Arachidonic Acid Activates Phosphatidylinositol 3-Kinase Signaling and Induces Gene Expression in Prostate Cancer

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Abstract
Essential fatty acids are not only energy-rich molecules; they are also an important component of the membrane bilayer and recently have been implicated in induction of fatty acid synthase and other genes. Using gene chip analysis, we have found that arachidonic acid, an ω-6 fatty acid, induced 11 genes that are regulated by nuclear factor-κB (NF-κB). We verified gene induction by ω-6 fatty acid, including COX-2, IkBα, NF-κB, GM-CSF, IL-1β, CXCL-1, TNF-α, IL-6, LTA, IL-8, PPARγ, and ICAM-1, using quantitative reverse transcription-PCR. Prostaglandin E2 (PGE2) synthesis was increased within 5 minutes of addition of arachidonic acid. Analysis of upstream signal transduction showed that within 5 minutes of fatty acid addition, phosphatidylinositol 3-kinase (PI3K) was significantly activated followed by activation of Akt at 30 minutes. Extracellular signal-regulated kinase 1 and 2, p38 and stress-activated protein kinase/c-Jun-NH2 kinase were not phosphorylated after ω-6 fatty acid addition. Thirty minutes after fatty acid addition, we found a significant 3-fold increase in translocation of NF-κB transcription factor to the nucleus. Addition of a nonsteroidal anti-inflammatory drug (NSAID) caused a decrease in COX-2 protein synthesis, PGE2 synthesis, as well as inhibition of PI3K activation. We have previously shown that NSAIDs cause an inhibition of arachidonic acid–induced proliferation; here, we have shown that arachidonic acid–induced proliferation is also blocked (P < 0.001) by PI3K inhibitor LY294002. LY294002 also significantly inhibited the arachidonic acid–induced gene expression of COX-2, IL-1β, GM-CSF, and ICAM-1. Taken together, the data suggest that arachidonic acid via conversion to PGE2 plays an important role in stimulation of growth-related genes and proliferation via PI3K signaling and NF-κB translocation to the nucleus.

Introduction
One of the hallmarks of cellular stimulation in response to hormone, growth factor, or phorbol ester activation is the induction of the immediate-early gene expression. There is increasing support to show that essential fatty acids stimulate cell growth; however, the mechanism is not fully understood. For many decades, fats were perceived simply as nutrient fuels and membrane components. Recently, it has been noted that nutrients can also serve as controllers of gene transcription. For instance, glucose can cause hormone secretion and polyunsaturated fatty acids have been shown to regulate fatty acid synthases, Spot 14, and ApoA1 expression in human adipocytes (1). Induction of c-fos is a primary event in growth induction by sera or growth factors and is one of the earliest known effects on gene expression by mitogens; we have previously shown that arachidonic acid induction of c-fos occurs within minutes of arachidonic acid addition (2–5). Taken together, these data implicate arachidonic acid as a growth mitogen. Omega-6 fatty acids are essential because they cannot be synthesized by mammals and must be supplied in the diet.

We have previously shown that cyclooxygenase-2 (COX-2) is induced by ω-6 fatty acids and that COX-2 is a feed-forward enzyme in prostate and colorectal cancers (5–7). In this report, we find that ω-6 fatty acids cause induction of 13 other nuclear factor-κB (NF-κB)-regulated genes, including Jun B oncogene (JUNB); B-cell chronic lymphocytic leukemia (BCL3); nuclear factor of κ light chain gene enhancer in B cells, α (NFKBIA); nuclear factor of κ light polypeptide (NFKB2); peroxisome proliferator-activated receptor (PPAR) δ; and PPARγ. In addition, examination of specific phosphorylation of kinase pathways revealed that two upstream regulators of the NF-κB pathway, phosphatidylinositol 3-kinase (PI3K) and Akt were activated within minutes of arachidonic acid addition. Translocation of NF-κB to the nucleus was significantly increased 3-fold with 30 minutes of treatment. Moreover, arachidonic acid was shown to induce proliferation of cancer cells within 24 hours after addition and this proliferation was inhibited by LY294002, a specific inhibitor of PI3K, suggesting a new mechanism of action for the ω-6 fatty acid induction of prostate cancer gene expression and growth.

Materials and Methods
Trypsin was from University of California San Francisco Cell Culture Facility (San Francisco, CA). Human lipoprotein-deficient serum and antibiotic-antimycotic solution (containing penicillin, streptomycin, and amphotericin B) were from Sigma Cell Culture (St. Louis, MO). Oligonucleotides were purchased from Operon Technologies, Inc. (Alameda, CA). Phospho-pI2/44 (phospho-Thr202/phospho-Tyr204) Mitogen-activated protein (MAP) kinase (ERK) and p42/44 MAP (ERK) kinase, phosphorylated p38 MAP kinase (MAPK; Thr180/Tyr182), phosphorylated pAkt (Ser473), p38 MAPK, and phosphorylated stress-activated protein kinase/c-Jun-NH2 kinase (SAPK/JNK; Thr183/Tyr185) kinase antibodies were purchased from Cell Signaling Technologies (Beverly, MA). Phosphorylated PI3K (Tyr458) and actin antibodies were purchased from Santa Cruz Biotechnologies (Santa Cruz, CA). Phosphorylated cAMP-responsive element binding protein (CREB; Ser133) antibodies were purchased from Upstate (Charlottesville, VA). Supersignal pico-enhanced chemiluminescence kits were purchased from Pierce (Rockford, IL). CyQuant kits were purchased from Molecular Probes (Eugene, OR). All

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other reagents were from Sigma-Aldrich (St. Louis, MO). COX-2 polyclonal antibodies and PGE$_2$ monoclonal ELISA assay kits were purchased from Cayman Chemical (Ann Arbor, MI). Actin goat polyclonal antibody was purchased from Santa Cruz Biotechnologies. Peroxidase-conjugated goat anti-rabbit and donkey anti-goat IgG were purchased from Jackson Immunoresearch Laboratories (West Grove, PA). The DC Protein Assay kit and broad range molecular weight marker were purchased from Bio-Rad (Hercules, CA). Four percent to 12% Bis-Tris gels were purchased from Invitrogen (Carlsbad, CA). Hybond-C extra nitrocellulose membranes were purchased from Amersham Pharmacia (Piscataway, NJ). Restore stripping buffer were purchased from Pierce-Endrogen (Rockford, IL). FCS was purchased from Hyclone Laboratories (Logan, UT). RPMI medium, l-glutamine, antibiotic, and PBS were purchased from Cellgro through Fisher Scientific (Pittsburgh, PA). TRI reagent, HEPES, and albumin were purchased from Sigma (St. Louis, MO).

**Cell culture.** The PC-3 human prostate cancer cell line was provided by the University of California San Francisco Cell Culture Facility. Twenty-four hours before cell plating, cell stocks were fed with fresh RPMI medium containing 10% FCS. Cells were plated and after attachment, medium was changed to 1% to 4% FCS and down-regulated for 24 to 64 hours depending on the amount of FCS present and visual condition of cell endoplasmic reticulum. For cell proliferation analysis, the cells were plated in 96-well plates and once attached were grown in RPMI containing 1% FCS for 51 hours. Cells were treated with 50 µmol/L of LYY294002 1 hour before arachidonic acid addition. Cells were then frozen 24 hours later and cell number was quantified using the CyQuant kit according to the protocol of the manufacturer. Nuclear isolation and preparation of nuclear extract was processed as described by Sheng et al. (8). Arachidonic acid was prepared by addition of arachidonic acid to albumin containing RPMI medium for a final concentration of 1.25 mg/mL of albumin. LY294002 (50 µmol/L), a PI3K inhibitor, or 25 to 50 µmol/L nonsteroidal anti-inflammatory drugs (NSAID) flurbiprofen or indomethacin were added to the cells 1 hour before treatment with arachidonic acid.

**RNA extraction and cleanup for microarrays.** Methods for extraction and cleanup and analysis of microarrays have been previously published (9, 10).

**Real-time quantitative PCR.** Two microliters of cDNA from the reverse transcription reaction were added to 20 µL real-time quantitative PCR mixture containing 10 µL of 2× SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA) and 12 pmol oligonucleotide primers. PCRs were carried out in a Bio-Rad MyQ Single-Color Real-Time PCR Detection System (Bio-Rad) or ABI prism 7900 HT Sequence Detection System (Foster City, CA). The thermal profile was 50°C for 2 minutes, 95°C for 10 minutes to activate the Taq polymerase, followed by 50 amplification cycles, consisting of denaturation at 95°C for 1:40 minutes, annealing at 63°C for 1:10 minutes, and elongation at

![Figure 1](image1.png)

**Figure 1.** Arachidonic acid–induced gene expression of COX-2, NF-κB2, and IκBα, and protein expression of COX-2, which is blocked by NSAID. A, PC-3 prostate cancer cells were activated with 5 µg/mL arachidonic acid (AA, in albumin (0.25 mm/mL containing medium) for 2 hours. Control cells were treated with albumin alone and remained inactivated. Total RNA was isolated and a two-step real-time RT-PCR was done. Columns, mean (n = 4) for each treatment corrected to actin internal standard; bars, SD. *, P < 0.01; **, P < 0.001, with two-tailed Student’s t test against control samples. B, PC-3 cells were grown to near confluence, down-regulated for 48 hours, and then treated with vehicle or vehicle plus arachidonic acid. One hour before treatment with fatty acids, flurbiprofen was added to a portion of the samples, control cells were treated with albumin alone, and remained inactivated. Protein was then isolated and separated by gel electrophoresis and then transferred to blot for COX-2 analysis. The two COX-2 bands are known glycosylated forms of COX-2, both being significantly increased by arachidonic acid. 1, control cells; 2, arachidonic acid–treated cells; 3, cells treated with arachidonic acid and 25 µmol/L NSAID. The membrane was reprobed against actin antibody. Columns, mean (n = 4) for each treatment corrected to actin internal standard; bars, SD. *, P < 0.01, against control samples; γ, P < 0.01 against arachidonic acid samples, with two-tailed Student’s t test.

![Figure 2](image2.png)

**Figure 2.** Arachidonic acid–induced phosphorylation of PI3K and Akt and translocation of NF-κB. A, PC-3 cells were grown to near confluence, down-regulated for 48 hours, and then treated with albumin or albumin plus arachidonic acid for the times shown. Polyclonal antibodies of actin, total p44/42 MAPK, phosphorylated p44/42 MAPK, total p38 MAPK, phosphorylated p38 MAPK, phosphorylated SAPK/JNK, phosphorylated 85s P38, and phosphorylated Akt were used. Columns, mean (n = 3) of phosphorylation of PI3K or Akt for each treatment corrected to actin internal standard; bars, SD. *, P < 0.05; **, P < 0.01 with two-tailed Student’s t test against control samples. B, cells were down-regulated before adding arachidonic acid or carrier (control) to the cells. Cells were collected 30 minutes after addition. Nuclear extracts were prepared as previously described (8). The nuclear extracts were analyzed for NF-κB using Western blots as described in Materials and Methods. Columns, mean; bars, SD. *, P < 0.03 (n = 3).
Table 1. Arachidonic acid significantly induces production of PGE\textsubscript{2} as early as 5 minutes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PGE\textsubscript{2} concentration (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>13.1 ± 6.4</td>
</tr>
<tr>
<td>AA</td>
<td>38.9 ± 8.1\textsuperscript{*}</td>
</tr>
<tr>
<td>AA + F</td>
<td>12.9 ± 2.6\textsuperscript{+}</td>
</tr>
<tr>
<td>AA + Indo</td>
<td>13.5 ± 8.0\textsuperscript{b}</td>
</tr>
</tbody>
</table>

 NOTE: Arachidonic acid (5 \mu g/mL) was added to down-regulated PC-3 cells. Cells (1 × 10\textsuperscript{5}) were seeded in each well. Three hours before addition of arachidonic acid, 25 \mu mol/L of flurbiprofen or 25 \mu mol/L of indomethacin were added to the cells. At 5 minutes after addition of arachidonic acid, medium was collected and PGE\textsubscript{2} enzyme immunoassay was done (n = 3).

 Abbreviations: AA, arachidonic acid; F, flurbiprofen; Indo, indomethacin.

\textsuperscript{*}P < 0.05 against control samples.

\textsuperscript{+}P < 0.05 against arachidonic acid samples with two-tailed Student’s t test.

\textsuperscript{b}P < 0.05 against arachidonic acid samples with two-tailed Student’s t test.

72°C for 1-40 minutes. Fluorescence was measured and used for quantitative purposes. At the end of the amplification period, melting curve analysis was done to confirm the specificity of the amplicon. RNA samples were normalized to cyclophilin internal standard. Relative quantification of genes was calculated by using the 2\textsuperscript{ΔΔCt} gene 0 hour / C\textsubscript{0} equation, where “C\textsubscript{t} gene T” represents the calculated threshold cycle (C\textsubscript{t}) of time point of each sample other than 0 hour or each treatment other than control.

Immunoblot analysis. Cells were lysed 15 minutes after the end of arachidonic acid incubation, using lysis buffer previously described (9–11). Membranes were probed with anti-phospho-p42/p44 MAPK (ERK; Thr\textsuperscript{202}/Tyr\textsuperscript{204}), anti-phospho-p42/p44 MAPK (ERK), anti-phospho PI3K (Tyr), anti-phospho-p38 MAPK (Thr\textsuperscript{180}/Tyr\textsuperscript{182}), anti-phospho SAPK/JNK (Thr\textsuperscript{183}/Tyr\textsuperscript{185}), anti-phospho-Akt (Ser\textsuperscript{473}), or actin antibodies. Proteins were detected by enhanced chemiluminescence (Supersignal Pico kit) and exposed on autoradiography film. Films were scanned and bands were quantified with UNSCANIT densitometry software (Silk Scientific, Orem, UT), with 25 \mu mol/L flurbiprofen blocked increased synthesis of the protein (P < 0.001).

Increased PI3K and Akt phosphorylation after incubation with arachidonic acid. To study early signal transduction in the arachidonic acid treatment, PC-3 cells were incubated with arachidonic acid for 0, 5, 10, and 30 minutes. There was a significant increase in phosphorylation of PI3K as detected by the phospho-85kDa antibody (Ty\textsuperscript{545}) and the pAkt (Ser\textsuperscript{473}) antibody. There was no detectable activation of ERK1 or ERK2, SAPK/JNK, or p38 kinases (Fig. 2A). Moreover, there was an increase in PGE\textsubscript{2} synthesis 5 minutes after addition of the arachidonic acid (Table 1).

Translocation of NF-κB increases with arachidonic acid treatment. To further analyze our observation that the NF-κB signaling pathway was being activated by arachidonic acid, we analyzed the nuclear extract of treated and untreated cells. As seen in Fig. 2B, there is over a 2-fold increase in translocation of NF-κB within 30 minutes of treatment. Each column represents mean ± SD (n = 4) for each treatment corrected to actin internal standard (\textsuperscript{+}P < 0.03 with two-tailed Student’s t test against control samples).

Quantitative RT-PCR analysis of other NF-κB–regulated genes. To understand and verify initial gene chip analysis, we verified the gene expression using quantitative RT-PCR. Figure 3A shows the quantitative RT-PCR analysis of gene induction in untreated controls and the arachidonic acid–treated PC-3 cells of known NF-κB-regulated genes previously described (12–18), including GM-CSF, IL-1β, CXL-1, TNF-α, IL-6, LTA, IL-8, PPAR\gamma, and ICAM-1. Figure 3B compares microarray analysis and quantitative RT-PCR analysis of arachidonic acid induction of the various genes in fold increase rounded up the closest integer.

The phosphorylation of PI3K induced by arachidonic acid is inhibited by NSAIDs. To further investigate the activation of PI3K, 50 \mu mol/L of indomethacin (an NSAID) was added to the cells 1 hour before addition of arachidonic acid to deplete the presence of PGE\textsubscript{2}. Protein was harvested 5 minutes after the addition of arachidonic acid. Western blotting analysis reveals that the phosphorylation of PI3K is affected by NSAIDs (Fig. 4A).

The induction of gene expression of COX-2, IL-1β, GM-CSF, and ICAM1 is inhibited by PI3K inhibitor LY294002. We examined the arachidonic acid–induced gene expression with 50 \mu mol/L of PI3K inhibitor LY294002 and found that the induction of COX-2, IL-1β, GM-CSF, and ICAM1 all required activation of PI3K (Fig. 4B).

COX-2 is the main arachidonic acid–metabolizing enzyme in PC-3 prostate cancer cells. We examined the other eicosanoid pathway enzymes in PC-3 cells, including COX-1, COX-2, 5-LO, and cytochrome P450. Only COX-2 had an abundance of expression that was up-regulated by arachidonic acid/PGE\textsubscript{2} (Table 2).

Arachidonic acid induced proliferation of PC-3 cells blocked by addition of LY294002. To assess whether the induction of gene expression by arachidonic acid led to a dose-responsive proliferation, we analyzed proliferation of PC-3 cells 24 hours after addition of arachidonic acid (5 \mu g/mL). We have previously reported that doses between 0.1 and 7.5 \mu g/mL of arachidonic acid induced proliferation as measured by CyQuant assay (5); the response was saturated at ~2.5 \mu g/mL. In the current study, we found that arachidonic acid caused significant increase in growth and a significant portion of the growth depended on PI3K activation because LY294002, a specific inhibitor of PI3K, significantly inhibited the arachidonic acid–induced proliferation of PC-3 cells (Fig. 4C).
Discussion

The influence of diet on prostate cancer may be important in the U.S. male population, which has a high rate of advanced prostate cancer. Mortality rates per 100,000 men are the highest in African-American men ages 80 to >85 (2,316) versus Caucasians (1,135). It is possible that this difference is determined by culturally related dietary habits. It has been suggested that deaths due to prostate cancers could be reduced by ~50% with a change in diet (19). For many decades, fats have been perceived simply as nutrient fuels and membrane components. There is increasing evidence showing that fatty acids stimulate cell growth (5, 6, 20–22). Recently, it has been noted that many nutrients serve as controllers of gene transcription. For instance, glucose can cause hormone secretion and polyunsaturated fatty acids have been shown to regulate fatty acid synthases. Spot 14, ApoA1, and COX-2 expression (1). COX-2 expression is increased in several cancers, including large bowel, lung, breast, bladder, and prostate (6, 7, 23–26). The ω-6 fatty acid, arachidonic acid, activates prostate cancer cell growth, COX-2 expression, and PGE2 synthesis in vivo and in vitro (5, 6, 20–22). Over the last 50 years, the dietary intake of ω-6:3 polyunsaturated fatty acids has increased from a ratio of 2:1 to 25:1 in Western cultures and this may be a factor in the activation of latent prostate tumors (27). The increase in ω-6 fatty acids is due primarily to the increased intake of the essential fatty acid oils that are derived from corn and other seed products.

We were the first to find that COX-2 was up-regulated in prostate tumors (28) and that ω-6 fatty acids induced COX-2 in prostate tumors (5, 6). Those findings were later confirmed by others both...
in vitro and in vivo (29–38). Furthermore, inhibition of COX-2 activity results in diminished angiogenesis and tumor growth (26, 29, 39) and NSAIDs are now being considered as a possible treatment for prostate cancer (40–42).

Recent evidence indicates that activation of PI3K may be key in progression of prostate cancer because constitutive activation of the PI3K pathway and its downstream effectors occurs in a high proportion of prostate cancers (43). In fact, long-term androgen ablation therapy for prostate cancer reinforces the PI3K/Akt pathway and impedes its inhibition, thus contributing to increased resistance of tumor cells to induction of apoptosis (44). Some PPAR ligands have been proposed as a new class of anti-inflammatory compounds and one 15dPGJ2 causes inhibition of the inflammatory response by inhibition of NF-κB signaling (45). The arachidonic acid product PGE2 induces PPARδ, suggesting that it is working through PGE2 receptors (46, 47). Here, we show that arachidonic acid induces NF-κB via PI3K signaling. We also found that PPARδ and PPARy are induced by presence of α-6 fatty acid, suggesting a dietary source of inflammation (Fig. 3B). Shukla et al. (48) have shown that PI3K, part of the NF-κB signaling pathway, is increased in TRAMP (transgenic adenocarcinoma of the mouse prostate) mice. Finally, Lin et al. (49) showed that feeding TRAMP mice a diet supplemented with 5% flaxseed by weight slowed progression of this prostate cancer model because flaxseed has a high level of the α-3 fatty acids, thus suggesting a role for α-6 fatty acids in promotion of carcinogenesis.

Here, we report that the α-6 fatty acids that can be converted to PGE2 act as signaling molecules, exerting their influence on synthesis within 5 minutes of arachidonic acid addition, PI3K phosphorylation within 5 minutes, early gene expression within 2 hours, and cell proliferation by 24 hours. Downstream activation of NF-κB is evidenced by the translocation of NF-κB into the nucleus within 30 minutes (see Fig. 5). Further evidence of NF-κB involvement is the arachidonic acid induction of 13 other genes that are regulated by this pathway. Further examination showed that the IκBα (the inhibitor subunit) was also significantly up-regulated 2 hours after arachidonic acid treatment, most likely due to replacement, because IκBα is degraded after translocation of the free NF-κB to the nucleus. The NF-κB pathway is important because the promoter region of COX-2 contains two NF-κB sites in addition to CRE (CREB from PKA) and an AP1 (fos/jun) site, making COX-2 a triple target for the α-6 fatty acid effects. The changes in gene expression point to a probable PI3K/Akt pathway activation by arachidonic acid, where COX-2 and 11 other NF-κB

**Table 2. Abundance of eicosanoid pathway enzymes in PC-3 cells**

<table>
<thead>
<tr>
<th>Relative abundance</th>
<th>Fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>AA</td>
</tr>
<tr>
<td>COX-2</td>
<td>14.59 ± 7.94</td>
</tr>
<tr>
<td>COX-1</td>
<td>4.82 ± 0.40</td>
</tr>
<tr>
<td>5-LO</td>
<td>16.09 ± 5.58</td>
</tr>
<tr>
<td>Cytochrome P450, subfamily II, polypeptide 2 (CYP2J2)</td>
<td>229.10 ± 93.32</td>
</tr>
</tbody>
</table>

NOTE: Arachidonic acid (5 μg/mL) was added to down-regulated PC-3 cells. At 2 hours after the addition of arachidonic acid, RNA was collected and quantitative RT-PCR was done (n = 3).

Abbreviation: NS, not significant.
regulated genes are induced by presence of ω-6 fatty acids. Treatment with the NSAIDs decreased PI3K activation. LY294002 also causes a reduction in arachidonic acid–induced proliferation as well as a reduction of many arachidonic acid–induced genes. Because the evidence points to a PGE2-mediated response, we would hypothesize that only ω-6 fatty acids, such as linoleic and arachidonic acids, which can be converted to PGE2 (not γ-linoleic acid) would activate this pathway.

Cancer progression is usually facilitated by independent growth signals that may lead to increased cell survival and evasion of apoptosis. PI3K and NF-κB are important signaling molecules that are key to prostate proliferation and oncogenesis. Proliferation of prostate cancer cells in prostatic tumors is slow, which may explain why prostate cancer is a disease of older men. However, after hormone relapse, proliferation increases and at that point the patient typically has <18 months to live. Strategies that would limit proliferation pathways, such as PI3K, may extend those precious months into years or even decades, which is a meaningful objective. Moreover, reduction of the abnormally high levels of ω-6 fatty acids in the modern diet may reduce the eicosanoid-mediated PI3K activation and slow the progression of prostate cancer. Consequently, reduction of ω-6 fatty acid intake and anti-PI3K/Akt inhibitors may be worth considering as future therapeutic approaches to battle prostate cancer.

Acknowledgments

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