Decreased $n$-6/$n$-3 fatty acid ratio reduces the invasive potential of human lung cancer cells by downregulation of cell adhesion/invasion-related genes

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Recent studies have shown opposing effects of $n$-6 and $n$-3 fatty acids on the development of cancer and suggest a role for the ratio of $n$-6 to $n$-3 fatty acids in the control of cancer. However, whether an alteration in the $n$-6/$n$-3 fatty acid ratio of cancer cells affects their invasive potential has not been well investigated. We recently developed a genetic approach to modify the $n$-6/$n$-3 ratio by expression of the Caenorhabditis elegans fat-1 gene encoding an $n$-3 desaturase that converts $n$-6 to $n$-3 fatty acids in mammalian cells. The objective of this study was to examine the effect of alteration in the $n$-6/$n$-3 fatty acid ratio on the invasive potential of human lung cancer A549 cells. Adenovirus-mediated gene transfer of the $n$-3 desaturase resulted in a marked reduction of the $n$-6/$n$-3 fatty acid ratio, particularly the ratio of arachidonic acid to eicosapentaenic acid. Cell adhesion assay showed that the cells expressing fat-1 gene had a delayed adhesion and retarded colonization. Matrigel assay for invasion potential indicated a 2-fold reduction of cell migration in the fat-1 transgenic cells when compared with the control cells. An increased apoptosis was also observed in the fat-1 transgenic cells. Microarray and quantitative polymerase chain reaction revealed a downregulation of several adhesion/invasion-related genes (MMP-1, integrin-α2 and nm23-H4) in the fat-1 transgenic cells. These results demonstrate that a decreased $n$-6/$n$-3 fatty acid ratio reduces the invasion potential of human lung cancer cells by probably downregulating the cell adhesion/invasion-related molecules, suggesting a role for the ratio of $n$-6 to $n$-3 fatty acids in the prevention and treatment of cancer.

Introduction

The ability of malignant tumors to metastasize is largely responsible for their lethality. Patients with metastatic disease from a solid tumor are almost invariably incurable. Thus, metastasis is a principal factor that affects the survival time and prognosis of patients with cancer, and the control of metastasis remains to be a major clinical challenge for the treatment of cancer. Development of safe and effective means to prevent or limit tumor metastasis is urgently needed.

Emerging evidence from epidemiological and experimental studies suggests a relationship between dietary fat and the risk of cancer (1–8). Specifically, it has been shown that a high dietary intake of omega-6 ($n$-6) polyunsaturated fatty acids (PUFAs), such as linoleic acid (18:2n-6), is associated with a high risk for cancer, whereas high intake of omega-3 ($n$-3) PUFAs from fish oils, such as eicosapentaenic acid (EPA) (20:5n-3) and docosahexaenoic acid (DHA) (22:6n-3), decreases the risk for cancers of breast, colon and possibly prostate (3–8). Experimental data show that the $n$-6 fatty acids stimulate carcinogenesis, tumor growth and metastasis, whereas the $n$-3 fatty acids exert suppressive effects (3–13). These findings suggest that the ratio of $n$-6 to $n$-3 fatty acids may be an important factor in controlling the development of tumors. Although previous studies have examined the effect of supplementation with $n$-3 fatty acids on tumor formation, cell proliferation and apoptosis, less information is available on the effect of these fatty acids on the tumor invasive potential and metastasis. A role for the $n$-6/$n$-3 fatty acid ratio in tumor invasion and metastasis has not been evaluated in well-qualified experimental models.

We recently developed a genetic approach to modify the $n$-6/$n$-3 ratio by expression of the Caenorhabditis elegans fat-1 gene encoding an $n$-3 desaturase that converts $n$-6 to $n$-3 fatty acids in mammalian cells (14). Human cells normally cannot produce $n$-3 from $n$-6 fatty acids due to a lack of the fat-1 gene, and must rely on exogenous supply. Our previous studies have shown that the adenovirus-mediated gene transfer of the C. elegans $n$-3 desaturase can quickly and dramatically modify the fatty acid composition ($n$-6/$n$-3), without the need for supplementation with exogenous fatty acids (14). In comparison with supplementation, this genetic approach is more effective in balancing the $n$-6/$n$-3 fatty acid ratio because it not only elevates the cellular concentrations of $n$-3 fatty acids, but also reduces the levels of endogenous $n$-6 fatty acids (as a result of the direct conversion of $n$-6 to $n$-3 fatty acids). Therefore, this can serve as a new model for the elucidation of the biological effects of $n$-3 as well as the $n$-6/$n$-3 fatty acid ratio. The objective of this study was to examine the effect of decreased/balanced $n$-6/$n$-3 fatty acid ratio on the invasive potential of human lung cancer A549 cells.

Materials and methods

Cell culture and adenovirus-mediated gene transfer

Human lung cancer cell line A549 was grown in Dulbecco’s modified medium/F-12 supplemented with 5% fetal bovine serum (FBS) and penicillin/streptomycin. The recombinant adenovirus (Ad) carrying the fat-1 cDNA was constructed as described previously (14). Cells were infected with Ad for experiments when they were grown to ~70% confluence by adding virus (108 particles/ml) (in the presence of 5% FBS). Initially, optimal viral concentration was determined by using Ad.GFP (control vector) to achieve an optimal balance of high gene expression.
and low viral titer to minimize cytotoxicity. Infection efficiency was determined by cell counting using a microscope under both white light and fluorescent light [Infection efficiency = number of green cells (under fluorescence)/cell number (under white light) × 100%]. In this study, only those cells with an infection efficiency of >90% were used for the further analysis.

Detection of fat-1 expression by immunofluorescence staining

Three days after infection, the expression of fat-1 gene in A549 cells was detected by a standard protocol of immunofluorescence. Briefly, the cells were cultured on sterilized glass cover slips to ~75% confluence, fixed by immersion in phosphate-buffered saline (PBS) containing 3% formaldehyde for 15 min, and permeabilized by 0.1% Triton X-100. Anti-fat-1 serum from rabbits (against a synthetic peptide) was used as the primary antibody (dilution, 1:300), Alex Fluor goat-anti-rabbit IgG (H+L) (dilution, 1:800) as the secondary antibody (Molecuar Probe, Eugene, OR). Images were captured with an Olympus fluorescence microscope equipped with a Spot CCD camera.

Analysis of fatty acid composition

The fatty acid composition of total tissue lipids was analyzed as described previously (15). Lipid was extracted with chloroform/methanol (2:1, v/v) containing 0.005% butylated hydroxyltoluene (as antioxidant). Fatty acid methyl esters were prepared using a 14% BF3/methanol reagent. Fatty acid methyl esters were analyzed by gas chromatography using a fully automated HP5890 system equipped with a flame-ionization detector. The chromatography utilized an Omegawax 250 capillary column (30 m × 0.25 mm ID). Peaks were identified by a comparison with fatty acid standards (Nu-chek-Prep, Elysian, MN), and the area percentage for all resolved peaks was analyzed using a Perkin-Elmer M1 integrator.

Cell proliferation assay

Cell proliferation was assessed using a MTT assay (Roche, Mannheim, Germany). At a series of time points after infection, the number of viable cells grown on a 96-well microtiter plate was estimated by adding 10 μl of MTT solution (5 mg/ml in PBS). After 4 h of incubation at 37°C, the stain was diluted with 100 μl of dimethyl sulfoxide. The optical densities were quantified at a test wavelength of 550 nm and a reference wavelength of 630 nm on a multimwell spectrophotometer.

Cells apoptosis assay

Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling (TUNEL) assay was used for apoptosis detection. After 72 h of infection with Ad.GFP or Ad.GFP-fat-1, the cells were fixed with 4% paraformaldehyde in PBS overnight at 4°C. The samples were washed three times in PBS and permeabilized by 0.2% Triton X-100 in PBS for 15 min on ice. After rinsing twice with PBS, the samples were incubated with the TUNEL reagent (Roche) at 37°C in the dark, according to the manufacturer’s instructions. Apoptotic cells were identified by microscopy.

Microarray assay

Total RNA was extracted from the cells after 48 h infection with Ad.GFP or Ad.GFP-fat-1 (infection efficiency was >90%), using an RNAeasy Mini kit (QIAGEN, Valencia, CA) according to the manufacturer’s suggested protocol. Concentration and purity of extracted RNA were determined using a Shimadzu 1600 spectrophotometer (Shimadzu, Kyoto, Japan). The quality of RNA was checked by the 1% agarose gel electrophoresis. Total RNA (5 μg) was used for the synthesis of cDNA probe according to the manufacturer’s protocol. Microarray assay was carried out by using the Human Cancer Pathway Finder Gene Array that contains 96 cancer-related genes (SuperArray Biosci. Corp., Frederick, MD). Hybridized arrays were scanned with HP ScanJet 5550. The images were quantified using the imaging software GeArray Analyzer from SuperArray Inc., and a smoothed T-value cutoff of 2.0 was used.

Real-time quantitative RT-PCR

Oligonucleotide primers were designed using the Primer Express software (Applied Biosystems) and synthesized by Sigma. Forward primers (5′-3′) were: AAGCGGAGAAATAGTGGCCC, CCGATTGAGGCAACAGCGAC-TCT, GGGATTGAGGCTACCTGCATTTT and TCTCGCAACCTCAACCTGCTTAG for matrix metalloproteinase-1 (MMP-1), NM23-H4, ITGα-2 and GAPDH, respectively. Reverse primers (5′-3′) were: TCCAGGCTTCTTG-CAAGCCA, CTGCTGATGGGCAAGCAAGT, GAGAGACGCTCT-ATTCTGAAAG and GCCCATGACTGTTGTCATGAGT for MMP-1, NM23-H4, ITGα-2 and GAPDH, respectively. The fluorescent dye SYBR green was ordered from Stratagene (La Jolla, CA). GAPDH gene was used as an endogenous control to normalize the expression of these genes. Quantitative real-time RT-PCR was performed in triplicate using a 96-well optical tray on an ABI Prism 7000 sequence detection system (Applied Biosystems).

The negative controls lacking template RNA were included in each experiment. PCR products were then run on a 1% agarose gel in order to confirm the presence of a single band with the expected size. Data collection and analysis were performed with the SDS version 1.7 software (Applied Biosystems). Data were then exported and further analyzed in Excel. Results, expressed as N-fold differences in the target gene expression relative to the control gene, termed ‘N’, were determined by the formula: N = 2ΔCtSample/AΔCtControl, where ΔCt value of the sample was determined by subtracting the average Ct value of the target gene from the average Ct value of the control gene. All Ct values of the samples were normalized by human GAPGH.

Cell attachment assay

After 48 h, the A549 cells infected with Ad.GFP or Ad.GFP-fat-1, were detached from the culture plates with 0.5% trypsin-EDTA and plated back on a new culture plate. After a period of 6 and 24 h, the cell attachment status and morphology were examined and the images of the cells were captured by using a fluorescence microscope.

Chemoinvasion assay

Chemoinvasion was determined using the 6-well BioCoat Matrigel invasion chambers (Becton Dickinson Labware, Bedford, MA) with an 8 μm pore polycarbonate filter coated with matrigel. The lower compartment contained 0.6 ml of DMEM/F12 medium with 5% FBS as chemoattractants or serum-free DMEM/F12 medium as a control. In the upper compartment, 5 × 104 cells/well were plated in triplicate and incubated for 24 h at 37°C in a humidified incubator with 5% CO2. After incubation, the cells that had passed through the filter into the lower wells were stained with crystal purple (Fisher Scientific, Orangeburg, NY) and counted under a microscope in five predetermined fields. All the assays were repeated at least three times. The differences in the invasion rates between the control Ad.GFP cells and the Ad.GFP-fat-1 cells were analyzed using a two-tailed Student’s t-test.

Statistical analysis

Results are mean ± SD. Statistical analysis was performed using Student’s t-test, and P-values < 0.05 were considered significant.

Results

Expression of fat-1 gene in A549 cells

After 72 h of viral infection, ~90% of the cells were infected based on the expression of GFP (as shown by green fluorescence, data not shown). To verify the existence of fat-1 product in the cells infected with Ad.GFP-fat-1, we performed an immunofluorescence staining. As shown in Figure 1, a strong immunofluorescent assay. After 60 h of the adenoviral gene transfer, the cells stain was observed in the cells infected with Ad.GFP-fat-1, but not in the control cells treated with Ad.GFP. These results indicate a high infection efficiency of the viral vectors and a high expression rate of the transgene (fat-1) in A549 cells.

Expression of fat-1 gene alters n-6/n-3 fatty acid ratio

After 48 h of infection, the total long chain unsaturated fatty acids were analyzed by gas chromatography. No difference in lipid profile was found between uninfected cells and...
GFP-virus infected cells (data not shown). As shown in Figure 2, eight PUFAs (4 \( n \)-6 and 4 \( n \)-3) were detected in the Ad.GFP cells and Ad.GFP-fat-1 cells. The expression of fat-1 cDNA in A549 cells resulted in the conversions of \( n \)-6 fatty acids to \( n \)-3 fatty acids, leading to a significant change in the ratio of \( n \)-6/\( n \)-3 fatty acids. In the fat-1 transgenic cells, the \( n \)-3 fatty acids ALA, EPA and DHA increased from 0.3, 0.4 and 3.1\% to 0.6, 7.6 and 4.5\%, respectively. Accordingly, the \( n \)-6 fatty acids LA, arachidonic acid (AA) reduce from 3.5 and 15.1\% to 1.4 and 3.5\%, respectively (Table I). Consequently, the ratio of \( n \)-6 to \( n \)-3 fatty acids dropped from 4.5 in the control cells to 0.4 in the fat-1 transgenic cells (AA/EPA + DHA decreased by 10-fold).

**Fat-1 expression inhibits the adhesion of A549 cells**

To examine the effect on cell adhesion, we detached the cells from culture plates with 0.5\% trypsin–EDTA and plated them back on a new culture plate. The same number of viable infected (green) cells in each group (Ad.GFP or Ad.GFP-fat-1) were plated. The rounded cells were the unattached cells. They all eventually attached and developed projections. At a given time point within 24 h, the higher percentage of round cells indicates the more unattached cells (a defect or delay in cell attachment). Figure 3 shows the difference in cell attachment between the control cells and fat-1 transgenic cells. Within 6 h, the majority of the control cells (infected with Ad.GFP) adhered firmly to the plate and developed projections (Figure 3B). Twenty-four hours later, these cells began to grow and form colonies (Figure 3D). In contrast, the cells infected with Ad.GFP-fat-1 still remained suspended after 6 h (Figure 3A) or only slightly attached to the plate 24 h after plating (Figure 3C). The fat-1 cells exhibited a round shape with no attachment projections (Figure 3A and C). Colonization of the fat-1 cells was retarded. These results indicate that the fat-1 transgenic cells have a lower adhesive capability than the control cells.

**Expression of fat-1 gene reduces invasive potential of A549 cells**

A matrigel assay was performed to examine the invasive potential of the lung cancer cells after fat-1 gene transfer.

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**Table I.** PUFA composition of total cellular lipids from cells infected with Ad-GFP and cells infected with Ad-GFP-fat-1

<table>
<thead>
<tr>
<th>Mol % of total fatty acids</th>
<th>Ad-GFP</th>
<th>Ad-GFP-fat-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 18:2n)-6</td>
<td>3.5(^a)</td>
<td>1.4(^b)</td>
</tr>
<tr>
<td>( 20:4n)-6</td>
<td>15.1(^a)</td>
<td>3.5(^b)</td>
</tr>
<tr>
<td>( 22:4n)-6</td>
<td>2.1(^a)</td>
<td>0.6(^b)</td>
</tr>
<tr>
<td>( 22:5n)-6</td>
<td>1.6(^a)</td>
<td>0.4(^b)</td>
</tr>
<tr>
<td>( 18:3n)-3</td>
<td>0.3(^b)</td>
<td>0.6(^a)</td>
</tr>
<tr>
<td>( 20:5n)-3</td>
<td>0.4(^b)</td>
<td>7.6(^a)</td>
</tr>
<tr>
<td>( 22:5n)-3</td>
<td>1.2(^b)</td>
<td>3.3(^a)</td>
</tr>
<tr>
<td>( 22:6n)-3</td>
<td>3.1(^b)</td>
<td>4.5(^a)</td>
</tr>
<tr>
<td>( n)-6/( n)-3 ratio</td>
<td>4.5(^a)</td>
<td>0.4(^b)</td>
</tr>
</tbody>
</table>

Values are means of three measurements. Values for each fatty acid with the same letter do not differ significantly (\( P \leq 0.01 \)) between Ad-GFP and Ad-GFP-fat-1.

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**Fig. 3.** Micrographs showing the effect of fat-1 gene transfer on the cell attachment of A549 cells. Following infection with Ad.GFP or Ad.GFP-fat-1 for 48 h, the cells were trypsinized and plated on a new culture dish. After a period of 6 and 24 h, the images were captured with a fluorescence microscope. (A and B) 6 h; (C and D) 24 h. (A and C) Cells infected with Ad.GFP-fat-1; (B and D) cells infected with Ad.GFP. (Magnification, \( \times 100 \)). See online supplementary material for a color version of this figure.
Fat-1 expression decreases the invasive potential of A549 cells. The cells that invaded through the matrigel-coated trans-well inserts toward chemotaxtractant were stained with 1% crystal purple as described in Materials and methods. Photographs were taken at a magnification of ×100. (A) Control cells infected with Ad.GFP; (B) transgenic cells infected with Ad.GFP-fat-1; and (C) the cells invading through the matrigel were counted under microscope in five predetermined fields at ×100. Each sample was assayed in triplicate. See online supplementary material for a color version of this figure.

Fat-1 expression increases apoptosis of A549 cells

We used the MTT reagent to detect the cell proliferation and found that during the first 4 days, the cell growth rate was not different between Ad.GFP and Ad.GFP-fat-1 cells. But after 96 h, the growth rate of the fat-1 transgenic cells was lower than that of the control cells (Figure 5). In addition, apoptosis assay (TUNEL) showed that the percentage of apoptotic cells in the fat-1 transgenic cells was higher than that in the control cells (P < 0.001) (Figure 6). Although some experiment-to-experiment variability might occur, the high expression and functional activity of fat-1 gene in the fat-1 transgenic cells but the zero background of the gene in the control cells made it not difficult to see the effect, if any, of the fat-1 expression. Indeed, the adenoviral infection and GFP expression somehow affected the cell survival after the 4-day infection. (This nonspecific effect is similar between Ad.GFP and Ad.GFP-fat-1 cells.) The difference in cell apoptosis observed at 72 h reflects the effect of fat-1 expression.

Expression of fat-1 gene downregulates adhesion/invasion-related genes in A549 cells

To examine if the fat-1-induced change in n-6/n-3 ratio has an effect on the expression of cancer-related genes in A549 cells, we characterized the gene-expression profiles of the transgenic and control cells using a low-density microarray (SuperArray) as the preliminary screening, which contains 96 cancer-related genes. The images were quantified using the imaging software GeArray Analyzer from SuperArray, Inc. (Figure 7). Eight genes were found to be downregulated in the fat-1 transgenic cells. Among them, the three genes, *MMP-1* (the intensity of signal of the gene on the array decreased from 27435 to 2988 counts), *ITG-α2* (the intensity decreased from 56821 to 20654) and *NM23-H4* (the intensity decreased from 60429 to 49218), which are involved in the adhesion or metastasis of cancer cells, showed the significant change. This downregulation was verified by a quantitative real-time RT-PCR. The results are shown in Table II.

**Discussion**

The present study demonstrates that the gene transfer of the n-3 fatty acid desaturase into human lung cancer A549 cells decreases the ratio of n-6 to n-3 fatty acids in these cells, inhibits their adhesion, migration, and proliferation, and downregulates the expression of *MMP-1*, *ITG-α2*, and *NM23-H4*. These results suggest that the decreased n-6/n-3 fatty acid ratio reduces the invasive potential of A549 cells through downregulation of the adhesion/invasion-related genes.

In this study, we used a genetic approach to modify the cellular n-6/n-3 fatty acid ratio by converting the endogenous n-6 to n-3 fatty acids, without the need for supplementation with exogenous fatty acids. Thus, this technique could eliminate the potential confounding factor of supplementation (which can cause cellular fatty acid volumes to be unequal between control and experimental cells—an increase in total lipid mass in the supplemented cells), and therefore may be able to provide more reliable results on the effect of change in the n-6/n-3 ratio. Our observation that the change of the cellular n-6/n-3 ratio from a relatively high to a low/balanced one exhibits
Fig. 6. Fat-1 expression induced apoptosis of A549 cells. After 72 h of infection with Ad.GFP or Ad.GFP-fat-1, apoptotic cells were detected by using TUNEL assay. Cells with yellow or red color are apoptotic cells. (Magnification, ×200).

Fig. 7. Microarray images showing the expression profiles of 96 cancer-related genes in A549 cells infected with Ad.GFP (A) or Ad.GFP-fat-1 (B). The arrows indicate the genes (1, ITG-α2; 2, MMP-1; 3, NM23-H4) that are downregulated in Ad.GFP-fat-1-treated cells.

Table II. Real-time RT-PCR showing fold change of target gene expression in A549 cells

<table>
<thead>
<tr>
<th>Genes</th>
<th>Ad.GFP-fat-1 Ct values</th>
<th>Ad.GFP Ct values</th>
<th>ΔCt</th>
<th>Fold changed</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAPDH</td>
<td>15.96 ± 0.079</td>
<td>15.14 ± 0.015</td>
<td>0.82 ± 0.094</td>
<td>—</td>
</tr>
<tr>
<td>NM23-H4</td>
<td>22.76 ± 0.161</td>
<td>20.68 ± 0.306</td>
<td>2.08 ± 0.195</td>
<td>2.40 ± 0.231</td>
</tr>
<tr>
<td>MMP-1</td>
<td>22.59 ± 0.098</td>
<td>20.81 ± 0.188</td>
<td>1.77 ± 0.286</td>
<td>1.93 ± 0.453</td>
</tr>
<tr>
<td>Integrin-α2</td>
<td>23.66 ± 0.036</td>
<td>20.73 ± 0.015</td>
<td>2.93 ± 0.051</td>
<td>4.32 ± 0.132</td>
</tr>
</tbody>
</table>

an inhibitory effect on the invasive potential of A549 cells, implies differential/opposing effects of n-6 and n-3 fatty acids on cancer metastasis and points to the importance of n-6/n-3 fatty acid ratio in the control of cancer.

It is not yet clear how the decreased n-6/n-3 fatty acid ratio causes inhibitory effects on the invasion of cancer cells. The mechanisms may be complex and probably involve multiple pathways. It is possible that the effects are mediated by the decreased production of n-6-derived eicosanoids and/or the increased generation of n-3 fatty acid metabolites. Regardless of peripheral mediators, the behavior of a cell is ultimately dictated by its genetic profile. Importantly, the results of the present study demonstrate for the first time that the decreased n-6/n-3 fatty acid ratio downregulates the expression of MMP-1, ITG-α2 and NM23-H4 in A549 cells. MMP-1 is a member of matrix metalloproteinases that collectively degrade most of the components of the extracellular matrix. It has been classically thought to contribute to the tissue destruction required for the cells to invade, intravasate, extravasate and migrate (16). More recent evidence suggests that MMP-1 also plays a role in the growth of benign and malignant tumors (17), angiogenesis (18) and the sustained growth of metastatic lesions (19). NM23-H4 belongs to human NM23/nucleoside diphosphate kinase gene family. NM23-H family genes (H1, H2, H3 and H4) play different roles in various types of carcinomas. Huang et al. found that NM23-H4 expressed in diffuse astrocytomas, but not in non-malignant brain tissue (20). Hayer et al. reported a strong overexpression of NM23-H4 in most colorectal carcinomas (21). NM23-H4 was also found to overexpress in the large cell anaplastic lymphoma (22) and renal tumors (21). ITG-α2, one of the first integrins to be identified and characterized, is a collagen receptor, although it can function as a dual collagen/ laminin receptor on some cell types. Numerous studies have implicated this integrin in a wide range of biological and pathological functions. Current studies have revealed that ITG-α2 plays a key role in tumor cell-induced platelet aggregation (23) and in adhesive interactions necessary for tumoral invasion and metastasis in breast carcinoma (24). The downregulation of these three genes may be the molecular basis for the inhibitory effects on cell adhesion, invasion (migration) and growth.

Lung cancer is one of the most common cancers and has the highest death rate, owing to its invasion and metastasis. Although currently available drug therapies may temporarily slow tumor growth, they lose their effectiveness and the genetic versatility of the cells allows them to become resistant. Some therapies may not be suitable for long-term use due to severe side-effects. Thus, it is important to develop additional effective and safe approaches for the treatment of cancer, which can be applied separately or in conjunction with current modalities. The results of the present study suggest a role for the n-6/n-3 fatty acid ratio in the control of cancer and provide insights into the development of a new therapeutic strategy by modulating the tissue n-6/n-3 fatty acid ratio for patients with lung cancer. Hardman et al. recently reported that the increased consumption of n-3 fatty acids from fish oil sensitized the A549 lung xenografts in mice to doxorubicin chemotherapy (25). In fact, recent studies have shown that the ratio of
n-6 to n-3 fatty acids in today’s diet is ~10–30:1, indicating that Western diets are deficient in n-3 fatty acids as compared with the diet on which humans evolved and their genetic patterns were established (n-6/n-3 = 1:1) (26). The excess n-6 fatty acids and the very high n-6/n-3 ratios may contribute to the increased incidence of modern diseases, including cancer (27). Thus, manipulating (balancing) the n-6/n-3 ratio of tissue lipids appears to be a feasible approach to the control of cancer.

In addition, the results of the present study showing the effectiveness of adenosine gene transfer of n-3 fatty acid desaturase in the modification of fatty acid composition indicate a novel and effective approach to the balance of n-6/n-3 fatty acid ratio in human cancer cells, and provide a basis for potential applications of this gene transfer as a gene therapy for patients with cancer.

Supplementary material

Supplementary material can be found at: http://www.carcin.oupjournals.org

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References


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