special report

International workshop on cellular and molecular aspects of ω-3 fatty acids and cancer[1]

William Stillwell* and Laura Jenski[2,†]

Department of Biology,* Indiana University-Purdue University, Indianapolis, 723 W. Michigan Street, Indianapolis, IN 46202-5132; and Department of Biological Sciences,† Marshall University, 1 John Marshall Drive, Huntington, WV 25755

The "Cellular and Molecular Aspects of ω-3 Fatty Acids and Cancer" workshop was held on June 28–30, 2001 at the Beaver Run Resort, Breckenridge, CO, USA. The conference organizing committee consisted of Laura Jenski, William Stillwell, Arthur Spector, and Robert Katz.

WORKSHOP OBJECTIVE

It is now well established that dietary ω-3 polyunsaturated fatty acids (ω-3 PUFAs) can reduce the incidence and/or severity of many cancers. The initial observations suggesting an anticancer role for ω-3 PUFAs were based on epidemiology studies that, by their very nature, do not indicate a mode of action. Subsequent dietary, cell culture, and model studies have produced a plethora of possible mechanisms of action for these fatty acids. It was the purpose of the "Cellular and Molecular Aspects of ω-3 Fatty Acids and Cancer" workshop to bring together investigators from diverse backgrounds who would not normally have the opportunity to interact to discuss the relationship between ω-3 PUFAs and cancer.

WORKSHOP SUMMARY

While the mechanism of action for ω-3 fatty acids is undoubtedly complex and still remains a mystery, it is agreed that understanding how these compounds function is essential for successfully employing them as anticancer agents. The workshop covered a vast array of possibilities that can be roughly divided into six, often overlapping, categories. Possible modes of action for ω-3 fatty acids discussed at the workshop are briefly summarized below.

Effect on membrane structure and function

The focus on the structural effects of ω-3 fatty acids on membranes was on docosahexaenoic acid (DHA), the longest (22 carbons) and most unsaturated (six double bonds) of the ω-3s. This fatty acid is rapidly incorporated into membrane phospholipids, phosphatidylethanolamines (PE), and cholines (PC) in tumor cells and phosphatidylserines (PS) in neuronal cells. Once incorporated, DHA has a profound effect on many membrane physical properties, including permeability, lateral diffusion, lipid packing, and domain formation. Alterations in basic membrane properties in turn affect the activity of resident proteins. Discussed at the workshop were the effect of ω-3 fatty acids on the G-protein coupled Metarhodopsin, Raf-1 kinase, ion channels, tyrosine kinases, adenyl cyclase, and class I major histocompatibility complex protein. Many of the discussed proteins are intimately involved in intracellular signaling events and may partially account for the anticancer properties of ω-3 fatty acids.

Effect on cell biology

DHA was reported to be involved in programmed cell death, increasing apoptosis in tumor cells, yet preventing apoptosis in neuronal cells. Perhaps this discrepancy is due to DHA accumulation primarily into PE and PC in the tumor cells and PS in neuronal cells. Another suggested role for DHA was as a competitor of arachidonic acid for cyclooxygenase (COX-2) and 5-lipoxygenase, reducing eicosanoid synthesis and depressing the growth of some cancers. Over-expression of COX-2 was anti-apoptotic and therefore tumorigenic.

Effect on transcription/translation

The effect of DHA on endothelial cells was attributed to reduction of COX-2 protein expression and enzyme activity by transcriptional regulation likely to involve NF-kB activation. The effect of other transcription factors, peroxisome proliferation activated receptor (PPAR), and sterol response element binding protein (SREBP), was also discussed.

[1] For additional information, see http://www.marshall.edu/n3confer

[2] To whom correspondence should be addressed.
e-mail: jenski@marshall.edu

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As source of lipid peroxidation products

The long chain PUFAs were shown to be highly susceptible to lipid peroxidation. In breast cancer cell lines, it was reported that DHA increased toxicity of anthracyclins (agents that generate oxidative stress) and increased lipid peroxides and that both were inhibited by the antioxidant vitamin E. Anticancer agents that have high peroxide-generating potential (e.g., doxorubicin and epirubicin) were shown to enhance cytotoxicity with DHA but not with oleic acid. Tumor growth was related to the generation of 13-hydroxyoctadecadienoic acid (13-HODE) and was reversed by a lipoxygenase inhibitor.

Effect on metabolism

PUFAs regulate the abundance and activities of PPAR and SREBP, both involved in the balance between hepatic fatty acid synthesis/storage and oxidation. Also discussed was the importance of fatty acid binding proteins (FABPs) in regulating cellular processes, perhaps through transporting the ω-3 fatty acids to the nucleus.

As components of novel anticancer drugs

It was reported that dietary fish oils improve responsiveness of human mammary carcinoma to chemotherapy with doxorubicin, mitomycin, and cyclophosphamide, probably by enhancing membrane permeability to the drugs. It was predicted that nutritional ω-3s improve the therapeutic index of these three drugs by enhancing pharmacological effects but also by lowering host toxicity. It was also demonstrated that ω-3 fatty acids may play a role in treatment of the cachexia associated with cancer and AIDS. Two novel DHA-containing anticancer agents were reported at the workshop. One involved a novel PC containing DHA as the *sn*-1 acyl-chain and methotrexate as the *sn*-2 chain. The second involved DHA conjugated to Paclitaxel. Both drugs were shown to have enhanced anticancer effects and had the further advantage of being less toxic and could be slowly released over time.

PROSPECTUS

During this workshop it became evident that many aspects of ω-3 fatty acids anticancer properties overlapped. Particularly striking was the involvement of the poorly understood lipid peroxidation products on cell signaling, apoptosis, and metabolism. It was evident that much better methods to detect the oxidation products of ω-3 fatty acids are desperately needed. Although being a relatively new area of research, the action of ω-3 fatty acids on transcription factors has the exciting potential to link nutritional studies to molecular biology. Many of the anticancer properties of ω-3 fatty acids must be related to some underlying basic biological principle such as membrane structure or gene expression. The workshop clearly demonstrated the need for collaborations between investigators working in vastly different research environments.