rapid communication

Identification of mouse and human macrophages as a site of synthesis of hepatic lipase

Herminia González-Navarro,[1,*] Zengxuan Nong,* Lita Freeman,* André Bensadoun,[2,†] Katherine Peterson,* and Silvia Santamarina-Fojo*

Molecular Disease Branch,* National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD 20892; and Division of Nutritional Sciences,† Cornell University, Ithaca, NY 14852

Abstract **Hepatic lipase (HL) is synthesized by the liver and is also present in steroidogenic tissues. As both a lipolytic enzyme and a ligand that facilitates the cellular uptake of lipoproteins, HL plays a major role in lipoprotein metabolism and may modulate atherogenic risk. However, HL has not been directly implicated in lesion development. In the present study we demonstrate that HL is also synthesized by mouse and human macrophages. Northern analysis and real time RT-PCR showed that HL mRNA is present in mouse peritoneal macrophages, RAW-264.7, and IC-21 cells. The levels of HL mRNA in mouse peritoneal macrophages were approximately 10–30% that of mouse liver. HL protein was identified by Western blot analyses in human monocyte-derived macrophages, THP, RAW-264.7, and mouse peritoneal macrophages following fractionation by heparin-sepharose affinity chromatography. These combined findings establish that HL is synthesized de novo by macrophages as well as liver, and raises the possibility that HL may have a direct role in the pathogenesis of atherosclerosis.**—González-Navarro, H., Z. Nong, L. Freeman, A. Bensadoun, K. Peterson, S. Santamarina-Fojo. **Identification of mouse and human macrophages as a site of synthesis of hepatic lipase.** ***J. Lipid Res.*** **2002.** 43: **671–675.**

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Hepatic lipase (HL) is a lipolytic enzyme primarily synthesized and secreted by the liver (1, 2) which is also present in steroidogenic tissues (2–5). HL plays a major role in the metabolism of circulating plasma lipoproteins by hydrolyzing triglycerides and phospholipids present in chylomicron remnants VLDL, IDL, and HDL (6–10). HL can also serve as a ligand that facilitates the uptake of lipoproteins by cell surface receptors or proteoglycans, as shown by in vitro (6–8, 11), animal (12–15), and human (16) studies.

While a role for HL in plasma lipoprotein metabolism has been clearly demonstrated, its role in modulating atherogenic risk remains controversial. Hepatic lipase activity has been inversely correlated with the development of atherosclerosis; however, other studies suggest a proatherogenic role for HL (6–11, 17, 18). Of particular interest has been the observation that HL deficiency in apolipoprotein E (apoE)-knockout mice (19) and in LCAT-Tg mice (20) markedly reduces aortic lesion formation despite significant increases in plasma total and apoB-containing lipoprotein cholesterol. These findings suggest that HL might modulate atherogenic risk through a pathway that does not involve changes in plasma lipoprotein metabolism. One attractive possibility is the cellular expression of HL in the vessel wall, which may influence the progression of atherosclerosis.

In the present report we establish that HL is expressed in mouse and human macrophages, thereby providing a new pathway by which HL may modulate atherosclerosis.

MATERIALS AND METHODS

Animals and cell lines

HL-KO (21) mice and C57BL/6J mice were housed in microisolator cages and fed a rodent autoclaved chow diet (NIH-07 chow diet 4.5% fat; Zeigler Brothers, Inc., Gardners, PA). Human hepatoma HepG2, human THP-1, T/G HA-VSMC, mouse IC-21, and mouse RAW 264.7 cells were obtained from ATCC (Manassas, VA). THP-1 cells were stimulated for 72 h with 50 nM PMA (Sigma, St. Louis, MO) before harvesting. Mouse peritoneal macrophages and human monocyte-derived macrophages were isolated and prepared as described (22, 23).

RNA isolation, Northern analysis, and quantitative RT-PCR

Total or poly(A)$^+$ RNA was isolated using an RNeasy kit (Qiagen, Valencia, CA) from all tissues as well as from primary and cultured cells, except for human liver RNA, which was purchased from Ambion Inc. (Austin, TX). Northern blot analyses followed by densitometric scanning (Molecular Dynamics Personal Densitometer, Sunnyvale, CA) was performed as described

Abbreviations: HL, hepatic lipase; apo, apolipoprotein.

[1] To whom correspondence should be addressed.
e-mail: gonza@mail.nih.gov
[2] Request for the anti-human hepatic lipase monoclonal antibodies may be addressed to André Bensadoun, Cornell University, Ithaca, NY.

(22). The membrane was hybridized to a digoxigenin-labeled HL riboprobe and detected using a DIG chemiluminescent detection kit (Roche, Indianapolis, IN). The HL riboprobe was generated by transcription of a 462 bp *Apa*I-*Eco*RI fragment of mouse HL cDNA subcloned into pBluescript II (Stratagene, La Jolla, CA). A ^{32}P-labeled 693 bp cyclophilin cDNA probe (Ambion) was used for normalization. Real-time quantitative RT-PCR was performed using a LightCycler and the Light Cycler-RNA Amplification Kit (SYBR Green I) from Roche (Roche Molecular Biochemicals, Mannheim, Germany). Fifty five amplification cycles (95°C, 0 s; 55°C, 5 s; 72°C, 10 s; 84°C, 1 s) were performed. The concentration of RNA in different samples was normalized by using 18S rRNA or β-actin primers. Serial 10-fold dilutions of normalized RNA, expressing similar amounts of 18S rRNA or β-actin, were then used as template for amplification of HL mRNA. The sequences of primers used for RT-PCR of exons 8 and 9 of mouse and human HL are available upon request.

Protein purification and Western blot analysis

Cellular extracts from tissue culture cells and mouse livers for purification of the HL protein were prepared as previously described (24). The supernatant was loaded into a HiTrap Heparin column (Amersham Pharmacia, Uppsala, Sweden) and equilibrated with 0.01 M phosphate buffer, pH 7.6, and 0.2 M NaCl (24). The total protein applied to the heparin-sepharose columns was as follows: mouse control (15 mg) and HL-KO (15 mg) livers, RAW 264.7 cells (84 mg), peritoneal macrophages (440 mg) and human HepG2 (120 mg), THP-1 (120 mg) and human monocyte-derived macrophages (140 mg). For Western blot analysis heparin-purified fractions, which eluted with 0.8 M NaCl buffer, were electrophoresed, transferred to an Immobilon membrane (Millipore, Bedford, MA), probed with HL antibodies (1 μg/ml) and detected by chemiluminescence (Supersignal West-Pico kit, PIERCE, Rockford, IL) after incubation with HRP-conjugated secondary antibody (Santa Cruz Biotechnology Inc., Santa Cruz, CA). The characterization of the human HL standard, mouse recombinant LPL standard, bovine LPL standard, as well as the anti-human HL and LPL monoclonal antibodies and anti-rat HL polyclonal antibody used, have been previously reported (24–26).

RESULTS

Identification of HL mRNA in macrophages

To determine whether macrophages transcribe the HL gene, RNA isolated from control and HL-KO mouse liver and macrophages were analyzed by Northern blotting (**Fig. 1A**). A 1.7 kb mRNA was detected in control mouse liver and peripheral macrophages, but was absent from HL-KO liver and peritoneal macrophages. HL mRNA was also present in the mouse macrophage-derived cell lines IC-21 and RAW 264.7. However, the HL mRNA present in poly(A)$^+$ RNA isolated from either THP or human-monocyte-derived macrophages was very low compared with that of total liver RNA (data not shown).

Quantification of HL mRNA in macrophages

The relative abundance of HL mRNA in macrophages and liver was determined by densitometric scanning of four independent Northern blots of RNA isolated from mouse peritoneal macrophages as well as two independent Northern blots of RNA isolated from IC-21 and RAW

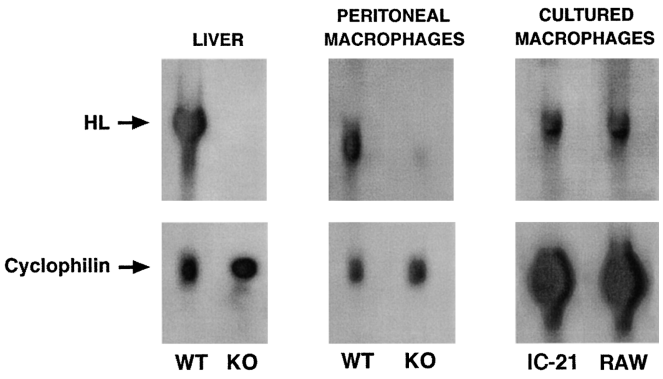

Fig. 1. Northern blot analysis of hepatic lipase (HL) expression in mouse macrophages. Total RNA from wild-type (WT; 20 μg) and HL-KO (20 μg) mouse liver, WT (20 μg) and HL-KO (20 μg) peritoneal macrophages, as well as poly(A)$^+$ RNA from cultured IC-21 (5 μg) and RAW 264.7 (5 μg) macrophages were electrophoresed and analyzed by Northern blot hybridization with a probe for either mouse HL (upper panel) or cyclophilin (lower panel).

cells. HL expression in each tissue or cell type was normalized to cyclophilin mRNA. A representative Northern is illustrated in Fig. 1A. The relative abundance of macrophage HL mRNA to that of liver HL mRNA was determined for mouse peritoneal macrophages (12–28%), IC-21 (0.5–1.5%), and RAW264.7 cells (0.5–1.5%). Real-time quantitative RT-PCR analyses (**Fig. 2A**) also indicated that HL mRNA was more abundant in mouse peritoneal macrophages than in RAW cells and confirmed that human macrophages transcribe the HL gene at low levels compared with human liver (Fig. 2B).

Analysis of HL protein in mouse and human macrophages

To determine whether mouse macrophages express HL, cell protein extracts were fractionated by heparin-sepharose chromatography and evaluated by Western blot analysis (**Fig. 3A**). An antibody previously shown to recognize mouse and rat HL but not LPL (25) detected two protein bands of approximately 59 and 56 kDa in peritoneal macrophages, RAW 264.7 cells, and C57BL mouse liver, but not in HL-KO mouse liver (Fig. 3A). The presence of these two polymorphic forms of HL has been previously reported in mouse and rat livers and shown to reflect different stages in the processing and/or glycosylation of HL (2, 25, 27, 28).

In order to determine if HL was also synthesized by human macrophages, Western blotting was performed on heparin-purified extracts of human monocyte-derived macrophages and human macrophage-derived cell lines (Fig. 3B). Although HL mRNA was low in human macrophages, immunoblot analysis readily detected expression of HL protein in human macrophages and human macrophage-derived cell lines (Fig. 3B). A single band of approximately 62 KDa was detected in heparin-purified extracts from HepG2 cells, PMA-stimulated THP-1 cells, and human primary monocyte-derived macrophages, but not from smooth muscle cells, by a monoclonal anti-human HL antibody (Fig. 3B). Neither the anti-human nor the anti-mouse HL antibody cross-reacted with either purified

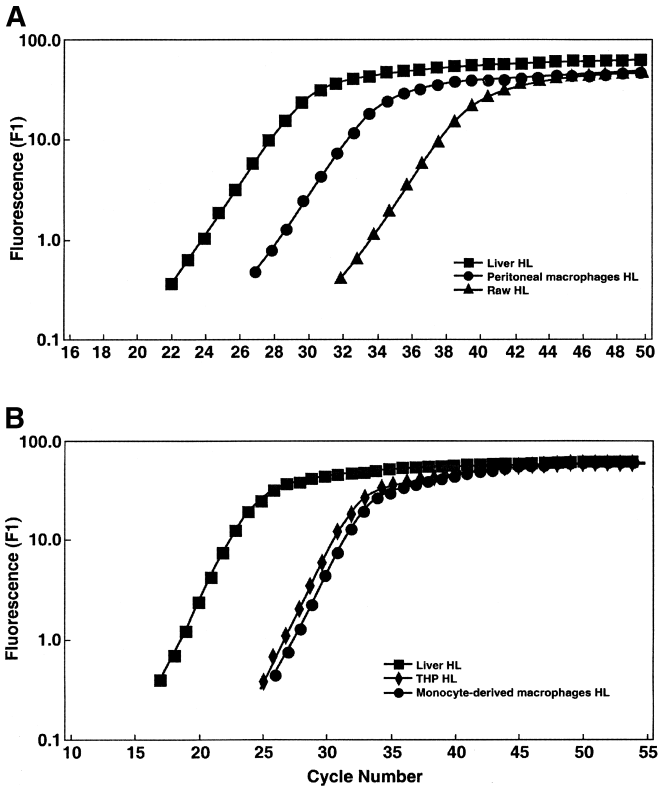

Fig. 2. Quantitative real-time RT-PCR analysis of HL expression in mouse and human macrophages. A: Dnase treated total RNA isolated from mouse liver, peritoneal macrophages, and RAW 264.7 cultured cells was reverse-transcribed and amplified using a primer pair for exons 8 and 9 of the mouse HL gene. B: Poly(A)$^+$ RNA from human liver, monocyte-derived macrophages, and PMA-stimulated THP-1 cells was reverse-transcribed and amplified using a primer pair for exons 8 and 9 of the human HL gene. The quantities of RNA used to amplify HL were normalized to give similar loads of 18S (A) or β-actin (B) RNA.

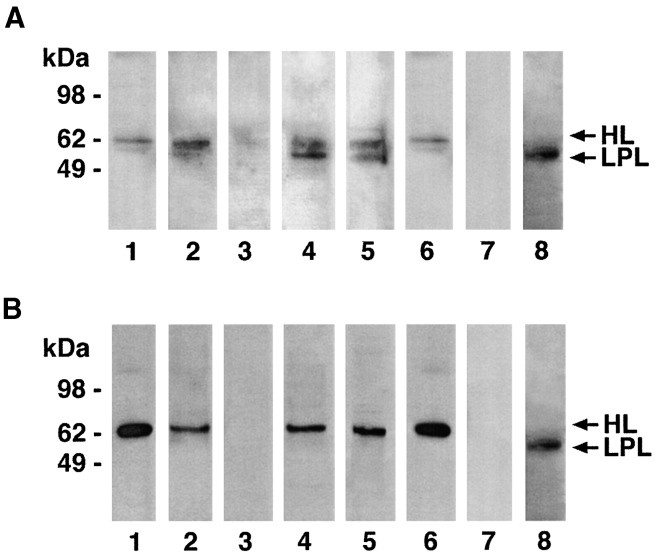

Fig. 3. Western blot analysis of HL isolated from mouse and human macrophages. Purified HL and LPL standards as well as partially purified proteins that were eluted from heparin-sepharose with 0.8 M NaCl were immunoblotted with either a goat anti-rat HL polyclonal antibody that detects mouse, rat, and human HL (25) (A), or a specific mouse monoclonal antibody against human HL (24) (B). Lanes 8 of both A and B were probed with the anti-human LPL monoclonal antibody, 5D2 (26). Protein loads were as follows: A: lane 1, human HL standard (0.2 ng); lane 2, control mouse liver (3 μg); lane 3, HL-KO mouse liver (3 μg); lane 4, RAW 264.7 (3 μg); lane 5, mouse peritoneal macrophages (2 μg); lane 6, human HL standard (0.2 ng); lane 7, mouse LPL standard (0.4 ng); and lane 8, bovine LPL standard (0.2 ng) probed with the 5D2 antibody (0.2 ng). B: lane 1, human HL standard (0.2 ng); lane 2, HepG2 (6 μg); lane 3, human T/G HA-VSCM (7 μg); lane 4, THP-1 (15 μg); lane 5, human monocyte-derived macrophages (5 μg); lane 6, human HL standard (0.2 ng); lane 7, bovine LPL standard (0.2 ng); and lane 8, bovine LPL standard (0.2 ng) probed with 5D2 antibody.

mouse or bovine LPL (Fig. 3A and B) or rat and human LPL standards (24, 25), confirming that the protein detected by the HL antibodies is HL and not LPL. These combined results establish that HL protein is synthesized by both human and mouse macrophages.

DISCUSSION

As both a lipolytic enzyme and a ligand that facilitates the cellular uptake of lipoproteins and lipoprotein lipids, HL has a major role in the metabolism of circulating plasma lipoproteins. However, our current understanding of the physiological role of HL cannot reconcile conflicting studies supporting both proatherogenic and antiatherogenic roles for HL (6–11, 17–20). In the present study we report the presence and synthesis of HL in macrophages, a finding that may help to clarify the role of HL in atherogenesis. The HL protein was identified by Western blot analysis in primary and cultured mouse as well as human macrophages (Fig. 3). HL mRNA in primary and cultured macrophages was detectable by both Northern analysis (Fig. 1) and RT-PCR (Fig. 2), indicating that the HL protein is synthesized de novo by macrophages.

While expression of the HL gene in macrophages is a novel finding, expression of this gene in tissues other than liver has been previously reported. HL in mouse adrenals has been demonstrated by immunohistochemistry (29) and HL has been found in rat ovaries and adrenals (2, 3). Both adrenals and ovaries from rat synthesize a variant mRNA that lacks exons 1 and 2 (4, 5). Although the functionality of the resulting truncated protein, which is predicted to lack a signal peptide, has not been elucidated, the presence of HL in steroidogenic tissues may play a role in the accumulation of cholesterol necessary for steroid hormone synthesis (30). Expression of HL in these tissues would not be expected to influence the development of atherogenesis.

In contrast, expression of HL in macrophages may very well clarify the role of HL in atherosclerosis. Macrophage expression of a related lipase, LPL, has been suggested to play an essential role in the progression of aortic lesions. Bone marrow transplantation experiments have demonstrated that localized expression of LPL by macrophages

present in the arterial wall increases atherosclerotic lesion formation without altering the lipoprotein profile (31, 32). Addition of both HL and LPL to cell cultures has been shown to promote lipoprotein internalization and lipid accumulation by macrophages (33). Like LPL (34, 35), HL may also contribute to foam cell formation and promote atherosclerosis by enhancing monocyte recruitment and retention in the arterial wall, facilitating the retention of lipoproteins in the subendothelial space, and/or enhancing the uptake of lipoprotein into macrophages. A localized proatherogenic function for HL in the arterial wall would explain the paradoxical finding that HL deficiency markedly reduces aortic atherosclerosis in LCAT-Tg and apoE-KO mice in spite of increased plasma levels of apoB-containing lipoproteins (14, 19). The direct proatherogenic effect of HL in the arterial wall is likely modulated by other HL-mediated processes that lead to increased remnant and HDL metabolism and changes in LDL density (9, 18). In humans, a subset of patients with HL deficiency have increased atherogenic risk (9). This finding suggests that in certain clinical circumstances the accumulation of remnant lipoproteins may offset the protective effects of HL deficiency in the arterial wall. In summary, we report for the first time de novo synthesis of HL by mouse and human macrophages. These findings raise the possibility that HL may be produced by macrophages residing in arterial lesions and provide the basis for future studies to evaluate a novel mechanism by which HL may play a direct role in the pathogenesis of atherosclerosis.

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