Nuclear Orphan Receptor NR4A2 Modulates Fatty Acid Oxidation Pathways in Colorectal Cancer*

Received for publication, September 13, 2010, and in revised form, July 7, 2011 Published, JBC Papers in Press, July 10, 2011, DOI 10.1074/jbc.M110.184697

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Although cancer cells have traditionally been thought to rely on the glycolytic pathway to generate ATP, recent studies suggest that cancer cells can shift to the fatty acid oxidation pathway as an alternative energy source. All of the factors that induce and regulate this adaptive shift in metabolism are not known. Cyclooxygenase-2-derived prostaglandin E₂ (PGE₂) is produced at high levels in colon cancer, and multiple lines of evidence from human-, animal-, and cell line-based studies indicate that PGE₂ plays a pro-oncogenic role in colorectal cancer progression. We have shown previously that exposure of colon cancer cells to PGE₂ promotes cell survival, in part by inducing the expression of the nuclear orphan receptor NR4A2. Here, we report that PGE₂-induced NR4A2 increased fatty acid oxidation by inducing the expression of multiple proteins in the fatty acid oxidation pathway. NR4A2 was found to bind directly to Nur77-binding response elements located within the regulatory region of these genes. Nur77-binding response element binding also resulted in the recruitment of transcriptional coactivators and induction of gene expression. Collectively, our findings suggest that NR4A2 plays a key role as a transcriptional integration point between the eicosanoid and fatty acid metabolic pathways. Thus, PGE₂ is a potential regulator of the adaptive shift to energy utilization via fatty acid oxidation that has been observed in several types of cancer.

Despite their extremely inefficient use of energy, cancer cells are able to generate sufficient ATP to maintain their survival. Although it has traditionally been thought that cancer cells rely solely on the glycolytic pathway to generate ATP (1), recent studies suggest that many types of cancer cells can adapt to alternative energy utilization pathways, especially in fluorodeoxyglucose positron emission tomography-negative tumors in which glucose metabolism is suppressed (2). For instance, an adaptive shift to fatty acid oxidation and metabolism as an alternative means to generate energy has been well documented in various malignancies that may be influenced by obesity (3–5). In fact, several fatty acyl β-oxidation proteins are elevated in a variety of tumors (5, 6). Moreover, a recent report provides evidence that cancer cells can be sensitized to apoptosis by the inhibition of fatty acid oxidation (7).

The transcription factor NR4A2 is an orphan member of the nuclear receptor superfamily and is an important regulator of dopaminergic neuronal pathways. Recent evidence has linked NR4A2 to the regulation of both glucose and fatty acid metabolism (8, 9). The NR4A family includes three members: Nur77 (NGIF-B/NR4A1), Nurr1 (NOT/NR4A2), and Nor-1 (MINOR/NR4A3). NR4A nuclear receptors can act as monomers to transactivate target genes by binding to the consensus Nur77-binding response element (NBRE; 2AAAGGTCA) (10).

Multiple lines of evidence from human-, animal-, and cell culture-based studies indicate that the cyclooxygenase-2 (COX-2) pathway plays an important role in colorectal carcinogenesis (11, 12). COX-2-derived prostaglandin E₂ (PGE₂) is one of the key mediators of the proinflammatory/procarcinogenic arm of the COX-2 pathway during cancer progression (12). We have previously identified NR4A2 as a PGE₂ regulated gene that is increased following treatment of colon cancer cells with PGE₂ (13). Consistent with our observation, NR4A2 expression has been shown to be up-regulated in colon cancer cells compared with normal colonic mucosa. Functional studies have confirmed that NR4A2 promotes colon cancer cell survival by inhibiting apoptosis (13). However, the mechanism by which PGE₂-induced NR4A2 expression promotes cell survival in colon cancer has not yet been established.

Given prior studies linking NR4A2 to energy metabolism and the documented importance of fatty acid oxidation as an alternative energy utilization pathway to promote cancer cell survival, we hypothesized that PGE₂ may promote cell survival in part by promoting a shift to fatty acid oxidation via NR4A2. Our results confirm that NR4A2 leads to the induction of multiple genes in the fatty acid oxidation pathway. Furthermore, mechanistic studies demonstrate that this adaptive shift occurs via NR4A2 binding to its cognate NBRE in the regulatory regions of genes involved in the fatty acid oxidation pathway, with subsequent recruitment of transcriptional coactivators and induction of gene expression.

**EXPERIMENTAL PROCEDURES**

Reagents—PGE₂, EP1 antagonist SC-19220, and EP2 antagonist AH 6809 were obtained from Cayman Chemical (Ann Arbor, MI). EP4 antagonist ONO-AE-3208 was obtained from...
ONO Pharmaceutical CO., Ltd. (Osaka, Japan). Antibodies to NR4A2, SRC-1, and PGC1α were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). β-Actin antiserum was obtained from Sigma.

**Cell Culture**—LS-174T and HCT-116 cells were purchased from American Type Culture Collection (Manassas, VA). These cells were maintained in McCoy’s 5A medium containing 10% fetal bovine serum, 100 units/ml penicillin, and 100 μg/ml streptomycin in a 5% CO2 atmosphere.

**Transient Transfection and Luciferase Assay**—For luciferase assays, 1.3 × 10^5 LS-174T or HCT-116 cells were cultured in a 12-well plate 24 h before transfection. Transfection was carried out using Lipofectamine (Invitrogen) in serum-free medium containing 300 ng of reporter plasmid and 5 ng of *Renilla* luciferase reporter plasmid pRL-SV40 as an internal control according to the manufacturer’s protocol. This transfection mixture was added to the cells, and the plates were incubated at 37 °C for 4 h. Prostaglandins and other reagents were added after 4 h, and the plates were incubated for an additional 16 h. Firefly and *Renilla* luciferase activities were measured using a Dual-Luciferase assay kit (Promega, Madison, WI) and a luminometer. Firefly luciferase values were normalized to *Renilla* luciferase values.

**Silencing NR4A2**—LS-174T and HCT-116 cells were seeded at 1.3 × 10^5 cells/well in a 12-well plate. After 24 h, the cells were transfected with control siRNA or NR4A2 siRNA pools (Stealth Select RNAi reagents, Invitrogen) using Lipofectamine 2000 reagent (Invitrogen).

**Western Blot Analysis**—Cells were washed with PBS and lysed with radioimmunoprecipitation assay buffer (50 mmol/liter Tris-Cl (pH 7.4), 150 mmol/liter NaCl, 1 mmol/liter EDTA, 1% Triton X-100, 1% sodium deoxycholate, 0.1% SDS, and protease inhibitors (Roche Diagnostics)). Proteins were then separated on SDS-polyacrylamide gels and electrotransferred onto nitrocellulose membranes. Membranes were blocked in 5% milk in TBS with 0.1% Tween 20 and incubated with primary antibody overnight at 4 °C. The membranes were then treated with horseradish peroxidase-conjugated secondary antibody and developed using an ECL kit (Amersham Biosciences).

**DNA Binding Assay**—Oligonucleotides containing different sequences were annealed and labeled with [γ-32P]dCTP using Klenow DNA polymerase. NR4A2 protein was made from T7-containing plasmid using a TNT quick coupled transcrip-

FIGURE 1. PGE2 induction of NR4A2 is mediated by the EP4 receptor. LS-174T cells were treated with different EP receptor antagonists (Ant; 1 μM) 1 h before the addition of PGE2. NR4A2 expression was measured by Western blotting (A) and qPCR (B). C, LS-174T cells were transiently transfected with a (NBRE)_3-luciferase construct. Transfected cells were treated with different EP receptor antagonists (10 μM) 1 h before the addition of PGE2 (1 μM) for 16 h prior to measurement of luciferase activity. DMSO, dimethyl sulfoxide; IB, immunoblot.

FIGURE 2. NR4A2 increases PPRE activity. LS-174T (A) and HCT-116 (B) cells were transiently transfected with an empty vector or an NR4A2-expressing vector and then transfected with a (PPRE)_3-thymidine kinase-luciferase reporter and *Renilla* normalization constructs. After 4 h, the medium was replaced with or without PGE2. Twenty-four hours after transfection, (PPRE)_3-thymidine kinase-luciferase reporter activity was measured and then normalized to *Renilla* luciferase activity. C, treatment of LS-174T and HCT-116 cells under serum-free conditions with an NR4A2-specific siRNA suppressed (PPRE)_3-thymidine kinase-luciferase reporter activity. The scrambled sequence had no effect on (PPRE)_3-thymidine kinase-luciferase reporter activity. DMSO, dimethyl sulfoxide.
tion/translation system (Promega). Nuclear extracts were prepared from LS-174T cells treated with or without PGE2 using standard protocols. A typical binding assay contained 50 μg of nuclear proteins derived from 50 ng of plasmid in 10 mmol/liter HEPES buffer (pH 7.9) containing 50 mmol/liter KCl, 1 mmol/liter DTT, 2.5 mmol/liter MgCl\textsubscript{2}, 5 μg of poly(dI-dC), and 20% glycerol in a final volume of 20 μl. The mixture was placed on ice for 15 min. A radiolabeled oligonucleotide (500,000 cpm) and/or an unlabeled competitor PPRE oligonucleotide was added, and the solution was incubated at 20 °C for 12 min. Reactions were loaded onto a prerun (30 min) 5% polyacrylamide gel equilibrated in 0.5 Tris borate/EDTA and electrophoresed for 2 h. The gels were dried and autoradiographed. The following double-strand oligonucleotide sequence was used for labeling: wild-type peroxisome proliferator response element (PPRE) sense strand, CAAAACTAGGTCAAAGGTCA.

Oligonucleotide Pulldown Assay—Nuclear proteins from LS-174T cells treated with or without PGE2 were incubated with 1 μg of consensus PPRE sequence biotinylated at the 5′-end (5′-TGCTGCTGACCTTTCCCCTACTTT-3′) or the mutant PPRE sequence (5′-TGCTGCTGCTTTCCCCTACCTTT-3′) in binding buffer containing 12 mM HEPES (pH 7.9), 4 mM Tris-Cl (pH 7.9), 150 mM KCl, 12% glycerol, 1 mM EDTA, and 1 mM DTT. The binding reaction was allowed to continue for 30 min at room temperature. The oligonucleotide and protein complex were precipitated with high capacity streptavidin-agarose beads (Thermo Scientific) for 4 h at 4 °C. Bound fractions were washed three times with binding buffer, eluted with denaturing buffer, and then analyzed by Western blotting.

Chromatin Immunoprecipitation Assay—ChIP analysis was performed with the EZ ChIP kit (Millipore) according to the manufacturer’s protocol. Briefly, LS-174T cells were serum-starved for 48 h prior to the addition of Me\textsubscript{2}SO or PGE2 (1 μmol/liter) for 2 h, followed by cross-linking with formaldehyde. Immunoprecipitates of cross-linked complexes were prepared with the antibodies specific for NR4A2, SRC-1, and PGC1α. Normal rabbit IgG (Santa Cruz Biotechnology) was used as a negative control. After purification by phenol/chloroform extraction and ethanol precipitation, DNA was used as a template for PCR amplification using the following sets of PCR primers: acyl-CoA oxidase, 5′-CTATTCAATGCTAAGTACCC-3′ and 5′-TAGTTTATTCTCTGTACCTGC-3′; and CPT1L (carnitine palmitoyltransferase 1, liver form), 5′-CACAGCGGTCAAGAGCAAGA-3′ and 5′-TGCCACCTGGA-GCCTACAAC-3′.

Establishment of Stable Cell Lines—Phoenix packaging cells were transfected with pBMNIGFP-NR4A2 or pBMNIGFP vector and transduced into LS-174T cells using 5 μg/ml hexadimethrine bromide (Sigma). After 48 h of treatment, LS-174T cells expressing GFP were sorted by fluorescence-activated cell sorting.

Fatty Acid Oxidation Assay—[9,10-3H]Palmitic acid was used as a substrate, and palmitic acid oxidation was assessed by measuring 3H\textsubscript{2}O produced in the cell culture medium as described previously (14). Briefly, LS-174T or HCT-116 cells

FIGURE 3. PGE\textsubscript{2} induces NR4A2 interactions with PPRE sequence. A, EMSA of in vitro transcribed NR4A2 binding to the PPRE. Purified NR4A2 protein or nuclear proteins from LS-174T cells treated with or without PGE\textsubscript{2} were analyzed for interactions with 32P-labeled PPRE DNA oligonucleotides in the absence or presence of an unlabeled (cold) competitor PPRE oligonucleotide. B, oligonucleotide pulldown assay using CPT1L promoter elements revealed that treatment of LS-174T cells with PGE\textsubscript{2} induced interactions of NR4A2 and PGC1α proteins with PPREs of CPT1L. IB, immunoblot.
were seeded at 1.3 × 10^5 cells/well in a 12-well plate. After 24 h, 50 μl of [9,10-3H]palmitic acid (50 Ci/mmol, 1 μCi/μl) was added in Hanks’ balanced salt solution containing 0.5 mg/ml fat-free bovine serum albumin. After 2 h, palmitic acid oxidation was assessed by measuring 3H2O released into the assay medium. The medium was collected (0.25 ml), and the cells were washed with 0.25 ml of medium. The supernatants were pooled and extracted twice with 1.25 ml of chloroform/methanol (1:1, v/v) and 0.5 ml of 2 mol/liter KCl/HCl (1:1, v/v). The aqueous phase containing 3H2O was collected and subjected to liquid scintillation counting. For the PGE2 treatment assay, cells were serum-starved for 48 h, and PGE2 (1 μmol/liter) was added for 2 h before the addition of [9,10-3H]palmitic acid.

RESULTS

PGE2 Induction of NR4A2 Is Mediated by the EP4 Receptor—We reported previously that NR4A2 is rapidly and transiently induced by PGE2 (13). As there are four known G protein-coupled PGE2 receptors (EP1–EP4), we investigated which EP receptor is involved in the regulation of NR4A2. We used receptor-specific antagonists (EP1, SC-19220; EP2, AH 6809; and EP4, ONO-AE-3208) and then completed Western blotting (Fig. 1A), quantitative PCR (qPCR) Fig. 1B), and luciferase (Fig. 1C) assays to show that EP4 is the main receptor responsible for regulating NR4A2 expression. These results corroborated our previous finding that induction of NR4A2 expression is mediated by cAMP (13).

PGE2 Treatment Increases NR4A2 Levels and Functional Activity—We have shown previously that PGE2 can induce the activity of a heterologous reporter system driven by a promoter containing the PPRE (13). Examination of the PPRE sequence revealed a consensus NBRE within the PPRE. Thus, PGE2 may regulate PPRE activity in part by up-regulating NR4A2. This NBRE-containing reporter system was used in a downstream assay to determine the functional activity of NR4A2 and the relevance of NBRE sites located within PPREs.

To determine the role of NR4A2 in this induction, we transfected LS-174T and HCT-116 colon cancer cell lines with an empty vector or an NR4A2 expression vector. We found that overexpression of NR4A2 in both colon cancer lines significantly increased reporter gene activity. Moreover, we observed that the combination of PGE2 and NR4A2 resulted in a synergistic increase in luciferase activity (Fig. 2, A and B). Loss-of-function studies using two different cell lines targeting NR4A2 siRNA revealed that intact NR4A2 is essential for PGE2 to activate gene expression using this PPRE-driven heterologous reporter system (Fig. 2C).

NR4A2 Binds to Its Cognate NBRE Located within PPRE Sequences—To confirm that NR4A2 could bind directly to the NBRE located within the PPRE sequence, we performed an EMSA. We found that in vitro transcribed NR4A2 could bind specifically to the NBRE located within the PPRE located in the acyl-CoA oxidase gene (Fig. 3A). In the absence of any ligand,
we observed interactions of NR4A2 with the PPRE (Fig. 3A, left panel, lane 2). Unlabeled PPRE oligonucleotide competed with NR4A2 (Fig. 3A, left panel, lanes 3–6), suggesting that NR4A2 can form tight but reversible associations with PPRE sequences. Incubation with anti-NR4A2 antibody showed a loss of the shifted band (Fig. 3A, left panel, lane 7). To establish the link between PGE$_2$ and NR4A2 further, we treated LS-174T cells with/or without PGE$_2$. The nuclear proteins were used for EMSA. NR4A2 induced by PGE$_2$ showed strong binding to PPRE sequences (Fig. 3A, right panel, lane 3), which were competed away by the identical unlabeled oligonucleotide (lane 5) or NR4A2-specific antibody (lane 7).

An oligonucleotide pulldown assay was used to confirm the EMSA results. Biotinylated oligomer sequences that contained the PPRE and the flanking sequences within the intron that occurs between exons 1b and 2 of CPT1 were used to pull down transcriptional complexes. These transcriptional complexes included NR4A2 as well as the transcriptional coactivator PGC1α (Fig. 3B). The specificity of NR4A2 binding was demonstrated using a mutant oligonucleotide that resulted in loss of NR4A2 binding (Fig. 3B).

NR4A2 Recruits Transcriptional Coactivators and Directly Occupies NBRE Sites within the Regulatory Region of Fatty Acid Oxidation Genes—To determine whether PGE$_2$-induced NR4A2 is functionally active, we conducted pulldown assays to test if NR4A2 can directly bind to the transcriptional coactivators PGC1α and SRC-1. Immunoprecipitation of either PGC1α or SRC-1 from LS-174T cell nuclear extracts following PGE$_2$ treatment showed specific binding of NR4A2 to either transcriptional coactivator (Fig. 4A).

ChIP analysis indicated that NR4A2 directly occupied the consensus NBRE within the PPRE of fatty acid oxidation genes. ChIP of NR4A2 from LS-174T cells treated with PGE$_2$ or HCT-116 cells (which have high basal levels of NR4A2) demonstrated directly that NR4A2 occupied endogenous targets involved in fatty acid metabolism, such as acyl-CoA oxidase, CPT1α, FABP2, and FABP4 (Fig. 4B). Specificity of NR4A2 binding to the PPRE of the target genes was confirmed using oligonucleotides designed to the 1-kb upstream sequence of the PPRE-binding site of the target genes with NR4A2 chromatin-immunoprecipitated DNA that completely lacked any amplification product (data not shown).

PGE$_2$ Induces Overexpression of NR4A2 in Conjunction with Increased Fatty Acid Oxidation and Fatty Acid Oxidation Pathway Genes—To determine the biologic relevance of PGE$_2$-induced NR4A2 with regard to energy utilization, we measured fatty acid oxidation in LS-174T and HCT-116 cells. We found that PGE$_2$ addition in both cell lines increased fatty acid oxidation (Fig. 5B). To confirm that the increased fatty acid oxidation is mediated by NR4A2, we knocked down NR4A2 using two different siRNAs (Fig. 5A). After siRNA-mediated knockdown of NR4A2, fatty acid oxidation was greatly reduced (Fig. 5B).

Finally, gain-of-function studies with NR4A2 were conducted to determine whether NR4A2 can directly activate the expression of genes involved in fatty acid oxidation. LS-174T and HCT-116 cells were selected for stable expression of vector or NR4A2. The expression of a panel of genes involved in the fatty acid oxidation pathway was measured in vector- or NR4A2-expressing cells. Our results revealed that expression of NR4A2 led to the up-regulation of genes involved in fatty acid transport and metabolism (Fig. 6, A and B).

DISCUSSION

This study is the first to link eicosanoid signaling and fatty acid metabolism through PGE$_2$-mediated up-regulation of NR4A2 receptors in colon cancer cells. Our results suggest that COX-2-derived PGE$_2$ is a potential regulator of an adaptive shift in metabolism and show that NR4A2 increases fatty acid oxidation by inducing several enzymes in the fatty acid pathway. Functionally, we observed a decrease in palmitate oxidation after knockdown of NR4A2 expression and an increase in metabolic activity following overexpression of NR4A2. We have also shown that NR4A2 binding to NBREs located within the regulatory region of these genes results in recruitment of transcriptional coactivators.

Tumor cells are subjected to severe metabolic stress and inflammatory insult in the tumor microenvironment (15, 16). Literature suggests that cancer cells rely solely on the rudimentary and inefficient glycolytic pathway to generate energy.

**FIGURE 5.** PGE$_2$-induced NR4A2 increases fatty acid oxidation. A, LS-174T and HCT-116 cells were transiently transfected with or without NR4A2 siRNA. Forty-eight hours later, cells were treated with PGE$_2$. NR4A2 expression was measured by Western blotting (WB) LS-174T (B) and HCT-116 (C) cells with and without NR4A2 siRNA were used to examine fatty acid oxidation of isotopically labeled palmitate. This method measured the conversion of $[^{3}H]$palmitate to $[^{3}H]$2O. The oxidation of palmitic acid was assessed by measuring $[^{3}H]$2O released into the culture medium. The results are expressed as cpm of water/min. *, $p < 0.05$ versus no PGE$_2$ selected for stable expression of an empty vector or NR4A2. Elevated mRNA synthesis of metabolic genes was determined by qPCR. DMSO, dimethyl sulfoxide.
However, the most efficient stored forms of energy are fatty acids that are catabolically released by β-oxidation. Recent studies support the notion that certain tumor types also utilize the fatty acid oxidation pathway to generate energy for continued growth.

Peroxisomal proliferator-activated receptors and retinoid X receptor heterodimers bind to the PPRE of fatty acid metabolism genes upon ligand binding to initiate transcription. The PPRE is a direct repeat of AGG(A/T)CA separated by a single base pair (DR-1) (17, 18). Our analyses revealed that a partial NBRE sequence (AAAGGTCA) overlaps with the consensus PPRE sequence (AGGTCAAAGGTCA). An important hypothesis tested here was whether NR4A2 alone is effective in interacting with PPREs to activate transcription. Our results show that NR4A2 binds directly to the reporter system containing the PPRE sequence, eliciting transcriptional activation. NR4A2 can function either as an unliganded monomer that activates transcription constitutively by interacting with the consensus NBRE sequence or as a heterodimer with liganded retinoid X receptor by interacting with DRs spaced by five nucleotides (DR-5) (19, 20). Our results with the PPRE (DR-1) indicate that NR4A2 activates the PPRE independent of the retinoid X receptor. Increased levels of PGE₂ in the tumor microenvironment result in induction of NR4A2, which may support fatty acid oxidation necessary for cells deprived of ATP.

Zagani et al. (21) used an NR4A2 siRNA knockdown approach to target osteopontin promoter-luciferase reporter activity. Importantly, they reported that COX-2-selective inhibitors suppress polyp formation in ApcΔ14/+ mice through an NR4A2-based mechanism that is dependent on NBREs. Even though PPRE-binding elements appear to be present in the osteopontin promoter, their significance is not yet fully understood. Our EMSA and ChIP data clearly suggest that NR4A2 monomers effectively interact with PPREs and recruit coactivators, particularly when forming complexes with DNA.

Our findings are consistent with those demonstrating the emerging role of NR4A nuclear receptors as key regulators of metabolic function (22). Moreover, we have identified the nuclear orphan receptor NR4A2 as a key transcriptional integrator that allows cross-talk between the prostaglandin and fatty acid oxidation pathways.

Acknowledgment—We gratefully acknowledge Dr. Lutfi Abu-Elheiga (Baylor College of Medicine) for valuable suggestions about the fatty acid oxidation studies.

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