PPARα Activators Inhibit Tissue Factor Expression and Activity in Human Monocytes

Nikolaus Marx, MD; Nigel Mackman, PhD; Uwe Schönbek, PhD; Nurcan Yilmaz, MS; Vinzenz Hombach, MD; Peter Libby, MD; Jorge Plutzky, MD

Background—Tissue factor (TF), expressed on the surface of monocytes and macrophages in human atherosclerotic lesions, acts as the major procoagulant initiating thrombus formation in acute coronary syndromes. Peroxisome proliferator–activated receptor-α (PPARα), a nuclear receptor family member, regulates gene expression in response to certain fatty acids and fibrac acid derivatives. Given that some of these substances reduce TF activity in patients, we tested whether PPARα activators limit TF responses in human monocytic cells.

Methods and Results—Pretreatment of freshly isolated human monocytes or monocyte-derived macrophages with PPARα activators WY14643 and eicosatetraynoic acid (ETYA) led to reduced lipopolysaccharide (LPS)-induced TF activity in a concentration-dependent manner (maximal reduction to 43±8% with 250 μmol/L WY14643 [P<0.05, n=5] and to 42±12% with 30 μmol/L ETYA [P>0.05, n=3]). Two different PPARγ activators (15-deoxyΔ12,14-prostaglandin J2 and BRL49653) lacked similar effects. WY14643 also decreased tumor necrosis factor-α protein expression in supernatants of LPS-stimulated human monocytes. Pretreatment of monocytes with WY14643 inhibited LPS-induced TF protein and mRNA expression without altering mRNA half-life. Transient transfection assays of a human TF promoter construct in THP-1 cells revealed WY14643 inhibition of LPS-induced promoter activity, which appeared to be mediated through the inhibition of nuclear factor-κB but not to be due to reduced nuclear factor-κB binding.

Conclusions—PPARα activators can reduce TF expression and activity in human monocytes/macrophages and thus potentially reduce the thrombogenicity of atherosclerotic lesions. These data provide new insight into how PPARα-activating fibrac acid derivatives and certain fatty acids might influence atherothrombosis in patients with vascular disease. (Circulation. 2001;103:213-219.)

Key Words: leukocytes ■ thrombosis ■ genes ■ coagulation

Tissue factor (TF) is an integral membrane protein, which binds to factor VII/VIIa and initiates the coagulation cascade.1,2 Expressed on the surface of lipid-laden monocytes, macrophages, and foam cells in human atherosclerotic lesions, TF acts as the major procoagulant for thrombus formation in acute coronary syndromes.3,4 The expression of TF in monocytes can be rapidly induced by lipopolysaccharide (LPS) and phorbol 12-myristate 13-acetate as well as by an inflammatory mediator found in atherosclerotic lesions, CD40L.5,6 TF activity of circulating monocytes appears controlled locally by its intrinsic inhibitor, TF pathway inhibitor (TFPI).7 LPS-induced monocyte TF expression is controlled locally by its intrinsic inhibitor, TF pathway inhibitor (TFPI).7 LPS-induced monocyte TF expression is regulated through a 56-bp promoter region (~227 through ~172 bp) containing 2 activator protein-1 (AP-1) binding sites and a nuclear factor (NF)-κB binding site, elements that bind c-fos/c-jun and c-Rel/p65 heterodimers, respectively.8,9 LPS-induced TF expression in cells of the monocyte lineage requires functional interaction between these transcription factors.10

Although the clinical course of acute coronary events may be influenced by reduced monocyte/macrophage TF expression,11 the mechanisms inhibiting TF expression in these cells remain largely unexplored. Animal studies suggest that a diet rich in polyunsaturated fatty acids (PUFAs) reduces TF expression in mononuclear cells, whereas dietary intake of PUFAs in humans reduces TF activity in unstimulated and LPS-stimulated monocytes.12 Thus, PUFAs seem to inhibit monocyte TF expression in vivo, although through unknown mechanisms. Interestingly, some of the PUFAs used in those studies (docosahexaenoic acid [DHA] and eicosatetraynoic acid [ETYA]) are ligands for the peroxisome proliferator–activated receptor-α (PPARα).14 PPARα, as well as the other members of the PPAR family, PPARγ and PPARδ, are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamity.15 PPARα can be activated by PUFAs as well as lipid-lowering fibrac acid derivatives, such as fenofibrate or WY14643.16 Although prior work focused...
on PPARα as a regulator of genes involved in lipid metabolism and fatty acid oxidation, recent studies have highlighted its anti-inflammatory role in vascular cells. The effect of PPARα activation on monocyte TF expression is unknown.

Given the clinical evidence that fibric acid drugs and PUFA-rich diets may reduce thrombotic complications of atherosclerosis, the present study tested whether PPARα activation limits inducible TF activity and expression in human cells of the monocytic lineage.

**Methods**

**Cell Culture**

Human monocytes isolated from freshly drawn blood of healthy volunteers by sequential Ficoll-Hypaque (Sigma) and Percoll (Sigma) gradient centrifugation were >85% pure. Monocyte-derived macrophages were obtained by culturing isolated human monocytes for 6 days (RPMI media, Gibco; 5% human serum, Sigma; and 1% penicillin-streptomycin, Gibco). The monocyte-like cell line THP-1, obtained from the American Tissue Culture Collection, was cultured as described before.

**Reverse Transcriptase–Polymerase Chain Reaction**

Total RNA from freshly isolated monocytes, monocyte-derived macrophages, or THP-1 cells was isolated by the guanidinium thiocyanate–phenol–chloroform method (RNAzol, Tel-Test). Reverse transcriptase (RT)–polymerase chain reaction (PCR) for PPARα and GAPDH was performed as described before.

**TF Activity Assay**

For TF activity assays, monocytes, monocyte-derived macrophages, or THP-1 cells were pretreated with PPARα activators (PPARα activators: ETYA, Sigma, and WY14643, Biomol; PPARγ activators: 15-deoxy-D12,14-prostaglandin J2 [15d-PGJ2], Calbiochem, and BRL49653, SmithKline Beecham) for 30 minutes at the concentrations indicated and then LPS-stimulated (100 μg/L for monocytes, 10 mg/L for THP-1 cells) for 5 hours. TF activity was determined by using a standard chromogenic assay (American Diagnostica).

**TNF-α ELISA**

Monocytes or THP-1 cells (1×10⁶ cells/mL) were pretreated with the PPARα activator WY14643 for 30 minutes before LPS stimulation at the concentrations indicated. Cells were cultured for 24 hours, and a tumor necrosis factor (TNF)-α ELISA (R&D Systems) was performed on cell-free supernatants by using a recombinant TNF-α standard curve.

**Western Blot Analysis**

For Western blot analysis of TF and TFPI expression, human monocytes or monocyte-derived macrophages were pretreated with WY14643 (30 minutes) at the concentrations indicated and stimulated with LPS (5 hours). Standard Western blot analysis on total cell lysates was performed by using mouse anti-human TF and mouse anti-human TFPI antibodies (monoclonal antibodies, American Diagnostica). Restaining with α-tubulin antibodies ensured equal loading of intact protein.

**RNA Extraction and Northern Blot Analysis**

For Northern blot experiments, cells were pretreated with the PPARα or PPARγ activators for 30 minutes and then LPS-stimulated (100 μg/L, 2 hours). Five micrograms of total RNA was used in standard Northern blot analysis with the use of TF, TNF-α, or GAPDH cDNA probes.

TF mRNA half-life was determined by stimulating monocytes with LPS for 2 hours before blocking transcription with actinomycin D (5 μg/L). Cells then received WY14643 for the times indicated, and mRNA levels were compared with untreated cells.

**Electrophoretic Mobility Shift Assay**

Nuclear extracts of THP-1 cells were prepared by using standard procedures. THP-1 cells were stimulated for 2 hours with LPS (10 μg/mL) with or without WY14643 (10 or 100 μmol/L) pretreatment before nuclear extract preparation. Oligonucleotides for the TF-specific NF-κB site (5′-GGCCGGAGTTCTCCTACC-3′) or the prototypic site from the murine Igκ gene were annealed with a complementary primer and radiolabeled with the use of [α-³²P]dCTP (ICN) as described. Protein-DNA complexes were separated from free DNA probe by electrophoresis (6% nondenaturing acrylamide gels/0.5× Tris-borate-EDTA), and autoradiography was performed.

**Assessment of Total Protein Synthesis**

To determine the effects of WY14643 on total protein synthesis in human monocytes, cells were treated with LPS in the absence or presence of WY14643 in media containing [³⁵S]methionine (0.2 g/L). Cells then received WY14643 for the times indicated, and protein synthesis was assessed by using an ELISA (R&D Systems).

**Effects of WY14643 on Human Monocytes**

<table>
<thead>
<tr>
<th>Cell viability, %</th>
<th>LPS (10 μg/L)</th>
<th>LPS (250 μmol/L/WY14643)</th>
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<td>&gt;95</td>
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Protein synthesis:

| Cell associated, ×10⁶ cpm/10⁵ cells | 40.4±8.4 | 61.5±21.2 |
| Secreted, ×10⁶ cpm/10⁵ cells        | 39.2±2.5 | 37.0±2.6 |

Values are mean±SEM.

*As [³⁵S]methionine incorporation after trichloroacetic acid precipitation.

**Transient Transfection Assays**

To investigate the effect of PPARα activators on TF or TNF-α promoter activity, we transiently transfected THP-1 cells with TF promoter constructs containing the luciferase reporter (pTF(−2106)-LUC and pTFN-α-LUC) as previously described. To determine the effect of PPARα on NF-κB activation, p(κB)LUC, a luciferase reporter construct containing 4 copies of the TF-κB site cloned upstream from the minimal simian virus 40 promoter was transfected into THP-1 cells. Transfected cells were cultured for 48 hours before stimulation with LPS (10 mg/L) for 5 hours. Cells were harvested, and luciferase activity was measured as described before.

![Figure 1. Cells of monocyte lineage express PPARα. RT-PCR reaction of PPARα and GAPDH RNA in freshly isolated human monocytes (Mo), monocyte-derived macrophages (MΦ), and monocytic THP-1 cells (THP) reveals appropriately sized cDNA fragment. Also shown are DNA ladder (MW) and negative control consisting of RT-PCR reactions lacking reverse transcriptase (Co).](image-url)
Ci/mL) (Table). After 5 hours, cells were harvested, and total protein synthesis in both lysates and supernatants was measured by counting radioactivity after cold trichloroacetic acid precipitation.  

**Statistical Analysis**

Results of the experimental studies are reported as mean ± SEM or mean ± SD. Differences were analyzed by 1-way ANOVA followed by the Fisher least significant difference test. A value of P < 0.05 was regarded as significant.

**Results**

**Cells of Monocyte Lineage Express PPARα**

To establish the expression of PPARα in cells of the monocyte lineage used in our experiments, RT-PCR was performed. Freshly isolated human monocytes, monocyte-derived macrophages, and monocyte-like THP-1 cells all contained PPARα mRNA as detected by a 276-bp RT-PCR product (Figure 1).

**PPARα Activators Inhibit LPS-Induced TF Activity and TNF-α Expression in Human Monocytes**

To determine the effect of PPARα activation on LPS-induced TF activity in freshly isolated human monocytes, purified cells were pretreated for 30 minutes with the PPARα activators WY14643 or ETYA at the concentrations indicated and then stimulated for 5 hours with LPS (100 µg/L) before TF activity assays were performed. As expected, monocyte TF activity markedly increased in response to LPS stimulation. Pretreatment of cells with the PPARα activators WY14643 (Figure 2A) and ETYA (Figure 2B) inhibited LPS-induced TF activity in a concentration-dependent manner, with a maximal reduction at 250 µmol/L WY14643 or 30 µmol/L ETYA to 43 ± 8% (P < 0.05, n = 5) or 42 ± 12% (P < 0.05, n = 3), respectively. Two different PPARγ activators, the naturally occurring ligand 15d-PGJ2 and the antidiabetic agent BRL49653 (rosiglitazone), had no significant effect (P = NS, n = 3; Figure 2B). PPARα activators alone also had no effect on TF activity (data not shown). Cell viability in all conditions was >95%, as determined by trypan blue exclusion, suggesting that enhanced cell death is not responsible for these observations. In addition, WY14643 did not affect total protein synthesis in LPS-treated human monocytes, thus making toxic effects of PPARα activators an unlikely explanation for our findings (Table).

To investigate whether PPARα alters other LPS-induced genes in human monocytes, we measured the effect of WY14643 on monocyte TNF-α protein secretion after LPS stimulation. Pretreatment of monocytes for 30 minutes with the PPARα activator WY14643 significantly reduced LPS-
induced TNF-α protein content in the supernatant (Figure 2C), with a maximal inhibition at 250 μmol/L WY14643 (7,696 ± 449 pg/mL in LPS-treated cells versus 4,490 ± 197 pg/mL in LPS- and WY14643-treated cells, P < 0.05; n = 3). As previously reported, 2 PPARγ activators had no effect on LPS-induced TNF-α secretion.

**PPARα Activation Inhibits TF Protein Expression in Human Monocytes**

To test whether the effect of PPARα on TF activity corresponded to changes in TF protein levels, human monocytes were pretreated and stimulated as indicated, and Western blot analysis was performed on total cell lysates. Stimulation of monocytes with LPS markedly increased TF protein expression, whereas 30-minute pretreatment with the PPARα activator WY14643 reduced cellular TF protein content in a concentration-dependent manner (Figure 3, top). In contrast, WY14643 did not reduce the expression of TFPI, the intrinsic inhibitor of TF activity (Figure 3, middle).

**PPARα, but Not PPARγ, Activators Reduce LPS-Induced TF mRNA Levels in Human Monocytes**

Northern blot analysis was used for the evaluation of a potential effect of PPARα ligands at the mRNA level. Increased TF mRNA levels after a 2-hour stimulation of human monocytes with LPS (100 μg/L) could be inhibited in a concentration-dependent manner by 30-minute pretreatment with the PPARα activator WY14643 (Figure 4A). In contrast, pretreatment of monocytes with 2 different PPARγ activators, 15d-PGJ2 (10 μmol/L) and BRL49653 (10 μmol/L), had no such effect (Figure 4B). In addition, WY14643 also decreased LPS-induced TNF-α mRNA expression (Figure 4C). Stimulation experiments in the presence of actinomycin D revealed that WY14643 did not significantly reduce TF mRNA half-life compared with the control condition (Figure 4D), indicating that PPARα activators affect TF transcription but not mRNA stability.

**WY14643 Reduces LPS-Induced TF Activity as Well as TF Protein and mRNA Expression in Monocyte-Derived Macrophages**

To determine whether PPARα activators had similar effects on TF activity in a more macrophage-like cell type, human monocyte–derived macrophages were used for stimulation experiments. As expected, these cells had higher baseline TF activity than did monocytes. Pretreatment of monocyte-derived macrophages with WY14643 reduced LPS-induced TF activity in a concentration-dependent manner with a maximal reduction at 100 μmol/L to 40.3 ± 7.6% (P < 0.05 compared with LPS-stimulated cells, Figure 5A). In addition, WY14643 also decreased LPS-induced TF protein (Figure 5B) and mRNA expression (Figure 5C) in these cells.

**WY14643 Inhibits LPS-Induced TF Activity and TNF-α Protein Expression in Monocyte-Like THP-1 Cells**

Because prior studies have successfully used monocytic THP-1 cells for investigating the regulation of TF expression, 9,19 we used this cell line to study responsiveness to PPARα agonism in anticipation of promoter analysis. Treatment of THP-1 cells with the PPARα activator WY14643 decreased LPS-induced (10 mg/L) TF activity as well as TNF-α protein expression in a concentration-dependent fashion (Figure 6). Maximal reduction of TF activity to 9.3 ± 0.4% was achieved in cells treated with 100 μmol/L WY14643 compared with LPS-stimulated cells. WY14643 decreased TNF-α protein expression from 1,396 ± 58 pg/mL in LPS-treated cells to 144 ± 8 pg/mL. These data indicate that the more readily transflectable monocyte-like THP-1 cells can be used to examine the effects of PPARα activators on TF and TNF-α.

**PPARα Activation Inhibits LPS-Induced TF and TNF-α Promoter Activity**

THP-1 cells were transiently transfected with TF (pTF-LUC) or TNF-α (pTNF-LUC) promoter-reporter constructs to de-

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**Figure 4.** PPARα activator WY14643 inhibits TF and TNF-α mRNA expression. A, Northern blot analysis for TF in human monocytes pretreated for 30 minutes with WY at concentrations shown before stimulation with LPS for 2 hours (100 μg/L) (top). B, Northern blot analysis for TF of human monocytes pretreated with PPARα (250 μmol/L WY) or PPARγ activators (10 μmol/L PGJ2 and 10 μmol/L BRL) for 30 minutes and then stimulated with LPS for 2 hours. C, TNF-α mRNA expression in human monocytes stimulated as indicated above. GAPDH mRNA expression confirmed equal loading of intact RNA in all experiments (A, B, and C, bottom). Three independent experiments yielded similar results. D, Graph showing that PPARα activation does not affect TF mRNA half-life. Actinomycin D and WY were added to human monocytes 2 hours after LPS stimulation (0 hours), and cells were harvested at times indicated. Amount of mRNA at each time point was compared with mRNA levels after 2 hours of LPS stimulation at time 0 (ordinate labeled as relative mRNA level). Co indicates control. Results are shown as mean ± SEM of 3 independent experiments.
termine the effects of PPARα activation on LPS-induced promoter activity. Stimulation of transfected cells with LPS (10 μg/mL) increased TF promoter activity 7.8 ± 1.8-fold, whereas 30-minute pretreatment with WY14643 reduced this increase to 3.3 ± 1.1-fold (Figure 7A). Similar results were obtained when cells were transfected with the TNF-α promoter construct (Figure 7B). WY14643 alone had no effect on TF or TNF-α promoter activity.

PPARα Activator WY14643 Reduces NF-κB Activation but Does Not Inhibit DNA Binding of NF-κB Transcription Factors p65/c-Rel

To assess the effect of PPARα activation on LPS-induced NF-κB activation, transient transfection experiments of reporter construct p(κB)LUC were performed. Stimulation of transfected cells with LPS (10 μg/mL) induced a 50 ± 5-fold increase in luciferase activity, which was reduced by 30% to 35 ± 7-fold by WY14643 (Figure 8A). To investigate whether PPARα activation inhibits binding of NF-κB transcription factors to the TF promoter, we performed gel-shift analysis (electrophoretic mobility shift assay) with the use of oligonucleotides corresponding to the TF NF-κB site. PPARα activation did not inhibit LPS-induced nuclear translocation and DNA binding of the NF-κB proteins to the TF promoter (Figure 8B, left) nor did PPARα activation alter binding of the NF-κB proteins p50/p65, known to regulate monocyte TNF-α gene expression (Figure 8B, right).

Discussion

The present study demonstrates inhibition of LPS-induced TF and TNF-α expression by PPARα activators in human monocytes and monocyte-derived macrophages. This effect is mediated through an inhibition of gene transcription, likely through changes in NF-κB activation.

Human monocytes and macrophages express PPARα as well as PPARγ,21–24 although the amount of PPARγ compared with PPARα may be lower in these cells.24 In monocytes, PPARγ increases during differentiation, and its stimulation can inhibit the expression of genes implicated in atherosclerosis.21–24 However, we did not observe any effects of PPARγ activators on LPS-induced TF or TNF-α expression. These findings concur with previous reports showing that PPARγ activators inhibit phorbol 12-myristate 13-acetate but not LPS-induced TNF-α expression.21 The lack of an effect by PPARγ activators on TF and TNF-α expression might result from lower levels of PPARγ in these cells or may indicate different PPAR subtype specificity. The PPARα

Figure 5. PPARα activator WY14643 reduces TF activity and expression in human monocyte–derived macrophages. A, TF activity assays for monocyte-derived macrophages were performed after 30-minute pretreatment with PPARα activator WY14643, followed by 5-hour stimulation with LPS (100 μg/mL). Results are expressed as percentage of LPS-stimulated cells (% control). Bars represent mean±SEM (n=3). *P<0.05 compared with control. B, Western blot analysis for TF protein expression in monocyte-derived macrophages (top). Equal loading of intact protein was confirmed by restaining membrane with α-tubulin antibodies (bottom). C, Northern blot analysis for TF in human monocyte–derived macrophages pretreated for 30 minutes with WY14643 at concentrations shown before stimulation with LPS (100 μg/mL) for 2 hours (top). GAPDH mRNA expression confirmed equal loading of intact RNA (bottom). Three independent experiments yielded similar results.

Figure 6. PPARα activator WY14643 reduces TF activity and TNF-α protein expression in THP-1 monocytoid cells. THP-1 cells were pretreated with WY14643 for 30 minutes at concentrations indicated before stimulation with LPS at 10 mg/L. After 5 hours, cellular TF activity and TNF-α protein content in cell-free supernatants were measured. Results are expressed in comparison with LPS-treated cells (% control) for TF activity. Bars represent mean±SEM (n=2).
coactivators might inhibit NF-κB expression levels in macrophages as previously described by Chi-netti et al.24 Lower concentrations of WY14643 yielded similar effects on TNF-α reduction LPS-induced expression and promoter activity of PPARα. This finding might reflect higher PPARα expression levels in macrophages as previously described by Chinetti et al.24

The reduction of TF activity, protein, and mRNA expression by PPARα activators likely results from inhibition of gene transcription given its inhibition of LPS-induced TF promoter activity as well as the lack of an effect of WY14643 on TF mRNA half-life. The reduction of NF-κB activity by PPARα parallels our observation that PPARα activators also decrease LPS-induced expression and promoter activity of TNF-α, another NF-κB–regulated gene. Gel-shift experiments suggest that PPARα does not inhibit LPS-induced nuclear translocation or DNA binding of NF-κB transcription factors to the TF promoter. Several models might account for the effect of PPARα on functional NF-κB activity independent of DNA-protein complex assembly. The NF-κB proteins c-Rel/p65 and PPARα have been shown to interact with several transcriptional coactivators, such as cAMP response element–binding protein or p30025,26; competition for such coactivators might inhibit NF-κB signaling through a “sequestering” effect. Alternatively, a direct protein-protein interaction between PPARα and c-Rel/p65 or between PPARα and another coactivator might allow binding of NF-κB proteins to the promoter but prevent functional activation of NF-κB, as suggested previously.27

Other mechanisms in addition to the ~30% inhibition of NF-κB activity suggested by the p(κB)αLUC construct experiments might account for the effects of PPARα on TF and TNF-α. Because AP-1 is implicated in TF expression, its inhibition by PPARα could also be involved.27 Alternatively, the effects of PPARα might engage a transcriptional repressor complex with corepressors such as N-CoR, as previously suggested in the context of the effects of retinoic acid receptor on TF expression.28

Our findings that PPARα activators reduce monocyte TF expression but not the expression of the intrinsic inhibitor of TF activity, TFPI, suggest a PPARα-mediated shift toward limiting a critical procoagulant in atherosclerosis, an effect with possible important in vivo relevance. Diets enriched in PPARα-activating PUFAs can limit the occurrence and course of acute coronary events,29 and clinical studies with fibric acid derivatives demonstrate reduced cardiovascular events in patients with coronary heart disease.30 The regulation by PPARα of monocyte and macrophage TF expression may contribute to these reported benefits, a particular intriguing possibility given recent data from the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), which demonstrated that fibric acid derivatives

![Figure 7](image)

**Figure 7.** PPARα activation inhibits TF and TNF-α promoter activity. THP-1 cells were transiently transfected with promoter reporter constructs pTF-LUC (A) and pTNF-LUC (B) and stimulated with LPS (10 mg/L) for 5 hours with or without PPARα activator WY (100 μmol/L) pretreatment. Results of luciferase activity are expressed as fold induction compared with unstimulated cells. Bars represent mean±SD (n=3).

![Figure 8](image)

**Figure 8.** PPARα activator WY14643 (WY) reduces nuclear NF-κB activity but does not inhibit DNA binding of NF-κB transcription factors. A, THP-1 cells transiently transfected with reporter construct p(κB)LUC containing 4 copies of TF NF-κB site. Transfected cells were stimulated as described above, and luciferase activity was determined. Results are expressed as fold induction compared with unstimulated cells. Bars represent mean±SD (n=3). B, Gel-shift analysis of THP-1 cells pretreated with WY14643 (WY, 100 μmol/L) and then stimulated with LPS (10 mg/L) for 2 hours. Electrophoretic mobility shift assays were performed by using NF-κB site of TF promoter (left) and prototypic NF-κB site of the murine Igκ gene (right).
decrease cardiac events in coronary heart disease patients with low LDL levels despite only a modest HDL increase. The observations reported in the present study may offer one molecular mechanism contributing to how PUFA-rich diets and fibrates might reduce acute coronary events.

Acknowledgments

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