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Review Article

The Janus Face of Lipids in Human Breast Cancer: How Polyunsaturated Fatty Acids Affect Tumor Cell Hallmarks

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For several years, lipids and especially $n-3$ and $n-6$ polyunsaturated fatty acids (PUFAs) receive much attention in human health. Epidemiological studies tend to correlate a PUFA-rich diet with a reduced incidence of cancer, including breast cancer. However, the molecular and cellular mechanisms supporting the effect of PUFAs in breast cancer cells remain relatively unknown. Here, we review some recent progress in understanding the impact that PUFA may have on breast cancer cell proliferation, apoptosis, migration, and invasion. While most of the results obtained with docosahexaenoic acid and/or eicosapentaenoic acid show a decrease of tumor cell proliferation and/or aggressivity, there is some evidence that other lipids, which accumulate in breast cancer tissues, such as arachidonic acid may have opposite effects. Finally, lipids and especially PUFAs appear as potential adjuvants to conventional cancer therapy.

1. Introduction

Breast cancer is one of the cancers most frequently observed in industrialized countries, and the one with the highest incidence in women. Epidemiological studies have shown that the rate of breast cancer is 4 to 5 times higher in Western countries that in Japan [1, 2] suggesting that diet, and particularly diet rich in $n-3$ and $n-6$ long-chain polyunsaturated fatty acids (PUFAs), may have an influence on tumor emergence [3–6]. Also high dietary intake of fish is associated with a lower incidence of cancers including breast cancer [7–9].

However cohort studies that examined the effect of $n-3$ PUFAs on breast cancer incidence yielded mixed results, and most of them did not show a significant association between $n-3$ PUFAs consumption and breast cancer risk [10, 11]. Nevertheless the Women's Intervention Nutrition Study (WINS) provided evidence that a reduction in dietary fat intake to 22% of total energy intake led to a 24% reduction in the recurrence rate of breast cancer [12]. Then, is fat beneficial or not? Probably not in excess, and mainly PUFAs rich fat rather than saturated fat.

Several authors have shown that $n-3$ PUFAs, namely, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have demonstrable anticancer properties both *in vitro* and *in vivo*. However, the mechanisms behind the benefits are not clear [13–16]. This paper aims to give a rapid overview of the effect of PUFAs on breast cancer cell proliferation, apoptosis, migration, and invasion.

2. Effect of $n-3$ PUFAs on Breast Cancer Cell Proliferation and Apoptosis

Several studies showed that DHA and EPA together or alone inhibit the growth of breast cancer cell lines [17–19]. Some additional evidence hints that DHA not only acts as an antiproliferative agent by lengthening the cell cycle between the G2/M transition [20], but is also a proapoptotic factor, increasing Bcl-2, procaspase-8, and caspase-3 activity in breast cancer cell lines [21–23]. In addition, DHA has been

shown to affect cell proliferation whatever it comes from fish oil or microalgae [24].

Activation of the p44/42 mitogen-activated protein kinase (MAPK) pathway plays a major role in regulating cell growth and survival in breast cancer cells [25] and is protective against apoptosis through phosphorylation of Bad [26]. DHA-induced apoptosis of breast cancer cells was also associated with up-regulation of the transmembrane heparan sulfate proteoglycan syndecan-1 [27]. Moreover increase of syndecan-1 impairs signaling of the MAPK pathway by inhibiting phosphorylation of MEK, Erk, and Bad, that results in apoptosis induction in breast cancer cells [28].

Incorporation of $n-3$ PUFAs in membranes decreased arachidonic acid (AA) content and $n-6/n-3$ PUFA ratio in the membranes, without modifying the unsaturation index [29]. Consequently, the modification of AA metabolism, especially the inhibition of the production of eicosanoids, may explain in part the antiproliferative and proapoptotic effect of $n-3$ PUFAs [16, 30]. Whereas low doses of DHA and EPA did not change cell susceptibility to oxidative stress [29], several works report increased lipid peroxidation and ROS production in $n-3$ PUFA-treated cancer cells associated with growth arrest and apoptosis [31–38]. Some differences between DHA and EPA may be noted as reported in glioblastoma cells where the levels of reactive oxygen species and thiobarbituric acid-reactive substances were significantly higher in DHA-treated cells than in EPA- and AA-treated groups [33]. Glutathione is a key molecule in cellular redox homeostasis, and its reduced form (GSH) content was decreased in DHA-supplemented cells [33, 35]. The activity of cytosolic glutathione peroxidase was decreased in breast cancer cells treated with DHA [37] whereas main antioxidant enzyme activities (i.e., superoxide dismutase and catalase) were increased [33, 37]. The use of various antioxidant molecules was shown to inhibit $n-3$ PUFA-induced apoptosis suggesting the involvement of lipid peroxidation-derived ROS [31–38].

Then PUFAs appeared as proliferation inhibitors and apoptosis inducers in breast cancer cell lines and animal models, at least in part through MAPK and ROS pathways [28, 39].

3. Effect of $n-3$ PUFAs on Lipid Rafts and Signaling in Breast Cancer Cells

The $n-3$ PUFAs may exert their growth inhibitory effects on cancer cells by altering the plasma membrane composition and associated signaling events [40]. One emerging view is that DHA-containing phospholipids modify the biophysical organization of the plasma membrane which in turn modifies protein activity and cellular function [41–45]. Model membrane studies suggest that the energetically less favorable interaction between cholesterol and PUFA, especially DHA, promotes lateral phase segregation into sterol-poor/PUFA-rich and sterol-rich/saturated fatty acid-rich microdomains [44, 46, 47]. Since lipid rafts are predominantly enriched in saturated fatty acids-containing sphingolipid and cholesterol, the incorporation of PUFA, especially DHA, determines in breast cancer cells a disruption of lipid rafts and a formation of the PUFA-rich/cholesterol-poor nonraft domains [43].

The effect of $n-3$ PUFAs on lipid rafts and their signaling pathways has been studied in several cell types with cancerous origin or not [48]. Particularly, the raft marker caveolin-1 is partially displaced on treatment with DHA and EPA [49, 50]. In the MDA-MB-231 breast cancer cell line, Altenburg and Siddiqui, 2009 showed that $n-3$ PUFAs exposure resulted in a decreased level of the chemokine receptor CXCR4, which requires intact lipid rafts for signaling [51]. Schley et al, 2007 have shown in the MDA-MB-231 cell line that a combination of EPA and DHA induces a modification in the lipid raft composition including fatty acids, phospholipids, cholesterol, ceramides, and DAG content of membrane rafts [52]. These alterations of lipid content are accompanied by a decrease of EGFR in rafts and an increased whole cells level of phosphorylated EGFR and p38 MAPK [52]. Increased phosphorylation of EGFR and p38 was already reported as a proapoptotic signal in cancer cells [53–55], and especially in the MDA-MB-231 breast cancer cell line [52, 56]. Furthermore DHA induces the upregulation of EGFR tyrosine phosphorylation and the increase of EGFR association with the Sos1 guanine nucleotide protein exchange factor in cancer cell lines including MDA-MB-231 [57]. These data suggest that EGF/Ras/Erk signaling is being disrupted in DHA-treated breast cancer cells by the exclusion of EGFR protein from lipid raft microdomains [52, 57].

Corsetto et al. have recently examined the PUFA incorporation in breast cancer lipid rafts and showed that PUFA are incorporated preferentially in phosphatidylinositol, phosphatidylserine, and phosphatidylcholine that may be relevant to the formation of biologically active metabolites such as prostaglandins, prostacyclins, leukotrienes, resolvines, and protectines [43]. These authors conclude that while EPA may contribute to cell apoptosis mainly through a decrease of AA concentration in lipid raft phospholipids, DHA may change the biophysical properties of lipid rafts decreasing the content of cholesterol and the distribution of key proteins such as EGFR, Src, heterotrimeric G-proteins subunits, or sphyngomyelinase. Indeed DHA decreases the sphingomyelin content in lipid rafts of breast cancer cell lines [43]. This might be due to an activation of sphingomyelinase, leading to the production of ceramide which is well known to be associated with apoptosis and cellular stress [58–61]. Increased activity of the neutral sphingomyelinase in response to EPA and DHA treatment was previously reported in Jurkat leukemic cells [16].

Recently $n-3$ PUFA-mediated alteration of lipid rafts was linked to oxidative stress modulation. The treatment of rat hepatocytes with EPA increases ethanol-induced oxidative stress via lipid raft aggregation and subsequent phospholipase Cγ translocation into these microdomains [41]. EPA incorporates preferentially into nonraft membrane region, leading to raft cholesterol increase [41]. In a different model, that is, human endothelial cells, DHA reduced oxidative-stress-induced calcium influx through modification of lipid raft composition [45]. Then what is

the effect of $n-3$ PUFA-mediated remodeling of lipid rafts in breast cancer cells with respect to oxidative stress?

4. PUFA-Induced Inhibition of Cell Migration and Invasiveness

Because metastasis is the leading cause of death from breast cancer, reducing the invasive potential of breast cancer cells is almost as important as destroying in the primary tumor. Recently, we showed that DHA reduces the invasive potential of the MDA-MB-231 breast cancer cell line [21]. Interestingly cholesterol levels in lipid rafts, which are altered by $n-3$ PUFA [52], are critical for the migration, invasion, and angiogenesis of breast cancer cells [62]. In this study, methyl-β-cyclodextrin reduced uPAR and matrix metalloproteinase-9 (MMP-9) colocalization in lipid rafts and inhibited breast carcinoma cell migration and invasion. The decreased expression of uPAR and MMP-9 was reversed by cholesterol supplementation [62]. In addition the DHA-induced reduction of breast cancer cells migration may also be due to inhibition of voltage-gated Na^+ channels [63, 64]. Indeed DHA inhibits voltage-gated Na^+ channels (neonatal $Na_v1.5$) in a dose-dependent manner, and tetrodoxin, a compound that specifically blocks this type of channels, reduces MDA-MB-231 cell migration at the same level that observed in the presence of DHA [64]. The authors concluded that DHA-induced suppression of cellular migration occurred primarily via down-regulation of voltage-gated Na^+ channel mRNA and functional protein expression [64]. Moreover voltage-gated Na^+ channels localization in lipid rafts, such as shown in cardiac cells [65], may be affected by PUFAs [63].

One of the hallmarks for breast cancer metastasis is the over expression of chemokine receptors, which leads to migration of the cancerous cells to surrounding tissues [66–68]. The transmembrane G protein-coupled receptor CXCR4 is the most prominent chemokine receptor expressed in breast cancer cells (but not in normal breast cells) and represent a major factor in breast cancer metastasis due to migration of the cancerous cells through signaling by its unique ligand (i.e., CXCL12) to surrounding tissues [67, 69–71]. Exposure of MDA-MB-231 breast cancer cells to $n-3$ PUFAs results in decreased surface levels of CXCR4 in a time- and dose-dependent manner [51]. Migration of cells toward the CXCR4 ligand CXCL12 was also significantly reduced on $n-3$ PUFA treatment [51]. These data suggest that the disruption of required lipid raft domains for CXCR4 signaling and the displacement of CXCR4 from the lipid raft domains are potential mechanisms behind the inhibited migratory response after DHA and EPA treatment [51].

5. $n-6$ PUFAs as Promoters of Breast Cancer Cell Proliferation and Invasiveness

Some recent studies focused on the negative effect lipids may have on breast cancer evolution and/or emergence. Both LDL and unsaturated fatty acids have been demonstrated to increase proliferation of estrogen receptor alpha negative (ER^-) breast cancer cells [72–74] suggesting that higher levels of circulating lipoproteins and free fatty acids, which are common in obesity, metabolic syndrome, and high-fat diets, may themselves promote aggressive characteristics of breast cancer. The observations by Antalis et al. that triple negative breast cancer cell lines (i.e., lacking ER, progesterone receptor, and ERBB2), namely, MDA-MB-231 and MDA-MB-436, had many more lipids droplets as compared to the ER^+ MCF-7 cell line leads to the investigation of neutral lipid composition and metabolism in these cells [75]. Elevated levels of triacylglycerol and cholesteryl esters were found, with a greater proportion of cholesteryl ester relative to triacylglycerol [75]. Moreover the acylCoA : cholesterol acyltransferase 1 (ACAT1) expression was upregulated as well as the LDL uptake in triple negative cells compared to ER^+ cells [75]. These data are in agreement with transcriptomic results showing that ACAT1 is more highly expressed in human breast cancer cell lines [76] and human breast tumors [77–80] that were characterized as basal, triple negative, or ER^-. Interestingly, LDL was shown to stimulate proliferation of ER-cells in a manner dependent from ACAT1 activity [75, 81]. High ACAT1 activity was associated with a higher expression of LDL receptor and both depletion in LDL and ACAT1 inhibition decreased cell migration [81]. This supports the association of lipid accumulation with aggressive behavior in ER-breast cancer cell lines.

Examining fatty acid composition of breast cancer tissues Chang et al. observed higher levels of AA, stearic acid, and DHA in tumoral tissue by comparison with healthy tissue of the same patient [82]. They also observed an increased expression of PPARα in breast cancer tissues [82]. Furthermore, the AA contents of the breast cancer tissues were positively correlated with mammary carcinogenesis [82–84]. Besides these *in vivo* data, AA was found to stimulate the growth rate of three breast cancer cell lines (one triple negative and two triple positive) in correlation with PPARα expression and activity [82]. Invasiveness of breast cancer cells is increased by AA and was recently shown to be dependent of TGF-β-activated kinase-1 [85] and ubiquitination of collagen-IV [86]. Treatment of MDA-MB-231 cells with AA also stimulates a signaling pathway dependent of phospholipase-A2-α, Src, Erk1/2, and lipoxygenase activities [87]. The mammalian target of rapamycin (mTOR) signaling pathway, which is upregulated in many cancers, was stimulated in breast cancer cultured cells treated with AA [88]. This mTOR pathway seems to be involved in AA-induced proliferation and angiogenesis of breast tumor [88]. In addition, esterification of AA by acyl-CoA synthetase-4 (ACSL4) may play a causal role in the aggressive phenotype of breast cancer cells through the compartmentalization of AA release in mitochondria, a mechanism that serves to drive the specific lipoxygenase metabolism of AA [89].

Like AA, linoleic acid promotes the proliferation and the migration of cancer cells. Linoleic acid induces expression of plasminogen activator inhibitor-1, proliferation, migration, and invasion of breast cancer cells [90, 91]. Linoleic acid also induces focal adhesion kinase, NF-κB activation, matrix metalloproteinase-2 and -9 secretion, and finally cell migration and invasion [92]. By contrast, conjugated linoleic

acid (CLA), converted from plant linoleic acid by rumen bacteria, displays the opposite anticancer effect [93]. CLA has been shown to promote breast cancer cell apoptosis through diverse signaling pathways such as estrogen receptor, MAPK, and PI3K/Akt signaling pathways [94–97]. Breast cancer cell invasion is reduced after treatment with CLA, and this may involve PPARγ and E-cadherin/β-catenin pathway and/or estrogen receptor and protein phosphatase-2A depending of the cell type [98, 99]. Caveolin-1 expression is also decreased in breast cancer cells treated with CLA [100], leading to lipid raft alteration as observed with $n-3$ PUFAs.

6. Breast Cancer Risk Associated with $n-6$ and $n-3$ PUFAs in Human

Animal models have demonstrated that long chain PUFAs have differential effects on mammary tumorigenesis based on double bond position and meta-analyses of mouse mammary tumor models have suggested that $n-6$ PUFAs, such as linoleic acid and AA have a tumor promoting effect [101–103]. A potential mechanism behind the cancer promoting effects of $n-6$ PUFAs is through the production of proinflammatory eicosanoids such as prostaglandin E_2, which promotes angiogenesis and hinders apoptosis. Alternatively, $n-3$ PUFAs, such as EPA and DHA are the precursor molecules to eicosanoids that are less inflammatory when compared to AA-derived prostanoids [42, 104]. In a case-control study with US women, Bagga et al. showed that total $n-6$ PUFAs may be contributing to the high risk of breast cancer in the US, and that $n-3$ PUFAs may have a protective effect [105]. A recent cohort study in China also shows a statistically significant interaction between $n-6$ PUFA intake, $n-3$ PUFA intake, and breast cancer risk. Women with lower intake of $n-3$ PUFA and higher intake of $n-6$ PUFA had an increased risk for breast cancer compared to women with higher intake of $n-3$ PUFAs and lower intake of $n-6$ PUFAs [106]. Accordingly a previous study points out an increased breast cancer risk in Singapore Chinese women belonging to the highest quartile of $n-6$ fatty acid consumption among subjects who consumed low levels of marine $n-3$ fatty acids [107]. To conclude, the relative amounts of $n-6$ PUFA to $n-3$ PUFAs may be more important for breast cancer risk than individual dietary amounts of these fatty acids.

7. Conclusion

High fat diets, obesity, and metabolic syndrome leading to high circulating level of lipoproteins are harmful for more than one aspect, but they may also be aggravating for breast cancer by stimulating tumor proliferation and metastasis. On the contrary PUFAs are generally regarded as safe compounds that are well tolerated and produce few side effects. Their effects on nontumorigenic cells have not been fully elucidated, but some studies suggest that when provided at concentrations that inhibit tumor cell growth, $n-3$ PUFA exert little or no cytotoxic effects on normal breast cells [17, 18, 108]. Clinical studies are ongoing to show the DHA-improved outcome of chemotherapy in patients with metastatic breast cancer [109, 110]. DHA may also have interesting synergistic effects with other compounds such as with curcumin [111]. Then $n-3$ PUFA may now be considered as powerful nontoxic adjuvant of canonical anticancer treatments [112], especially for patient suffering from late stage metastatic breast cancer. However, further investigation will be required to determine whether the effects observed in the breast cancer cell lines or animal models will be replicated with primary breast cancer cells, and moreover to see if the *in vitro* observed effects will be translated *in vivo*. Also, it will be important to determine the ratio of $n-3$ versus $n-6$ PUFAs needed to be consumed for the beneficiary effect to be achieved.

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