

# Effects of Native and Modified Low-Density Lipoproteins on Monocyte Recruitment in Atherosclerosis

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Atherosclerosis is a chronic inflammatory disease of the arterial wall<sup>1–3</sup> with enormous epidemiological relevance.<sup>4,5</sup> Recruitment of monocytes to the vascular wall is a key feature in the pathogenesis of atherosclerotic lesions. Through a complex cascade of interactions between adhesion molecules and chemotactic factors, monocytes enter the subendothelial space, where they develop into macrophages, foam cells, and dendritic cells under the influence of cytokines, growth factors, and lipoproteins.<sup>6–8</sup> Foam cells eventually undergo secondary necrosis and form the lipid core of advanced atherosclerotic plaques. When exposed by rupture or erosion, it triggers acute thrombotic events leading to myocardial infarction and strokes.<sup>9</sup>

Elevated serum levels of low-density lipoprotein (LDL) (see the Table for abbreviations) are a major risk factor for the development of atherosclerosis.<sup>4</sup> Apart from epidemiological evidence for the proatherogenic role of lipoproteins, mechanistic studies suggest that they play a role in monocyte recruitment to the vessel wall and the progression of macrophages to foam cells. LDL does not only occur in its native form, but modified forms of LDL—eg, by oxidation, aggregation, or other processes—are thought to be even more proatherogenic.<sup>10–13</sup>

Even though numerous reviews have focused on monocyte recruitment to the arterial wall<sup>14–16</sup> or on effects of LDL on foam cell formation<sup>7,14</sup> in atherogenesis, no recent review has specifically addressed the effects of native and modified LDL on monocyte recruitment to the vessel wall. Here, we discuss the molecular effects of LDL on monocyte recruitment to the arterial wall as a crucial step in the pathogenesis of atherosclerosis.

## Monocyte Recruitment to the Arterial Wall

Recruitment of leukocytes to the vessel wall is a multi-step process consisting of capture, rolling, arrest, adhesion, and transmigration through the endothelium. These steps require expression and interaction of adhesion molecules and their ligands on the vascular endothelium and on the monocyte surface. Four groups of adhesion molecules have been identified in this process: selectins, selectin ligands, integrins, and immunoglobulin-like adhesion molecules.<sup>17,18</sup> In addition to

these adhesion molecules, chemokines play an important role in monocyte recruitment.<sup>19</sup> The mechanisms of monocyte recruitment to the vessel wall have been reviewed.<sup>14,16</sup>

## Native and Modified Forms of LDL

LDL is a heterogeneous class of lipoprotein particles consisting of a hydrophobic core containing triglycerides and cholesterol esters in a hydrophilic shell of phospholipids, free cholesterol, and apolipoproteins (predominantly B-100), the latter acting as ligands for lipoprotein receptors. The density of LDL ranges from 1.019 to 1.063 g/mL, its diameter is between 20 and 25 nm.<sup>20</sup> LDL binds to and is internalized by a specific LDL receptor (LDLR)<sup>21</sup> expressed on endothelial cells, monocytes, macrophages, and smooth muscle cells in atherosclerotic lesions.<sup>22</sup> LDLR expression is downregulated by elevated serum LDL levels.<sup>23</sup>

Apart from native LDL, modified forms of LDL occur in vitro and in vivo, displaying characteristics different from native LDL that make them even more atherogenic. LDL can be oxidized by exposure to copper salts or by coincubation with other cell types like endothelial cells, smooth muscle cells, monocytes, or macrophages expressing 5-, 12-, and 15-lipoxygenase.<sup>24,25</sup> There is evidence for the presence of oxLDL in atherosclerotic lesions in humans.<sup>26</sup> Enzymatic modification of LDL by hydrolytic enzymes has been discussed,<sup>27</sup> and there is some evidence that enzymatically modified LDL may play a role in atherogenesis in vivo.<sup>28</sup> Other ways of LDL modification are glycation<sup>13</sup> and incorporation in immune complexes.<sup>11,13,29</sup> LDL is thought to be modified in the subendothelial space even though modification in the blood stream cannot be completely ruled out<sup>10</sup> (Figure 1). Depending on the degree of oxidation, minimally-modified LDL (mmLDL) can be differentiated from fully oxidized LDL (oxLDL).<sup>30</sup>

In contrast to native LDL, mmLDL is bound and internalized not only by the LDLR but also by a number of scavenger receptors, whereas oxLDL exclusively binds to scavenger receptors<sup>31</sup> including scavenger receptor class A (SR-AI and SR-AII<sup>32</sup>), class B (CD36<sup>33,34</sup>), class D (CD68<sup>35</sup>), class E (oxidized LDL receptor [LOX-1]<sup>36</sup>), or class G CXCL16 (scavenger receptor that binds phosphatidylserine and oxi-

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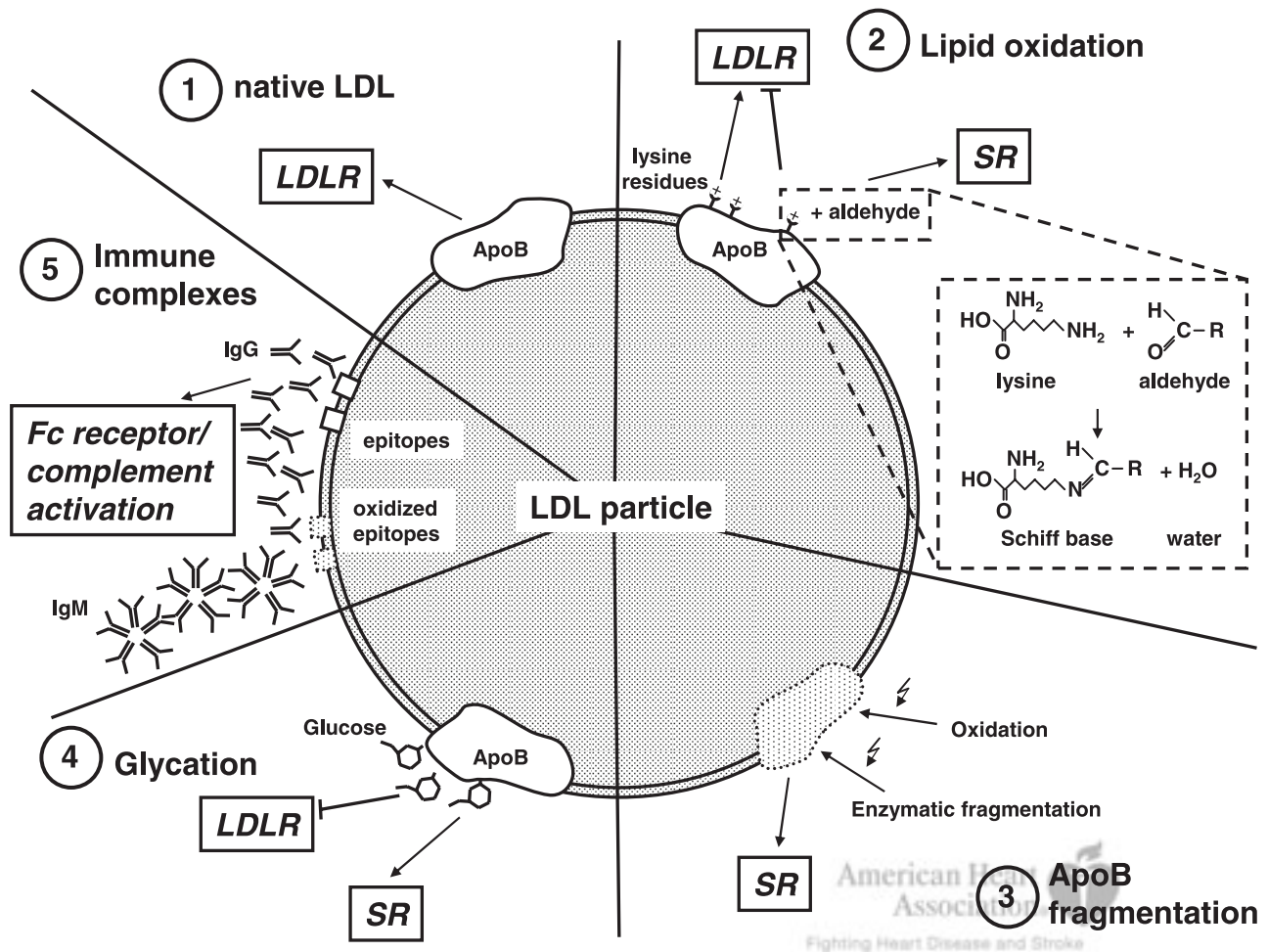
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**Figure 1.** Modification of low-density lipoproteins by various interventions. Binding of native LDL to the LDL receptor is mediated by apolipoprotein B (ApoB) (1). Modification of ApoB by (2) blocking of lysine residues through formation of Schiff bases, (3) fragmentation of ApoB by oxidation or enzymatic modification, (4) glycation, or (5) incorporation in immune complexes interferes with LDLR binding, thus modified LDL is bound and taken up by scavenger receptors (2–4). Immune complexes containing oxLDL bind to Fc $\gamma$  receptor or activate complement (5).

dized lipoprotein SR-PSOX<sup>37</sup>). LDL incorporated in immune complexes is bound and internalized by the Fc $\gamma$  receptor or activates complement.<sup>29</sup> LDLR and scavenger receptors are expressed in macrophages, and some are found in platelets and smooth muscle cells.<sup>22,38</sup> Unlike LDLR, scavenger receptors are not downregulated by elevated serum LDL levels.

### Effects of Modified Forms of LDL

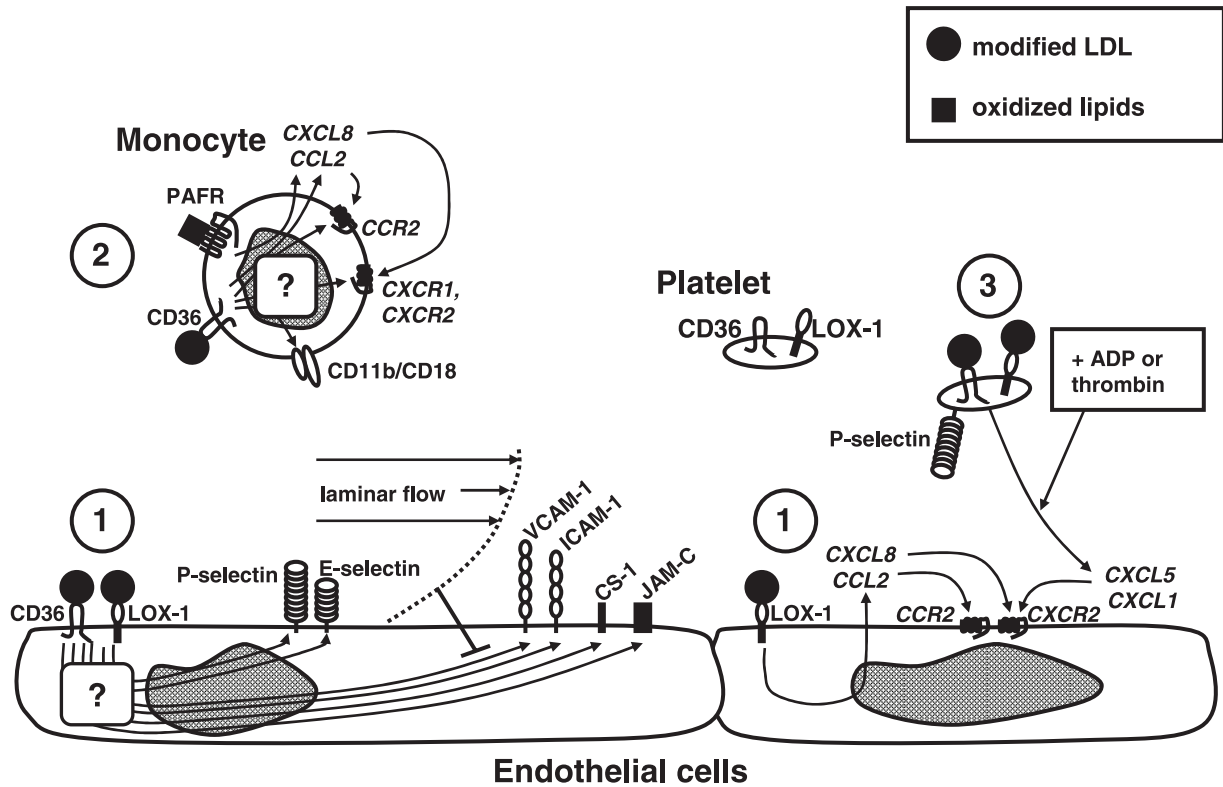
Modified forms of LDL like mmLDL and oxLDL are more proatherogenic than native LDL. mmLDL and oxLDL increase adherence of monocytes to the endothelium *in vivo*.<sup>39–41</sup> In human fetal aortas, retention and oxidation of LDL has been demonstrated to precede accumulation of monocytes and formation of fatty streaks.<sup>42</sup> Several mechanisms for increased monocyte recruitment attributable to presence of modified LDL in the arterial wall have been identified: (1) modified LDL enhances monocyte adhesion to the endothelium by inducing expression of adhesion molecules, chemotactic and growth factors in endothelial cells, (2) modified LDL exerts effects on monocytes inducing their adherence to the endothelium, and (3) modified LDL activates platelets, thereby promoting platelet-monocyte aggre-

gates and increasing monocyte adherence to the endothelium (Figure 2).

### Endothelium

Two scavenger receptors mediate effects of oxLDL on endothelial cells: CD36<sup>43</sup> and LOX-1.<sup>44</sup> Intracellular events induced by oxLDL include upregulation of adenylate cyclase generating cAMP as second messenger, but there is no direct evidence for CD36 or LOX-1 to be involved.<sup>45</sup> Ligation of LOX-1 induces NF $\kappa$ B in cultured human endothelial cells.<sup>45–48</sup> Intracellular signaling in endothelial cells after stimulation with mmLDL involves protein kinase-C (PKC)  $\beta$ ,<sup>49</sup> 12-lipoxygenase,<sup>50</sup> and intracellular free calcium.<sup>50</sup>

Depending on the degree of oxidation, LDL induces expression of P-selectin in human umbilical vein endothelial cells (HUVECs), which increases adhesion of monocytes.<sup>51</sup> Exposure of human aortic endothelial cells (HAECs) to mmLDL increases cell surface P-selectin protein expression as measured by immunofluorescence but has no significant effect on P-selectin message.<sup>52</sup> Exposure of human aortic endothelial cells to mmLDL suppresses transforming growth factor (TGF)- $\beta$  secretion



**Figure 2.** Schematic summary of effects of modified low-density lipoprotein on monocyte recruitment to the arterial wall (1): Induction of adhesion molecules (VCAM-1, ICAM-1, CS-1 containing form of fibronectin, JAM-C) and chemokines (CCL2, CXCL8) in endothelial cells, (2) induction of chemokines, chemokines receptors, and adhesion molecules in monocytes, (3) amplification of platelet activation in combination with other activators (ADP, thrombin). Question marks indicate that exact mechanisms are still unclear.

through a LOX-1–dependent process; TGF- $\beta$  appears to inhibit oxLDL-dependent monocyte adhesion under static conditions.<sup>53</sup>

In HUVECs and HAECs, oxLDL enhances tumor necrosis factor (TNF)- $\alpha$ -induced expression of vascular cell adhesion molecule (VCAM)-1 with a peak at 6 hours but not E-selectin.<sup>54</sup> VCAM-1<sup>48</sup> and intercellular adhesion molecule-1 (ICAM-1)<sup>48,53</sup> expression in HAEC is increased after stimulation with oxLDL. 13-HPODE shows a similar effect, suggesting that this component of oxLDL might be responsible for the enhanced VCAM-1 and ICAM-1 expression.<sup>54</sup> oxLDL increases adhesion of THP-1 cells (a human cell line derived from a patient with monocytic leukemia, which has phagocytotic capacities, produces lysozyme, and to some extent activates T cells<sup>55</sup>) to HAECs by 50% under static conditions which is reduced to below baseline by flow.<sup>48</sup> Interestingly, VCAM-1 but not ICAM-1 expression is suppressed by flow. In vivo, endothelial VCAM-1 expression is rapidly induced by an atherogenic diet.<sup>56</sup> In rabbits, induction of ICAM-1 expression in endothelial cells was confirmed beginning 24 hours after injection of native LDL, which was trapped and oxidized in the arterial wall as demonstrated by histological analysis.<sup>57</sup> Conversely, lowering of lipids in rabbits resulted in reduction of endothelial VCAM-1 expression.<sup>58</sup> These in vivo data support an effect of modified LDL on monocyte recruitment by upregulation of endothelial adhesion molecules.

Human secreted phospholipase A2 has been shown to hydrolyze LDL resulting in formation of lysophosphatidyl-

choline (lyso-PC), which has specific chemotactic effects on monocytes but not on resident macrophages.<sup>59</sup> In cultured rabbit and human endothelial cells, lyso-PC induces ICAM-1 and VCAM-1 expression resulting in increased attachment of the monocytic cell lines THP-1 and U937 (a human histiocytic lymphoma cell line<sup>60</sup>).<sup>61</sup> It has recently been shown that this modification of LDL can be achieved by human group X enzyme, one of the secreted phospholipases A2. Lyso-PC activates MAP kinase in HUVECs and induces doubling of ICAM-1, VCAM-1, and E-selectin expression resulting in significantly increased adhesion of monocytes under static conditions.<sup>62</sup>

Similarly, LDL modified by trypsin, cholesterol esterase, or neuraminidase induces monocyte adhesion and transmigration in vitro even more than oxLDL or native LDL, an effect mediated by upregulation of P-selectin, E-selectin, and ICAM-1.<sup>63</sup> Immunoreactivity for enzymatically modified LDL was found in human atherosclerotic lesions supporting its role in atherogenesis.<sup>28</sup> These results suggest that the effects of modified LDL depend on the result of modification (eg, fragmentation of apolipoprotein B).

mmLDL can induce monocyte adhesion to HAECs independently of VCAM-1 expression by interaction of connecting segment-1 (CS-1), an alternatively spliced form of fibronectin expressed on the endothelial surface, with  $\alpha_4\beta_1$  integrin.<sup>64</sup> Furthermore, junctional cell adhesion molecule-C (JAM-C) has been suggested to play a role in oxLDL-mediated increased adhesion of monocytes to HAECs. ox-

## Abbreviations Used in the Text

ADP	adenosine 5'-diphosphate
AP-1	activator protein-1
ApoB	apolipoprotein-B
CCL2	macrophage chemotactic protein-1 (MCP-1)
CCL5	regulated upon activation, normal T-cell expressed, and presumably secreted (RANTES)
CCR2	macrophage chemotactic protein-1 receptor
CS-1	connecting segment-1 (fibronectin peptide)
CXCL1	growth-related oncogene-alpha (GRO- $\alpha$ )
CXCL4	platelet factor-4 (PF-4)
CXCL5	epithelial neutrophils-activating protein-78 (ENA-78)
CXCL8	interleukin-8 (IL-8)
CXCL16	scavenger receptor that binds phosphatidylserine and oxidized lipoprotein (SR-PSOX)
CXCR2	interleukin-8 receptor 1 (type B)
HAEC	human aortic endothelial cell
HO-1	heme oxygenase-1
HSVEC	human saphenous vein endothelial cell
HUVEC	human umbilical vein endothelial cell
ICAM-1	intercellular adhesion molecule-1
JAM-C	junctional cell adhesion molecule-C
LDL	low density lipoprotein
LDLR	low density lipoprotein receptor
LOX-1	lectin-like oxidized LDL receptor-1
Lp(a)	lipoprotein(a)
Lyso-PC	lysophosphatidylcholine
M-CSF	macrophage-colony stimulating factor
mmLDL	minimally modified low density lipoprotein
oxLDL	oxidized low density lipoprotein
PAFR	platelet activating-factor receptor
PBMC	peripheral blood mononuclear cells
PKC	protein kinase-C
SR	scavenger receptor
VCAM-1	vascular cell adhesion molecule-1

LDL significantly upregulates JAM-C expression in HUVECs, resulting in increased adherence and transmigration of THP-1 cells mediated by Mac-1 (CD11b/CD18) and ICAM-1.<sup>65</sup>

Coculture-modified LDL, which has biological and chemical properties comparable to those of mmLDL, induces expression of heme oxygenase-1 (HO-1) in HAECs cocultured with human aortic smooth muscle cells, an effect mediated by arachidonic acid-containing phospholipids<sup>66</sup> but not by lyso-PC.<sup>67</sup> HO-1 induction in endothelial cells inhibits monocyte transmigration potentially by increased levels of biliverdin, a HO-1 product known to inhibit chemotaxis.<sup>66</sup> Induction of HO-1, which is known to have a number of antiatherogenic effects,<sup>68</sup> might represent a protective mechanism of the endothelium.

Lipoprotein(a) (Lp(a)) and its apolipoprotein A have chemotactic effects on monocytes and induce monocyte adhesion through interaction with the  $\beta_2$  integrin Mac-1 (CD11b/

CD18).<sup>69</sup> Apolipoprotein CIII has been identified to be one constituent of oxLDL responsible for enhanced adhesion of THP-1 cells to human saphenous vein endothelial cells (HSVECs) in a dose- and time-dependent manner. This effect is mediated by upregulation of ICAM-1 and VCAM-1 on the endothelium.<sup>49</sup>

Several studies have demonstrated that oxLDL itself can act as chemoattractant for monocytes and T cells.<sup>70,71</sup> In addition, modified LDL induces a number of chemotactic and growth factors in various cell types. Thus, in endothelial cells modified LDL can induce release of CCL2 (MCP-1) and M-colony stimulating factor (CSF)<sup>45,72-74</sup> as well as CXCL8 (IL-8).<sup>74,75</sup> Transendothelial migration of monocytes has been described to be induced by mildly oxidized LDL attributable to endothelial CCL2 synthesis.<sup>76</sup> Blocking of the scavenger receptor LOX-1 with antisense oligonucleotides reduces oxLDL-dependent induction of CCL2 in HAECs.<sup>44</sup> mmLDL-induced expression of CCL2 and M-CSF by endothelial cells has been confirmed in vivo in mice.<sup>77</sup> Conversely, lowering of lipid serum levels in rabbits results in a decrease of CCL2 production in the endothelium<sup>58</sup> suggesting an effect of modified LDL on endothelial chemokine production.

There is strong genetic variability in endothelial responses to modified LDL as shown by differences in the level of upregulation of M-CSF, CCL2, and HO-1 by mmLDL in various inbred mouse strains.<sup>78</sup> These findings suggest that human populations may also display various endothelial cell responses to modified LDL.

### Monocytes and Macrophages

In addition to exerting effects on the endothelial cell layer, modified LDL increases monocyte recruitment to the vascular wall by directly acting on monocytes. oxLDL has long been known to contain lipids with chemotactic activity toward human monocytes.<sup>79</sup> oxLDL and mmLDL increase monocyte CD11b expression in a PKC-dependent manner.<sup>80</sup> Blocking of CD11a (LFA-1 $\alpha$ ), CD11b (Mac-1 $\alpha$ ), or CD18 (common  $\beta$  chain) partially reduces oxLDL-induced monocyte adhesion to HUVECs under static conditions.<sup>81</sup> In hairless mice, injection of oxLDL but not native LDL induces an increase in leukocyte interaction with the endothelium, which is reduced by blocking antibodies against the integrin CD11b/CD18.<sup>82</sup> Oxidation of LDL generates biologically active lipids that bind to the platelet activating-factor receptor (PAFR). The role of PAFR expression on monocytes has been demonstrated in hamster experiments, where oxLDL-induced increase of leukocyte rolling is significantly attenuated when a PAFR antagonist is injected.<sup>83</sup>

Modified LDL induces expression of chemokines and chemokine receptors in monocytes and macrophages. Thus, blocking studies suggest that PAFR is crucial for oxLDL-dependent induction of CCL2 and CXCL8 in monocytes and macrophages.<sup>84</sup> Similarly, in rabbit peritoneal macrophages oxLDL induces CCL2.<sup>85</sup> Furthermore, oxLDL stimulates the release of CXCL8, CXCL5 (epithelial neutrophil-activating protein-78 [ENA-78]), and CXCL1 from peripheral blood mononuclear cells (PBMCs).<sup>86</sup>

In Mono-Mac-6 cells (a human cell line established from acute monoclonal leukemia exhibiting oxidative burst,

phagocytotic capacities as well as expression of mature monocytic markers<sup>87</sup>), oxLDL prevents the decreased CCR2 expression induced by TNF- $\alpha$  and thereby restores chemotaxis of monocytes toward CCL2 and other CCR2 ligands.<sup>88</sup> In THP-1 cells, CCR2 expression is increased after incubation with native LDL. In contrast, CCR2 is downregulated in these cells after incubation with oxLDL via a PPAR $\gamma$ -dependent pathway,<sup>89,90</sup> which may represent an additional antiinflammatory effect of PPAR $\gamma$  agonists widely used for treating diabetes mellitus. These different effects of oxLDL may simply reflect the use of different cell lines derived from patients with monocytic leukemia, neither of which behaves like primary monocytes. In primary human monocytes, exposure of oxLDL induces CCR2 message and protein in a dose-dependent fashion.<sup>89</sup> In blood samples of hypercholesterolemic subjects, CCR2 message is doubled versus control subjects,<sup>89</sup> indicating that modified LDL most likely increases CCR2 expression *in vivo*. oxLDL also upregulates CXCR2 expression in human monocytes as well as the human monocytic cell line U937 and to thereby increase chemotaxis toward CXCL8.<sup>91</sup>

### Platelets

Increasing evidence shows that platelets are involved in atherogenesis by mediating leukocyte recruitment to the endothelium. Thus, activated platelets induce expression of adhesion molecules like E-selectin, ICAM-1, and VCAM-1 and chemokines like CCL2 or CXCL8 on endothelial cells.<sup>92</sup> Deposition of CCL5 (RANTES) and CXCL4 (PF-4) on the endothelium by activated platelets triggers arrest of monocytes.<sup>93–96</sup> CCL5 has also been shown also to be delivered to the endothelium by platelet microparticles.<sup>97</sup>

Candidate oxLDL receptors on platelets include CD36<sup>98,99</sup> and LOX-1.<sup>100</sup> oxLDL increases cytoplasmic calcium levels in platelets<sup>101</sup> and amplifies platelet aggregation in response to ADP, thrombin, and other activating agents.<sup>102,103</sup> Similar findings were reported with mmLDL.<sup>104</sup> *In vivo*, hypercholesterolemia increases expression of P-selectin in platelets and enhances adhesion of platelets to the vessel wall in a P-selectin-dependent manner.<sup>105</sup> In addition, oxLDL induces release of CXCL5 and CXCL1 (GRO- $\alpha$ ) from platelets.<sup>86</sup> The importance of platelets in hypercholesterolemia-induced leukocyte recruitment to the arterial wall has been demonstrated in mice, where treatment with a platelet-depleting antibody at least partially reduced leukocyte adherence to the endothelium.<sup>106</sup> In summary, these effects of modified LDL bear the potential to increase atherosclerotic lesions by enhancing monocyte recruitment to the vessel wall.

### Effects of Native LDL

Modification of LDL substantially increases its proinflammatory effects.<sup>12,24,107</sup> It is controversial whether native unmodified LDL plays a role in atherogenesis and monocyte recruitment to the vascular wall. The fact that native LDL may be modified during *in vitro* or *in vivo* experiments makes it challenging to determine whether any effects seen are attributable to native or at least partially modified LDL. Furthermore, native LDL can aggregate and enter the macrophage through patocytosis.<sup>11,108</sup> Thus, aggregation of LDL

may account for some of the effects seen with what is believed to be native LDL. In HUVECs *in vitro* as well as in the murine aortic endothelium *in vivo*, LDL has been shown to bind to the LDL receptor and to induce intracellular signal transduction involving activator protein-1 (AP-1).<sup>109,110</sup>

Exposure of HUVECs to LDL results in increased adherence of monocytes to the endothelium.<sup>111</sup> Native LDL has been shown to increase adherence of monocytes to HUVECs by induction of P-selectin (only at high concentration and thus potentially an effect of traces of oxLDL)<sup>51</sup> as well as by increased ICAM-1 expression.<sup>112</sup> Similarly, native LDL has been demonstrated to induce VCAM-1 expression in cultured human coronary artery or pig aortic endothelial cells. Native LDL triggers a modest increase of VCAM-1 and E-selectin in human aortic endothelial cells through a rise in intracellular calcium acting as second messenger; increased VCAM-1 expression results in increased monocyte binding.<sup>113</sup> Native LDL at physiological concentrations induces a mild increase in VCAM-1 and P-selectin expression in HACECs.<sup>114</sup> This effect was abrogated by blocking LDL receptor, which suggests that the LDL used was native or at least only mildly modified, because LDLR does not bind oxLDL.<sup>21</sup> Treatment of endothelial cells with a calcium chelator showed that the calcium acting as second messenger derives from intracellular calcium stores.<sup>114</sup>

In monocytes and macrophages, native LDL is bound and internalized by the LDL receptor which in contrast to scavenger receptors is downregulated by cholesterol loading.<sup>23</sup> Native LDL has been shown to upregulate monocyte CCR2 expression *in vitro* and *in vivo* and to thereby increase chemotaxis.<sup>89</sup> Similarly, LDL induced CD11b in human monocytes resulting in CD11b-dependent adhesion to endothelial monolayers, however only after stimulation with CCL2.<sup>115</sup>

### Conclusion and Future Directions

LDL and especially modified forms of LDL support the development of atherosclerotic lesions not only by their effects on foam cell formation in the atherosclerotic plaques<sup>9,116</sup> but also at earlier stages by increasing monocyte recruitment to the vessel wall. Three major mechanisms have emerged as likely contributors: (1) Modified LDL induces adhesion molecules and chemokines in endothelial cells; (2) Modified LDL has direct effects on monocytes; (3) OxLDL promotes platelet interaction with both monocytes and endothelial cells leading to more efficient monocyte recruitment. These effects enhance and accelerate the formation of atherosclerotic lesions and may cause existing lesions to become more vulnerable. The significance of different scavenger receptors for monocyte recruitment is still largely unclear. The specific components of modified LDL responsible for its increased atherogenicity remain to be identified. Models are needed to test the role of these LDL components under controlled conditions *in vivo*.

Therapeutically, lowering of LDL serum levels is the most valuable tool available for lowering the risk of atherosclerosis in the population at large.<sup>117</sup> Better understanding of the mechanisms how LDL and modified forms of LDL increase

monocyte recruitment to the vascular wall might result in new approaches for primary and secondary prevention.

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### Disclosures

None.

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