Effects of Infection and Inflammation on Lipid and Lipoprotein Metabolism: Mechanisms and Consequences to the Host

Weerapan Khovidhunkit*, Min-Sun Kim, Riaz A. Memon, Judy K. Shigenaga, Arthur H. Moser, Kenneth R. Feingold, and Carl Grunfeld**

Department of Medicine, University of California, San Francisco and Metabolism Section, Medical Service, Department of Veterans Affairs Medical Center, San Francisco, California

* Current address: Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

** Deceased

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Correspondence Address: Carl Grunfeld, M.D., Ph.D. and Kenneth R. Feingold, M.D.

Metabolism Section (111F)

Department of Veterans Affairs Medical Center

4150 Clement Street, San Francisco, CA 94121

TEL: (415) 750-2005

FAX: (415) 750-6927

Email: grunfld@itsa.ucsf.edu, kfngld@itsa.ucsf.edu

This paper is dedicated to the memory of Dr. Riaz A. Memon.

Abbreviations: ABC, ATP-binding cassette; ACC, acetyl CoA carboxylase; ACS, acyl-CoA synthetase; AIDS, acquired immune deficiency syndrome; aP2, adipocyte P2; Apo, apolipoprotein; APR, acute-phase response; BEF-1, BK virus enhancer factor-1; BSEP, bile salt export pump; CAD, coronary artery disease; CAR, constitutive androstane receptor; CETP, cholesterol ester transfer protein; CNTF, ciliary neurotropic factor; CPT, carnitine palmitoyl transferase; CRP, C-reactive protein; CYP7A1, cholesterol 7α-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; CYP8B1, sterol 12α-hydroxylase; CYP27A1, sterol 27-hydroxylase; DR, direct repeat; ERK, extracellular signal-related kinase; EL, endothelial lipase; FA, fatty acid; FABP, fatty acid binding protein; FAS, fatty acid synthase; FAT, fatty acid translocase; FATP, fatty acid transport protein; FXR, farnesoid X receptor; GlcCer, glucosylceramide; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSL, glycosphingolipid; HIV, human immunodeficiency virus; HL, hepatic lipase; HMG-CoA, hydroxymethylglutaryl coenzyme A; HNF, hepatocyte nuclear factor; HSL, hormone-sensitive lipase; IFN, interferon; IL, interleukin; IR, inverted repeat; JAK-STAT, Janus kinase-signal transducers and activators of transcription; KB, ketone body; KGF, keratinocyte growth factor; LBP, lipopolysaccharide-binding protein; LCAT, lecithin:cholesterol acyltransferase; LIF, leukemia inhibitory factor; Lp(a), lipoprotein(a); LPC,

lysophosphatidylcholine; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LRH-1, liver receptor homolog-1; LTA, lipoteichoic acid; LXR, liver X receptor; M-CSF, macrophage colony-stimulating factor; MDR3, multidrug resistance-3; MEK, mitogen-activated protein kinase kinase; MRP2, multidrug resistance-associated protein-2; NF-κB, nuclear factor-kappa B; NF-IL6, nuclear factor interleukin-6, NGF, nerve growth factor; NTCP, sodium taurocholate cotransporting protein; OATP, organic anion transporting protein; oxPAPC, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine; PAF, platelet-activating factor; PAF-AH, platelet-activating factor acetylhydrolase; PGC-1, PPAR-^{3} co-activating factor-1; PKA, protein kinase A; PLTP, phospholipid transfer protein; PON1, paraoxonase1; PPAR, peroxisome proliferator-activated receptor; PTHrP, parathyroid hormone-related protein; PXR, pregnane X receptor; RCT, reverse cholesterol transport; RXR, retinoid X receptor; SAA, serum amyloid A; SHP, small heterodimer partner; $sPLA_2$, secretory phospholipase A_2; SPT, serine palmitoyltransferase; SR-BI, scavenger receptor class B type I; TG, triglyceride; TLF, trypanosome lytic factor; TNF, tumor necrosis factor; TR, thyroid hormone receptor.

ABSTRACT

Infection and inflammation induce the acute-phase response (APR), leading to multiple alterations in lipid and lipoprotein metabolism. Plasma triglyceride levels rise from increased VLDL secretion due to adipose tissue lipolysis, increased de novo hepatic fatty acid synthesis, and suppression of fatty acid oxidation. With more severe infection, VLDL clearance decreases secondary to decreased lipoprotein lipase and apo E in VLDL. In rodents, hypercholesterolemia occurs due to increased hepatic cholesterol synthesis and decreased LDL clearance, conversion of cholesterol to bile acids, and secretion of cholesterol into the bile. Marked alterations in proteins important in HDL metabolism lead to decreased reverse cholesterol transport and increased cholesterol delivery to immune cells. Oxidation of LDL and VLDL increases, while HDL becomes a pro-inflammatory molecule. Lipoproteins become enriched in ceramide, glucosylceramide and sphingomyelin, enhancing uptake by macrophages. Thus, many of the changes in lipoproteins are pro-atherogenic. The molecular mechanisms underlying the decrease in many of the proteins during the APR involve coordinate decreases in several nuclear hormone receptors including PPAR, LXR, FXR, and RXR. APR-induced alterations initially protect the host from the harmful effects of bacteria, viruses, and parasites. However, if prolonged, these changes in the structure and function of lipoproteins will contribute to atherogenesis.

Supplementary keywords: acute-phase response, endotoxin, lipopolysaccharide, cytokine, atherosclerosis

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I. Introduction

The acute-phase response (APR), an early, highly complex reaction of the host is induced by injurious stimuli including infection and inflammation, as well as trauma, burns, ischemic necrosis and malignant growth (1). The APR is accompanied by specific changes in concentration of plasma proteins. Proteins that increase by at least 25 percent during the APR are positive acute-phase proteins e.g., C-reactive protein, serum amyloid A, and fibrinogen, while proteins that decrease are negative acute-phase proteins e.g., albumin, transferrin, and alpha-fetoprotein (1). Changes in acute-phase protein concentrations are largely due to alterations in their rate of synthesis in the liver, although similar changes occur in extra-hepatic tissues. Microarrays of mouse liver following endotoxin treatment demonstrate that approximately 7% of the genes respond to endotoxin challenge (2). These changes in acute-phase proteins are often species-specific with regard to magnitude and direction of changes.

The APR induced during infection/inflammation protects the host from further injury (1). Changes in acute-phase proteins neutralize invading microorganisms, minimize the extent of tissue damage, participate in the local immune response and tissue regeneration, and replenish proteins utilized in the inflammatory process. These changes if present for a prolonged period of time can lead to detrimental consequences to the host, such as development of systemic amyloidosis after chronic infection or inflammation.

Changes in acute-phase protein synthesis are mediated by cytokines produced in response to a variety of stimuli of multiple cell types including macrophages, monocytes, T-lymphocytes, and

endothelial cells (1). Key cytokines responsible for coordination of both immune and inflammatory responses include tumor necrosis factors (TNF-α and -β), interleukins (ILs), and interferons (IFN-α, -β and -γ) (1). Redundancy classically occurs in essential parts of the host response, as several structurally different cytokines may exert similar biological effects even though they bind to different receptors. Combinations of certain cytokines produce additive or synergistic effects, whereas other cytokines may have inhibitory effects indicating the complex nature of the host response (3-5).

Infection and inflammation are accompanied by similar cytokine-induced alterations in lipid and lipoprotein metabolism. Of note, inflammatory cytokines are elevated and play a pathogenic role in a variety of very common disorders, such as diabetes, obesity, metabolic syndrome, hypertension, chronic heart failure, chronic renal failure, and atherosclerosis (6-12). Many of these disorders display abnormalities in lipid metabolism that are similar to those that occur during infection and inflammation.

This review summarizes the changes in lipid and lipoprotein during infection/inflammation and their molecular mechanisms. Most mechanistic studies were carried out in animal models of infection using endotoxin (lipopolysaccharide or LPS), a well-characterized inducer of cytokines and the APR, or the pro-inflammatory cytokines (TNF and IL-1), which mediate the APR. We describe the role of transcription factors in regulating lipid metabolism during infection/inflammation. Finally, we discuss both the beneficial effects and deleterious consequences to the host of APR-induced changes in lipid and lipoprotein metabolism.

II. Changes in lipid and lipoprotein metabolism during infection and inflammation

An early and consistent metabolic alteration during infection/inflammation is increased serum triglyceride (TG) levels, characterized by an increase in VLDL levels (13). Multiple mechanisms produce hypertriglyceridemia during the APR; several cytokines are capable of producing these changes. Whether an increase in glucocorticoid levels during infection plays a role in lipid metabolism is unclear.

The effects of infection and inflammation on TG metabolism are similar in all species, whereas changes in cholesterol metabolism differ between rodents and primates. In rodents, there is an increase in serum total cholesterol levels and hepatic cholesterol synthesis, whereas non-human primates and humans have either no change or a decrease in serum cholesterol and LDL levels (13). The mechanism underlying this species difference is not known. HDL levels are decreased in both rodents and primates during the APR, and there are marked changes in proteins associated with HDL metabolism (14). Finally, infection produces alterations in the composition and function of lipoproteins, including changes in sphingolipid concentrations, decreased reverse cholesterol transport, and increased oxidation of lipids.

A. Triglyceride metabolism

Patients with gram-negative or gram-positive bacterial infections and viral infections have increased serum TG levels (15-17). In animals, administration of LPS, a major component of the cell wall of gram-negative bacteria, or lipoteichoic acid (LTA), a component of the cell wall of gram-positive bacteria, produces hypertriglyceridemia (18-28)(**Table 1**). Multiple cytokines

increase serum TG levels in rodents and in humans (29-40). The hypertriglyceridemic effect of LPS and cytokines is rapid, occurring within 2 hours after administration and is sustained for at least 24 hours (26, 29). The doses of LPS or cytokines that produce hypertriglyceridemia in rodents are similar to those that produce fever, anorexia and changes in acute-phase protein synthesis, suggesting that hypertriglyceridemia is a very sensitive, physiological part of the host response to infection rather than a manifestation of toxicity (26).

The increased VLDL is secondary to either increased VLDL production or decreased VLDL clearance, depending upon the dose of LPS (26). At low doses, VLDL production increases as a result of increased hepatic fatty acid (FA) synthesis, activation of adipose tissue lipolysis, and suppression of FA oxidation and ketogenesis. All of these mechanisms provide more FA substrate in the liver for esterification into TG and secretion as VLDL. At higher doses of LPS, VLDL clearance is decreased due to decreases in the activity of lipoprotein lipase (LPL), the enzyme responsible for the catabolism of TG-rich lipoproteins, and levels of apolipoprotein (apo) E.

Serum TG levels are increased by multiple cytokines, including TNF, IL-1, IL-2, IL-6, IFN, leukemia inhibitory factor (LIF), ciliary neurotropic factor (CNTF), nerve growth factor (NGF), keratinocyte growth factor (KGF), platelet-activating factor (PAF) and parathyroid hormone-related protein (PTHrP) (30, 32-39, 41-47) (**Table 1**), suggesting redundancy. IL-4, an anti-inflammatory cytokine, opposes the action of some, but not all, of these cytokines (48). The effects of cytokines on TG metabolism are likely direct and not mediated by hormones like insulin, cortisol or catecholamines, as TNF increases serum TG levels in insulinopenic diabetic animals and

adrenalectomized rats (49, 50). Moreover, TNF also raises serum TG levels under various dietary conditions from high sucrose, which stimulates endogenous FA synthesis, to high fat, which suppresses endogenous FA synthesis (51, 52).

1. Increased VLDL production

a. Increased de novo FA and TG synthesis

LPS and several cytokines, including TNF-α, TNF-β (lymphotoxin), IL-1, IL-6, IFN-α, LIF, CNTF, NGF, PAF, and PTHrP, rapidly induce de novo FA synthesis and hepatic TG synthesis in rodents (26, 29, 31, 32, 34, 43, 44, 47, 50, 53)(**Table 1**). Hepatic secretion of apo B also increases (54), resulting in an increased number of VLDL particles secreted. In contrast, other cytokines, such as IL-2, IL-4, and IFN-γ, do not stimulate hepatic FA synthesis (31, 48).

TNF rapidly increases hepatic FA synthesis within an hour after administration, which is sustained for at least 17 hours (29). The time course for stimulation of hepatic FA synthesis and VLDL secretion is consistent with the time course for TNF-induced hypertriglyceridemia (29, 55). However, TNF does not acutely increase total activity of the rate-limiting enzymes of FA synthesis i.e., acetyl CoA carboxylase (ACC) and FA synthase (FAS), nor alter the phosphorylation state of ACC, a mechanism that regulates ACC activity (56). Instead, TNF acutely increases intracellular concentrations of citrate, an allosteric activator of ACC (56)(**Fig. 1**). IL-1 and IL-6 increase hepatic FA synthesis by increasing hepatic citrate levels, whereas IFN-±, which also increases hepatic FA synthesis, has no effect on citrate levels suggesting a different mechanism (53). The stimulatory effects of TNF or IL-1 and IFN-± on hepatic FA synthesis are additive or synergistic, whereas

there is no such synergy between TNF and IL-1 or TNF and IL-6 (53). Finally, IL-4, an anti-inflammatory cytokine, inhibits the stimulatory effects of TNF, IL-1 and IL-6 on hepatic FA synthesis by blocking the increase in hepatic citrate levels (48). In contrast, IL-4 does not block the stimulatory effect of IFN-± on FA synthesis in liver (48). Thus, analogous to cytokine regulation of the immune response, there are complex interactions among the metabolic effects of cytokines that may be additive, synergistic, or antagonistic.

The late effects of TNF on hepatic FA synthesis are accompanied by modest increases in hepatic ACC and FAS activities (56). Late increases in ACC activity in rat liver occur in a sepsis model induced by cecal ligation and puncture (57). Whether gene expression of ACC and/or FAS increases in the liver is currently not known.

b. Increased adipose tissue lipolysis

Adipose tissue lipolysis also provides FA for increased hepatic TG synthesis during infection. The mobilized FA are delivered to the liver and, instead of being oxidized, become re-esterified into TGs and secreted into the circulation as VLDL.

LPS, LTA, and several cytokines induce adipose tissue lipolysis in both intact animals and 3T3-L1 adipocytes (26, 28, 34, 37, 43, 45, 52, 58-63). The effects of different cytokines are specific and dependent upon the nutritional status of the host (**Table 1**). TNF acutely induces lipolysis in chow-fed but not in sucrose-fed animals (52). IL-1 does not stimulate lipolysis; its effect on serum TG levels is due to enhanced hepatic FA synthesis and TG secretion (32). IL-6, LIF, and CNTF, which act through the same receptor transducer (gp130), stimulate both hepatic FA

synthesis and adipose tissue lipolysis (34, 43). On the other hand, KGF stimulates lipolysis but has no effect on hepatic FA synthesis (45). Finally, both IFN-± and IFN-γ stimulate lipolysis, but those peripherally-derived FA do not contribute to increased TG synthesis in the liver, as they are oxidized producing ketone bodies (KB) (63).

Lipolysis in adipose tissue is primarily driven by hormone-sensitive lipase (HSL), which is regulated either by alteration in its phosphorylation state or by induction of gene expression. Several cytokines that induce lipolysis including TNF, IFN-±, and IFN-γ produce a marked decrease in HSL mRNA (64), indicating that gene regulation of HSL does not play a role in cytokine-induced lipolysis. Rather, lipolysis is likely due to phosphorylation of HSL or its associated proteins. TNF-induced lipolysis in cultured human adipocytes is associated with activation of mitogen-activated protein kinase kinase (MEK)-extracellular signal-related kinase (ERK) (65), leading to decreases in cyclic nucleotide phosphodiesterase 3B, an enzyme that hydrolyzes cAMP. Increased intracellular cAMP consequently activates cAMP-dependent protein kinase A (PKA), which phosphorylates perilipins, phosphoproteins located at the surface of lipid droplets in adipocytes. Phosphorylation of perilipin A or B modifies lipid surfaces, allowing access of lipases to the lipid droplets, promoting lipolysis. Activation of MEK-ERK pathway and PKA has also been shown to phosphorylate HSL and increase its lipolytic activity (65, 66).

LPS and cytokines may also induce lipolysis by decreasing expression of acyl-CoA synthetase (ACS) in adipose tissue (64). ACS catalyzes activation of long chain FA to acyl-CoA esters that are subsequently metabolized in anabolic or catabolic pathways depending on the type of

tissue, nutritional status, and the hormonal milieu of the host. While FA transport across biological membranes is a bi-directional process, activation of FA to acyl-CoA esters prevents efflux of FA from cells and hence renders FA transport uni-directional. In adipose tissue, ACS is primarily associated with microsomes to support synthesis of TG for storage of energy. During the APR, there is a coordinate decrease in the mRNA expression of FA transport proteins and ACS mRNA and activity in adipose tissue (67, 68) that likely prevents activation and storage of FA and may promote the mobilization of FA.

c. Decreased hepatic FA oxidation and ketogenesis

Bacterial infections are accompanied by suppression of hepatic FA oxidation (69, 70). Increased FA substrate provided by increased hepatic FA synthesis and adipose tissue lipolysis is then directed away from oxidation and channeled towards reesterification. This concept is supported by demonstration that LPS, TNF, and IL-1 decrease mitochondrial but increase microsomal ACS activity in the liver (68). Decreased mitochondrial ACS prevents activation of FA for entry into mitochondria for oxidation, whereas increased microsomal ACS enhances reesterification of FA for TG synthesis.

LPS and cytokines differentially regulate hepatic mRNA expression of membrane-associated FA transport proteins involved in the uptake of peripherally derived FA. LPS and cytokines increase the expression of CD36/FA translocase (FAT), while decreasing the mRNA levels of FA transport protein (FATP) in the liver suggesting that these proteins may be involved in directing FA to different intracellular locations (67)(**Fig. 1**). We propose that CD36/FAT transports

FA to cytosol for reesterification, which is enhanced during the APR, whereas FATP transports FA towards mitochondria for oxidation, which is suppressed during the APR. LPS also decreases the mRNA and protein levels of cytosolic fatty acid binding protein (FABP) in liver, heart and muscle (71). Because FABPs are thought to facilitate transport of FA to the site of utilization in the cell, the decrease in FABP may also contribute to decreased FA oxidation during infection. The fact that TNF does not acutely increase the activities of regulatory enzymes of TG synthesis such as glycerol phosphate acyltransferase and diacylglycerol acyltransferase (52) also suggests that the acute increase in TG synthesis is driven by increased FA substrate.

Mitochondrial ACS converts FA into fatty acyl CoA, which is subsequently metabolized by mitochondrial carnitine palmitoyl transferase-I (CPT-I) into acylcarnitine. CPT-II subsequently metabolizes acylcarnitine into acyl-CoA, which allows FA entrance into the mitochondria where it undergoes ²-oxidation. Hepatic expression of both CPT-I, the rate-limiting enzyme for mitochondrial FA oxidation, and CPT-II are decreased during sepsis (72, 73)(**Fig. 1**). LPS, IL-1, and TNF increase levels of hepatic malonyl-CoA, an allosteric inhibitor of CPT-I, which inhibits the remaining CPT-I decreasing FA oxidation (74)(**Table 1**). IFN-± at high doses increases hepatic malonyl-CoA levels (63), whereas IFN-γ does not affect hepatic malonyl-CoA levels (63).

Given the decrease in FA oxidation, infection is associated with suppression of hepatic KB production (69, 70). Serum KB levels are regulated by their rates of synthesis in the liver and utilization in peripheral tissues. Infection decreases KB production through inhibition of FA oxidation, but also likely by increased peripheral KB utilization.

Various cytokines have different effects on KB metabolism (**Table 1**). Both TNF and IL-1 acutely decrease serum KB levels in mice (30, 74). In the fed state, IL-1 increases hepatic malonyl-CoA levels, inhibiting CPT-I, preventing KB production. During fasting, IL-1 inhibits lipolysis, reducing FA substrate to the liver for KB synthesis (74). Although TNF raises hepatic malonyl-CoA levels, it stimulates peripheral lipolysis, increasing flux of FA substrate to the liver, with no net effect on hepatic KB levels (74), suggesting TNF decreases serum KB through changes in KB catabolism. IL-6 has no effect on serum KB levels (34). IFN-± has biphasic effects: low doses of IFN-± 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 coordinate 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.

2. 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 due 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 LIF also require several hours to decrease LPL activity in vivo in mouse adipose tissue (80). IFN-± and IFN-γ increase serum TG levels in humans (38, 39), but do not raise 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 decreased clearance of TG with high doses of LPS. Low doses of LPS enhance hepatic VLDL secretion and raise 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 post-heparin plasma LPL activity and LPL activity in adipose tissue and muscle (80).

LPS and cytokines also decrease apo E mRNA in many tissues including the liver, and VLDL has lower amounts of apo E during infection (54, 85, 86). Because apo E is required for

clearance of TG-rich lipoproteins, decreased apo E could contribute to the delayed clearance observed in rats with bacteremia (87).

B. Cholesterol metabolism

There are marked alterations in metabolism of cholesterol, LDL, HDL and reverse cholesterol transport 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.

1. 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 16 hours after administration (27). LPS stimulates hepatic cholesterol synthesis by increasing the transcription rate, mRNA expression, protein mass, and activity of hydroxymethylglutaryl coenzyme A (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 up-regulates 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 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 non-sterol pathways, which include 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 non-sterol 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 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 non-sterol pathways during the APR.

In primates including humans, infection/inflammation decrease serum cholesterol due to decreases in both LDL and HDL cholesterol (16, 17, 24, 25). LPS, TNF, IL-2, IFN-², granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) 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 apo B 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 apo B secretion, whereas IL-6 increases cholesterol synthesis but decreases cholesterol secretion (98). IFN-² also decreases apo B synthesis (99).

2. 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 post-transcriptional regulation occurs during the APR (101). In a rat model of gram-negative sepsis, the rate of apo B 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 species-specific response in cholesterol metabolism commonly seen during the APR.

3. 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 7α-hydroxylase (CYP7A1) that converts cholesterol into 7α-hydroxycholesterol, which is subsequently converted into primary bile acids. The alternate or acidic pathway is initiated by mitochondrial sterol 27-hydroxylase (CYP27A1) that converts cholesterol into 27-hydroxycholesterol, which is then converted into 7α, 27-dihydroxycholesterol by oxysterol 7α-hydroxylase (CYP7B1) and subsequently metabolized into primary bile acids. The alternate 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 solubilization of lipids from the canalicular membrane, resulting in secretion of biliary phospholipids and cholesterol.

As polarized cells, hepatocytes contain multiple transporters at the basolateral (sinusoidal) and the apical (canalicular) surfaces (106). Basolateral bile salt uptake from the portal circulation is primarily mediated by sodium taurocholate cotransporting protein (NTCP). Several organic anion transporting proteins (OATPs), including OATP1, OATP2, and OATP4, are also involved in the 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 in order 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 ABCC2) 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 minutes of LPS administration and is sustained for at least 16 hours (109). LPS also decreases mRNA expression and activity of CYP27A1, the rate-limiting enzyme in the alternate 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 hours after LPS administration and persist for at least 24 hours, suggesting that both the classic and alternate pathways of bile acid synthesis are sequentially down-regulated 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 due 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 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. **Fig. 3** summarizes the effect of APR on bile acid metabolism.

The coordinate down-regulation of both pathways of bile acid synthesis during the APR is in contrast to most other situations including studies in knockout animals, where during the

suppression or absence of one pathway of bile acid synthesis, the enzymes of the other pathway are up-regulated to compensate for the deficiency. The decreases in the regulatory enzymes of both classic and alternate 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 down-regulated in order to limit the elimination of cholesterol from the body. A decrease in cholesterol catabolism would make cholesterol more available for hepatic lipoprotein production.

4. Lipoprotein(a)

Lipoprotein(a) or Lp(a) is a distinct lipoprotein consisting of an LDL particle attached to apolipoprotein(a) (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 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), while others reported no changes or a reduction (122, 123). These conflicting data may be due to the specificity of the assays used to measure Lp(a) levels or the interindividual variation in plasma Lp(a) levels in the population.

5. HDL metabolism and decreased reverse cholesterol transport

During infection and inflammation, there is a marked decrease in serum levels of HDL and apo A-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 HDL_3; its radius extending into the HDL_2 range, but has a density comparable to HDL_3 (125). Acute-phase HDL is depleted in cholesterol ester but enriched in free cholesterol, TG, and free FAs (24, 25, 27, 125-127). Phospholipid content of acute-phase HDL was increased in some studies (24, 27) but decreased in others (124, 125). In patients who underwent bypass surgery, acute-phase HDL had the same phospholipid/neutral lipids ratio, a decrease in phosphatidylethanolamine and phosphatidylinositol, and an increase in isoprostane-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 apo serum amyloid A (SAA) (24, 124, 125, 129, 130) and a decrease in apo A-I content (24, 124, 127, 130)(**Table 3**). The content of apo A-II and apo Cs is decreased (24, 124, 130, 131), while apo E was found to be increased in some (24, 132) but decreased in other studies (130). HDL-associated apo J is increased during inflammation and infection in rodents and humans (133-135). In contrast, several other proteins including lecithin:cholesterol acyltransferase (LCAT) (24, 25, 136), cholesterol 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 A_2 ($sPLA_2$), 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 apo A-I have also been reported (145). We recently found that apo A-IV and apo A-V levels are increased in acute-phase HDL (Khovidhunkit et al., unpublished observations).

Although it is well established that infection and inflammation are associated with a reduction in serum HDL and apo A-I levels, the exact mechanism has not yet been established. Since apo SAA can displace apo A-I from HDL (146, 147) and apo SAA-rich HDL particles are rapidly cleared from the circulation (148), it has been assumed that the several-fold increase in apo SAA content in HDL is the mechanism for the decrease in apo A-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 apo SAA levels were markedly increased to levels comparable to those seen in infection found no changes in HDL cholesterol or apo A-I levels (149). Thus, high levels of SAA per se do not decrease HDL or apo A-I levels in the absence of the other changes that occur during infection and inflammation.

An increase in $sPLA_2$ has also been proposed to contribute to the reduction in HDL during infection/inflammation. Mice overexpressing $sPLA_2$ have reduced HDL concentrations (150), and HDL from these mice is catabolized more rapidly than HDL from normal mice (151). Although apo

SAA is known to activate $sPLA_2$, overexpression of SAA in addition to $sPLA_2$ does not cause a greater reduction in levels of HDL or apo A-I (152), further suggesting that the reduction of HDL during infection is not caused by an increase in apo SAA.

Endothelial lipase (EL) has been shown to regulate HDL metabolism (153-155). EL is synthesized by the endothelial cells and possesses phospholipase A1 activity. Overexpression of EL reduces HDL cholesterol levels (153), while inhibition of EL increases HDL levels (156). Treatment of cultured endothelial cells with TNF-± or IL-1² has been shown to increase 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 due to 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 rapid clearance of apo A-I (159). Which of these changes contributes to the reduction of HDL and apo A-I during the APR is not yet established, but none accounts for the early decrease.

HDL metabolism is tightly linked to reverse cholesterol transport (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**). Apo A-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 cholesterol ester, assists in cholesterol efflux by an aqueous diffusion mechanism. CETP then mediates exchange of cholesterol ester in HDL for TG in TG-rich lipoproteins. PLTP transfers phospholipids from TG-rich lipoproteins into HDL and promotes 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 selective uptake of cholesterol ester whereas ^{2}-chain of ATP synthase mediates endocytosis of HDL particles.

During infection and inflammation, there is a reduction in RCT due to multiple changes at each step in the pathway (**Table 3**). ABCA1 mRNA and protein levels in macrophages are decreased by LPS and cytokines (117, 162), impairing cholesterol efflux from cells. The decreases in apo A-I, HDL, and LCAT impair acceptance of cellular cholesterol (163). The decrease in CETP activity limits the transfer of cholesterol 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 cholesterol 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.

C. 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.

Metabolism of sphingolipids and GSLs is altered during infection and inflammation. LPS stimulates hepatic ceramide and sphingomyelin synthesis by increasing 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), while 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 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 towards aggregation.

LPS also up-regulates mRNA expression and activities of SPT and GlcCer synthase in extra-hepatic tissues, including spleen and kidney (166). The content of ceramide in spleen or kidney, however, is not increased, suggesting that newly synthesized ceramide is utilized as a substrate for increasing 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 for regulating cellular proliferation and modulating the immune response.

In addition to activating the enzymes that synthesize sphingolipids and GSLs, LPS and cytokines also induce enzymes involved in hydrolysis of sphingolipids (**Fig. 5**). Treatment with LPS, TNF, or IL-1 acutely increases serum activity of secretory sphingomyelinase (168). Serum ceramide levels are elevated 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 de novo synthesis of ceramide and its downstream metabolites or in the hydrolysis of

ceramide are induced by LPS and cytokines. Since 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. **Fig. 5** summarizes the effects of LPS and APR-inducing cytokines on sphingolipid and GSL metabolism.

III. Role of nuclear hormone receptors in the regulation of lipid metabolism during infection and inflammation

A. Nuclear hormone receptors and lipid metabolism

Most, if not all, of the changes in lipid metabolism that are induced by infection and inflammation are due 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, while the IL-6 family of cytokines increase class 2 positive acute-phase proteins (173, 174). Activation of nuclear factor-ºB (NF-ºB) and nuclear factor interleukin-6 (NF-IL-6) mediates IL-1-stimulated increases in acute-phase protein transcription, while activation of NF-IL-6 and the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway mediates IL-6 family stimulation of acute-phase protein transcription (174). Much less is understood regarding the mechanism of the down-regulation 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, increased activity of these receptors regulates transcription of a large number of genes involved in a 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 will be 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 down-regulation of these liposensors plays a key role in those changes.

B. 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 hours) 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 (Kim et al., unpublished observations). Furthermore, LPS administration also significantly reduces hepatic nuclear DNA-binding activity of RXR homodimers to an RXR response element (183).

In addition to inhibiting 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, PXR (pregnane X receptor), and CAR (constitutive androstane receptor) (183-185). These decreases were associated with reductions in nuclear-binding activity to a DR-1 PPAR response element, a DR-4 LXR response element, and an IR-1 FXR response element (183, 184). In contrast, mRNA levels of PPAR-β/δ and LXR-β were not significantly altered in the liver following LPS treatment.

In adipose tissue, PPAR-γ levels decrease following the administration of LPS or TNF (186)(**Table 4**). Treatment of adipocytes in vitro with TNF, IFN-^{3}, 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, while the levels of liposensors are regulated in tissues that play a major role in the alterations in 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.

C. Consequences of decreased expression of liposensors

While 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 coordinate 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.

1. 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-^{3} has been shown to directly regulate genes that promote the storage of fat in adipose tissue, including adipocyte P2 (aP2), 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-^{3} activity in adipose tissue contributes to the changes in these proteins that would reduce fat storage and enhance lipolysis.

Likewise, down-regulation 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, H-FABP, CPT-Iβ, 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.

Down-regulation 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, L-FABP, and CPT-Iα (ACS is decreased in mitochondria but not endoplasmic reticulum) (67, 68, 70, 71)(**Table 4**). In contrast, many proteins involved in re-esterification of FA and secretion of VLDL from the liver are not decreased and they 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 elevated serum TG levels (201), and FXR has been shown to regulate the hepatic expression apo C-II and apo E (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 et al. (204, 205) have shown that IL-1- and IL-6-induced decreases in apo E mRNA levels in HepG2 cells are associated with the phosphorylation of BK virus enhancer factor-1 (BEF-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 apo E 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 apo E expression. Likewise, we recently found that PPAR-³ co-activating factor-1 (PGC-1), which interacts with PPAR-±, PPAR-³, hepatocyte nuclear factor-4 (HNF-4) and other nuclear hormone receptors, is reduced during the APR (Kim, 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.

2. Reverse Cholesterol Transport (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.

a. 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 the 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 induction of LXR target genes, including ABCA1 (209). This crosstalk between LXR and toll-like receptor signaling decreases cholesterol efflux from macrophages (209). In addition, LPS-induced decreases in expression of CYP27A1 would decrease production of 27-hydroxycholesterol, a likely endogenous ligand of LXR, further explaining the effect of LPS on LXR target genes (110).

b. Enzymes and transfer proteins in the serum

CETP mediates the transfer of cholesterol ester from HDL to apo B-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**).

c. Receptors in the liver

SR-BI mediates selective uptake of cholesterol 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**).

d. Hepatic synthesis of bile acids

Cholesterol 7α-hydroxylase (CYP7A1) is the key rate-limiting enzyme in the neutral bile acid synthetic pathway (105). CYP7A1 is regulated by both LXR and FXR in rodents, but not

humans (216-218) (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 lowering 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 12α-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 following 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 sterol 27-hydroxylase (CYP27A1), a key enzyme in the both the classical 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.

e. 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 by ABCG5/ABCG8, and the secretion of phospholipids 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-± 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 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.

IV. Pro-atherogenic 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, and chronic bronchitis, infections in which the microorganisms are not localized to the vessel wall (240-242). Finally, there is an increased incidence of CAD in patients with inflammatory diseases such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus (243-246). While 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 pro-atherogenic changes in lipoproteins, a vicious cycle could develop resulting in worsening of atherosclerosis.

A. VLDL metabolism

Evidence is accumulating that TG-rich lipoproteins are pro-atherogenic (247-249). VLDL from hypertriglyceridemic 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). VLDL secreted by the liver after LPS administration is also enriched in sphingolipids (128). Since 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 pro-atherogenic.

B. 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 LDL (subclass pattern B) (253). These LDL particles are more pro-atherogenic 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 LDL can cross the endothelial barrier more effectively and bind to proteoglycans in the vascular

wall intima, resulting in LDL retention (255). Additionally, small dense LDL are more susceptible to oxidative modifications resulting in rapid uptake and cholesterol accumulation in the macrophages (256). The increase in small dense LDL 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).

C-reactive protein (CRP) is a classical 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 formation of foam cells using the oxidized LDL.

During infection and inflammation, increases in $sPLA_2$ are likely to promote atherosclerosis. $sPLA_2$ 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, $sPLA_2$-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 $sPLA_2$ exhibit significant atherosclerosis even when maintained on a low-fat diet (265).

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 of plasma PAF-AH activity is found on HDL (266). Plasma PAF-AH degrades PAF, a pro-inflammatory phospholipid mediator produced during infection and inflammation. However, PAF-AH also hydrolyzes lipoprotein-associated phosphatidylcholine, generating LPC, a molecule that exerts several pro-atherogenic 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 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 pro-atherogenic consequences.

Circulating LDL is more enriched in several sphingolipids including sphingomyelin, ceramide, and glucosylceramide during infection/inflammation (27, 128). Sphingolipid enrichment may increase atherogenic potential of LDL, as LDL isolated from atherosclerotic lesions is enriched in sphingomyelin, ceramide, and glucosylceramide (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 generation of small dense LDL, increased susceptibility towards oxidation, increased CRP, $sPLA_2$-induced hydrolysis of LDL phospholipids, high plasma PAF-AH activity, and LDL enrichment with TG, cholesterol, LPC and sphingolipids. These alterations alter the structure and function of LDL, rendering it more pro-atherogenic.

C. HDL metabolism

Many changes in HDL metabolism occur during infection/inflammation that can impair the anti-atherogenic functions of HDL. As discussed above, several HDL-associated proteins involved in RCT pathway are decreased, including apo A-I, LCAT, CETP, HL, and SR-BI (**Table 3**). During the APR, cholesterol removal from cells is decreased (163, 277, 278) due to a reduction in LCAT in acute-phase HDL (163). Moreover, cholesterol ester delivery to hepatocytes is decreased due to a decrease in SR-BI (164, 279). While an initial decrease in RCT during the APR may be

beneficial as it redirects cholesterol towards 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 apo A-I possess anti-oxidant activity. Their removal or inactivation increases the susceptibility of LDL towards oxidation (280, 281), although the in vivo contribution of each is not yet established. During infection and inflammation, HDL loses its anti-oxidant function and becomes pro-oxidant (134, 135).

PON is 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 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 pro-oxidant role (283, 284). In contrast, transferrin levels decrease during infection (285). Transferrin, which binds iron, may be anti-oxidant, 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 anti-oxidant function during the APR, converting HDL into a pro-oxidant, pro-inflammatory, and pro-atherogenic 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 risk of atherosclerosis. LPS and cytokines (TNF and IL-1) activate macrophages to accumulate lipids (286-288). LPS-stimulated macrophages accumulate more TGs and cholesterol ester from lipoproteins than 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.

V. 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 anti-infective 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. The following sections will discuss these actions of lipoproteins with reference to changes that occur in the APR.

A. 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 ±-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 due 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 minutes 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 was induced by cecal ligation and puncture (313).

Further evidence of lipoprotein protection comes from models of hypolipidemia or hyperlipidemia. Hypolipidemic rats, produced by 4-aminopyrolo-(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 apo A-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. Raising lipoprotein levels may be a viable therapeutic strategy to block or neutralize toxic effects of LPS. Although the LPS-binding capacity of lipoproteins is 10-1000-fold above 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 is favored. As a result, TG-rich fat emulsions could not inhibit the inflammatory response to LPS (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. While 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 selective inhibition of NF-ºB, 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 attenuate 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, has been 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, apo A-I, apo E, and apo A-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.

Apo A-I or apo A-IV alone decreases the activation of macrophages by LPS (327, 340). LPS preincubated with apo A-I in vitro reduces the febrile response in animals (298). Transgenic mice overexpressing apo A-I are resistant to LPS-induced lethality and severe gram-negative infections (315). Secretion of cytokines from lymphocytes of apo A-IV transgenic mice was less pronounced than that of control animals (340). Similarly, injection of apo E reduces the production of cytokines and death induced by LPS (341). Although apo E-deficient mice have high levels of

cholesterol, they are more susceptible to endotoxemia and gram negative infections (342). The fact that high levels of cholesterol could not protect apo E-deficient mice from toxic effects of LPS and that these mice develop defects in the phagocytic activity of granulocytes suggests that apo E may have additional effects on the immune system (343). It is of interest that macrophages themselves make and secrete apo E (344). Apo A-IV is recently found to be increased in HDL during the APR (Khovidhunkit, et al., unpublished observations).

Thus, more than one component of lipoproteins may induce 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).

B. Lipoproteins, lipoprotein receptors, and viruses

Lipoproteins also bind and neutralize a wide variety of enveloped and non-enveloped 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 only for 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 due 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 ±-helix peptides. Because apo A-I and synthetic amphipathic peptide analogues inhibit virus-induced cell fusion (352), it has been proposed that the amphipathic peptides of apo A-I and other apolipoproteins may interfere with membrane fusion and entry of the virus into the host cell. Displacement of apo A-I on HDL by apo SAA during infection may provide free apo A-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 GSL are exploited as receptors by a number of microorganisms, including viruses and bacteria (361). Because acute-phase lipoproteins are enriched in GSL (128), they may prevent entry of these organisms.

Viral infection leads to 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, which 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.

C. 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 apo A-I and haptoglobin-related protein with trace amounts of apo A-II, haptoglobin and PON. TLF2, in contrast, is a lipid-poor lipoprotein complex composed of apo A-I, haptoglobin-related protein, and immunoglobulin M. TLF2 accounts for most of the TLF activity in

serum, as physiologic 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 apo L-I, another HDL-associated protein, as a trypanosome-lytic factor in serum (369). Apo L-I interacts with serum resistance associated protein in the lysosome of trypanosomes. Depletion of apo L-I from normal serum abolished the trypanolytic activity, whereas addition of native or recombinant apo L-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). Beside platelets, activated monocytes can kill schistosomula. Because LDL and oxidized 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 for 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 development. 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 high fat diet compared to those on chow diet, suggesting that high levels of lipoproteins inhibit sporozoite infectivity in mice (372).

D. 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-ºB activation in monocytes/macrophages and endothelial cells by disrupting caveolae and inhibiting 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).

E. Lipoproteins and redistribution of lipids to immune cells

During infection/inflammation, there is an increase in TG-rich VLDL particles, which could provide lipid substrates 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 to 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 down-regulated in the heart, muscle, and

adipose tissue. As a result, fat oxidation in the heart and skeletal muscle decreases, while 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 apo SAA on acute-phase HDL helps redirect cholesterol away from catabolism by hepatocytes and delivers cholesterol to other cells, such as macrophages (376). Upregulation of $sPLA_2$ increases cholesterol 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.

VI. 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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References

1. Gabay, C., and I. Kushner. 1999. Acute-phase proteins and other systemic responses to inflammation. *N. Engl. J. Med.* **340**: 448-454.

2. Yoo, J. Y., and S. Desiderio. 2003. Innate and acquired immunity intersect in a global view of the acute-phase response. *Proc. Natl. Acad. Sci. USA.* **100**: 1157-1162.

3. Okusawa, S., J. A. Gelfand, T. Ikejima, R. J. Connolly, and C. A. Dinarello. 1988. Interleukin 1 induces a shock-like state in rabbits. Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition. *J. Clin. Invest.* **81**: 1162-1172.

4. Yokota, T., N. Arai, J. de Vries, H. Spits, J. Banchereau, A. Zlotnik, D. Rennick, M. Howard, Y. Takebe, S. Miyatake, F. Lee, and K. Arai. 1988. Molecular biology of interleukin 4 and interleukin 5 genes and biology of their products that stimulate B cells, T cells and hemopoietic

cells. *Immunol. Rev.* **102**: 137-187.

5. de Waal Malefyt, R., H. Yssel, M. G. Roncarolo, H. Spits, and J. E. de Vries. 1992. Interleukin-10. *Curr. Opin. Immunol.* **4**: 314-320.

6. Pickup, J. C., and M. A. Crook. 1998. Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia.* **41**: 1241-1248.

7. Pradhan, A. D., and P. M. Ridker. 2002. Do atherosclerosis and type 2 diabetes share a common inflammatory basis? *Eur. Heart J.* **23**: 831-834.

8. Huerta, M. G., and J. L. Nadler. 2002. Role of inflammatory pathways in the development and cardiovascular complications of type 2 diabetes. *Curr. Diab. Rep.* **2**: 396-402.

9. Grimble, R. F. 2002. Inflammatory status and insulin resistance. *Curr. Opin. Clin. Nutr. Metab. Care.* **5**: 551-559.

10. Yudkin, J. S., M. Kumari, S. E. Humphries, and V. Mohamed-Ali. 2000. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis.* **148**: 209-214.

11. Sharma, R., F. O. Al-Nasser, and S. D. Anker. 2001. The importance of tumor necrosis factor and lipoproteins in the pathogenesis of chronic heart failure. *Heart Fail. Monit.* **2**: 42-47.

12. Young, J. L., P. Libby, and U. Schonbeck. 2002. Cytokines in the pathogenesis of atherosclerosis. *Thromb. Haemost.* **88**: 554-567.

13. Hardardóttir, I., C. Grunfeld, and K. R. Feingold. 1995. Effects of endotoxin on lipid metabolism. *Biochem. Soc. Trans.* **23**: 1013-1018.

14. Khovidhunkit, W., R. A. Memon, K. R. Feingold, and C. Grunfeld. 2000. Infection and

inflammation-induced proatherogenic changes of lipoproteins. *J. Infect. Dis.* **181**: S462-S472.

15. Gallin, J. I., D. Kaye, and W. M. O'Leary. 1969. Serum lipids in infection. *N. Engl. J. Med.* **281**: 1081-1086.

16. Sammalkorpi, K., V. Valtonen, Y. Kerttula, E. Nikkila, and M. R. Taskinen. 1988. Changes in serum lipoprotein pattern induced by acute infections. *Metabolism.* **37**: 859-865.

17. Grunfeld, C., M. Pang, W. Doerrler, J. K. Shigenaga, P. Jensen, and K. R. Feingold. 1992. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J. Clin. Endocrinol. Metab.* **74**: 1045-1052.

18. Fiser, R. H., T. D. Shultz, R. B. Rindsig, and W. R. Beisel. 1973. Alterations in plasma and brain lipid metabolism during endotoxemia in the neonatal rat. *Biol. Neonate.* **22**: 155-160.

19. Kaufmann, R. L., C. F. Matson, and W. R. Beisel. 1976. Hypertriglyceridemia produced by endotoxin: role of impaired triglyceride disposal mechanisms. *J. Infect. Dis.* **133**: 548-555.

20. Sakaguchi, O., and S. Sakaguchi. 1979. Alterations of lipid metabolism in mice injected with endotoxin. *Microbiol. Immunol.* **23**: 71-85.

21. Scholl, R. A., C. H. Lang, and G. J. Bagby. 1984. Hypertriglyceridemia and its relation to tissue lipoprotein lipase activity in endotoxemic, Escherichia coli bacteremic, and polymicrobial septic rats. *J. Surg. Res.* **37**: 394-401.

22. Gaal, D., T. Kremmer, Z. Balint, L. Holczinger, L. Bertok, and A. Nowotny. 1984. Effects of bacterial endotoxins and their detoxified derivatives on serum and liver lipids in mice. *Toxicol.*

Appl. Pharmacol. **75**: 437-443.

23. Kawakami, M., T. Murase, H. Itakura, N. Yamada, N. Ohsawa, and F. Takaku. 1986. Lipid metabolism in endotoxic rats: decrease in hepatic triglyceride lipase activity. *Microbiol. Immunol.* **30**: 849-854.

24. Auerbach, B. J., and J. S. Parks. 1989. Lipoprotein abnormalities associated with lipopolysaccharide-induced lecithin: cholesterol acyltransferase and lipase deficiency. *J. Biol. Chem.* **264**: 10264-10270.

25. Ettinger, W. H., L. D. Miller, J. J. Albers, T. K. Smith, and J. S. Parks. 1990. Lipopolysaccharide and tumor necrosis factor cause a fall in plasma concentration of lecithin: cholesterol acyltransferase in cynomolgus monkeys. *J. Lipid Res.* **31**: 1099-1107.

26. Feingold, K. R., I. Staprans, R. A. Memon, A. H. Moser, J. K. Shigenaga, W. Doerrler, C. A. Dinarello, and C. Grunfeld. 1992. Endotoxin rapidly induces changes in lipid metabolism that produce hypertriglyceridemia: low doses stimulate hepatic triglyceride production while high doses inhibit clearance. *J. Lipid Res.* **33**: 1765-1776.

27. Feingold, K. R., I. Hardardottir, R. Memon, E. J. Krul, A. H. Moser, J. M. Taylor, and C. Grunfeld. 1993. Effect of endotoxin on cholesterol biosynthesis and distribution in serum lipoproteins in Syrian hamsters. *J. Lipid Res.* **34**: 2147-2158.

28. Nonogaki, K., A. H. Moser, X. M. Pan, I. Staprans, C. Grunfeld, and K. R. Feingold. 1995. Lipoteichoic acid stimulates lipolysis and hepatic triglyceride secretion in rats in vivo. *J. Lipid Res.* **36**: 1987-1995.

29. Feingold, K. R., and C. Grunfeld. 1987. Tumor necrosis factor-alpha stimulates hepatic lipogenesis in the rat in vivo. *J. Clin. Invest.* **80**: 184-190.

30. Argiles, J. M., F. J. Lopez-Soriano, R. D. Evans, and D. H. Williamson. 1989. Interleukin-1 and lipid metabolism in the rat. *Biochem. J.* **259**: 673-678.

31. Feingold, K. R., M. Soued, M. K. Serio, A. H. Moser, C. A. Dinarello, and C. Grunfeld. 1989. Multiple cytokines stimulate hepatic lipid synthesis in vivo. *Endocrinology.* **125**: 267-274.

32. Feingold, K. R., M. Soued, S. Adi, I. Staprans, R. Neese, J. Shigenaga, W. Doerrler, A. Moser, C. A. Dinarello, and C. Grunfeld. 1991. Effect of interleukin-1 on lipid metabolism in the rat. Similarities to and differences from tumor necrosis factor. *Arterioscler. Thromb.* **11**: 495-500.

33. Memon, R. A., C. Grunfeld, A. H. Moser, and K. R. Feingold. 1993. Tumor necrosis factor mediates the effects of endotoxin on cholesterol and triglyceride metabolism in mice. *Endocrinology.* **132**: 2246-2253.

34. Nonogaki, K., G. M. Fuller, N. L. Fuentes, A. H. Moser, I. Staprans, C. Grunfeld, and K. R. Feingold. 1995. Interleukin-6 stimulates hepatic triglyceride secretion in rats. *Endocrinology.* **136**: 2143-2149.

35. Sherman, M. L., D. R. Spriggs, K. A. Arthur, K. Imamura, E. Frei, 3rd, and D. W. Kufe. 1988. Recombinant human tumor necrosis factor administered as a five-day continuous infusion in cancer patients: phase I toxicity and effects on lipid metabolism. *J. Clin. Oncol.* **6**: 344-350.

36. Malmendier, C. L., J. F. Lontie, J. P. Sculier, and D. Y. Dubois. 1988. Modifications of plasma lipids, lipoproteins and apolipoproteins in advanced cancer patients treated with

recombinant interleukin-2 and autologous lymphokine-activated killer cells. *Atherosclerosis.* **73**: 173-180.

37. Starnes, H. F., Jr., R. S. Warren, M. Jeevanandam, J. L. Gabrilove, W. Larchian, H. F. Oettgen, and M. F. Brennan. 1988. Tumor necrosis factor and the acute metabolic response to tissue injury in man. *J. Clin. Invest.* **82**: 1321-1325.

38. Kurzrock, R., M. F. Rohde, J. R. Quesada, S. H. Gianturco, W. A. Bradley, S. A. Sherwin, and J. U. Gutterman. 1986. Recombinant gamma interferon induces hypertriglyceridemia and inhibits post-heparin lipase activity in cancer patients. *J. Exp. Med.* **164**: 1093-1101.

39. Olsen, E. A., G. R. Lichtenstein, and W. E. Wilkinson. 1988. Changes in serum lipids in patients with condylomata acuminata treated with interferon alfa-n1 (Wellferon). *J. Am. Acad. Dermatol.* **19**: 286-289.

40. Naeem, M., B. R. Bacon, B. Mistry, R. S. Britton, and A. M. Di Bisceglie. 2001. Changes in serum lipoprotein profile during interferon therapy in chronic hepatitis C. *Am. J. Gastroenterol.* **96**: 2468-2472.

41. Chajek-Shaul, T., G. Friedman, O. Stein, E. Shiloni, J. Etienne, and Y. Stein. 1989. Mechanism of the hypertriglyceridemia induced by tumor necrosis factor administration to rats. *Biochim. Biophys. Acta.* **1001**: 316-324.

42. Rosenzweig, I. B., D. A. Wiebe, J. A. Hank, J. J. Albers, J. L. Adolphson, E. Borden, E. S. Shrago, and P. M. Sondel. 1990. Effects of interleukin-2 (IL-2) on human plasma lipid, lipoprotein, and C-reactive protein. *Biotherapy.* **2**: 193-198.

43. Nonogaki, K., X. M. Pan, A. H. Moser, J. Shigenaga, I. Staprans, N. Sakamoto, C. Grunfeld, and K. R. Feingold. 1996. LIF and CNTF, which share the gp130 transduction system, stimulate hepatic lipid metabolism in rats. *Am. J. Physiol.* **271**: E521-528.

44. Nonogaki, K., A. H. Moser, J. Shigenaga, K. R. Feingold, and C. Grunfeld. 1996. Beta-nerve growth factor as a mediator of the acute phase response in vivo. *Biochem. Biophys. Res. Commun.* **219**: 956-961.

45. Nonogaki, K., X. M. Pan, A. H. Moser, I. Staprans, K. R. Feingold, and C. Grunfeld. 1995. Keratinocyte growth factor increases fatty acid mobilization and hepatic triglyceride secretion in rats. *Endocrinology.* **136**: 4278-4284.

46. Evans, R. D., V. Ilic, and D. H. Williamson. 1991. Effects of platelet-activating factor on lipid metabolism in rats in vivo. Origin of the hypertriglyceridaemia. *Biochem. J.* **280**: 541-543.

47. Funk, J. L., A. H. Moser, C. Grunfeld, and K. R. Feingold. 1997. Parathyroid hormone-related protein is induced in the adult liver during endotoxemia and stimulates the hepatic acute phase response. *Endocrinology.* **138**: 2665-2673.

48. Grunfeld, C., M. Soued, S. Adi, A. H. Moser, W. Fiers, C. A. Dinarello, and K. R. Feingold. 1991. Interleukin 4 inhibits stimulation of hepatic lipogenesis by tumor necrosis factor, interleukin 1, and interleukin 6 but not by interferon-alpha. *Cancer Res.* **51**: 2803-2807.

49. Feingold, K. R., M. Soued, I. Staprans, L. A. Gavin, M. E. Donahue, B. J. Huang, A. H. Moser, R. Gulli, and C. Grunfeld. 1989. Effect of tumor necrosis factor (TNF) on lipid metabolism in the diabetic rat. Evidence that inhibition of adipose tissue lipoprotein lipase activity is not

required for TNF-induced hyperlipidemia. *J. Clin. Invest.* **83**: 1116-1121.

50. Evans, R. D., and D. H. Williamson. 1991. Comparison of effects of platelet-activating factor and tumour necrosis factor-alpha on lipid metabolism in adrenalectomized rats in vivo. *Biochim. Biophys. Acta.* **1086**: 191-196.

51. Feingold, K. R., M. Soued, M. K. Serio, S. Adi, A. H. Moser, and C. Grunfeld. 1990. The effect of diet on tumor necrosis factor stimulation of hepatic lipogenesis. *Metabolism.* **39**: 623-632.

52. Feingold, K. R., S. Adi, I. Staprans, A. H. Moser, R. Neese, J. A. Verdier, W. Doerrler, and C. Grunfeld. 1990. Diet affects the mechanisms by which TNF stimulates hepatic triglyceride production. *Am. J. Physiol.* **259**: E177-184.

53. Grunfeld, C., M. Soued, S. Adi, A. H. Moser, C. A. Dinarello, and K. R. Feingold. 1990. Evidence for two classes of cytokines that stimulate hepatic lipogenesis: relationships among tumor necrosis factor, interleukin-1 and interferon-alpha. *Endocrinology*. **127**: 46-54.

54. Tripp, R. J., A. Tabares, H. Wang, and S. Lanza-Jacoby. 1993. Altered hepatic production of apolipoproteins B and E in the fasted septic rat: factors in the development of hypertriglyceridemia. *J. Surg. Res.* **55**: 465-472.

55. Feingold, K. R., M. K. Serio, S. Adi, A. H. Moser, and C. Grunfeld. 1989. Tumor necrosis factor stimulates hepatic lipid synthesis and secretion. *Endocrinology*. **124**: 2336-2342.

56. Grunfeld, C., J. A. Verdier, R. Neese, A. H. Moser, and K. R. Feingold. 1988. Mechanisms by which tumor necrosis factor stimulates hepatic fatty acid synthesis in vivo. *J. Lipid Res.* **29**: 1327-1335.

57. Kiuchi, S., N. Matsuo, N. Takeyama, and T. Tanaka. 1993. Accelerated hepatic lipid synthesis in fasted septic rats. *Eur. Surg. Res.* **25**: 146-154.

58. Hikawyj-Yevich, I., and J. A. Spitzer. 1977. Endotoxin influence on lipolysis in isolated human and primate adipocytes. *J. Surg. Res.* **23**: 106-113.

59. Spitzer, J. J. 1979. Lipid metabolism in endotoxic shock. *Circ. Shock.* **Suppl 1**: 69-79.

60. Green, A., S. B. Dobias, D. J. Walters, and A. R. Brasier. 1994. Tumor necrosis factor increases the rate of lipolysis in primary cultures of adipocytes without altering levels of hormone-sensitive lipase. *Endocrinology.* **134**: 2581-2588.

61. Kawakami, M., T. Murase, H. Ogawa, S. Ishibashi, N. Mori, F. Takaku, and S. Shibata. 1987. Human recombinant TNF suppresses lipoprotein lipase activity and stimulates lipolysis in 3T3-L1 cells. *J. Biochem. (Tokyo).* **101**: 331-338.

62. Hauner, H., T. Petruschke, M. Russ, K. Rohrig, and J. Eckel. 1995. Effects of tumour necrosis factor alpha (TNF alpha) on glucose transport and lipid metabolism of newly-differentiated human fat cells in cell culture. *Diabetologia.* **38**: 764-771.

63. Memon, R. A., K. R. Feingold, A. H. Moser, W. Doerrler, and C. Grunfeld. 1992. In vivo effects of interferon-alpha and interferon-gamma on lipolysis and ketogenesis. *Endocrinology.* **131**: 1695-1702.

64. Doerrler, W., K. R. Feingold, and C. Grunfeld. 1994. Cytokines induce catabolic effects in cultured adipocytes by multiple mechanisms. *Cytokine.* **6**: 478-484.

65. Zhang, H. H., M. Halbleib, F. Ahmad, V. C. Manganiello, and A. S. Greenberg. 2002.

Tumor necrosis factor-alpha stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP. *Diabetes.* **51**: 2929-2935.

66. Greenberg, A. S., W. J. Shen, K. Muliro, S. Patel, S. C. Souza, R. A. Roth, and F. B. Kraemer. 2001. Stimulation of lipolysis and hormone-sensitive lipase via the extracellular signal-regulated kinase pathway. *J. Biol. Chem.* **276**: 45456-45461.

67. Memon, R. A., K. R. Feingold, A. H. Moser, J. Fuller, and C. Grunfeld. 1998. Regulation of fatty acid transport protein and fatty acid translocase mRNA levels by endotoxin and cytokines. *Am. J. Physiol.* **274**: E210-217.

68. Memon, R. A., J. Fuller, A. H. Moser, P. J. Smith, K. R. Feingold, and C. Grunfeld. 1998. In vivo regulation of acyl-CoA synthetase mRNA and activity by endotoxin and cytokines. *Am. J. Physiol.* **275**: E64-72.

69. Beylot, M., M. Guiraud, G. Grau, and P. Bouletreau. 1989. Regulation of ketone body flux in septic patients. *Am. J. Physiol.* **257**: E665-674.

70. Takeyama, N., Y. Itoh, Y. Kitazawa, and T. Tanaka. 1990. Altered hepatic mitochondrial fatty acid oxidation and ketogenesis in endotoxic rats. *Am. J. Physiol.* **259**: E498-505.

71. Memon, R. A., N. M. Bass, A. H. Moser, J. Fuller, R. Appel, C. Grunfeld, and K. R. Feingold. 1999. Down-regulation of liver and heart specific fatty acid binding proteins by endotoxin and cytokines in vivo. *Biochim. Biophys. Acta.* **1440**: 118-126.

72. Barke, R. A., S. Birklid, R. B. Chapin, S. Roy, P. S. Brady, and L. J. Brady. 1996. The effect

of surgical treatment following peritoneal sepsis on hepatic gene expression. *J. Surg. Res.* **60**: 101-106.

73. Andrejko, K. M., and C. S. Deutschman. 1997. Altered hepatic gene expression in fecal peritonitis: changes in transcription of gluconeogenic, beta-oxidative, and ureagenic genes. *Shock.* **7**: 164-169.

74. Memon, R. A., K. R. Feingold, A. H. Moser, W. Doerrler, S. Adi, C. A. Dinarello, and C. Grunfeld. 1992. Differential effects of interleukin-1 and tumor necrosis factor on ketogenesis. *Am. J. Physiol.* **263**: E301-309.

75. Romanosky, A. J., G. J. Bagby, E. L. Bockman, and J. J. Spitzer. 1980. Free fatty acid utilization by skeletal muscle after endotoxin administration. *Am. J. Physiol.* **239**: E391-395.

76. Romanosky, A. J., G. J. Bagby, E. L. Bockman, and J. J. Spitzer. 1980. Increased muscle glucose uptake and lactate release after endotoxin administration. *Am. J. Physiol.* **239**: E311-316.

77. Lanza-Jacoby, S., K. Feagans, and A. Tabares. 1989. Fatty acid metabolism in the heart during Escherichia coli sepsis in the rat. *Circ. Shock.* **29**: 361-370.

78. Friedman, G., V. Barak, T. Chajek-Shaul, J. Etienne, A. J. Treves, O. Stein, and Y. Stein. 1991. Recombinant human interleukin-1 suppresses lipoprotein lipase activity, but not expression of lipoprotein lipase mRNA in mesenchymal rat heart cell cultures. *Biochim. Biophys. Acta.* **1089**: 83-87.

79. Enerback, S., H. Semb, J. Tavernier, G. Bjursell, and T. Olivecrona. 1988. Tissue-specific regulation of guinea pig lipoprotein lipase; effects of nutritional state and of tumor necrosis factor

on mRNA levels in adipose tissue, heart and liver. *Gene.* **64**: 97-106.

80. Feingold, K. R., M. Marshall, R. Gulli, A. H. Moser, and C. Grunfeld. 1994. Effect of endotoxin and cytokines on lipoprotein lipase activity in mice. *Arterioscler. Thromb.* **14**: 1866-1872.

81. Beutler, B., and A. Cerami. 1986. Cachectin and tumour necrosis factor as two sides of the same biological coin. *Nature.* **320**: 584-588.

82. Patton, J. S., H. M. Shepard, H. Wilking, G. Lewis, B. B. Aggarwal, T. E. Eessalu, L. A. Gavin, and C. Grunfeld. 1986. Interferons and tumor necrosis factors have similar catabolic effects on 3T3 L1 cells. *Proc. Natl. Acad. Sci. USA.* **83**: 8313-8317.

83. Grunfeld, C., R. Gulli, A. H. Moser, L. A. Gavin, and K. R. Feingold. 1989. Effect of tumor necrosis factor administration in vivo on lipoprotein lipase activity in various tissues of the rat. *J. Lipid Res.* **30**: 579-585.

84. Feingold, K. R., M. Soued, S. Adi, I. Staprans, J. Shigenaga, W. Doerrler, A. Moser, and C. Grunfeld. 1990. Tumor necrosis factor-increased hepatic very-low-density lipoprotein production and increased serum triglyceride levels in diabetic rats. *Diabetes.* **39**: 1569-1574.

85. Hardardóttir, I., J. Sipe, A. H. Moser, C. J. Fielding, K. R. Feingold, and C. Grünfeld. 1997. LPS and cytokines regulate extra hepatic mRNA levels of apolipoproteins during the acute phase response in Syrian hamsters. *Biochim. Biophys. Acta.* **1344**: 210-220.

86. Lanza-Jacoby, S., S. H. Wong, A. Tabares, D. Baer, and T. Schneider. 1992. Disturbances in the composition of plasma lipoproteins during gram- negative sepsis in the rat. *Biochim.*

Biophys. Acta. **1124**: 233-240.

87. Phetteplace, H., M. Maniscalco, and S. Lanza-Jacoby. 1994. The catabolism of apolipoprotein B from very low density lipoprotein and triglyceride-rich lipoprotein remnants in fasted septic rats. *Shock.* **1**: 217-220.

88. Feingold, K. R., A. S. Pollock, A. H. Moser, J. K. Shigenaga, and C. Grunfeld. 1995. Discordant regulation of proteins of cholesterol metabolism during the acute phase response. *J. Lipid Res.* **36**: 1474-1482.

89. Memon, R. A., I. Shechter, A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 1997. Endotoxin, tumor necrosis factor, and interleukin-1 decrease hepatic squalene synthase activity, protein, and mRNA levels in Syrian hamsters. *J. Lipid Res.* **38**: 1620-1629.

90. Mookerjea, S., T. Coolbear, and M. L. Sarkar. 1983. Key role of dolichol phosphate in glycoprotein biosynthesis. *Can. J. Biochem. Cell. Biol.* **61**: 1032-1040.

91. Sarkar, M., and S. Mookerjea. 1988. Differential effect of inflammation and dexamethasone on dolichol and dolichol phosphate synthesis. *Biochem. Cell. Biol.* **66**: 1265-1269.

92. Hardardóttir, I., A. H. Moser, R. Memon, C. Grünfeld, and K. R. Feingold. 1994. Effects of TNF, IL-1, and the combination of both cytokines on cholesterol metabolism in Syrian hamsters. *Lymphokine Cytokine Res.* **13**: 161-166.

93. Spriggs, D. R., M. L. Sherman, H. Michie, K. A. Arthur, K. Imamura, D. Wilmore, E. Frei, 3rd, and D. W. Kufe. 1988. Recombinant human tumor necrosis factor administered as a 24-hour intravenous infusion. A phase I and pharmacologic study. *J. Natl. Cancer Inst.* **80**: 1039-1044.

94. Rosenzweig, I. B., D. A. Wiebe, E. C. Borden, B. Storer, and E. S. Shrago. 1987. Plasma lipoprotein changes in humans induced by beta-interferon. *Atherosclerosis.* **67**: 261-267.

95. Nimer, S. D., R. E. Champlin, and D. W. Golde. 1988. Serum cholesterol-lowering activity of granulocyte-macrophage colony-stimulating factor. *J. Am. Med. Assoc.* **260**: 3297-3300.

96. Stoudemire, J. B., and M. B. Garnick. 1991. Effects of recombinant human macrophage colony-stimulating factor on plasma cholesterol levels. *Blood.* **77**: 750-755.

97. Ettinger, W. H., L. A. Miller, T. K. Smith, and J. S. Parks. 1992. Effect of interleukin-1 alpha on lipoprotein lipids in cynomolgus monkeys: comparison to tumor necrosis factor. *Biochim. Biophys. Acta.* **1128**: 186-192.

98. Ettinger, W. H., V. K. Varma, M. Sorci-Thomas, J. S. Parks, R. C. Sigmon, T. K. Smith, and R. B. Verdery. 1994. Cytokines decrease apolipoprotein accumulation in medium from Hep G2 cells. *Arterioscler. Thromb.* **14**: 8-13.

99. Schectman, G., S. Kaul, R. A. Mueller, E. C. Borden, and A. H. Kissebah. 1992. The effect of interferon on the metabolism of LDLs. *Arterioscler. Thromb.* **12**: 1053-1062.

100. Xu, N., and A. Nilsson. 1996. Endotoxin inhibits catabolism of low density lipoproteins in vivo: an experimental study in the rat. *Scand. J. Clin. Lab. Invest.* **56**: 53-61.

101. Liao, W., M. Rudling, and B. Angelin. 1999. Endotoxin suppresses mouse hepatic low-density lipoprotein-receptor expression via a pathway independent of the toll-like receptor 4. *Hepatology*. **30**: 1252-1256.

102. Moorby, C. D., E. Gherardi, L. Dovey, C. Godliman, and D. E. Bowyer. 1992. Transforming

growth factor-beta 1 and interleukin-1 beta stimulate LDL receptor activity in Hep G2 cells. *Atherosclerosis.* **97**: 21-28.

103. Liao, W., and C. H. Floren. 1993. Tumor necrosis factor up-regulates expression of low-density lipoprotein receptors on HepG2 cells. *Hepatology.* **17**: 898-907.

104. Bjorkhem, I., and G. Eggertsen. 2001. Genes involved in initial steps of bile acid synthesis. *Curr. Opin. Lipidol.* **12**: 97-103.

105. Russell, D. W. 2003. The enzymes, regulation, and genetics of bile acid synthesis. *Annu. Rev. Biochem.* **16**: 16.

106. Trauner, M., and J. L. Boyer. 2003. Bile salt transporters: molecular characterization, function, and regulation. *Physiol. Rev.* **83**: 633-671.

107. Yu, L., R. E. Hammer, J. Li-Hawkins, K. Von Bergmann, D. Lutjohann, J. C. Cohen, H. H. Hobbs, K. E. Berge, J. D. Horton, G. A. Graf, W. P. Li, R. D. Gerard, I. Gelissen, and A. White. 2002. Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion. *Proc. Natl. Acad. Sci. USA.* **99**: 16237-16242.

108. Yu, L., J. Li-Hawkins, R. E. Hammer, K. E. Berge, J. D. Horton, J. C. Cohen, H. H. Hobbs, G. A. Graf, W. P. Li, R. D. Gerard, I. Gelissen, and A. White. 2002. Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. *J. Clin. Invest.* **110**: 671-680.

109. Feingold, K. R., D. K. Spady, A. S. Pollock, A. H. Moser, and C. Grunfeld. 1996. Endotoxin, TNF, and IL-1 decrease cholesterol 7 alpha-hydroxylase mRNA levels and activity. *J.*

Lipid Res. **37**: 223-228.

110. Memon, R. A., A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 2001. In vivo and in vitro regulation of sterol 27-hydroxylase in the liver during the acute phase response. potential role of hepatocyte nuclear factor-1. *J. Biol. Chem.* **276**: 30118-30126.

111. Green, R. M., D. Beier, and J. L. Gollan. 1996. Regulation of hepatocyte bile salt transporters by endotoxin and inflammatory cytokines in rodents. *Gastroenterology.* **111**: 193-198.

112. Moseley, R. H., W. Wang, H. Takeda, K. Lown, L. Shick, M. Ananthanarayanan, and F. J. Suchy. 1996. Effect of endotoxin on bile acid transport in rat liver: a potential model for sepsis-associated cholestasis. *Am. J. Physiol.* **271**: G137-146.

113. Trauner, M., M. Arrese, H. Lee, J. L. Boyer, and S. J. Karpen. 1998. Endotoxin downregulates rat hepatic ntcp gene expression via decreased activity of critical transcription factors. *J. Clin. Invest.* **101**: 2092-2100.

114. Hartmann, G., A. K. Cheung, and M. Piquette-Miller. 2002. Inflammatory cytokines, but not bile acids, regulate expression of murine hepatic anion transporters in endotoxemia. *J. Pharmacol. Exp. Ther.* **303**: 273-281.

115. Vos, T. A., G. J. Hooiveld, H. Koning, S. Childs, D. K. Meijer, H. Moshage, P. L. Jansen, and M. Muller. 1998. Up-regulation of the multidrug resistance genes, Mrp1 and Mdr1b, and down-regulation of the organic anion transporter, Mrp2, and the bile salt transporter, Spgp, in endotoxemic rat liver. *Hepatology.* **28**: 1637-1644.

116. Tygstrup, N., K. Bangert, P. Ott, and H. C. Bisgaard. 2002. Messenger RNA profiles in liver

injury and stress: a comparison of lethal and nonlethal rat models. *Biochem. Biophys. Res. Commun.* **290**: 518-525.

117. Khovidhunkit, W., A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 2003. Endotoxin down-regulates ABCG5 and ABCG8 in mouse liver and ABCA1 and ABCG1 in J774 murine macrophages: differential role of LXR. *J. Lipid Res.* **44**: 1728-1736.

118. Scanu, A. M. 2003. Lipoprotein(a) and the atherothrombotic process: mechanistic insights and clinical implications. *Curr. Atheroscler. Rep.* **5**: 106-113.

119. Karabina, S. A., M. C. Elisaf, J. Goudevenos, K. C. Siamopoulos, D. Sideris, and A. D. Tselepis. 1996. PAF-acetylhydrolase activity of Lp(a) before and during Cu(2+)-induced oxidative modification in vitro. *Atherosclerosis.* **125**: 121-134.

120. Maeda, S., A. Abe, M. Seishima, K. Makino, A. Noma, and M. Kawade. 1989. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis.* **78**: 145-150.

121. Wallberg-Jonsson, S., A. Uddhammar, G. Dahlen, and S. Rantapaa-Dahlqvist. 1995. Lipoprotein(a) in relation to acute phase reaction in patients with rheumatoid arthritis and polymyalgia rheumatica. *Scand. J. Clin. Lab. Invest.* **55**: 309-315.

122. Andreassen, A. K., K. Berg, and H. Torsvik. 1994. Changes in Lp(a) lipoprotein and other plasma proteins during acute myocardial infarction. *Clin. Genet.* **46**: 410-416.

123. Mooser, V., M. M. Berger, L. Tappy, C. Cayeux, S. M. Marcovina, R. Darioli, P. Nicod, and R. Chiolero. 2000. Major reduction in plasma Lp(a) levels during sepsis and burns. *Arterioscler. Thromb. Vasc. Biol.* **20**: 1137-1142.

124. Cabana, V. G., J. N. Siegel, and S. M. Sabesin. 1989. Effects of the acute phase response on the concentration and density distribution of plasma lipids and apolipoproteins. *J. Lipid Res.* **30**: 39-49.

125. Clifton, P. M., A. M. Mackinnon, and P. J. Barter. 1985. Effects of serum amyloid A protein (SAA) on composition, size, and density of high density lipoproteins in subjects with myocardial infarction. *J. Lipid Res.* **26**: 1389-1398.

126. Cabana, V. G., J. R. Lukens, K. S. Rice, T. J. Hawkins, and G. S. Getz. 1996. HDL content and composition in acute phase response in three species: triglyceride enrichment of HDL a factor in its decrease. *J. Lipid Res.* **37**: 2662-2674.

127. Pruzanski, W., E. Stefanski, F. C. de Beer, M. C. de Beer, A. Ravandi, and A. Kuksis. 2000. Comparative analysis of lipid composition of normal and acute-phase high density lipoproteins. *J. Lipid Res.* **41**: 1035-1047.

128. Memon, R. A., W. M. Holleran, A. H. Moser, T. Seki, Y. Uchida, J. Fuller, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 1998. Endotoxin and cytokines increase hepatic sphingolipid biosynthesis and produce lipoproteins enriched in ceramides and sphingomyelin. *Arterioscler. Thromb. Vasc. Biol.* **18**: 1257-1265.

129. Hoffman, J. S., and E. P. Benditt. 1982. Changes in high density lipoprotein content following endotoxin administration in the mouse. Formation of serum amyloid protein-rich subfractions. *J. Biol. Chem.* **257**: 10510-10517.

130. Lindhorst, E., D. Young, W. Bagshaw, M. Hyland, and R. Kisilevsky. 1997. Acute

inflammation, acute phase serum amyloid A and cholesterol metabolism in the mouse. *Biochim. Biophys. Acta.* **1339**: 143-154.

131. Sakaguchi, S. 1982. Metabolic disorders of serum lipoproteins in endotoxin-poisoned mice: the role of high density lipoprotein (HDL) and triglyceride-rich lipoproteins. *Microbiol. Immunol.* **26**: 1017-1034.

132. Barlage, S., D. Frohlich, A. Bottcher, M. Jauhiainen, H. P. Muller, F. Noetzel, G. Rothe, C. Schutt, R. P. Linke, K. J. Lackner, C. Ehnholm, and G. Schmitz. 2001. ApoE-containing high density lipoproteins and phospholipid transfer protein activity increase in patients with a systemic inflammatory response. *J. Lipid Res.* **42**: 281-290.

133. Hardardóttir, I., S. T. Kunitake, A. H. Moser, W. T. Doerrler, J. H. Rapp, C. Grünfeld, and K. R. Feingold. 1994. Endotoxin and cytokines increase hepatic messenger RNA levels and serum concentrations of apolipoprotein J (clusterin) in Syrian hamsters. *J. Clin. Invest.* **94**: 1304-1309.

134. Van Lenten, B. J., S. Y. Hama, F. C. de Beer, D. M. Stafforini, T. M. McIntyre, S. M. Prescott, B. N. La Du, A. M. Fogelman, and M. Navab. 1995. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. *J. Clin. Invest.* **96**: 2758-2767.

135. Van Lenten, B. J., A. C. Wagner, D. P. Nayak, S. Hama, M. Navab, and A. M. Fogelman. 2001. High-density lipoprotein loses its anti-inflammatory properties during acute influenza a infection. *Circulation.* **103**: 2283-2288.

136. Ly, H., O. L. Francone, C. J. Fielding, J. K. Shigenaga, A. H. Moser, C. Grunfeld, and K. R.

Feingold. 1995. Endotoxin and TNF lead to reduced plasma LCAT activity and decreased hepatic LCAT mRNA levels in Syrian hamsters. *J. Lipid Res.* **36**: 1254-1263.

137. Masucci-Magoulas, L., P. Moulin, X. C. Jiang, H. Richardson, A. Walsh, J. L. Breslow, and A. Tall. 1995. Decreased cholesteryl ester transfer protein (CETP) mRNA and protein and increased high density lipoprotein following lipopolysaccharide administration in human CETP transgenic mice. *J. Clin. Invest.* **95**: 1587-1594.

138. Hardardóttir, I., A. H. Moser, J. Fuller, C. Fielding, K. Feingold, and C. Grünfeld. 1996. Endotoxin and cytokines decrease serum levels and extra hepatic protein and mRNA levels of cholesteryl ester transfer protein in syrian hamsters. *J. Clin. Invest.* **97**: 2585-2592.

139. Feingold, K. R., R. A. Memon, A. H. Moser, J. K. Shigenaga, and C. Grunfeld. 1999. Endotoxin and interleukin-1 decrease hepatic lipase mRNA levels. *Atherosclerosis.* **142**: 379-387.

140. Feingold, K. R., R. A. Memon, A. H. Moser, and C. Grunfeld. 1998. Paraoxonase activity in the serum and hepatic mRNA levels decrease during the acute phase response. *Atherosclerosis.* **139**: 307-315.

141. Memon, R. A., J. Fuller, A. H. Moser, K. R. Feingold, and C. Grunfeld. 1999. In vivo regulation of plasma platelet-activating factor acetylhydrolase during the acute phase response. *Am. J. Physiol.* **277**: R94-R103.

142. Jiang, X. C., and C. Bruce. 1995. Regulation of murine plasma phospholipid transfer protein activity and mRNA levels by lipopolysaccharide and high cholesterol diet. *J. Biol. Chem.* **270**: 17133-17138.

143. Hudgins, L. C., T. S. Parker, D. M. Levine, B. R. Gordon, S. D. Saal, X. C. Jiang, C. E. Seidman, J. D. Tremaroli, J. Lai, and A. L. Rubin. 2003. A single intravenous dose of endotoxin rapidly alters serum lipoproteins and lipid transfer proteins in normal volunteers. *J. Lipid Res.* **44**: 1489-1498.

144. Pruzanski, W., P. Vadas, and J. Browning. 1993. Secretory non-pancreatic group II phospholipase A2: role in physiologic and inflammatory processes. *J. Lipid Mediat.* **8**: 161-167.

145. Cabana, V. G., C. A. Reardon, B. Wei, J. R. Lukens, and G. S. Getz. 1999. SAA-only HDL formed during the acute phase response in apoA-I+/+ and apoA-I-/- mice. *J. Lipid Res.* **40**: 1090-1103.

146. Husebekk, A., B. Skogen, and G. Husby. 1988. High-density lipoprotein has different binding capacity for different apoproteins. The amyloidogenic apoproteins are easier to displace from high-density lipoprotein. *Scand. J. Immunol.* **28**: 653-658.

147. Coetzee, G. A., A. F. Strachan, D. R. van der Westhuyzen, H. C. Hoppe, M. S. Jeenah, and F. C. de Beer. 1986. Serum amyloid A-containing human high density lipoprotein 3. Density, size, and apolipoprotein composition. *J. Biol. Chem.* **261**: 9644-9651.

148. Hoffman, J. S., and E. P. Benditt. 1983. Plasma clearance kinetics of the amyloid-related high density lipoprotein apoprotein, serum amyloid protein (apoSAA), in the mouse. Evidence for rapid apoSAA clearance. *J. Clin. Invest.* **71**: 926-934.

149. Hosoai, H., N. R. Webb, J. M. Glick, U. J. Tietge, M. S. Purdom, F. C. de Beer, and D. J. Rader. 1999. Expression of serum amyloid A protein in the absence of the acute phase response

does not reduce HDL cholesterol or apoA-I levels in human apoA-I transgenic mice. *J. Lipid Res.* **40**: 648-653.

150. de Beer, F. C., M. C. de Beer, D. R. van der Westhuyzen, L. W. Castellani, A. J. Lusis, M. E. Swanson, and D. S. Grass. 1997. Secretory non-pancreatic phospholipase A2: influence on lipoprotein metabolism. *J. Lipid Res.* **38**: 2232-2239.

151. Tietge, U. J., C. Maugeais, W. Cain, D. Grass, J. M. Glick, F. C. de Beer, and D. J. Rader. 2000. Overexpression of secretory phospholipase A(2) causes rapid catabolism and altered tissue uptake of high density lipoprotein cholesteryl ester and apolipoprotein A-I. *J. Biol. Chem.* **275**: 10077-10084.

152. Tietge, U. J., C. Maugeais, S. Lund-Katz, D. Grass, F. C. DeBeer, and D. J. Rader. 2002. Human secretory phospholipase A(2) mediates decreased plasma levels of HDL cholesterol and apoA-I in response to inflammation in human apoA-I transgenic mice. *Arterioscler. Thromb. Vasc. Biol.* **22**: 1213-1218.

153. Jaye, M., K. J. Lynch, J. Krawiec, D. Marchadier, C. Maugeais, K. Doan, V. South, D. Amin, M. Perrone, and D. J. Rader. 1999. A novel endothelial-derived lipase that modulates HDL metabolism. *Nat. Genet.* **21**: 424-428.

154. Ma, K., M. Cilingiroglu, J. D. Otvos, C. M. Ballantyne, A. J. Marian, and L. Chan. 2003. Endothelial lipase is a major genetic determinant for high-density lipoprotein concentration, structure, and metabolism. *Proc. Natl. Acad. Sci. USA.* **100**: 2748-2753.

155. Ishida, T., S. Choi, R. K. Kundu, K. Hirata, E. M. Rubin, A. D. Cooper, and T.

Quertermous. 2003. Endothelial lipase is a major determinant of HDL level. *J. Clin. Invest.* **111**: 347-355.

156. Jin, W., J. S. Millar, U. Broedl, J. M. Glick, and D. J. Rader. 2003. Inhibition of endothelial lipase causes increased HDL cholesterol levels in vivo. *J. Clin. Invest.* **111**: 357-362.

157. Jin, W., G. S. Sun, D. Marchadier, E. Octtaviani, J. M. Glick, and D. J. Rader. 2003. Endothelial cells secrete triglyceride lipase and phospholipase activities in response to cytokines as a result of endothelial lipase. *Circ. Res.* **92**: 644-650.

158. Kuivenhoven, J. A., H. Pritchard, J. Hill, J. Frohlich, G. Assmann, and J. Kastelein. 1997. The molecular pathology of lecithin:cholesterol acyltransferase (LCAT) deficiency syndromes. *J. Lipid Res.* **38**: 191-205.

159. Lamarche, B., K. D. Uffelman, A. Carpentier, J. S. Cohn, G. Steiner, P. H. Barrett, and G. F. Lewis. 1999. Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL apo A-I in healthy men. *J. Clin. Invest.* **103**: 1191-1199.

160. Fielding, C. J., and P. E. Fielding. 1995. Molecular physiology of reverse cholesterol transport. *J. Lipid Res.* **36**: 211-228.

161. von Eckardstein, A., J. R. Nofer, and G. Assmann. 2001. High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. *Arterioscler. Thromb. Vasc. Biol.* **21**: 13-27.

162. Baranova, I., T. Vishnyakova, A. Bocharov, Z. Chen, A. T. Remaley, J. Stonik, T. L. Eggerman, and A. P. Patterson. 2002. Lipopolysaccharide down regulates both scavenger receptor

B1 and ATP binding cassette transporter A1 in RAW cells. *Infect. Immun.* **70**: 2995-3003.

163. Khovidhunkit, W., J. K. Shigenaga, A. H. Moser, K. R. Feingold, and C. Grunfeld. 2001. Cholesterol efflux by acute-phase high density lipoprotein. Role of lecithin:cholesterol acyltransferase. *J. Lipid Res.* **42**: 967-975.

164. Khovidhunkit, W., A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 2001. Regulation of scavenger receptor class B type I in hamster liver and Hep3B cells by endotoxin and cytokines. *J. Lipid Res.* **42**: 1636-1644.

165. Memon, R. A., W. M. Holleran, Y. Uchida, A. H. Moser, S. Ichikawa, Y. Hirabayashi, C. Grunfeld, and K. R. Feingold. 1999. Regulation of glycosphingolipid metabolism in liver during the acute phase response. *J. Biol. Chem.* **274**: 19707-19713.

166. Memon, R. A., W. M. Holleran, Y. Uchida, A. H. Moser, C. Grunfeld, and K. R. Feingold. 2001. Regulation of sphingolipid and glycosphingolipid metabolism in extrahepatic tissues by endotoxin. *J. Lipid Res.* **42**: 452-459.

167. Kawano, T., J. Cui, Y. Koezuka, I. Toura, Y. Kaneko, K. Motoki, H. Ueno, R. Nakagawa, H. Sato, E. Kondo, H. Koseki, and M. Taniguchi. 1997. CD1d-restricted and TCR-mediated activation of valpha14 NKT cells by glycosylceramides. *Science.* **278**: 1626-1629.

168. Wong, M. L., B. Xie, N. Beatini, P. Phu, S. Marathe, A. Johns, P. W. Gold, E. Hirsch, K. J. Williams, J. Licinio, and I. Tabas. 2000. Acute systemic inflammation up-regulates secretory sphingomyelinase in vivo: a possible link between inflammatory cytokines and atherogenesis. *Proc. Natl. Acad. Sci. USA.* **97**: 8681-8686.

169. Delogu, G., G. Famularo, F. Amati, L. Signore, A. Antonucci, V. Trinchieri, L. Di Marzio, and M. G. Cifone. 1999. Ceramide concentrations in septic patients: a possible marker of multiple organ dysfunction syndrome. *Crit. Care Med.* **27**: 2413-2417.

170. Drobnik, W., G. Liebisch, F. X. Audebert, D. Frohlich, T. Gluck, P. Vogel, G. Rothe, and G. Schmitz. 2003. Plasma ceramide and lysophosphatidylcholine inversely correlate with mortality in sepsis patients. *J. Lipid Res.* **44**: 754-761.

171. Nikolova-Karakashian, M., E. T. Morgan, C. Alexander, D. C. Liotta, and A. H. Merrill, Jr. 1997. Bimodal regulation of ceramidase by interleukin-1beta. Implications for the regulation of cytochrome p450 2C11. *J. Biol. Chem.* **272**: 18718-18724.

172. Xia, P., J. R. Gamble, K. A. Rye, L. Wang, C. S. Hii, P. Cockerill, Y. Khew-Goodall, A. G. Bert, P. J. Barter, and M. A. Vadas. 1998. Tumor necrosis factor-alpha induces adhesion molecule expression through the sphingosine kinase pathway. *Proc. Natl. Acad. Sci. USA.* **95**: 14196-14201.

173. Baumann, H., K. R. Prowse, S. Marinkovic, K. A. Won, and G. P. Jahreis. 1989. Stimulation of hepatic acute phase response by cytokines and glucocorticoids. *Ann. N. Y. Acad. Sci.* **557**: 280-295.

174. Kishimoto, T., T. Taga, and S. Akira. 1994. Cytokine signal transduction. *Cell.* **76**: 253-262.

175. Mangelsdorf, D. J., and R. M. Evans. 1995. The RXR heterodimers and orphan receptors. *Cell.* **83**: 841-850.

176. Blumberg, B., and R. M. Evans. 1998. Orphan nuclear receptors--new ligands and new

possibilities. *Genes Dev.* **12**: 3149-3155.

177. Kliewer, S. A., J. M. Lehmann, and T. M. Willson. 1999. Orphan nuclear receptors: shifting endocrinology into reverse. *Science.* **284**: 757-760.

178. Chawla, A., J. J. Repa, R. M. Evans, and D. J. Mangelsdorf. 2001. Nuclear receptors and lipid physiology: opening the X-files. *Science.* **294**: 1866-1870.

179. Lee, C. H., P. Olson, and R. M. Evans. 2003. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. *Endocrinology.* **144**: 2201-2207.

180. Peet, D. J., B. A. Janowski, and D. J. Mangelsdorf. 1998. The LXRs: a new class of oxysterol receptors. *Curr. Opin. Genet. Dev.* **8**: 571-575.

181. Edwards, P. A., H. R. Kast, and A. M. Anisfeld. 2002. BAREing it all: the adoption of LXR and FXR and their roles in lipid homeostasis. *J. Lipid Res.* **43**: 2-12.

182. Francis, G. A., E. Fayard, F. Picard, and J. Auwerx. 2003. Nuclear receptors and the control of metabolism. *Annu. Rev. Physiol.* **65**: 261-311.

183. Beigneux, A. P., A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 2000. The acute phase response is associated with retinoid X receptor repression in rodent liver. *J. Biol. Chem.* **275**: 16390-16399.

184. Kim, M. S., J. Shigenaga, A. Moser, K. Feingold, and C. Grunfeld. 2003. Repression of farnesoid X receptor during the acute phase response. *J. Biol. Chem.* **278**: 8988-8995.

185. Beigneux, A. P., A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 2002. Reduction in cytochrome P-450 enzyme expression is associated with repression of CAR

(constitutive androstane receptor) and PXR (pregnane X receptor) in mouse liver during the acute phase response. *Biochem. Biophys. Res. Commun.* **293**: 145-149.

186. Hill, M. R., M. D. Young, C. M. McCurdy, and J. M. Gimble. 1997. Decreased expression of murine PPARgamma in adipose tissue during endotoxemia. *Endocrinology.* **138**: 3073-3076.

187. Zhang, B., J. Berger, E. Hu, D. Szalkowski, S. White-Carrington, B. M. Spiegelman, and D. E. Moller. 1996. Negative regulation of peroxisome proliferator-activated receptor-gamma gene expression contributes to the antiadipogenic effects of tumor necrosis factor-alpha. *Mol. Endocrinol.* **10**: 1457-1466.

188. Xing, H., J. P. Northrop, J. R. Grove, K. E. Kilpatrick, J. L. Su, and G. M. Ringold. 1997. TNF alpha-mediated inhibition and reversal of adipocyte differentiation is accompanied by suppressed expression of PPARgamma without effects on Pref-1 expression. *Endocrinology.* **138**: 2776-2783.

189. Perrey, S., S. Ishibashi, N. Yahagi, J. Osuga, R. Tozawa, H. Yagyu, K. Ohashi, T. Gotoda, K. Harada, Z. Chen, Y. Iizuka, F. Shionoiri, and N. Yamada. 2001. Thiazolidinedione- and tumor necrosis factor alpha-induced downregulation of peroxisome proliferator-activated receptor gamma mRNA in differentiated 3T3-L1 adipocytes. *Metabolism.* **50**: 36-40.

190. Waite, K. J., Z. E. Floyd, P. Arbour-Reily, and J. M. Stephens. 2001. Interferon-gamma-induced regulation of peroxisome proliferator-activated receptor gamma and STATs in adipocytes. *J. Biol. Chem.* **276**: 7062-7068.

191. Meng, L., J. Zhou, H. Sasano, T. Suzuki, K. M. Zeitoun, and S. E. Bulun. 2001. Tumor

necrosis factor alpha and interleukin 11 secreted by malignant breast epithelial cells inhibit adipocyte differentiation by selectively down-regulating CCAAT/enhancer binding protein alpha and peroxisome proliferator-activated receptor gamma: mechanism of desmoplastic reaction. *Cancer Res.* **61**: 2250-2255.

192. Feingold, K., M. S. Kim, J. Shigenaga, A. Moser, and C. Grunfeld. 2004. Altered expression of nuclear hormone receptors and coactivators in mouse heart during the acute-phase response. *Am. J. Physiol. Endocrinol. Metab.* **286**: E201-207.

193. Fajas, L., M. B. Debril, and J. Auwerx. 2001. Peroxisome proliferator-activated receptor-gamma: from adipogenesis to carcinogenesis. *J. Mol. Endocrinol.* **27**: 1-9.

194. Willson, T. M., M. H. Lambert, and S. A. Kliewer. 2001. Peroxisome proliferator-activated receptor gamma and metabolic disease. *Annu. Rev. Biochem.* **70**: 341-367.

195. Fruchart, J. C., P. Duriez, and B. Staels. 1999. Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. *Curr. Opin. Lipidol.* **10**: 245-257.

196. Wang, Y. X., C. H. Lee, S. Tiep, R. T. Yu, J. Ham, H. Kang, and R. M. Evans. 2003. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell.* **113**: 159-170.

197. Lehman, J. J., and D. P. Kelly. 2002. Gene regulatory mechanisms governing energy metabolism during cardiac hypertrophic growth. *Heart Fail. Rev.* **7**: 175-185.

198. Schoonjans, K., B. Staels, and J. Auwerx. 1996. Role of the peroxisome proliferator-

activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. *J. Lipid Res.* **37**: 907-925.

199. Bagby, G. J., and J. A. Spitzer. 1980. Lipoprotein lipase activity in rat heart and adipose tissue during endotoxic shock. *Am. J. Physiol.* **238**: H325-330.

200. Bagby, G. J., and J. A. Spitzer. 1981. Decreased myocardial extracellular and muscle lipoprotein lipase activities in endotoxin-treated rats. *Proc. Soc. Exp. Biol. Med.* **168**: 395-398.

201. Sinal, C. J., M. Tohkin, M. Miyata, J. M. Ward, G. Lambert, and F. J. Gonzalez. 2000. Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell.* **102**: 731-744.

202. Kast, H. R., C. M. Nguyen, C. J. Sinal, S. A. Jones, B. A. Laffitte, K. Reue, F. J. Gonzalez, T. M. Willson, and P. A. Edwards. 2001. Farnesoid X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids. *Mol. Endocrinol.* **15**: 1720-1728.

203. Mak, P. A., H. R. Kast-Woelbern, A. M. Anisfeld, and P. A. Edwards. 2002. Identification of PLTP as an LXR target gene and apoE as an FXR target gene reveals overlapping targets for the two nuclear receptors. *J. Lipid Res.* **43**: 2037-2041.

204. Berg, D. T., D. S. Calnek, and B. W. Grinnell. 1995. The human apolipoprotein E gene is negatively regulated in human liver HepG2 cells by the transcription factor BEF-1. *J. Biol. Chem.* **270**: 15447-15450.

205. Berg, D. T., D. S. Calnek, and B. W. Grinnell. 1996. Trans-repressor BEF-1

phosphorylation. A potential control mechanism for human ApoE gene regulation. *J. Biol. Chem.* **271**: 4589-4592.

206. Oram, J. F., and R. M. Lawn. 2001. ABCA1. The gatekeeper for eliminating excess tissue cholesterol. *J. Lipid Res.* **42**: 1173-1179.

207. Venkateswaran, A., B. A. Laffitte, S. B. Joseph, P. A. Mak, D. C. Wilpitz, P. A. Edwards, and P. Tontonoz. 2000. Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. *Proc. Natl. Acad. Sci. USA.* **97**: 12097-12102.

208. Costet, P., Y. Luo, N. Wang, and A. R. Tall. 2000. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J. Biol. Chem.* **275**: 28240-28245.

209. Castrillo, A., S. B. Joseph, S. A. Vaidya, M. Haberland, A. M. Fogelman, G. Cheng, and P. Tontonoz. 2003. Crosstalk between LXR and toll-like receptor signaling mediates bacterial and viral antagonism of cholesterol metabolism. *Mol. Cell.* **12**: 805-816.

210. Tall, A. R., X. Jiang, Y. Luo, and D. Silver. 2000. 1999 George Lyman Duff memorial lecture: lipid transfer proteins, HDL metabolism, and atherogenesis. *Arterioscler. Thromb. Vasc. Biol.* **20**: 1185-1188.

211. Luo, Y., and A. R. Tall. 2000. Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. *J. Clin. Invest.* **105**: 513-520.

212. Urizar, N. L., D. H. Dowhan, and D. D. Moore. 2000. The farnesoid X-activated receptor mediates bile acid activation of phospholipid transfer protein gene expression. *J. Biol. Chem.* **275**: 39313-39317.

213. Krieger, M. 2001. Scavenger receptor class B type I is a multiligand HDL receptor that influences diverse physiologic systems. *J. Clin. Invest.* **108**: 793-797.

214. Malerod, L., M. Sporstol, L. K. Juvet, A. Mousavi, T. Gjoen, and T. Berg. 2003. Hepatic scavenger receptor class B, type I is stimulated by peroxisome proliferator-activated receptor gamma and hepatocyte nuclear factor 4alpha. *Biochem. Biophys. Res. Commun.* **305**: 557-565.

215. Lambert, G., M. J. Amar, G. Guo, H. B. Brewer, Jr., F. J. Gonzalez, and C. J. Sinal. 2003. The farnesoid X-receptor is an essential regulator of cholesterol homeostasis. *J. Biol. Chem.* **278**: 2563-2570.

216. Lehmann, J. M., S. A. Kliewer, L. B. Moore, T. A. Smith-Oliver, B. B. Oliver, J. L. Su, S. S. Sundseth, D. A. Winegar, D. E. Blanchard, T. A. Spencer, and T. M. Willson. 1997. Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. *J. Biol. Chem.* **272**: 3137-3140.

217. Peet, D. J., S. D. Turley, W. Ma, B. A. Janowski, J. M. Lobaccaro, R. E. Hammer, and D. J. Mangelsdorf. 1998. Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. *Cell.* **93**: 693-704.

218. Makishima, M., A. Y. Okamoto, J. J. Repa, H. Tu, R. M. Learned, A. Luk, M. V. Hull, K. D. Lustig, D. J. Mangelsdorf, and B. Shan. 1999. Identification of a nuclear receptor for bile acids. *Science.* **284**: 1362-1365.

219. Chen, J. Y., B. Levy-Wilson, S. Goodart, and A. D. Cooper. 2002. Mice expressing the human CYP7A1 gene in the mouse CYP7A1 knock-out background lack induction of CYP7A1

expression by cholesterol feeding and have increased hypercholesterolemia when fed a high fat diet. *J. Biol. Chem.* **277**: 42588-42595.

220. Lu, T. T., M. Makishima, J. J. Repa, K. Schoonjans, T. A. Kerr, J. Auwerx, and D. J. Mangelsdorf. 2000. Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. *Mol. Cell.* **6**: 507-515.

221. Gupta, S., W. M. Pandak, and P. B. Hylemon. 2002. LXR alpha is the dominant regulator of CYP7A1 transcription. *Biochem. Biophys. Res. Commun.* **293**: 338-343.

222. Chiang, J. Y. 2002. Bile acid regulation of gene expression: roles of nuclear hormone receptors. *Endocr. Rev.* **23**: 443-463.

223. Wang, B., S. R. Cai, C. Gao, F. M. Sladek, and K. P. Ponder. 2001. Lipopolysaccharide results in a marked decrease in hepatocyte nuclear factor 4 alpha in rat liver. *Hepatology.* **34**: 979-989.

224. Beigneux, A. P., A. H. Moser, J. K. Shigenaga, C. Grunfeld, and K. R. Feingold. 2003. Sick euthyroid syndrome is associated with decreased TR expression and DNA binding in mouse liver. *Am. J. Physiol. Endocrinol. Metab.* **284**: E228-236.

225. del Castillo-Olivares, A., and G. Gil. 2000. Alpha 1-fetoprotein transcription factor is required for the expression of sterol 12alpha -hydroxylase, the specific enzyme for cholic acid synthesis. Potential role in the bile acid-mediated regulation of gene transcription. *J. Biol. Chem.* **275**: 17793-17799.

226. Zhang, M., and J. Y. Chiang. 2001. Transcriptional regulation of the human sterol 12alpha-

hydroxylase gene (CYP8B1): roles of hepatocyte nuclear factor 4alpha in mediating bile acid repression. *J. Biol. Chem.* **276**: 41690-41699.

227. Burke, P. A., M. Drotar, M. Luo, M. Yaffe, and R. A. Forse. 1994. Rapid modulation of liver-specific transcription factors after injury. *Surgery.* **116**: 285-292.

228. Garuti, R., M. A. Croce, L. Piccinini, R. Tiozzo, S. Bertolini, and S. Calandra. 2002. Functional analysis of the promoter of human sterol 27-hydroxylase gene in HepG2 cells. *Gene.* **283**: 133-143.

229. Roe, A. L., S. M. Poloyac, G. Howard, S. I. Shedlofsky, and R. A. Blouin. 2001. The effect of endotoxin on hepatocyte nuclear factor 1 nuclear protein binding: potential implications on CYP2E1 expression in the rat. *J. Pharm. Pharmacol.* **53**: 1365-1371.

230. Ananthanarayanan, M., N. Balasubramanian, M. Makishima, D. J. Mangelsdorf, and F. J. Suchy. 2001. Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. *J. Biol. Chem.* **276**: 28857-28865.

231. Kast, H. R., B. Goodwin, P. T. Tarr, S. A. Jones, A. M. Anisfeld, C. M. Stoltz, P. Tontonoz, S. Kliewer, T. M. Willson, and P. A. Edwards. 2002. Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J. Biol. Chem.* **277**: 2908-2915.

232. Repa, J. J., K. E. Berge, C. Pomajzl, J. A. Richardson, H. Hobbs, and D. J. Mangelsdorf. 2002. Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta. *J. Biol. Chem.* **277**: 18793-18800.

233. Kok, T., V. W. Bloks, H. Wolters, R. Havinga, P. L. Jansen, B. Staels, and F. Kuipers. 2003. Peroxisome proliferator-activated receptor alpha (PPARalpha)-mediated regulation of multidrug resistance 2 (Mdr2) expression and function in mice. *Biochem. J.* **369**: 539-547.

234. Libby, P., D. Egan, and S. Skarlatos. 1997. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. *Circulation.* **96**: 4095-4103.

235. Epstein, S. E., Y. F. Zhou, and J. Zhu. 1999. Infection and atherosclerosis: emerging mechanistic paradigms. *Circulation.* **100**: e20-28.

236. Becker, A. E., O. J. de Boer, and A. C. van Der Wal. 2001. The role of inflammation and infection in coronary artery disease. *Annu. Rev. Med.* **52**: 289-297.

237. Leinonen, M., and P. Saikku. 2002. Evidence for infectious agents in cardiovascular disease and atherosclerosis. *Lancet Infect. Dis.* **2**: 11-17.

238. Saikku, P., M. Leinonen, L. Tenkanen, E. Linnanmaki, M. R. Ekman, V. Manninen, M. Manttari, M. H. Frick, and J. K. Huttunen. 1992. Chronic Chlamydia pneumoniae infection as a risk factor for coronary heart disease in the Helsinki Heart Study. *Ann. Intern. Med.* **116**: 273-278.

239. Melnick, J. L., E. Adam, and M. E. Debakey. 1993. Cytomegalovirus and atherosclerosis. *Eur. Heart J.* **14 Suppl K**: 30-38.

240. Mendall, M. A., P. M. Goggin, N. Molineaux, J. Levy, T. Toosy, D. Strachan, A. J. Camm, and T. C. Northfield. 1994. Relation of Helicobacter pylori infection and coronary heart disease. *Br. Heart J.* **71**: 437-439.

241. DeStefano, F., R. F. Anda, H. S. Kahn, D. F. Williamson, and C. M. Russell. 1993. Dental

disease and risk of coronary heart disease and mortality. *Brit. Med. J.* **306**: 688-691.

242. Jousilahti, P., E. Vartiainen, J. Tuomilehto, and P. Puska. 1996. Symptoms of chronic bronchitis and the risk of coronary disease. *Lancet.* **348**: 567-572.

243. Monson, R. R., and A. P. Hall. 1976. Mortality among arthritics. *J. Chronic Dis.* **29**: 459-467.

244. McDonald, C. J., and P. Calabresi. 1978. Psoriasis and occlusive vascular disease. *Br. J. Dermatol.* **99**: 469-475.

245. Asanuma, Y., A. Oeser, A. K. Shintani, E. Turner, N. Olsen, S. Fazio, M. F. Linton, P. Raggi, and C. M. Stein. 2003. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N. Engl. J. Med.* **349**: 2407-2415.

246. Roman, M. J., B. A. Shanker, A. Davis, M. D. Lockshin, L. Sammaritano, R. Simantov, M. K. Crow, J. E. Schwartz, S. A. Paget, R. B. Devereux, and J. E. Salmon. 2003. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N. Engl. J. Med.* **349**: 2399-2406.

247. Havel, R. J. 2000. Remnant lipoproteins as therapeutic targets. *Curr. Opin. Lipidol.* **11**: 615-620.

248. Malloy, M. J., and J. P. Kane. 2001. A risk factor for atherosclerosis: triglyceride-rich lipoproteins. *Adv. Intern. Med.* **47**: 111-136.

249. Ginsberg, H. N. 2002. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation.* **106**: 2137-2142.

250. Gianturco, S. H., S. G. Eskin, L. T. Navarro, C. J. Lahart, L. C. Smith, and A. M. Gotto, Jr. 1980. Abnormal effects of hypertriacylglycerolemic very low-density lipoproteins on 3-hydroxy-3-methylglutaryl-CoA reductase activity and viability of cultured bovine aortic endothelial cells. *Biochim. Biophys. Acta.* **618**: 143-152.

251. Gianturco, S. H., M. P. Ramprasad, R. Song, R. Li, M. L. Brown, and W. A. Bradley. 1998. Apolipoprotein B-48 or its apolipoprotein B-100 equivalent mediates the binding of triglyceride-rich lipoproteins to their unique human monocyte-macrophage receptor. *Arterioscler. Thromb. Vasc. Biol.* **18**: 968-976.

252. Redgrave, T. G., V. Rakic, B. C. Mortimer, and J. C. Mamo. 1992. Effects of sphingomyelin and phosphatidylcholine acyl chains on the clearance of triacylglycerol-rich lipoproteins from plasma. Studies with lipid emulsions in rats. *Biochim. Biophys. Acta.* **1126**: 65-72.

253. Feingold, K. R., R. M. Krauss, M. Pang, W. Doerrler, P. Jensen, and C. Grunfeld. 1993. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. *J. Clin. Endocrinol. Metab.* **76**: 1423-1427.

254. Nigon, F., P. Lesnik, M. Rouis, and M. J. Chapman. 1991. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cellular LDL receptor. *J. Lipid Res.* **32**: 1741-1753.

255. Hurt-Camejo, E., G. Camejo, B. Rosengren, F. Lopez, O. Wiklund, and G. Bondjers. 1990. Differential uptake of proteoglycan-selected subfractions of low density lipoprotein by human

macrophages. *J. Lipid Res.* **31**: 1387-1398.

256. Chait, A., R. L. Brazg, D. L. Tribble, and R. M. Krauss. 1993. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am. J. Med.* **94**: 350-356.

257. Steinberg, D., S. Parthasarathy, T. E. Carew, J. C. Khoo, and J. L. Witztum. 1989. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N. Engl. J. Med.* **320**: 915-924.

258. Memon, R. A., I. Staprans, M. Noor, W. M. Holleran, Y. Uchida, A. H. Moser, K. R. Feingold, and C. Grunfeld. 2000. Infection and inflammation induce LDL oxidation in vivo. *Arterioscler. Thromb. Vasc. Biol.* **20**: 1536-1542.

259. Liuba, P., J. Persson, J. Luoma, S. Yla-Herttuala, and E. Pesonen. 2003. Acute infections in children are accompanied by oxidative modification of LDL and decrease of HDL cholesterol, and are followed by thickening of carotid intima-media. *Eur. Heart J.* **24**: 515-521.

260. Pepys, M. B., and G. M. Hirschfield. 2003. C-reactive protein: a critical update. *J. Clin. Invest.* **111**: 1805-1812.

261. de Beer, F. C., A. K. Soutar, M. L. Baltz, I. M. Trayner, A. Feinstein, and M. B. Pepys. 1982. Low density lipoprotein and very low density lipoprotein are selectively bound by aggregated C-reactive protein. *J. Exp. Med.* **156**: 230-242.

262. Libby, P., and P. M. Ridker. 1999. Novel inflammatory markers of coronary risk : theory versus practice. *Circulation.* **100**: 1148-1150.

263. Chang, M. K., C. J. Binder, M. Torzewski, and J. L. Witztum. 2002. C-reactive protein binds to both oxidized LDL and apoptotic cells through recognition of a common ligand: Phosphorylcholine of oxidized phospholipids. *Proc. Natl. Acad. Sci. USA.* **99**: 13043-13048.

264. Hakala, J. K., K. Oorni, M. O. Pentikainen, E. Hurt-Camejo, and P. T. Kovanen. 2001. Lipolysis of LDL by human secretory phospholipase A(2) induces particle fusion and enhances the retention of LDL to human aortic proteoglycans. *Arterioscler. Thromb. Vasc. Biol.* **21**: 1053-1058.

265. Ivandic, B., L. W. Castellani, X. P. Wang, J. H. Qiao, M. Mehrabian, M. Navab, A. M. Fogelman, D. S. Grass, M. E. Swanson, M. C. de Beer, F. de Beer, and A. J. Lusis. 1999. Role of group II secretory phospholipase A2 in atherosclerosis: 1. Increased atherogenesis and altered lipoproteins in transgenic mice expressing group IIa phospholipase A2. *Arterioscler. Thromb. Vasc. Biol.* **19**: 1284-1290.

266. Stafforini, D. M., T. M. McIntyre, M. E. Carter, and S. M. Prescott. 1987. Human plasma platelet-activating factor acetylhydrolase. Association with lipoprotein particles and role in the degradation of platelet-activating factor. *J. Biol. Chem.* **262**: 4215-4222.

267. Steinbrecher, U. P., and P. H. Pritchard. 1989. Hydrolysis of phosphatidylcholine during LDL oxidation is mediated by platelet-activating factor acetylhydrolase. *J. Lipid Res.* **30**: 305-315.

268. Quinn, M. T., S. Parthasarathy, and D. Steinberg. 1988. Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. *Proc. Natl. Acad. Sci. USA.* **85**: 2805-2809.

269. Kugiyama, K., S. A. Kerns, J. D. Morrisett, R. Roberts, and P. D. Henry. 1990. Impairment

of endothelium-dependent arterial relaxation by lysolecithin in modified low-density lipoproteins. *Nature.* **344**: 160-162.

270. Khovidhunkit, W., R. A. Memon, J. K. Shigenaga, M. Pang, M. Schambelan, K. Mulligan, K. R. Feingold, and C. Grunfeld. 1999. Plasma platelet-activating factor acetylhydrolase activity in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Metabolism.* **48**: 1524-1531.

271. Packard, C. J., D. S. O'Reilly, M. J. Caslake, A. D. McMahon, I. Ford, J. Cooney, C. H. Macphee, K. E. Suckling, M. Krishna, F. E. Wilkinson, A. Rumley, and G. D. Lowe. 2000. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N. Engl. J. Med.* **343**: 1148-1155.

272. Schissel, S. L., J. Tweedie-Hardman, J. H. Rapp, G. Graham, K. J. Williams, and I. Tabas. 1996. Rabbit aorta and human atherosclerotic lesions hydrolyze the sphingomyelin of retained low-density lipoprotein. Proposed role for arterial-wall sphingomyelinase in subendothelial retention and aggregation of atherogenic lipoproteins. *J. Clin. Invest.* **98**: 1455-1464.

273. Mukhin, D. N., F. F. Chao, and H. S. Kruth. 1995. Glycosphingolipid accumulation in the aortic wall is another feature of human atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **15**: 1607-1615.

274. Jeong, T., S. L. Schissel, I. Tabas, H. J. Pownall, A. R. Tall, and X. Jiang. 1998. Increased sphingomyelin content of plasma lipoproteins in apolipoprotein E knockout mice reflects combined production and catabolic defects and enhances reactivity with mammalian sphingomyelinase. *J.*

Clin. Invest. **101**: 905-912.

275. Jiang, X. C., F. Paultre, T. A. Pearson, R. G. Reed, C. K. Francis, M. Lin, L. Berglund, and A. R. Tall. 2000. Plasma sphingomyelin level as a risk factor for coronary artery disease. *Arterioscler. Thromb. Vasc. Biol.* **20**: 2614-2618.

276. Xu, X. X., and I. Tabas. 1991. Sphingomyelinase enhances low density lipoprotein uptake and ability to induce cholesteryl ester accumulation in macrophages. *J. Biol. Chem.* **266**: 24849-24858.

277. Artl, A., G. Marsche, S. Lestavel, W. Sattler, and E. Malle. 2000. Role of serum amyloid A during metabolism of acute-phase HDL by macrophages. *Arterioscler. Thromb. Vasc. Biol.* **20**: 763-772.

278. Pussinen, P. J., M. Jauhiainen, T. Vilkuna-Rautiainen, J. Sundvall, M. Vesanen, K. Mattila, T. Palosuo, G. Alfthan, and S. Asikainen. 2004. Periodontitis decreases the antiatherogenic potency of high density lipoprotein. *J. Lipid Res.* **45**: 139-147. Epub 2003 Sep 2016.

279. Artl, A., G. Marsche, P. Pussinen, G. Knipping, W. Sattler, and E. Malle. 2002. Impaired capacity of acute-phase high density lipoprotein particles to deliver cholesteryl ester to the human HUH-7 hepatoma cell line. *Int. J. Biochem. Cell. Biol.* **34**: 370-381.

280. Kunitake, S. T., M. R. Jarvis, R. L. Hamilton, and J. P. Kane. 1992. Binding of transition metals by apolipoprotein A-I-containing plasma lipoproteins: inhibition of oxidation of low density lipoproteins. *Proc. Natl. Acad. Sci. USA.* **89**: 6993-6997.

281. Shih, D. M., L. Gu, Y. R. Xia, M. Navab, W. F. Li, S. Hama, L. W. Castellani, C. E.

Furlong, L. G. Costa, A. M. Fogelman, and A. J. Lusis. 1998. Mice lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. *Nature.* **394**: 284-287.

282. Goldstein, I. M., H. B. Kaplan, H. S. Edelson, and G. Weissmann. 1982. Ceruloplasmin: an acute phase reactant that scavenges oxygen-derived free radicals. *Ann. N. Y. Acad. Sci.* **389**: 368-379.

283. Ehrenwald, E., G. M. Chisolm, and P. L. Fox. 1994. Intact human ceruloplasmin oxidatively modifies low density lipoprotein. *J. Clin. Invest.* **93**: 1493-1501.

284. Lamb, D. J., and D. S. Leake. 1994. Acidic pH enables caeruloplasmin to catalyse the modification of low- density lipoprotein. *FEBS Lett.* **338**: 122-126.

285. Buttenschoen, K., D. C. Buttenschoen, D. Berger, C. Vasilescu, S. Schafheutle, B. Goeltenboth, M. Seidelmann, and H. G. Beger. 2001. Endotoxemia and acute-phase proteins in major abdominal surgery. *Am. J. Surg.* **181**: 36-43.

286. Oiknine, J., and M. Aviram. 1992. Increased susceptibility to activation and increased uptake of low density lipoprotein by cholesterol-loaded macrophages. *Arterioscler. Thromb.* **12**: 745-753.

287. Funk, J. L., K. R. Feingold, A. H. Moser, and C. Grunfeld. 1993. Lipopolysaccharide stimulation of RAW 264.7 macrophages induces lipid accumulation and foam cell formation. *Atherosclerosis.* **98**: 67-82.

288. Ruan, X. Z., Z. Varghese, S. H. Powis, and J. F. Moorhead. 2001. Dysregulation of LDL receptor under the influence of inflammatory cytokines: a new pathway for foam cell formation.

Kidney Int. **60**: 1716-1725.

289. Kalayoglu, M. V., and G. I. Byrne. 1998. A Chlamydia pneumoniae component that induces macrophage foam cell formation is chlamydial lipopolysaccharide. *Infect. Immun.* **66**: 5067-5072.

290. Rall, D. P., J. R. Gaskins, and M. G. Kelly. 1957. Reduction of febrile response to bacterial polysaccharide following incubation with serum. *Am. J. Physiol.* **188**: 559-562.

291. Skarnes, R. C., F. S. Rosen, M. J. Shear, and M. Landy. 1958. Inactivation of endotoxin by a humoral component. II. Interaction of endotoxin with serum and plasma. *J. Exp. Med.* **108**: 685-699.

292. Ulevitch, R. J., A. R. Johnston, and D. B. Weinstein. 1979. New function for high density lipoproteins. Their participation in intravascular reactions of bacterial lipopolysaccharides. *J. Clin. Invest.* **64**: 1516-1524.

293. Munford, R. S., C. L. Hall, J. M. Lipton, and J. M. Dietschy. 1982. Biological activity, lipoprotein-binding behavior, and in vivo disposition of extracted and native forms of Salmonella typhimurium lipopolysaccharides. *J. Clin. Invest.* **70**: 877-888.

294. Van Lenten, B. J., A. M. Fogelman, M. E. Haberland, and P. A. Edwards. 1986. The role of lipoproteins and receptor-mediated endocytosis in the transport of bacterial lipopolysaccharide. *Proc. Natl. Acad. Sci. USA.* **83**: 2704-2708.

295. Harris, H. W., C. Grunfeld, K. R. Feingold, and J. H. Rapp. 1990. Human very low density lipoproteins and chylomicrons can protect against endotoxin-induced death in mice. *J. Clin. Invest.* **86**: 696-702.

296. Eichbaum, E. B., H. W. Harris, J. P. Kane, and J. H. Rapp. 1991. Chylomicrons can inhibit endotoxin activity in vitro. *J. Surg. Res.* **51**: 413-416.

297. Harris, H. W., E. B. Eichbaum, J. P. Kane, and J. H. Rapp. 1991. Detection of endotoxin in triglyceride-rich lipoproteins in vitro. *J. Lab. Clin. Med.* **118**: 186-193.

298. Emancipator, K., G. Csako, and R. J. Elin. 1992. In vitro inactivation of bacterial endotoxin by human lipoproteins and apolipoproteins. *Infect. Immun.* **60**: 596-601.

299. Netea, M. G., N. de Bont, P. N. Demacker, B. J. Kullberg, L. E. Jacobs, T. J. Verver-Jansen, A. F. Stalenhoef, and J. W. Van der Meer. 1998. Lipoprotein(a) inhibits lipopolysaccharide-induced tumor necrosis factor alpha production by human mononuclear cells. *Infect. Immun.* **66**: 2365-2367.

300. Parker, T. S., D. M. Levine, J. C. Chang, J. Laxer, C. C. Coffin, and A. L. Rubin. 1995. Reconstituted high-density lipoprotein neutralizes gram-negative bacterial lipopolysaccharides in human whole blood. *Infect. Immun.* **63**: 253-258.

301. Grunfeld, C., M. Marshall, J. K. Shigenaga, A. H. Moser, P. Tobias, and K. R. Feingold. 1999. Lipoproteins inhibit macrophage activation by lipoteichoic acid. *J. Lipid Res.* **40**: 245-252.

302. Bhakdi, S., J. Tranum-Jensen, G. Utermann, and R. Fussle. 1983. Binding and partial inactivation of Staphylococcus aureus alpha-toxin by human plasma low density lipoprotein. *J. Biol. Chem.* **258**: 5899-5904.

303. Levels, J. H., P. R. Abraham, A. van den Ende, and S. J. van Deventer. 2001. Distribution and kinetics of lipoprotein-bound endotoxin. *Infect. Immun.* **69**: 2821-2828.

304. Levels, J. H., P. R. Abraham, E. P. van Barreveld, J. C. Meijers, and S. J. van Deventer. 2003. Distribution and kinetics of lipoprotein-bound lipoteichoic acid. *Infect. Immun.* **71**: 3280-3284.

305. Kitchens, R. L., and P. A. Thompson. 2003. Impact of sepsis-induced changes in plasma on LPS interactions with monocytes and plasma lipoproteins: roles of soluble CD14, LBP, and acute phase lipoproteins. *J. Endotoxin Res.* **9**: 113-118.

306. Kitchens, R. L., P. A. Thompson, R. S. Munford, and G. E. O'Keefe. 2003. Acute inflammation and infection maintain circulating phospholipid levels and enhance lipopolysaccharide binding to plasma lipoproteins. *J. Lipid Res.* **44**: 2339-2348. Epub 2003 Aug 2316.

307. Eggesbo, J. B., T. Lyberg, T. Aspelin, I. Hjermann, and P. Kierulf. 1996. Different binding of 125I-LPS to plasma proteins from persons with high or low HDL. *Scand. J. Clin. Lab. Invest.* **56**: 533-543.

308. Harris, H. W., C. Grunfeld, K. R. Feingold, T. E. Read, J. P. Kane, A. L. Jones, E. B. Eichbaum, G. F. Bland, and J. H. Rapp. 1993. Chylomicrons alter the fate of endotoxin, decreasing tumor necrosis factor release and preventing death. *J. Clin. Invest.* **91**: 1028-1034.

309. Hubsch, A. P., F. S. Powell, P. G. Lerch, and J. E. Doran. 1993. A reconstituted, apolipoprotein A-I containing lipoprotein reduces tumor necrosis factor release and attenuates shock in endotoxemic rabbits. *Circ. Shock.* **40**: 14-23.

310. Hubsch, A. P., A. T. Casas, and J. E. Doran. 1995. Protective effects of reconstituted high-

density lipoprotein in rabbit gram-negative bacteremia models. *J. Lab. Clin. Med.* **126**: 548-558.

311. Casas, A. T., A. P. Hubsch, and J. E. Doran. 1996. Effects of reconstituted high-density lipoprotein in persistent gram-negative bacteremia. *Am. Surg.* **62**: 350-355.

312. Read, T. E., C. Grunfeld, Z. Kumwenda, M. C. Calhoun, J. P. Kane, K. R. Feingold, and J. H. Rapp. 1995. Triglyceride-rich lipoproteins improve survival when given after endotoxin in rats. *Surgery.* **117**: 62-67.

313. Read, T. E., C. Grunfeld, Z. L. Kumwenda, M. C. Calhoun, J. P. Kane, K. R. Feingold, and J. H. Rapp. 1995. Triglyceride-rich lipoproteins prevent septic death in rats. *J. Exp. Med.* **182**: 267-272.

314. Feingold, K. R., J. L. Funk, A. H. Moser, J. K. Shigenaga, J. H. Rapp, and C. Grunfeld. 1995. Role for circulating lipoproteins in protection from endotoxin toxicity. *Infect. Immun.* **63**: 2041-2046.

315. Levine, D. M., T. S. Parker, T. M. Donnelly, A. Walsh, and A. L. Rubin. 1993. In vivo protection against endotoxin by plasma high density lipoprotein. *Proc. Natl. Acad. Sci. USA.* **90**: 12040-12044.

316. Netea, M. G., P. N. Demacker, B. J. Kullberg, O. C. Boerman, I. Verschueren, A. F. Stalenhoef, and J. W. van der Meer. 1996. Low-density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe gram-negative infections. *J. Clin. Invest.* **97**: 1366-1372.

317. Netea, M. G., P. N. Demacker, B. J. Kullberg, L. E. Jacobs, T. J. Verver-Jansen, O. C.

Boerman, A. F. Stalenhoef, and J. W. Van der Meer. 1998. Bacterial lipopolysaccharide binds and stimulates cytokine-producing cells before neutralization by endogenous lipoproteins can occur. *Cytokine.* **10**: 766-772.

318. Pajkrt, D., J. E. Doran, F. Koster, P. G. Lerch, B. Arnet, T. van der Poll, J. W. ten Cate, and S. J. van Deventer. 1996. Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. *J. Exp. Med.* **184**: 1601-1608.

319. Harris, H. W., J. A. Johnson, and S. J. Wigmore. 2002. Endogenous lipoproteins impact the response to endotoxin in humans. *Crit. Care Med.* **30**: 23-31.

320. van der Poll, T., C. C. Braxton, S. M. Coyle, M. A. Boermeester, J. C. Wang, P. M. Jansen, W. J. Montegut, S. E. Calvano, C. E. Hack, and S. F. Lowry. 1995. Effect of hypertriglyceridemia on endotoxin responsiveness in humans. *Infect. Immun.* **63**: 3396-3400.

321. Read, T. E., H. W. Harris, C. Grunfeld, K. R. Feingold, M. C. Calhoun, J. P. Kane, and J. H. Rapp. 1993. Chylomicrons enhance endotoxin excretion in bile. *Infect. Immun.* **61**: 3496-3502.

322. Kumwenda, Z. L., C. B. Wong, J. A. Johnson, J. E. Gosnell, W. J. Welch, and H. W. Harris. 2002. Chylomicron-bound endotoxin selectively inhibits NF-kappaB activation in rat hepatocytes. *Shock.* **18**: 182-188.

323. Flegel, W. A., A. Wolpl, D. N. Mannel, and H. Northoff. 1989. Inhibition of endotoxin-induced activation of human monocytes by human lipoproteins. *Infect. Immun.* **57**: 2237-2245.

324. Cavaillon, J. M., C. Fitting, N. Haeffner-Cavaillon, S. J. Kirsch, and H. S. Warren. 1990. Cytokine response by monocytes and macrophages to free and lipoprotein-bound

lipopolysaccharide. *Infect. Immun.* **58**: 2375-2382.

325. Baumberger, C., R. J. Ulevitch, and J. M. Dayer. 1991. Modulation of endotoxic activity of lipopolysaccharide by high-density lipoprotein. *Pathobiology.* **59**: 378-383.

326. Weinstock, C., H. Ullrich, R. Hohe, A. Berg, M. W. Baumstark, I. Frey, H. Northoff, and W. A. Flegel. 1992. Low density lipoproteins inhibit endotoxin activation of monocytes. *Arterioscler. Thromb.* **12**: 341-347.

327. Flegel, W. A., M. W. Baumstark, C. Weinstock, A. Berg, and H. Northoff. 1993. Prevention of endotoxin-induced monokine release by human low- and high-density lipoproteins and by apolipoprotein A-I. *Infect. Immun.* **61**: 5140-5146.

328. Kitchens, R. L., G. Wolfbauer, J. J. Albers, and R. S. Munford. 1999. Plasma lipoproteins promote the release of bacterial lipopolysaccharide from the monocyte cell surface. *J. Biol. Chem.* **274**: 34116-34122.

329. Victorov, A. V., N. V. Medvedeva, E. M. Gladkaya, A. D. Morozkin, E. A. Podrez, V. A. Kosykh, and V. A. Yurkiv. 1989. Composition and structure of lipopolysaccharide-human plasma low density lipoprotein complex. Analytical ultracentrifugation, 31P-NMR, ESR and fluorescence spectroscopy studies. *Biochim. Biophys. Acta.* **984**: 119-127.

330. Yan, J. J., J. S. Jung, J. E. Lee, J. Lee, S. O. Huh, H. S. Kim, K. C. Jung, J. Y. Cho, J. S. Nam, H. W. Suh, Y. H. Kim, and D. K. Song. 2004. Therapeutic effects of lysophosphatidylcholine in experimental sepsis. *Nat. Med.* **10**: 161-167. Epub 2004 Jan 2011.

331. Park, C. T., and S. D. Wright. 1996. Plasma lipopolysaccharide-binding protein is found

associated with a particle containing apolipoprotein A-I, phospholipid, and factor H-related proteins. *J. Biol. Chem.* **271**: 18054-18060.

332. Wurfel, M. M., S. T. Kunitake, H. Lichenstein, J. P. Kane, and S. D. Wright. 1994. Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. *J. Exp. Med.* **180**: 1025-1035.

333. Vreugdenhil, A. C., A. M. Snoek, C. van 't Veer, J. W. Greve, and W. A. Buurman. 2001. LPS-binding protein circulates in association with apoB-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. *J. Clin. Invest.* **107**: 225-234.

334. Vreugdenhil, A. C., C. H. Rousseau, T. Hartung, J. W. Greve, C. van 't Veer, and W. A. Buurman. 2003. Lipopolysaccharide (LPS)-binding protein mediates LPS detoxification by chylomicrons. *J. Immunol.* **170**: 1399-1405.

335. Vreugdenhil, A. C., M. A. Dentener, A. M. Snoek, J. W. Greve, and W. A. Buurman. 1999. Lipopolysaccharide binding protein and serum amyloid A secretion by human intestinal epithelial cells during the acute phase response. *J. Immunol.* **163**: 2792-2798.

336. Dentener, M. A., A. C. Vreugdenhil, P. H. Hoet, J. H. Vernooy, F. H. Nieman, D. Heumann, Y. M. Janssen, W. A. Buurman, and E. F. Wouters. 2000. Production of the acute-phase protein lipopolysaccharide-binding protein by respiratory type II epithelial cells: implications for local defense to bacterial endotoxins. *Am. J. Respir. Cell. Mol. Biol.* **23**: 146-153.

337. Jack, R. S., X. Fan, M. Bernheiden, G. Rune, M. Ehlers, A. Weber, G. Kirsch, R. Mentel, B. Furll, M. Freudenberg, G. Schmitz, F. Stelter, and C. Schutt. 1997. Lipopolysaccharide-binding

protein is required to combat a murine gram-negative bacterial infection. *Nature.* **389**: 742-745.

338. Lamping, N., R. Dettmer, N. W. Schroder, D. Pfeil, W. Hallatschek, R. Burger, and R. R. Schumann. 1998. LPS-binding protein protects mice from septic shock caused by LPS or gram-negative bacteria. *J. Clin. Invest.* **101**: 2065-2071.

339. Hailman, E., J. J. Albers, G. Wolfbauer, A. Y. Tu, and S. D. Wright. 1996. Neutralization and transfer of lipopolysaccharide by phospholipid transfer protein. *J. Biol. Chem.* **271**: 12172-12178.

340. Recalde, D., M. A. Ostos, E. Badell, A. L. Garcia-Otin, J. Pidoux, G. Castro, M. M. Zakin, and D. Scott-Algara. 2004. Human Apolipoprotein A-IV Reduces Secretion of Proinflammatory Cytokines and Atherosclerotic Effects of a Chronic Infection Mimicked by Lipopolysaccharide. *Arterioscler. Thromb. Vasc. Biol.* **29**: 29.

341. Van Oosten, M., P. C. Rensen, E. S. Van Amersfoort, M. Van Eck, A. M. Van Dam, J. J. Breve, T. Vogel, A. Panet, T. J. Van Berkel, and J. Kuiper. 2001. Apolipoprotein E protects against bacterial lipopolysaccharide-induced lethality. A new therapeutic approach to treat gram-negative sepsis. *J. Biol. Chem.* **276**: 8820-8824.

342. de Bont, N., M. G. Netea, P. N. Demacker, I. Verschueren, B. J. Kullberg, K. W. van Dijk, J. W. van der Meer, and A. F. Stalenhoef. 1999. Apolipoprotein E knock-out mice are highly susceptible to endotoxemia and Klebsiella pneumoniae infection. *J. Lipid Res.* **40**: 680-685.

343. de Bont, N., M. G. Netea, P. N. Demacker, B. J. Kullberg, J. W. van der Meer, and A. F. Stalenhoef. 2000. Apolipoprotein E-deficient mice have an impaired immune response to

Klebsiella pneumoniae. *Eur. J. Clin. Invest.* **30**: 818-822.

344. Mahley, R. W. 1988. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science.* **240**: 622-630.

345. Allen, R. G., J. T. Barrett, and B. J. Campbell. 1971. Lipoprotein inhibitor of Newcastle disease virus from chicken lung. *Appl. Microbiol.* **21**: 53-60.

346. Halonen, P. E., P. Toivanen, and T. Nikkari. 1974. Non-specific serum inhibitors of activity of haemagglutinins of rabies and vesicular stomatitis viruses. *J. Gen. Virol.* **22**: 309-318.

347. Seganti, L., M. Grassi, P. Mastromarino, A. Pana, F. Superti, and N. Orsi. 1983. Activity of human serum lipoproteins on the infectivity of rhabdoviruses. *Microbiologica.* **6**: 91-99.

348. Shortridge, K. F., W. K. Ho, A. Oya, and M. Kobayashi. 1975. Studies on the inhibitory activities of human serum lipoproteins for Japanese encephalitis virus. *Southeast Asian J. Trop. Med. Public Health.* **6**: 461-466.

349. Shortridge, K. F., and W. K. Ho. 1976. Comparison of the activities in inhibition of haemagglutination by different togaviruses for human serum lipoproteins and their constituents. *J. Gen. Virol.* **33**: 523-527.

350. Chisari, F. V., L. K. Curtiss, and F. C. Jensen. 1981. Physiologic concentrations of normal human plasma lipoproteins inhibit the immortalization of peripheral B lymphocytes by the Epstein-Barr virus. *J. Clin. Invest.* **68**: 329-336.

351. Huemer, H. P., H. J. Menzel, D. Potratz, B. Brake, D. Falke, G. Utermann, and M. P. Dierich. 1988. Herpes simplex virus binds to human serum lipoprotein. *Intervirology.* **29**: 68-76.

352. Srinivas, R. V., B. Birkedal, R. J. Owens, G. M. Anantharamaiah, J. P. Segrest, and R. W. Compans. 1990. Antiviral effects of apolipoprotein A-I and its synthetic amphipathic peptide analogs. *Virology.* **176**: 48-57.

353. Owens, B. J., G. M. Anantharamaiah, J. B. Kahlon, R. V. Srinivas, R. W. Compans, and J. P. Segrest. 1990. Apolipoprotein A-I and its amphipathic helix peptide analogues inhibit human immunodeficiency virus-induced syncytium formation. *J. Clin. Invest.* **86**: 1142-1150.

354. Martin, I., M. C. Dubois, T. Saermark, and J. M. Ruysschaert. 1992. Apolipoprotein A-1 interacts with the N-terminal fusogenic domains of SIV (simian immunodeficiency virus) GP32 and HIV (human immunodeficiency virus) GP41: implications in viral entry. *Biochem. Biophys. Res. Commun.* **186**: 95-101.

355. Kane, J. P., D. A. Hardman, J. C. Dimpfl, and J. A. Levy. 1979. Apolipoprotein is responsible for neutralization of xenotropic type C virus by mouse serum. *Proc. Natl. Acad. Sci. USA.* **76**: 5957-5961.

356. Singh, I. P., A. K. Chopra, D. H. Coppenhaver, G. M. Ananatharamaiah, and S. Baron. 1999. Lipoproteins account for part of the broad non-specific antiviral activity of human serum. *Antiviral Res.* **42**: 211-218.

357. Ho, W. K. 1977. Serum lipoproteins as inhibitors of haemafflutination by rubella virus. *Lipids.* **12**: 85-91.

358. Mastromarino, P., L. Seganti, and N. Orsi. 1980. Relationship between enzymatic modifications of serum low density lipoproteins and their haemagglutination inhibiting activity

towards Sindbis virus. *Arch. Virol.* **65**: 37-44.

359. Mastromarino, P., C. Conti, S. Rieti, and N. Orsi. 1988. Identification of lipid components of human serum lipoproteins involved in the inhibition of Sindbis virus infectivity, hemagglutination, and hemolysis. *Arch. Virol.* **103**: 243-252.

360. Mastromarino, P., C. Conti, S. Rieti, and N. Orsi. 1989. Involvement of lipids in the interaction of Sindbis virus with goose erythrocytes. *Microbiologica.* **12**: 113-120.

361. Karlsson, K. A. 1989. Animal glycosphingolipids as membrane attachment sites for bacteria. *Annu. Rev. Biochem.* **58**: 309-350.

362. Fischer, D. G., N. Tal, D. Novick, S. Barak, and M. Rubinstein. 1993. An antiviral soluble form of the LDL receptor induced by interferon. *Science.* **262**: 250-253.

363. Marlovits, T. C., T. Zechmeister, M. Gruenberger, B. Ronacher, H. Schwihla, and D. Blaas. 1998. Recombinant soluble low density lipoprotein receptor fragment inhibits minor group rhinovirus infection in vitro. *FASEB J.* **12**: 695-703.

364. Marlovits, T. C., C. Abrahamsberg, and D. Blaas. 1998. Very-low-density lipoprotein receptor fragment shed from HeLa cells inhibits human rhinovirus infection. *J. Virol.* **72**: 10246-10250.

365. Hofer, F., M. Gruenberger, H. Kowalski, H. Machat, M. Huettinger, E. Kuechler, and D. Blass. 1994. Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. *Proc. Natl. Acad. Sci. USA.* **91**: 1839-1842.

366. Monazahian, M., I. Bohme, S. Bonk, A. Koch, C. Scholz, S. Grethe, and R. Thomssen.

1999. Low density lipoprotein receptor as a candidate receptor for hepatitis C virus. *J. Med. Virol.* **57**: 223-229.

367. Raper, J., R. Fung, J. Ghiso, V. Nussenzweig, and S. Tomlinson. 1999. Characterization of a novel trypanosome lytic factor from human serum. *Infect. Immun.* **67**: 1910-1916.

368. Raper, J., M. P. Portela, E. Lugli, U. Frevert, and S. Tomlinson. 2001. Trypanosome lytic factors: novel mediators of human innate immunity. *Curr. Opin. Microbiol.* **4**: 402-408.

369. Vanhamme, L., F. Paturiaux-Hanocq, P. Poelvoorde, D. P. Nolan, L. Lins, J. Van Den Abbeele, A. Pays, P. Tebabi, H. Van Xong, A. Jacquet, N. Moguilevsky, M. Dieu, J. P. Kane, P. De Baetselier, R. Brasseur, and E. Pays. 2003. Apolipoprotein L-I is the trypanosome lytic factor of human serum. *Nature.* **422**: 83-87.

370. Bout, D., M. Joseph, M. Pontet, H. Vorng, D. Deslee, and A. Capron. 1986. Rat resistance to schistosomiasis: platelet-mediated cytotoxicity induced by C-reactive protein. *Science.* **231**: 153-156.

371. Xu, X., H. G. Remold, and J. P. Caulfield. 1993. Potential role for scavenger receptors of human monocytes in the killing of Schistosoma mansoni. *Am. J. Pathol.* **142**: 685-689.

372. Sinnis, P., T. E. Willnow, M. R. Briones, J. Herz, and V. Nussenzweig. 1996. Remnant lipoproteins inhibit malaria sporozoite invasion of hepatocytes. *J. Exp. Med.* **184**: 945-954.

373. Walton, K. A., A. L. Cole, M. Yeh, G. Subbanagounder, S. R. Krutzik, R. L. Modlin, R. M. Lucas, J. Nakai, E. J. Smart, D. K. Vora, and J. A. Berliner. 2003. Specific phospholipid oxidation products inhibit ligand activation of toll-like receptors 4 and 2. *Arterioscler. Thromb. Vasc. Biol.*

23: 1197-1203.

374. Bochkov, V. N., A. Kadl, J. Huber, F. Gruber, B. R. Binder, and N. Leitinger. 2002. Protective role of phospholipid oxidation products in endotoxin-induced tissue damage. *Nature.* **419**: 77-81.

375. Hauton, D., and R. D. Evans. 2002. Utilisation of fatty acid and triacylglycerol by rat macrophages: the effect of endotoxin. *Cell. Physiol. Biochem.* **12**: 293-304.

376. Kisilevsky, R., and L. Subrahmanyan. 1992. Serum amyloid A changes high density lipoprotein's cellular affinity. A clue to serum amyloid A's principal function. *Lab. Invest.* **66**: 778-785.

377. Tietge, U. J., C. Maugeais, W. Cain, and D. J. Rader. 2003. Acute inflammation increases the selective uptake of HDL-cholesteryl esters into adrenals of mice overexpressing human secretory phospholipase A2. *Am. J. Physiol. Endocrinol. Metab.* **11**: 11.

378. Cuthbert, J. A., and P. E. Lipsky. 1987. Regulation of lymphocyte proliferation by cholesterol: the role of endogenous sterol metabolism and low density lipoprotein receptors. *Int. J. Tissue React.* **9**: 447-457.

Figure Legends

Fig. 1. Changes in hepatic fatty acid (FA) metabolism during the acute-phase response (APR). LPS and cytokines increase CD36/FAT (fatty acid translocase), while decreasing FATP (fatty acid transport protein) in the liver. CD36/FAT may transport long chain FA (LCFA) to cytosol for reesterification, which is enhanced during infection and inflammation, whereas FATP may transport FA towards mitochondria for oxidation, which is suppressed during infection. Cytokines, such as TNF and IL-1, increase hepatic FA synthesis by increasing hepatic citrate levels. Modest increases in acetyl CoA carboxylase (ACC) and FA synthase (FAS) are also observed. The expression of carnitine palmitoyl transferase-I (CPT-I) and CPT-II are decreased during sepsis. In addition, LPS and cytokines increase the levels of hepatic malonyl CoA, which further inhibits CPT-I, the rate-limiting enzyme in FA oxidation, resulting in decreased FA oxidation and suppressed ketone body (KB) production in the liver. PM, plasma membrane; CYT, cytosol; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; MM, mitochondrial matrix; TG, triglyceride; ACS, acyl-CoA synthetase.

Fig. 2. Changes in cholesterol metabolism during the acute-phase response (APR). Infection and inflammation are associated with an increase in hydroxymethylglutaryl coenzyme A (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 non-sterol pathways, such as dolichols.

Fig. 3. Changes in bile acid metabolism during the acute-phase response (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 CYP7A1, CYP27A1, CYP7B1, and CYP8B1. 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 (NCTP) and organic anion transporting proteins (OATPs). Furthermore, LPS decreases the excretion of cholesterol and phospholipids into the bile by down-regulating ABCG5/ABCG8 and multidrug resistance 3 (MDR3), respectively.

Fig. 4. Changes in reverse cholesterol transport during the acute-phase response (APR). LPS and cytokines decrease ABCA1 and cholesterol efflux from peripheral cells to HDL. LPS also decreases several enzymes involved in HDL metabolism, including lecithin:cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP), and hepatic lipase (HL). In addition, LPS and cytokines down-regulate hepatic scavenger receptor class B type I (SR-BI), resulting in a decrease in cholesterol ester uptake into the liver.

Fig. 5. Changes in sphingolipid metabolism during the acute-phase response (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 elevated levels of ceramide in serum.

Table 1. Effects of LPS, LTA, and cytokines on TG metabolism in intact animals

	LPS	LTA	TNF	IL-1	IL-6	IFN-α	IFN-γ	
Serum TG	↑	↑	↑	↑	↑	↔	↔	
Hepatic FA synthesis	↑	↑	↑	↑	↑	↑	↔	
TG secretion	↑	↑	↑	↑	↑	ND		
ND								
Lipolysis	↑	↑	↑	↔	↑	↑	↑	
FA oxidation	↓	ND	↓	↓	ND	ND	ND	
Serum KB	↓	ND	↓	↓	↔	↑[a],↔[b]	↑	
TG clearance	↔[a],↓[b]	↔	↔	↔	↔	ND	ND	
LPL activity	↓	↔	↓,↔[c]	↓	↓	↓	↓	

ND: not determined; a: low doses; b: high doses; c: some but not most tissues.

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

	LPS	LTA	TNF	IL-1		IL-6	IFN-α	IFN-γ
Serum CH	↑,↓[a]	↑	↑,↓[a]	↑,↔[a]	↑		↔	↔
Hepatic CH synthesis	↑	ND	↑	↑	ND	↔		↑
HMG CoA reductase activity	↑	ND	↑	↑	ND	ND		↔
LDL receptor protein	↓,↔[b]	ND	↔[b]	↔[b]	ND	ND		ND
Bile acid synthesis	↓	ND	↓	↓	ND	ND		ND

Data are in rats and mice unless otherwise noted. a; primates, b; hamsters, ND; not determined.

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

Proteins	Effects
Increased	
Apo SAA	Decreases cholesterol uptake by hepatocytes; increases cholesterol uptake into macrophages
$sPLA_2$	Decreases phospholipid content of HDL and impairs cholesterol removal from cells
Apo J	Not known
PAF-AH	Increases LPC production
LBP	Increases neutralization of endotoxin by HDL
Apo E	Increases cholesterol delivery to cells, redirects endotoxin from

	macrophages to hepatocytes
Apo A-IV	Decreases endotoxin-induced stimulation of monocytes
Apo A-V	Not known
Ceruloplasmin	Enhances LDL oxidation

Decreased

Apo A-I	Impairs cholesterol removal from cells
Apo A-II	Not known
LCAT	Impairs cholesterol removal from cells
CETP	Impairs cholesterol transfer to apo B-containing lipoproteins
HL	Decreases pre^2-HDL generation
PON1	Decreases the ability of HDL to protect against LDL oxidation
Transferrin	Decreases the ability of HDL to protect against LDL oxidation

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 ↓	Fat storage

		LPL ↓	Triglyceride catabolism
		FATP ↓	Fatty acid transport
		CD36/FAT ↓	Fatty acid and oxidized LDL uptake
		ACS ↓	Fatty acid esterification
Heart	PPAR-α ↓	LPL ↓	Triglyceride catabolism
	PPAR-β/δ ↓	FATP ↓	Fatty acid transport
		CD36/FAT ↓	Oxidized LDL uptake
		H-FABP ↓	Fatty acid transport
		CPT-Iβ ↓	Fatty acid oxidation
		ACS ↓	Fatty acid esterification
Skeletal	PPAR-α ?	LPL ↓	Triglyceride catabolism
muscle	PPAR-β/δ ?	FATP ↓	Fatty acid transport
		CD36/FAT ↓	Oxidized LDL uptake
		H-FABP ↓	Fatty acid transport
		ACS ↓	Fatty acid esterification
Liver	PPAR-α ↓	FATP ↓	Fatty acid transport
	PPAR-γ ↓	CD36/FAT ↓	Oxidized LDL uptake
		H-FABP ↓	Fatty acid transport
		CPT-Iα ↓	Fatty acid oxidation
	FXR ↓	Apo C-II ↓	Increases LPL activity

Apo E	↓	Lipoprotein metabolism

↓ : decreased levels of mRNA after LPS treatment; ? : not determined

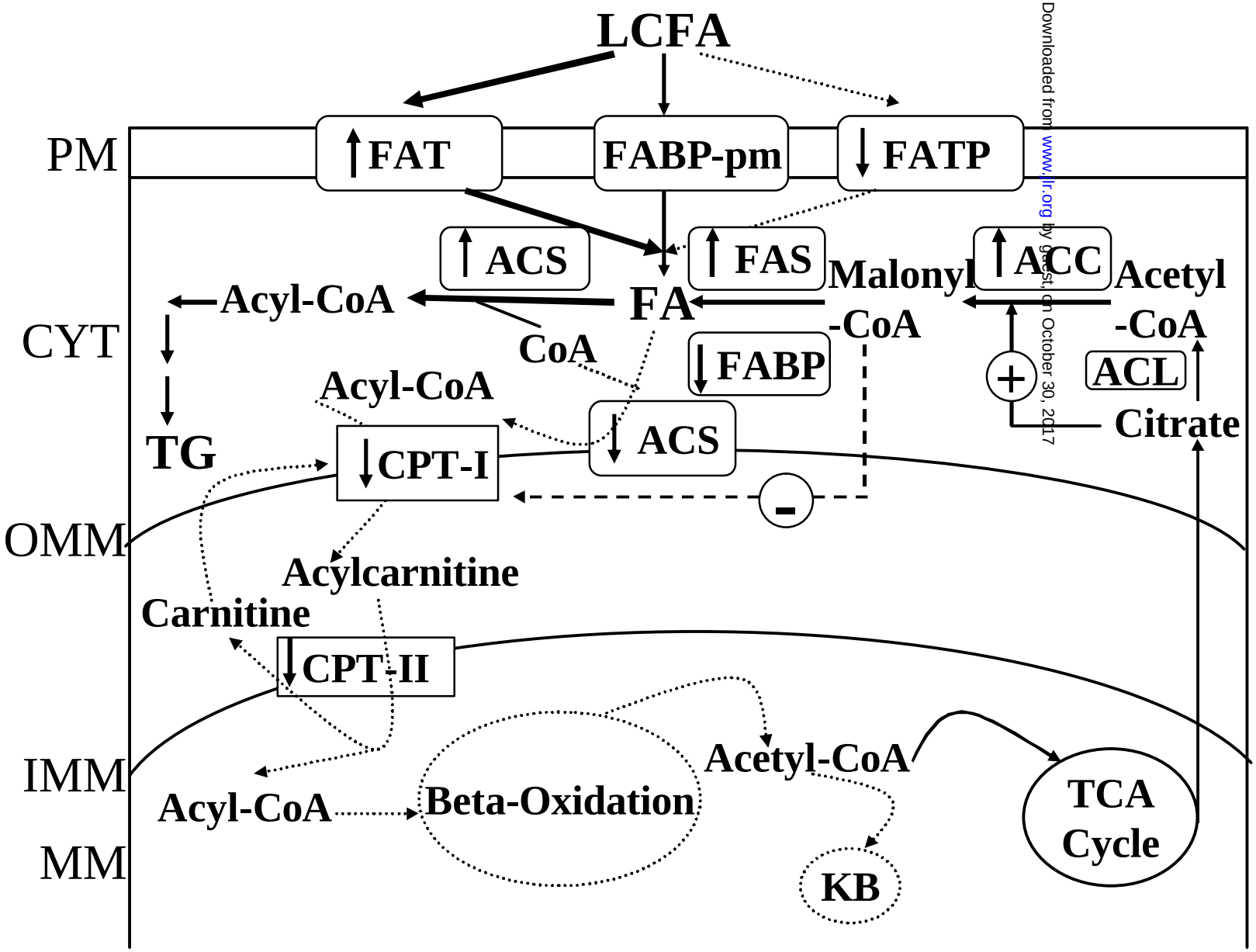
Table 5. Changes in nuclear hormone receptors and their target genes involved in reverse cholesterol transport during infection and inflammation

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

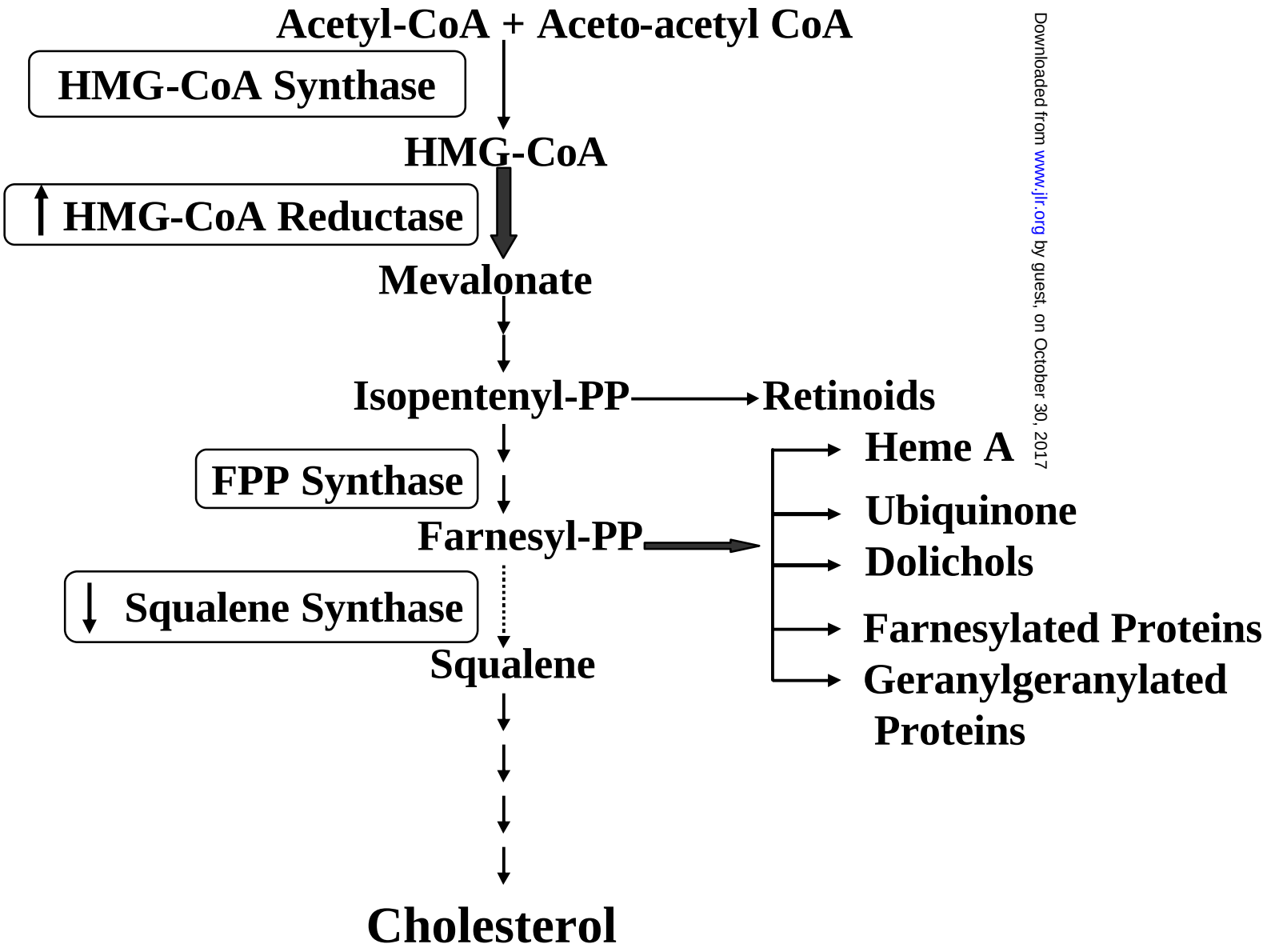
HNF-1* ↓	CYP27A1 ↓	Bile acid synthesis

↔: unchanged; ↓: decreased; *: not nuclear hormone receptor

Hepatic FA metabolism during the APR



Cholesterol metabolism during the APR



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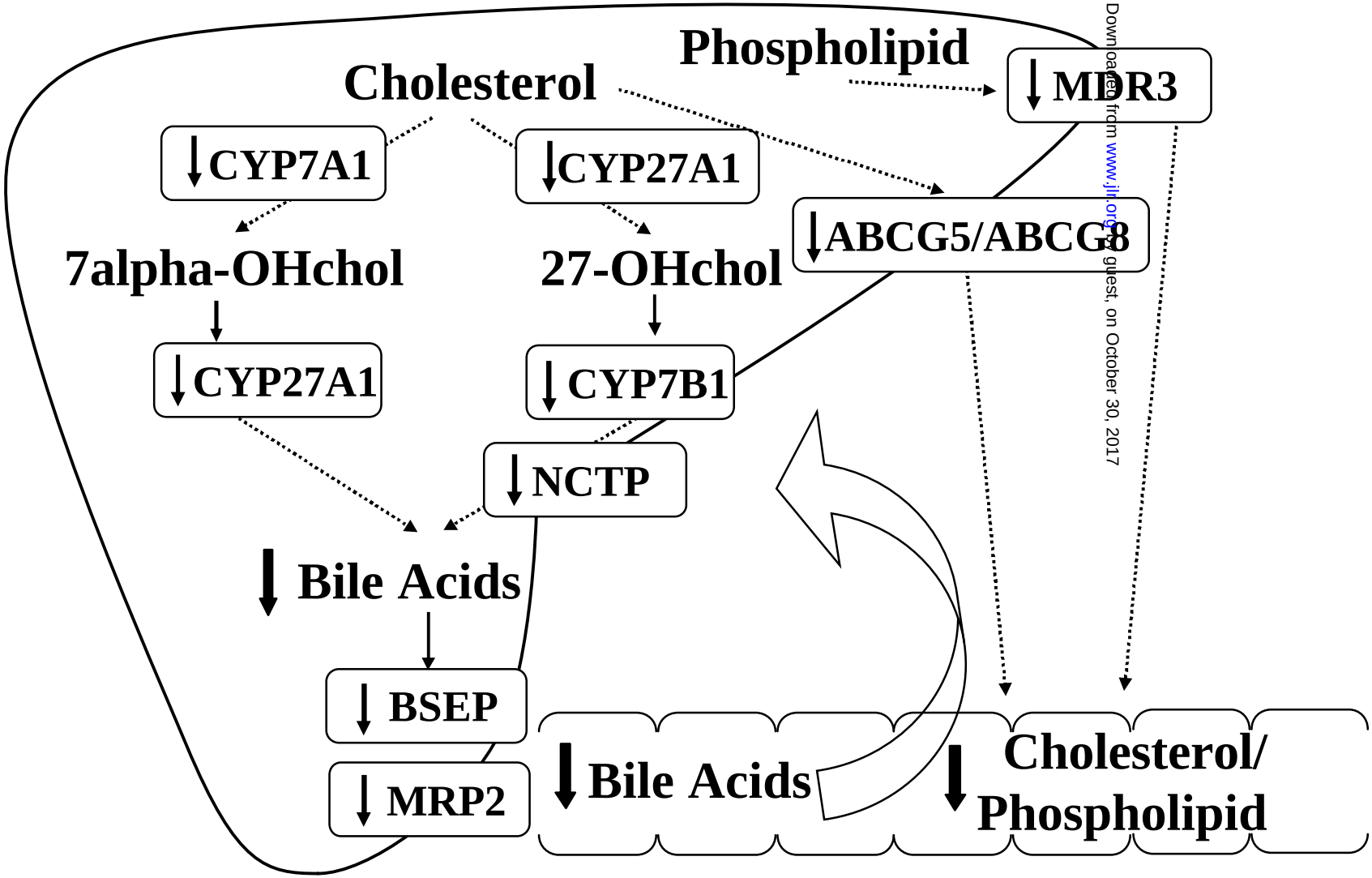
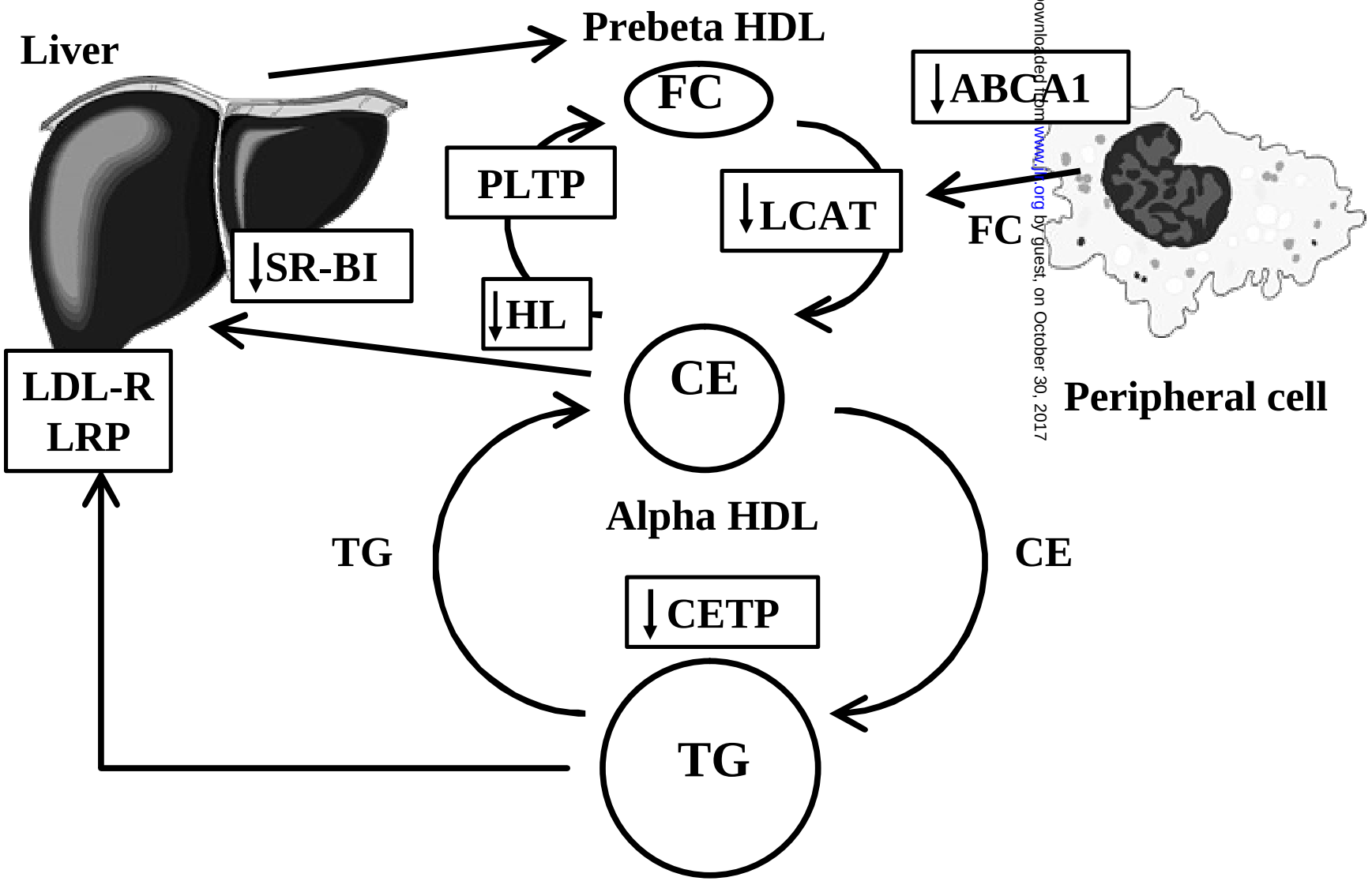


Reverse Cholesterol Transport during the APR



Sphingolipid metabolism during the APR