

Effects of ω -3 PUFA-enriched diet on growth parameters in a syngenic murine model of breast adenocarcinoma: a possible role for estrogen receptor alpha

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Background: Breast cancer (BC) is the most common tumour among women and 75% of BC are estrogen receptor (ER)-dependent. In particular, ER α promotes tumour growth, while ER β has an anti-proliferative effect [1]. Epidemiological data have linked ω -3 polyunsaturated fatty acid (PUFA) consumption to lower incidence of BC and several experimental studies showed the anti-proliferative effects of ω -3 fish oil in different tumour models [2,3]. Chia seed oil is rich in α -linolenic acid (ALA 18:3 ω -3), while corn oil is rich in linoleic acid (LA 18:2 ω -6), precursors of eicosapentaenoic acid (EPA) and arachidonic acid (AA), respectively. Based on substrate availability, these FAs give rise to different eicosanoid signatures with opposite effects in cancer [4]. ω -3 PUFAs generate both anti-inflammatory prostanoids and reactive oxygen species (ROS), which in turn could affect NF- κ B. Indeed, NF- κ B belongs to a family of transcription factors with a key role in inflammation and oxidative stress, but its role in tumour development is still controversial [5]. The aim of the study was to determine possible processes that are activated by dietary lipids regulating BC growth and metastasis.

Methods: 40 BALB/c mice were divided in 2 groups and fed 1) an experimental diet enriched with Chia Oil (ChO) as a source of ω -3, or 2) a control diet with Corn Oil (CO) as a source of ω -6. Afterwards, mice were inoculated with mouse BC cells (LM3) and tumour parameters were recorded after 35 days. FA incorporation into cell membranes was analyzed by gas chromatography, whereas eicosanoid production was evaluated by HPLC. Mitotic or apoptotic figures were assessed in haematoxylin/eosin-stained tumour sections. Western blotting for p-I κ B α /I κ B α , as an index of NF- κ B activation, and ER α /ER β was performed in tumour lysates. ROS release was evaluated in LM3 cells after treatment with either AA or DHA by flow cytometry in the presence of DCFHDA.

Results: Tumour incidence was higher in CO-fed mice (100%) compared with ChO-fed mice (85%). Tumour weight (1.0 \pm 0.2 vs 2.2 \pm 0.2 g, p<0.05) and volume (4.4 \pm 0.4 vs 7.2 \pm 1.0 mm, p<0.05) as well as metastasis number (7.4 \pm 0.8 vs 10.0 \pm 0.1, p<0.05) were lower, whereas tumour latency time (22 \pm 1 vs 15 \pm 2 d, p<0.05) was higher in ChO-fed mice. Accordingly, a lower number of mitosis and a higher number of apoptotic figures were recorded in tumours from ChO-compared with CO-fed mice. Cell membranes of tumours from ChO-fed mice showed a higher percentage of ω -3 PUFAs compared with those from CO-fed mice and generated lower amounts of ω -6 pro-inflammatory eicosanoids 13-HODE (25.1 \pm 2.8 vs 43.1 \pm 4.8 ng/10⁷cells, p<0.05), 15-HETE (13.2 \pm 0.8 vs 86.8 \pm 5.4 ng/10⁷cells, p<0.05) and 5-HETE (11.0 \pm 0.7 vs 95.7 \pm 6.9 ng/10⁷cells, p<0.05). Unexpectedly, the p-I κ B α /I κ B α ratio was higher in tumor lysates from ChO group. Consistently, ROS production was higher in tumor cells challenged with ω -3 with respect to ω -6 PUFAs. Finally, ER α amount was down-regulated by ω -3 PUFAs (-65%, p<0.005) in tumor lysates, while ER β was unaffected.

Conclusion: ω -3 PUFA incorporation into cell membranes shifted lipid mediator profile toward an anti-inflammatory, anti-tumour effect. In addition, ω -3 PUFAs produced higher ROS amounts with respect to ω -6 PUFAs in vitro, consistent with increased NF- κ B activation in vivo. Finally, the ω -3 PUFA-enriched diet profoundly down-regulated ER α without affecting ER β expression. Overall, these data support a potential role for dietary ω -3 PUFAs in BC treatment in association with antiestrogens.

References

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