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Individual Variation of Scavenger Receptor Expression in Human Macrophages with Oxidized Low-Density Lipoprotein Is Associated with a Differential Inflammatory Response

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Atherosclerosis is an inflammatory disease in which oxidized low-density lipoprotein (oxLDL) plays important roles. Scavenger receptors (SR) CD36, SR-A, and LOX-1 uptake over 90% of the oxLDL leading to foam cell formation and secretion of inflammatory cytokines. To investigate whether the interindividual differences in macrophage SR gene expression could determine the inflammatory variability in response to oxLDL, we quantified the gene and protein expression of SR and inflammatory molecules from macrophages isolated from 18 volunteer subjects and incubated with oxLDL for 1, 3, 6, and 18 h. The individual gene expression profile of the studied SR at 1 h of incubation was highly variable, showing a wide fold-change range: CD36: −3.57–4.22, SR-A: −5.0–4.43, and LOX-1: −1.56–75.32. We identified subjects as high and low responders depending on whether their SR gene expression was above or below the median, showing a different inflammatory response pattern. CD36 and LOX-1 gene expression correlated positively with IL-1β; SR-A correlated negatively with IL-8 and positively with PPARγ and NF-κBIA. These results were confirmed in the same subjects 3 mo after the first sampling. Furthermore, a negative correlation existed between CD36 and SR-A at protein level after 18 h of oxLDL incubation (r = −0.926, p = 0.024). These data would suggest that the type of SR could determine the macrophage activation: more proinflammatory when associated to CD36 and LOX-1 than when associated with SR-A. The Journal of Immunology, 2007, 179: 3242–3248.

Macrophage pattern recognition receptors include: TLRs, which behave as signaling receptors triggering the expression of proinflammatory cytokines, and scavenger receptors (SR), endocytic cell surface receptors that bind and internalize pathogen-associated molecular patterns, such as oxLDL, bacterial components, or apoptotic cells. oxLDL is rapidly recognized and internalized by macrophage SR, which in contrast with the LDL receptor, do not down-regulate in response to an increased cellular cholesterol content, leading to foam-cell formation, the first hallmark of atherosclerotic plaque development (4).

SR are a group of transmembrane proteins with large sequence variation, which are classified in eight classes (A–H). However, one class A SR (SR-A), one class B SR (CD36), and the class E SR (lectin-like oxLDL-receptor-1, LOX-1) account for over 90% of oxLDL uptake (5, 6). Circulating monocytes express SR at very low levels, but they are highly up-regulated by the oxLDL located in the subendothelial space, leading to macrophage activation, foam-cell formation and secretion of proinflammatory cytokines and activation of adaptive immunity. However, there is a great human interindividual variation in the vascular (7) and systemic inflammation (8) associated with oxLDL. Moreover, a large variation in human foam-cell formation (9), intracellular cholesterol content, and cytokine gene expression (10) in individuals exists when induced by oxLDL “in vitro,” suggesting that this differential response is due to individual characteristics. Thus, the magnitude and type of macrophage responses to oxLDL could determine part of the observed interindividual inflammatory variability associated with hypercholesterolemia and oxLDL, and could be helpful to improve individual cardiovascular risk, which is closely related with the levels of systemic inflammation (11). We hypothesized that interindividual variability of macrophage SR gene expression in response to oxLDL and the subsequent...
induced intracellular signals could determine the observed inflammatory variability in response to oxLDL. Our work supports this concept and indicates that SR expression in vitro varies among individuals, is highly reproducible, and is associated with a differential inflammatory response.

Materials and Methods

Study subjects

Eighteen individuals, aged 20–55 years, 11 male and 7 female volunteers were recruited. Five of these (3 male and 2 female) were smokers and 4 (1 male and 3 female) had a positive family history of coronary artery disease. Exclusion criteria included: acute infectious disease in the previous week, active chronic inflammatory disease, and anti-inflammatory drug consumption, including oral steroids and nonsteroidal anti-inflammatory drug in the previous week. All subjects gave written informed consent and the ethical committee of our institution approved the study.

Isolation and oxidation of LDL

LDL was isolated from one homozygous familial hypercholesterolemia patient who is regularly treated with dextran sulfate LDL apheresis. The apolipoprotein B-containing lipoproteins retained by dextran sulfate were eluted from the column with 0.702 M NaCl, subjected to a single vertical spin density gradient ultracentrifugation in a VTI 50 rotor (Beckman Coulter), and dialyzed at 4°C for 24 h against EDTA-free PBS. The protein content of LDL was determined by the Bradford method. Oxidation of LDL was performed by incubation at 37°C with 8 μM CuCl₂ for 24 h. The reaction was stopped by adding 1 mM EDTA and storing at 4°C. Oxidation of LDL was confirmed by Sudan Black LDL staining and agarose gel electrophoresis and conjugated diene formation assessment by spectrophotometry at 234 nm.

Isolation and culture of human monocyte-derived macrophages

Human mononuclear cells from the selected subjects were isolated by density gradient centrifugation on Ficoll-Paque separating solution (Amer sham Biosciences) from 40 ml of peripheral blood with 10 U/ml lithium heparin, as described previously (10). Briefly, mononuclear cells were washed twice with RPMI 1640, re-suspended in complete RPMI 1640 (with GlutaMAX I) containing 1% heat-inactivated autologous serum, and plated at a density of 1.8 × 10⁶ cells/ml distributed among five 25-cm² culture flasks for each subject. Cell viability was >95% in all experiments, as assessed by trypan blue. After 2 h at 37°C in 5% CO₂, adherent monocytes were incubated for 24 h with complete RPMI 1640 with 10% heat-inactivated autologous serum. After 24 h, monocytes were incubated in macrophage serum-free medium (Invitrogen Life Technologies). Monocyte purity was assessed by flow cytometric analysis of CD14 using an Epics XL cytometer (Beckman Coulter) and was routinely found to be >90%. On the ninth day, 50 µg/ml oxLDL was added to four of five flasks for 1, 3, 6, and 18 h of incubation. The remaining culture was incubated with PBS instead of oxLDL, and was used as a control.

RNA isolation

After 10 days of culture, total RNA was isolated from macrophages using an RNeasy kit (Qiagen), following the manufacturer’s instructions. Total RNA was quantified by spectrophotometry at 260 nm and its purity was assessed by the ratio A₂₆₀nm/A₂₈₀nm. RNA integrity was verified by visualization of ethidium bromide-stained 1% agarose gels.

Relative quantitative real-time RT-PCR

Two micrograms of each total RNA sample were treated with 1 U of DNase I (Ambion) and it was reverse transcribed with 200 U of Super-Script III RNase H⁻ reverse transcriptase (Invitrogen Life Technologies) using 150 ng of random hexamer primers (Invitrogen Life Technologies) to prime cDNA synthesis. Real-time RT-PCR was conducted using the ABI Prism 7000 HT Sequence Detection System (Applied Biosystems), TaqMan Universal PCR Master Mix, unlabeled PCR primers, and TaqMan MGB probes (FAM dye-labeled) from Assay-on-Demand (IL-1β, Hs00174097_m1; IL-6, Hs00232935_m1; TNF-α, Hs00266577_m1; and GAPDH, Hs00265627_m1).
FIGURE 3. Inflammatory molecule gene expression after incubation with oxLDL. Mean gene expression data ± SD at 1, 3, 6, and 18 h of oxLDL incubation for PPARγ, IL-1β, CXCL3, TPS, NF-κBIA, TNF-α, and IL-8 genes are shown.

CXCL3, Hs00171061_m1; PPARγ, Hs00234592_m1; IL-8, Hs00174103_m1; TNF-α, Hs00174128_m1; NF-κBIA, Hs00153283_m1; CD36, Hs00169627_m1; LOX-1, Hs00254028_m1; SR-A, Hs00234007_m1; 18srRNA, Hs99999901_s1; RPLP0, Hs99999902_m1; and HPRT1, Hs99999909_m1 and Assay-on-Design (tryptase α2, design based on sequence AF206665 (position 320–653 bp)) gene expression products, according to the manufacturer’s recommendations (Applied Biosystems). All samples were run in triplicate.

Sequence detector software (SDS; Applied Biosystems) was used for data analysis. A threshold cycle (Ct) value was determined from each amplification plot. The relative expression ratios or fold changes of target genes were calculated using the comparative ΔCt method. Expression of target genes was normalized by the endogenous reference genes 18srRNA, RPLP0, and HPRT1, using the geNorm method (12, 13).

Cytokine production
Quantification of IL-8, IL-1β, and TNF-α was conducted in cell-free supernatants from control and 18 h of incubation with oxLDL macrophage cultures, by quantitative ELISA (R&D Systems), according to the manufacturer’s instructions. All measurements were conducted in duplicate and all samples were analyzed in the same microplate to minimize run-to-run variability.

FACS analysis
For these analyses, macrophages were divided in two 75-cm² culture flasks for 18 h of incubation. The remaining flask was incubated with PBS instead of oxLDL and was used as a control. After incubation, macrophages were scraped with a rubber policeman, centrifuged at 1000 rpm for 5 min, and resuspended in 1.1 ml of PBS/0.2% BSA. Macrophages were scrapes with a rubber policeman, centrifuged at 1000 rpm for 5 min, and resuspended in 1.1 ml of PBS/0.2% BSA. Inflammatory molecule gene expression was performed with the Pearson’s test of log transformed data. Correlation between SR and inflammatory molecule gene expression was performed with the Pearson’s test of log transformed data. Correlation between CD36 and SR-A proteins was performed with the Pearson’s test. A value of p < 0.05 was considered statistically significant for all analyses.

Results
SR gene expression
The gene expression pattern of analyzed SRs in response to oxLDL was highly variable throughout the studied incubation times with oxLDL. The highest expression of CD36, SR-A, and LOX-1 genes occurred at short incubation times with oxLDL, 1 h for CD36 and SR-A, and 3 h for LOX-1. Mean gene expression data (fold-change) ± SD for SR genes after 1 h of incubation with oxLDL were as follows: CD36: -1.01 ± 0.06; SR-A: 1.03 ± 0.05; LOX-1: 5.44 ± 0.095.

| Table I. Correlation of SR gene expression at 1 h of oxLDL incubation with inflammation molecule gene expression at indicated incubation times |
|-----------------|--------|----------------|----------------|----------------|----------------|
|                  | PPARγ | IL-8 | IL-1β | CXCL3 | TPS | NF-κBIA | TNF-α |
| 1 h              |       |      |       |       |     |         |       |
| CD36 (1 h)       | 0.308 | 0.259 | 0.667 | 0.480 | 0.028 | 0.399 | 0.577 |
| SR-A (1 h)       | 0.505 | 0.140 | 0.527 | 0.507 | 0.277 | 0.706 | 0.579 |
| LOX-1 (1 h)      | 0.288 | 0.245 | 0.458 | 0.487 | 0.119 | 0.373 | 0.019 |
| 6 h              |       |      |       |       |     |         |       |
| CD36 (1 h)       | -0.477| -0.440| -0.179| -0.300| -0.496| 0.005 | 0.236 |
| SR-A (1 h)       | -0.366| -0.541| -0.236| -0.083| -0.279| 0.238 | 0.110 |
| LOX-1 (1 h)      | -0.436| -0.308| -0.225| -0.143| -0.375| -0.176| -0.382 |

*Pearson’s coefficients are shown.
 Value of p < 0.001.
 Value of p < 0.05.
The individual gene expression profile of the analyzed SRs, CD36, SR-A, and LOX-1, at 1 h of incubation was highly variable, as shown in Fig. 1. The expression of the CD36 gene ranged from −3.57 to 4.22 times, the SR-A gene varied from −5.0 to 4.43 times, and the LOX-1 gene ranged from −1.56 to 72.32.

Based on these data, we divided the studied subjects in two groups: high and low responders, depending on whether their SR gene expression was above or below the median. As Fig. 2 shows, differences between both groups are maintained at every time of incubation with oxLDL, being statistically significant for CD36 and SR-A at 1 h and for LOX-1 at every time of incubation with oxLDL.

Inflammatory molecule gene expression

We analyzed the gene expression pattern of several inflammatory molecules in response to different incubation times with oxLDL. As shown in Fig. 3, IL-1β, CXCL3, tryptase (TPS), and TNF-α reached their maximum gene expression after short incubation times with oxLDL (1 h), diminishing progressively over time. PPARγ and NF-κBIA gene expression diminished at short and long incubation times. However, IL-8 gene expression increased progressively over time, reaching the maximum at 18 h of incubation with oxLDL.

We also found a wide interindividual variability in the expression of these inflammatory genes: the gene expression (fold-change) at 1 h of incubation with oxLDL of PPARγ ranged from −4.76 to 3.72, IL-8 at 18 h, from 6.48 to 800.63, IL-1β at 1 h, from 1.00 to 32.13, CXCL3 at 1 h, from 2.05 to 70.11, TPS at 1 h, from −11.11 to 29.17 times, and TNF-α at 1 h, from −50.0 to 4.05 times.

The mean expression values (fold-change) ± SD at short incubation times with oxLDL, 1 h, were as follows: PPARγ, 0.84 ± 0.06; IL-1β, 5.93 ± 0.31; TNF-α, 0.97 ± 0.08; IL-8, 5.93 ± 0.47; CXCL3, 8.89 ± 0.56; and TPS, 1.26 ± 0.13. The mean expression values (fold-change) ± SD at long incubation times, 6 h, were as follows: PPARγ, −1.78 ± 0.03; IL-1β, −2.38 ± 0.02; TNF-α, −5.55 ± 0.01; IL-8, 7.27 ± 0.65; CXCL3, 6.57 ± 0.67; and TPS, −1.66 ± 0.04.

Correlation of SR and inflammatory molecule gene expression

In Table I, we show the correlation of SR gene expression at 1 h and inflammatory molecule gene expression at 1 h (short) and 6 h (long) incubation times with oxLDL. CD36 gene expression at 1 h correlated positively with IL-1β (R = 0.667, p < 0.01) and TNF-α (R = 0.577, p < 0.05) gene expressions at short incubation times with oxLDL, and negatively with TPS at long incubation times (R = −0.496, p < 0.05). SR-A gene expression correlated positively at short incubation times with the PPARγ gene (R = 0.595, p < 0.05), the IL-1β gene (R = 0.527, p < 0.05), the CXCL3 gene (R = 0.507, p < 0.05), the NF-κBIA gene (R = 0.706, p < 0.01), and the TNF-α gene (R = 0.579, p < 0.05). At long incubation times, SR-A was negatively correlated with the IL-8 gene (R = −0.541, p < 0.05). LOX-1 gene expression correlated positively with IL-1β and CXCL3 genes (R = 0.458, R = 0.487), although it was not statistically significant.

To better characterize the relationship of SR gene expression with inflammatory genes, we divided the studied subjects into two groups: high (n = 9) and low responders (n = 9), depending on whether the level of their SR gene expression was above or below the median; we analyzed the gene expression of inflammatory molecules in each group. We did not find any differences between these groups in terms of sex, age, smoking, or another illnesses like a positive family history for cardiovascular artery disease. Of the nine high-responder subjects for CD36, six were in the high-responder group for SR-A and seven were in the high-responder group for LOX-1. Of the nine low-responder subjects for CD36, five were in the low-responder group for SR-A and six were in the same group for LOX-1. Therefore, we consider that the subjects were homogeneously divided in the different groups. As Fig. 4 shows, positive correlation of CD36 (1 h) with IL-1β (1 h), as well as LOX-1 (1 h) with IL-1β (1 h), is demonstrated. SR-A (1 h) was positively correlated with PPARγ (1 h) and NF-κBIA (1 h) and negatively with IL-8 (6 h).

Table II. Correlation of gene expression results of analyzed genes between first sample and 3 mo later

| Genes       | Correlation (r) | p <  
|-------------|-----------------|------
| CD36        | 0.739           | 0.001|
| SR-A        | 0.806           | 0.001|
| PPARγ       | 0.564           | 0.05 |
| CXCL3       | 0.589           | 0.05 |
| NF-κBIA     | 0.575           | 0.05 |
| IL-8        | 0.792           | 0.05 |

r, Pearson’s correlation coefficient between first and second sampling.

FIGURE 4. Inflammatory molecule gene expression in SR high- and low-expressing subjects; CD36 (A), SR-A (B), and LOX-1 (C). Mean gene expression data ± SD for analyzed genes are shown. □, Gene expression above the median (high responders). ■, Gene expression below the median (low responders). *, p < 0.05 for Mann-Whitney U test.
Cytokine production

To know the cytokine production of macrophage cultures of both control and 18 h incubation with oxLDL, we measured the IL-8, IL-1β, and TNF-α concentration in cell-free supernatants by ELISA. In the control unstimulated macrophage cultures, no IL-1β nor TNF-α was detected. However, IL-8 production was observed in these cultures, although no significant differences between groups of low and high responders according their level of SR gene expression was observed. In macrophage cultures incubated during 18 h with oxLDL, neither IL-1β nor TNF-α levels were detectable, but IL-8 concentration was significantly increased after 18 h of oxLDL incubation. Moreover, a positive correlation between IL-8 gene expression at 1 h of incubation with oxLDL and IL-8 concentration in culture medium of macrophages incubated during 18 h with oxLDL was observed ($R = 0.611, p < 0.05$).

In relation with SR gene expression, a positive correlation between CD36 gene expression at 1 h of incubation with oxLDL and the IL-8 concentration in supernatant after 18 h of oxLDL incubation was observed ($R = 0.386$), although it did not reach statistical significance. Also, a statistical significant positive correlation between LOX-1 gene expression at 1 h of incubation with oxLDL and IL-8 produced after 18 h of oxLDL incubation was identified ($R = 0.651, p < 0.05$). However, no correlation was found between SR-A gene expression and the production of IL-8 by macrophage cultures incubated with oxLDL.

Reproducibility of the gene expression patterns

To verify the reproducibility and consistency of our results, we analyzed the gene expression pattern 3 mo after the first sampling. The analyzed genes were CD36 and SR-A and the following inflammatory genes: PPARγ, CXCL3, IL-8, and NF-κBIA. Five subjects were chosen, belonging to both groups of high and low responders of CD36 and SR-A gene expression. In Table II, correlation of gene expression results of analyzed genes after 3 mo are shown. These correlations were very high for all analyzed genes and all of them reached statistical significance.

Scavenger receptor protein quantification

Changes in SR protein from high-responder ($n = 4$) and low-responder ($n = 2$) subjects after 18 h of incubation with oxLDL was further analyzed by FACS analysis. Results for an individual subject are shown in Fig. 5. This subject was a high responder for the CD36 gene and a low responder for the SR-A gene. As Fig. 5A shows, the MFI for CD36 SR was higher after 18 h of incubation with oxLDL than the control situation (25.18 and 16.35 RFU, respectively). Fig. 5B shows the MFI results for SR-A in the same subject, being lower after 18 h of incubation with oxLDL than the control situation (19.18 and 30.68 RFU, respectively). Therefore, the SR protein results are in agreement with the SR gene expression results in the analyzed subjects.

Fig. 6 shows gene expression and protein content of high- and low-responder groups for the three SR analyzed. The high-responder group for the CD36 gene showed a higher content of CD36 surface protein (ratio 2.51 ± 1.35) than the low-responder...
group (ratio 0.68 ± 0.02) (Fig. 6A), and the same occurred with SR-A (ratio 1.45 ± 0.34 vs 0.60 ± 0.01) (Fig. 6B). However, an elevated rate of LOX-1 gene expression observed in the high-responder group (ratio 46.6 ± 0.85) was not correlated with LOX-1 protein (ratio 0.96 ± 0.43) (Fig. 6C). As with gene expression level, CD36 and SR-A followed a different protein expression pattern (Fig. 6D). A negative correlation existed between both SRs at the protein level ($r = -0.926$, $p = 0.024$), and, therefore, individuals with a high level of surface protein CD36 had a low level of surface protein SR-A and vice versa, suggesting a different response to oxLDL depending on the type of SR activation.

Discussion

In this work, we demonstrate that macrophage inflammatory gene expression is highly variable among individuals when macrophages are exposed to oxLDL and that this individual response is highly reproducible. No previous work had studied the human interindividual variation in the SR and inflammatory response to oxLDL.

We think that our data are important for several reasons. First, our data suggest that at least part of the variability of the inflammatory state induced by LDL cholesterol could be associated with the macrophage individual response to oxLDL. No differences in cytokine production were observed at basal situation, suggesting that macrophages from different subjects were not differently activated before oxLDL incubation. It has been previously demonstrated that there are large interindividual variations in foam cell formation with modified LDL, but little variation over a 10 mo period in each individual subject (9). Large interindividual variations in neutral lipid content in macrophages after oxLDL loading in vitro was also demonstrated by our group in subjects with familial hypercholesterolemia (10).

Second, our data indicate that part of the individual variation could be related to differential SR expression in response to oxLDL. It is well-established that CD36, SR-A, and LOX-1 are the main SR involved in the macrophage uptake of oxLDL in humans. However, no previous studies had faced the SR variation among individuals against the same oxLDL. Our data indicate that most subjects increase the expression of SR after exposure to oxLDL, but it can vary among them as much as 70 times after 1 or 3 h of exposure, and actually, some subject showed a decrease in some SR. SR gene expression is well-correlated with receptor activity in human macrophages (14, 15) and, therefore, this differential expression probably indicate differences in oxLDL uptake.

Third, our study indicates that the macrophage inflammatory response is partly dependent of the type of SR activation. There was a highly significant correlation between CD36 and LOX-1 gene expression and expression of proinflammatory genes, such as IL-1$\beta$ or IL-8 (Table 1), and with IL-8 production at the protein level. This type of response is probably mediated throughout a MAPK cascade that finally activates NF-κB (16) and later, by involving Th1 cells, tends to promote and amplify the same kind of inflammatory responses induced by macrophages (17). Because Th1 adaptive responses and Th1 cytokines clearly promote atherogenesis (18), these inflammatory responses could have an important role in the origin of atherosclerosis.

By contrast, SR-A gene expression was associated with lower proinflammatory cytokine gene expression and much higher PPARγ gene expression, a well-established anti-inflammatory product. The precise mechanism is poorly understood, but it has been reported that the anti-inflammatory action of PPARγ agonists is made through antagonizing the activities of AP-1, NF-κB, and Stat 1 transcription factors (19).

The major function of SR-A gene products is to control ligand uptake rather than intracellular signaling. Recent data indicate that SR-A mediates uptake of oxLDL for presentation to T cells, participating in the immune recognition of oxidized protein Ags (20). Macrophage SR-A could be responsible, after uptake and processing of modified LDL, for Ag presentation to specific Th2 cells. Mechanism of oxLDL Ag-derived presentation to T cells is not clearly established, but several lines of evidence indicate that this process could be related to the evolution and complication of atherosclerosis lesions. For example, it is well-established in animal models that a Th2 type of response associated ameliorates the progression of atherosclerosis (3).

Therefore, a different balance between CD36, SR-A, and LOX-1 uptake of oxLDL could have important consequences with respect to the evolution of atherosclerosis plaques. This is also in agreement with the fact that CD36 expression is hardly observed in the human arterial wall without atherosclerosis, in contrast to SR-A, and that the distribution of CD36 and SR-A is different from each other in lipid-laden macrophages. Within plaques, macrophages tend to more abundantly express CD36 protein (21). Our results are in agreement with this different regulation between these two SRs, as we have demonstrated that CD36 and SR-A showed an opposite profile of response to oxLDL at the gene level as well as at the protein level. However, the LOX-1 gene had a higher rate of expression than LOX-1 protein, which could be due to posttranslational modifications of LOX-1 (22).

Prospective studies have demonstrated that inflammatory markers, especially C-reactive protein (CRP), independently predict the risk of first or recurrent cardiovascular events at all levels of LDL cholesterol (23, 24). However, there is no correlation between baseline LDL cholesterol and CRP concentration, neither between LDL cholesterol and CRP reductions during statin treatments, which vary greatly from patient to patient (11). It has been speculated that reduction of inflammatory markers associated with statins is due to their anti-inflammatory effects (11, 25), but it could be simply related to differences in the inflammatory stimulus induced by LDL. In fact, CRP reduction can be obtained with other LDL cholesterol-lowering agents different from statins (26, 27). All these facts clearly show not only that inflammation plays a major role in the progression and complications of atherosclerosis mediated by LDL cholesterol, but also that the relationship between inflammation and LDL cholesterol is complex and highly variable among individuals.

In conclusion, when studied in vitro, SR gene expression is highly variable: it varies greatly from subject to subject when macrophages are exposed to oxLDL. A proinflammatory type of response is associated in CD36 and LOX-1 high responders. By contrast, PPARγ expression was highly correlated with SR-A expression. All these data would suggest that the type of SR, which would mediate in the uptake of oxLDL, could be associated with the immune response, and could lead to the development of more comprehensive predictors of the relationship among LDL, inflammation, and coronary heart disease.

Disclosures

The authors have no financial conflict of interest.

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