Omega-3 Polyunsaturated Fatty Acids Regulate Syndecan-1 Expression in Human Breast Cancer Cells

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Abstract

Human epidemiologic studies and animal model studies support a role for n-3 polyunsaturated fatty acids (n-3 PUFA) in prevention or inhibition of breast cancer. However, mechanisms for this protection remain unclear. Syndecan-1 is a heparan sulfate proteoglycan, expressed on the surface of mammary epithelial cells and known to regulate many biological processes, including cytoskeletal organization, growth factor signaling, and cell-cell adhesion. We studied effects of n-3 PUFA on syndecan-1 expression in human mammary cell lines. PUFA were delivered to cells by low-density lipoproteins (LDL) isolated from the plasma of monkeys fed diets enriched in fish oil (n-3 PUFA) or linoleic acid (n-6 PUFA). Proteoglycan synthesis was measured by incorporation of [35S]-sodium sulfate. No effect of either LDL was observed in nontumorigenic MCF-10A cells, whereas in MCF-7 breast cancer cells, treatment with n-3–enriched LDL but not n-6–enriched LDL resulted in significantly greater synthesis of a proteoglycan identified by immunoprecipitation as syndecan-1. Using real-time reverse transcription-PCR (RT-PCR), it was shown that n-3–enriched LDL significantly increased the expression of syndecan-1 mRNA in a dose-dependent manner and maximal effective time at 8 hours of treatment. The effect was mimicked by an agonist for peroxisome proliferator-activated receptor γ (PPARγ) and eliminated by the presence of PPARγ antagonist suggesting a role for PPARγ in syndecan enhancement. Our studies show that n-3 LDL modifies the production of syndecan-1 in human breast cancer cells and suggest that biological processes regulated by syndecan-1 may be modified through LDL delivery of n-3 PUFA. (Cancer Res 2005; 65(10): 4442-7)

Introduction

Human epidemiologic studies have shown that dietary intake of fish oil may protect against the development of certain cancers including breast, colon, and prostate (1–4). In support of this, animal studies have indicated that diets enriched in fish oil or its component n-3 fatty acids, docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3), significantly inhibit breast cancer cell growth (5–7) and metastases (8, 9). In spite the potential importance of n-3 polyunsaturated fatty acids (PUFA) in prevention or inhibition of breast cancer, there is little understanding of the key molecular targets of n-3 PUFA that may play a role in the tumor-inhibitory properties.

Syndecan-1 (SDC-1) is a member of the syndecan family of transmembrane heparan sulfate proteoglycans and has been shown to act as a tumor suppressor molecule by induction of apoptosis and inhibition of cell growth (10–12). Expression of SDC-1 in S115 mouse mammary epithelial tumor cells was shown to restore their epithelial phenotype (13). SDC-1 expression was markedly reduced in squamous cell carcinoma and there was an inverse relationship between SDC-1 expression and tumor aggressiveness (14). Similarly, SDC-1 expression was reduced in human hepatocellular carcinoma with high metastatic potential (15) and the survival rate in patients with SDC-1–negative colorectal tumors was decreased significantly (16). Loss of tumor cell SDC-1 was associated with poor prognostic outcome in head and neck cancer (17, 18), laryngeal cancer (19), malignant mesothelioma (20), and lung cancer (21). In vitro studies have shown that SDC-1 inhibited the invasion of tumor cells into type I collagen (22, 23) and that expression of SDC-1 in myeloma cells suppressed matrix metalloproteinase-9 (24). Thus, decreased SDC-1 expression may be an important step in progression of carcinoma cells to the metastatic phenotype.

Factors regulating SDC-1 expression are not well understood. An intriguing finding is that the proximal promoter of the SDC-1 gene contains a functional DR-1 element (25) which is recognized by several members of the nuclear hormone superfamily receptors including peroxisome proliferator-activated receptors (PPAR). PPARs are monitors of intracellular nonesterified fatty acid level and change the transcription of many genes (26). Fatty acids are known to bind and activate PPARs (27–29). The three PPAR isotypes (α, β/δ, and γ) are involved in diverse physiologic processes, including cell proliferation and differentiation, apoptosis, inflammatory response, and lipid and glucose homeostasis (reviewed in refs. 30, 31). Distinct tissue distribution and developmental expression suggests distinct functions for different PPARs but clear evidence is lacking. In human breast cancer cell lines, activation of PPARs (32) and PPARα/δ (33) stimulated proliferation, whereas ligands for PPARγ were growth inhibitory (34).

We have previously reported that n-3 PUFA inhibited growth and induced apoptosis in MCF-7 human breast cancer cells (35). In the present studies, we sought to determine whether SDC-1 may be a molecular target for n-3 PUFA through activation of the PPARγ transcriptional pathway and thereby provide a molecular mechanism for tumor protection by these fatty acids.

Materials and Methods

Preparation of low-density lipoproteins. Low-density lipoprotein (LDL) was isolated from plasma of adult African Green monkeys fed n-3 PUFA–enriched (fish oil) or n-6 PUFA–enriched (linoleic acid) diets for 3 to 5 years and whose maintenance and clinical measurements are published (36). Blood samples drawn from the femoral vein of anesthetized animals after an overnight (18 hours) fast, were placed into chilled tubes containing 0.1% EDTA and protease inhibitor cocktail (Sigma Chemical Co., St Louis, MO) at pH 7.4. Plasma was immediately isolated by low-speed centrifugation and LDL was isolated from plasma by sequential density gradient
ultracentrifugation, filter sterilized, and cryopreserved in 10% sucrose under argon at −70°C until use (37). LDL protein was measured by the method of Lowry (38). LDL chemical compositions were measured by enzymatic and chemical assays (35). LDL fatty acids were determined after lipid extraction, saponification, and methylation, and fatty acid methyl esters were measured by gas-liquid chromatography. Based on the phospholipid/protein molar ratio and the fatty acid percent composition of the LDL (33), 100 μg/mL LDL (as protein) contained ~30 μmol/L EPA and 15 μmol/L DHA.

Preparation of fatty acid–bovine serum albumin complexes. Fatty acid–free bovine serum albumin (BSA, Sigma Chemical) was prepared as a 125 μmol/L solution in DMEM/Ham’s F-12. EPA, DHA, and linoleic acid, purchased as sodium salts (Sigma Chemical), were solubilized to 600 μmol/L stocks in the BSA medium and stored in aliquots at −20°C under argon (35).

Cell culture. MCF-7 and MCF-10A cell lines, obtained from American Type Culture Collection (Rockville, MD) were maintained in DMEM/F12 supplemented with 5% fetal bovine serum (FBS), 10 mg/mL porcine insulin (Sigma Chemical), penicillin/streptomycin, and 1-glutamine at 37°C in 5% CO2. In experiments measuring proteoglycan synthesis, cells were plated in 24-well plates at a density of 1.3 × 105 cells per well in growth medium. After 6 hours, the medium was changed to DMEM/F12 with 0.5% FBS for 18 hours to up-regulate LDL receptors. Proteoglycans were metabolically radiolabeled with 30 μCi/mL [35S]-sodium sulfate (Perkin-Elmer, Billerica, MA) in DMEM/F12 containing 0.5% FBS and indicated concentrations of LDL, BSA-fatty acids, or PPAR ligands troglitazone and GW298662 (Cayman Chemicals, Ann Arbor, MI) for 4 to 24 hours. For experiments measuring mRNA levels, cells were plated in 6-well plates at 1 × 106 cells per well.

**RNA isolation and cDNA synthesis.** Total RNA was isolated using TRIZOL (Life Technologies Chemical, Ann Arbor, MI) according to manufacturer’s protocol, and RNA concentrations were measured at A260. Total RNA (2 μg) was used for first-strand cDNA synthesis using Omniscript RT kit (Qiagen, Valencia, CA), Oligo (dT)12-18 Primer (Invitrogen, Carlsbad, CA), and RNase inhibitor (Promega, Madison, WI).

**Real-time PCR.** Real-time PCR was done using SYBR Green PCR master Mix (Applied Biosystems, Foster City, CA) on an ABI PRISM 7000 Sequence Detection System. Primers specific for SDC-1 and peptidyl prolyl isomerase B (PPIB) housekeeping gene were designed using Primer3 (39). SDC-1 primers were 5'-GGAGGACGAGCTTACACCTTG (upper) and 5'-CTCCAGCACCTCTTCTCTCT (lower). PPIB primers were 5'-GGCCAAGATTACCCGTCAA (upper) and 5'-TCCGAGAGACCAAAGATCAC (lower). PCR reactions contained 100 μmol/L of primers and 10 ng of reverse transcribed total RNA in 25 μL PCR was done with an initial 10-minute denaturation at 95°C followed by 40 cycles of PCR (15 seconds at 95°C and 1 minute at 60°C). SDC-1 data was normalized to the housekeeping control PPIB.

Preparation of fatty acid–bovine serum albumin complexes. Fatty acid–free bovine serum albumin (BSA, Sigma Chemical) was prepared as a 125 μmol/L solution in DMEM/Ham’s F-12 supplemented with 5% fetal bovine serum (FBS), 10 mg/mL porcine insulin (Sigma Chemical), penicillin/streptomycin, and 1-glutamine at 37°C in 5% CO2. In experiments measuring proteoglycan synthesis, cells were plated in 24-well plates at a density of 1.3 × 105 cells per well in growth medium. After 6 hours, the medium was changed to DMEM/F12 with 0.5% FBS for 18 hours to up-regulate LDL receptors. Proteoglycans were metabolically radiolabeled with 30 μCi/mL [35S]-sodium sulfate (Perkin-Elmer, Billerica, MA) in DMEM/F12 containing 0.5% FBS and indicated concentrations of LDL, BSA-fatty acids, or PPAR ligands troglitazone and GW298662 (Cayman Chemicals, Ann Arbor, MI) for 4 to 24 hours. For experiments measuring mRNA levels, cells were plated in 6-well plates at 1 × 106 cells per well.

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**Results**

**Effect of n-3 polyunsaturated fatty acids–enriched low-density lipoproteins on SDC-1 expression.** MCF-7 and MCF-10A cells. To determine effects of n-3 PUFA on proteoglycan production, MCF-10A and MCF-7 cells were incubated in medium containing varying concentrations of n-3– and n-6–enriched LDL and [35S]-sodium sulfate. In the absence of LDL, proteoglycan synthesis was threefold higher in MCF-10A cells than that in MCF-7 cells (Fig. 1A). This confirms our recent report of significantly lower proteoglycan production in the MCF-7 compared with MCF-10A cells.1 All levels of n-3 LDL but not n-6 LDL caused a significant increase in proteoglycan synthesis, whereas no effect of either LDL was observed in MCF-10A cells. In MCF-7 cells, n-3 LDL induced a ~2-fold increase in proteoglycans.

Our previous studies have identified SDC-1 as the major species of proteoglycans produced by both of these human mammary cell lines.1 To show that the n-3 LDL specifically up-regulated SDC-1 production in the MCF-7 cells, [35S] sulfate–labeled proteoglycans produced in the presence or absence of n-3 LDL were immunoprecipitated with an antibody to SDC-1. As shown in Fig. 1B, significantly more SDC-1 was measured in preparations from n-3 LDL–treated cells than control cells. SDC-4, another member of the syndecan family of proteoglycans present mammary epithelial cells did not increase when MCF-7 cells were grown in the presence of n-3 LDL (Fig. 1B).

**Effects of n-3 low-density lipoproteins on SDC-1 gene expression.** The observed increase in [35S] sulfate incorporation was not simply a result of increased sulfation of glycosaminoglycan chains in the n-3 LDL–treated cells because double labeling with [35S] sulfate and [3H] serine resulted in increased incorporation of [3H] serine (90.8 ± 4.6 versus 132.4 ± 19.0 dpm/μg cell protein) and [35S] sulfate (8.5 ± 1.4 versus 11.0 ± 1.5 dpm/μg cell protein) for control and n-3 LDL–treated cells, respectively. Moreover, the ratio of [35S] sulfate to [3H] serine was similar (0.094 ± 0.014 and 0.085 ± 0.014, mean ± SE, P = 0.35) in proteoglycans from control and n-3 LDL–treated cells, indicating that the n-3 LDL–induced increase in [35S] sulfate incorporation represented an increase in intact proteoglycans rather than induction of proteoglycan structural changes.

To determine whether n-3 LDL stimulation of SDC-1 production is due to transcriptional regulation of SDC-1, real-time reverse transcription-PCR (RT-PCR) was used to measure SDC-1 expression in MCF-7 cells grown in the presence or absence of n-3 LDL. Previous experiments shown in Fig. 1 had clearly shown an increase in SDC-1 protein by 24 hours of n-3 LDL treatment. To define a window of time in which LDL exerts its effects, MCF-7 cells were treated with n-3 LDL for 4, 8, 12, and 24 hours. As shown in Fig. 2A, the maximal effect was achieved by 8 hours but SDC-1 expression was still significantly higher in n-3 LDL–treated cells

at 24 hours. The optimal concentration of n-3 LDL in regulating SDC-1 gene expression of was 100 μg/mL (Fig. 2B) which was also the optimal dose for proteoglycan production (Fig. 1). The marked drop in SDC-1 expression at 200 μg/mL LDL suggests toxicity of the LDL at this high concentration.

**Effect of eicosapentaenoic acid and docosahexaenoic acid on SDC-1 expression.** LDL from n-3 PUFA-fed animals is enriched with two n-3 PUFA, EPA and DHA (35). To determine whether one or both of these PUFA are active in regulating the SDC-1 gene, studies were conducted with albumin-bound EPA and DHA. As shown in Fig. 3A, 30 μmol/L EPA had no effect on SDC-1 expression. This was also true for 15 and 60 μmol/L EPA (data not shown). DHA at 30 μmol/L (Fig. 3A) or 60 mol/L (data not shown) significantly (P < 0.005) increased the level of SDC-1 mRNA to a level similar to that of n-3 LDL. A combination of EPA + DHA (30 μmol/L each) did not increase the level of SDC-1 expression beyond that of DHA alone. These results suggest that regulation of SDC-1 by n-3 LDL may be primarily an effect of DHA. To confirm that the DHA-induced increase in SDC-1 mRNA resulted in an increase in SDC-1 product, a parallel study examined 35S sulfate incorporation into newly synthesized proteoglycans (Fig. 3B). Consistent with the effects on SDC-1 message levels, DHA enhanced proteoglycan synthesis to a level similar to that of n-3 LDL whereas EPA had no effect either as a separate treatment or in combination with DHA. In addition, neither n-6 LDL nor its principal component PUFA linoleic acid was effective in stimulating proteoglycan synthesis.

**Regulation of SDC-1 expression by peroxisome proliferator-activated receptor γ.** To investigate the transcriptional pathway for regulation of SDC-1 production by n-3 LDL or DHA, MCF-7 cells were incubated for 24 hours with [35S]-sodium sulfate and PPARγ agonist, troglitazone or PPARγ agonist, GW610742. (Fig. 4A and B). Both troglitazone and n-3 LDL were effective stimulators of proteoglycan synthesis, whereas the PPARγ agonist had no effect. The effect of troglitazone was dose dependent (B) with maximal stimulation observed at 10 μmol/L. Higher concentrations (30 μmol/L) of both troglitazone and GW610742 resulted in significant cell death (data not shown). Parallel experiments using real-time RT-PCR indicated that SDC-1 expression by 10 μmol/L troglitazone was regulated at the level of transcription (Fig. 4C). To more directly implicate PPARγ in n-3 LDL stimulation of SDC-1, cells were treated with n-3 LDL in the presence of the PPARγ antagonist GW259662. As shown in Fig. 5A, the n-3 LDL–induced increase in proteoglycan production was eliminated at all concentrations of the PPARγ antagonist. Real-time RT-PCR confirmed that the PPARγ antagonist inhibited the n-3 LDL effect on SDC-1 mRNA (Fig. 5B). This suggests that regulation of the SDC-1 gene by n-3 LDL is mediated by the PPARγ transcriptional pathway.
In spite of considerable evidence for a protective role for n-3 PUFA in breast cancer, mechanisms remain unclear. In the present studies, we report the novel finding that in human breast cancer cells, SDC-1, a multifunctional regulator of cell behavior, is a molecular target for n-3 PUFA. Expression of this proteoglycan may have important consequences in the interaction of the tumor cell and its environment.

A unique feature of these studies is the use of two delivery routes for the n-3 PUFA. Both are physiologically relevant since mammary cells in vivo receive essential fatty acids from two major sources: (a) albumin/fatty acids complexes formed following lipolysis of chylomicrons and very low density lipoproteins; (b) receptor-mediated uptake and intracellular hydrolysis of internalized LDL. The significant increase in LDL receptor activity in neoplastic tissues (41–43) suggests that the LDL pathway may be the major route for dietary fatty acids uptake by tumor cells. As shown in our previous studies, LDL delivery of n-3 PUFA has significant effects on cell growth, apoptosis and global gene regulation (35). In the present study, we have shown that at concentrations slightly lower than those found in fasted human plasma, n-3 LDL up-regulates the expression of SDC-1, that regulation is at the level of transcription and involves the PPARγ transcriptional pathway.

Interest in n-3 PUFA effects on SDC-1 was generated by the potential importance of SDC-1 in processes important to tumorigenesis (10–12, 22–24). SDC-1 is a transmembrane proteoglycan, expressed predominantly on the surface of epithelial cells. In mouse mammary epithelial cells, the SDC-1 ectodomain can bear both heparan sulfate and chondroitin sulfate glycosaminoglycan chains (44). Primarily through the heparan sulfate chains, SDC-1 interacts with extracellular matrix proteins including fibronectin (45), interstitial collagens (46), and thrombospondin (47), and with growth factors, notably fibroblast growth factor -2 (48). When the extracellular domain of SDC-1 is cross-linked by ligands, the cytoplasmic domain associates with F actin (49), suggesting that SDC-1 may be involved in extracellular-intracellular signaling. In addition, there is mounting evidence that SDC-1 is a key regulator of the migratory and invasive behavior of both normal and tumor cells (reviewed in ref. 50).

Our results showed that SDC-1 levels were significantly lower in MCF-7 breast cancer cells than in nontumorigenic MCF-10A cells. This is consistent with reduced SDC-1 in a number of malignancies (14–21) and most evidence suggests that loss of SDC-1 is directly involved in induction of the tumor cell phenotype. In mouse mammary epithelial tumor cells lacking SDC-1, epithelial morphology was restored and malignant growth properties were...
eliminated by re-expression of SDC-1 (13). In addition, SDC-1 synthetic analogues, termed neoglycans were shown to reduce cell viability and induce apoptosis in human myeloma and breast cancer cells (12). This highlights the importance of identifying pathways and mechanisms by which native SDC-1 production may be restored or enhanced in tumor cells.

When MCF-7 cells were grown in the presence of n-3 LDL, SDC-1 was increased up to 2-fold. The effect was associated with n-3 PUFA enrichment of the LDL, because n-6 LDL was not similarly effective. The two major long-chain n-3 PUFA in n-3–enriched LDL from these animals are EPA and DHA (35). When cells were exposed to these fatty acids bound to albumin, only DHA-BSA was able to mimic the stimulatory effect of n-3 LDL on SDC-1 production in spite of the fact that these MCF-7 cells are able to convert EPA to DHA (35). Interestingly, EPA-BSA was able to inhibit growth of MCF-7 cells although to a lesser degree than n-3 LDL (35). MCF-10A cells did not respond to the n-3 LDL by increased SDC-1. One possible explanation is that MCF-10A cell surface SDC-1 is sufficiently high that the cells are refractory to further SDC-1 induction. Another would be that some cells are more sensitive to n-3 PUFA than others.

One potential mechanism by which n-3 LDL may affect gene transcription in MCF-7 cells is by alteration in redox state. We did not measure this nor try to control it by antioxidant supplementation. The LDL was isolated from animals whose diets were supplemented with vitamins including α-tocopherol. Previous studies have shown that in LDL from similar groups of animals, the α-tocopherol remained associated with the LDL particles throughout the isolation procedure and offered protection against oxidation (51). In those studies, α-tocopherol levels were similar among the different diet groups. Nevertheless, the lipid environment did have subtle effects on in vitro oxidation of the LDL with n-6 PUFA–enriched LDL more resistant to initiation of oxidation but oxidizing at a faster rate than n-3 PUFA–enriched LDL. Clearly, effects of LDL lipids on redox state of the tumor cells would be an important area for future study.

In the present studies, both mRNA and proteoglycan were analyzed to determine effects of n-3 PUFA on SDC-1. Incorporation of both GAG and core protein precursors were increased in n-3 LDL–treated cells and proteoglycan from n-3 LDL–treated and control cells had similar ratios of core protein to GAG chains indicating that the n-3 PUFA was stimulating the production of intact proteoglycan rather than inducing structural variations in the proteoglycans. Analysis of mRNA indicated that n-3 PUFA was regulating SDC-1 expression at the level of transcription.

Our study is the first to investigate the transcriptional pathway by which n-3 PUFA regulates SDC-1 expression. Results showed that the PPARγ agonist troglitazone and n-3 LDL induced similar up-regulation of SDC-1 transcription and that the PPARγ antagonist, GW259662, was able to block the LDL induction of SDC-1. These data strongly implicate PPARγ in n-3 PUFA regulation of SDC-1. PPARs are known to monitor intracellular nonesterified fatty acid level and use fatty acids as ligands for regulating gene transcription (27, 31), but data are lacking on specific gene targets of specific fatty acids in different tissues. In a previous report, darglitazone, a ligand for both PPARγ and PPARδ was shown to inhibit PUFA-stimulated expression of the proteoglycan decorin in arterial smooth muscle cells (52). Our data indicate that PPARγ agonist ligands increase rather than decrease the production of SDC-1 in MCF-7 cells. An interesting finding is that although EPA, DHA, and linoleic acid have all been shown to bind PPARγ (28), only DHA was able to regulate SDC-1 expression. This is consistent with reports that binding does not necessarily induce PPRE transactivation. Linoleic acid and arachidonic acid were both shown to bind PPARγ but did not induce transcriptional activation of PPARγ. EPA and DHA showed similar binding activity to PPARδ but only EPA induced activation (28). In solving the co-crystal structure of PPARδ bound to EPA, Xu et al. (27) suggested that its acyl chain length and the five cis double-bonds were important both in fitting the EPA into the PPAR pocket and in producing the numerous hydrophobic interactions required to stabilize the interaction. One speculation would be that DHA is a better fit than EPA for PPARγ although we are not aware of evidence to support this. Another possible reason for a differential result between binding and activation may be that there are indirect effects based on the fatty acids serving as precursors to more active compounds (28).

Activation of specific PPAR has been shown to result in distinct regulation of biological processes. Of great interest and relevance to the present studies are reports that in human breast cancer cell lines, including MCF-7, activation of PPARα, and PPARδ-stimulated proliferation (32, 33), whereas the PPARγ agonist troglitazone significantly inhibited growth (34). Our recent studies have shown that n-3 PUFA inhibit the growth of these cells (35). Although further investigations are needed to confirm this, we would propose, based on present studies, that the n-3 LDL–induced growth inhibition is
mediated by PPARγ. Moreover, because exogenous SDC-1 ectodomain has been shown to suppress the growth of MCF-7 cells (10), we propose that the n-3 PUFA-induced inhibition of cell growth is mediated by a mechanism involving up-regulation of endogenous SDC-1 synthesis via the PPARγ transcriptional pathway.

Acknowledgments


Grant support: American Institute for Cancer Research.

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References

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