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ARTICLES

Atherosclerosis: Basic Mechanisms

Oxidation, Inflammation, and Genetics

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Abstract

Abstract The clinical events resulting from atherosclerosis are directly related to the oxidation of lipids in LDLs that become trapped in the extracellular matrix of the subendothelial space. These oxidized lipids activate an NFκB-like transcription factor and induce the expression of genes containing NFκB binding sites. The protein products of these genes initiate an inflammatory response that initially leads to the development of the fatty streak. The progression of the lesion is associated with the activation of genes that induce arterial calcification, which changes the mechanical characteristics of the artery wall and predisposes to plaque rupture at sites of monocytic infiltration. Plaque rupture exposes the flowing blood to tissue factor in the lesion, and this induces thrombosis, which is the proximate cause of the clinical event. There appear to be potent genetically determined systems for preventing lipid oxidation, inactivating biologically important oxidized lipids, and/or modulating the inflammatory response to oxidized lipids that may explain the differing susceptibility of individuals and populations to the development of atherosclerosis. Enzymes associated with HDL may play an important role in protecting against lipid oxidation in the artery wall and may account in part for the inverse relation between HDL and risk for atherosclerotic clinical events.

atherosclerosis lipids genes antioxidants lipoproteins

At one time, atherosclerosis was thought to be a degenerative disease that was an inevitable consequence of aging. Research in the last two decades has shown that atherosclerosis is neither a degenerative disease nor inevitable. On the contrary, atherosclerosis seems to be a chronic inflammatory condition that is converted to an acute clinical event by the induction of plaque rupture, which in turn leads to thrombosis.[1] What are the basic mechanisms that induce this sequence of events? Fig 1⇓ depicts a model of the sequence of changes in the artery wall that lead to a clinical event. The underlying hypothesis presented here is that components of the earliest lesion, the fatty streak, which itself is not clinically significant, are also responsible for the latter events that lead to clinically significant disease

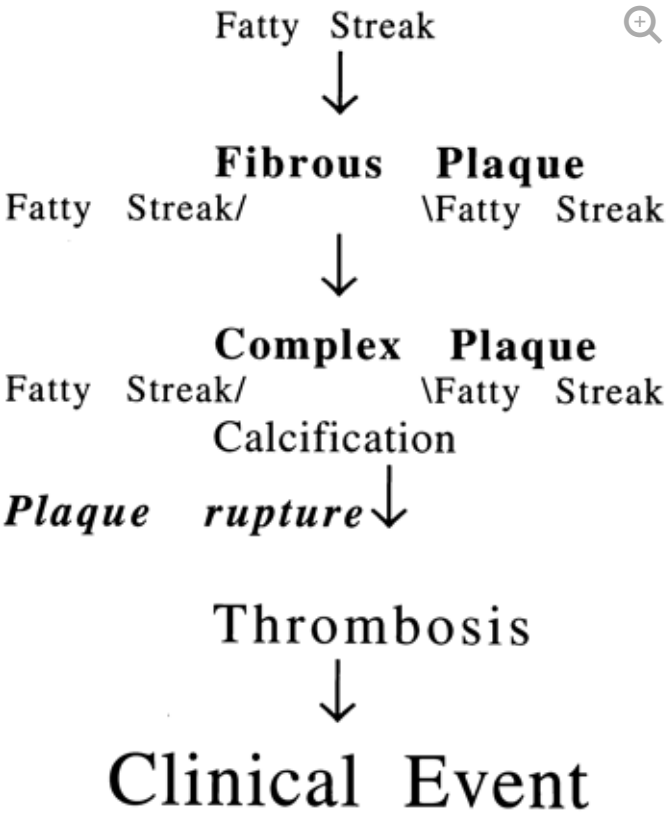

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Figure 1.

Model showing the sequence of events from fatty streak to clinical event.

Lipids and Atherogenesis

Table 1⇓ depicts some of the steps in fatty streak development. The first is lipoprotein transport into the artery wall. This concentration-dependent process does not require receptor-mediated endocytosis.[2 3] The seminal findings by Brown and Goldstein[4] that atherosclerosis is induced in multiple species by mutations that involve a single gene, the LDL receptor, provide strong evidence that elevations in LDL levels are sufficient to induce all the components of the atherosclerotic reaction.

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Table 1.

Development of the Fatty Streak

Step	
1	Lipoprotein transport

2	Lipoprotein retention
3	Lipoprotein modification
4	Monocyte adherence
5	Monocyte migration (chemotaxis)
6	Monocyte differentiation
7	Foam cell formation

Lipoprotein Retention in the Artery Wall

Schwenke and her late colleague Carew[5 6] provided convincing evidence that for any given lipoprotein concentration in the plasma, lipoprotein retention in the artery wall was more important than the rate of transport into the artery wall. Kruth[7] and Simionescu et al[8] first reported early changes in the lipoproteins retained in the artery wall. Frank and Fogelman[9] extended these findings with state-of-the-art ultrastructural techniques and demonstrated that LDL was rapidly transported across an intact endothelium and became trapped in the three-dimensional cage work of fibers and fibrils secreted by the artery wall cells.[10] The intimate association of LDL[11] with the extracellular matrix of the subendothelial space explains how the concentration of apolipoprotein B (apoB), the major protein of LDL, is found in higher concentrations in the artery wall than in the plasma.[12 13 14] Early lesions appear to develop at sites of predilection[15 16 17 18 19 20 21 22] that are related to hemodynamic and mechanical factors.[23 24 25]

Lipoprotein Oxidation

The cells of the artery wall secrete oxidative products from multiple pathways that can seed the LDL trapped in the subendothelial space and initiate lipid oxidation.[26 27 28 29] Studies by Navab and colleagues[30] with serum containing cocultures of human artery wall cells in which an endothelial monolayer was maintained on multilayers of smooth muscle cells indicated that the matrix provided by these artery wall cells could produce microenvironments that could exclude the water-soluble antioxidants of plasma. It is not surprising then that oxidative modification of the trapped lipoproteins does, in fact, occur, as was suggested more than a decade ago[31 32 33 34 35] and subsequently proved in the late 1980s.[36 37 38 39]

Mildly and Highly Oxidized LDL

The oxidative modification of the trapped LDL is thought to occur in two stages. The first stage occurs before monocytes are recruited and results in the oxidization of lipids in LDL with little change in apoB. The second stage begins when monocytes are recruited to the lesion, convert into macrophages, and contribute their enormous oxidative capacity. In this second stage, the LDL lipids are further oxidized, but the protein portion of LDL is also modified, leading to a loss of recognition by the LDL receptor and a shift to recognition by the scavenger receptors and/or the oxidized LDL receptor.[40 41 42] This shift in receptor recognition leads to cellular uptake of the LDL by receptors that are not regulated by the cholesterol content of the cell. The result is a massive accumulation of cholesterol. Such cholesterol-loaded cells have a foamy cytoplasm and have been called foam cells; they are the hallmark of the arterial fatty streak.

Oxidized LDL Is a Potent Inducer of Inflammatory Molecules

What are the mechanisms by which the oxidation of LDL leads to this inflammatory reaction? Berliner and colleagues[43] reported that the mild oxidation of LDL yielded oxidized lipids that induced monocytes but not neutrophils to bind to endothelial cells. Treatment of endothelial cells with this oxidized lipid induced changes in molecules that affect all three stages[44] of monocyte binding: tethering, activation, and attachment (Table 2⇓). Levels of the tethering molecule P-selectin are increased intracellularly by mildly oxidized LDL and can be released by a variety of substances, including highly oxidized LDL.[45] In vivo studies have also suggested that P-selectin can be released by oxidized LDL,[46] and P-selectin expression has been shown to be increased in human lesions.[45 47] Moreover, mildly oxidized LDL induced endothelial cells to produce the potent monocyte activators monocyte chemoattractant protein 1 (MCP-1),[48] monocyte colony stimulating factor (M-CSF),[49] and GRO.[50] While M-CSF and MCP-1 appear to be soluble molecules, GRO was found bound to heparin-like molecules on the endothelial cell surface.[50] Another adhesion molecule, VCAM-1, has been implicated in the development of fatty streaks in rabbits.[51] Mildly oxidized LDL does not induce VCAM-1 or ICAM-1 expression,[52] and the adhesion molecule induced by mildly oxidized LDL has yet to be completely identified. Navab and colleagues[30] demonstrated that LDL added to cocultures of human aortic endothelial and smooth muscle cells also led to the production of MCP-1 and monocyte migration into the subendothelial space. Rajavashisth and colleagues[49] demonstrated the presence of M-CSF in atherosclerotic lesions in rabbits. Subsequent to these findings, others reported that MCP-1 and M-CSF were present in lesions from animals and humans.[53 54] Studies by Cushing and Fogelman[55] suggested that differentiating monocytes also produced MCP-1 that could amplify their own recruitment into lesions. Consistent with this hypothesis was the finding by Neiken and colleagues[56] that MCP-1 was expressed most in lesion areas where monocyte density was greatest. Charo and colleagues[57] recently cloned the receptor for MCP-1, providing a potential new target for interrupting this reaction.

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Table 2.

Molecules Mediating Adhesion That Are Increased by MM-LDL

Molecule	mRNA	Protein
MCP-1	24-Fold	20-Fold
M-CSF	4-Fold	10-Fold
GRO-KC	30-Fold	20-Fold
P-selectin	2-Fold	2.5-Fold

MM-LDL indicates mildly oxidized LDL; MCP-1, monocyte chemoattractant protein 1; M-CSF, monocyte colony stimulating factor; and GRO-KC, a C-X-C chemokine.

How does mildly oxidized LDL induce a set of genes with protein products that lead to monocyte adherence, migration, and conversion into macrophages without inducing a neutrophilic or lymphocytic reaction? Parhami and colleagues[58] reported that mildly oxidized LDL induces elevated levels of cAMP by a G protein–mediated

mechanism. These high levels of cAMP decrease the expression of ELAM-1 (a receptor to which neutrophils bind) while increasing the molecules noted above. Mildly oxidized LDL induces these inflammatory molecules both by inducing increased rates of gene transcription and by stabilizing the mRNA for these genes.[59]

HDL May Protect by Inhibiting LDL Oxidation

HDL was found to protect against LDL oxidation by metal ions in vitro[60 61] and to prevent the production of mildly oxidized LDL by the artery wall cells in a coculture model.[30] However, HDL obtained either from patients undergoing surgery or after myocardial infarction in which apolipoprotein A-I was displaced from the HDL by the acute phase reactant serum amyloid A not only was not protective against LDL modification but actually enhanced LDL modification by the cocultures.[62] Two enzyme systems associated with normal HDL have been reported to inhibit LDL oxidation in vitro. Stafforini and colleagues[63] reported that the platelet activating factor acetylhydrolase was effective in preventing metal ion–dependent oxidation of LDL. Mackness and colleagues[64] reported that a second enzyme associated with HDL, paraoxonase, also inhibited LDL oxidation in vitro. Both enzymes have been found to protect against LDL modification in the coculture system.[65 66] Thus, the inverse relation between risk for atherosclerotic events and HDL levels may be due to enzymes associated with HDL that protect against LDL oxidation and the putative role of HDL in reverse cholesterol transport.[67] Moreover, because these enzymes are associated with only a small fraction of HDL particles, this may, in part, explain why some patients with low levels of total HDL cholesterol may not have clinically significant atherosclerosis and others with relatively normal levels of HDL cholesterol may have premature atherosclerosis. However, this hypothesis has yet to be tested.

Oxidation and Lesion Progression

Fig 2⇓ depicts in cartoon form some of the molecular and cellular mechanisms responsible for the sequence of events described in Fig 1⇑. This scheme would predict that conditions that increased the oxidative waste of artery wall cells would increase the seeding of LDL trapped in the subendothelial space, as suggested by Witztum and Steinberg[26 29] and Parthasarathy.[27 28] Increased levels of HDL containing enzymes that prevented the formation of or destroyed the biologically active lipids generated in the mildly oxidized LDL would prevent the ensuing inflammatory reaction. Once started, however, the reaction would tend to amplify itself. Navab et al[68] reported that artery wall cells interacted with monocytes by inducing mRNA for the gap junction protein connexin43, which was accompanied by increased production of matrix molecules and involved interleukin-1 (IL-1) and interleukin-6. Ross[69] demonstrated that monocyte macrophages are a potent source of a powerful smooth muscle cell growth factor and chemoattractant platelet-derived growth factor (PDGF). This would explain, in part, the migration of smooth muscle cells into the lesion. Products of lipoprotein oxidation have also been shown to affect other events associated with atherogenesis. The secretion of IL-1, a growth factor for smooth muscle cells, has been shown to be stimulated by oxidized lipids.[70] Lysophosphatidylcholine, a product of LDL oxidation, has been shown to be a chemoattractant for monocytes[71] and T-lymphocytes,[72] to induce the adhesion molecules VCAM-1 and ICAM-1,[73] and to increase levels of PDGF and heparin-binding epidermal growth factor mRNA in endothelial cells[74] and smooth muscle cells.[75] Highly oxidized LDL also can inhibit endothelial cell migration and may impair the repair of ulcerated plaques in advanced lesions.[76] Highly oxidized LDL has also been shown to be toxic to macrophages[77] and as a result may contribute to amplification of the inflammatory process and the formation of the necrotic core found in advanced lesions. With the death of some of the macrophage foam cells, lipid droplets could be released and phagocytized by the smooth muscle cells, producing smooth muscle cell foam cells, as suggested by Wolfbauer and colleagues.[78] The involvement of the immune system in the development of lesions[79 80 81] may increase[82] or decrease[83 84] the inflammatory reaction.

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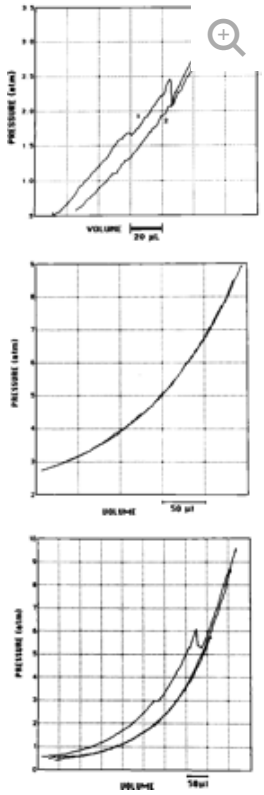

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Figure 3.

Line graphs showing pressure-volume recordings during inflation of angioplasty balloon. Pressure-volume recordings were made as described by Demer.[98] Top, Upper curve is from a human during the first balloon inflation in an atherosclerotic coronary artery. Note the break in the curve, indicating plaque fracture. The lower curve was recorded from the same patient at the same site at the end of the procedure. Note that the curve is smooth and shifted to the right, indicating a return toward normal distensibility. Middle, A pressure-volume recording during balloon inflation in the aorta of a cholesterol-fed Watanabe heritable hyperlipidemic (WHHL) rabbit.[98] Note that the curves are smooth and superimposed and do not have a break. This trend is identical to that of the curve obtained during balloon inflation in a normal rabbit aorta.[98] Bottom, Upper curve represents balloon inflation in the aorta of a cholesterol-fed WHHL rabbit after the aorta was induced to

calcify.[98] The lower curve was recorded from the same rabbit at the same site at the end of the procedure. Note the similarity in the fracture patterns obtained in the calcified rabbit aorta (bottom) and the atherosclerotic human coronary artery (top).

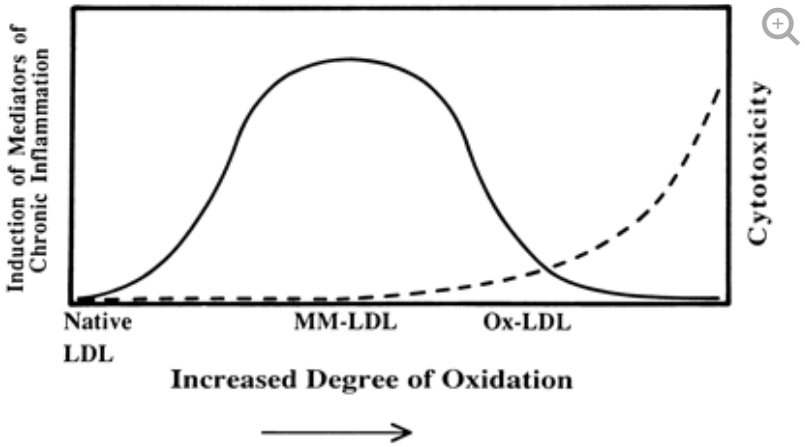

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Figure 4.

Diagram of the change in the biological activities of LDL with increasing degrees of oxidation. The solid line represents the level of induction of mediators of chronic inflammation; dashed line, the level of cytotoxicity. MM-LDL indicates mildly oxidized LDL; Ox-LDL, oxidized LDL.

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Figure 2.

This page and facing page, Schematics showing molecular and cellular mechanisms for some events described in Fig 1⇑. A, Development of the fatty streak. B, Progression to advanced lesion. Small grey cells with round black nuclei represent lymphocytes; red droplets in cells, lipid inclusions. C, Advanced lesion with plaque rupture and thrombus. D, Cross section of artery corresponding to panel A. E, Cross section of artery corresponding to panel B. F, Cross section of artery corresponding to panel C. EC indicates endothelial

cells; IEL, internal elastic lamina; SMC, smooth muscle cells; MM-LDL, mildly oxidized LDL; Ox-LDL, highly oxidized LDL; +, positive induction; X-LAM, adhesion molecule induced by MM-LDL; MCP-1, monocyte chemoattractant protein-1; M-CSF, monocyte colony stimulating factor; ROS, reactive oxygen species; and Ca, calcification resulting from the action of the pericyte-like cells. Adapted with permission in part from Fig 1⇑, page 374, Berliner JA, Haberland ME. The role of oxidized low density lipoprotein in atherogenesis. *Curr Opin Lipidol*. 1993;4:373-381.

Glagov et al[85] demonstrated that in all species the lesion grows out toward the adventitia until a critical point is reached, at which time the lesion can no longer expand outward at the expense of the normal media and then begins to encroach on the lumen. The lesion grows by the migration of new mononuclear cells that enter at the shoulder regions of the lesion,[86] the proliferation of both monocyte macrophages[87] and smooth muscle cells,[88] the production of an exuberant extracellular matrix,[89] and the accumulation of extracellular lipid in a necrotic core.[7 90]

Genetic Factors Affecting Lipid Oxidation and Inflammation

Liao and colleagues[91] reasoned that if oxidized lipids were responsible for the induction of a set of genes that induced the chronic inflammatory response characteristic of the fatty streak, these genes might be induced in any tissue that accumulated the oxidized lipids. They used mouse livers as a convenient tissue for detailed genetic studies. Mice that readily develop fatty streaks in their aortas on an atherogenic diet (C57BL/6) were compared with mice that never developed fatty streaks on the same atherogenic diet (C3H/HeJ), despite the fact that the two strains develop similar levels of the atherogenic apoB-containing lipoproteins in their blood on this diet. On the atherogenic diet, both strains accumulated substantial amounts of total lipid, cholesterol, and triglycerides in their livers that did not significantly differ between the two strains. However, the fatty streak–susceptible strain (C57BL/6) accumulated significantly more oxidized lipid than did the fatty streak–resistant strain (C3H/HeJ). Associated with these higher levels of oxidized lipids was the activation of an NFκB-like transcription factor and the expression of genes that contain NFκB binding sites: *JE*, the mouse homologue of MCP-1, colony stimulating factors, serum amyloid A, and heme oxygenase in the fatty streak–susceptible C57BL/6 mice but not in the fatty streak–resistant C3H/HeJ mice.[91 92] Injection of mildly oxidized LDL into the mice induced the same set of genes in the liver.[91 93] These results were consistent with the hypothesis that the atherogenic diet resulted in the accumulation of oxidized lipids in certain tissues (eg, liver and arteries), with the resulting inflammatory response to this oxidative stress genetically determined.[94] While these data were suggestive of a genetically determined rate of formation or destruction of oxidized lipids or that the intensity of the inflammatory response to these lipids was genetically determined, the association or lack of association of these phenomena with two genetically distinct strains did not directly prove a genetic link. Fortunately, recombinant inbred strains derived from the parental strains were available to directly test the hypothesis. Crossbreeding of the parental strains allowed the genomes of the two strains to be extensively intermingled because of chromosomal crossover. If the level of oxidized lipids, the activation of the NFκB-like transcription factor, the expression of the inflammatory genes, and the development of aortic fatty streaks all cosegregated together as the two genomes were randomly distributed by extensive crossbreeding, it would be strong evidence that these phenomena were genetically linked. Results of the analysis revealed that indeed there was cosegregation and suggested that a major gene contributing to aortic lesion development in this mouse model, previously termed *Ath-1*, may control either the accumulation of lipid peroxides in tissues or the cellular responses to such lipid peroxides.[95]

Calcification and Plaque Rupture

Recent evidence suggests that the site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process regardless of the dominant plaque morphology.[96 97] It is thought that mechanical factors are involved in the actual rupture of the plaque at such sites of structural

weakness. Demer[98] reported that the mechanical characteristics of atherosclerotic plaque are due to calcification of the lesions. Fig 3⇑ demonstrates that the mechanical characteristics observed in human coronary arteries were not reproduced in the aorta of rabbits with LDL receptor deficiency even when they were placed on a cholesterol-rich diet and had extensive aortic atherosclerosis. However, as Fig 3⇑ shows, when the aortas of these animals were induced to calcify, they had mechanical characteristics identical to those seen in atherosclerotic human coronary arteries. Demer et al[99] argued that the presence of a soft plaque with a point of weakness induced by inflammation sitting on an area of calcification predisposes to plaque rupture because of the presence of a tissue interface of differing physical properties that is subjected to the pulsatile changes of the arterial blood pressure. “Hardening of the arteries” has long been thought to be an inevitable consequence of aging. However, Demer and her colleagues[99] reported that this is no more an inevitable degenerative change than is the development of other components of the inflammatory reaction. Bostrom et al[100] and Watson et al[101] demonstrated that a heretofore unrecognized cell in large and medium arteries is responsible for calcification. This cell has many of the characteristics of pericytes found in the microcirculation. These cells, called calcifying vascular cells, were induced to calcify by expression of the same set of genes as those expressed during bone formation. The expression of these genes was induced by tissue growth factor-β and oxysterol, two agents known to be present in the fatty streak and the developing atherosclerotic lesion. It is possible that other chronic inflammatory reactions such as tuberculosis may induce calcification by similar mechanisms. In the artery wall, however, the calcification-induced changes in the mechanical characteristics of the tissue predispose to plaque rupture.[102 103 104 105 106] Recent studies in mice indicate that arterial calcification may be under genetic control.[107] The changes in the mechanical characteristics of the arterial tissue induced by calcification are superimposed on changes in the matrix that result from increased expression of matrix metalloproteinases and matrix degrading activity in the shoulder region of the lesion.[108 109] Thus, mechanical forces are applied to an area of structural weakness and predispose to plaque rupture.

Thrombosis

The endothelium usually has anticoagulant properties. The potent coagulant, tissue factor, usually is expressed only in the adventitia. (This makes teleological sense because one would want to induce clotting if the artery were opened to the adventitial side.) Oxidized LDL has been shown to induce endothelial cells[110 111] and monocytes[112] to express high levels of tissue factor. In addition, Drake and colleagues[113] demonstrated that there is abundant tissue factor in the intima of atherosclerotic lesions. Plasminogen activator inhibitor levels are also increased when endothelial cells are exposed to oxidized LDL.[114] Consequently, plaque rupture would expose the flowing blood to these high levels of tissue factor and result in clotting with the induction of a clinical event. The normal response to thrombin formation is vasodilation,[115] which would favor the mechanical removal of a clot. Oxidized LDL has been shown to induce the expression of endothelin,[116] to inhibit the expression of nitric oxide synthase, and to inhibit the resulting vasodilation.[117 118 119] Thus, LDL further contributes to arterial occlusion by thrombus. In addition to the local reduction in nitric oxide, it is also quite clear that platelet accumulation and local increases in thromboxane A_2, serotonin, ADP, platelet activating factor, and activated thrombin, together with a local reduction in prostacyclin, contribute to thrombosis.[120 121]

Oxidation of LDL Produces Oxidized Lipids With Differing Biological Activities

Atherosclerotic lesions contain multiple oxidized lipids derived from the lipids in LDL.[122] The biological properties of the lipids in mildly oxidized LDL have been seen to be different from those induced by the lipids in highly oxidized LDL (eg, the expression of tissue factor by endothelial cells was induced by mildly oxidized LDL but not by highly oxidized LDL[110] ; the lipids in highly oxidized LDL were cytotoxic,[123] whereas the lipids in mildly oxidized LDL were not[43]). Fig 4⇑ depicts a scheme in which LDL undergoes various degrees of oxidation. The activation of the NFκB-like transcription factor and the increase in the genes induced by mildly oxidized LDL are due to the appearance of specific oxidized lipids that appear to be oxidized phospholipids but are as yet

unidentified.[65 66] With continued oxidation, these bioactive lipids are presumed to be destroyed and new ones formed that account for the different biological activity of highly oxidized LDL. These latter lipids include lysophosphatidylcholine and oxidized sterols.[71 73 74 75 123] The final identification of the specific biologically active lipids in mildly oxidized LDL will likely yield new targets of opportunity for intervention. One possibility is that these lipids are by chance similar to lipids in bacteria that evoke similar chronic inflammatory responses such as *Mycobacterium tuberculosis*.[124]

Pharmacological Intervention at the Level of the Artery Wall

The prevention and treatment of atherosclerosis currently are appropriately directed to lowering LDL levels and raising HDL levels. As we understand the basic mechanisms more fully, new strategies may emerge.[125] We may learn how to specifically raise the levels of HDL subfractions that carry the enzymes that prevent the formation of or destroy the biologically active lipids in oxidized LDL. If we can identify the major genes that control the formation of biologically active oxidized lipids or control the intensity of the response to these lipids, we may be able to devise strategies that will favorably modify the functions controlled by these genes. As we understand the basic mechanisms of arterial calcification, we may be able to devise strategies that will allow us to maintain normal artery wall mechanics and prevent plaque rupture. So far, at least one anti-inflammatory compound has been identified that inhibits in vitro the formation of biologically active mildly oxidized LDL and smooth muscle proliferation without inhibiting endothelial cell proliferation.[126 127] The future will undoubtedly reveal a number of new strategies for preventing and treating atherosclerosis.

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