

Molecular effects of docosahexaenoic acid on carcinogenesis and tumor progression processes

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n-3 polyunsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), present at high levels in fish products, are one of the most relevant nutritional factors able to affect etiological mechanisms of several pathological conditions, producing human health benefits. PUFA intake, both as nutrition component or at higher pharmacological doses, is significantly related to risk and outcome of cardiovascular diseases. Moreover, these compounds have been shown to affect the mechanisms involved in some types of malignancies, including breast cancer. However, molecular mechanisms by which n-3 PUFA may affect breast carcinogenic processes have not been completely clarified. Therefore, the aim of our study was to further analyze the effects of these nutrients on the mechanisms underlying breast cancer development, through the comparison of the DHA effects in human breast cell lines (MCF-10A, MCF-7, ZR-75-1, SK-BR-3) with different degree of differentiation and biochemical characteristics. In particular, MCF-10A is a not neoplastic, but an immortalized cell line and therefore comparable to an epithelial mammary cell in an early stage of transformation. Other used cell models are all derived from breast cancer. In addition to their specific intrinsic molecular microenvironment, these cell lines also present a variable growing malignancy level.

Following treatments with two concentrations of DHA (100 and 300 μ M) for 24, 48 and 72 h, we examined cell viability, apoptosis, and cell cycle progression in each cell line. Therefore, we first analyzed cell proliferation by MTT assay, recognizing two most sensitive (MCF-10A and SK-BR-3) and two not very responsive (MCF-7 and ZR-75-1) cell lines to DHA treatments. Through flow cytometry analysis, we then identified two different DHA-mediated phenomena underlying the observed cell growth inhibitions: a strong G0/G1 cell cycle arrest (obtained in MCF-10A cell line) and a cell death induction (in SK-BR-3 cells). To assess involved molecular mechanisms explaining the observed differential cellular effects of DHA, we analyzed the activation of ERK 1/2 and STAT3 pathways and the expression of some molecules involved in cell cycle regulation (p21 and p53), assaying protein products by western blot and mRNA levels by Real time RT-PCR. Results showed as also these molecular targets are differentially regulated by DHA treatments in each cell model. These findings suggest a role of DHA in the etiology and in the development of breast cancer. However, it is impossible to describe an univocal and definitive antitumor mechanism of action for this nutrient because it appears different in different cell lines, even if each one was obtained from the same type of human tissue. It is also not possible correlate the differential observed effects of DHA treatments to the cellular transformation degree since the nutrient inhibited cell viability of both a partial and a fully transformed cell line (MCF-10A and SK-BR-3, respectively). Thus DHA role in breast cancer mechanisms is likely dependent from both molecular properties and degree of malignancy of each clinical case. Nevertheless, taken together, the achieved data appear promising since they suggest a potential contribution of DHA to chemotherapeutic but also to chemopreventive treatments of breast neoplasia.