Reduced In Vivo Aortic Uptake of Radiolabeled Oxidation-Specific Antibodies Reflects Changes in Plaque Composition Consistent With Plaque Stabilization

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Objective—Labeled oxidation-specific antibodies (Ox-AB) detect, quantify, and noninvasively image lipid-rich atherosclerotic lesions. However, it is unknown whether Ox-AB detect plaque stabilization.

Methods and Results—The aortic uptake of intravenously injected 125I-MDA2 (Ox-AB to malondialdehyde [MDA]–low-density lipoprotein [LDL]) was quantitated in: (1) LDL receptor−/− mice with established atherosclerosis continued on Western diet (Progression) or switched to chow (Regression) or chow + vitamins E and C (Regression-VIT) for 6 months; and (2) Watanabe rabbits (3- to 57-month-old) with naturally evolved atherosclerotic lesions. In mice, the Progression group had more extensive atherosclerosis, higher 125I-MDA2 uptake, high concordance of Sudan (lipid)-staining and 125I-MDA2 uptake, and stronger oxidized LDL (OxLDL) and macrophage immunostaining than both Regression groups. In contrast, the Regression groups showed Sudan-positive lesions with focally diminished 125I-MDA2 uptake, which coincided with reduced OxLDL and macrophages but more smooth muscle cells (SMCs) and collagen. In rabbits, areas of increased 125I-MDA2 uptake were associated with high Sudan concordance and strong immunostaining for OxLDL and macrophages. Interestingly, advanced lesions with focally diminished 125I-MDA2 uptake showed stronger immunostaining for SMCs and collagen, particularly at the fibrous cap.

Conclusion—Ox-AB uptake is focally diminished in plaques displaying accepted features of plaque stability. Imaging techniques to detect the presence and depletion of OxLDL may be useful in assessing plaque stabilization. (Arterioscler Thromb Vasc Biol. 2004;24:2307-2312.)

Key Words: oxidation ■ lipoproteins ■ radionuclide ■ imaging ■ antibodies

Human atherosclerotic plaques susceptible to rupture or disruption contain thin, mechanically weak fibrous caps, an abundance of inflammatory cells, and a large quantity of extracellular lipid.1 The mechanisms of plaque rupture are not fully defined, but a key etiologic component is the underlying inflammatory milieu, which is significantly enhanced by oxidized lipids and multiple other triggering mechanisms.2 In vitro studies have demonstrated that oxidized low-density lipoprotein (OxLDL) is proinflammatory and upregulates the synthesis and release of collagen-degrading metalloproteinases from macrophages that amplify the underlying inflammatory state, leading to collagen degradation and plaque disruption.2 Studies in humans and animals have shown that OxLDL and oxidized phospholipids are present in significant amounts within atherosclerotic lesions and may contribute to plaque instability by inducing proinflammatory pathways.3,4 Several invasive and noninvasive techniques are being intensively evaluated for detection of such plaques.5 OxLDL and oxidation-specific epitopes, which are relatively accessible targets, particularly when present in the form of large extracellular deposits in the lipid core,6–8 are rational targets for imaging and may serve as markers of plaque vulnerability.

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We have shown previously that intravenously injected, radiolabeled oxidation-specific antibodies (Ox-AB), such as the murine monoclonal antibody (MAB) MDA2, which detects malondialdehyde (MDA)–lysine epitopes, have a strong and specific predilection for atherosclerotic lesions but not normal arteries.9,10 Aortic uptake of 125I-MDA2 is enhanced in lipid-rich lesions and reduced in lesions of LDL receptor−/− (LDLR−/−) mice on dietary/antioxidant diets.10 99mTc-labeled MDA2 noninvasively images atherosclerotic lesions in live animals.5 However, it is unknown whether plaque uptake of radiolabeled Ox-AB may reflect the changes that occur when plaques become more stable, a property that would potentially enhance the utility of this imaging approach in patients at risk for plaque rupture. The present study therefore assessed the rela-
tionship between the in vivo plaque uptake of $^{125}$I-MDA2 and immunohistologic features of plaque stability.

Materials and Methods

Animal Models

Mice

The experimental protocol used in this study was reported previously.\textsuperscript{10} Starting at 6 to 12 months of age, 43 LDLR/−/− mice were fed 20% milk fat supplemented with 1.25% cholesterol for 6 months. After atherosclerosis was established (25% of the aortic surface area documented in a subgroup of 13 mice), the remaining mice were fed for an additional 6 months the atherogenic diet as above (Progression), normal mouse chow (Regression), or mouse chow supplemented with 1.0% vitamin E and 0.05% vitamin C added to the drinking water (Regression-VIT). One mouse died in the Progression and Regression-VIT groups before the end of the study, and 2 mice in the Regression group had poor tail vein injection and 1 inadequate aorta preparation. The final cholesterol levels in the Progression, Regression, and Regression-VIT groups were 1526±858, 334±56, and 406±149 mg/dL, respectively.

Mice were injected intravenously with 10 μCi $^{125}$I-MDA2, and aortic uptake (percentage injected dose per gram aortic tissue [%ID/g]) was determined at 24 hours by placing the entire aorta in a gamma counter.\textsuperscript{10} Aortas were stained with Sudan IV staining, and computer-assisted determination of atherosclerosis surface area followed established protocols.\textsuperscript{10} After atherosclerosis quantitation, 3 aortas from each group that had lesions representative of the whole group were placed in autoradiography cassettes for 2 weeks to assess $^{125}$I-MDA2 distribution. Aortas used for autoradiography were not used for immunostaining. Cross-sectional atherosclerosis area measurement and comparative immunohistochimistry were performed in 3 mouse aortas (9 lesions per group) from each group with lesions in the arch, thoracic, and abdominal aorta, obtaining a sample from each aortic segment.

Rabbits

Nineteen Watanabe heritable hyperlipidemic (WHHL) rabbits aged 3 to 57 months on normal rabbit chow were studied to assess the “natural history” of atherosclerotic plaques and their relationship to $^{125}$I-MDA2 uptake. Cholesterol levels were not measured in experimental rabbits, but in a contemporaneous group of rabbits (n=24) of the same age and gender distribution, the mean total cholesterol levels were 699±83 mg/dL (range 626 to 964).\textsuperscript{9}

Rabbits were intravenously injected with 100 μCi $^{125}$I-MDA2, and $^{125}$I-MDA2 uptake, Sudan staining, and autoradiography (3- to 5-day exposure at –4°C) were performed as described previously.\textsuperscript{9,10} Aortas were visually inspected for concordance or discordance of plaque distribution (Sudan) and $^{125}$I-MDA2 uptake (corresponding autoradiographs). Those aortas with total concordance of Sudan staining and autoradiography signal were designated as Plaque=Ox-AB, and those with clearly visibly diminished $^{125}$I-MDA2 uptake in areas of Sudan-positive lesions were designated as Plaque≠Ox-AB.

Immunohistochemical analysis to define histological differences in areas that had normal versus reduced $^{125}$I-MDA2 uptake was performed in 4 of 13 rabbits (12 lesions, 1 from each segment of the aorta of each rabbit) in the Plaque=Ox-AB and in 4 of 6 rabbits (15 lesions, 7 concordant and 8 discordant) in the Plaque≠Ox-AB. These studies were approved by the animal subjects committee of the University of California, San Diego.

Immunohistochemistry

Serial 8-μm-thick sections of paraffin-embedded mouse and rabbit aortas were rehydrated. Three oxidation-specific epitopes were detected immunohistochemically: (1) MDA–lysine epitopes were detected with unlabeled murine MAB MDA2A in rabbit aortas and by guinea pig antiserum MAL2\textsuperscript{21} in mouse aortas (1:500 dilution), (2) oxidized phospholipid epitopes were detected with MAB E06\textsuperscript{12} (1:400 dilution), and (3) a unique oxidation-specific epitope common to MDA–lysine and copper-oxidized phospholipids and prevalent in necrotic cores was detected by biotinylated IK17, a human IgG Fab (1:100 dilution).\textsuperscript{7} Apolipoprotein B-100 (apoB-100) was detected by MAB MB–47 (1:500 dilution). Smooth muscle cells (SMCs) were detected by MAB 1A4 (Sigma), recognizing the α-smooth muscle actin isoform (1:20 dilution). Rabbit macrophages were detected with MAB RAM-11 (1:500 dilution) and mouse macrophages with rat IgG\textsubscript{2a} clone BM8 (Acris, Inc.) at 0.5 μg/mL after antigen retrieval by enzymatic digestion with proteinase K. Collagen content was determined by Trichrome staining.

MABs MDA2A, MAL2A, E06, MB–47, and RAM-11 bound to tissue on slides were detected using appropriate secondary antibodies and an avidin-biotin–alkaline phosphatase system (Vector Laboratories). Immunostaining of murine tissues with the MAB E06 was performed using the Vector M.O.M. immunodetection kit (Vector Laboratories). Biotinylated IK17 was detected as described previously.\textsuperscript{7} Slides were counterstained with methyl green or hematoxylin. In the absence of each primary antibody, no specific staining was noted.

Quantitative Immunohistological Analysis in LDLR/−/− Mice

Quantitative immunostaining for oxidation-specific epitopes (MDA–lysine epitopes), SMCs, and macrophages was determined as the percentage of cells (primarily macrophages but also SMCs) stained by MDA2A, 1A4, and clone BM8, respectively, divided by total number of all cells present in an entire lesion, which was identified by the presence of hematoxylin-counterstained nuclei. Quantitation of colagen staining was performed by choosing a same-color threshold for the specific bright blue color in all specimens. Collagen staining was expressed as percent immunopositive area divided by total plaque area. One experienced operator (M.T.), blinded to the treatment regimens, performed all determinations.

Statistical Analysis

Analysis of quantitative parameters in mice was performed with 1-way ANOVA with the post hoc Tukey–Kramer multiple comparison test. Differences between the 2 WHHL rabbit groups (Plaque=Ox-AB and Plaque≠Ox-AB) were assessed by Student t test. Correlation between $^{125}$I-MDA2 uptake and aortic plaque weight was assessed by linear regression analysis. P<0.05 was considered significant.

Results

LDLR/−/− Mouse Regression Study

Aortic Lesion Composition and $^{125}$I-MDA2 Uptake in LDLR/−/− Mice

En face preparations of Sudan-stained aortas and autoradiographs from the Progression group showed near-perfect concordance between plaque and $^{125}$I-MDA2 distribution (Figure 1A), whereas both regression groups showed distinct areas containing Sudan-positive lesions that did not yield autoradiography signal (Figure 1B and 1C, arrowheads), indicating diminished or absent $^{125}$I-MDA2 uptake. Immunohistochemical staining of representative lesions demonstrates intense OxLDL (Figure 2A, pink/purple) and macrophage (Figure 2B, black) staining throughout the lesion in the Progression group. SMCs were infrequent and primarily in the subendothelial area (Figure 2C, pink). Collagen was present in moderate amounts throughout the lesion (Figure 2D, light blue). In contrast, both regression groups (Figure 2G through 2J and 2M through 2P) showed significantly reduced OxLDL and macrophage immunostaining, but enhanced presence of SMCs, particularly at the subendothelial area and the base of the lesion, and collagen accumulation throughout the lesions. Immunostaining with Ox-AB IK17 (pink color) and E06\textsuperscript{13} (brown color) also showed significantly stronger im-
munostaining for different and distinct oxidation-specific epitopes in lesions of the Progression group (Figure 2E and 2F) compared with those in the regression groups (Figure 2K, 2L, 2Q, and 2R).

Quantitative Immunohistochemistry in LDLR−/− Mice

The Progression group had greater cross-sectional lesion area than the Regression and Regression-VIT groups (398±140 μm² versus 129±70 and 61±29; P<0.05; Figure 3A). 125I-MDA2 uptake was significantly greater in the Progression group, even when corrected by the tissue weight (ie, a measure that should correct for differences in lesion sizes [3.6±1.3% ID/g versus 1.7±0.5 and 2.0±1.0; P<0.01; Figure 3B]). Consistent with the findings of immunostaining, quantitative immunohistochemistry indicated that the lesions of the Progression group had a significantly greater relative content of OxLDL (MDA–lysine epitope) compared with the Regression and Regression-VIT groups, respectively (83±6% of all cells stained positive for MDA–lysine versus 22±3% and 17±3%; P<0.01; Figure 3C). Similarly, the Progression group had more macrophage content than both Regression groups (71±5.3% versus 14.7±2.2% and 14.1±2.7%; P<0.001; Figure 3D). In contrast, plaques in the Progression group had significantly reduced percentage of SMCs (25±7% cells staining positive for α-actin versus 55±3% and 48±9%; P<0.05; Figure 3E) and collagen content (50±4% of total plaque area versus 60±4% and 68±4%; P<0.01; Figure 3F). No significant differences were noted between the Regression and Regression-VIT groups.

WHHL Rabbit Study

We examined the concordance of 125I-MDA2 uptake with extent of Sudan staining in 19 WHHL rabbits of varying age (mean age 30.9±16.7, range 3 to 57 months), thus providing an assessment of these parameters over a wide range of naturally progressing lesions. In 13 of 19 rabbits, we observed (visually) almost total concordance of plaque distribution indicated by Sudan staining and 125I-MDA2 uptake detected by autoradiography (Plaque=Ox-AB; Figure 4). In contrast, in 6 of 19 rabbits, there was discordance between Sudan-stained areas and 125I-MDA2 uptake (Plaque≠Ox-AB; Figure 5). In these discordant arteries, only 71% of the Sudan-positive atherosclerotic surface area was reflected by the autoradiography signal (Table I, available online at http://atvb.ahajournals.org), and overall aortic 125I-MDA2 uptake was diminished. The Plaque=Ox-AB group was significantly younger and had less overall atherosclerosis burden, measured by aortic weight and percent atherosclerotic surface area, but interestingly had 58% greater 125I-MDA2 uptake than the Plaque≠Ox-AB group.

A representative aorta from the Plaque≠Ox-AB group is shown in Figure 5. Sections were compared by immunohistochemistry from the right edge (arrow) of the divided aortic arch, where fairly strong autoradiography signal is noted, and from the left edge (arrowhead), which yielded diminished signal in the middle of the plaque. The staining pattern from the right arch showed diffuse OxLDL, macrophage, and apoB-100 staining but minimal SMC and moderate collagen staining (Figure 5A through 5E). In contrast, the similar-sized plaque from the left side showed significantly weaker OxLDL staining, and the macrophage and apoB-100 staining was present primarily in the deep, necrotic area of the plaque. Conversely, collagen and SMC staining abounded in the fibrous cap and toward the luminal side (Figure 5I and 5J). The discordant plaques from the Plaque≠Ox-AB group
Figure 3. Quantitative analyses of lesion size (A), 125I-MDA2 uptake (as %ID/g; B), cell-associated OxLDL immunostaining (MDA-lysine epitope; C), macrophages (D), SMCs (E), and interstitial collagen (F) in LDLR−/− mice. The 125I-MDA2 uptake was determined in the entire aorta for all mice and the other parameters in 9 lesions per group. *P<0.05; **P<0.01; ***P<0.0001, all compared with Progression group.

Discussion

The novel finding of this study is that aortic uptake of intravenously injected 125I-MDA2, a prototype Ox-AB, reflects changes in plaque composition that are consistent with established features plaque stabilization.4,13 Interestingly, these features were also associated with a loss of oxidation-specific epitopes and macrophages of established lesions. We have shown previously that aortic uptake of Ox-AB provides a measure of the presence and extent of atherosclerosis7,10 and can also be used to noninvasively image atherosclerosis with appropriate radiolabels.9 This study suggests that serial imaging with labeled Ox-AB may allow the detection of reductions in plaque content of OxLDL that coincide with features of plaque stability.

Several recent studies have shown that the presence of OxLDL in coronary and carotid plaques is associated with plaque vulnerability.14,15 Importantly, Nishi et al15 explicitly demonstrated that carotid plaques, derived from asymptomatic patients undergoing carotid endarterectomy, displaying pathologically confirmed features of plaque instability such as increased plaque rupture, intraplaque hemorrhage, fibrous cap thinning, and macrophage infiltration, have a 25-fold higher content of OxLDL than stable plaques and 70-fold higher levels than plasma OxLDL levels. These studies are also in agreement with recent observations in patients showing that increased levels of OxLDL in plasma, including levels of OxLDL-E06 (LDL containing oxidized phospholipid epitopes, measured by the antibody E0616) are strongly associated with clinical features of plaque instability.3,14,17 In addition, we have shown recently that OxLDL-E06 levels are markedly elevated immediately after percutaneous coronary intervention, which appears to emanate from mechanically disrupted plaques.18 During lipid-lowering therapy with atorvastatin and pravastatin, respectively, it has been shown that OxLDL levels are significantly reduced in plasma (measured as OxLDL-E0619 and within carotid plaques (measured as OxLDL-NA59),20 respectively.

The underlying mechanisms involved in plaque regression or stabilization have not been well defined. Early animal studies of atherosclerosis regression have shown that cholesterol esters and macrophage foam cells are depleted within 6 months but that up to 2 years may be required to solubilize and deplete cholesterol crystals.21 Changes in vessel wall content of OxLDL during dietary-induced atherosclerosis regression have only recently been evaluated. It was demonstrated previously that Ox-AB uptake is enhanced in progressing atherosclerotic lesions but reduced in lesions undergoing dietary regression of LDLR−/− mice.10 In this study, LDLR−/− mice showed reduced 125I-MDA2 uptake in conjunction with reduction in several distinct oxidation-specific epitopes of OxLDL and reduced macrophage content but enhanced SMCs and collagen. In WHHL rabbits, there was evidence of thickened fibrous caps and redistribution of OxLDL and macrophage immunostaining to the deeper areas within lesions. In support of these findings, Aikawa et al4 demonstrated recently that dietary lipid lowering in hypercholesterolemic rabbits was associated with preferential depletion of OxLDL, measured by immunostaining with antibody MDA2, compared with LDL. Commensurate with these changes, there was a downregulation of metalloproteinases and increased collagen formation, which is thought to enhance matrix stability.13,22,23 Our current findings suggest that with appropriate development of imaging methods, such changes may be imaged in patients, which may ultimately have significant clinical utility.

In the LDLR−/− mouse study, evidence was provided for a transition to a “stable” atherosclerotic lesion phenotype in conjunction with reduced 125I-MDA2 uptake after robust...
showing excellent colocalization of plaque distribution and 125I-
lead to lesion regression. Rabbits with focally reduced 125I-
esterolemic, even in the absence of conditions that normally
observed despite the fact that these rabbits were very hypercho-
and increased histological markers of plaque stability were
yielding a weaker autoradiography signal appeared to have
plaque burden. Even among lesions of the same size, lesions
MDA2 uptake were older and, interestingly, had increased
physical regression of lesions with statins,26 plaque stability has
been inferred mainly from a significant reduction in clinical
events, and no conclusive data have proven, thus far, that
“plaque stabilization” (thicker fibrous caps and reduced oxida-
tion, lipid, and macrophage content) occurs in humans.

Interestingly, addition of vitamins E and C after switching to
a chow diet in this very hypercholesterolemic model (mean
cholesterol levels 1526 mg/dL) did not result in additional
reductions in 125I-MDA2 uptake and vessel wall OxLDL or
increased SMCs and collagen compared with chow alone. This
suggests that reduction in the substrate for oxidation (LDL and
other lipids) is a more powerful mediator of reduction in OxLDL
seemed to be redistributed to the deeper part of aortic
plaques may suggest that these epitopes were inaccessible to the
injected 125I-MDA2, a condition that may also favor prevention of
thrombotic occlusion.

Limitations of this study include the fact that the content of
OxLDL was detected by immunostaining and by 125I-MDA2
uptake but not directly measured by elution of apoB-100 from
atherosclerotic lesions. However, we used the colocalization
of 3 antibodies to distinct oxidation-specific epitopes and
apoB-100 as a surrogate measure of OxLDL in plaques.
Because many of these oxidation-specific epitopes are not
limited exclusively to apoB-100 but are present on many
which are more likely to result in fixed obstructive lesions and
stable angina compared with smaller plaques that result in acute
coronary syndromes.27 Interestingly, in pathological studies of
human coronary arteries obtained after death from myocardial
infarction,28,29 fibrous tissue is generally the major component of
atherosclerotic plaques when viewed in total; although specific
lesions that rupture are more enriched in inflammatory cells and
lipid.1 In this study, the fact that many of the macrophages and
OxLDL seemed to be redistributed to the deeper part of aortic
plaques may suggest that these epitopes were inaccessible to the
injected 125I-MDA2, a condition that may also favor prevention of
thrombotic occlusion.

In the WHHL rabbit study, focally reduced 125I-MDA2 uptake
and increased histological markers of plaque stability were
observed despite the fact that these rabbits were very hypercho-
lesterolemic, even in the absence of conditions that normally
lead to lesion regression. Rabbits with focally reduced 125I-
MDA2 uptake were older and, interestingly, had increased
plaque burden. Even among lesions of the same size, lesions
yielding a weaker autoradiography signal appeared to have
characteristics of more stable plaques, as indicated by increased
collagen and SMCs and a redistribution of OxLDL and macro-
phages to the core. A parallel situation may occur in humans for
whom progression of atheroma to complex atherosclerotic le-
sons may lead to a similar configuration of advancing plaques,
nonlipid-associated matrix proteins anchored to the vessel wall, this type of assessment may more globally reflect the presence of oxidative stress. Second, cholesterol levels were not measured in the WHHH rabbits, which limited our ability to assess whether changes in cholesterol levels with aging affected plaque characteristics.

Translation of these findings to human imaging may provide a means to monitor changes in lesion characteristics. After plaques are identified and quantitated, plaque stabilization may be detected by absence of signal in a previously detected site. Potential clinical applications may include surveillance of plaque changes after treatment with novel agents for treatment or prevention of atherosclerosis, earlier and improved diagnosis of oxidation-rich plaques, particularly in high-risk asymptomatic individuals, and potentially deriving prognostic information if borne out by clinical trials.

Acknowledgments

This study was supported by National Heart, Lung, and Blood Institute grant HL-59089 (La Jolla Specialized Center of Research in Molecular Medicine and Atherosclerosis), the Donal W. Reynolds Foundation, and the Regensburger Forschungsförderung in der Medizin (M.T.). We thank Mercedes Silvestre, Florencia Casanada, and Jennifer Pattison for excellent technical assistance.

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Arterioscler Thromb Vasc Biol. 2004;24:2307-2312; originally published online November 4, 2004;
doi: 10.1161/01.ATV.0000149378.98458.fe
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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<th>Plaque=Ox-AB</th>
<th>Plaque≠Ox-AB</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Age (months)</td>
<td>24 ± 14</td>
<td>46 ± 11</td>
<td>0.006</td>
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<tr>
<td>Aortic weight (mg)</td>
<td>965 ± 408</td>
<td>1720 ± 452</td>
<td>0.002</td>
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<tr>
<td>$^{125}$I-MDA2 uptake (%ID/g)</td>
<td>0.066 ± 0.028</td>
<td>0.028 ± 0.013</td>
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</tr>
<tr>
<td>Atherosclerosis (% surface area)</td>
<td>63 ± 29</td>
<td>90 ± 7</td>
<td>0.04</td>
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<tr>
<td>Autoradiography area (% of Sudan-positive atherosclerotic area)</td>
<td>100</td>
<td>71 ± 13</td>
<td>&lt;0.001</td>
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