Activation of CAAT Enhancer-binding Protein δ (C/EBPδ) by Interleukin-1 Negatively Influences Apolipoprotein C-III Expression*

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Systematic injury, or infections, trigger a complex series of regulatory mechanisms that eventually lead to dramatic alterations in the serum levels of several proteins that are predominantly synthesized in the liver (1, 2). These characteristic changes involving proteins that have protective or regulatory roles in the inflammatory response define the hepatic acute phase reaction, an important host defense mechanism to maintain physiological homeostasis, prior to the onset of the inflammatory reaction (3–5). A number of cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor, which are released from activated monocytes and macrophages, transmit their signals to hepatocytes through binding to specific cell surface receptors. These interactions trigger a multistep process eventually leading to the activation of distinct combinations of transcription factors that recognize well defined response elements in the promoters of acute phase genes (6). Members of the C/EBP, STAT, and NFκB transcription factor family, or combinations of them, have been implicated as the main mediators of the cytokine-induced activation of several hepatic genes including C-reactive protein (7), haptoglobin (10, 11), α2-macroglobulin (12, 13), serum amyloid A (14–18), α1-acid glycoprotein (19), and the third component of complement (C3) (20, 21).

Previous studies on the IL-1-dependent regulation of several hepatic genes have shown that the main mediators of the response belong to different gene families, including members of the NFκB (22) and C/EBP (23–26) family. NFκB has been found to be involved in the IL-1-mediated regulation of complement factor B (27), angiotensinogen (28), and serum amyloid A (14) genes. C/EBP proteins have been demonstrated to play an important role in the IL-1-dependent activation of the IL-6 gene (24), the complement 3 gene (20), and serum amyloid A gene (18). Of particular interest is the recent finding that NFκB can physically interact with C/EBP proteins (29, 30). The functional consequence of this association can be either synergistic activation (14, 16, 30, 31) or inhibition of NFκB-mediated transactivation by C/EBP proteins (28).

The recent finding of a potential NFκB binding site in the proximal region of the apoC-III promoter (32) raised the possibility that the expression of this gene may be modulated during the IL-1 signaling pathway. ApoC-III is a major component of chylomicrons and very low density lipoprotein particles and a minor component of HDL. In vitro, ApoC-III inhibits the hydrolysis of triglycerides by lipoprotein lipase (33), and it causes the inhibition of apoE-mediated clearance of lipoproteins from the serum (34), suggesting that it plays a critical role in the regulation of plasma triglyceride levels through its effect on the catabolism of lipoproteins (35–37). Therefore changes in apoC-III expression levels in response to extracellular signals may have important physiological consequences.

In this paper we demonstrate that IL-1 treatment of HepG2 cells causes an inhibition of apoC-III expression. We present evidence that C/EBPδ is the main mediator of the IL-1-dependent down-regulation of apoC-III transcription. We propose a mechanism that involves disruption of the synergistic interactions between enhancer binding factors and HNF-4, as a result of indirect interaction of C/EBPδ with the I element of the apoC-III enhancer.
Fig. 1. Treatment of HepG2 cells by IL-1 inhibits apoC-III expression. Total RNAs from HepG2 cells treated with 100 ng/ml IL-1 for 0–48 h were prepared and analyzed by Northern blot hybridization using the apoC-III cDNA (top panel) or the 18S rRNA (bottom panel) as a probe. After densitometric quantification, the values obtained by the apoC-III cDNA probe were divided by those obtained by the 18S rRNA probe and expressed as a percentage of the normalized values of untreated cells (bar graph).

MATERIALS AND METHODS

Plasmids—The different apoC-III promoter constructs apoC-III-890-CAT, apoC-686-CAT, apoC-99-CAT, apoC-IIID-CAT, and apoC-IIIDCAT were used in this study. [CII J-F] ML-44-CAT, and apoCIII-G380 have been described before (38–41). CIIID, and III-I oligonucleotides into the SalI site of AdML-CAT, and plasmids containing three concatamerized oligonucleotides were selected. The expression vectors pRSV-C/EBPb (25), pRSV-C/EBPb (26), and pRSV-C/EBPb (9) were generously provided by Drs. S. McKnight (Tularic Inc.), R. Cortese (IRBM, Rome, Italy), and G. Ciliberto (IRBM), respectively. RecMV p50 and RecMV p65 (42) were kind gifts from Dr. L. Schmitz (Genzentrum, Munich, Germany).

Northern Blot Analysis—Total RNA from untreated and IL-1-treated HepG2 cells were prepared by the hot phenol method (43) and separated on formaldehyde/containing 1% agarose gels (43). After capillary transfer onto GeneScreen membranes, the blot was used for hybridization with the cDNA probe encompassing the apoC-III coding region. Hybridization and washings were performed as described previously (44). Specific hybridization signals were visualized by autoradiography and quantitated by densitometry.

In Vitro DNA Binding Assays—Nuclear extracts from HepG2 and COS-1 cells were prepared by a modification of the Dignam method (45). Protein concentrations were determined according to Bradford (46). Double-stranded oligonucleotides were labeled by filling in the overhanging ends with Sequenase (U. S. Biochemical Corp.) in the presence of [α-32P]dATP and [α-32P]dCTP. DNA binding reactions were performed in 15-μl volumes containing 20 mM Hepes, pH 7.9, 50 mM KCI, 2 mM MgCl2, 4 mM spermidine, 0.02 mM zinc acetate, 0.1 mg/ml bovine serum albumin, 10% glycerol, 0.5 mM dihydrotestosterone, 2 μg of poly(dI-dC), and 5–10 μg of nuclear extract. When indicated 100-fold molar excess of cold competitor oligonucleotide was also included. In supershift experiments the nuclear extracts were preincubated with 1 μl (diluted at 1:6 ratio) C/EBPb, C/EBPb, Sp1 (Santa Cruz), or C/EBPb and p50 (kindly provided by Sheng-Chung Lee (National University, Taiwan, Republic of China) and A. Israel (Pasteur Institute, Paris, France), respectively) antibodies prior to the binding reaction. Protein-bound and free probes were separated by electrophoresis in 6% native polyacrylamide gels and visualized by autoradiography.

The following oligonucleotides were used in this study: CIIID, 5′-CTCAGTCCTCTAGGGATTTCCACCTCCTCCCAGGCTACCTCCTCATTGTCGCTCACG (40); CIII-I, 5′-GAGACCCAGCTCCTCCTCCCAAGGGGTTATGATCGTGGGTCGAC (40, 41); IM-1, 5′-GAGACCCAATGATCCTGGAGATTCTGACGATCGGTCCAG (41); IM-2, 5′-GAGACCCAATCCTCCTCCACCTCATTAGTTATCGTGGGTCGAC (41); AbD, 5′-TTGGTATAGTTTGTATATGGGGTGAGGA-3′ (47); α2-macroglobulin, 5′-TCGAATCTCTGGAGAATTCTTGGC-3′ (13); Ig-domain, 5′-ACAGAGGGGACTTTCCGAGAATATCTCAGGGG (48); CIII-I, 5′-TCGATCGTATGACTGGGCGGGGCGGAAC (47); and Sp1, 5′-TCGATCGTATGACTGGGCGGGGCGGAAC (47).

For Western blot analysis 50 μg of nuclear extracts or immunoprecipitated proteins were separated on 12% polyacrylamide/SDS gel, electrophoresed to nitrocellulose membrane, and probed with C/EBPb antibody at 1/200 dilution or 0.5 μg/ml horseradish peroxidase-conjugated anti-phosphotyrosine (PY20, ICN) as described previously (49).

Cell Culture and Transfections—HepG2 cells were grown and transfected with the indicated amount of plasmid constructs together with 3 μg of pcMV-bgal plasmid using the calcium phosphate coprecipitation method (49, 50). In some experiments the cells were treated with 100 ng/ml human recombinant IL-1 (R & D Systems) in serum-free medium 12 h after transfection and grown for additional 24 h before harvest. Chloramphenicol acetyltransferase activities using constant amounts of protein were determined as described previously (49, 50). β-Galactosidase activities were measured according to Edlund et al. (51), and the values were used to normalize variations in the transfection efficiency.

RESULTS

Down-regulation of ApoC-III Expression by Interleukin-1—Total RNAs from HepG2 cells treated with 100 ng/ml IL-1 for various time intervals were prepared, and Northern blot hybridizations were carried out using the human apoC-III cDNA as a probe. As shown in Fig. 1, IL-1 induced a dramatic decrease of apoC-III mRNA. The inhibition was evident as early as 4 h after exposure to IL-1 and continued during the subsequent 48 h to the level of 20% of the control, indicating that apoC-III expression is negatively regulated during IL-1 signal transduction pathway.

Negative Regulation of the ApoC-III Promoter Activity by IL-1 and C/EBPb—The effect of IL-1 on the activity of the apoC-III promoter was assessed in transient transfection experiments using the C-III-890-CAT promoter construct. This construct contains all the regulatory elements required for expression of apoC-III in liver and intestinal transcription of the apoC-III gene (40, 41). IL-1 treatment of HepG2 cells inhibited apoC-III promoter activity to approximately 39% of the control (Fig. 2), suggesting that, at least in part, the specific decrease of apoC-III mRNA levels in response to this cytokine can be ascribed to suppression of apoC-III transcription. To identify the putative mediator of the IL-1-induced repression, we have performed cotrans-
fection experiments using expression vectors for C/EBP and NFκB family members, which have been implicated as the main mediators of IL-1-induced transcription of several genes (6). C/EBPa and p65 expression vectors had a small (1.5- and 1.3-fold) stimulatory effect, while C/EBPb and p50 expression vectors did not change apoC-III promoter activity (Fig. 2). On the other hand, overexpression of C/EBPδ decreased apoC-III promoter activity to about 36% of the control (Fig. 2). To identify the putative IL-1 response elements in the apoC-III promoter, we have analyzed the C/EBPδ-dependent transactivation of different deletion mutants. As shown in Fig. 3A, deletion mutants lacking the entire or part of the apoC-III enhancer (CIII-214-CAT, CIII-686-CAT) were activated 6- and 4-fold by C/EBPδ. These data raised the possibility of two potential response elements that function in an opposite manner: one is located in the proximal promoter region (−2214 to −124 nucleotides) and the other in the distal part of the apoC-III enhancer (−890 to −686 nucleotides). As shown in Fig. 3B, the deletion mutant lacking site D (CIIIΔD-CAT) was repressed more efficiently by C/EBPδ or IL-1 treatment. On the other hand, mutation of the −278 to −274-nt part of the footprint region I (CIII-IM2-CAT) abolished both IL-1-mediated repression and C/EBPδ-mediated transrepression, but no significant change was observed with CIII-IM1-CAT that contains a mutated Sp1 binding site (Fig. 3B) or constructs containing other enhancer mutations (data not shown). IL-1 treatment further enhanced C/EBPδ-induced repression of the wild type, CIIIΔD and CIII-IM1 mutants by a factor of about 2 (Fig. 3B), suggesting the importance of an IL-1-dependent modification of C/EBPδ.

These data suggest that activated C/EBPδ acts as a negative regulator when it interacts with site I of the upstream apoC-III enhancer, while its potential interaction with proximal element D partially relieves repression. Transfection experiments using chimeric promoter constructs containing three copies of site D, or site I, or the entire apoC-III enhancer in front of the minimal AdML promoter further supported this hypothesis. The 3×D ML-44-CAT reporter gene activity was induced 8-fold by treatment of the cells with IL-1 and 155-fold by cotransfection with C/EBPδ (Fig. 4). In contrast, the apoC-III enhancer-driven activity was inhibited by both IL-1 treatment or overexpression of C/EBPδ to about 45% of the control. Interestingly, the activity of 3×CIII-I ML44 CAT was increased by C/EBPδ cotransfection and IL-1 treatment 31- and 1.9-fold, respectively, showing that CIII-I acts as a negative response element only in the context of the intact enhancer. Therefore, the underlying mechanism must be due to the inhibition of a higher order enhancer complex formed between factors binding to CIII-I and adjacent sites, rather than direct repression resulting from the displacement of another factor binding to CIII-I element.

Taken together, these results suggest that C/EBPδ is the main mediator of IL-1-dependent inhibition of apoC-III transcription. Although depending on the regulatory region it acts on, C/EBPδ can modulate the apoC-III promoter in both a positive and negative direction; the negative effect brought about by its interaction with the enhancer element I dominates
 Activation of C/EBPδ

were performed in the presence of antibodies raised against C/EBPα-related factors (28, 47). The other competitor (Igκ light chain) was synthesized from the Igκ light chain promoter and can bind proteins that belong to the NFκB family, but not C/EBP-related proteins (48). The formation of the IL-1-induced complex (CHID3) as well as the two other complexes (CHID1 and CHID2) was not inhibited by 100-fold molar excess of IgκB oligonucleotide (Fig. 5B). In addition, antibodies raised against the p50 subunit of NFκB did not affect the electrophoretic mobility profile of CHID-binding proteins (data not shown), indicating that members of the NFκB family do not bind to site D of the apoC-III promoter in IL-1-induced or uninduced HepG2 cells. The APRF/STAT3 binding site oligonucleotide (α2-macroglobulin) (12, 13) also failed to prevent the formation of D binding complexes (Fig. 5B). On the other hand, complete competition of all three DNA binding activities was observed with the AlbD oligonucleotide (Fig. 5B), suggesting that CHID1, CHID2, and CHID3 may represent homo- and heterodimers of C/EBP-related factors. Antibodies specific to individual C/EBP proteins were used in supershift assays to determine which members of this family were involved in complex formation. The C/EBPα-specific antibody supershifted CHID1 and some of the CHID2 complex present in both untreated and IL-1 treated HepG2 extracts, but did not affect CHID3 binding activity (Fig. 5C). Similarly, an antibody to C/EBPβ supershifted only a small amount of CHID1 protein in both extracts, but not CHID2 or CHID3 (Fig. 5C). The formation of the IL-1-inducible complex (CHID3) was neutralized only by the antibody raised against C/EBPδ (Fig. 5C), which did not affect CHID1 and CHID2. Therefore, we conclude that in untreated HepG2 cells C/EBPα and C/EBPβ are the main binding activities interacting with the apoC-IIID site, while IL-1 treatment induces the binding of an additional factor which was identified as C/EBPδ.

No changes in the steady state protein levels of C/EBPδ were

over the positive effect resulting from its binding to the proximal elements D.

In Vitro Analysis of the Transcription Factors Interacting with the IL-1 Response Elements of the ApoC-III Promoter—To determine if in hepatic cells the binding of C/EBP and NFκB factors to site D are induced, mobility shift assays were carried out with extracts prepared from IL-1-treated HepG2 cells. Two major DNA binding activities were detected in untreated cell extracts (CHID1 and CHID2), while a novel faster moving complex (CHID3) was also observed when extracts from IL-1-stimulated cells were analyzed (Fig. 5A). A similar pattern was observed with the AlbD probe (data not shown). We used specific competitors and antibodies recognizing NFκB and C/EBP family proteins to reveal the identity of the different binding activities. The competitor oligonucleotide AlbD (derived from the −115 to −90 nt region of the rat albumin promoter) is a high affinity binding site for C/EBP and does not bind NFκB-related factors (28, 47). The other competitor (IgκB) synthesized from the Igκ light chain promoter is able to bind proteins that belong to the NFκB family, but not C/EBP-related proteins (48). The formation of the IL-1-induced complex (CHID3) as well as the two other complexes (CHID1 and CHID2) was not inhibited by 100-fold molar excess of IgκB oligonucleotide (Fig. 5B). In addition, antibodies raised against the p50 subunit of NFκB did not affect the electrophoretic mobility profile of CHID-binding proteins (data not shown), indicating that members of the NFκB family do not bind to site D of the apoC-III promoter in IL-1-induced or uninduced HepG2 cells. The APRF/STAT3 binding site oligonucleotide (α2-macroglobulin) (12, 13) also failed to prevent the formation of D binding complexes (Fig. 5B). On the other hand, complete competition of all three DNA binding activities was observed with the AlbD oligonucleotide (Fig. 5B), suggesting that CHID1, CHID2, and CHID3 may represent homo- and heterodimers of C/EBP-related factors. Antibodies specific to individual C/EBP proteins were used in supershift assays to determine which members of this family were involved in complex formation. The C/EBPα-specific antibody supershifted CHID1 and some of the CHID2 complex present in both untreated and IL-1 treated HepG2 extracts, but did not affect CHID3 binding activity (Fig. 5C). Similarly, an antibody to C/EBPβ supershifted only a small amount of CHID1 protein in both extracts, but not CHID2 or CHID3 (Fig. 5C). The formation of the IL-1-inducible complex (CHID3) was neutralized only by the antibody raised against C/EBPδ (Fig. 5C), which did not affect CHID1 and CHID2. Therefore, we conclude that in untreated HepG2 cells C/EBPα and C/EBPβ are the main binding activities interacting with the apoC-IIID site, while IL-1 treatment induces the binding of an additional factor which was identified as C/EBPδ.

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observed between uninduced and IL-1-induced HepG2 cells (Fig. 6A). In addition, we could not detect the existence or induction of a truncated C/EBPδ isoform, suggesting that post-translational modification may play a role in C/EBPδ activation. Previous studies using the specific tyrosine phosphatase inhibitor sodium orthovanadate have suggested that C/EBPδ may be tyrosine-phosphorylated in BNL CL2 hepatic cells under acute phase conditions (18). To test whether such modification is induced by IL-1, C/EBPδ was immunoprecipitated from untreated and IL-1-treated HepG2 cells and Western blots of the immunoprecipitates were probed with a monoclonal antibody against phosphotyrosine. A 29-kDa tyrosine-phosphorylated band was observed in the extracts from IL-1-treated cells, but not in the extracts from untreated cells (Fig. 6B). When the nuclear extracts were pretreated with protein phosphatase, binding of C/EBPδ to CIIID probe (CIIID3) was eliminated, indicating that in IL-1-induced cells phosphorylation of C/EBPδ is important for DNA binding activity (Fig. 6C). Over-expression of C/EBPδ without IL-1 treatment still had a repression effect on apoC-III promoter (Figs. 2 and 3), raising the possibility of an IL-1-independent activation pathway. It is more likely, however, that this effect is rather due to the presence of small amounts of active cytokines in the serum, which is sufficient to induce modification in part of the overexpressed proteins during the first 12-h period after transfection.

Previous work in our laboratory has shown that the upstream element I is mainly recognized by Sp1 and related factors and to a lesser extent by two other so far unidentified activities named CIII-I3 and CIII-I5 (41). Binding of C/EBP factors to the upstream element I was assayed by electrophoretic mobility shift experiments. We did not observe any differences in the pattern of DNA-protein complexes produced by untreated or IL-1 treated HepG2 cell extracts (Fig. 7A). In addition, no competition was observed when excess concentrations of the high affinity C/EBP binding oligonucleotides (AlbD and CIIID) were included in the reaction mixture, and antibodies raised against C/EBPα, β, and δ failed to supershift or neutralize the binding of the different activities on CIII-I (Fig. 7, B and C). Furthermore, we did not observe any specific DNA-protein interaction in experiments using extracts prepared from C/EBPα, β, and δ transfected COS-1 cells except a complex formed by an endogenous activity presumably related to Sp1 (data not shown). These results suggest that C/EBPα, β, and δ cannot directly bind to the CIII-I element. Taking into account the response of this element to IL-1 and C/EBPδ in transfection experiments, we assume that indirect protein-protein interaction between C/EBPδ and CIII-I binding factors may occur in vivo that may not be stable enough to be detected in vitro by electrophoretic mobility shift assays.

**DISCUSSION**

The molecular mechanisms responsible for the rapid but reversible induction of several positive acute phase genes have been well studied. In all documented cases increased expression of these genes in response to a variety of humoral factors
is mainly due to transcriptional activation. On the other hand, there are proteins whose plasma levels decrease during the hepatic acute phase reaction, e.g. albumin and apolipoprotein A-I (52). Their expression is inhibited via a posttranscriptional mechanism affecting the stability and turnover of the respective mRNAs (52). A precedent example of another class of negative acute phase genes is transthyretin, whose expression is decreased during 12-O-tetradecanoylphorbol-13-acetate-induced acute phase response (53). Down-regulation of transthyretin expression was shown to be due to decreased expression of HNF-3α, an essential activator of this gene (53).

The results presented in this paper establish a novel mechanism that may be involved in the negative regulation of acute phase genes, in which the activation of a positive transcription factor is implicated. We show that apolipoprotein C-III is a target for IL-1-induced response. Its mRNA levels and promoter activity are decreased in IL-1-treated HepG2 cells, suggesting that this cytokine negatively regulates apoC-III expression at the translational level. Because IL-1 is a potent inducer of NFκB in a variety of cell types (14, 16, 27, 28), and the presence of a putative NFκB regulatory element on the apoC-III promoter, members of this family were thought to play a role in the modulation of the apoC-III gene expression (32). In line with this latter report we found that the proximal element D is a potential binding site for at least two subunits (p50 and p65) of the NFκB transcription factor (data not shown). However, DNA binding and transactivation experiments clearly showed that these factors do not participate in the IL-1-dependent down-regulation of the apoC-III gene. We cannot rule out however that under other physiological conditions induced by different combinations of signal transducers, NFκB may modulate apoC-III transcription.

Several lines of evidence suggest that C/EBPδ is the main mediator of the IL-1 response of the apoC-III gene. First, under our experimental conditions IL-1 treatment induced a new DNA binding activity, which was identified as C/EBPδ. In agreement with previous studies (18), we found that activation of C/EBPδ in HepG2 cells involves posttranslational mechanism. In addition, there is a positive correlation between IL-1-induced phosphorylation of C/EBPδ and its DNA binding or transrepression activity. Second, C/EBPδ inhibited apoC-III promoter activity in cotransfection experiments, while other members of the C/EBP family did not have significant effect. Third, the activities of the different mutant promoter constructs analyzed in this study were affected in the same direction by IL-1 treatment or overexpression of C/EBPδ.

In all cases that have been described, C/EBPδ elicits transcriptional activation of the genes containing one or more C/EBP regulatory element (9, 18, 20, 54). The apoC-III gene therefore serves as a paradigm for a puzzling phenomenon: it is negatively regulated by an otherwise positive transcription factor. To understand the molecular mechanism responsible for this surprising effect, we have analyzed the transrepression potential of C/EBPδ on different constructs containing dissected parts of the apoC-III promoter. The results suggest that in the context of the full promoter C/EBPδ causes a net inhibition mainly through its action on the apoC-III enhancer element I. In contrast to proximal element D, we could not observe direct protein-DNA interaction between element I and C/EBPδ. On the other hand our results clearly show that C/EBPδ can exert a negative effect on apoC-III transcription through this site and a positive effect when this region is placed into a heterologous promoter context. This controversy can be explained by assuming that in vitro C/EBPδ may indirectly bind to element I through protein-protein interaction with factors that can recognize this element. A similar situation has been reported recently for the human C/EBPα promoter (55), showing that direct binding of C/EBPα to the promoter of its own gene is not required for the observed positive autoregulation. Protein-protein interaction between C/EBPδ and upstream stimulatory factor (USF) was suggested as an underlying mechanism, since C/EBPδ transactivated its own promoter through a USF binding site (55).

The site-dependent dual mode of action of C/EBPδ provides an interesting example for the changes of the regulatory phenotype of a given promoter element, depending on the complex modular arrangement of neighboring cis-acting DNA sequences. The promoter context-dependent negative effect of C/EBPδ may thus be ascribed to its ability to interfere with the formation of a stronger transcriptionally active complex, rather than acting as a bona fide repressor.

Apolipoprotein C-III plays an important role in the regulation of triglyceride metabolism. Several studies suggested the existence of a strong positive correlation between plasma triglyceride and apoC-III levels. Overexpression of apoC-III in transgenic mice results of hypertriglyceridaemia (34, 35), while targeted disruption of the apoC-III gene results in hypotriglyceridaemia (37). These changes are in agreement with the proposed functions of apoC-III, such as inhibition of plasma triglyceride-rich lipoprotein catabolism by the inhibition of lipoprotein lipase-mediated intravascular lipolysis or their receptor-mediated uptake. During tumor necrosis factor- or IL-1-induced acute phase reaction, serum triglyceride concentrations are increased, which is correlated with increased de novo hepatic fatty acid synthesis (56). The biological significance of the reduced apoC-III expression in response to IL-1 may therefore be to provide a balancing mechanism to prevent the hyperaccumulation of plasma lipids during conditions that promote the acute phase reaction.

The genes encoding the human apolipoprotein A-I, C-III, and A-IV are closely linked in the long arm of chromosome 11 (57). Recent studies have suggested that the upstream region of apoC-III gene may function as a common enhancer for all three physically linked apolipoprotein genes in the apoA-I/apoC-III/ApoA-IV cluster (39, 58, 59). Since C/EBPδ inhibits the activity of this common enhancer, one may expect that besides apoC-III, the expression of apoA-I and apoA-IV may also be influenced. In this way, the negative regulation of the apoC-III enhancer by C/EBPδ may induce profound changes in the production and/or utilization of different classes of lipoproteins that may lead to complete remodeling of lipoprotein metabolism during IL-1-induced hepatic acute phase reaction.

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