thematic review

Thematic review series: The Immune System and Atherogenesis

Lipoprotein-associated inflammatory proteins: markers or mediators of cardiovascular disease?

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Abstract **In humans, a chronically increased circulating level of C-reactive protein (CRP), a positive acute-phase reactant, is an independent risk factor for cardiovascular disease. This observation has led to considerable interest in the role of inflammatory proteins in atherosclerosis. In this review, after discussing CRP, we focus on the potential role in the pathogenesis of human vascular disease of inflammation-induced proteins that are carried by lipoproteins. Serum amyloid A (SAA) is transported predominantly on HDL, and levels of this protein increase markedly during acute and chronic inflammation in both animals and humans. Increased SAA levels predict the risk of cardiovascular disease in humans. Recent animal studies support the proposal that SAA plays a role in atherogenesis. Evidence is accruing that secretory phospholipase A_2, an HDL-associated protein, and platelet-activating factor acetylhydrolase, a protein associated predominantly with LDL in humans and HDL in mice, might also play roles both as markers and mediators of human atherosclerosis. In contrast to positive acute-phase proteins, which increase in abundance during inflammation, negative acute-phase proteins have received less attention. Apolipoprotein A-I (apoA-I), the major apolipoprotein of HDL, decreases during inflammation. Recent studies also indicate that HDL is oxidized by myeloperoxidase in patients with established atherosclerosis. These alterations may limit the ability of apoA-I to participate in reverse cholesterol transport. Paraoxonase-1 (PON1), another HDL-associated protein, also decreases during inflammation. PON1 is atheroprotective in animal models of hypercholesterolemia. Controversy over its utility as a marker of human atherosclerosis may reflect the fact that enzyme activity rather than blood level (or genotype) is the major determinant of cardiovascular risk. Thus, multiple lipoprotein-associated proteins that change in concentration during acute and chronic inflammation may serve as markers of cardiovascular disease. In future studies, it will be important to determine whether these proteins play a causal role in atherogenesis.**—Chait, A., C. Y. Han, J. F. Oram, and J. W. Heinecke. **Lipoprotein-associated inflammatory proteins: markers or mediators of cardiovascular disease?** ***J. Lipid Res.*** **2005.** 46: **389–403.**

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In the face of infection, tissue damage, or acute inflammation, the host undergoes a series of biochemical and physiological changes termed the acute-phase response. This response plays a critical role in limiting tissue injury and in the innate immune response. The innate immune system provides a rapid, first-line defense against injurious insults, compared with the adaptive immune system, which uses slower and more specific B- and T-cell responses. The innate immune system uses a number of pattern recognition receptors that sense conserved structures and molecules characteristic of harmful agents. Pattern recognition receptors are important for triggering the activation of cells of the innate immune system and removing potentially injurious pathogens (1, 2).

A key component of the acute-phase response is altered hepatic synthesis of a wide array of proteins involved in coagulation, lipid metabolism, and the complement system (3). Various cytokines regulate changes in the concentrations of these proteins in blood. A low level of systemic inflammation can also chronically perturb blood levels of the inflammatory proteins that participate in the acute-phase response. Importantly, the magnitude of the chronic change is often considerably less than that observed in response to acute injury or infection. Moreover, many lines of evidence suggest that chronic, small changes in inflammatory protein levels might be detrimental rather than beneficial to the host.

The acute-phase reaction occurs rapidly in response to tissue injury or infection. For example, levels of C-reactive protein (CRP; so named because it reacts with the C-polysaccharide protein of *Streptococcus pneumoniae*) can increase

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1,000-fold within 48 h after an acute-phase stimulus. This is the largest increase achieved by any of the known acute-phase proteins. It is also important to note that concentrations of several proteins decrease in blood and the liver during the acute-phase response (3). These proteins are referred to as negative acute-phase proteins. A variety of functions have been attributed to the various positive and negative acute-phase proteins. For example, CRP activates the complement pathway and binds to Fc receptors on macrophages, which may be important for host defense.

Epidemiological and clinical studies have shown independent relationships between circulating levels of certain of these inflammatory proteins and cardiovascular disease, supporting the view that increased levels of CRP and other inflammatory proteins provide an independent assessment of the risk for cardiovascular events. These observations have reinforced basic science studies demonstrating that atherosclerosis is a chronic inflammatory process (2). Thus, one possibility is that altered levels of these inflammatory proteins reflect the presence of inflammation in the artery wall (4–6) or elsewhere in the body that might increase the risk for atherosclerosis. If so, these proteins might serve as potential markers of atherosclerosis. More recently, it has been proposed that inflammatory proteins may play a pathogenic role in atherosclerosis by promoting vascular injury. In this view, inflammatory proteins directly affect biological processes in the artery wall, or perhaps elsewhere, that in turn contribute to atherogenesis. This proposal raises the possibility that inflammatory proteins might be direct mediators of atherosclerosis.

In this review, we evaluate the roles of several positive and negative inflammatory proteins as markers or mediators of atherosclerosis. After discussing the role of CRP, we focus our attention on lipoprotein-associated proteins implicated in atherogenesis, including serum amyloid A (SAA), group II secretory phospholipase A_2 ($sPLA_2$), platelet-activating factor acetylhydrolase (PAF-AH), apolipoprotein J (apoJ; also known as clusterin), paraoxonase-1 (PON1), and apolipoprotein A-I (apoA-I). Several recent reviews provide information on the potential atherogenic role of non-lipoprotein-associated inflammatory proteins, such as complement, fibrinogen, ferritin, and ceruloplasmin (7–10).

ROLE OF PROTEINS INFLUENCED BY INFLAMMATION IN ATHEROGENESIS

CRP

CRP, a member of the pentraxin family of proteins, contains five noncovalently linked protomers surrounding a central pore. It is transported free in plasma rather than bound to circulating lipoproteins, although it can interact with oxidized phospholipids and oxidized lipoproteins in vitro (11). CRP activates complement and binds to Fc receptors, which may facilitate the uptake and clearance of apoptotic and necrotic cells during the acute-phase response (12).

Predictor of clinical cardiovascular events. CRP was the first acute-phase protein identified and thus is the best studied marker of inflammation in humans. Increased levels of CRP predict first clinical events, recurrent events, coronary heart disease end points, and stroke (reviewed in 13). In certain studies, CRP was a more powerful predictor of cardiovascular risk than traditional risk factors such as LDL (14). Indeed, CRP appeared to predict risk independently of LDL and HDL cholesterol (13, 15) and to provide predictive power beyond that derived from using Framingham risk scores (14). CRP levels are also increased in conditions that are associated with increased cardiovascular risk, including obesity (16–20), insulin resistance (17, 18), hypertension (21, 22), the metabolic syndrome (16, 23–25), type 2 diabetes (16, 17, 26), hypertriglyceridemia (24, 27, 28), a low level of HDL cholesterol (17, 24, 28), and smoking (28, 29). CRP levels are also increased in other chronic inflammatory conditions, such as periodontal disease (30, 31) and rheumatoid arthritis (32), which are more weakly associated with increased risk for cardiovascular disease. CRP is less well associated with measures of atherosclerosis than with clinical outcomes (33–35).

Several risk factors associated with increased CRP are also components of the metabolic syndrome, which greatly increases the risk of clinically significant atherosclerosis (36–39). Insulin resistance, diabetes, low HDL, visceral obesity, and hypertension are the hallmarks of the metabolic syndrome (40). Indeed, CRP adds prognostic information even when components of the metabolic syndrome are taken into account (41), although the magnitude of risk is attenuated after adjusting for these risk factors in some studies (42). However, the metabolic syndrome is unlikely to be the sole reason for the association between CRP and cardiovascular risk, because levels also are increased in conditions such as familial hypercholesterolemia (43), in which the prevalence of the metabolic syndrome is unlikely to be increased.

Although increased CRP has been regarded as one of the strongest predictors of risk for future cardiovascular events, the magnitude of this risk was recently called into question. In the Reykjavik Prospective Cohort Study (44), multivariate analysis suggested that measuring CRP added less to the predictive power than previous studies had suggested and less than traditional risk factors. After adjustment for factors such as smoking status, body mass index, and total blood cholesterol, participants in the highest tertile of CRP had only a 1.5-fold higher risk for coronary artery disease than those in the lowest tertile. In contrast, the odds ratio was 2.4 for subjects with increased cholesterol and 1.9 for smokers. Strengths of this study included the large number of subjects (>20,000, the largest number reported to date), the large number of cardiovascular events, the length of follow-up (20 years), and low rates of dropout in the study population (44). These observations suggest that CRP might contribute less to predictions than traditional risk factors of cardiovascular disease.

Two recent studies suggest that statins reduce CRP in patients with established cardiovascular disease and that clinical improvements in these patients is independent of changes in lipid levels (45, 46). These observations raise the possibility that inflammation plays a causal role in atherosclerosis and confirm that blood levels of CRP serve as

a marker for the risk of cardiovascular disease that is independent of traditional risk factors. However, the magnitude of this risk may have been overestimated in earlier studies, and uncertainties remain about the clinical utility of measuring CRP.

Atherogenic effects. Most of our understanding of the potential atherogenic mechanisms of CRP is based on model systems using cultured cells, especially endothelial cells. Proposed mechanisms include impaired production of cardioprotective molecules [e.g., endothelial nitric oxide (47) and prostacyclin (48)] and increased production of potentially atherogenic molecules [e.g., endothelin-1 (49), various cell adhesion molecules (47, 49, 50), monocyte chemoattractant protein 1 (51), interleukin-8 (52), and plasminogen activator inhibitor-1 (53)]. CRP induces macrophages to secrete tissue factor (54) and increases their production of reactive oxygen species (55) and proinflammatory cytokines (56). It also promotes monocyte adhesion and chemotaxis (57, 58), increases the uptake of oxidized LDL (11), and stimulates the expression of matrix metalloproteinases by macrophages (59). In vascular smooth muscle cells, CRP induces nitric oxide synthase, activates nuclear factor κB and mitogen-activated protein kinase, and promotes cell proliferation (60). These latter effects may be partly attributable to upregulation of the angiotensin type-1 receptor (61). These studies have been reviewed recently (62).

It is important to note that these studies of cultured cells usually did not assess the purity of the CRP used, utilized high concentrations of the protein, and often failed to use relevant controls to demonstrate the specificity of the response. These are important issues because commercial CRP can be contaminated with other proteins and it can adopt a variety of properties in vitro that may not be physiologically relevant (63). However, if these in vitro studies are valid, CRP could be involved at multiple stages of early and late atherosclerosis: endothelial cell injury, impairment of vasodilation, enhanced monocyte adhesion and chemotaxis, lipid accumulation by monocyte-macrophages, smooth muscle cell proliferation, thrombosis, and plaque rupture. Moreover, CRP has been detected immunohistochemically in atherosclerotic lesions (11, 64, 65).

Remarkably little is known about CRP's effects in animal models of atherosclerosis. Because CRP is not an acute-phase protein in mice (66, 67), transgenic mouse models of accelerated atherosclerosis offer useful opportunities to directly test its atherogenic role. A recent study using apoE-deficient mice demonstrated that atherosclerosis was enhanced when animals overexpressed human CRP (68). However, the effects on lesion formation were modest and were confined to males, suggesting that even high levels of CRP might have little direct effect on the initiation and progression of atherosclerosis in hypercholesterolemic mice. In pioneering studies, Pepys and colleagues (69) demonstrated that human CRP promotes myocardial infarction in a rat model of acute ischemic injury. The increase in infarct size caused by CRP was abrogated by depleting complement in vivo, suggesting that complement activation by CRP plays a role in tissue injury.

CRP interacts with the complement and coagulation systems, and thrombosis is centrally important in triggering clinical events in human atherosclerotic vascular disease (70). Indeed, CRP colocalizes with activated complement in ischemic human myocardial tissue (71). In contrast, most animal models of hypercholesterolemia do not develop myocardial infarction or exhibit a major thrombotic component. The fact that CRP is more strongly associated with cardiovascular end points than with measures of atherosclerosis raises questions regarding whether its major effect is on thrombosis and plaque rupture rather than on atherogenesis.

Thus, although CRP might be an independent marker for cardiovascular disease risk, the role of CRP as a mediator of atherogenesis remains to be established. In future studies, it will be important to determine whether CRP directly promotes atherogenesis in animal models and to explore the possibility that it exacerbates vascular disease by other mechanisms, perhaps involving the complement and coagulation systems.

SAA

SAA is an amphipathic, α-helical apolipoprotein that is transported in the circulation primarily in association with HDL (72–74). Like CRP levels, SAA levels increase rapidly in the blood of humans suffering from acute inflammation (75). They also increase in response to inflammation in mice (75).

The SAA gene family clusters on chromosome 11 in humans and chromosome 7 in mice. In mice, there are four functional *Saa* genes (*Saa1* to *Saa4*). The liver produces SAA1 and SAA2 in response to systemic inflammation. Extrahepatic cells, such as macrophages and adipocytes, are the major source of SAA3, which also is produced in response to inflammatory stimuli (76, 77). SAA4 is produced in the liver constitutively (75). In humans, there are only three functional *SAA* genes, because *SAA3* is a pseudogene that is not transcribed. Although most SAA is produced by the liver, SAA1, SAA2, and SAA4 also can be produced by extrahepatic sources (78). It is of interest that mRNA for SAA has been detected in all of the major cell types present in atherosclerotic lesions (78), which contain both acute-phase and constitutive forms of SAA protein (79).

Predictor of clinical cardiovascular events. The concentration of SAA in blood increases dramatically during acute inflammation in humans and animals (75). In several observational and prospective studies, the risk of cardiovascular disease associated with SAA changed in parallel with that seen with CRP (80–83), although the absolute level of risk was generally smaller. Moreover, SAA levels are increased in conditions associated with increased cardiovascular risk, including obesity (17, 80), insulin resistance (17, 84), the metabolic syndrome (85), diabetes (17, 84, 86), and rheumatoid arthritis (32). Thus, a chronic modest increase in SAA level also appears to be associated with an increased risk of cardiovascular disease. Although additional studies are needed, these observations raise the possibility that SAA might serve as a marker for an increased risk of cardiovascular disease in humans.

Atherogenic effects. In vitro studies have suggested a number of pathways for the involvement of SAA in host defense mechanisms and inflammation. For example, in vitro experiments and studies in experimental animals indicate that apolipoprotein SAA can induce the expression of proteinases thought to degrade extracellular matrix (87, 88), which might be important during tissue injury. Moreover, it can act as a chemoattractant for inflammatory cells such as monocytes, polymorphonuclear leukocytes, and T-lymphocytes (89, 90), all of which are involved in host defense mechanisms. Lipoprotein-associated SAA may play a role in cholesterol transport by increasing the delivery of cholesterol to peripheral cells (91, 92), which might be important for lipid metabolism in injured cells. In contrast, liposome-associated SAA2 promotes the efflux of cholesterol from cells, a property not shared by SAA1 (93). Non-HDL-associated SAA promotes cholesterol efflux by both ABCA1-dependent and -independent mechanisms (94). When SAA circulates in the blood, it is bound to HDL, but it is conceivable that SAA not associated with lipoproteins could be formed from HDL in the artery wall or secreted directly by artery wall cells (78). Thus, lipoprotein-associated and non-lipoprotein-associated SAA might play different roles in the delivery and removal of cholesterol from cells at inflamed or injured sites. SAA has been shown to displace apoA-I from HDL in vitro (95). Moreover, remodeling of HDL occurs after the induction of acute inflammation with lipopolysaccharide (LPS) in mice (96). HDL protein composition also may be regulated by inflammation-induced changes in the hepatic expression of some HDL apolipoproteins, particularly SAA, apoA-I, and PON1 (see below). These compositional changes are likely to have functional consequences.

A rapid increase in SAA level is likely beneficial during infection and acute inflammation. However, modest but chronic increases of SAA, as often occur in the metabolic syndrome, type 2 diabetes, and other chronic inflammatory disorders, might be deleterious. Potential consequences include the stimulation of monocyte adhesion and chemotaxis into the artery wall and increased delivery of cholesterol to artery wall cells, two processes that might contribute to the initiation and progression of atherosclerotic lesions. Because SAA binds to proteoglycans (97, 98), chronic inflammation might facilitate the binding of SAA-containing HDL to extracellular vascular proteoglycans, which would favor the retention and modification of HDL by the vascular matrix. Retention of lipoproteins by vascular proteoglycans is believed to play an important role in the formation of macrophage foam cells but has also been implicated in all stages of atherogenesis (99, 100). Retention could prevent HDL from participating in reverse cholesterol transport and inhibiting oxidative processes in the artery wall. Moreover, modification of the lipid and protein components of trapped HDL might increase its interactions with macrophage scavenger receptors and render the lipoprotein atherogenic, similar to what happens with LDL (101).

Recent studies suggest that SAA may play a role in atherosclerosis in mouse models of hyperlipidemia. A study of LDL receptor-deficient mice showed that supplementing a high-fat diet with cholesterol increases SAA levels without adversely affecting circulating lipid and lipoprotein concentrations (102). Circulating SAA levels in these mice, but not lipid levels, were strongly associated with the extent of atherosclerosis in the aorta. Binding of HDL to proteoglycans correlated with the SAA content of the lipoprotein, and SAA colocalized with apoA-I and proteoglycans in atherosclerotic lesions (102). Surprisingly, this study showed that a fraction of the SAA was carried in VLDL and its remnants in addition to HDL, the usual transporter of SAA through plasma (72, 74). These findings are consistent with the hypothesis that SAA might be atherogenic because it tethers SAA-containing lipoproteins to vascular proteoglycans. Its ability to stimulate the expression of matrix-degrading enzymes, such as collagenases and matrix metalloproteinases (88), also could contribute to plaque instability and plaque rupture, although this has not been tested in animal models.

These animal studies suggest that SAA is a mediator of atherosclerosis as well as a marker for cardiovascular disease. In future studies, it will be important to further explore the proposal that SAA plays a causal role in atherogenesis using additional animal models. One powerful test would be to overexpress the different SAA genes in hyperlipidemic mice that are not in an inflammatory state.

$sPLA_2$

$sPLA_2$ is another family of proteins that become more abundant in response to inflammatory stimuli. These enzymes hydrolyze phospholipids at the *sn*-2 position to generate lysophospholipids and free fatty acids. The best studied $sPLA_2$ with respect to its role in inflammation and atherogenesis is the group IIA enzyme. Like SAA and apoJ (see below), it also can be bound to HDL (103). Most studies of the role of $sPLA_2$ in atherogenesis have focused on the group IIA enzyme, and we will focus our review on this family member.

Predictor of clinical cardiovascular events. Circulating levels of $sPLA_2$ increase dramatically during infection and inflammation (104). Moreover, plasma levels are increased in patients with cardiovascular disease (105–108), consistent with a link between plasma $sPLA_2$ and atherosclerosis. However, it has yet to be determined whether this enzyme is an independent predictor of cardiovascular disease.

Atherogenic effects. In vitro studies indicate that $sPLA_2$ hydrolyzes phospholipids in both LDL and HDL. It converts LDL into small, dense particles of the type that are associated with an increased risk of cardiovascular disease in clinical studies (109, 110). Small, dense LDLs have an enhanced tendency to interact with proteoglycans (111). Moreover, $sPLA_2$ is also present in the artery wall, where it may act locally to promote the development of atherosclerosis. It is synthesized by vascular smooth muscle cells. Synthesis of the enzyme by vascular smooth muscle cells in vitro is induced by a variety of proinflammatory cytokines, although the specific cytokines involved appear to differ from smooth muscle cells of different species (105). In nonatherosclerotic arteries, $sPLA_2$ type IIA associates mainly

with smooth muscle cells (112, 113). In both humans and experimental animals, immunohistochemical studies have detected the enzyme in atherosclerotic lesions in association with macrophages, the necrotic lipid core, and extracellular vascular proteoglycans (112, 113), to which the enzyme binds with high affinity (114). The presence of $sPLA_2$ in the artery wall suggests that it might play a direct role in the development of vascular disease.

Several mechanisms might allow $sPLA_2$ to facilitate atherogenesis (reviewed in 105). When the enzyme modifies lipids of LDL and VLDL, two lipoproteins that contain apolipoprotein B-100, it generates lysophospholipids and free fatty acid. The resulting lipoproteins bind strongly to extracellular vascular proteoglycans (114). Once retained in the vascular matrix, these lipoproteins could undergo further enzymatic and nonenzymatic modifications, including oxidative modification. $sPLA_2$ also causes lipoproteins to aggregate and fuse (115), which further increases the binding of lipoproteins to extracellular proteoglycans (116). Aggregated lipoproteins can be taken up by LDL receptor-mediated phagocytosis (117–119). Because many molecules of lysophospholipids and free fatty acids can be generated when a single lipoprotein particle is hydrolyzed, high concentrations of these highly bioactive proinflammatory compounds might be achieved locally.

Lysophospholipids exert several potentially atherogenic effects. Lysophosphatidylcholine (lysoPC) is chemotactic for macrophages in vitro (120). Exposing vascular smooth muscle cells to lysoPC in vitro increased the expression of biglycan and the length of its glycosaminoglycan chains. These modified glycosaminoglycans increased the retention of unmodified LDL (121). Smooth muscle cells exposed to lysoPC also secreted the proteoglycan form of monocyte-macrophage colony-stimulating factor (M-CSF), the predominant proteoglycan produced by macrophages (121). M-CSF may play a role in lipoprotein retention and macrophage maturation and differentiation (122).

Endocytic uptake of lysoPC mediated by macrophage scavenger receptors plays a major role in oxidized LDL-induced macrophage growth (123, 124). LysoPC also can upregulate the expression of adhesion molecules for monocytes (125, 126) and stimulate the expression of growth factors, such as heparin binding epidermal growth factor and the platelet-derived growth factor A and B chains (127–129), all of which may play important roles in atherogenesis. Lysophosphatidic acid, which can be produced by hydrolysis of the polar head group of lysoPC, stimulates platelet aggregation, cell proliferation, and smooth muscle cell contraction (130, 131). Thus, phospholipid hydrolysis by $sPLA_2$ could produce high, localized concentrations of potentially toxic products in the milieu of the artery wall.

Mice in the C57Bl/6 genetic background, which are commonly used to study atherosclerosis, have a point mutation in the $sPLA_2$ gene that renders the enzyme nonfunctional (132). This defect ameliorates the reduction of HDL that normally occurs after an injection of LPS, a widely used model of acute inflammation. Transgenic mice that overexpress $sPLA_2$ are more susceptible to atherosclerosis than control mice (133, 134). Most likely, this partly reflects the fact that overexpression of $sPLA_2$ reduces HDL levels in mice (135). Increased levels of $sPLA_2$ might similarly decrease HDL levels in humans suffering from acute or chronic inflammation. Transplanting bone marrow cells from $sPLA_2$ transgenic mice into LDL receptor-deficient mice also enhanced atherosclerosis (133), suggesting that the local presence of the enzyme in the artery wall milieu can facilitate atherogenesis, independently of its effect on HDL levels.

The role of $sPLA_2$ in mouse atherosclerosis has recently been questioned. The C57Bl/K mouse strain has an intact $sPLA_2$ gene ($sPLA_2^{+/+}$) and its genome is highly homologous to that of the C57Bl/6 mouse (136). When C57Bl/K mice were crossed with C57Bl/6 mice deficient in apoE ($apoE^{-/-}$), there were no differences in the extent of atherosclerosis (monitored by cholesteryl ester levels in the aorta) or HDL levels (quantified by fast-protein liquid chromatography) in siblings that were either $apoE^{-/-}$ $sPLA_2^{+/+}$ or $apoE^{-/-}$ $sPLA_2^{-/-}$ (136). Enzyme assays confirmed that there was no active $sPLA_2$ in the $apoE^{-/-}$ $sPLA_2^{-/-}$ mice. These observations raise questions about the impact of $sPLA_2$ on atherosclerosis in this animal model of hypercholesterolemia.

Several factors might account for the differences observed in the different mouse models of atherosclerosis. The transgenic mice that exhibited decreased HDL levels and increased atherosclerosis exhibited much higher blood levels of $sPLA_2$ than is observed in humans, raising questions about the physiological relevance of the model. The transgenic mouse studies also used the human enzyme, whereas the mouse enzyme was deficient in the $apoE^{-/-}$ $sPLA_2^{-/-}$ mice. It is noteworthy that mice in the C57Bl/6 genetic background, which have a point mutation in the $sPLA_2$ gene that renders the enzyme nonfunctional, are nonetheless susceptible to atherosclerosis. Finally, it is important to note that the C57Bl/K mice and the C57Bl/6 mice are not congenic strains and that other genetic differences also might contribute to their susceptibilities to atherosclerosis.

Collectively, these observations indicate that overexpression of the active enzyme in macrophages promotes atherosclerosis in hypercholesterolemic mice, raising the possibility that local expression of the enzyme in the artery wall might be atherogenic. It is less clear whether the enzyme plays a critical role in decreasing HDL levels during acute inflammation in mice and perhaps chronic inflammation in humans. Thus, these animal model studies suggest that $sPLA_2$ has the potential to promote vascular disease by a variety of mechanisms, raising the possibility that this enzyme directly mediates atherosclerosis in humans.

Secretory phospholipases other than group IIA $sPLA_2$ also may play a role in atherogenesis. Group V $sPLA_2$, which also can be increased by the injection of LPS, has proteoglycan-binding sites, facilitates LDL aggregation, and can promote foam cell formation in vitro (137). Moreover, it binds phosphatidylcholine more avidly than the group II enzymes and preferentially appears to hydrolyze phospholipids in HDL rather than LDL (138). By so doing, it may reduce the atheroprotective properties of HDL and render it potentially

atherogenic during inflammation. However, it is unclear whether this enzyme is normally present in atherosclerotic lesions and whether it plays a role in atherogenesis.

PAF-AH

PAF-AH (also known as lipoprotein-associated PLA_2) is another circulating PLA_2 that is transported in both LDL and HDL (139). In humans it is present mainly on LDL, whereas HDL is the preferred carrier in mice (reviewed in 140, 141). PAF-AH hydrolyzes both the acetyl group in the *sn*-2 position of PAF (a potent inflammatory mediator) and short-chain oxidized fatty acids in the *sn*-2 position of oxidized phospholipids. However, it is unclear whether PAF-AH is an acute-phase response protein, because studies have shown levels of the enzyme to be either increased or decreased after inflammatory stimuli in animal models (142, 143). Because of its ability to deactivate oxidized phospholipids in the potent proinflammatory and prothrombotic molecule PAF, the enzyme has been considered to have a potentially protective role in atherogenesis (144). However, epidemiological studies favor a proatherogenic role for the enzyme (see below), raising questions regarding its precise role in cardiovascular disease.

Predictor of clinical cardiovascular events. Despite the proposed antiatherogenic properties of PAF-AH, clinical studies have shown that an increased PAF-AH level is an independent predictor of cardiovascular risk (145–147). Moreover, PAF-AH levels do not correlate with CRP levels (145). Because of its uncertainty as a protein that changes during inflammation, it is unclear whether PAF-AH should be considered a marker for inflammatory cardiovascular disease, although high circulating levels appear to predict clinical events.

Atherogenic effects. PAF-AH has a potentially ambiguous role with respect to atherosclerosis. It might promote atherosclerosis by many of the same mechanisms proposed for $sPLA_2$. Conversely, it might be cardioprotective if it degrades oxidized phospholipids with atherogenic and thrombogenic properties. PAF, which is a substrate for PAF-AH, blocked the conversion of monocytes into migrating cells and favored their subendothelial retention in an in vitro model (148). Normal migration was restored by HDL-associated PAF-AH (149). It has been suggested that PAF-AH that is associated with HDL, as occurs predominantly in rodent species, might be an atheroprotective form of the enzyme, whereas LDL-associated PAF-AH, as occurs in humans, might be atherogenic (140).

Little is known about PAF-AH's influence on atherogenesis in animal models of vascular disease. However, reduced PAF-AH levels in apoE-deficient mice fed a Western diet were accompanied by an increase in circulating oxidized phospholipids (150). Transfer of the PAF-AH gene into skeletal muscle of apoE-deficient mice was associated with an increase in arterial wall thickness (151). Therefore, it remains to be firmly established whether the enzyme plays a causal role in cardiovascular disease.

PON1

The paraoxonases are a family of enzymes that protect cells from damage by organophosphate toxins (152, 153). There are three known paraoxonase genes: *PON1*, *PON2*, and *PON3*. PON1 is synthesized in the liver and transported through plasma in HDL (154). PON2 is a ubiquitously expressed intracellular protein that can protect cells against oxidative damage (155). PON3 is the least well studied. It also is transported in HDL (156, 157), but it has different substrate specificities than PON1 (157). PON1 activity and/or protein levels are inhibited during the acute-phase response in animals (158, 159) and also in humans (160). Other studies have demonstrated a reduction in paraoxonase expression in HepG2 cells exposed to oxidized LDL (161) and in livers of mice exposed to an atherogenic diet (162). In contrast, PON3 does not appear to be regulated by either inflammation or exposure of liver cells to oxidized lipids (157).

Predictor of clinical cardiovascular events. Polymorphisms in *PON1* partly control the enzyme's activity in humans. An amino acid substitution at position 192 gives rise to two allozymes that have markedly different activities with certain artificial substrates in vitro. Some studies have found an association between the position 192 polymorphism and the risk for cardiovascular disease, but this association remains controversial (163–165).

It is noteworthy that PON1 activity in serum varies widely by mechanisms that are poorly understood but are independent of the known polymorphisms. This has led to the proposal that enzyme activity rather than genotype plays a role in cardiovascular disease. Case-control and prospective studies of humans support this hypothesis. Thus, PON1 may also serve as a marker for cardiovascular disease risk in humans, but enzyme activity rather than genotype or protein level appears to correlate most highly with the degree of risk (164).

Atheroprotective effects. In vitro studies suggest that HDL-associated PON1 inhibits lipid peroxidation or degrades biologically active oxidized lipids in LDL (143, 166–170). LDL oxidation is thought to be one important mechanism for converting the lipoprotein to a form that promotes the formation of lipid-laden macrophages, the cellular hallmark of the early atherosclerotic lesion (171). HDL inhibits LDL oxidation by metal ions in vitro (172), leading to the suggestion that this pathway represents one potential cardioprotective function of HDL.

A deficiency of PON1 enhanced atherosclerosis in hypercholesterolemic mice and was associated with an increase in oxidized phospholipids (173). Cell culture studies suggest that LDL isolated from these animals is enriched in potentially atherogenic oxidized lipids (174). Moreover, mice that overexpress PON1 appear to be protected from atherosclerosis, and LDL isolated from these animals appears to contain less oxidized lipid (175). Collectively, these observations led to the suggestion that HDL-associated PON1 prevents atherosclerosis by inhibiting lipid oxidation (166, 176). They also strongly support the proposal that HDL can affect atherosclerosis by a mechanism independent of reverse cholesterol transport.

Although PON1 clearly has atheroprotective properties in animal models of hypercholesterolemia (173, 175), recent studies have raised questions regarding the precise mechanism of this effect. For example, low levels of PAF-AH were

detected in purified PON1, and biochemical studies suggested that PAF-AH was responsible for degrading biologically active oxidized lipids (177). Thus, the phospholipase activity of PON1 is not likely to be the main basis for the atheroprotection observed in the genetic mouse models. Moreover, the role of PON1 in the inhibition of LDL oxidation catalyzed by copper or peroxyl radical has been questioned (178). Thus, the precise physiological function of PON1 remains unclear. Nonetheless, the genetic experiments in mice clearly indicate that it has atheroprotective functions.

ApoJ

ApoJ, also known as clusterin, travels through plasma while bound to HDL, and its level increases in response to inflammatory stimuli (179). Although little is known about its precise function, its presence in atherosclerotic lesions but not in normal arteries (180) suggests a role in the atherosclerosis associated with chronic inflammatory states. Its colocalization in lesions with apoA-I and apoE (180) suggests that it may enter lesions in association with HDL particles, which can be retained by vascular proteoglycans if they contain positively charged apolipoproteins such as apoE (181, 182) or SAA (102). Like SAA, apoJ can be synthesized by vascular cells, especially arterial smooth muscle cells and foam cells (180). It also is released during the platelet aggregation (183) that occurs during thrombosis and plaque rupture.

Predictor of clinical cardiovascular events. Circulating levels of apoJ increase with aging, in inflammatory states, and in diabetes (184, 185), suggesting that this apolipoprotein may be a potential marker for atherosclerosis in humans. Two studies, however, have failed to find a significant association between plasma apoJ levels and risk for coronary events (186, 187). Thus, it appears unlikely that apoJ is a strong independent predictor of cardiovascular disease.

Atherogenic effects. In animals, apoJ levels increase in situations in which PON1 levels decrease. For example, the apoJ/PON1 ratio is increased by feeding mice an atherogenic diet, by injecting mildly oxidized LDL into mice that are susceptible to atherosclerosis, or by inducing inflammation in rabbits (161). Exposing hepatocytes to mildly oxidized LDL also promotes apoJ expression and PON1 suppression in vitro (161). In a small clinical study, the apoJ/PON1 ratio in patients with coronary artery disease predicted whether HDL would protect LDL from becoming oxidized and inducing monocyte adherence and chemotaxis in vitro (161). These results suggest that apoJ may have a deleterious effect on the antioxidation activity of PON1, although the latter has recently been called into question (178).

These human and animal model studies have not yet established a role for apoJ in either facilitating or protecting against human atherosclerosis. Studies using mice with altered apoJ expression would provide a powerful tool for determining the influence of this protein on atherogenesis.

ApoA-I

Although apoA-I, HDL's major protein, is not widely regarded as an inflammatory molecule, apoA-I levels clearly decrease during the acute inflammatory response in rabbits (188), mice (135), and humans (189). HDL is one of the major blood components that bind to bacterial LPS (190), and high HDL levels protect animals from LPS-induced septic shock (191). Studies suggest that HDL also has potent anti-inflammatory and antioxidant properties (reviewed in 166, 170), although the mechanisms are incompletely understood.

Predictor of clinical cardiovascular events. Numerous population studies have demonstrated an inverse relationship between plasma HDL levels and cardiovascular disease risk, establishing low HDL levels as a strong independent marker for atherosclerosis (192–194). Both the hepatic production rate and peripheral catabolism of apoA-I can influence plasma levels of HDL, and it is unclear to what extent these two different mechanisms contribute to low HDL levels during inflammation. It is noteworthy, however, that a low HDL level is one of the features of the metabolic syndrome (195), a condition strongly associated with increased levels of CRP and an increased risk of cardiovascular disease. The acute-phase reactant, SAA, can displace apoA-I from HDL in vitro (95). Moreover, HDL is remodeled to a considerable extent during inflammation (96). Such compositional changes are likely to be associated with altered functional properties. Therefore, it is likely that many atherogenic inflammatory states are associated with low plasma HDL and apoA-I levels and with altered HDL composition.

In addition to its plasma concentrations, apoA-I may be a marker for atherosclerosis when it is oxidized. Chlorinated HDL and nitrated HDL appear in human atherosclerotic lesions (196–199), and in vitro experiments indicate that these abnormal forms of the lipoprotein arise when apoA-I is oxidized by myeloperoxidase (200), a heme enzyme produced by macrophages. Moreover, tandem mass spectrometric analysis identified myeloperoxidase as a component of lesion HDL (196), suggesting that the enzyme and lipoprotein interact in the artery wall. Protein chlorination and nitration were impaired in myeloperoxidase-deficient mice (201, 202), strongly implicating myeloperoxidase in generating chlorinating and nitrating intermediates in vivo. 3-Chlorotyrosine and 3-nitrotyrosine were also detected in circulating HDL, and the levels of these oxidized amino acids were increased in HDL isolated from the blood of humans with established coronary artery disease (196–198). These observations raise the possibility that circulating levels of chlorinated and nitrated HDL are novel markers for clinically significant atherosclerosis.

Atheroprotective effects. Many lines of evidence indicate that HDL protects the artery wall from atherosclerosis. In one important pathway, apoA-I removes cellular cholesterol and phospholipids by an active transport process mediated by ABCA1 (203–205). In vivo, ABCA1 is critical for removing cholesterol from macrophages, and lipid-laden macrophages are the cellular hallmark of atherosclerotic lesions. HDL particles are also capable of clearing excess cholesterol from macrophages through their interaction with other cell surface proteins, such as scavenger recep-

tor B1 and ABCG1. The cardioprotective effects of HDL may occur by other mechanisms, including inhibiting LDL oxidation (172), reducing LDL lipid hydroperoxides (143) and oxidized phospholipids (170), and transporting oxidized lipids to the liver for elimination in the bile (206). HDL can also block the expression of adhesion molecules on endothelial cells (207, 208), thus blocking the recruitment of monocytes into the artery wall. HDL also can neutralize CRP's proinflammatory activity (209). It is likely that both lipids and proteins in HDL mediate these diverse atheroprotective effects.

The atheroprotective effects of HDL may be uniquely targeted for damage by inflammatory pathways. As discussed above, remodeling of HDL by SAA could convert it into an atherogenic particle. HDL or apoA-I exposed to HOCl or myeloperoxidase (the only enzyme known to generate HOCl in humans) loses its ability to remove cholesterol from cultured cells by the ABCA1 pathway (196). Impaired ABCA1 activity strongly associates with apoA-I chlorination but not nitration (196, 197, 210). It is noteworthy that bacterial products and cytokines are potent stimulants for oxidant generation by macrophages and other phagocytic white blood cells. It is possible, therefore, that HDL is targeted for oxidation in chronic inflammation and that HDL chlorination promotes atherosclerosis by inhibiting ABCA1-dependent cholesterol efflux from cells of the artery wall.

Taken together, these studies indicate that HDL could have direct anti-inflammatory effects that protect the artery wall from atherogenesis and that multiple inflammatory processes that alter HDL or apoA-I could play a direct role in atherogenesis, either by generating atherogenic particles or by impairing cholesterol efflux from arterial macrophages. It will be important to confirm these observations in larger clinical studies and with additional animal models.

REGULATION OF HEPATIC PRODUCTION OF PROTEINS DURING INFLAMMATION

Levels of CRP and SAA tend to increase in parallel during the acute inflammatory response, in chronic inflammatory conditions, and in conditions associated with an increased risk of cardiovascular disease (13, 75, 80–83). Therefore, it is not surprising that their synthesis and secretion by the liver are regulated in a similar manner. Both CRP and the inflammatory forms of SAA are secreted by the liver primarily in response to inflammatory stimuli such as interleukin-6, tumor necrosis factor-α, and interleukin-1 (12, 75). All of these cytokines are produced by macrophages (reviewed in 75). However, other cell types, particularly adipocytes (211, 212), can also synthesize and release these proteins. Indeed, it has been suggested that cytokines derived from adipose tissue are the major source of the increased levels of inflammatory markers seen in obesity (29, 213, 214). The recent suggestion that macrophages accumulate in adipose tissue of obese mice and humans (211, 212) may change our understanding of the role of these cells in generating cytokines and other inflammatory mediators in adipose tissue. The 3T3 adipocyte cell line also can secrete SAA directly (215). Moreover, macrophages present in adipose tissue from obese subjects may be a direct source of cytokines that induce the hepatic expression of molecules such as CRP and SAA or may secrete proteins such as SAA directly (75). These observations suggest an additional potential mechanism linking obesity, inflammation, and atherosclerosis.

Many other inflammatory stimuli prompt macrophages and other cells to generate cytokines, which in turn could result in the overproduction in the liver of acute-phase proteins such as CRP and SAA. One potential mechanism involves chronic infection with bacterial or viral pathogens, including *Chlamydia pneumoniae* (216–218), herpes simplex virus (217, 219), cytomegalovirus (217, 218), and *Helicobacter pylori* (218). However, epidemiological studies and intervention studies with antibiotics have yielded conflicting results regarding the role of chronic infection in atherosclerosis. However, cytokine levels are also increased in chronic inflammatory conditions such as periodontal disease, rheumatoid arthritis, and systemic lupus erythematosus. Under these conditions, cytokines might also induce increases of inflammatory proteins that promote atherosclerotic vascular disease.

CRP and SAA levels are increased in patients with the metabolic syndrome (16, 17, 24, 41). Their production in the liver could be stimulated by cytokines from the increased visceral adipose tissue that characterizes this disorder. As noted above, macrophages in adipose tissue may be a source of the cytokines that stimulate the hepatic production of inflammatory proteins or may even secrete some of these proteins directly. Moreover, adipocytes themselves can be the source of cytokines (211) and inflammatory molecules (215). Insulin resistance has also been proposed to regulate the levels of inflammatory molecules, although the mechanism is unclear. However, it is difficult to separate the role of insulin resistance from that of obesity, because the two are clearly interdependent. Nonetheless, subjects whose insulin resistance decreased when they lost weight had decreased levels of circulating CRP and SAA, whereas there was little change in these acute-phase proteins in subjects who lost weight but did not increase their insulin sensitivity (18). These observations raise the question of whether insulin resistance may regulate the circulating levels of inflammatory molecules independently of their association with obesity.

A wide variety of enzymes involved in hepatic lipid metabolism are regulated during acute inflammation. Indeed, a decreased level of blood cholesterol, together with variable changes in triglyceride levels, is one of the metabolic hallmarks of acute inflammation (220). Array analyses of mRNAs isolated from mice injected with LPS demonstrated coordinated downregulation of enzymes involved in cholesterol synthesis, triglyceride synthesis, and mitochondrial fatty acid oxidation (221). These observations indicate that acute inflammation affects levels of proatherogenic and antiatherogenic lipoproteins, raising the possibility that chronic inflammation also alters levels of these lipoproteins.

In humans, apoA-I and HDL levels are also reduced during acute inflammation (189) as well as in conditions associated with chronic inflammation, such as obesity and the metabolic syndrome (222–224). HDL levels are also low in patients suffering from type 2 diabetes, a major risk factor for accelerated vascular disease. LPS and the inflammatory cytokines interleukin-1, tumor necrosis factor-α, and interleukin-6 inhibit apoA-I expression by the liver (225, 226). Moreover, these cytokines resulted in reciprocal regulation of the expression of apoA-I and SAA in murine hepatocytes, such that apoA-I expression was inhibited and SAA expression was coordinately increased (226). These effects appear to be regulated by nuclear factor κB, which inhibits the peroxisome proliferator-activated receptor α (225, 226). The net effect of inflammation may be to reduce HDL's ability to participate in reverse cholesterol transport and to perform its other atheroprotective functions.

CONCLUSIONS

There is mounting evidence that the chronic increase of proteins that participate in the acute inflammatory response may not only predict the onset of clinical cardiovascular events but may actually play a causal role in mediating atherosclerotic disease. The best studied of these is CRP. Increased levels of CRP appear to be an independent risk factor for cardiovascular disease, although the absolute magnitude of this risk remains to be established. Basic studies have identified a number of potential roles for CRP in atherogenesis, but additional studies need to be undertaken to determine whether CRP directly promotes vascular disease. SAA levels also appear to predict the risk of cardiovascular disease in humans, and recent animal studies support the proposal that this acute-phase protein plays a role in atherogenesis. It will be important to further investigate its potential role as a marker or mediator of atherosclerotic vascular disease. Less is known about the roles of $sPLA_2$, PAF-AH, and apoJ in atherogenesis, although evidence is accruing that $sPLA_2$ and PAF-AH also might play roles in the pathogenesis of atherosclerosis.

Negative acute-phase proteins such as apoA-I and PON1 have received less attention as markers of inflammation than have positive acute-phase proteins such as CRP and SAA. ApoA-I, the major apolipoprotein of HDL, decreases during both acute and chronic inflammation. It is well established that low levels of HDL are a major risk factor for accelerated atherosclerosis. Recent studies strongly suggest that levels of chlorinated and nitrated HDL are increased in patients with established cardiovascular disease. In vitro studies suggest that the ability of chlorinated apoA-I to promote cholesterol efflux by the ABCA1 pathway is markedly impaired. In larger clinical studies, it will be of great interest to examine the potential of oxidized HDL to serve as a marker for cardiovascular disease. PON1, another HDL-associated protein, also decreases during inflammation. It is clearly atheroprotective in animal models of hypercholesterolemia, and controversy over its utility as a marker of human atherosclerosis may reflect the fact that enzyme activity rather than blood level (or genotype) is the major determinant of cardiovascular risk. The underlying mechanism may involve the degradation of oxidized phospholipids by PON1. However, recent studies have raised questions regarding this proposal. It will be important to clarify the underlying mechanism whereby PON1 protects animals from atherosclerosis.

Thus, many proteins that participate in the acute-phase response are implicated in the diagnosis and pathogenesis of clinically significant atherosclerotic vascular disease. By better understanding the pathophysiology of these proteins, we will begin to identify the pathways that promote atherosclerosis. These findings should provide new clinical tools for identifying patients at risk for cardiovascular disease and identify therapies that act by mechanisms that differ from those of traditional lipid-lowering therapies.

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