Scavenger receptor-mediated recognition of maleyl bovine plasma albumin and the demaleylated protein in human monocyte macrophages

(ligand-receptor interaction/malondialdehyde low density lipoprotein)

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Communicated by Richard J. Havel, December 27, 1984

ABSTRACT Maleyl bovine plasma albumin competed on an equimolar basis with malondialdehyde low density lipoprotein (LDL) in suppressing the lysosomal hydrolysis of ^{125}I -labeled malondialdehyde LDL mediated by the scavenger receptor of human monocyte macrophages. Maleyl bovine plasma albumin, in which 94% of the amino groups were modified, exhibited an anodic mobility in agarose electrophoresis 1.7 times that of the native protein. Incubation of maleyl bovine plasma albumin at pH 3.5 regenerated the free amino groups and restored the protein to the same electrophoretic mobility as native albumin. The demaleylated protein suppressed 75% of the hydrolysis of ^{125}I -labeled malondialdehyde LDL and >80% of ^{125}I -labeled maleyl bovine plasma albumin. The ability of the demaleylated protein to compete was abolished after treatment with guanidine hydrochloride. Although ligands recognized by the scavenger receptor typically are anionic, we propose that addition of new negative charge achieved by maleylation, rather than directly forming the receptor binding site(s), induces conformational changes in albumin as a prerequisite to expression of the recognition domain(s). The altered conformation of the modified protein apparently persists after removal of the maleyl groups. We conclude that the primary sequence of albumin, rather than addition of new negative charge, provides the recognition determinant(s) essential for interaction of maleyl bovine plasma albumin with the scavenger receptor.

The scavenger receptor of macrophages binds a diverse array of polyanionic macromolecules, including modified human low density lipoprotein (LDL), maleyl-albumin (the half-cystyl derivative of bovine plasma albumin that has been modified by maleic anhydride), polyinosinic acid, and fucoidin (see review in ref. 1). Several cellular responses occur as a consequence of incubation of macrophages with certain of these ligands. Johnson *et al.* (2) have shown that addition of maleyl-albumin or fucoidin induces secretion of neutral proteases, plasminogen-activating factor, and tumor cytolytic factor by primed murine peritoneal macrophages. Goldstein *et al.* (3) have demonstrated that receptor-mediated internalization of acetyl-LDL in unstimulated murine peritoneal macrophages results in a rapid accumulation of cholesteryl esters. Because the activity of the scavenger receptor of macrophages is not down-regulated by intracellular levels of cholesterol (3, 4), the continued internalization and lysosomal hydrolysis of acetyl-LDL generate large quantities of free cholesterol, a portion of which is reesterified in the cytoplasm for storage in lipid droplets (5). Several other cholesteryl ester-rich lipoprotein complexes have been identified that bind to the scavenger receptor of macrophages and promote the intracellular accumulation of cholesteryl es-

ters. These include LDL modified by malondialdehyde (6, 7), diketene (8), or endothelial cells (9, 10); particulate complexes of bovine serum albumin with cholesteryl ester (11); and lipid-protein particles extracted from human atherosclerotic aortas (11).

The site(s) promoting interaction of macromolecules with the scavenger receptor have yet to be characterized. Brown and Goldstein and colleagues (1, 3, 12) have proposed that a specific cluster of multiple negative charges may be necessary for binding of the ligand to the receptor. This proposal was based on the ability of certain polyanionic macromolecules to prevent the binding and uptake of ^{125}I -labeled acetyl-LDL by murine peritoneal macrophages (3, 12). In particular, maleyl human serum albumin was an effective competitive inhibitor, whereas acetyl albumin was not. Since maleylation results in the addition of net negative charge to peptidyl lysines, and acetylation acts to neutralize the positive charge of lysyl residues, it was postulated that the addition of new negative charges by maleylation was necessary to convert albumin into a molecule bound by the scavenger receptor (3).

We have recently compared the ability of several lysine-specific reagents to convert LDL into a ligand bound by the scavenger receptor of human monocyte macrophages (13, 14). Based on these studies, we have proposed that modification of LDL to produce a molecule recognized by the scavenger receptor effects a conformational transition of the apoB polypeptides, and that modification of the charge of specific critical peptidyl lysines results in expression of the receptor binding site(s) formed by the primary amino acid sequence of the LDL protein.

These results prompted us to examine whether the negative charge provided by maleylation of the lysyl residues of bovine plasma albumin was essential for interaction of albumin with the scavenger receptor of human monocyte macrophages. In this report, we demonstrate that both maleyl-albumin and the demaleylated protein competitively inhibit the uptake and hydrolysis of ^{125}I -labeled malondialdehyde LDL mediated by the scavenger receptor of human monocyte macrophages.

MATERIALS AND METHODS

Materials. Sodium [^{125}I]iodide (15 mCi/ μg ; 1 Ci = 37 GBq) and 1-fluoro-2,4-dinitro[3,5- ^3H]benzene (16.6 Ci/mmol) were purchased from Amersham. Polyinosinic acid was obtained from Sigma, maleic anhydride was from Aldrich, crystallized bovine plasma albumin (cat. no. 2266-01) was from Armour (Kankakee, IL), human serum albumin (cat. no. 10881) was from United States Biochemical (Cleveland,

OH), and guanidine hydrochloride (ultrapure) was from Schwarz/Mann. All other supplies and reagents were obtained from sources previously reported (15).

Subjects. Normal subjects were recruited from the staff and student body at the University of California. No one received drugs that might have affected serum cholesterol levels or lipid metabolism. All had normal hematocrits, leukocyte and differential counts, serum cholesterol, and triglycerides. Informed consent was obtained in writing from each person.

Separation of Cells. Five hundred milliliters of blood was taken after an overnight fast, and the monocytes were separated from 300 ml of blood by using counterflow centrifugation (method BB in ref. 4).

Cell Culture. Cells were suspended in 30% autologous serum in Dulbecco's modified Eagle's medium supplemented with 24 mM NaHCO_3 /10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid/8 μg of insulin per ml/0.25 μg of fungizone per ml (called medium B to be consistent with our previous publications; refs. 4 and 15). Samples (0.5 ml) of the cell suspension containing 0.5×10^6 cells were transferred to 2.0-cm² polystyrene wells (Falcon 3047) and incubated at 37°C in a humidified 5% CO_2 /95% air incubator. The medium was aspirated and replaced with fresh medium of the same composition twice weekly.

Classification and Viability of the Cells. The cells were classified and their viability was determined as described (16). Because of the media changes and the washes prior to beginning each experiment, the cells were $\geq 99\%$ monocyte macrophages before the radioactive lipoproteins were added. More than 95% of the cells were viable at the end of the incubation.

Preparation of Sera. Autologous serum was prepared from 200 ml of blood as described (4).

Preparation and Chemical Modification of Proteins. Human LDL (d 1.019 to 1.063 g/ml) was isolated from the serum of individual healthy human subjects by ultracentrifugation. LDL was modified by malondialdehyde as described (6, 14) and dialyzed against 0.01 M sodium phosphate, pH 7.4/0.15 M sodium chloride/0.01% EDTA (buffer A).

The half-cystyl derivative of crystallized bovine plasma albumin (3 g) was prepared by the method of King and Spencer (17) and dialyzed for 36 hr at 4°C against 0.2 M sodium phosphate (pH 9.0). Maleylation of half-cystyl bovine plasma albumin was conducted according to the method of Butler and Hartley (18), using recrystallized maleic anhydride. The maleylated protein was dialyzed for 48 hr at 4°C against 0.01 M ammonium bicarbonate, lyophilized, and stored at -10°C. Desired samples were reconstituted in buffer A and dialyzed for 16 hr at 4°C against buffer A prior to use.

Demaleylation was performed according to Butler and Hartley (18) by addition of acetic acid (30%, wt/wt) to the sterile-filtered (0.45 μm) protein solution (5–10 mg/ml) to adjust the pH to 3.5, chloroform (5% vol/vol) was added to prevent bacterial growth, and the preparation was incubated in a glass-sintered top conical tube for 96 hr at 37°C. Both the unmodified and maleylated half-cystyl bovine plasma albumin precipitated under these conditions. The precipitated proteins were resolubilized by adding 1 M sodium hydroxide to adjust the preparations to pH 6.4. Portions of the acid-treated samples were placed at 4°C, either with or without dialysis for 16 hr against buffer A, and then used in cellular assays within 21 days after termination of the demaleylation procedure. For those studies using guanidine hydrochloride, the lyophilized protein was reconstituted in buffer A containing 6 M guanidine hydrochloride and, as required, the procedure for demaleylation was initiated. The soluble protein at pH 3.5 (demaleyl-protein) or at pH 7.4 (maleyl-albumin) was renatured by dialysis against sequential dilutions of guanidine hydrochloride (6, 4, 2, 1, 0.5 M) in buffer A and

exhaustively dialyzed against buffer A. Analyses of all preparations were comparable to those given in Table 1.

Reaction of the several preparations of albumin with 1-fluoro-2,4-dinitro[3,5-³H]benzene (696 dpm/nmol) was conducted according to the method of Sanger (19). The insoluble [³H]dinitrophenylated proteins were sequentially extracted with ether, acetone, and ethanol. After a final extraction with ether, the precipitated proteins were solubilized in 1 M sodium hydroxide, and 10 M urea was added to give a final concentration of 0.1 M sodium hydroxide/9 M urea. The modified proteins were then dialyzed against the same solution at room temperature, and the samples were removed for determination of the amount of radioactivity by scintillation spectrophotometry (29.3% efficiency of counting). Each sample (0.5 mg) included <13% (wt/wt) of radioiodinated protein ($0.15\text{--}2.6 \times 10^5$ cpm) to permit radiochemical determination by γ emission of the concentration of the [³H]dinitrophenylated protein. Corrections for the radioemission of ¹²⁵I detected by scintillation spectrophotometry were made prior to calculating the molar ratios of dinitrophenylation; ¹²⁵I radioemission contributed 40% (albumin), 53% (maleyl albumin), and 4% (demaleyl protein) of the counts determined by scintillation spectrophotometry.

Labeling of LDL and maleyl-albumin with ¹²⁵I was performed by the method of McFarlane (20) as modified by Bilheimer *et al.* (21).

Assays of Chemical Modification. The malondialdehyde adduct of LDL was quantitated by colorimetric assay with thiobarbituric acid as reported (6, 14). The extent of lysine modification was determined by the method of Habeeb (22) with trinitrobenzenesulfonic acid as the difference in lysyl residues of modified and unmodified protein preparations. Molar ratios were calculated assuming a total molecular weight of 500,000 for the protein of LDL (23), 66,210 for half-cystyl bovine plasma albumin (24), 68,900 for the maleylated albumin, and 66,210 for the demaleylated protein. Chemical derivatization of LDL by malondialdehyde typically resulted in modification of 38%–48% of the lysyl residues of the apoB polypeptides; maleylation of albumin resulted in modification of >94% of the peptidyl lysines. The concentrations of protein samples used in cellular assay, given in molar terms, were calculated from the molecular weights stated above and the protein concentrations were determined by the method of Lowry *et al.* (25) with bovine plasma albumin as a standard.

Agarose electrophoresis was conducted in Tris-HCl/barbital/sodium barbital, pH 8.4, using Biogram A slides (Bio-Rad); the radioiodinated protein samples were diluted to a concentration of 1 mg/ml with buffer A and were subjected to electrophoresis for 9 min at 150 V. After fixation, the slide was wrapped in Saranwrap and exposed at -76°C to Kodak XAR-5 film, using an intensifying screen. Positions detected by autoradiography were confirmed by Coomassie blue stain (0.025%) for protein.

Cellular Assays. Prior to initiating studies, the cells were washed 3 times with 1-ml vol of Dulbecco's modified Eagle's medium containing 10 mM 4-(2-hydroxyethyl) 1-piperazineethanesulfonic acid (medium C). Radioactive proteins were added in medium C supplemented with 25 mM NaHCO_3 and 2 mg of glucose per ml (medium D) to the cells, and the cells were returned to the incubator for the indicated times. The proteolytic degradation of ¹²⁵I-labeled protein was measured by assaying the amount of ¹²⁵I-labeled trichloroacetic acid-soluble (noniodide) material formed by the cells and excreted into the culture medium as described by Goldstein and Brown (26). Corrections were made for the small amounts (<0.01% of total radioactivity added) of ¹²⁵I-labeled acid-soluble material that was formed in parallel incubations without cells. The protein content of cells solubilized by 0.1 M sodium hydroxide was measured by the method of Lowry *et al.*

(25) with bovine plasma albumin as a standard. Statistical analyses were conducted by methods previously cited (4).

RESULTS

A total of 60 mol of free amino groups (provided by the lysyl side chains and the single amino terminus) per mol of bovine plasma albumin has been determined by amino analysis and primary sequence (24). In this study, quantitation of free amino groups either by reaction with 1-fluoro-2,4-dinitro[3,5-³H]benzene (19) or by colorimetric determination with trinitrobenzenesulfonic acid (22) was in good agreement with the theoretical number expected (Table 1). Maleylation of bovine plasma albumin resulted in modification of 94% (56 mol) of the available amino groups per mol of albumin. Maleyl-albumin migrated as a discrete band on agarose electrophoresis, with an anodic mobility 1.7 times that of native albumin. Regeneration of the free amino groups can be accomplished by subjecting the maleyl-protein to acid conditions; reversal of the modification, or demaleylation, occurs with a half-life of 11–12 hr at pH 3.5 and 37°C (18). Incubation of maleyl-albumin for 96 hr under these conditions resulted in efficient regeneration of the free amino groups and in a protein of the same electrophoretic mobility as native bovine albumin. Each of the proteins, whether or not reduced by dithiothreitol, migrated as a single band in sodium dodecyl sulfate/polyacrylamide gel electrophoresis (7%–17% gradient), indicating that no protein scission occurred as the result of acid treatment of the maleyl-protein (data not shown).

It has been proposed by Goldstein and co-workers (1, 3, 12) that a cluster of negative charge may constitute a portion of the recognition site(s) required for binding of ligand by the scavenger receptor of macrophages. On this basis, it has been considered that the maleyllysine derivatives of modified albumin may directly form the anionic site(s) necessary for receptor binding. Given the efficient demaleylation of the derivatized albumin achieved in this study (Table 1), the opportunity existed to examine the role of negative charge provided by maleylation with respect to ligand–receptor interaction.

The receptor-mediated uptake and hydrolysis of ¹²⁵I-labeled maleyl-albumin by human monocyte macrophages at 37°C (data not shown) show the same concentration dependence previously described in murine peritoneal macrophages (27). Fig. 1 presents experiments in which the human cells were incubated with ¹²⁵I-labeled maleyl-albumin in the presence of increasing concentrations of potential competitors of the ligand–receptor interaction. Nonradioactive ma-

FIG. 1. Competitive inhibition of the degradation of ¹²⁵I-labeled maleyl-albumin (maleyl-BPA) by the demaleylated form of maleyl-albumin. Normal human monocytes were cultured in 30% autologous serum in 0.5 ml of medium B for 7 days and were prepared for studies at 37°C as described. Each well received 0.5 ml of medium D containing 145 pmol of ¹²⁵I-labeled maleyl-albumin per ml (26,299 cpm/pmol) and the indicated concentrations of nonradioactive maleyl-albumin (○), the demaleylated form of maleyl-albumin (▲), or native albumin (Δ). After incubation for 4 hr at 37°C, the medium was removed and the content of ¹²⁵I-labeled acid-soluble material was determined. The 100% value for the rate of degradation in the absence of competing molecules was 5.5 pmol of ¹²⁵I-labeled maleyl-albumin per 4 hr per mg of cell protein. Values shown are means of triplicate determinations.

leil-albumin effectively suppressed >70% of the hydrolysis of ¹²⁵I-labeled maleyl-albumin, whereas native albumin failed to compete. Demaleylation of the modified albumin resulted in a protein that suppressed >80% of the degradation of ¹²⁵I-labeled maleyl-albumin. However, as compared to maleyl-albumin, a 15-fold higher concentration of the demaleyl-protein was required to produce inhibition of 50% of the degradation of ¹²⁵I-labeled maleyl-albumin.

¹²⁵I-labeled demaleyl-albumin (145 pmol/ml) was hydrolyzed at a rate (4.9 pmol per 4 hr per mg of cell protein) similar to that of ¹²⁵I-labeled maleyl-albumin. The degradation of the ¹²⁵I-labeled demaleyl-protein was reduced >88% by a 5-fold molar excess of nonradioactive maleyl-albumin.

We have previously demonstrated that human LDL in which >16% of the lysines have been modified by malondialdehyde is selectively recognized and internalized by the scavenger receptor of human monocyte macrophages (13, 14). As shown in Fig. 2, increasing concentrations of maleyl-albumin suppressed >92% of the hydrolysis of ¹²⁵I-labeled malondialdehyde LDL. Maleyl-albumin competed on a mol-for-mol basis as effectively as nonradioactive malondialdehyde LDL in preventing the degradation of ¹²⁵I-labeled malondialdehyde LDL. Maleyl human albumin was identical to maleyl bovine albumin as an effective competitor (data not shown). These results confirmed that maleyl-albumin from both bovine and human sources competes with modified LDL for uptake mediated by the scavenger receptor (3).

The ability of increasing concentrations of the demaleyl-protein to compete with the hydrolysis of ¹²⁵I-labeled malondialdehyde LDL was also determined (Fig. 2). The demaleyl-protein readily suppressed 75% of the rate of degradation of the modified LDL. As compared to maleyl-albumin, a 7-fold higher concentration of the demaleyl-protein was required to inhibit 50% of the hydrolysis of ¹²⁵I-labeled malondialdehyde LDL. The increased concentrations of the demaleyl-protein necessary to produce suppression of 50% of the degradation of both ¹²⁵I-labeled maleyl-albumin (Fig. 1) and ¹²⁵I-labeled malondialdehyde LDL (Fig. 2) suggested that the demaleyl-protein bound to the scavenger receptor with a lower affinity than the maleyl-albumin.

Table 1. Characterization of bovine plasma albumin, maleyl-albumin, and the demaleyl-protein

Parameter	Bovine plasma albumin	Maleyl-albumin	Demaleyl-albumin
Relative mobility*	1.0	1.7	1.0
NH ₂ groups/protein†			
TNBS	60.4 ± 0.4	4.2 ± 0.2	59.5 ± 0.5
[³ H]DNFB	57.3 ± 1.0	4.0 ± 0.2	57.9 ± 1.0

*Anodic mobility in agarose electrophoresis at pH 8.4 of the radioiodinated samples was determined relative to that of bovine plasma albumin, as detected by both autoradiography and Coomassie blue staining of the protein.

†A value of 60 mol of amino groups provided by lysine and the single amino terminus per mol of bovine plasma albumin has been determined by amino acid analysis and primary sequence (24). The molar ratio of amino groups was determined by colorimetric assay with trinitrobenzenesulfonic acid (TNBS) or by reaction with 1-fluoro-2,4-dinitro[3,5-³H]benzene ([³H]DNFB). Values given are mean ± 1 SD of triplicate determinations.

FIG. 2. Inhibition of the degradation of ^{125}I -labeled malondialdehyde LDL (MDA-LDL) by potential competitors derived from bovine plasma albumin. Normal human monocytes were cultured in 30% autologous serum in 0.5 ml of medium B for 7 days and were prepared for studies at 37°C as described. Each well received 0.5 ml of medium D containing 10 pmol of ^{125}I -labeled malondialdehyde LDL per ml (117,500 cpm/pmol) and the indicated concentration of nonradioactive malondialdehyde LDL (●), maleyl-albumin (○), the demaleylated form of maleyl-albumin (▲), the guanidine hydrochloride-treated and renatured demaleyl-protein (■), or native albumin (△). After incubation for 4 hr at 37°C , the medium was removed and the content of ^{125}I -labeled acid-soluble material was determined. The 100% value for the rate of degradation in the absence of competing molecules was 1.48 pmol of ^{125}I -labeled malondialdehyde LDL per 4 hr per mg of cell protein. Values shown are means of triplicate determinations.

Several explanations could account for the ability of the demaleyl-protein to compete with these ligands for interaction with the scavenger receptor. It could be argued that, although regeneration of the free amino groups by acid treatment of the maleyl-albumin had been efficient (Table 1), a small remaining proportion of maleyllysine could be sufficient to promote ligand-receptor interaction. A second and more likely explanation is based on the versatility with which bovine plasma albumin can adopt different conformational structures—e.g., the classic N-F transition that occurs at pH values <5 (reviewed in ref. 28) or the expansion of the several globular disulfide-bonded domains of albumin that occurs after modification of the lysines by succinic anhydride (29), the chemically reduced form of maleic anhydride. It could be argued that a conformational isomer of albumin was produced by maleylation and that the receptor recognition domains of this conformational isomer were retained after demaleylation and rapid resolubilization of the protein. It might be expected then that the structure of the conformational isomer of the demaleyl-protein could be disrupted by the addition of guanidine hydrochloride (30) and that the receptor-inactive conformation of native albumin could be regenerated after renaturation.

Fig. 2 shows experiments in which human monocyte macrophages were incubated with ^{125}I -labeled malondialdehyde LDL in the presence of increasing concentrations of the demaleyl-protein renatured after treatment with guanidine hydrochloride. The guanidine hydrochloride-treated and renatured protein failed to compete with the hydrolysis of the ^{125}I -labeled malondialdehyde LDL. These results demonstrated that the ability of the demaleyl-protein to interact with the scavenger receptor was dependent on the conformation of the albumin molecule.

Maleyl-albumin incubated with 6 M guanidine hydrochloride at pH 7.4 for 96 hr at 37°C and subsequently renatured competed with the hydrolysis of ^{125}I -labeled malondialdehyde LDL essentially the same as the untreated maleyl-albumin (data not shown). Neither native albumin (Fig. 2) nor

albumin incubated at pH 3.5 for 96 hr at 37°C (data not shown) was effective as an inhibitor of the degradation of ^{125}I -labeled malondialdehyde LDL.

DISCUSSION

The new negative charge provided by interaction of maleic anhydride with the ϵ -amino groups of lysyl residues of albumin has previously been considered to constitute a portion of the recognition site(s) required for the interaction of maleyl-albumin with the scavenger receptor of macrophages (1, 3, 12). Our data clearly demonstrate that both maleyl-albumin and the demaleylated protein suppress the degradation of ^{125}I -labeled malondialdehyde LDL by this receptor in human monocyte macrophages (Fig. 2) as well as the hydrolysis of ^{125}I -labeled maleyl-albumin (Fig. 1). Thus, the new negative charge provided by maleylation itself does not appear essential for ligand-receptor association.

We propose that domain(s) recognized by the scavenger receptor are formed by the primary sequence of albumin as a consequence of conformational changes induced by maleylation. The addition of negative charge to the lysyl residues of albumin is but a mechanism for inducing this conformational change. Once achieved, the hydrophobic and/or electrostatic forces maintaining the new secondary and tertiary structures apparently are sufficient that the altered conformation of the protein persists after removal of the maleyl groups. Disruption of the conformational isomer can be achieved by addition of the chaotropic reagent guanidine hydrochloride, resulting in conversion of the receptor-active to a receptor-inactive protein (Fig. 2).

Goldstein and Brown and colleagues (1, 3, 12) have proposed that a specific cluster of negatively charged groups provided by the ligand is essential for interaction with the scavenger receptor. Our studies indicate that such a cluster may be provided by the amino acids of bovine plasma albumin. Support for this proposal is derived from earlier studies conducted by Goldstein *et al.* (11). These investigators demonstrated that coacervates of bovine plasma albumin and cholesteryl ester formed by sonication were recognized in part by the scavenger receptor of murine peritoneal macrophages. Sonication of albumin in the presence of cholesteryl esters may result in exposure and stabilization of the recognition domain(s) formed by the primary sequence of bovine plasma albumin.

We have also recently investigated the interaction of LDL modified by several lysine-specific reagents with the scavenger receptor, and we have proposed that the recognition site(s) of modified LDL promoting receptor binding are formed by the primary sequence of the apoB polypeptides of the lipoprotein complex (13). These data, together with the current studies, suggest that the recognition of protein-containing ligands by the scavenger receptor of macrophages may be dependent on a specific configuration of amino acid residues. Such residues could be present in a continuous stretch of primary sequence to generate a sequence-dependent site, or they could be spatially clustered to produce a conformation-dependent domain.

Kaiser and Kezdy (31) have recently addressed the relationship of protein structure to biological activity. These investigators have designed and constructed several synthetic peptides as models for naturally occurring surface-active proteins such as the apoA1 polypeptide of human high density lipoprotein, bee melittin, and human β -endorphin. For each of these proteins, they demonstrated that synthetic proteins that lacked homology in the primary sequence with the parent protein could provide the steric configuration of functional groups necessary to equal or excel the biological activity of the naturally occurring protein. It is our current view that the recognition domain(s) provided by the primary se-

quence of albumin and of the apoB polypeptides of LDL may likewise be similar in terms of the steric display of functional groups necessary for interaction with the scavenger receptor. Consequently, it would not be essential for the amino acids in the recognition domain(s) of these two different proteins to be identical in order to achieve the steric configuration of hydrophilic and hydrophobic groups necessary for binding of these ligands by the scavenger receptor.

We thank Christopher Olch, Ronald Rasmussen, Joan Burns, and Erin Burnham for expert technical assistance, and Molly Williams and Therese Sonnenfeld for the preparation of this manuscript. This work was supported in part by U.S. Public Health Service Grants HL 30568 and RR 865, a grant from the American Heart Association, Greater Los Angeles Affiliate (649P5), the Laubisch Fund, and the M. K. Grey Fund.

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