Infection and Inflammation-Induced Proatherogenic Changes of Lipoproteins

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Epidemiologic studies suggest a link between infection/inflammation and atherosclerosis. During the acute-phase response to infection and inflammation, cytokines induce tissue and plasma events that lead to changes in lipoprotein. Many of these changes are similar to those proposed to promote atherogenesis. The changes of lipoproteins during infection and inflammation are reviewed with a focus on those that are potentially proatherogenic. Hypertriglyceridemia, elevated triglyceride-rich lipoproteins, the appearance of small dense low-density lipoproteins, increased platelet-activating factor acetylhydrolase activity, and secretory phospholipase A_2, sphingolipid-enriched lipoproteins, and decreased high-density lipoprotein (HDL) cholesterol are changes that could promote atherogenesis. Moreover, alterations of proteins associated with HDL metabolism (e.g., paraoxonase, apolipoprotein A-I, lecithin:cholesterol acyltransferase, cholesterol ester transfer protein, hepatic lipase, phospholipid transfer protein, and serum amyloid A) could decrease the ability of HDL to protect against atherogenesis through antioxidation and reverse cholesterol transport mechanisms. These proatherogenic changes of lipoproteins may contribute to the link between infection/inflammation and atherosclerosis.

Epidemiologic data suggest a link between atherosclerosis and chronic infections and inflammatory conditions. For example, Chlamydia pneumoniae, cytomegalovirus, Helicobacter pylori, dental infections, chronic bronchitis, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis have been associated with an increased risk of atherosclerosis [1–8]. Increased plasma C-reactive protein, a marker of systemic inflammation, predicts future risk of coronary events [9, 10]. Furthermore, measurement of plasma C-reactive protein can add to the predictive value achieved by assessment of plasma lipid levels alone [11]. Although some infectious agents are found in the arterial wall and atheromatous lesions, it is unclear how other infections and inflammatory states (i.e., H. pylori infection in the stomach) are linked to atherosclerosis [12].

During infection and inflammation, a wide range of alterations in metabolism occur. These are part of the body’s reaction known as the acute-phase response (APR). The APR characteristically induces changes in the concentration of specific plasma proteins, which help protect the host from further injury, and facilitates the repair process [13]. Levels of positive acute-phase proteins (e.g., C-reactive protein and serum amyloid A) increase during the APR, whereas levels of negative acute-phase proteins (e.g., albumin and transferrin) decrease. The increase in acute-phase proteins modulates the inflammatory response by directly neutralizing foreign agents, minimizing the extent of tissue damage, and participating in tissue regeneration. However, these metabolic changes, if present for prolonged periods, can lead to detrimental consequences on the host, a typical example of which is the development of secondary amyloidosis after chronic infection or inflammation. Cytokines, such as tumor necrosis factor (TNF) or interleukin (IL)-1, are recognized as prime mediators of these metabolic changes during infection and inflammation [13]. The APR is species specific with both the magnitude and directions of changes varying from species to species.

Infection and inflammation can also perturb lipoprotein metabolism and produce a wide variety of changes in the plasma concentrations of lipids and lipoproteins [14]. Increased triacylglyceride levels due to an increase in very low-density lipoprotein (VLDL) and reduced high-density lipoprotein (HDL) cholesterol levels are characteristic changes during infection and inflammation [15, 16]. Although low-density lipoprotein (LDL) cholesterol levels decrease during infection and inflammation in humans, there is an appearance of small dense LDL [17], a particle believed to be more proatherogenic [18]. Because these lipoprotein changes are similar to those proposed to promote
Atherosclerosis is a complex process, and atherosclerotic lesions in the arterial wall are characterized by lipid accumulation in macrophages, resulting in foam cell formation [19]. The development of lipid-filled foam cells is primarily regulated by two major determinants: lipid uptake and lipid removal.

Several risk factors for atherosclerosis have been identified in epidemiologic studies. Hypercholesterolemia, especially elevated levels of LDL cholesterol, is one major risk factor for coronary artery disease (CAD), and therapeutic reductions of total and LDL cholesterol levels result in a decrease in cardiovascular morbidity and mortality [20–23]. Hypertriglyceridemia and elevated levels of triglyceride-rich lipoproteins (e.g., VLDL and remnants) have recently reemerged as risk factors for atherosclerosis [24, 25]. On the other hand, plasma levels of HDL cholesterol are inversely correlated with the risk of atherosclerosis [26]. In agreement with these concepts, therapies that raise HDL and decrease triglyceride reduce the morbidity and mortality from CAD [27, 28]. These intervention trials support the concept that LDL and possibly VLDL play a pivotal role in lipid uptake and that HDL is a key lipoprotein in lipid removal from macrophage foam cells in the arterial wall.

Although LDL is a major risk factor for CAD, experiments have shown that incubation of macrophages with native LDL does not result in foam cell formation, a characteristic feature of atheromatous lesions [19]. However, LDL is chemically modified, rapid uptake occurs, leading to cholesterol accumulation in the macrophage with subsequent foam cell formation. These data suggest that LDL modification is a necessary step in atherogenesis. Oxidized LDL can induce foam cell formation, and oxidative modification of LDL is now recognized as an important process that occurs in vivo [29]. Different subclasses of LDL have been isolated based on size or density. Compared with large buoyant particles, small dense LDL are more susceptible to oxidation [30]. Furthermore, small dense LDL have poorer binding affinity to the LDL receptor, resulting in increased plasma half-life in the circulation and decreased clearance [31]. In addition, because of the smaller size, small dense LDL can efficiently penetrate the endothelial barrier into the arterial intima and interact with intima proteoglycans, leading to retention in the arterial wall [32]. Therefore, small dense LDL are considered more proatherogenic.

Recent studies also show that the presence of small dense LDL can predict subsequent CAD [33, 34]. Evidence is accumulating for the pathologic role for triglyceride-rich lipoproteins, especially VLDL, in atherosclerosis. Although intact triglyceride-rich lipoproteins do not effectively cross the intact endothelial barrier into the intima, similar particles have been isolated from atherosclerotic lesions [35]. In addition, they are toxic to endothelial cells [36]. Once triglyceride-rich particles are in the intima, they can interact with lipoprotein receptors on the macrophage. VLDL from patients with hypertriglyceridemia, but not from subjects with normal plasma triglyceride levels, can bind to receptors on the macrophage, resulting in rapid lipid uptake and accumulation [37, 38]. Because of the larger size, triglyceride-rich lipoproteins can deliver more cholesterol per particle than LDL [39].

Plasma HDL cholesterol levels, on the contrary, inversely correlate with the risk of CAD. Therefore, several antiatherogenic effects of HDL have been postulated [40]. HDL is thought to protect LDL against oxidative modification. In addition, HDL is proposed to mediate the removal of cholesterol from cells and the return of cholesterol to the liver for elimination, a phenomenon known as “reverse cholesterol transport” (RCT). Several proteins and enzymes associated with HDL appear to mediate these functions of HDL.

**Infection/Inflammation and Lipoprotein Changes**

Infection and inflammation are associated with alterations in triglyceride and cholesterol metabolism. In addition to changes in circulating levels of lipids and lipoproteins, the composition of the lipoprotein particles is also altered. Furthermore, there are changes in the level and activity of a variety of plasma proteins involved in metabolism and function of these lipoproteins (table 1).

**Changes of Triglyceride and VLDL Metabolism**

The most typical change in lipoprotein metabolism during infection and inflammation is hypertriglyceridemia [41]. An increase in plasma triglyceride levels is due to an increase in VLDL, which can be the result of either increased VLDL production or decreased VLDL clearance. In patients with human immunodeficiency virus (HIV) infection and AIDS, an increase in plasma triglyceride in the VLDL fraction has been observed [42]. Increased plasma triglyceride levels, increased hepatic lipogenesis, and decreased triglyceride clearance are all correlated with interferon (IFN)-α levels [16, 43]. Therefore, IFN-α may contribute to hypertriglyceridemia by both increasing triglyceride production and decreasing clearance.

By using lipopolysaccharide (LPS) and lipoteichoic acid (LTA) to mimic gram-negative and gram-positive infections in animals, respectively, we found that low doses of LPS and higher doses of LTA stimulate VLDL production, whereas high
doses of LPS inhibit VLDL clearance [44, 45]. Experiments in rats and mice showed that low doses of LPS rapidly stimulate VLDL production by increasing adipose tissue lipolysis, increasing hepatic de novo fatty acid synthesis, and decreasing hepatic fatty acid oxidation, all of which provide fatty acid substrate for esterification into triglyceride and assembly into VLDL particles in the liver [46, 47]. LTA, like low-dose LPS, also induces hypertriglyceridemia in rats by increasing hepatic VLDL triglyceride secretion by similar mechanisms [45]. In contrast, high-dose LPS does not increase hepatic VLDL synthesis. Rather, it decreases the activity of lipoprotein lipase, an enzyme responsible for clearance of triglyceride-rich lipoproteins [44]. A concomitant reduction of tissue expression of apo-lipoprotein (apo) E during infection would further limit the clearance, as apo E facilitates lipoprotein uptake of VLDL particles by the LDL receptor and LDL receptor-related protein [48].

The effects of LPS and LTA on triglyceride metabolism are mediated through cytokines. Like LPS and LTA, a number of cytokines, including TNF, IL-1, IL-6, and IFN-α, rapidly stimulate hepatic fatty acid synthesis, resulting in increased VLDL production and hypertriglyceridemia in rats and mice [46, 49–55]. Of note, TNF and IL-1 are key cytokines in bacterial infection, and IL-1 is the primary mediator of noninfectious inflammation, whereas IFN-α is primarily activated by viral infection. Despite different pathways of cytokine activation, different types of infection or inflammation result in similar effects on triglyceride metabolism.

In addition to changes in the level of VLDL and triglyceride, the composition of VLDL is altered during infection and inflammation. Although VLDL produced by the liver after LPS and TNF administration have normal particle size and apolipoprotein composition, triglyceride, cholesterol, and phospholipid composition, they are enriched in sphingolipids [54, 56]. Sphingolipid-enriched lipoproteins are potentially proatherogenic. For example, sphingomyelin can retard the clearance of triglyceride-rich lipoproteins, which could result in accumulation of proatherogenic remnant particles [57]. Other proatherogenic effects of sphingolipid-enriched lipoproteins are discussed below.

### Changes of Cholesterol and LDL Metabolism

Several changes in LDL could promote atherogenesis during infection and inflammation (table 1). Among subclasses of LDL, small dense LDL has smaller particle size but higher density than large buoyant LDL. Small dense LDL is believed to be proatherogenic because it is particularly susceptible to oxidation and can penetrate the endothelium and bind to intima proteoglycans more effectively than large buoyant LDL, resulting in retention in the arterial wall [30, 32]. In addition, small dense LDL have a poor binding affinity to LDL receptor,

<table>
<thead>
<tr>
<th>Changes</th>
<th>Effects</th>
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<tr>
<td>Increased VLDL levels</td>
<td>Provides lipid substrates for macrophage uptake</td>
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<td>Decreased LPL and HL</td>
<td>Decreases clearance of triglyceride-rich lipoproteins</td>
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<tr>
<td>Increased sphingolipid content</td>
<td>Decreases clearance of triglyceride-rich lipoproteins</td>
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<tr>
<td>Decreased tissue apo E expression</td>
<td>Decreases lipoprotein clearance</td>
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<tr>
<td>Increased small dense LDL</td>
<td>Increases susceptibility to oxidation; increases LDL penetration through endothelium; increases interaction with arterial wall proteoglycans and LDL retention in arterial wall</td>
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<tr>
<td>Increased PAF-AH activity</td>
<td>Increases LPC production</td>
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<td>Increased sPLA₂</td>
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<td>Increased sphingolipid content</td>
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<td>Decreased LCAT</td>
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<td>Decreased CETP</td>
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<td>Decreased HL</td>
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<td>Decreased PLTP</td>
<td>Reduces pre-β HDL generation; decreases HDL phospholipid content and impairs cholesterol removal by increasing cholesterol flux from HDL into cells</td>
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<tr>
<td>Increased SAA</td>
<td>Decreases availability of cholesterol in HDL to be metabolized by hepatocytes; increases cholesterol uptake into macrophages</td>
</tr>
<tr>
<td>Increased sPLA₂</td>
<td>Decreases HDL phospholipid content and impairs cholesterol removal by increasing cholesterol flux from HDL into cells</td>
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<tr>
<td>Increased PAF-AH activity</td>
<td>Increases LPC production</td>
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<tr>
<td>Decreased PON</td>
<td>Decreases ability of HDL to protect against LDL oxidation</td>
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<tr>
<td>Decreased transferrin</td>
<td>Impairs the ability of HDL to prevent LDL oxidaation</td>
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<tr>
<td>Increased apo J</td>
<td>Increases smooth muscle cell differentiation in arterial wall</td>
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NOTE. apo, apolipoprotein; CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; LPC, lysophosphatidylcholine; LPL, lipoprotein lipase; PAF-AH, platelet-activating factor acetylhydrolase; sPLA₂, secretory phospholipase A₂; PLTP, phospholipid transfer protein; PON, paraoxonase; VLDL, very low-density lipoprotein; SAA, serum amyloid A.
leading to decreased clearance [31]. In patients with AIDS, a decrease in LDL cholesterol level is associated with the appearance of small dense LDL (subclass pattern B) [16, 17]. Consistent with this finding, infection in animals is associated with increased oxidation of LDL [58].

Platelet-activating factor (PAF) is a proinflammatory phospholipid secreted by activated platelets, leukocytes, and endothelial cells during infection and inflammation [59]. PAF exerts several biologic effects, including activation of inflammatory cells, increased vascular permeability, and hypotension. In the plasma, PAF is degraded by PAF acetylhydrolase (PAF-AH), an enzyme that catalyzes the hydrolysis of the acetyl group at the sn-2 position [60]. Of note, PAF-AH also hydrolyzes oxidized fatty acids from phospholipids. Plasma PAF-AH circulates in the blood as a complex with lipoproteins. In humans, most plasma PAF-AH activity (60%-70%) is found in LDL; the rest is in HDL.

The role of PAF-AH in atherosclerosis is controversial. On one hand, PAF-AH hydrolyzes PAF, a mediator of inflammation, and other oxidized phospholipids. This reaction removes oxidized fatty acids from the sn-2 position of phospholipids in LDL, which could protect LDL against further oxidation. However, PAF-AH also hydrolyzes phosphatidylcholine, resulting in the generation of lysophosphatidylcholine (LPC) [61], a molecule that may mediate various biologic effects of oxidized LDL, including chemotaxis of monocytes, induction of adhesion molecules, and impairment of relaxation of blood vessels [62, 63]. Therefore, PAF-AH may have both antiatherogenic and proatherogenic properties.

We recently found an increase in plasma and LDL-associated PAF-AH activity in patients with HIV infection [64]. The increase is not reversed by highly active antiretroviral therapy containing an HIV protease inhibitor. Whether the increase in LDL-associated PAF-AH activity in HIV-infected persons renders them more or less prone to the development of atherosclerosis is not clear. It is possible that an acute increase in PAF-AH may be beneficial to protect against LDL oxidation and prevent cellular uptake of oxidized LDL that may occur during chronic infections, but a prolonged increase in PAF-AH may eventually promote atherogenesis.

Secretory nonpancreatic phospholipase A2 (sPLA2) is another acute-phase protein that is induced during acute infection or inflammation [65]. sPLA2 hydrolyzes phospholipids, mainly phosphatidylethanolamine, at the sn-2 position, liberating polyunsaturated fatty acids. Increased activity of sPLA2 could be potentially atherogenic because sPLA2 provides fatty acid substrate for oxidation, resulting in oxidized fatty acids. These oxidized fatty acids can further modify LDL to become oxidized LDL [66]. In fact, transgenic mice overexpressing human sPLA2 exhibit significant atherosclerosis even when maintained on a low-fat diet [67].

LPS administration to nonprimates increases triglyceride and cholesterol content in LDL, resulting in triglyceride and cholesterol-rich particles [68]. This LDL is also enriched in sphingolipids, including sphingomyelin and ceramide [56]. The increase in total sphingolipid content in lipoproteins results from an up-regulation of serine palmitoyltransferase, the rate-limiting enzyme in sphingolipid synthesis in the liver, and leads to increased hepatic sphingomyelin and ceramide production. Of note, sphingomyelin is a substrate for ceramide formation by sphingomyelinase in the arterial wall [69]. Therefore, increased sphingomyelin synthesis can further enhance ceramide production. In addition, infection through cytokines increases secretion of sphingomyelinase by macrophages and endothelial cells and therefore induces ceramide generation [69, 70].

An increase in sphingolipid content in lipoproteins has been proposed to increase the atherogenicity of LDL. For example, an increase in ceramide levels in LDL facilitates LDL aggregation and stimulates LDL uptake by macrophages, which can lead to foam cell formation [71]. LDL isolated from atherosclerotic lesions is also enriched in ceramide compared with plasma LDL and has an increased tendency to aggregate [69].

LPS administration increases sphingomyelin, ceramide, and especially glucosylceramide content of lipoproteins [56]. LPS, TNF, and IL-1 increase the hepatic mRNA level and activity of glucosylceramide synthase, the enzyme that catalyzes the first glycosylation step of glycosphingolipid pathway [72]. An increase in glucosylceramide content in lipoproteins can also increase their atherogenic potential, and glucosylceramide accumulates in human atherosclerotic plaques [73, 74].

Changes of HDL Metabolism

Infection and inflammation are associated with a decrease in HDL cholesterol levels [15, 16, 68, 75, 76]. The mechanism for the decrease in HDL cholesterol levels during infection and inflammation has not been firmly established. Nevertheless, a persistently low level of HDL cholesterol in chronic infection and inflammation suggests that this change may be undesirable, since data from epidemiologic studies have shown a greater risk of CAD in subjects with low HDL cholesterol levels.

The function of HDL is mediated through a variety of apolipoproteins associated with HDL particles. Moreover, HDL metabolism is regulated by several enzymes and transfer proteins that can affect various functions of HDL. During infection and inflammation, not only do HDL cholesterol levels decrease, but there are also a wide range of changes in these apolipoproteins, enzymes, and transfer proteins. As a result, there are marked changes in lipid and protein composition of HDL, which can theoretically lead to alterations in function of HDL.

HDL that circulate during infection and inflammation (also termed acute-phase HDL) are depleted in cholesterol ester but enriched in free cholesterol, triglyceride, and sphingolipids [56, 68, 76, 77]. In addition, HDL-associated apo A-I and paraoxonase (PON) levels decrease, but apo J and serum amyloid A (SAA) levels increase [16, 78–80]. Moreover, there are reduc-
Acute-Phase HDL and RCT Pathway

RCT is a pathway by which cholesterol from peripheral cells is transported back to the liver for metabolism and/or excretion [97]. This pathway is thought to play a key role in removing cholesterol from cells in atherosclerotic lesions, such as macrophage foam cells. The first step of RCT is cholesterol removal from cells, and two major mechanisms of cholesterol removal have been proposed: an apolipoprotein-mediated mechanism and a diffusion mechanism [98, 99] (figure 1). In the apolipoprotein-mediated mechanism, cholesterol is removed from plasma membrane of peripheral cells to small, lipid-poor 

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HDL particles. Recent data suggest that this step requires apo A-I on HDL and an ATP-binding cassette transporter 1 (ABCI) on the cell surface [100–103]. Free cholesterol can also move from plasma membrane to HDL by the diffusion mechanism. LCAT plays a key role by converting free cholesterol in HDL into cholesterol ester, thus maintaining a free cholesterol gradient so that continuous diffusion of free cholesterol from plasma membrane to HDL can occur. Cholesterol ester generated by LCAT then moves into the core of HDL particles, resulting in larger \(\alpha\) HDL (figure 1).

After free cholesterol is esterified, cholesterol ester in HDL can be transported to the liver for elimination via several routes.
Free cholesterol (FC) removal from cells is the first step of reverse cholesterol transport. FC from peripheral cells (e.g., macrophage foam cells) can be removed to pre-β high-density lipoprotein (HDL) by apolipoprotein-mediated mechanism. Membrane-spanning ATP-binding cassette transporter 1 (ABC1) plays role in this cholesterol removal pathway. FC can also move from plasma membrane of cells to HDL by diffusion mechanism. Lecithin:cholesterol acyltransferase (LCAT) in HDL creates FC gradient by converting FC into cholesterol ester (CE) for continuous diffusion to occur. In presence of CE transfer protein, CE in HDL is exchanged for triglyceride in triglyceride-rich lipoproteins. Triglyceride in α HDL is then metabolized by hepatic lipase (HL) and pre-β HDL is regenerated.

In the presence of CETP, cholesterol ester from HDL is transferred to triglyceride-rich lipoproteins in exchange for triglyceride. HDL can also be directly endocytosed into liver parenchymal cells as intact particles. In addition, cholesterol ester in HDL can be exclusively taken up without proteins by a non-endocytic process called selective uptake of cholesterol ester (figure 2).

During infection and inflammation, there is a reduction in HDL cholesterol concentrations, apo A-I levels, and plasma PLTP activity (table 1). As HDL and apo A-I are acceptors of cellular cholesterol, the decrease in HDL and apo A-I levels could impair apolipoprotein-mediated cholesterol removal from cells. PLTP mediates a transfer of phospholipids and cholesterol between triglyceride-rich lipoproteins and HDL, and a reduction in PLTP activity results in lower HDL levels [104]. Therefore, a reduction in PLTP activity could presumably decrease cellular cholesterol removal as well.

Plasma LCAT activity is reduced during infection and inflammation [81]. This reduction could potentially impair cholesterol removal, because free cholesterol gradient is not efficiently maintained for diffusion to occur. In addition, LCAT is required for the conversion of free cholesterol into cholesterol ester so that cholesterol ester can move into the core of HDL. Plasma activities of CETP and HL also decrease during infection [82, 83]. CETP mediates the exchange of cholesterol ester in HDL for triglyceride in triglyceride-rich lipoproteins; therefore, a decrease in CETP activity could limit the transfer of cholesterol to triglyceride-rich lipoproteins, an important step for the delivery of cholesterol to the liver. Both reductions in LCAT and CETP activities during infection and inflammation could retard the RCT pathway.

After the exchange of HDL cholesterol ester for triglyceride, HL catabolizes triglyceride in HDL, leading to a decrease in HDL size and regeneration of pre-β HDL. A decrease in HL activity could potentially reduce the generation of pre-β HDL, which could in turn impair the transfer of cellular cholesterol to HDL. Plasma sPLA₂, increases during infection [65]. Increased activity of sPLA₂ could also be potentially atherogenic because it hydrolyzes phospholipids in HDL, leading to decreased HDL phospholipid content, which could increase cholesterol flux from HDL into cells [105].

SAA and apo J increase during infection [79, 106]. SAA is a classic acute-phase protein preferentially associated with HDL. SAA-rich HDL are more rapidly cleared from the cir-
Reverse cholesterol transport process is decreased during infection and inflammation. Decrease in high-density lipoprotein (HDL) and apolipoprotein (apo) A-I levels would impair free cholesterol (FC) removal from cells. Decrease in lecithin:cholesterol acyltransferase (LCAT) activity further impairs cholesterol removal by limiting FC gradient in absence of esterification. Decrease in cholesterol ester (CE) transfer protein (CETP) activity limits transfer of cholesterol to triglyceride (TG)-rich lipoproteins. Decrease in hepatic lipase (HL) and phospholipid transfer protein (PLTP) reduces regeneration of pre-β HDL, major cholesterol acceptor from cells. Different pathways of lipoprotein uptake by liver may also be affected by changes in hepatic lipoprotein receptors, such as low-density lipoprotein (LDL) receptor-related protein (LRP) or scavenger receptor class B type I (SR-BI). LDL receptor (LDL-R) protein levels do not change during infection and inflammation but decrease in apo E expression in tissues during infection and inflammation could limit uptake of lipoproteins by LDL-R and LRP.

Apo J (clusterin) is a glycoprotein associated with HDL in the plasma. Apo J is produced by a wide variety of cells, and many physiologic functions have been proposed, including lipid transport, plasma membrane protection, complement regulation, endocrine secretion, and initiation of apoptosis [108]. Plasma levels of apo J increase in response to infection and inflammation [79]; however, its role in atherogenesis is uncertain. It is believed that apo J may bind potentially toxic fatty acids generated during cell damage to prevent oxidative injury to phospholipids in LDL and plasma membrane. However, apo J expression is found in atherosclerotic lesions, especially in smooth muscle cells [109]. Because smooth muscle cells are a component of atherosclerotic lesions, and a recent study showed...
that apo J regulates vascular smooth muscle cell differentiation in vitro [110], it can be postulated that apo J may be a mediator in the propagation of atherosclerotic lesions by inducing smooth muscle cell differentiation and reorganization in the arterial wall.

Given the marked changes in HDL metabolism during infection and inflammation, it is likely that the function of HDL in RCT is affected. As a result, a defect in cellular cholesterol removal and further steps in RCT could lead to accumulation of cholesterol in cells. Together with an inability of acute-phase HDL to protect LDL against oxidation, this may lead to foam cell formation and atheromatous lesions in the arterial wall.

Summary

Infection and inflammation produce a variety of changes in lipoproteins (table 1) as a part of the APR through actions of cytokines. These changes mimic those proposed to be proatherogenic. Hypertriglyceridemia occurs as the result of increased VLDL production and/or decreased VLDL clearance. Recent evidence indicates that these triglyceride-rich lipoproteins could render HDL proatherogenic. An enrichment of triglyceride and sphingolipids in LDL, the appearance of small dense LDL, and increased PAF-AH, sPLA₂, and ceruloplasmin could increase the atherogenic potential of LDL during infection and inflammation. A decrease in plasma HDL cholesterol levels, marked changes in HDL composition, and alterations of several proteins associated with HDL metabolism and function could also render HDL proatherogenic. An increase in PAF-AH and ceruloplasmin and a decrease in PON and transferrin could have significant effects on the ability of HDL to protect against LDL oxidation. In addition, a decrease in plasma apo A-I, LCAT, CETP, HL, and PLTP, together with an increase in SAA and sPLA₂, could significantly affect the function of HDL in RCT. Moreover, an increase in apo J may enhance the progression of atherosclerotic lesions by inducing smooth muscle cell differentiation. These proatherogenic changes of lipoproteins during infection and inflammation may be the potential mechanisms that account for the epidemiologic observations linking chronic infections and inflammatory conditions and atherosclerosis.

References


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