

changes in KB catabolism. IL-6 has no effect on serum KB levels (34). IFN- α has biphasic effects: low doses of IFN- α increase serum KB levels by mobilization of FA substrate, whereas higher doses have no effect (63). IFN- γ stimulates adipose tissue lipolysis, increasing serum and hepatic KB levels (63).

FA uptake and oxidation decrease in heart and skeletal muscle during the APR, shifting their metabolism from FA as the preferred fuel substrate to glucose, whose uptake and utilization are increased (75–77). This makes more FA available to liver and other tissues, such as those of the immune system. IL-1, but not TNF, decreases LPL activity in the heart (78–80). LPS, TNF, and IL-1 decrease the mRNA expression of FA transport and binding proteins and ACS in heart and muscle (67, 71). It is likely that this coordinated decrease in FA transport and binding proteins and ACS is the mechanism for the decreased uptake and utilization of FA in heart and muscle during infection/inflammation.

Decreased VLDL clearance. Infection may also increase serum TG levels by decreasing VLDL clearance. Early *in vitro* studies showed that TNF decreases LPL expression in cultured adipocytes (81, 82). *In vivo*, however, there is little evidence that hypertriglyceridemia is attributable to decreased LPL activity. First, although TNF reduces LPL activity in epididymal fat pads in rodents (80, 83), this decrease requires many hours, whereas the TNF-induced increase in serum TG levels occurs very rapidly (29). Second, TNF administration does not decrease LPL activity in other adipose tissue sites or in muscle (41, 83). Third, TNF-neutralizing antibodies block the LPS-induced increase in serum TG levels in mice but they do not block LPS-induced inhibition of LPL in mouse adipose tissue, again dissociating the LPS-induced increase in serum TGs from changes in LPL activity (33). Finally, TNF does not decrease the clearance of chylomicrons or VLDL from the circulation, the mechanism by which changes in LPL might influence TG levels (41, 49, 84).

Like TNF, IL-1, IL-6, and LPS also require several hours to decrease LPL activity *in vivo* in mouse adipose tissue (80). IFN- α and IFN- γ increase serum TG levels in humans (38, 39) but do not increase TG levels in rodents, despite decreasing LPL activity in cultured murine 3T3-L1 fat cells (64, 82), again showing discordance between LPL activity and TG levels.

There may be a role for the decreased clearance of TG with high doses of LPS. Low doses of LPS enhance hepatic VLDL secretion and increase serum TG levels without affecting TG clearance in rats. In contrast, high doses of LPS inhibit the clearance of TG-rich lipoproteins (26). Moreover, high doses of LPS decrease postheparin plasma LPL activity and LPL activity in adipose tissue and muscle (80).

LPS and cytokines also decrease apoE mRNA in many tissues, including the liver, and VLDL has lower amounts of apoE during infection (54, 85, 86). Because apoE is required for the clearance of TG-rich lipoproteins, decreased apoE could contribute to the delayed clearance observed in rats with infection (87).

Cholesterol metabolism

There are marked alterations in the metabolism of cholesterol, LDL, HDL, and RCT during infection. LPS and cytokines decrease total serum cholesterol levels in primates, whereas in rodents they increase cholesterol levels by stimulating *de novo* cholesterol synthesis, decreasing lipoprotein clearance, and decreasing the conversion of cholesterol into bile acids. Such species-specific responses in the APR are common, but the underlying mechanisms responsible for these differences are not yet understood. There are baseline differences in serum cholesterol levels among species, with rodents having low LDL levels and primates having relatively high LDL levels. Baseline levels are often related to the direction of changes in the APR. There are classic positive acute-phase proteins that are expressed at baseline in some species, and they do not increase during the APR in those species.

Hepatic cholesterol synthesis. In rodents, LPS stimulates hepatic cholesterol synthesis (27) (Table 2). In contrast to the acute effect of LPS on *de novo* FA synthesis, the effect of LPS on hepatic cholesterol synthesis is delayed, occurring 10 h after administration (27). LPS stimulates hepatic cholesterol synthesis by increasing the transcription rate, mRNA expression, protein mass, and activity of HMG-CoA reductase, the rate-limiting enzyme in the biosynthetic pathway of cholesterol liver (27, 88). The effect of LPS on HMG-CoA reductase is specific, as the mRNA expression of several other enzymes in the cholesterol synthetic pathway, including HMG-CoA synthase and farnesyl pyrophosphate synthase, which are usually coordinately regulated with HMG-CoA reductase under nutritional or pharmacological manipulations, is not altered by LPS treatment (2, 88) (Fig. 2). Moreover, LPS still upregulates HMG-CoA reductase mRNA expression when its basal expression is increased by treatment with bile acid binding resins or decreased by feeding a high-cholesterol diet (88). Thus, the stimulatory effect of LPS on HMG-CoA reductase is independent of dietary regulation and persists over a wide range of basal expression.

Despite a marked increase in HMG-CoA reductase activity, LPS only produces a modest increase in hepatic cholesterol synthesis and serum cholesterol levels (27). The reason is that LPS produces a decrease in the mRNA expression and activity of squalene synthase (89), the first

TABLE 2 Effects of LPS, LTA, and cytokines on cholesterol metabolism in intact animals

Variable	LPS	LTA	TNF	IL-1	IL-6	IFN- α	IFN- γ
Serum cholesterol	↑, ↓*	↑	↑, ↓*	↑, ↔*	↑	↔	↔
Hepatic cholesterol synthesis	↑	ND	↑	↑	ND	↔	↑
HMG-CoA reductase activity	↑	ND	↑	↑	ND	ND	↔
LDL receptor protein	↓, ↔*	ND	↔*	↔*	ND	ND	ND
Bile acid synthesis	↓	ND	↓	↓	ND	ND	ND

Data are for rats and mice unless otherwise noted.

* Primates.

† Hamsters.

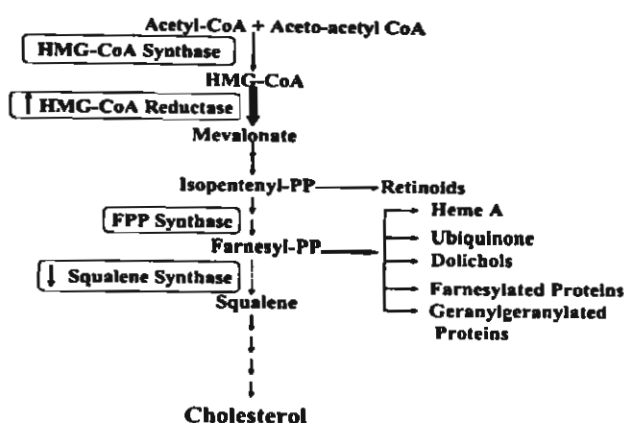


Fig. 2. Changes in cholesterol metabolism during the APR. Infection and inflammation are associated with an increase in HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis in the liver. However, there is a decrease in the expression of enzymes downstream of the mevalonate pathway, including squalene synthase. As a result, there is only a modest increase in hepatic cholesterol synthesis, and other mevalonate metabolites are redirected into nonsterol pathways, such as dolichols, FPP, farnesyl pyrophosphate.

committed enzyme in cholesterol synthesis located at a branch point in the mevalonate pathway (Fig. 2), and other enzymes downstream of mevalonate pathway (2). Regulation of squalene synthase plays an important role in regulating the flux of metabolic intermediates to the sterol or nonsterol pathways, which include the synthesis of retinoids, dolichols, ubiquinone, and prenylated proteins. It is likely that the LPS-induced increase in HMG-CoA reductase coupled with a decrease in squalene synthase maintains adequate cholesterol synthesis while redirecting mevalonate metabolites into nonsterol pathways (Fig. 2). Indeed, the synthesis of dolichol phosphate is increased in the liver during inflammation (90, 91). Dolichol is required for the glycosylation of proteins, and the synthesis of several glycosylated plasma proteins is markedly increased in the liver during the APR (90, 91).

Like LPS, several cytokines, including TNF, IL-1, IL-6, KGF, and NGF, produce a delayed increase in serum cholesterol levels in rodents (29, 32, 34, 44, 45) (Table 2). TNF- α , TNF- β , IL-1, and IFN- γ stimulate hepatic cholesterol synthesis in mice, whereas IFN- α and IL-2 have no such effect (31). Like LPS, both TNF and IL-1 stimulate *de novo* hepatic cholesterol by increasing the activity and mRNA expression of HMG-CoA reductase (88, 92). TNF and IL-1 decrease squalene synthase activity and mRNA expression (89); they may also divert the flux of mevalonate metabolites into nonsterol pathways during the APR.

In primates, including humans, infection/inflammation decreases serum cholesterol as a result of decreases in both LDL and HDL cholesterol (16, 17, 24, 25). LPS, TNF, IL-2, IFN- β , granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor decrease serum cholesterol, whereas IL-1 has no effect (24, 25, 36, 42, 93–97). The decrease in cholesterol is accompanied by a reduction in serum apoB levels.

The mechanism by which infection/inflammation decreases cholesterol levels has not been thoroughly studied in intact primates. Most of the mechanistic studies were performed *in vitro* using human hepatoma HepG2 cells. IL-1 inhibits cholesterol synthesis and decreases cholesterol and apoB secretion, whereas IL-6 increases cholesterol synthesis but decreases cholesterol secretion (98). IFN- β also decreases apoB synthesis (99).

LDL clearance. In rats, LPS significantly inhibits the clearance of LDL from the circulation (100). LPS decreases the expression of hepatic LDL receptor protein (Table 2), but the decrease in protein levels could not be explained by changes in mRNA levels, suggesting that posttranscriptional regulation occurs during the APR (101). In a rat model of gram-negative sepsis, the rate of apoB degradation is decreased (87). In hamsters, however, LPS, IL-1, and TNF either have no effect or produce a slight increase in hepatic LDL receptor mRNA and protein levels (27). In human HepG2 cells, IL-1 and TNF increase LDL receptor activity (102, 103). The differences may explain the species-specific response in cholesterol metabolism commonly seen during the APR.

Decreased hepatic cholesterol catabolism and excretion. Equipped with a number of enzymes and transporters, hepatocytes secrete bile salts, phospholipids, cholesterol, organic anions, and cations into the bile. Cholesterol returned to the liver is primarily metabolized into bile acids, representing the major pathway for the elimination of cholesterol from the body. There are two distinct pathways of bile acid synthesis in mammalian liver (104, 105). The classic or neutral pathway is initiated by microsomal cholesterol 7 α -hydroxylase (CYP7A1) that converts cholesterol into 7 α -hydroxycholesterol, which is subsequently converted into primary bile acids. The alternative or acidic pathway is initiated by mitochondrial sterol 27-hydroxylase (CYP27A1) that converts cholesterol into 27-hydroxycholesterol, which is then converted into 7 α ,27-dihydroxycholesterol by oxysterol 7 α -hydroxylase (CYP7B1) and subsequently metabolized into primary bile acids. The alternative pathway may contribute as much as 50% to total bile acid synthesis (104, 105). Primary bile acids synthesized in hepatocytes are conjugated with taurine and glycine. At physiological pH, these conjugates exist in the anionic salt form; therefore, they are called bile salts. Secretion of bile salts mediates the solubilization of lipids from the canalicular membrane, resulting in the secretion of biliary phospholipids and cholesterol.

As polarized cells, hepatocytes contain multiple transporters at the basolateral (sinusoidal) and apical (canalicular) surfaces (106). Basolateral bile salt uptake from the portal circulation is primarily mediated by sodium taurocholate-cotransporting protein. Several organic anion-transporting proteins (OATPs), including OATP1, OATP2, and OATP4, are also involved in sodium-independent bile salt uptake. At the canalicular surface, bile salt secretion into the bile duct is mediated by members of the ATP binding cassette (ABC) superfamily. An ABC transporter hydrolyzes intracellular ATP to transport biliary components against the concentration gradient into the

bile. The canalicular bile salt export pump (BSEP or ABCB11) secretes monovalent bile salts, whereas multidrug resistance-associated protein-2 (MRP2 or ABCG2) secretes divalent bile salts. Once secreted into the bile, bile salts stimulate the secretion of phospholipids and cholesterol from the canalicular membrane, forming micelles. Multidrug resistance-3 (MDR3 or ABCB4 in humans or MDR2 in rodents) is a phospholipid transporter. Secretion of intact cholesterol into bile is mediated by a heterodimer of two ABC transporters, ABCG5 and ABCG8 (107, 108). These transporters are transcriptionally regulated by a variety of nuclear hormone receptors (106).

LPS and cytokines decrease the catabolism and excretion of cholesterol. In the liver, LPS markedly decreases the mRNA expression and activity of CYP7A1, the rate-limiting enzyme in the classic pathway of bile acid synthesis (109) (Fig. 3). This effect is very rapid, occurring within 90 min of LPS administration, and is sustained for at least 16 h (109). LPS also decreases the mRNA expression and activity of CYP27A1, the rate-limiting enzyme in the alternative pathway of bile acid synthesis, and mRNA levels of CYP7B1 in the liver (110) (Fig. 3). The decreases in CYP27A1 and CYP7B1 occur 8–16 h after LPS administration and persist for at least 24 h, suggesting that both the classic and alternative pathways of bile acid synthesis are sequentially downregulated during infection and inflammation. Like LPS, both TNF and IL-1 also decrease hepatic CYP27A1 and CYP7B1 mRNA expression (110).

Infection is associated with intrahepatic cholestasis that may be attributable to effects on biliary transport. LPS administration in rodents reduces bile salt uptake, bile salt

secretion, and bile flow, which are mediated by decreases in the expression of several transporters involved in the hepatocellular uptake, including NCTP, OATP1, and OATP2 (111–114), and canalicular excretion of bile salts, including BSEP and MRP2 (114, 115). LPS and cytokines also decrease the expression of MDR2 in rats, which mediates phospholipid secretion into bile (114, 116). Moreover, LPS coordinately decreases hepatocyte mRNA levels for ABCG5 and ABCG8, which mediate cholesterol excretion into the bile (117). Thus, biliary secretion of bile salts, phospholipids, and cholesterol are all impaired during infection. Figure 3 summarizes the effect of APR on bile acid metabolism.

The coordinated downregulation of both pathways of bile acid synthesis during the APR is in contrast to most other situations, including studies in knockout animals, in which during the suppression or absence of one pathway of bile acid synthesis the enzymes of the other pathway are upregulated to compensate for the deficiency. The decreases in the regulatory enzymes of both the classic and alternative pathways of bile acid synthesis as well as the decrease in ABCG5 and ABCG8 induced by LPS and cytokines suggest that during infection the body's need to conserve cholesterol is so essential that all of these pathways are downregulated to limit the elimination of cholesterol from the body. A decrease in cholesterol catabolism would make cholesterol more available for hepatic lipoprotein production.

Lipoprotein [a]. Lipoprotein [a] (Lp[a]) is a distinct lipoprotein consisting of an LDL particle attached to apo[a] that is present in primates but not in rodents and most other species (118). Lp[a] is cholesterol-rich; increased serum levels have been associated with a higher risk for atherosclerosis. The physiological role of Lp[a] is not known, but it is thought to be involved in wound healing. The structure of apo[a] resembles plasminogen, and apo[a] has been found in the lesions during early stages of wound healing. Alternatively, Lp[a] may act as a scavenger of oxidized lipids, as Lp[a] contains platelet-activating factor acetylhydrolase (PAF-AH) (119), an enzyme that inactivates PAF and oxidized lipids.

Whether Lp[a] is an acute-phase reactant is unclear. Some studies showed that levels of Lp[a] are increased during stress (120, 121), whereas others reported no changes or a reduction (122, 123). These conflicting data may be attributable to the specificity of the assays used to measure Lp[a] levels or to interindividual variation in plasma Lp[a] levels in the population.

HDL metabolism and decreased RCT. During infection and inflammation, there is a marked decrease in serum levels of HDL and apoA-I (16, 17, 27, 124). Furthermore, circulating HDL during infection, known as acute-phase HDL, has different characteristics from normal HDL. Acute-phase HDL is larger than normal HDL₃, its radius extending into the HDL₂ range, but it has a density comparable to that of HDL₃ (125). Acute-phase HDL is depleted in cholesteryl ester but enriched in free cholesterol, TG, and free FAs (24, 25, 27, 125–127). The phospholipid content of acute-phase HDL was increased in some studies (24,

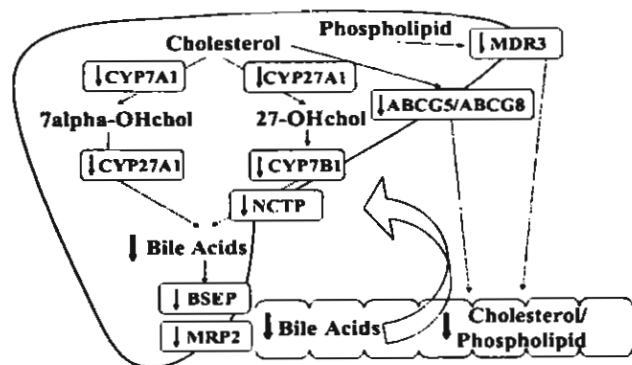


Fig. 3. Changes in bile acid metabolism during the APR. LPS and cytokines decrease the catabolism and excretion of cholesterol in the liver by decreasing the expression and activities of enzymes in both the classic pathway and the neutral pathway, including cholesterol 7 α -hydroxylase (CYP7A1), sterol 27-hydroxylase (CYP27A1), oxysterol 7 α -hydroxylase (CYP7B1), and sterol 12 α -hydroxylase. LPS also decreases the expression of several protein transporters involved in the canalicular excretion of bile salts, such as bile salt export pump (BSEP) and multidrug resistance-associated protein-2 (MRP2), and those in the hepatocellular uptake of bile salts, including sodium taurocholate-cotransporting protein and organic anion-transporting proteins. Furthermore, LPS decreases the excretion of cholesterol and phospholipids into the bile by downregulating ABCG5/ABCG8 and multidrug resistance-3 (MDR3), respectively.

27) but decreased in others (124, 125). In patients who underwent bypass surgery, acute-phase HDL had the same phospholipid-neutral lipid ratio, a decrease in phosphatidylethanolamine and phosphatidylinositol, and an increase in isoprostone-containing phosphatidylcholine and lysophosphatidylcholine (LPC) (127). In humans, there was a decrease in HDL sphingomyelin content (127), but an increase was observed in hamsters (128).

The hallmark of acute-phase HDL is an increase in apoSAA (24, 124, 125, 129, 130) and a decrease in apoA-I content (24, 124, 127, 130) (Table 3). The content of apoA-II and apoCs is decreased (24, 124, 130, 131), whereas apoE is found to be increased in some studies (24, 132) but decreased in others (130). HDL-associated apoJ is increased during inflammation and infection in rodents and humans (133–135). In contrast, several other proteins, including LCAT (24, 25, 136), cholesteryl ester transfer protein (CETP) (137, 138), hepatic lipase (HL) (139), and paraoxonase 1 (PON1) (134, 140), are decreased during the APR. The activity of HDL-associated plasma PAF-AH is acutely increased during inflammation in several rodent species (141), but a late decrease has also been reported in rabbits and mice (134, 135). Phospholipid transfer protein (PLTP) is decreased in rats injected with LPS (142), but data in humans are conflicting (132, 143). Finally, secretory phospholipase A₂ (sPLA₂), a phospholipase enzyme that hydrolyzes phospholipids in HDL, and LPS-binding protein (LBP) are markedly induced during infection and inflammation (144). SAA-rich HDL particles that are devoid of apoA-I have also been reported (145). We recently found that apoA-IV and apoA-V levels are increased in acute-phase HDL (our unpublished observations).

Although it is well established that infection and inflammation are associated with a reduction in serum HDL and apoA-I levels, the exact mechanism has not yet been established. Because apoSAA can displace apoA-I from HDL (146, 147) and apoSAA-rich HDL particles are rapidly cleared from the circulation (148), it has been assumed

that the several-fold increase in apoSAA content in HDL is the mechanism for the decrease in apoA-I and HDL levels. However, we have shown that the decrease in HDL is very rapid, occurring before the increase in SAA (136). Furthermore, a study in mice in which apoSAA levels were markedly increased to levels comparable to those seen in infection found no changes in HDL cholesterol or apoA-I levels (149). Thus, high levels of SAA per se do not decrease HDL or apoA-I levels in the absence of the other changes that occur during infection and inflammation.

An increase in sPLA₂ has also been proposed to contribute to the reduction in HDL during infection/inflammation. Mice overexpressing sPLA₂ have reduced HDL concentrations (150), and HDL from these mice is catabolized more rapidly than HDL from normal mice (151). Although apoSAA is known to activate sPLA₂, overexpression of SAA in addition to sPLA₂ does not cause a greater reduction in the levels of HDL or apoA-I (152), further suggesting that the reduction of HDL during infection is not caused by an increase in apoSAA.

Endothelial lipase (EL) has been shown to regulate HDL metabolism (153–155). EL is synthesized by the endothelial cells and possesses phospholipase A-I activity. Overexpression of EL reduces HDL cholesterol levels (153), whereas inhibition of EL increases HDL levels (156). Treatment of cultured endothelial cells with TNF- α or IL-1 β has been shown to increase the expression of EL (157). If similar effects occur in vivo, it may provide another mechanism for the reduction in HDL levels during infection.

The decrease in LCAT activity during infection may decrease HDL cholesterol levels caused by impaired esterification, similar to what is found in humans or animals with mutations in the LCAT gene (158). The decrease in HL may reduce pre- β HDL generation. Moreover, TG enrichment of HDL during infection may lead to the rapid clearance of apoA-I (159). Which of these changes contributes to the reduction of HDL and apoA-I during the APR is not yet established, but none accounts for the early decrease.

TABLE 3. Changes in proteins involved in HDL metabolism during infection and inflammation

Proteins	Effects
Increased	
Apolipoprotein serum amyloid A	Decreases cholesterol uptake by hepatocytes; increases cholesterol uptake into macrophages
Secretory phospholipase A ₂	Decreases phospholipid content of HDL and impairs cholesterol removal from cells
ApoJ	Not known
PAF-AH	Increases lysophosphatidylcholine production
LPS binding protein	Increases neutralization of endotoxin by HDL
ApoE	Increases cholesterol delivery to cells; redirects endotoxin from macrophages to hepatocytes
ApoA-IV	Decreases endotoxin-induced stimulation of monocytes
ApoA-V	Not known
Ceruloplasmin	Enhances LDL oxidation
Decreased	
ApoA-I	Impairs cholesterol removal from cells
ApoA-II	Not known
LCAT	Impairs cholesterol removal from cells
CETP	Impairs cholesterol transfer to apoB-containing lipoproteins
Hepatic lipase	Decreases pre- β HDL generation
Paraoxonase 1	Decreases the ability of HDL to protect against LDL oxidation
Transferrin	Decreases the ability of HDL to protect against LDL oxidation

apoJ, apolipoprotein J; CETP, cholesteryl ester transfer protein; PAF-AH, platelet-activating factor acetylhydrolase.

HDL metabolism is tightly linked to RCT, a process by which cholesterol is removed from peripheral cells and transported to the liver for metabolism and/or excretion (160, 161). Several HDL-associated proteins and a number of cell surface receptors play a key role in RCT (Fig. 4). ApoA-I on HDL and ABCA1 in the plasma membrane are required for apolipoprotein-mediated cholesterol efflux. Subsequently, LCAT, which converts free cholesterol on HDL into cholesteryl ester, assists in cholesterol efflux by an aqueous diffusion mechanism. CETP then mediates the exchange of cholesteryl ester in HDL for TG in TG-rich lipoproteins. PLTP transfers phospholipids from TG-rich lipoproteins into HDL and promotes the remodeling of HDL. HL hydrolyzes TG and phospholipids in large α -HDL, generating small pre- β HDL particles that are efficient acceptors of cholesterol from plasma membrane. In the liver, scavenger receptor class B type I (SR-BI) plays a key role in the selective uptake of cholesteryl ester, whereas the β -chain of ATP synthase mediates endocytosis of HDL particles.

During infection and inflammation, there is a reduction in RCT attributable to multiple changes at each step in the pathway (Fig. 4). ABCA1 mRNA and protein levels in macrophages are decreased by LPS and cytokines (117, 162), impairing cholesterol efflux from cells. The decreases in apoA-I, HDL, and LCAT impair the acceptance of cellular cholesterol (163). The decrease in CETP activity limits the transfer of cholesteryl ester to TG-rich lipoproteins, further retarding the RCT pathway (138). HL activity is decreased (139), which would reduce the generation of pre- β HDL particles. In addition, during the APR, mRNA expression and protein levels of SR-BI in the liver are markedly decreased, which is accompanied by decreased cholesteryl ester uptake into hepatocytes (164). Therefore, during infection and inflammation, RCT is affected at the level of cholesterol removal from cells, transfer among particles, and uptake by the liver.

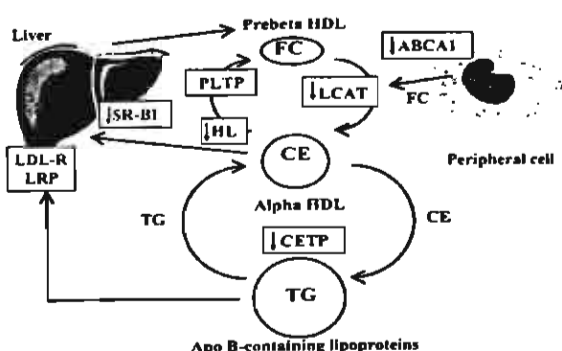


Fig. 4. Changes in reverse cholesterol transport during the APR. LPS and cytokines decrease ABCA1 and cholesterol efflux from peripheral cells to HDL. LPS also decreases several enzymes involved in HDL metabolism, including LCAT, cholesteryl ester transfer protein (CETP), and hepatic lipase (HL). In addition, LPS and cytokines downregulate hepatic scavenger receptor class B type I (SR-BI), resulting in a decrease in cholesteryl ester (CE) uptake into the liver. FC, free cholesterol; LDL-R, LDL receptor; LRP, LDL receptor related protein; PLTP, phospholipid transfer protein.

Sphingolipid metabolism

Sphingolipids such as ceramide and sphingomyelin are important constituents of plasma membranes. Glycosphingolipids (GSLs) are complex sphingolipids that contain a hydrophobic ceramide moiety and a hydrophilic oligosaccharide residue. Both sphingolipids and GSLs are components of plasma lipoproteins and are involved in several biological processes, including cell recognition and proliferation, signal transduction, interaction with bacterial toxins, and modulation of the immune response.

The metabolism of sphingolipids and GSLs is altered during infection and inflammation. LPS stimulates hepatic ceramide and sphingomyelin synthesis by increasing the mRNA expression and activity of serine palmitoyltransferase (SPT), the first and rate-limiting enzyme in sphingolipid synthesis that catalyzes the condensation of serine with palmitoyl-CoA (128) (Fig. 5). LPS increases the transcription rate, mRNA expression, and activity of glucosylceramide (GlcCer) synthase, the first committed enzyme in the GSL synthesis pathway, in the liver (165). GlcCer is the precursor of all neutral GSLs as well as sialic acid-containing acidic GSLs or gangliosides. The LPS-induced increase in GlcCer expression occurs earlier than the increase in SPT mRNA levels. It is possible that the increase in hepatic GlcCer production during the APR is the primary event, which then signals for more substrate, resulting in the induction of SPT and subsequent increase in ceramide synthesis. This hypothesis is supported by the fact that steady-state levels of GlcCer and its distal metabolites, including ceramide trihexoside and ganglioside GM3, are increased in the liver after LPS treatment (165), whereas in contrast, the content of ceramide, the substrate for GlcCer synthesis, is decreased in the liver despite the increase in SPT (165). Like LPS, TNF and IL-1 also increase both SPT and GlcCer mRNA expression in the

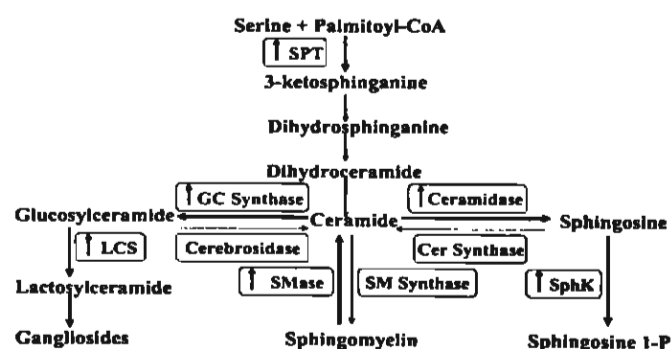


Fig. 5. Changes in sphingolipid metabolism during the APR. LPS and cytokines stimulate ceramide (Cer) and sphingomyelin (SM) synthesis in the liver by increasing the expression and activity of serine palmitoyltransferase (SPT), the rate-limiting enzyme in sphingolipid synthesis. LPS also increases the activity of glucosylceramide (GC) synthase, the first committed enzyme in the glycosphingolipid synthesis pathway. As a result, lipoproteins are enriched with ceramide, sphingomyelin, and glycosphingolipids. In addition, LPS and cytokines increase the activity of secretory sphingomyelinase (SMase) in the serum, resulting in increased levels of ceramide in serum. 1-P, 1-phosphate.

liver, suggesting that these cytokines mediate the LPS effect (128, 165).

Likely as a consequence of the LPS-induced increase in hepatic sphingolipid synthesis, all lipoprotein fractions isolated from LPS-treated animals contain significantly higher levels of ceramide, sphingomyelin, and GlcCer (128). An increase in ceramide content in LDL may enhance the susceptibility of LDL toward aggregation.

LPS also upregulates the mRNA expression and activities of SPT and GlcCer synthase in extrahepatic tissues, including spleen and kidney (166). The content of ceramide in spleen or kidney, however, is not increased, suggesting that newly synthesized ceramide is used as a substrate to increase GlcCer synthesis (166). Specific GSLs are ligands for a T-cell receptor expressed on natural killer T-lymphocytes, and GSLs stimulate the proliferation of specific subsets of lymphocytes (167). One can speculate that the LPS-induced increase in GSL content of these tissues is used to regulate cellular proliferation and modulate the immune response.

In addition to activating the enzymes that synthesize sphingolipids and GSLs, LPS and cytokines also induce enzymes involved in the hydrolysis of sphingolipids (Fig. 5). Treatment with LPS, TNF, or IL-1 acutely increases the serum activity of secretory sphingomyelinase (168). Serum ceramide levels are increased in animals treated with LPS and in patients with sepsis (128, 169, 170). The APR also activates ceramide-metabolizing enzymes. IL-1 activates both neutral and acid ceramidases in cultured rat hepatocytes, resulting in increased formation of sphingosine (171), whereas in cultured endothelial cells, TNF induces sphingosine kinase activity and increases the formation of sphingosine-1-phosphate (172). These studies suggest that several enzymes involved either in the *de novo* synthesis of ceramide and its downstream metabolites or in the hydrolysis of ceramide are induced by LPS and cytokines. Because ceramide and its metabolites are involved in signal transduction and cellular regulation, particularly in cells of the immune system, it makes sense that several anabolic and catabolic pathways of sphingolipid metabolism are induced during infection and inflammation to maintain a delicate balance between ceramide and its metabolites in the cell. Figure 5 summarizes the effects of LPS and APR-inducing cytokines on sphingolipid and GSL metabolism.

ROLE OF NUCLEAR HORMONE RECEPTORS IN THE REGULATION OF LIPID METABOLISM DURING INFECTION AND INFLAMMATION

Nuclear hormone receptors and lipid metabolism

Most, if not all, of the changes in lipid metabolism that are induced by infection and inflammation are attributable to changes in gene transcription (13). The mechanisms by which gene transcription is increased during the APR have been extensively studied. Class 1 positive acute-phase proteins are increased by IL-1-type cytokines, whereas the IL-6 family of cytokines increase class 2 positive acute-

phase proteins (173, 174). Activation of nuclear factor κ B (NF- κ B) and nuclear factor interleukin-6 (NF-IL-6) mediates IL-1-stimulated increases in acute-phase protein transcription, whereas activation of NF-IL-6 and the Janus kinase-signal transducers and activators of transcription pathway mediates IL-6 family stimulation of acute-phase protein transcription (174). Much less is understood regarding the mechanism of the downregulation of transcription of negative acute-phase proteins during the APR, and many of the changes in lipid metabolism seen in infection and inflammation are mediated by decreases in proteins and their transcription (13).

Nuclear hormone receptors are a large family of transcription factors, characterized by a central DNA binding domain that targets the receptor to specific DNA sequences (response elements) and a C-terminal portion that includes a ligand binding domain, which recognizes specific hormones, vitamins, drugs, or other lipophilic compounds (175–178). Several nuclear hormone receptors, including the peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), and farnesoid X receptor (FXR), bind and are activated by lipids (176–181). Furthermore, the increased activity of these receptors regulates the transcription of a large number of genes involved in multiple aspects of lipid and lipoprotein metabolism (182). Because of their abilities to sense intracellular lipid levels and orchestrate changes in lipid metabolism, these nuclear hormone receptors have been recognized as liposensors (178). Finally, these liposensors (PPARs, LXRs, and FXR) heterodimerize with retinoid X receptors (RXRs) for efficient gene regulation (175). As discussed in detail below, most of the genes of lipid metabolism that decrease during the APR are regulated by these liposensors and related transcription factors, and the downregulation of these liposensors plays a key role in those changes.

Regulation of liposensors during infection and inflammation

In hamsters and mice, LPS administration decreases both protein and mRNA levels of RXR- α , - β , and - γ in the liver (183) (Table 4). The decrease in RXR occurs rapidly (within 4 h) and is sustained. Administering TNF and IL-1 reproduces these LPS effects. Similar reductions in RXR isoforms are seen in Hep3B cells treated with TNF and IL-1 but not IL-6, indicating that the decreases are directly induced by the cytokines (M-S. Kim, J. K. Shigenaga, A. H. Moser et al., unpublished observations). Furthermore, LPS administration also significantly reduces the hepatic nuclear DNA-binding activity of RXR homodimers to an RXR response element (183).

In addition to inhibiting the expression of the obligate liposensor heterodimer partner RXR, LPS and cytokine administration also reduces hepatic mRNA levels of PPAR- α and - γ , LXR- α , FXR, pregnane X receptor (PXR), and constitutive androstane receptor (CAR) (183–185). These decreases were associated with reductions in nuclear binding activity to a direct repeat-1 (DR-1) PPAR response element, a DR-1 LXR response element, and an in-

TABLE 4. Changes in nuclear hormone receptors and their target genes involved in FA and TG metabolism during infection and inflammation

Tissue	Nuclear Receptor	Target Genes	Function
Adipocytes	PPAR- γ ↓	AP2 ↓ LPL ↓ FATP ↓ CD36/FAT ↓ ACS ↓	Fatty acid transport (intracellular) TG catabolism Fatty acid transport Fatty acid and oxidized LDL uptake Fatty acid esterification
Heart	PPAR- α ↓ PPAR- β/δ ↓	LPL ↓ FATP ↓ CD36/FAT ↓ H-FABP ↓ CPT-1 β ↓ ACS ↓	TG catabolism Fatty acid transport Oxidized LDL uptake Fatty acid transport (intracellular) Fatty acid oxidation Fatty acid esterification
Skeletal muscle	PPAR- α ? PPAR- β/δ ?	LPL ↓ FATP ↓ CD36/FAT ↓ H-FABP ↓ ACS ↓	TG catabolism Fatty acid transport Oxidized LDL uptake Fatty acid transport (intracellular) Fatty acid esterification
Liver	PPAR- α ↓ PPAR- γ ↓ FXR ↓	FATP ↓ CD36/FAT ↓ H-FABP ↓ CPT-1 α ↓ ApoC-II ↓ ApoE ↓	Fatty acid transport Oxidized LDL uptake Fatty acid transport (intracellular) Fatty acid oxidation Increases LPL activity Lipoprotein metabolism

ACS, acyl-CoA synthetase; AP2, adipocyte P2; CPT, carnitine palmitoyl transferase; FABP, fatty acid binding protein; FAT, fatty acid translocase; FATP, fatty acid transport protein; FXR, farnesoid X receptor; H-FABP, heart-FABP; PPAR, peroxisome proliferator-activated receptor; ↓, decreased levels of mRNA after LPS treatment.

verted repeat-1 FXR response element (183, 184). In contrast, mRNA levels of PPAR- β/δ and LXR- β were not significantly altered in the liver after LPS treatment.

In adipose tissue, PPAR- γ levels decrease after the administration of LPS or TNF (186) (Table 4). Treatment of adipocytes in vitro with TNF, IFN- γ , and IL-11 decreases mRNA levels of PPAR- γ (187–191). The effect of LPS and cytokines on RXR isoforms and other liposensors in adipose tissue remains to be determined. In cardiac muscle, our laboratory recently reported that LPS administration decreases RXR- α , - β , and - γ and PPAR- α and - β/δ expression (192) (Table 4). To our knowledge, studies of the effect of inflammation and infection on the expression of RXR, PPAR, and other liposensors in skeletal muscle have not been carried out. Lastly, although the levels of liposensors are regulated in tissues that play a major role in the alterations of lipid metabolism during the APR, recent studies by our laboratory have shown that changes in the levels of RXR, PPARs, and LXRs were not found in the small intestine, an organ in which lipid metabolism is not significantly altered during infection and inflammation (117). Thus, liposensor levels specifically change in the tissues that exhibit changes in lipid metabolism during the APR.

Consequences of decreased expression of liposensors

Although it is likely that many factors influence the diverse changes in lipid and lipoprotein metabolism that occur in response to infection/inflammation, alterations in the activity of nuclear hormone receptor liposensors are likely to play a pivotal role in the coordinated regulation of FA and cholesterol metabolism that occurs during the APR, as can be seen by examining the effects on genes that liposensors are known to regulate.

FA and TG metabolism. As discussed earlier, infection/inflammation is characterized by an increase in lipolysis and a decrease in FA oxidation in adipose tissue, contributing to hypertriglyceridemia (26). PPAR- γ has been shown to directly regulate genes that promote the storage of fat in adipose tissue, including adipocyte P2, LPL, FATP, CD36/FAT, and ACS (179, 193, 194). As discussed above, during infection and inflammation the expression of these genes is decreased, and it is likely that the reduction in PPAR- γ activity in adipose tissue contributes to the changes in these proteins that would reduce fat storage and enhance lipolysis.

Likewise, downregulation of RXR- α , - β , and - γ and PPAR- α and - β/δ in cardiac muscle would be expected to reduce FA oxidation. Activation of PPAR- α and - β/δ induces the expression of many key enzymes required for FA oxidation, including LPL, FATP, CD36/FAT, heart-FABP (H-FABP), CPT-1 β , and ACS (179, 195–198). One can postulate that a reduction in PPAR- α and - β/δ activity in the heart during the APR contributes to the decreased expression of these genes (67, 68, 71, 199) (Table 4). In skeletal muscle, there is also a decrease in FA oxidation, which is associated with a decrease in LPL, FATP, CD36/FAT, H-FABP, and ACS (67, 68, 71, 200). Whether levels of RXR- α , - β , and - γ and PPAR- α and - β/δ change in skeletal muscle during the APR remains to be determined.

Downregulation of RXR- α , - β , and - γ and PPAR- α and - γ in the liver during the APR could also reduce hepatic FA oxidation, as a number of key PPAR-regulated proteins required for FA oxidation are decreased, including FATP, CD36/FAT, liver-FABP, and CPT-1 α (ACS is decreased in mitochondria but not in endoplasmic reticulum) (67, 68, 70, 71) (Table 4). In contrast, many proteins involved in the reesterification of FA and the secretion of VLDL

from the liver are not decreased and are not regulated by the PPARs.

Decreased hepatic FXR activity could also contribute to the increase in serum TGs during infection (184). FXR-deficient mice have increased serum TG levels (201), and FXR has been shown to regulate the hepatic expression of apoC-II and apoE (202, 203), both of which are decreased during the APR (85, 184).

Regulation of gene transcription is complex, involving multiple transcription factors. Therefore, changes in PPARs, FXR, and RXR are unlikely to be the only transcription factors that regulate the genes of interest during the APR. For example, Berg, Calnek, and Grinnell (204, 205) have shown that IL-1- and IL-6-induced decreases in apoE mRNA levels in HepG2 cells are associated with the phosphorylation of BK virus enhancer factor-1, a member of the NF-1 family of nuclear factors, to its isoform B1. An increase in B1 is associated, by unknown mechanisms, with decreases in apoE mRNA levels (205). Thus, an increase in the B1 isoform coupled with the reduction in FXR activity during infection and inflammation may together result in the decrease in apoE expression. Likewise, we recently found that PPAR- γ coactivating factor-1 (PGC-1), which interacts with PPAR- α , PPAR- γ , hepatocyte nuclear factor-4 (HNF-4), and other nuclear hormone receptors, is reduced during the APR (M-S. Kim, J. K. Shigenaga, A. H. Moser, et al., unpublished observations).

Thus, decreases in RXR, PPARs, LXR, and related transcription factors in adipose tissue, muscle, and liver could be mechanisms by which the characteristic changes in TG and FA metabolism that occur during infection and inflammation are induced.

RCT. RCT is a complex process that involves transporters in peripheral tissues and liver, enzymes and transfer proteins in the serum, receptors in the liver, the synthesis of bile acids in the liver, and the secretion of cholesterol

and bile acids into the bile (160, 161). Many of the proteins essential for RCT are regulated by liposensors (181), whose changes could mediate the reduction in RCT that occurs during infection and inflammation.

PERIPHERAL TISSUES. ABCA1 transporters play a dominant role in the movement of cholesterol from cells to HDL and are regulated by LXR (206–208). Treatment of macrophages with LPS or cytokines decreases ABCA1 (117, 162). However, no change in RXR or LXR that could account for the reduction in ABCA1 expression was found in macrophages (117, 209) (Table 5). Recently, bacterial infection was found to activate Toll-like receptor 4, inhibiting the induction of LXR target genes, including ABCA1 (209). This cross-talk between LXR and Toll-like receptor signaling decreases cholesterol efflux from macrophages (209). In addition, LPS-induced decreases in the expression of CYP27A1 would decrease the production of 27-hydroxycholesterol, a likely endogenous ligand of LXR, further explaining the effect of LPS on LXR target genes (110).

ENZYMES AND TRANSFER PROTEINS IN THE SERUM. CETP mediates the transfer of cholesteryl ester from HDL to apoB-containing lipoproteins (210). CETP expression is regulated by LXR activity (211); decreased RXR/LXR activity in the liver likely contributes to the reduced CETP expression seen during the APR. PLTP mediates the transfer of phospholipids and cholesterol from TG-rich lipoproteins to HDL. PLTP expression in the liver is regulated by FXR activity (212); decreased RXR/FXR activity in the liver could contribute to the reduction in hepatic PLTP expression during the APR (142) (Table 5).

RECEPTORS IN THE LIVER. SR-BI mediates the selective uptake of cholesteryl esters from HDL into the liver (213). PPARs and FXR regulate the expression of SR-BI (214, 215). Therefore, the decrease in PPAR/RXR and FXR/RXR activity in the liver could mediate the decrease in SR-BI expression during the APR (Table 5).

TABLE 5. Changes in nuclear hormone receptors and their target genes involved in reverse cholesterol transport during infection and inflammation

Tissue	Nuclear Receptor	Target Genes	Function
Macrophage	LXR $\leftrightarrow$	ABCA1 $\downarrow$	Cholesterol efflux
Liver	LXR $\downarrow$	CETP $\downarrow$	Cholesteryl ester transfer
		ABCG5/ABCG8 $\downarrow$	Cholesterol and phytosterol efflux
		CYP7A1 $\downarrow$	Bile acid synthesis
	FXR $\downarrow$	PLTP $\downarrow$	Phospholipid transfer
		MDR-2 $\downarrow$	Phospholipid secretion
		SHP $\downarrow$	Inhibits bile acid synthesis
		BSEP $\downarrow$	Canalicular bile salt excretion
		SR-BI $\downarrow$	Cholesteryl ester uptake
	PPAR- α $\downarrow$	MDR-2 $\downarrow$	Phospholipid secretion
	PXR $\downarrow$	MDR-2 $\downarrow$	Phospholipid secretion
	LRH-1 $\downarrow$	CYP7A1 $\downarrow$	Bile acid synthesis
		CYP8B1 $\downarrow$	Cholic acid synthesis
	HNF-4 $\downarrow$	CYP8B1 $\downarrow$	Cholic acid synthesis
	HNF-1 α $\downarrow$	CYP27A1 $\downarrow$	Bile acid synthesis

BSEP, bile salt export pump; CYP7A1, cholesterol 7 α -hydroxylase; CYP8B1, sterol 12 α -hydroxylase; CYP27A1, sterol 27-hydroxylase; HNF, hepatocyte nuclear factor; LRH-1, liver receptor homolog-1; LXR, liver X receptor; MDR-2, multidrug resistance-2; PLTP, phospholipid transfer protein; PXR, pregnane X receptor; SHP, small heterodimer partner; SR-BI, scavenger receptor class B type 1; $\leftrightarrow$, unchanged; $\downarrow$, decreased.

* Not a nuclear hormone receptor.

HEPATIC SYNTHESIS OF BILE ACIDS. CYP7A1 is the key rate-limiting enzyme in the neutral bile acid synthetic pathway (105). CYP7A1 is regulated by LXR in rodents and FXR in rodents and humans (216–219). In contrast, increases in FXR/RXR activation reduce CYP7A1 activity by increasing small heterodimer partner (SHP), which in turn blocks the ability of the transcription factor liver receptor homolog-1 (LRH-1), to stimulate CYP7A1 expression (220).

During infection/inflammation, RXR, LXR, FXR, SHP, LRH-1, and other transcription factors decrease, with the net result being a decrease in CYP7A1 activity, despite the decreases in FXR and SHP (183, 184). There are several possible explanations for the decrease in CYP7A1 activity during the APR. First, LXR/RXR activation may be a dominant factor in regulating the transcription of CYP7A1 (221); hence, the reduction in LXR/RXR activity may result in decreased CYP7A1 expression. Second, the decrease in FXR/RXR activity and SHP may not be crucial in the complex setting of inflammation; their decrease would normally result in an increase in the activity of LRH-1, but during the APR LRH-1 is independently reduced (184), thereby decreasing CYP7A1. Lastly, expression of CYP7A1 is regulated by a number of other transcription factors, such as HNF-4, PXR, and thyroid hormone receptor (TR) (222); our laboratory and others have shown that these transcription factors are also down-regulated during the APR (185, 223, 224). Thus, multiple factors may produce the decrease in CYP7A1 expression (Table 5).

Sterol 12 α -hydroxylase (CYP8B1) is an enzyme in the bile synthetic pathway responsible for cholic acid synthesis (105). Unpublished studies by our laboratory have shown that mRNA levels of CYP8B1 decrease after LPS administration. Two key transcription factors that increase the expression of CYP8B1 are LRH-1 and HNF-4 (225, 226), both of which are decreased during the APR (184, 223, 227), which could account for the decrease in CYP8B1 mRNA (Table 5).

During the APR, expression of CYP27A1, a key enzyme in both the classic and alternative pathways of bile acid synthesis, is decreased (110). HNF-1, the transcription factor regulating the expression of CYP27A1 (228), is decreased during the APR (110, 227, 229), which could account for the changes (Table 5). HNF-4 stimulates the expression of HNF-1; the decrease in HNF-4 that occurs in the APR could explain the decrease in HNF-1.

SECRETION OF CHOLESTEROL AND BILE ACIDS INTO THE BILE. As discussed above, the secretion of bile acids into the bile is mediated by BSEP and MRP2, the secretion of cholesterol is mediated by ABCG5/ABCG8, and the secretion of phospholipids is mediated by MDR2 (106, 107). Expression of these transporters is regulated by liposensors. Specifically, FXR activation increases BSEP expression (230), FXR, PXR, and CAR activation increase MRP2 expression (231), LXR activation increases ABCG5 and ABCG8 expression (232), and PPAR- α activation increases MDR2 expression (233). Thus, the decreases in FXR, LXR, PPAR- α , PXR, and CAR during the APR (183–185) are

likely to contribute to decreases in these transporters and to decreased secretion of lipids into the bile (Table 5).

As summarized in Tables 4 and 5, these data demonstrate that the reduction in the nuclear hormone liposensors (PPARs, LXR, and FXR) could account for many of the changes in lipid and lipoprotein metabolism that occur during infection and inflammation. However, we have also shown that changes occur in several related transcription factors, and it is likely that other transcription factors are also involved in the complex regulation that occurs during the APR. Lastly, as additional regulatory functions of PPARs, LXR, FXR, RXR, PXR, CAR, and TR are recognized, the decrease in these nuclear hormone receptors may be shown to mediate other changes in metabolism that occur during the APR, such as changes in glucose, bilirubin, steroid hormone, and drug metabolism.

PROATHEROGENIC CHANGES IN LIPID AND LIPOPROTEIN METABOLISM DURING INFECTION AND INFLAMMATION

The forgoing has demonstrated that during the course of infection and inflammation, a multitude of changes occur in the structure, composition, and function of lipoproteins. Many of these changes in lipoproteins are similar to those proposed to promote atherogenesis. Several epidemiological studies have suggested that the risk and/or incidence of coronary artery disease (CAD) is higher in patients with infections and/or chronic inflammatory diseases (234–237). Some studies have suggested that specific infectious agents, such as *Chlamydia pneumoniae* and cytomegalovirus, play a direct role in the vessel wall in the formation of atherosclerotic lesions (238, 239). However, the prevalence of CAD is also higher in patients with *Helicobacter pylori* infection, chronic dental infection, chronic urinary tract infections, and chronic bronchitis, infections in which the microorganisms are not localized to the vessel wall (240–242, 242a). The presence of circulating endotoxin also predicts future atherosclerosis (242a). Finally, there is an increased incidence of CAD in patients with inflammatory diseases such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus (243–246). Although all of these infections and inflammatory conditions have a distinct etiological origin, they are associated with a common, sustained systemic APR. In addition, more common diseases that predispose to atherosclerosis, such as diabetes, obesity, and metabolic syndrome, are also associated with inflammation (6–10). We have proposed that the APR-associated structural and functional changes in lipoproteins could be one possible link between infection/inflammation and atherosclerosis (14). Because atherosclerosis itself is an inflammatory disease and inflammation causes proatherogenic changes in lipoproteins, a vicious cycle could develop, resulting in worsening of atherosclerosis.

VLDL metabolism

Evidence is accumulating that TG-rich lipoproteins are proatherogenic (247–249). VLDLs from hypertriglyceri-

demic individuals are toxic to endothelial cells (250). They can interact with LDL receptors and receptors for apoB-48 on the monocytes/macrophages, resulting in enhanced lipid uptake and foam cell formation (251). VLDLs secreted by the liver after LPS administration are also enriched in sphingolipids (128). Because sphingomyelin enrichment can decrease the clearance of TG-rich lipoproteins (252), the increase in VLDL sphingolipids during infection and inflammation can result in the accumulation of atherogenic remnant particles. Thus, the APR-associated changes in TG and VLDL metabolism can be proatherogenic.

LDL metabolism

Although circulating levels of total and LDL cholesterol in humans decrease during infection, other changes in LDL metabolism could promote atherogenesis. In patients with acquired immune deficiency syndrome (AIDS), a decrease in LDL levels is associated with a decrease in particle size, resulting in small dense LDLs (subclass pattern B) (253). These LDL particles are more proatherogenic because they have a lower binding affinity for the LDL receptor, which leads to impaired clearance and increased circulation time for these particles (254). Moreover, small dense LDLs can cross the endothelial barrier more effectively and bind to proteoglycans in the vascular wall intima, resulting in LDL retention (255). Additionally, small dense LDLs are more susceptible to oxidative modifications, resulting in rapid uptake and cholesterol accumulation in the macrophages (256). The increase in small dense LDLs is likely the consequence of hypertriglyceridemia during infection (253).

Oxidative modification of LDL plays a central role in the pathogenesis of atherosclerosis (257). We have shown that the levels of several markers of lipid peroxidation, including conjugated dienes, thiobarbituric acid-reactive substances, lipid hydroperoxides, and LPC, are increased in serum and/or circulating LDL in animals treated with LPS (258). Moreover, LDL isolated from LPS-treated animals is more susceptible to oxidation *in vitro* (258). Children with infection have increased antibodies to oxidized LDL, and their LDL may be more susceptible to further oxidation in the vessel wall (259).

CRP is a classic acute-phase protein that binds phosphorylcholine residues of phospholipids or microbial products (260). CRP is associated with VLDL and LDL and is present in atherosclerotic lesions (261). High levels of CRP have been shown to be an independent risk factor for CAD, which is thought to represent the inflammatory nature of atherosclerosis (262). CRP binds oxidized LDL and oxidized phospholipids, which then enhances uptake by macrophages (263), promoting the formation of foam cells using the oxidized LDL.

During infection and inflammation, increases in sPLA₂ are likely to promote atherosclerosis. sPLA₂ hydrolyzes phospholipids in LDL at the *sn*-2 position, generating polyunsaturated FAs that can be oxidized (144). These oxidized FAs can further modify LDL to yield oxidized LDL. In addition, sPLA₂-induced lipolysis of LDL phospholipid

increases LDL particle fusion and enhances LDL binding to proteoglycans (264), both of which promote atherogenesis. Transgenic mice expressing human sPLA₂ exhibit significant atherosclerosis even when maintained on a low-fat diet (265).

The protein and lipid composition of LDL particles is altered during infection/inflammation. In humans, the majority of plasma PAF-AH activity is associated with LDL, whereas in rodents, most plasma PAF-AH activity is found on HDL (266). Plasma PAF-AH degrades PAF, a proinflammatory phospholipid mediator produced during infection and inflammation. However, PAF-AH also hydrolyzes lipoprotein-associated phosphatidylcholine, generating LPC, a molecule that exerts several proatherogenic effects (267–269). During the LPS and cytokine-induced APR, there is an acute increase in plasma and HDL-associated PAF-AH activity in several rodent species (141). Moreover, in patients with chronic human immunodeficiency virus (HIV) infection, plasma PAF-AH activity is increased, mainly in LDL (270). There is also a marked increase in the LPC content of circulating LDL in animal models of infection (258). In humans, circulating levels of PAF-AH are a strong and independent risk factor for CAD (271). Thus, increased plasma PAF-AH activity during the APR could have proatherogenic consequences.

Circulating LDL is more enriched in several sphingolipids, including sphingomyelin, ceramide, and GlcCer, during infection/inflammation (27, 128). Sphingolipid enrichment may increase the atherogenic potential of LDL, as LDL isolated from atherosclerotic lesions is enriched in sphingomyelin, ceramide, and GlcCer (272, 273). Plasma sphingomyelin levels are also increased in animal models of atherosclerosis and in humans with CAD (274, 275). When sphingomyelin on LDL is delivered into the arterial wall, it can be partly converted into ceramide by an arterial wall sphingomyelinase. Because LPS and cytokines increase the circulating levels of secretory sphingomyelinase (168), they may enhance the production of ceramide; ceramide promotes lipoprotein aggregation, stimulating LDL uptake by macrophages (276). Similarly, ceramide-rich LDL extracted from atherosclerotic lesions is either aggregated or has an increased tendency to aggregate (272). Thus, the various sphingolipids that are increased during the APR enhance the atherogenicity of lipoproteins in multiple ways.

In summary, during infection/inflammation several changes occur in LDL, such as the generation of small dense LDLs, increased susceptibility toward oxidation, increased CRP, sPLA₂-induced hydrolysis of LDL phospholipids, high plasma PAF-AH activity, and LDL enrichment with TG, cholesterol, LPC, and sphingolipids. These alterations change the structure and function of LDL, rendering it more proatherogenic.

HDL metabolism

Many changes in HDL metabolism occur during infection/inflammation that can impair the antiatherogenic functions of HDL. As discussed above, several HDL-associated proteins involved in the RCT pathway are decreased,

including apoA-I, LCAT, CETP, HL, and SR-BI (Table 3). During the APR, cholesterol removal from cells is decreased (163, 277, 278) as a result of a reduction in LCAT in acute-phase HDL (163). Moreover, cholesteryl ester delivery to hepatocytes is decreased as a result of a decrease in SR-BI (164, 279). Although an initial decrease in RCT during the APR may be beneficial as it redirects cholesterol toward macrophages for host defense (see below), a prolonged or sustained APR, as seen in chronic infection and inflammation, may continually impair RCT, thus leading to cholesterol deposition in macrophages and promoting atherogenesis.

Another key physiological function of HDL is protecting LDL against oxidation. Several HDL-associated proteins, including PON1, PON3, ceruloplasmin, transferrin, and apoA-I, possess antioxidant activity. Their removal or inactivation increases the susceptibility of LDL toward oxidation (280, 281), although the *in vivo* contribution of each is not yet established. During infection and inflammation, HDL loses its antioxidant function and becomes prooxidant (134, 135).

PONs constitute a group of enzymes that hydrolyze phospholipids with longer acyl chains and are capable of protecting LDL against oxidation *in vitro*. Depletion of PON1 results in the loss of antioxidant function of HDL, and addition of PON1 restores the protective function of HDL (134). Lipoproteins isolated from PON1-deficient mice are more susceptible to oxidation than lipoproteins isolated from their wild-type littermates, and PON1-deficient mice are more susceptible to atherosclerosis, suggesting that PON1 plays a role in preventing lipoprotein oxidation and atherogenesis (281). Acute-phase HDL has lower PON1 activity and is unable to protect LDL against *in vitro* oxidation (134). Moreover, during the LPS- and cytokine-induced APR, hepatic PON1 mRNA expression and serum PON1 activity decrease (134, 140), which precede the appearance of oxidized LDL (258), raising the possibility that the decreased PON1 activity during the APR contributes to the increased LDL oxidation *in vivo*.

Levels of two other HDL-associated proteins, ceruloplasmin and transferrin, change during infection and could contribute to increased LDL oxidation. Ceruloplasmin is a copper binding protein whose levels increase during the APR (282). Ceruloplasmin increases LDL oxidation in cell-free systems as well as in cultured cell lines, suggesting a prooxidant role (283, 284). In contrast, transferrin levels decrease during infection (285). Transferrin, which binds iron, may be antioxidant, as removal of HDL particles that contain transferrin activity reduces the ability of HDL to protect against LDL oxidation (280). Thus, three independent changes in HDL-associated proteins, a decrease in PON activity, an increase in ceruloplasmin, and a decrease in transferrin, could deplete HDL of its antioxidant function during the APR, converting HDL into a prooxidant, proinflammatory, and proatherogenic lipoprotein that is compounded by its decreased effectiveness in RCT, enhancing the atherogenic process (Table 3).

There are also direct effects of infection on macrophages, which could increase the risk of atherosclerosis.

LPS and cytokines (TNF and IL-1) activate macrophages to accumulate lipids (286–288). LPS-stimulated macrophages accumulate more TGs and cholesteryl ester from lipoproteins than do unstimulated cells. *Chlamydia pneumoniae* infection of human-derived macrophages induces foam cell formation in the presence of LDL (289). Therefore, synergistic changes in lipoproteins and host cells during infection and inflammation could promote atherogenesis.

BENEFICIAL EFFECTS OF CHANGES IN LIPID AND LIPOPROTEIN METABOLISM DURING INFECTION AND INFLAMMATION

We have proposed that the changes in lipid and lipoprotein metabolism that occur during the host response to infection/inflammation include antiinfective and anti-inflammatory effects that contribute to the host defense (13). Indeed, there is ample evidence that lipoproteins are part of innate immunity, the immediate protection against infection and inflammation. Below, we discuss these actions of lipoproteins with reference to changes that occur in the APR.

Lipoproteins and bacterial endotoxin

A humoral component other than antibody and complement was initially found to inactivate LPS in serum (290, 291). Subsequent studies have shown that lipoproteins, including HDL, chylomicrons, VLDL, LDL, and Lp[a], have the ability to bind and neutralize LPS *in vitro* (292–300). In addition, lipoproteins can bind LTA and α -toxin from *Staphylococcus aureus* (301, 302). When purified LPS was added to normal human whole blood *in vitro*, the majority of LPS was detected in HDL (60%), followed by LDL (25%) and VLDL (12%) (303). Similar results were found with LTA (304). However, during sepsis, when HDL levels decrease, LPS binding shifts to VLDL (305, 306). Isolation of plasma lipoproteins from normal healthy volunteers using strict apyrogenic techniques found LPS associated with VLDL, suggesting that the interaction between lipoproteins and LPS may be operative *in vivo* and is not simply attributable to contamination during isolation (295). The use of different anticoagulants for plasma preparation (e.g., heparin vs. EDTA) affects the distribution of LPS among classes of lipoproteins (307).

Binding of LPS to lipoproteins protects animals from LPS-induced fever, hypotension, and death (292, 293, 295, 308). Infusion of reconstituted HDL protects against endotoxic shock and gram-negative bacteremia in rabbits (309–311). Improved survival occurs when infusions of chylomicron or synthetic TG-rich lipid emulsion were given to animals up to 30 min after LPS, indicating that lipoproteins may have a therapeutic role during endotoxemia (312). Additionally, TG-rich lipoproteins protect rats from death when gram-negative sepsis is induced by cecal ligation and puncture (313).

Further evidence of lipoprotein protection comes from models of hypolipidemia or hyperlipidemia. Hypolipidemic rats, produced by 4-aminopyrrole-(3,4-d)pyrimide

(which prevents the hepatic secretion of lipoproteins) or estradiol (which increases hepatic receptors, leading to increased lipoprotein clearance), are more sensitive to LPS-induced lethality (314). Administration of exogenous lipoproteins to these hypolipidemic rats, increasing serum lipid concentrations into the physiological range, reverses the increased mortality to levels similar to those of control animals. In contrast, transgenic mice overexpressing apoA-I, which have high HDL levels, and LDL receptor-deficient mice, which have high LDL levels, are resistant to LPS-induced lethality and severe gram-negative infections (315, 316).

Taken together, these animal studies provide strong evidence that circulating lipoproteins play a vital role in host defense during endotoxemia. Increasing lipoprotein levels may be a viable therapeutic strategy to block or neutralize the toxic effects of LPS. Although the LPS-binding capacity of lipoproteins is 10- to 1,000-fold above the maximal concentrations of LPS observed in patients with sepsis, it is not sufficient to inhibit the effects of LPS during massive infection (315). In the circulation, LPS binds and activates monocytes more rapidly than lipoprotein binding and neutralization occur. However, an increase in the lipoprotein/LPS molar ratio, as occurs during infusion of lipoproteins, can accelerate the kinetics of the neutralization of LPS, providing some advantage (317).

Lipoproteins protect against harmful effects of LPS in humans. Reconstituted HDL decreases flu-like symptoms, changes in leukocyte counts, and cytokine release during endotoxemia (318). When LPS was preincubated with fasting or hypertriglyceridemic whole blood, the majority of LPS was bound to lipoproteins and the host response to LPS was attenuated (319). However, when LPS was infused into the circulation without preincubation, the interaction between leukocytes and LPS was favored. As a result, TG-rich fat emulsions could not inhibit the inflammatory response to LPS in humans (320).

Several potential mechanisms for the protective effect of lipoproteins against LPS have been found. When lipoprotein-bound LPS is injected into animals, the fate of LPS is altered. LPS bound to chylomicrons is cleared more rapidly than LPS alone (308). When LPS enters the circulation, the liver is the primary site of clearance; LPS is primarily taken up by hepatic macrophages (Kupffer cells), which are activated and secrete cytokines. Although cytokines play a role in host defense, high levels of cytokine secretion are the cause of septic shock. However, binding of LPS by lipoproteins decreased uptake by hepatic macrophages and increased uptake by hepatocytes, resulting in rapid secretion of LPS into the bile (308, 312, 321). Consistent with these findings, circulating levels of TNF were lower (308). Uptake of chylomicron-bound LPS into hepatocytes is also associated with the selective inhibition of NF- κ B, a mediator of LPS activation (322).

Similarly, *in vitro* studies demonstrate that lipoproteins can prevent the activation of peripheral monocytes/macrophages by LPS, decreasing cytokine synthesis and secretion (323–327). Additionally, infusion of HDL reduces CD14 expression on monocytes (318). Once LPS is bound

to monocytes, lipoproteins have been shown to promote the release of LPS from the cell surface, further attenuating the cellular response to LPS (328). Collectively, these studies suggest that lipoproteins can help neutralize the lethal effects of LPS by accelerating its clearance from the plasma, redirecting it away from monocytes and macrophages, decreasing immune cell activation, and reducing the release of cytokines, thus attenuating LPS toxicity.

Although it is now established that lipoproteins can bind and inactivate LPS, the nature of this interaction is not completely understood. Furthermore, conflicting evidence exists regarding the necessary component(s) of lipoproteins (lipid vs. protein) that attenuates the toxic effects of LPS. Lipid emulsions, which are devoid of proteins, demonstrate LPS-neutralizing effects similar to those of TG-rich lipoproteins, suggesting that the protein component of the lipoproteins may not be necessary (295, 312, 313). Ultrastructural studies of the LPS-LDL complex also show that the fatty acyl chain of the toxic lipid A moiety of LPS is inserted into the phospholipid surface of lipoproteins, thus masking the active site of LPS (329). Furthermore, the phospholipid content, but not cholesterol, TG, or protein, correlates with the ability of lipoproteins to neutralize LPS (300). Recently, LPC, an endogenous phospholipid, was shown to protect mice from experimental sepsis (330).

On the other hand, certain proteins associated with lipoproteins can bind and help modulate the inactivation of LPS by lipoproteins. These proteins include LBP, PLTP, apoA-I, apoE, and apoA-IV.

LBP is a positive acute-phase protein carried on lipoproteins (331). During infection, the concentration of LBP in the circulation increases many-fold. LBP is associated with HDL, VLDL, LDL, and chylomicrons (332–334). LBP binds lipid A of LPS, modulating its effect. At low concentrations, LBP catalyzes the transfer of LPS to CD14 on the surface of monocytes and macrophages, resulting in cellular activation and enhancement of the effects of LPS. At higher concentrations, however, LBP transfers LPS to lipoproteins, where neutralization occurs (333). LBP is also produced in the intestine and in the lung, where it may play a role in local responses to bacterial LPS (335, 336). LBP-deficient mice are more susceptible to gram-negative bacterial infection (337), whereas systemic injection of LBP into animals treated with LPS or infected with bacteria reduces cytokine release and decreases mortality (338). PLTP, another HDL-associated protein, can also bind and transfer LPS to HDL (339). However, the role of PLTP in neutralizing the effects of LPS in intact animals is not known.

ApoA-I or apoA-IV alone decreases the activation of macrophages by LPS (327, 340). LPS preincubated with apoA-I *in vitro* reduces the febrile response in animals (298). Transgenic mice overexpressing apoA-I are resistant to LPS-induced lethality and severe gram-negative infections (315). Secretion of cytokines from lymphocytes of apoA-IV transgenic mice was less pronounced than that of control animals (340). Similarly, injection of apoE reduces the production of cytokines and death induced by

LPS (341). Although apoE-deficient mice have high levels of cholesterol, they are more susceptible to endotoxemia and gram-negative infections (342). The facts that high levels of cholesterol could not protect apoE-deficient mice from the toxic effects of LPS and that these mice develop defects in the phagocytic activity of granulocytes suggest that apoE may have additional effects on the immune system (343). It is of interest that macrophages themselves make and secrete apoE (344). ApoA-IV was recently found to be increased in HDL during the APR (our unpublished observations).

Thus, more than one component of lipoproteins may induce the binding and inactivation of LPS. The interaction between LPS and lipoproteins may involve lipids, but proteins, such as LBP, may help catalyze the process. The metabolism of lipoprotein-bound LPS is altered such that it is shunted away from the activation of the monocytes/macrophages, ameliorating its toxic effect and accelerating clearance. The increases in TG-rich lipoproteins and LBP during sepsis may therefore be beneficial to the host during bacterial infection.

Besides LPS from gram-negative bacteria, lipoproteins also neutralize the toxic effects of LTA from gram-positive bacteria (301). Native lipoproteins or synthetic lipids inhibited the activation of macrophages by LTA. Similarly, this effect of lipoproteins on LTA requires LBP (301).

Lipoproteins, lipoprotein receptors, and viruses

Lipoproteins also bind and neutralize a wide variety of enveloped and nonenveloped DNA and RNA viruses. These include New Castle disease virus, Rabies virus, Vesicular stomatitis virus, Japanese encephalitis virus, Rubella virus, Epstein-Barr virus, Herpes simplex virus, HIV, Simian immunodeficiency virus, Xenotropic virus, Sindbis virus, Vaccinia virus, Coxsackie virus, Poliovirus, and Mengo virus (345–356). VLDL and LDL are particularly active against certain viruses, such as togaviruses (Japanese encephalitis virus and Rubella virus) and rhabdoviruses (Rabies virus and Vesicular stomatitis virus), whereas HDL displays a broader antiviral activity (347, 349, 356). However, it is estimated that HDL accounts for only a modest degree of total antiviral activity in serum (356).

When lipoproteins were separated into lipid and protein components, it was found that neutralization of some viruses was attributable to lipid moieties, especially phospholipid and cholesterol (351, 357–360). However, apolipoproteins also bind and inactivate viruses. Certain viruses possess envelope glycoproteins that contain amphipathic α -helix peptides. Because apoA-I and synthetic amphipathic peptide analogs inhibit virus-induced cell fusion (352), it has been proposed that the amphipathic peptides of apoA-I and other apolipoproteins may interfere with membrane fusion and entry of the virus into the host cell. Displacement of apoA-I on HDL by apoSAA during infection may provide free apoA-I for this purpose. When cells were infected with viruses in the presence of HDL, viruses were retained on the cell surface, suggesting that HDL inhibits viral penetration into cells (356).

Cellular GSLs are exploited as receptors by a number of microorganisms, including viruses and bacteria (361). Because acute-phase lipoproteins are enriched in GSLs (128), they may prevent the entry of these organisms.

Viral infection leads to the induction of IFNs, which in turn induce several antiviral proteins. One of these proteins is a soluble form of LDL receptor comprising the ligand binding domain, which displays antiviral activity by interfering with virus assembly or budding (362). A recombinant soluble LDL receptor fragment has been found to inhibit human rhinovirus infection (363). An increase in LDL in rodents during infection may help compete with viruses for cellular uptake, protecting the host against viral infection. Besides soluble LDL receptor, cells infected with virus also shed a VLDL receptor fragment that binds human rhinovirus, inhibiting viral infection of cells (364). Because viruses, such as rhinovirus and hepatitis C virus, use the LDL receptor for entry into cells (365, 366), the increases in VLDL in all animal species and increases in LDL in rodents may help compete with these or similar viruses for cellular uptake, protecting the host against viral infection.

Lipoproteins and parasites

Lipoproteins protect from certain parasitic infections. Trypanosomes are unicellular parasites that cause sleeping sickness in animals. Humans are susceptible to infection by *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. However, the closely related subspecies *Trypanosoma brucei brucei* does not cause infection in humans because those trypanosomes are subject to lysis by human serum. Two distinct serum trypanosome lytic factors (TLFs), TLF1 and TLF2, have been characterized (367). TLF1 is a subset of lipid-rich HDL that contains mostly apoA-I and haptoglobin-related protein with trace amounts of apoA-II, haptoglobin, and PON. TLF2, in contrast, is a lipid-poor lipoprotein complex composed of apoA-I, haptoglobin-related protein, and immunoglobulin M. TLF2 accounts for most of the TLF activity in serum, as physiological levels of haptoglobin present in serum inhibit endogenous TLF1 activity (367). The mechanism of trypanolysis by TLFs is currently not known; evidence does not support the hypothesis that peroxidation is involved (368). Recent work implicates apoL-I, another HDL-associated protein, as a TLF in serum (369). ApoL-I interacts with serum resistance-associated protein in the lysosome of trypanosomes. Depletion of apoL-I from normal serum abolished the trypanolytic activity, whereas addition of native or recombinant apoL-I restored the activity (369).

Schistosomiasis is a parasitic infection of the hepatic portal system caused by schistosomes. Resistance to *Schistosoma* infection may be mediated by lipoproteins through several mechanisms. In rats, *Schistosoma* infection causes an increase in serum levels of CRP, a positive acute-phase protein associated with VLDL and LDL. CRP has been shown to activate platelets and render them cytotoxic to schistosomula in vitro (370). Besides platelets, activated monocytes can kill schistosomula. Because LDL and oxi-

dized LDL bind to the surface of schistosomula, it is thought that activated monocytes generate toxic oxygen species, which oxidize parasite-bound LDL, allowing endocytosis of the oxidized LDL into monocytes via the scavenger receptor (371). Removal of bound LDL exposes the parasites to further attack by activated monocytes and other immune cells.

Malaria infection is initiated after injection of malaria sporozoites into the bloodstream by mosquitoes. Hepatic invasion of malaria sporozoites is an initial step in the life cycle of the parasite. Malaria sporozoites and remnant lipoproteins of chylomicrons and VLDL are cleared from plasma using similar mechanisms (372). Malaria sporozoites are less infectious in LDL receptor-deficient mice maintained on a high-fat diet compared with those on a chow diet, suggesting that high levels of lipoproteins inhibit sporozoite infectivity in mice (372).

Oxidized phospholipids and LPS signaling

Infection and inflammation are associated with increased oxidized lipids (258). One of the oxidized phospholipids, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (oxPAPC), inhibits LPS-stimulated NF- κ B activation in monocytes/macrophages and endothelial cells by disrupting caveolae and inhibiting the assembly of the LPS signaling complex in lipid rafts (373). In addition, oxPAPC blocks the binding of LPS to LBP and CD14 (374). As a result, the LPS-induced expression of IL-8, IL-12, monocyte chemoattractant protein-1, and E-selectin is reduced. The ability of oxidized phospholipids to modulate the LPS signaling could be beneficial to the host during infection/inflammation. In fact, oxidized phospholipids have been shown to decrease an inflammatory process in mice treated with LPS, protecting them from endotoxic shock (374).

Lipoproteins and redistribution of lipids to immune cells

During infection/inflammation, there is an increase in TG-rich VLDL particles, which could provide lipid substrate for the activated immune system. In the presence of LPS, macrophages accumulated more TG and cholesterol (286, 287). VLDL produced during endotoxemia also provided more TG to macrophages compared with control VLDL, and these TGs were selectively stored as cellular lipids (375). During the APR, proteins involved in the uptake and metabolism of FA, such as FABP, FATP, and LPL, are coordinately downregulated in the heart, muscle, and adipose tissue. As a result, fat oxidation in the heart and skeletal muscle decreases, whereas adipose tissue does not store fat but rather provides FA for use by other tissues.

Similarly, during infection there is a decrease in HDL and the RCT pathway, which helps conserve cholesterol at peripheral sites. An increase in apoSAA on acute-phase HDL helps redirect cholesterol away from catabolism by hepatocytes and delivers cholesterol to other cells, such as macrophages (376). Upregulation of sPLA₂ increases cholesteryl ester uptake into the adrenal glands during the APR, presumably for increased steroid hormone synthesis

(377). Cholesterol may also be used for lymphocyte activation and proliferation (378). Furthermore, infection is often associated with cellular injury, and areas of injury may need extra cholesterol for new membrane synthesis.

CONCLUSION

Infection and inflammation are associated with marked changes in lipid and lipoprotein metabolism. Besides their role in lipid transport, lipoproteins participate in innate immunity, which is the first line of host defense against invading microorganisms. Many of the changes in lipoproteins during infection/inflammation help protect the host from harmful effects of the stimuli. In cases of chronic infection, inflammatory diseases, diabetes, obesity, metabolic syndrome, and heart failure, however, these cytokine-induced changes in the structure and function of lipoproteins could be deleterious and may contribute to the development of atherosclerosis. Further studies of the interface between infection/inflammation and lipoproteins could provide new insights into not only atherogenesis but also the innate immune system and the complex interaction between them. **■**

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