Inhibition of Macrophage Scavenger Receptor Activity by Tumor Necrosis Factor-α Is Transcriptionally and Post-translationally Regulated*

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Regulation of expression of the scavenger receptor is thought to play a critical role in the accumulation of lipid by macrophages in atherosclerosis. Tumor necrosis factor-α (TNF-α) has been shown to suppress macrophage scavenger receptor function (van Lenten, B. J., and Fogelman, A. M. (1992) J. Immunol. 148, 112-116). However, the mechanism by which it does so is unknown. We evaluated the mechanism by which TNF-α inhibited macrophage scavenger receptor surface expression and binding of acetylated low density lipoprotein (aLDL). Binding of aLDL to phorbol 12-myristate 13-acetate (PMA)-differentiated THP-1 macrophages was suppressed by TNF-α in a dose-dependent manner. Inhibition of aLDL binding was paralleled by a reduction of macrophage scavenger receptor protein as detected by the Western blot. TNF-α partially decreased macrophage scavenger receptor mRNA steady state levels in PMA-differentiated THP-1 macrophages, a result that was confirmed by reverse transcription-polymerase chain reaction. PMA increased the luciferase activity driven by the macrophage scavenger receptor promoter in the transfected cells, whereas TNF-α partially reduced luciferase activity. However, macrophage scavenger receptor mRNA half-life was dramatically reduced in cells treated with TNF-α relative to untreated cells. Reduction in macrophage scavenger receptor message in response to TNF-α was dependent on new protein synthesis because it was blocked by cycloheximide. These results indicate that TNF-α regulates macrophage scavenger receptor expression in PMA-differentiated THP-1 macrophages by transcriptional and post-transcriptional mechanisms but principally by destabilization of macrophage scavenger receptor mRNA.

Macrophage scavenger receptors bind oxidized low density lipoprotein (LDL)1 and acetylated LDL (aLDL), as well as other polyanionic ligands, and were initially identified by their ability to bind charge modified LDL but not native LDL (2). Unlike the LDL receptor, expression of the macrophage scavenger receptor is not down-regulated by high levels of intracellular cholesterol. Because of the potential role of this receptor in mediating cholesteryl ester accumulation by macrophages during atherosclerosis, the regulation of expression of these receptors is of considerable important and interest. Circulating monocytes express little or no macrophage scavenger receptor, but receptor mRNA and surface expression are dramatically increased because monocytes differentiate into macrophages in tissue culture. Treatment of monocytes or THP-1 cells (a human monocytic cell line) with phorbol-12 myristate 13-acetate (PMA) also promotes differentiation and induces macrophage scavenger receptor expression (3). Similarly, macrophage colony-stimulating factor (M-CSF) augments macrophage scavenger receptor expression (4).

Inhibition of macrophage scavenger receptor expression and activity has been reported in response to interferon-γ (IFN-γ) (5, 6), transforming growth factor-β1 (TGF-β1) (7), all-trans retinoic acid, dexamethasone (8), platelet secretory products (9–11), and lymphocyte culture supernatants (12). Bacterial lipopolysaccharide (LPS), a potent activator of mononuclear phagocytes, can inhibit scavenger receptor activity in human macrophages (13). Most of the inhibitory activity of LPS on the macrophage scavenger receptor could be blocked with an antibody to TNF-α (1), suggesting that TNF-α, which is synthesized in response to LPS, mediates the LPS effect. However, the molecular mechanism(s) by which TNF-α inhibits macrophage scavenger receptor activity have not been elucidated. In this study, we demonstrate that TNF-α inhibits macrophage scavenger receptor binding activity, surface protein expression, and mRNA levels, with subsequent down-regulation of macrophage scavenger receptor-mediated ACAT activity and cholesterol esterification in PMA-differentiated THP-1 macrophages. Although macrophage scavenger receptor transcriptional activity was modestly reduced in response to TNF-α, in the presence of actinomycin D, macrophage scavenger receptor mRNA half-life was significantly reduced, implying that TNF-α inhibits macrophage scavenger receptor expression principally by post-transcriptional decreases in macrophage scavenger receptor mRNA stability.

EXPERIMENTAL PROCEDURES

Materials—Disposable tissue culture materials were purchased from Corning Glass Works (Corning, NY). Medium RPMI 1640 medium, l-glutamine, penicillin, streptomycin, and fetal calf serum were purchased from Life Technologies, Inc. A 100-base pair DNA ladder was purchased from Life Technologies, Inc., MD. 123I was obtained from ICN transferase; PMA, phorbol 12-myristate 13-acetate; IFN-γ, interferon-γ; TGF-β1, transforming growth factor-β1.
mild reducing conditions (boiling for 5 min in the presence of 2-mercaptoethanol). Protein was loaded in each lane, separated by SDS-polyacrylamide gel electrophoresis, and transferred to an Immobilon membrane. The presence of macrophage scavenger receptor protein was examined by incubation the membrane with hSRI-2 anti-macrophage scavenger receptor peptide antibody (a rabbit polyclonal anti-human macrophage scavenger receptor antibody), which recognizes the collagen-like domain that is shared between types SR-AI and SR-AII macrophage scavenger receptor proteins (14). Blots were stained with a donkey anti-rabbit IgG-horseradish peroxidase conjugate. Protein visualization was performed with Renaissance®, DuPont Western blot Chemiluminescence Reagent, (DuPont NEN). Manufacturer-provided protocols were followed.

Reverse Transcription Reaction and Polymerase Chain Reaction Amplification for Human Macrophage Scavenger Receptor—The reagents in PCR kit for RT-PCR amplification were purchased from Perkin-Elmer. The oligonucleotides for the primers (26, 35) and the procedures for RT-PCR amplification were as described (35) with some modification. After electrophoresis on 2% agarose gels, the PCR products were stained with ethidium bromide and visualized on a UV transilluminator. Quantitative analysis of PCR products was performed by using Southern blot, and the membranes were hybridized with the 32P-labeled internal probe as described (35) and quantified using a Phosphorimager®. Differences in intensity of PCR product bands were calculated by 10-fold serial dilution of cDNA samples to ensure comparability and that the plateau of amplification had not been reached as described (36).

Protein Assay—Protein amounts were determined by the method of Lowry et al. (37) or the Bio-Rad protein assay.

Statistical Analysis—Statistical differences between the experimental groups were examined by analysis of variance, and statistical significance was determined at a p level of <0.05. All data are expressed as the means ± S.E.

RESULTS

PM and M-CSF equivalently increased the specific binding (4°C) of 125I-aLDL to THP-1 monocytes compared with untreated THP-1 monocytes (Fig. 1A). Co-treatment of PM- or M-CSF-differentiated THP-1 cells with TNF-α reduced specific binding of 125I-aLDL to baseline (control) levels (Fig. 1A) in a dose-dependent manner (Fig. 2). The effect of TNF-α on 125I-aLDL binding resulted from a decrease in the number of binding sites (Bmax) without significant change in receptor affinity (Kd). Scatchard analysis (Fig. 1B) demonstrated that PM or M-CSF increased Bmax by 6- or 7-fold, respectively, as compared with undifferentiated THP-1 monocytes (undifferentiated THP-1 monocytes (control) = 1.66 × 105 sites/cell; PM-differentiated THP-1 monocytes = 9.71 × 105 sites/cell; M-CSF-differentiated THP-1 monocytes = 10.6 × 105 sites/cell). The Bmax of undifferentiated THP-1 monocytes (control), PM-differentiated THP-1 monocytes treated with TNF-α (PMA + TNF-α), as well as THP-1 monocytes treated with TNF-α and M-CSF-differentiated THP-1 monocytes treated with TNF-α (data not shown) were equivalent (each approximately 1.23–1.66 × 105 sites/cell). Kd values were not significantly altered by any treatment (Fig. 1B).

Western analysis (Fig. 3) revealed that little or no macrophage scavenger receptor protein was expressed in THP-1 monocytes. PMA-differentiated THP-1 monocytes expressed scavenger receptor protein, but TNF-α suppressed the expression of macrophage scavenger receptor protein when THP-1 cells co-incubated with PMA, TNF-α did not cause any signs of general cellular toxicity. Cells treated with PMA/TNF-α remained adherent and morphologically similar to PMA-treated cells (THP-1 monocytes). Furthermore, there was no decrease in protein content or cell number or any increase in the uptake of trypan blue (data not shown).

To dissect the molecular mechanisms by which TNF-α suppressed macrophage scavenger receptor protein expression, we initially examined the influence of TNF-α on macrophage scavenger receptor mRNA levels. Northern blot analyses of PMA-differentiated THP-1 monocytes revealed a time-dependent

Biochemicals (Costa Mesa, CA). EGTA, leupeptin, aprotinin and DNA molecular weight marker V were obtained from Boehringer Mannheim. Sodium orthovanadate was obtained from Aldrich. HEPES, NaCl, glyc- erol, Triton X-100, MgCl2, phenylmethylsulfonyl fluoride, PMA, actino- mycin D, cycloheximide, and bovine serum albumin (Fraction V) were purchased from Sigma. Immobilon membrane was purchased from Mi- lipore. Western blot Chemiluminescence Reagent, (DuPont NEN), was a nonradioactive light-emitting system, was purchased from DuPont NEN.

Growth Factors and Antibodies—Human recombinant TNF-α and human recombinant M-CSF were obtained from R & D Systems (Min- neapolis, MN). Rabbit polyclonal anti-human macrophage scavenger receptor (hSRI-2 anti-macrophage scavenger receptor antibody), which recognizes the collagen-like domain that is shared between types SR-AI and SR-AII macrophage scavenger receptor proteins (14). Blots were stained with a donkey anti-rabbit IgG-horseradish peroxidase conjugate. Protein visualization was performed with Renaissance®, DuPont Western blot Chemiluminescence Reagent, (DuPont NEN). Manufacturer-provided protocols were followed.

Cell Culture—The human monocyte macrophage THP-1 cell line (15, 16) was purchased from ATCC (Rockville, MD) and followed the ATCC protocol to grow. Cells were incubated in 5% CO2 in air at 37°C. In this paper, human suspension monotypic THP-1 cell was referred to as THP-1 monocyte; for PMA-differentiated adhesion macrophage-like THP-1 cell is referred to as PMA-differentiated THP-1 macrophage or THP-1 macrophage as described (7, 16–18). THP-1 monocytes (control) were subpassaged the day before transfection and replaced with fresh medium containing egg phosphatidylcholine (31).

RNA Isolation and Northern Analysis—Total RNA was isolated from the guianium isothiocyanate method (23). Northern blot analyses were performed as described (24, 25). The CDNA for the human macrophage scavenger receptor was a gift from Dr. T. Kodama (University of Tokyo, Tokyo, Japan) (26). The cDNA for human 28 S ribosomal RNA was a gift from Dr. Iris L. Gonzalez (Hahnemann University, Philadelphia, PA). RNA from Northern blots was quantified using a PhosphorImager®. Differences in intensity of PCR product bands were calculated by 10-fold serial dilution of cDNA samples to ensure comparability and that the plateau of amplification had not been reached as described (36).

Protein Assay—Protein amounts were determined by the method of Lowry et al. (37) or the Bio-Rad protein assay.

Statistical Analysis—Statistical differences between the experimental groups were examined by analysis of variance, and statistical significance was determined at a p level of <0.05. All data are expressed as the means ± S.E.
increase in macrophage scavenger receptor mRNA steady state levels in response to PMA (Fig. 4, A and B). Expression peaked at 48 h. Macrophage scavenger receptor mRNA was not detected in undifferentiated THP-1 monocytes (not treated with PMA), and TNF-\( \alpha \) had no effect on this baseline expression. TNF-\( \alpha \) decreased macrophage scavenger receptor mRNA expression by 80% (at 20 h) and 70% (at 48 h), respectively, in PMA-differentiated cells relative to PMA-treated cells, and TNF-\( \alpha \) had no effect on this baseline expression. RT-PCR demonstrated that TNF-\( \alpha \) decreased both human macrophage scavenger receptor types SR-AI and SR-AII mRNA in PMA-treated THP-1 macrophages (Fig. 4, A and B). Dose response experiments showed that maximal inhibition of macrophage scavenger receptor mRNA levels (similar to macrophage scavenger receptor surface expression as determined by aLDL binding) by TNF-\( \alpha \) occurred at 200 units/ml (data not shown).

To examine if decreased macrophage scavenger receptor mRNA expression in response to TNF-\( \alpha \) in PMA-differentiated THP-1 macrophages resulted from decreased transcription of the macrophage scavenger receptor gene, assays for luciferase activity driven by macrophage scavenger receptor gene promoter were performed. THP-1 cells were transiently transfected by the DEAE-dextran sulfate method with plasmid MSR-Luc luciferase construct consisting of 5' upstream sequences of the macrophage scavenger receptor promoter region. Luciferase activity was measured in untreated cells, cells treated with PMA, and cells treated with PMA + TNF-\( \alpha \) (200 units/ml). PMA induced luciferase activity driven by the macrophage scavenger receptor gene promoter by 3.5-fold. TNF-\( \alpha \) reduced luciferase activity by 20% after 12 h (Fig. 5).

To determine if TNF-\( \alpha \) reduced the level of macrophage scavenger receptor mRNA by increasing its rate of degradation, we measured the half-life of macrophage scavenger receptor mRNA in the presence of the transcription inhibitor actinomycin D (5 \( \mu \)g/ml). TNF-\( \alpha \) shortened the half-life of macrophage scavenger receptor mRNA from 40 ± 3 to 10 ± 2 h (Figs. 6, A, B, and C). Therefore, the reduction in macrophage scavenger receptor mRNA by TNF-\( \alpha \) appears to be mediated primarily by a post-transcriptional mechanism, namely, accelerating the degradation of macrophage scavenger receptor mRNA. Moreover, incubation of cells with the protein synthesis inhibitor cycloheximide (10 \( \mu \)g/ml) prevented the decrease of macrophage scavenger receptor mRNA at both 3 and 6 h in TNF-\( \alpha \)-treated samples (Fig. 7). These findings suggest that the effect(s) of TNF-\( \alpha \) on macrophage scavenger receptor mRNA destabilization requires new protein synthesis.

Lastly, we characterized the role of TNF-\( \alpha \) in macrophage scavenger receptor-mediated CE metabolism by evaluating pa-
FIG. 4. TNF-α decreases MSR mRNA synthesis in PMA-differentiated THP-1 macrophages at steady state level. A, total RNA was isolated from THP-1 cells grown in serum-free medium (Control, THP-1 monocytes, samples 1 and 5), medium containing PMA (150 nM) (PMA, THP-1 macrophages, samples 2 and 6), medium containing PMA (150 nM) + TNF-α (200 units/ml) (PMA + TNF-α, samples 3 and 7), or medium containing TNF-α (200 units/ml) (TNF-α, samples 4 and 8) for 20 and 48 h, respectively. Northern blots were hybridized with 32P-labeled cDNAs of MSR or 28 S. The respective autoradiograms with MSR and 28 S bands are labeled and indicated with arrows. B, histograms represent quantification by PhosphorImager® of MSR mRNA normalized by comparison with 28 S ribosomal RNA. All data are expressed as a percentage of sample 2, i.e. PMA-differentiated THP-1 macrophages. Similar results were obtained in three separate experiments.

FIG. 5. TNF-α down-regulates MSR gene transcriptional activity in PMA-differentiated THP-1 macrophages. THP-1 cells were transfected by the DEAE-dextran sulfate method with plasmid MSR-Luc luciferase construct consisting of 5’ upstream sequences of the promoter region from MSR gene of THP-1 macrophages (e.g. plasmids HACL DL Xba-A1-luc promoter or HACL DL Xba-A1-luc Enhancer) or control plasmid and co-transfected with β-galactosidase. After 24 h post-transfection, cells were treated with PMA (150 nM) or PMA (150 nM) + TNF-α (200 units/ml). The luciferase activities of transfected cells were measured at the indicated time. The data are expressed as the means of quadruplicate samples ± S.E. (p < 0.05) and are representative of three separate experiments.

DISCUSSION

Expression of the macrophage scavenger receptor (acetylated LDL receptor) occurs as monocytes differentiate into macrophages in tissue culture over a period of several days, a process that mimics what is thought to occur as blood monocytes enter tissue to become tissue macrophages. These differentiation events can be mimicked by treating monocytes or some (but not all) monocyctic cell lines, such as THP-1 cells, with PMA. PMA activates protein kinase C (8, 38) in THP-1 cells concomitantly with the differentiation of this cell type into macrophage-like cells (7, 17, 18).

Fogelman and his colleagues had previously shown that LPS inhibited scavenger receptor activity in human macrophages (13) and that this inhibitory effect could be blocked with an antiby to TNF-α (1). We utilized PMA-differentiated THP-1 macrophages to evaluate the molecular mechanisms by which TNF-α inhibited macrophage scavenger receptor expression. The inhibitory effect of TNF-α on macrophage scavenger receptor expression and activity is comparable with previously demonstrated inhibitory effects of IFN-γ and TGF-β1 on the macrophage scavenger receptor. TNF-α inhibited macrophage scavenger receptor activity (aLDL binding, Fig. 1), protein synthesis (Fig. 3), and mRNA steady state levels (Fig. 4). TNF-α caused a 6-fold decrease in macrophage scavenger receptor number without affecting receptor affinity in PMA-differentiated THP-1 macrophages. IFN-γ inhibited macrophage scavenger receptor activity in human (5) or mouse monocyte-derived macrophages (6). IFN-γ inhibited binding, internalization, and degradation of aLDL and reduced macro...
Inhibition of macrophage scavenger receptor expression in THP-1 monocytes was performed. We found that TNF-α destabilizes the expression of both macrophage scavenger receptor isoforms (SR-AI and SR-AII) during the differentiation of THP-1 monocytes to THP-1 macrophages (Fig. 4C). To further determine the effect of TNF-α on the differential expression of the macrophage scavenger receptor gene subtypes, RT-PCR amplification for human macrophage scavenger receptor types SR-AI and SR-AII, on human macrophages (including PMA-differentiated THP-1 macrophages) are encoded by a single gene that gives rise to an alternatively spliced primary transcript (41–43). To further determine the effect of TNF-α on the differential expression of the macrophage scavenger receptor gene subtypes, RT-PCR amplification for human macrophage scavenger receptor types SR-AI and SR-AII, on human macrophages (including PMA-differentiated THP-1 macrophages) are encoded by a single gene that gives rise to an alternatively spliced primary transcript (41–43).

Glass and his colleagues have studied transcriptional regulation of the macrophage scavenger receptor gene in PMA-differentiated THP-1 macrophages (8, 28, 44). They have identified transcription factor binding sites for AP-1, SP-1, and Ets in the promoter of macrophage scavenger receptor gene from THP-1 macrophages (8). Furthermore, the mechanisms for development and cell-specific expression of macrophage scavenger receptor gene have been investigated. Complicated growth- and differentiation-related regulatory pathways of macrophage scavenger receptor gene transcription in THP-1 macrophages have been proposed (28, 44). Specifically, positive transcriptional control of the macrophage scavenger receptor mRNA steady state levels in comparison with untreated cells. This resulted in a reduction of cholesterol and CE content. Inhibition of binding resulted from decreased numbers of aLDL binding sites without a significant change in receptor affinity. Similarly, TGF-β1 inhibited macrophage scavenger receptor activity and mRNA in PMA-differentiated THP-1 macrophages (7) and caused a decrease in binding of aLDL, degradation of aLDL, and ACAT activity relative to PMA-differentiated THP-1 cells. TGF-β1 caused a 2-fold decrease in macrophage scavenger receptor number as well as a decrease in receptor affinity.

Inhibition of macrophage scavenger receptor expression in response to cytokines is cell-specific. TNF-α and IFN-γ increased scavenger receptor activity and mRNA in rabbit vascular smooth muscle cells (39). TGF-β, in combination with other cytokines, increased scavenger receptor activity in rabbit smooth muscle cells (40). The mechanism for the divergent effects of these cytokines on these two cell types (macrophages and smooth muscle cells) is unknown. However, it may reflect the fact that basal level of scavenger receptor expression in these two cell types is markedly different. Macrophages constitutively express macrophage scavenger receptor, whereas smooth muscle cells express little or no scavenger receptor mRNA or protein unless induced by cytokines, growth factors, or PMA (39, 40).

2 H.-Y. Hsu, A. C. Nicholson, and D. P. Hajjar, unpublished data.
TNF-α reduces macrophage scavenger receptor mRNA half-life.

**Fig. 8.** A, effect of TNF-α on ACAT activity in PMA-differentiated THP-1 macrophages. PMA-differentiated THP-1 macrophages were co-incubated with TNF-α (200 units/ml for 12 and 24 h) and homogenized after washing with ice-cold phosphate-buffered saline. Homogenates were assayed for ACAT activity as described under “Experimental Procedures.” All of the data derived from the group of THP-1 macrophages treated with TNF-α (asterisks) are significantly (p < 0.05) different from the group of THP-1 macrophages. The data represent the means of quadruplicate wells ± S.E. This figure is representative of three such experiments. B, esterification of cholesterol is decreased in PMA-treated macrophages (asterisks) are significantly (p < 0.05) different from the group of THP-1 macrophages. The data represent the means of quadruplicate wells ± S.E. This figure is representative of three such experiments.

Macrophage scavenger receptor mRNA is dependent on the combinatorial interactions of multiple positive factors (including Spi-1/PU.1, which binds to the region I, and a ternary complex of c-jun, c-fos, and an ets2-like protein, which binds to the region IV) and negative factors (undefined inhibitory elements, which bind to the regions II, III, and VI) (44). Moreover, the ternary complex binding to the region IV is a target for transcriptional activation following stimulation of THP-1 monocyes by PMA.

Decreased expression of macrophage scavenger receptor mRNA in response to TNF-α resulted, in part, from decreased transcriptional activity of macrophage scavenger receptor gene. Specifically, PMA increased macrophage scavenger receptor mRNA in THP-1 monocytes via the transcriptional activation of the macrophage scavenger receptor gene as shown (Fig. 5) and as described (44). TNF-α reduced macrophage scavenger receptor mRNA transcription by 20% (Fig. 5). TNF-α has shown to decrease the transcriptional rate of many genes (45–47). However, other genes are induced in response to TNF-α mediated by the induction of transcription factors such as NFkB, AP-1, IRF-1, and NF-GMa (48). Whether the effect of TNF-α on transcriptional down-regulation of macrophage scavenger receptor mRNA alters the combinatorial interactions of positive and negative factors as described (44) remains to be further investigated.

Our results demonstrate that in the presence of actinomycin D (an inhibitor of transcription), TNF-α inhibited macrophage scavenger receptor mRNA principally by reducing macrophage scavenger receptor mRNA half-life (Fig. 6). Although both IFN-γ (5, 6) and TGF-β1 (7) inhibited macrophage scavenger receptor mRNA steady state levels, it was undetermined if these cytokines reduced macrophage scavenger receptor transcription or if the reduction in mRNA steady state levels was due to increased mRNA degradation. The TNF-α reduction in macrophage scavenger receptor mRNA half-life was inhibited by cycloheximide, implying that new protein synthesis was necessary and suggesting that TNF-α induced expression of protein(s) that accelerated macrophage scavenger receptor mRNA degradation (Fig. 7). A reduction of endothelial cell nitric oxide synthase mRNA half-life has also been demonstrated in response to TNF-α (49–51) and was dependent on protein synthesis (49).

To assess the effects of TNF-α on cholesterol trafficking in THP-1 macrophages, the role of TNF-α in macrophage scavenger receptor-mediated CE metabolism was characterized by evaluating parameters in the CE cycle. TNF-α decreased ACAT activity (Fig. 8A) and esterification of free cholesterol (Fig. 8B) by 65% as compared with untreated cells and paralleled the decrease in aLDL binding. Decreased ACAT activity most likely resulted from decreased substrate (e.g. cholesterol) availability to the enzyme. However, we cannot rule out the possibility that decreased ACAT activity in response to TNF-α may occur through phosphorylation of ACAT by protein kinase (52). CE hydrolytic enzymes such as acid CE hydrolase and neutral CE hydrolase activities were unaffected by TNF-α treatment.

These findings may have physiologic significance in the pathogenesis of atherosclerosis. Scavenger receptors are expressed by macrophages in atherosclerotic lesions and are believed to mediate the binding and uptake of modified LDL including oxidized LDL. Cytokines produced by cells comprising the atheroma (macrophages, endothelial cells, smooth muscle cells, and lymphocytes) modulate macrophage scavenger receptor expression in vitro and are thought to participate in modulating expression in vivo. The expression of TNF-α is increased in atherosclerotic tissue (53, 54) in comparison with normal vascular tissue. TNF-α within the atherosclerotic lesion could have a modulatory or inhibitory effect on macrophage scavenger receptor-mediated accumulation of oxidized lipoprotein by macrophages. We have previously demonstrated that TNF-α can up-regulate expression of the LDL receptor by HepG2 cells (55) by increasing LDL receptor gene transcription. This study and our previous work (55) demonstrate how cytokines can modulate transcriptional and post-transcriptional regulation of lipoprotein receptors. These regulatory effects may potentially alter lipoprotein metabolism in vascular and hepatic tissues and alter pathophysiologic processes.

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