenomenon. This research might even help determine what specific fatty acid products can affect what specific types of cell, since the actions of fatty acid oxidation products appear to be cell type dependent.[9] Also of interest are studies addressing the interaction of oxidative species with immune system components (lymphocytes, neutrophils, natural killer cells).

Other areas may also require further research. The nature of the different oxidative species formed by the oxidation of fish oil in vivo or absorbed from the diet remains to be determined. Assays with the capability to separate contributions of oxidative species generated from nonenzymatic lipid metabolism from those generated by enzymatic activity of the cellular lipoxygenase or cycloxygenase systems need to be developed. Also, more studies are needed in the area of tumor growth kinetics, specifically in relation to cell loss and cell proliferation. Preliminary results pointing at cell loss as a more important tumor growth kinetic parameter than cell proliferation need to be verified. Also of in-

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terest is the effect of different fats on fatty acid metabolism enzymes, such as the desaturases (6-desaturase system has been reported[10] to be frequently modified in malignant cells). Further studies in these previously mentioned areas may clarify important details of the physio-biochemical pathways that fats undertake in order to affect tumor growth. It is conceivable that an interplay of various mechanisms are operative in the suppression of mammary gland tumorigenesis by omega-3 PUFAs.

Clinical Implications

At present, fats contribute close to 40% of the total kilocalories in the average American diet. Fats are involved in numerous biochemical processes. Thus, the amount and type of dietary fat can influence normal physiological functions and also can contribute to the pathogenesis of various diseases. General consensus supports the recommendations that many Americans should consume less fat in their diet. However, less settled is the issue of the appropriate type(s) of fat. It is clear that different fats have distinct biochemical/physiological functions in normal and/or pathological processes.

The substitution of foods with high levels of saturated fats with marine products has been recommended for health promotion and even treatment of certain diseases. Epidemiological and experimental data indicate that fish oils, which contain high levels of omega-3 PUFAs may help in the prevention and treatment of various clinical diseases,[1113] which includes breast cancer. In relation to fish oil, it is clear that the level of omega-3 PUFAs required to produce an antitumor effect is much higher than would normally be achieved from the diet alone. Nevertheless, the fish oil appears to have an anti-tumor effect similar to many conventional cytotoxic drugs with the added benefit of no toxic short term side effects. Furthermore, the possibility of utilizing omega-3 PUFAs as an effective adjuvant therapy (thereby using less chemo-therapeutic agents, thus producing less side effects without sacrificing treatment effectiveness) seems now within reach. This renewed interest in fish oil as both a preventive and a therapeutic substance for various conditions has overlooked potential detrimental side effects. These secondary effects may include: oxidation of low density lipoproteins (LDL)[14] which can be conduscent to coronary artery disease, suppression of the immune response[15] via oxidation of omega-3 fatty acids in the lymphocyte membrane and the oxidation of infant lipid emulsions and formulas[16] which can contribute to premature lung injuries and damage to the central nervous system and retina. In contrast to these detrimental effects, supplementation with fish oil has been found to be of benefit in reducing plasma triglycerides, reducing platelet aggregability[17] and possible therapeutic roles in hypertension,[18] inflammatory diseases[19] and cancer.[5] Although mechanisms for these actions remain uncertain, it is clear that lipid peroxidation cannot be ignored in our assessment of the role of long chain omega-3 PUFAs in normal and pathological processes.

Dedication

To the memory of Juan and Luz Guzman

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