Expression of Scavenger Receptor B-I*

Oxidized Low Density Lipoprotein Decreases Macrophage Expression of Scavenger Receptor B-I*

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Scavenger receptor class B type I (SR-BI) has recently been identified as a high density lipoprotein (HDL) receptor that mediates bidirectional flux of cholesterol across the plasma membrane. We have previously demonstrated that oxidized low density lipoprotein (OxLDL) will increase expression of another class B scavenger receptor, CD36 (Han, J., Hajjar, D. P., Febbraio, M., and Nicholson, A. C. (1997) J. Biol. Chem. 272, 21654–21659). In studies reported herein, we evaluated the effects of OxLDL on expression of SR-BI in macrophages to determine how exposure to this modified lipoprotein could alter SR-BI expression and cellular lipid flux. OxLDL decreased SR-BI expression in a dose- and time-dependent manner. Incubation with OxLDL had no effect on the membrane distribution of SB-BI, and it decreased expression of both cytosolic and membrane protein. Consistent with its effect on SR-BI protein expression, OxLDL decreased SR-BI mRNA in a dose-dependent manner. The ability of OxLDL to decrease SR-BI expression was dependent on the degree of LDL oxidation. OxLDL decreased both [3H]cholesteryl oleate/HDL uptake and efflux of [14C]cholesterol to HDL in a time-dependent manner. Incubation of macrophages with 7-ketocholesterol, but not free cholesterol, also inhibited expression of SR-BI. Finally, we demonstrate that the effect of OxLDL on SR-BI is dependent on the differentiation state of the monocyte/macrophage. These results imply that in addition to its effect in inducing foam cell formation in macrophages through increased uptake of oxidized lipids, OxLDL may also enhance foam cell formation by altering SR-BI-mediated lipid flux across the cell membrane.

Reverse cholesterol transport, defined as the flux of cholesterol from peripheral tissues to the liver, where it is excreted in the form of bile salts, is an important mechanism in the removal of cholesterol from sites of lipid deposition (1). The receptor mediating HDL binding is now well characterized as scavenger receptor class B type I (SR-BI) (2, 3) and its human homologue CLA-1 (CD36 and lysosomal integral membrane protein-II Analogous-I) (4). SR-BI belongs to the family of class B scavenger receptors that includes CD36 (5) and lysosomal integral membrane protein-II (6). SR-BI binds HDL with high affinity (2) but can also bind native low density lipoprotein (LDL), acetylated LDL, oxidized LDL, and anionic phospholipid vesicles (7).

SR-BI mediates bidirectional flux of cholesterol across the plasma membrane. SR-BI can bind HDL reversibly and mediate cholesterol efflux (8) and cholesteryl ester uptake (2, 9). When varying cell types were screened for the expression level of SR-BI, a direct relationship between the efflux rate of cholesterol to HDL and the level of SR-BI was observed (8). In studies with stably transfected Chinese hamster ovary cells or transiently transfected COS cells, expression of SR-BI stimulates both the efflux of cell cholesterol and influx of HDL cholesterol (10). Studies with genetically engineered mice have demonstrated that SR-BI has an essential role in cholesterol uptake in liver and steriodogenic tissues (11). Overexpression of SR-BI in liver reduces HDL levels, increases reverse cholesterol transport (12, 13), and decreases susceptibility to atherosclerosis (14). By contrast, inhibition of SR-BI activity in apoE-null mice accelerates the onset of atherosclerosis (15).

SR-BI/CLA-1 is highly expressed in liver, adrenal gland, ovary (16), atherosclerotic lesions of apoE-deficient mice (8, 17), and human atherosclerotic lesions (18). SR-BI is expressed in human monocytes (19), macrophages (18), and monocytic cell lines (19, 20). We and others have shown that expression of CD36 is increased in macrophages exposed to oxidized LDL (21–23). It has been subsequently shown that the mechanism by which oxidized low density lipoprotein (OxLDL) up-regulates CD36 involves activation of the transcription factor, PPAR-γ (24, 25). In the present study, we evaluate expression of SR-BI in macrophages to determine how it is regulated in response to OxLDL.

MATERIALS AND METHODS

Cell Culture—Raw264.7 cells, a murine macrophage cell line (ATCC, Manassas, VA), were cultured in RPMI 1640 medium containing 10% fetal calf serum, 50 μg/ml each of penicillin and streptomycin, and 2 mM glutamine. Cells were switched to serum-free medium for 3–5 h when the confluence was about 85%. Cells received treatments in serum-free medium. Human monocytes were isolated from the pooled blood of volunteer donors by Ficoll-Hypaque density gradient centrifugation. Monocytes were cultured in RPMI 1640 medium containing 10% human serum (Bioreclamation, Hixsville, NY), 50 μg/ml each of penicillin and streptomycin, and 2 mM glutamine. Non-adherent cells were removed by washing after 2 h of incubation.

Isolation of HDL and LDL and Preparation of OxLDL—LDL (1.019–1.063 g/ml) and HDL (1.063–1.210 g/ml) were isolated...
from normal human plasma by sequential ultracentrifugation. They were dialyzed against PBS containing 0.3 mM EDTA, sterilized by filtration through a 0.22-μm filter, and stored under nitrogen gas at 4 °C. Protein content was determined by the method of Lowry et al. (26).

OxLDL was prepared by dialysis of 500 μg/ml of LDL in PBS containing 5 μM CuSO4 for 12 h, or other indicated times) at 37 °C, followed by dialysis in PBS containing 0.3 mM EDTA for 2 × 12 h. The purity and charge of both LDL and OxLDL were evaluated by examining electrophoretic migration in agarose gel. The degree of oxidation of LDL and OxLDL was determined by measuring the amount of thiobarbituric acid-reactive substances (TBAR). LDL had TBAR values of <1 nmol/mg. OxLDL had TBAR values of >10 and <30 nmol/mg. All lipoproteins were used for experiments within 3 weeks after preparation.

Isolation of Total RNA, Purification of Poly(A+)
RNA, and Northern Blotting—Cells were lysed in RNAzol™ B (Tel-Test, Inc.) and chloroform-extracted, and total cellular RNA was precipitated in isopropyl alcohol. After washing with 80 and 100% ethanol, the dried pellet of total RNA was dissolved in distilled water and quantified. The poly(A+)
RNA was purified from about 80 μg of total RNA by using the Poly(A)Tract® mRNA Isolation System III (Promega, Madison, WI).

Poly(A+)
RNA was loaded on 1% formaldehyde-agarose gel. After electrophoresis, poly(A+)
RNA was transferred to a Zeta-probe® GT Genomic Testbed Blotting Membrane (Bio-Rad) in 10× SSC by capillary force for overnight. The blot was UV cross-linked for 2 min and then prehybridized with Hybrisol II (Oncor, Inc., Gaithersburg, MD) for 30 min before the addition of 32P-randomly labeled priming probe for mouse SR-BI or glyceraldehyde-3-phosphate dehydrogenase. After overnight hybridization, the membrane was washed for 2 × 20 min with 2× SSC and 0.2% SDS and for 2 × 20 min with 0.2× SSC and 0.2% SDS at 55 °C. The blot was autoradiographed by exposure to an x-ray film (X-Omat AR, Eastman Kodak Co.). The semiquantitative assay of autoradiograms was assessed by densitometric scanning using a UMAX (Santa Clara, CA) UC630 flatbed scanner attached to a Macintosh IIci (Apple Computer, Cupertino, CA) running NIH Image software (National Institutes of Health, Bethesda, MD). The probe for mouse SR-BI was generated by reverse transcription-polymerase chain reaction based on the published sequence. The sequences of 5′- and 3′-oligonucleotides used were TCG-GCCTTGCTAGTATGCTTC (positions 121–141) and GGT-TCATATGACGAGCTGG (positions 551–571), respectively (2).

Analysis of SR-BI by Western Blotting—After treatment, macrophages were washed twice with cold PBS and then scraped and lysed in ice-cold lysis buffer (50 mM Tris, pH 7.5, 150 mM NaCl, 1% Triton X-100, 1% sodium deoxycholate, 1 mM phenylmethylsulfonyl fluoride, 50 mM sodium fluoride, 1 mM sodium orthovandate, 50 μg/ml aprotinin, and 50 μg/ml leupeptin). Lysate was sonicated for 20 cycles and then microcentrifugated for 15 min at 4 °C, and supernatant was transferred to a new test tube. For the isolation of cytosolic protein, cells were lysed in the lysis buffer in the absence of detergent followed by sonication. To extract membrane protein, the pellet, after removal of cytosolic protein, was relysed in lysis buffer containing detergent and sonicated. After centrifugation, the supernatant was collected as membrane fraction. Proteins were separated on a SDS-PAGE and then transferred onto nylon-enhanced nitrocellulose membrane. Membranes were blocked with a solution of 0.1% Tween 20/PBS (PBS-T) containing 5% fat-free milk for 1 h and then incubated with rabbit polyclonal anti-SR-BI (Novus Biological, Inc., Littleton, CO) for 2 h at room temperature followed by washing for 3 × 10 min with PBS-T buffer. The blot was reblocked with PBS-T containing 5% milk followed by incubation with hors eradish peroxidase-conjugated goat anti-rabbit IgG for another 1 h at room temperature. After washing three times for 10 min each with PBS-T, the membrane was incubated for 1 min in a mixture of equal volumes of Western blot chemiluminescence reagents 1 and 2. The membrane was then exposed to film before development.

Determination of Efflux of Free Cholesterol and Influx of Cholesteryl Ester—[3H]Cholesterol was obtained from Perkin-Elmer Life Sciences. For influx study, macrophages were cultured in 24-well plates until ~85% confluence. After treatment, cells were washed with PBS and then incubated with a mixture of [3H]cholesteryl oleate (200 nCi/ml) and HDL (100 μg/ml) in serum-free RPMI 1640 medium. At the indicated times, medium was removed, and cells were washed twice with PBS and then lysed by the addition of 0.1 N NaOH. Radioactivity and protein content in lysate were determined. To study the efflux, macrophages were cultured in 24-well plates in complete medium containing free [14C]cholesterol (80 nCi/ml) until ~85% confluence. Cells then were switched into serum-free medium or medium containing 50 μg/ml OxLDL for 24 h. After washing twice with PBS, cells were incubated with 400 μg/ml HDL in serum-free RPMI medium. Free [14C]cholesterol (cholesterol efflux) was determined in the media collected at the indicated times.

Preparation of Methylated β-Cyclodextrin-Cholesterol Complexes—Methylated β-cyclodextrin (MeβCD), cholesterol and 7-ketocholesterol were purchased from Sigma.

To prepare the complexes of MeβCD-cholesterol, cholesterol or 7-ketocholesterol was dissolved in a mixture of methanol and chloroform (1:1) at a concentration of 100 μM. An ~0.5-ml solution of cholesterol or 7-ketocholesterol was dried under N2, and then 20 ml of 10 μM MeβCD solution was added. The dried cholesterol was suspended in solution by scraping off the wall of the tube. The suspension of cholesterol was sonicated for 5 min on ice and rotated in a 37 °C oven overnight. After adjusting the pH to 7.4, the mixture was filtered through a 0.22-μm filter. The concentration of cholesterol in the prepared solution was about 250–300 μg/ml as determined by a cholesterol assay kit (Sigma).

RESULTS
To investigate the effects of various lipoproteins on SR-BI expression, macrophages were treated with OxLDL (10 and 50 μg/ml), LDL (50 μg/ml), or HDL (50 μg/ml) for 16 h. The protein was extracted in lysis buffer containing detergent and analyzed for changes of SR-BI protein expression. OxLDL, at both 10 and 50 μg/ml, significantly decreased SR-BI protein (Fig. 1). LDL had no effect and HDL slightly increased SR-BI expression. Concentration and time course analyses showed that OxLDL decreased SR-BI expression in a dose-dependent manner (Fig. 2A). Decreased expression of SR-BI by OxLDL occurred by 4 h after initiation of treatment (Fig. 2B) with a maximum inhibition occurring at 8 h. OxLDL had no effect on the membrane distribution of SR-BI and decreased expression of both membrane and cytosolic protein (Fig. 3).

To determine the mechanism by which OxLDL down-regulated SR-BI expression, we next evaluated steady state mRNA levels of SR-BI in macrophages treated with varying concentrations of OxLDL. Consistent with its effect on SR-BI protein expression, OxLDL decreased SR-BI mRNA in a dose-dependent manner (Fig. 4).

We next determined if the degree of LDL oxidation affected its ability to modulate SR-BI expression. The degree of LDL oxidation was increased with increasing times of dialysis in PBS containing 5 μM CuSO4. Oxidation was stopped by the...
addition of EDTA and dialysis in cold PBS containing EDTA. Oxidation was quantified by assessment of TBAR and migration in agarose gel (data not shown). The ability of OxLDL to decrease SR-BI expression increased with the length of time of LDL oxidation (Fig. 5).

We next evaluated the functional consequences of decreased SR-BI expression in response to OxLDL. Both the efflux of free cholesterol and influx of cholesteryl ester were evaluated in macrophages following incubation with OxLDL. OxLDL decreased both [14C]cholesteryl oleate/HDL uptake (Fig. 6A) and efflux of [14C]cholesterol to HDL in a time-dependent manner (Fig. 6B). The relatively small changes seen in both HDL-mediated influx and efflux in response to OxLDL do not parallel the degree of down-regulation of SR-BI expression in response to OxLDL. The reasons for this are not completely clear but may reflect alterations in both receptor- and nonreceptor-mediated effects of OxLDL on cholesterol trafficking. Without blocking SR-BI, it is not possible to directly attribute the effects of OxLDL on either influx or efflux of cholesterol to SR-BI.

To investigate the mechanism(s) by which OxLDL inhibited SR-BI expression and to determine if changes in SR-BI could be mimicked by incubation of macrophages with cholesterol or an oxysterol, we evaluated SR-BI expression in cells incubated with these lipids. We have previously demonstrated that changes in cellular cholesterol levels following incubation of macrophages with β-Cyclodextrins can alter expression of CD36 (27). β-Cyclodextrins are cyclic oligosaccharides that encapsulate insoluble hydrophobic compounds and allow them to become soluble in aqueous solutions (28). Cyclodextrins are efficient at removing cholesterol from cells in culture (29, 30) and have also been used to deliver cholesterol (in the form of...
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**FIG. 6.** OxLDL decreases HDL-mediated influx of cholesteryl ester and efflux of free cholesterol. A, macrophages cultured in 24-well plates were incubated with 50 μg/ml OxLDL for 24 h. After washing with PBS, cells were incubated with [14C]cholesteryl oleate (200 nCi/ml) and HDL (100 μg/ml) in serum-free RPMI 1640 medium. At the indicated times, the medium was removed. Cells were washed twice with PBS and then lysed by the addition of 0.1 N NaOH. Radioactivity and protein content were determined in the lysate (n = 4). B, macrophages were cultured in 24-well plates in medium containing free [14C]cholesterol (80 nCi/ml). Cells then were switched into serum-free medium with 50 μg/ml OxLDL for 24 h. After washing twice with PBS, cells were incubated with 400 μg/ml HDL in serum-free RPMI medium. At the indicated times, the medium was collected, and [14C]cholesterol was quantified in the media (n = 3).

**DISCUSSION**

We demonstrate that macrophage expression of SR-BI is inhibited in response to OxLDL, resulting in reduced HDL-cholesteryl ester uptake and HDL-mediated cholesterol efflux. Our data are consistent with previous data demonstrating that intracellular cholesterol levels regulate SR-BI expression and that there is an inverse relationship between SR-BI expression and cellular cholesterol pools (32). This inverse relationship between cellular cholesterol content and SR-BI expression was also seen in an adrenal cell line (Y1-BS1) treated with β-cyclodextrin to deplete cellular cholesterol stores (33). As cellular cholesterol was reduced over time, SR-BI expression increased (33). Using a similar technique, we demonstrated a direct effect (increased cellular cholesterol was associated with increased expression) of cholesterol levels on expression of the macrophage class B scavenger receptor, CD36 (27). However, in the present study, 7-ketocholesterol, but not cholesterol, reduced SR-BI expression. 7-Ketocholesterol is a prominent oxysterol produced during the oxidation of LDL (34) but is not a peroxisome proliferator-activated receptor-γ ligand (25). Further studies are needed to determine the specific mechanism by which this oxysterol inhibits SR-BI expression.

The effects of cholesterol on SR-BI expression may be cell type-dependent. Rats given a 2-week high cholesterol diet had decreased SR-BI expression in hepatic parenchymal cells, while the expression in Kupffer cells was increased (35). In steroidogenic tissues (adrenal gland, testes), SR-BI expression is also hormonally regulated. Both adrenocorticotrophic hormone (ACTH) and human chorionic gonadotropin increase SR-BI expression. In rats, estrogen treatment inhibits hepatic SR-BI expression (16). The human SR-BI gene contains the consensus site for steroidogenic factor-1, an orphan member of the nuclear hormone receptor family involved in the regulation of steroidogenesis (36).

SR-BI is expressed in macrophage-rich areas in foam cells within atherosclerotic lesions of apoE-deficient mice (8, 17) and in human atherosclerotic lesions (18). Several reports document the expression of SR-BI/CLA-1 in monocytes, macrophages, and monocytic cell lines; however, its function in lipid metabolism in these cells and in cholesterol accumulation or efflux in atherosclerotic lesions remains unclear. There is conflicting data addressing the regulation of SR-BI/CLA-1 in monocyte/macrophages. Murao et al. reported that CLA-1 mRNA is expressed in human monocytes and TPH-1 cells, a human promonocytic leukemia cell line (19). Expression of CLA-1 was higher in freshly isolated monocytes than in macrophages, and expression in TPH-1 cells decreased following differentiation with phorbol 12-myristate 13-acetate (19). Con-
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Contrary to these findings, other groups find that expression of CLA-1 is low in freshly isolated human monocytes but increased upon differentiation of these cells in tissue culture (17, 20). CLA-1 was induced in monocytes treated with macrophage colony-stimulating factor and fetal calf serum (20) and was inhibited in both monocytes and macrophages by treatment with interferon-γ, lipopolysaccharide, and tumor necrosis factor (20).

In contrast to our data, Hirano et al. (18) demonstrated that incubation of human monocyte-derived macrophages with either OxLDL or acetylated LDL increased SR-BI expression by 4-fold. The reason for this discrepancy with our data and with data demonstrating an inverse relationship between cellular cholesterol content and SR-BI expression (33) is undetermined, but it may relate to the preparation of the OxLDL or the time frame of cell treatment. In our experiments, macrophages were treated for 2–10 h, a time frame in which we do not observe significant lipid accumulation in our cells. Hirano et al. (18) incubated macrophages with modified lipoproteins for 24–48 h. Thus, their results may be the result of lipid accumulation that may subsequently affect expression of this receptor by other mechanisms. More likely, these differences relate to the differentiation state of the monocyte/macrophage. Our data in human monocyte-derived macrophages demonstrate that the OxLDL is acting as a differentiating agent in monocyte/macrophages that are not fully differentiated. We and others have shown that OxLDL induces expression of a differentiation-linked surface antigen, CD14 (Fig. 8A) (25). At this early stage of macrophage differentiation, OxLDL up-regulates SR-BI expression (Fig. 8A). However, in fully differentiated macrophages, a state more likely to reflect macrophages in atherosclerotic tissue, OxLDL inhibits SR-BI but has no effect on CD-14.

It is clear from many lines of evidence that oxidation of low density lipoproteins is a critical early event in the pathogenesis of atherosclerosis (37). OxLDL is present in human atheroma (38) and is the proximal source of lipid that accumulates within cells of the atherosclerotic lesion (37). Two macrophage scavenger receptors, the type A scavenger receptor and CD36, have been implicated in the pathogenesis of atherosclerosis based on their presence in human lesions (22, 39) and inhibition of lesion formation when they are deleted by homologous recombination in murine models of atherosclerosis (40, 41). Insight into the role of SR-BI in atherosclerosis is provided by murine models of atherosclerosis. SR-BI protects against development of vascular lesions in atherosclerosis-prone mice; however, the mechanism by which it functions in this role remains unclear. Attenuation of SR-BI accelerated the development of atherosclerosis in ApoE knockout mice (15). Conversely, atherosclerotic lesion size is reduced in LDL receptor knockout mice overexpressing the SR-BI transgene (14). It is tempting to speculate that atherosclerosis in these murine models is either enhanced or repressed by altering HDL-mediated reverse cholesterol transport. However, since SR-BI can also act as a scavenger receptor, binding oxidized LDL, acetylated LDL, and anionic phospholipids (3, 7, 19), it is possible that alterations in SR-BI expression may alter circulating levels and/or binding of these proatherogenic lipids.

In conclusion, our data showing that macrophage expression of SR-BI is inhibited in response to OxLDL have potential implications for atherosclerosis. We believe, based on our data, that oxidized LDL may play a dual role in macrophage lipid accumulation. Oxidized lipid probably accumulates in macrophages through scavenger receptor-mediated binding and uptake. However, our data also imply that OxLDL may inhibit SR-BI-mediated efflux, which would act in a synergistic manner to promote lipid retention within macrophages.

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