Stimulation of Interleukin-8 Production in Human THP-1 Macrophages by Apolipoprotein(a)

EVIDENCE FOR A CRITICAL INVOLVEMENT OF ELEMENTS IN ITS C-TERMINAL DOMAIN*

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In the vessel wall, macrophages are among the cells that upon activation contribute to the atherosclerotic process. Low density lipoproteins (LDL) can mediate this activation but only after enzymatic or oxidative modification. Lipoprotein(a) (Lp(a)) is an LDL variant that has been shown to have an atherogenic potential by no clearly established mechanisms. In the present study we examined whether native Lp(a) can activate macrophages and, if so, identify the structural elements involved in this action. For this purpose, we utilized human THP-1 macrophages, prepared by treating THP-1 monocytes with phorbol ester, and we exposed them to Lp(a) and its two derivatives, apo(a)-free LDL (Lp(a)-) and free apo(a). We also studied apo(a) fragments, F1 (N terminus) and F2 (C terminus) and subfragments thereof, obtained by leukocyte elastase digestion. By Northern blot analyses, Lp(a), but not Lp(a)-, caused up to a 12-fold increase in interleukin 8 (IL-8) mRNA as compared with untreated cells. Free apo(a) also induced the production of IL-8 mRNA; however, the effect was 3–4-fold higher than that of Lp(a). The increase in mRNA was associated with the accumulation of IL-8 protein in the culture medium. F1 had only a minimal effect, whereas F2 was 1.5–2-fold more potent than apo(a), an activity mostly contained in the Kringle V protease region. A monoclonal antibody specific for Kringle V inhibited the apo(a)-mediated effect on IL-8. We conclude that Lp(a) via elements contained in the C-terminal domain of apo(a) causes in THP-1 macrophages an increased production of IL-8, a chemokine with pro-inflammatory properties, an event that may be relevant to the process of atherosclerosis.

Lipoprotein(a) (Lp(a))† represents a low density lipoprotein (LDL) variant in which apoB100 is linked by a single disulfide bond to apolipoprotein(a) (apo(a)), a multikringle structure shown to have a high degree of homology with plasminogen (1, 2). Lp(a) has been associated with an increased risk for coronary heart (3, 4), cerebrovascular (5–7), and peripheral vascular disease (8–10) by still poorly defined mechanisms. Whether the whole Lp(a) particle is required for the pathogenicity is unclear. The potential contribution by the LDL moiety of Lp(a) to the cardiovascular risk has received relatively limited attention, although based on the information available on authentic LDL, it is likely to be dependent on LDL particle size and type and extent of modifications due to oxidative, lipolytic, or proteolytic events. On the contrary, free apo(a), either derived from parent Lp(a) or as a recombinant, has been reported to be an active component of Lp(a) in many cellular systems and in binding to members of the vascular extracellular matrix. In an endothelial cell system, native Lp(a), via apo(a), has been shown to stimulate the production of adhesion molecules such as intercellular adhesion molecule (11), vascular cell adhesion molecule-1 (12), and E-selectin (12), as well as endothelin-1 (13) and I-309, a potent chemotactant for monocytes (14). Native Lp(a) has also been reported to enhance endothelial plasminogen activator inhibitor-1 expression (15, 16), although those data have not been corroborated by other studies (13, 17). Moreover, in a vascular smooth muscle cell system, native Lp(a), and particularly apo(a), was shown to inhibit the proteolytic activation of transforming factor β via a decrease in cell surface generation of plasmin, resulting in increased vascular smooth muscle cells proliferation (18). There is also evidence that the proteolytic fragment of apo(a), namely F2 which corresponds to the C-terminal domain of apo(a), may exhibit pro-inflammatory properties in that it binds in vitro to the members of the vascular extracellular matrix (19, 20), is present in vivo in unstable atheromatous carotid plaques (21), and stimulates the production of monocyte chemoattractant 1-309 in cultured endothelial cells (14).

Macrophages play a pivotal role in atherosclerosis as cellular components of the underlying chronic inflammatory process. These cells, derived from blood monocytes, are virtually absent in the normal artery but are abundant in unstable plaques, where they exhibit an increased expression of pro-inflammatory elements that contribute to the progression of the atherosclerotic lesion (22). At this time, it is unclear whether Lp(a) in its native form has pro-inflammatory properties. In the current study we tested this hypothesis by examining the effect of Lp(a) and some of its derivatives on the production of inflammatory mediators, using as a model system human THP-1 macrophages obtained by phorbol ester stimulation of THP-1 monocytes. This cell line is highly differentiated and, upon stimulation with phorbol ester, is known to acquire properties similar to those of human monocyte-derived macrophages (23, 24). We
show here that in the chosen cell system, Lp(a), Lp(a)-derived apo(a), and its C-terminal domain, all cause, although to a different degree, an increased production of interleukin (IL)-8, a potent pro-inflammatory chemokine. We also show that this effect is exhibited by neither the LDL isolated from parent Lp(a) nor by authentic LDL isolated from the plasma that served as a source of Lp(a).

**EXPERIMENTAL PROCEDURES**

**Materials—**All the tissue culture reagents, cholera toxin, and pertussis toxin were obtained from Life Technologies, Inc., and were of low endotoxin grade. Phorbol 12-myristate 13-acetate, 5,6-dichlorobenzimida-zole (DRB), e-aminocaproic acid (EACA), diisopropyl fluorophosphate (DFP), EDTA, dithioerythritol (DTE), b-mercaptoethanol, SDS, porcine pancreatic elastase (EC 1.4.19.36), trehalose, formamide, and formaldehyde were purchased from Sigma. Kallikrein inactivator (KI) was purchased from Calbiochem. Nuclease-free water and the RNase-free plasticware were from Ambion, Inc. (Austin, TX). Human Glu-plasminogen was purchased from Enzyme Research Laboratories (South Bend, IN). Rabbit affinity-purified antibodies to Lp(a), apo(a), and LDL and anti-KV monoclonal antibody were prepared as described previously (25). Anti-Lp(a) and anti-apo(a) did not react against LDL and plasminogen, and anti-LDL was unreactive to apo(a).

**Preparation of Human Lp(a), Lp(a–), and LDL—**The plasma from a healthy donor with a single apo(a) isoform of 289 kDa (26) was obtained by plasmapheresis performed in the Blood Bank of the University of Chicago. The steps for Lp(a) and LDL isolation were carried out immediately after blood drawing using the procedure outlined below. To prevent lipoprotein degradation, the plasma was adjusted with 0.15% EDTA, 0.01% sodium azide, 10,000 units/liter KI, and 1 mM phenylmethylsulfonyl fluoride. Lp(a) was isolated by sequential ultracentrifugation and Western blot criteria. Lp(a–), as described previously (28) and assessed to have no apo(a) by electrophoresis, was analyzed using the amoebocyte lysate assay (Sigma) and was estimated to be less than 0.25 pg/g apo(a).

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**Preparation of Apo(a)—**Apo(a) was isolated from Lp(a) under mild reductive conditions in the presence of 1.5–2 mM DTE as described by Edelstein et al. (26). The final preparation of apo(a) was assessed for purity by Western blot with an anti-apo(a) and stored in 10 mM phosphate buffer containing 1 mM EDTA, 0.02% sodium azide, and 125 mM trehalose at −80°C. The concentration of apo(a) was determined either by ELISA or using an extinction coefficient (ε278 = 1.31 ml mg⁻¹ cm⁻¹) established previously for apo(a) (30). The purity of the product was assessed by electrophoresis on precast 1% agarose gels (Ciba-Corning, Palo Alto, CA) and Western blots employing anti-Lp(a) and anti-LDL. The LDL preparations used precast 1% agarose gels (Ciba-Corning, Palo Alto, CA) and Western blot criteria. Lp(a–) was isolated by sequential ultracentrifugation and Western blot criteria. Lp(a–) was isolated by sequential ultracentrifugation and Western blot criteria.

**Preparation of Apo(a) Fragments—**Apo(a) fragments were prepared by digestion of apo(a) with pancreatic elastase as described previously by Edelstein et al. (19). Briefly, apo(a) in 50 mM Tris-HCl, 100 mM NaCl, pH 8.0, KI (200 units/ml) was digested with porcine pancreatic elastase (EC 1.4.19.36) at a molar ratio of 25:1 (protein/enzyme) at 22°C for 2 h, and the reaction was terminated by the addition of 5 mM DFP with further incubation for 20 min. The digest was applied to a lysine-Sepharose affinity column that was then washed sequentially with 3 column volumes of PBS, 500 mM NaCl, and 200 mM EACA. Fragment F1 eluted with PBS and F2 with EACA. The PBS and EACA fractions containing these fragments were each pooled, dialyzed against 10 mM phosphate buffer, pH 7.4, containing 1 mM EDTA, 0.02% sodium azide, and concentrated using Centriprep membranes (Amicon Corp., Beverly, MA).

**Cell Culture—**Human monocytic leukemia cell line, THP-1, was purchased from the American Type Culture Collection. The cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, penicillin (50 units/ml), streptomycin (50 μg/ml), gentamicin (50 μg/ml), and 50 μM mercaptoethanol at 37°C, 5% CO₂. To prepare THP-1 macrophages, monocytes were plated in 6-well plates at the density of 1.1×10^6 cells/ml (2 ml per well) and incubated in the complete growth medium in the presence of 100 μM phorbol 12-myristate 13-acetate. After 72 h, the cells were washed once with RPMI 1640 serum-free medium and incubated with a new aliquot of the serum-free medium for 16 h. At this point, the medium was replaced with a fresh serum-free medium containing the indicated amounts of Lp(a), Lp(a–), LDL, apo(a), or the apo(a) fragments and incubated with THP-1 macrophages for the indicated times. In some experiments, cells were preincubated for 30 min with cholera or pertussis toxins (1 μg/ml) prior to the addition of apo(a). At the end of incubation, the cells were immediately processed for the isolation of RNA as described below. The supernatants
from each well were collected, centrifuged to eliminate debris, and either used for determination of the concentration of IL-8 or frozen at −20 °C until further analysis. At the concentrations of apo(a) and lipoproteins used in our studies, cell viability was >95% as assessed by trypan blue exclusion. All the experiments were conducted in duplicate and were repeated at least twice.

**Analysis of RNA**—Total cellular RNA was isolated using the TRIZOL reagent (Life Technologies, Inc.). Quality of the RNA preparations was verified by 1% denatured formaldehyde agarose gel electrophoresis as described by Sambrook et al. (31). Microarray analysis of total RNA samples isolated from both control and treated cells, 5-μg aliquots, was performed using the human inflammatory response cytokines GE array kit from Super Array, Inc. (Bethesda, MD) according to the manufacturer’s instructions. This array is composed of 23 genes involved in inflammatory response including a variety of cytokines, growth factors, and interleukins such as IL-1β, IL-2, IL-6, IL-10, TNF-α, IL-1 receptor antagonist, and IL-12A, -12B, -16, -17, and -18. It also includes two housekeeping genes, β-actin and glyceraldehyde-3-phosphate-dehydrogenase (G3PDH). The relative mRNA level of each gene was normalized against the levels of both housekeeping genes and expressed as a ratio of sample to control.

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**RESULTS**

**Effect of Apo(a) on the Expression of Genes Involved in the Inflammatory Response of THP-1 Monocytes and THP-1 Macrophages**—In this preliminary work we used apo(a) because according to our previous studies (19, 20) it is the active component of Lp(a). Human THP-1 monocytes and THP-1 macrophages were incubated in the presence and absence of apo(a), 220 nM, for 24 h at 37 °C, and the gene expression in these cells was analyzed by the human inflammatory response cytokines microarray (Super Array, Inc., Bethesda, MD). Among the 23 genes examined, a 6-fold stimulation was observed for IL-8 mRNA in the apo(a)-treated THP-1 macrophages as compared with the untreated cells. This apo(a) effect on IL-8 was not observed in the THP-1 monocytes. Based on these results, we set out to identify in more detail the elements of Lp(a) responsible for the IL-8 stimulation.

**Studies on the Effect of Lp(a), Lp(a−), Authentic LDL, and Apo(a)−**—These products were obtained from the same donor. We first incubated THP-1 macrophages with various concentrations of Lp(a) and then evaluated the level of IL-8 expression by both Northern blot analysis and ELISA. As shown in Fig. 2, treatment of the THP-1 macrophages with this lipoprotein resulted in a dose-dependent induction of both IL-8 mRNA.

**Fig. 2.** Concentration-dependent effect of Lp(a), apo(a), and Lp(a−) on the production of IL-8 by THP-1 macrophages. The cells were incubated with the various products at the indicated concentrations for 24 h at 37 °C. A, Northern blot analysis of total cellular RNA extracted at the end of the incubation. Lane C indicates non-treated cells. B, relative intensity of IL-8 mRNA bands shown in A. The values are expressed as a fold difference over untreated cells. The closed circles indicate cells treated with apo(a); the closed squares indicate cells treated with Lp(a); the open squares indicate cells treated with Lp(a−). C, concentration of IL-8 released into the cell culture medium determined by ELISA. The symbols are as indicated in B. The data are representative of two independent experiments each conducted in duplicate.
The evidence that F2 studied as a fragment is the domain responsible for the action of apo(a) on the production of IL-8 in THP-1 macrophages, prompted us to determine whether this also applies to F2 as a part of apo(a). To this end, we exposed apo(a) to different concentrations of a monoclonal antibody specific for KV, prior to the incubation with the cells. As shown in Fig. 4, this antibody caused a concentration-dependent inhibition of the IL-8 mRNA production. In turn, no inhibition was observed when an irrelevant mouse IgG was used (data not shown).

**Effect of Apo(a) on the Stability of IL-8 mRNA**—For this purpose, we performed experiments using DRB, an inhibitor of RNA polymerase II. THP-1 macrophages were cultured in either the presence or absence of apo(a) for 20 h and then exposed to DRB for various time intervals. As shown in Fig. 5, following the arrest of transcription, the rate of decay of IL-8 mRNA in both apo(a)-treated and untreated cells was similar indicating that apo(a) had no effect on the degradation and stability of IL-8 mRNA, suggesting an induction of expression at the transcriptional level.

**Effect of Cholera and Pertussis Toxins on the Apo(a)-mediated Induction of IL-8 mRNA**—These experiments were carried out to determine whether the G-proteins were required for the action of apo(a) on IL-8 production. For this purpose, THP-1 macrophages were incubated with apo(a) in either the presence or absence of either cholera toxin (inhibitor of stimulatory G protein, Gs) or pertussis toxin (inhibitor of inhibitory G protein, Gi). Cholera toxin totally inhibited the apo(a)-mediated induction (Fig. 3). Pertussis toxin only partially inhibited the apo(a)-mediated induction of IL-8 mRNA (Fig. 5B). However, none of those fragments was individually as potent as the whole F2. Of note, plasminogen exhibited only a minimal effect regarding IL-8 induction (Fig. 3)

Inhibition of the Apo(a) Effect on IL-8 by a Monoclonal Antibody Directed against KV—The evidence that F2 studied as a fragment is the domain responsible for the action of apo(a) on the production of IL-8 in THP-1 macrophages, prompted us to determine whether this also applies to F2 as a part of apo(a). To this end, we exposed apo(a) to different concentrations of a monoclonal antibody specific for KV, prior to the incubation with the cells. As shown in Fig. 4, this antibody caused a concentration-dependent inhibition of the IL-8 mRNA production. In turn, no inhibition was observed when an irrelevant mouse IgG was used (data not shown).

**Effect of Apo(a) on IL-8 Production in THP-1 Macrophages**—Apo(a), 220 nM, was exposed to different concentrations of the antibody for 1 h at room temperature and subsequently incubated with THP-1 macrophages for 24 h at 37 °C. A Northern blot analysis of total cellular RNA extracted at the end of the incubation. B, relative intensity of IL-8 mRNA bands shown in A. The values are expressed as the percentage of the amount of IL-8 mRNA measured in the apo(a)-treated cells without the addition of the antibody. The data are representative of two independent experiments each conducted in duplicate.

Apo(a) caused a dose-dependent increase in the production of IL-8 mRNA (up to 32-fold) and protein (up to 6-fold) into the culture medium. Apo(a) also caused a dose-dependent increase in the production of IL-8 mRNA (up to 32-fold) and protein (up to 22-fold), indicating a greater stimulating efficiency compared with its parent Lp(a). Because bacterial endotoxin is a potent inducer of IL-8 expression in macrophages (32, 33), we determined the endotoxin content of Lp(a) and apo(a) by using the Limulus amoebocyte lysate assay. The amount of endotoxin in Lp(a) and apo(a) was extremely small (less than 0.3 pg/μg for Lp(a) protein and 0.25 pg/μg for apo(a)), a value that is in the same order of magnitude that reported for the LDL preparations used by other investigators (34, 35) in this cell system. Neither Lp(a−/−) (Fig. 2) nor LDL (endotoxin 0.2 pg/μg of LDL protein) had an effect on IL-8 production. Taken together, these results indicate that the increased production of IL-8 by THP-1 macrophages induced by Lp(a) was due to apo(a) and was not endotoxin-related.

Studies on F1 and F2 Fragments—To define the region on apo(a) responsible for the effect on IL-8 in THP-1 macrophages, we used in our assay the two main proteolytic fragments of apo(a), F1 and F2, along with a full-length apo(a). We first established that apo(a), upon incubation with THP-1 macrophages, remained intact as assessed by Western blot analysis of the immunoreactive apo(a) present in the culture medium (data not shown). F2 also remained intact and was 1.5–2-fold more potent than apo(a) both in terms of IL-8 RNA and protein induction (Fig. 3). In contrast, F1 exhibited only a limited activity.

Studies on Subfragments of F2—To define the region in F2 responsible for the IL-8 induction, we studied non-overlapping apo(a) fragments of F2 obtained by elastase digestion, namely F5, F6, and F7 (see Fig. 1). Of them, F7, located in the C-terminal portion of F2, stimulated IL-8 production more efficiently than F5 and F6 (Fig. 3). However, none of those fragments was individually as potent as the whole F2. Of note, plasminogen exhibited only a minimal effect regarding IL-8 induction (Fig. 3).

Western blot analysis of total cellular RNA extracted at the end of the incubation. The values are expressed as a fold difference over untreated cells. C, concentration of IL-8 released into the cell culture medium as determined by ELISA. The data are representative of two independent experiments each conducted in duplicate.
pertussis toxin (Fig. 6). These results suggest that the stimulatory G protein signal transduction pathway might have been responsible for the apo(a)-mediated effect.

**DISCUSSION**

In the present study we have shown that in THP-1 macrophages, Lp(a) under low endotoxin conditions is an inducer of IL-8, a major pro-inflammatory chemokine (36). We have also shown that this effect is at both the mRNA and protein levels and that apo(a) is responsible for the action of Lp(a). This stimulation was macrophage-specific because no effect was elicited when apo(a) was incubated with the unstimulated THP-1 monocytes. In inducing IL-8, apo(a) was markedly more efficient than parent Lp(a) possibly due to the masking of the apo(a)-active site(s) by the LDL moiety. In this vein, we have shown previously that in vitro apo(a) is more efficient than parent Lp(a) in binding to lysine-Sepharose (26), fibrinogen (19, 37), fibronectin (19), and decorin (20). The importance of apo(a) in the Lp(a) action was also supported by the finding that both Lp(a−) and authentic LDL from the same subject had little or no effect on the production of IL-8 by THP-1 macrophages even at very high lipoprotein concentrations. Of note, our finding regarding authentic LDL is in agreement with the previous observations by Wang et al. (34) in THP-1 macrophages and Terkeltaub et al. (35) in THP-1 monocytes. In both studies, LDL needed to undergo either oxidative (34, 35), acetylation (34), or phospholipase A2-induced modification (35) to stimulate production of IL-8. Of note, in the studies by Terkeltaub et al. (35) the stimulatory effect of oxidized LDL was mediated by oxidized lipid end products. In turn, our studies with unmodified Lp(a) demonstrated that the action on IL-8 was protein- and not lipid-dependent pointing at important functional differences between LDL and Lp(a) when studied in their native state.

By using proteolytic derivatives of apo(a), we also provided evidence that F2 was the domain responsible for the IL-8 stimulatory effect and that this effect was 1.5–2-fold higher than that exhibited by intact apo(a). There are two possible explanations for these findings. First, F2, as an isolated frag-

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2 O. Klezovitch and A. M. Scanu, unpublished observations.
Of the 13 interleukins examined, IL-8 was the one that was stimulated by apo(a) in our cell system. IL-8 is a known pro-inflammatory chemokine that is expressed in macrophage-rich areas of human coronary atheromas as assessed by both immunohistochemical techniques and in situ hybridization studies (34). The pathogenicity of this chemokine is mostly attributed to its chemotactic activity toward neutrophils (39), T-cells (40), monocytes (41), smooth muscle (42, 43), and endothelial cells (44), as well as to its mitotic (43) and angiogenic properties (44). IL-8 is also a long-lived chemokine resistant to proteolytic degradation compared with the other cytokines produced by macrophages (45). Thus, we may speculate that the apo(a)-dependent increased production and secretion of IL-8 by activated macrophages and its subsequent accumulation in the vascular extracellular matrix may contribute to the progression of the chronic inflammation process in atheromas.

The mechanism by which apo(a)/fragments stimulate IL-8 production remains to be established. Our current data with DRB, an inhibitor of transcription, suggest that apo(a) stimulated an involvement of the G protein signal transduction pathway in the Lp(a)/apo(a) action. These promising leads and the potential pleiotropic effects of Lp(a) justify further mechanistic studies utilizing larger scale microarray systems comprising a variety of genes relevant to the general areas of inflammation and atherosclerosis.

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