

Abstract

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DHA induces ER stress and growth arrest in human colon cancer cells: associations with cholesterol and calcium homeostasis.

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BACKGROUND: Polyunsaturated fatty acids (PUFAs) are normal constituents of the diet, but have properties different from other fatty acids (e.g., through generation of signaling molecules). **N-3 PUFAs reduce cancer cell growth**, but no unified mechanism has been identified.

OBJECTIVE: We show that docosahexaenoic acid (DHA; 22:6 n-3) causes extensive changes in gene expression patterns at mRNA level in the colon cancer cell line SW620.

RESULTS: Early changes include unfolded protein response (UPR) and increased levels of phosphorylated eIF2alpha as verified at protein level. The latter is considered a hallmark of **endoplasmic reticulum (ER) stress** and is abundantly present already after 3 h. It may coordinate many of the downstream changes observed, including signaling pathways for cell cycle arrest/apoptosis, calcium homeostasis, cholesterol metabolism, ubiquitination, and proteasomal degradation. Also, **eicosapentaenoic acid (EPA), but not oleic acid (OA), induced key mediators of ER stress** and UPR at protein level. Accumulation of esterified cholesterol was not compensated for by increased total levels of cholesterol, and mRNAs for cholesterol biosynthesis as well as de novo synthesis of cholesterol were reduced.

CONCLUSION: These results suggest that cytotoxic effects of DHA are associated with signaling pathways involving lipid metabolism and ER stress.

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