Review

The Many Faces of Cholesterol: How Modifications in LDL and HDL Alter Their Potential to Promote or Prevent Atherosclerosis

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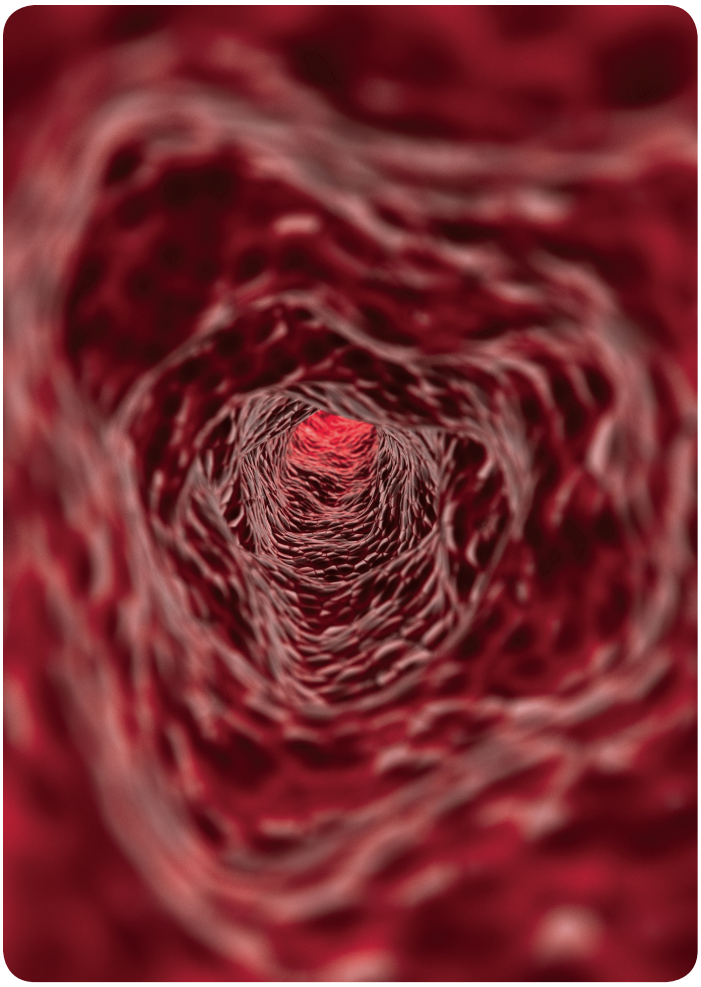

The mechanisms for processing and transporting cholesterol within the cell are intricate. Lipoproteins that carry cholesterol exist in multiple forms, including low density lipoprotein (LDL) and high density lipoprotein (HDL). LDL is required to transport cholesterol from the liver to tissues, and HDL is involved in the reverse transport of cholesterol from the tissues back to the liver. These two processes work together to regulate the cholesterol levels and ensure that this molecule is available for cellular use. This paper will review the notable modifications to LDL and HDL that are important for their homeostasis and discuss their essential relationship to the development of atherosclerotic related diseases.

INTRODUCTION

Most individuals who consult their physicians for conditions arising from atherosclerosis have probably heard about the "good" and "bad" cholesterol. The traditional school of thought identifies HDL as the beneficial form of cholesterol, with levels inversely related to risk of atherosclerotic diseases. LDL is the harmful form of cholesterol, and its levels are directly related to the risk of developing atherosclerotic disease. However, an accumulating body of evidence indicates that high LDL and low HDL are not necessarily good predictors of atherosclerosis. While high LDL and low HDL levels in plasma are associated epidemiologically with increased probability of atherosclerosis, an individual patient's risk cannot be reliably determined based on the levels of circulating lipoprotein. Only 40% of patients with coronary artery disease have high LDL values, and in the original Framingham study, 40% of men and 43% of women with coronary artery disease had higher than normal HDL values (Gordon et al., 1977). Recent research suggests both LDL and HDL undergo biochemical modification and provides an explanation for the discrepancy.

WHY IS MODIFIED LDL HARMFUL?

Prior to modification, LDL binds to the LDL receptor on hepatocytes and various other cell types. This binding induces receptor-mediated endocytosis of LDL, and the cholesterol is removed from the LDL for use in the diverse metabolic processes required by healthy functioning cells. However, modified LDL is not recognized by the LDL receptor and is instead taken up by scavenger receptors on macrophages. These scavenger receptors normally take up elements that are harmful to the organism and break them down, but the uptake of modified LDL by macrophages does not lead to its degradation. Instead, it accumulates in the macrophages in the form of cholesteryl esters and converts them to foam cells, which amass in the sub-endothelial space, contributing to the formation of atherosclerotic plaques (Goldstein et al., 1979).

HOW IS LDL MODIFIED TO BECOME HARMFUL?

Several different pathways and processes can lead to the harmful modification of LDL. One significant detrimental alteration is the addition of reactive oxygen species to an LDL molecule, an oxidative process designated "seeding" (Figure 1). Interestingly, endothelial cells of the artery walls often mediate the seeding of LDL. In tissue culture experiments, endothelial cells are capable of forming microenvironments that attract these reactive oxygen species and exclude antioxidants (Navab et al., 1991; Navab et al., 1991). This intriguing observation may explain why antioxidants such as tocopherol or vitamin E have not proven beneficial in decreasing atherogenesis. These microenvironments also trap LDL and enable the addition of the reactive oxygen species to it. Modified LDL stimulates the endothelial cells to release monocyte chemoattractant protein 1 (MCP-1). The monocyte colony stimulating factor (MCSF) attracts monocytes to these environments, where they take up the oxidized LDL and develop into foam cells (Berliner et al., 1990; Cushing et al., 1990; Rajavashisth et al., 1990; Cushing et al., 1992).

WHAT DRIVES LDL TO BECOME HARMFUL?

Evolutionarily speaking, what drives LDL oxidation? In isolated mice, IgM antibodies recognize the oxidized phospholipids that are found on modified LDL molecules and in atherosclerotic lesions (Hörkkö et al., 1999). The antigen-binding domain of these antibodies is similar to that of naturally occurring antibodies in humans known as T15 antiphospholipid antibodies. T15 antibodies confer resistance to virulent strains of Streptococcus pneuomiae, an organism that can cause sepsis. Sepsis is particularly threatening to fetuses and newborns and is a major cause of mortality (Shaw et al., 2000). Therefore, hypercholesterolemia in mothers may evolutionarly be favored to provide potential protection for children against sepsis. Since, the oxidation of LDL stimulates the production of T15 antibodies and protects against bacterial

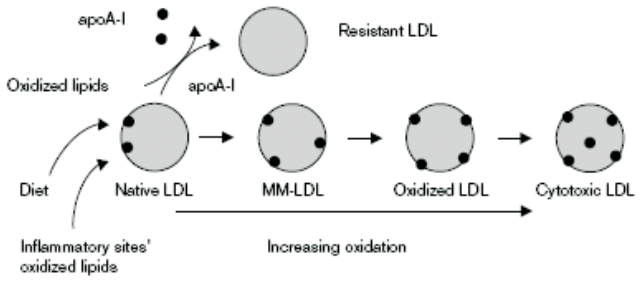

Figure 1. Formation of oxidized LDL. LDL can receive lipid oxidation products from diet, from cell membranes, or from inflammatory sites in the body, potentially resulting in the formation of oxidized LDL with various degrees of oxidation and bioactivity. Apolipoprotein (apo)A-I can remove these oxidized lipids from LDL, rendering LDL highly resistant to oxidation. MM-LDL stands for mildly modified/oxidized LDL.

infections such as Streptococcus pneuomiae, it may impart an evolutionary advantage.

WHAT ARE THE MECHANISMS FOR LDL MODIFICATION?

Of the numerous pathways that contribute to lipid formation, one of the most notable is the lipoxygenase pathway. Fogelman and colleagues have shown that this pathway metabolizes arachidonic acid to produce malondialdehyde (Figure 2). Malondialdehyde reacts with lysine residues on apolipoprotein B, leading to its oxidative modification (Fogelman et al., 1980). There is significant evidence substantiating the importance of this pathway in inducing atherogenesis. Overexpression of the 12/15-lipoxygenase gene in endothelial cells of mice led to higher levels of atherosclerosis (Harats et al., 2000). Conversely, deletion of this gene decreased atherogenesis in mice that had knockout mutations for the LDL receptor and were therefore more susceptible to hypercholesterolemia than the wild type mice (George et al., 2001). Furthermore, transgenic mice that were engineered to express the lipoxygenase gene at slightly higher levels than normal had a 2.5 times greater risk of aortic fatty streak formation (Reilly et al., 2004). In mice that had knockout mutations in the LDL receptor and were also deficient in apo-B editing catalytic polypeptide-1 enzyme, deletion of the 12/15-lipoxygenase gene decreased atherosclerosis significantly (Zhao et al., 2002). Finally, pharmacological inhibition of 12/15-lipoxygenease in rabbits led to a significant reduction in atherosclerosis. The lipoxygenase pathway generates phospholipids that are highly oxidized and the activity of this gene has been implicated in the formation of atherosclerotic plaques. This suggests that this enzyme is capable of generating oxidized phospholipids involved in atherosclerosis. In one conflicting experiment, rabbits were engineered to overexpress lipoxygenase but showed decreased levels of atherosclerosis (Shen et al., 1996). However, the evidence favoring the notion that lipoxygenase can induce atherosclerosis heavily outweighs the evidence refuting it.

Another enzyme responsible for the generation of oxidized phospholipids is myeloperoxidase. The phospholipids generated by this enzyme have proinflammatory properties (Poliakov et al., 2003; Carr et al., 2000; Zhang et al., 2002; Brennan et al., 2003) and may drive the innate immune response to produce the antiphospholipid antibodies mentioned above. The products of this enzymatic pathway have been found in atherosclerotic lesions (Thukkani et al., 2003), further proving that

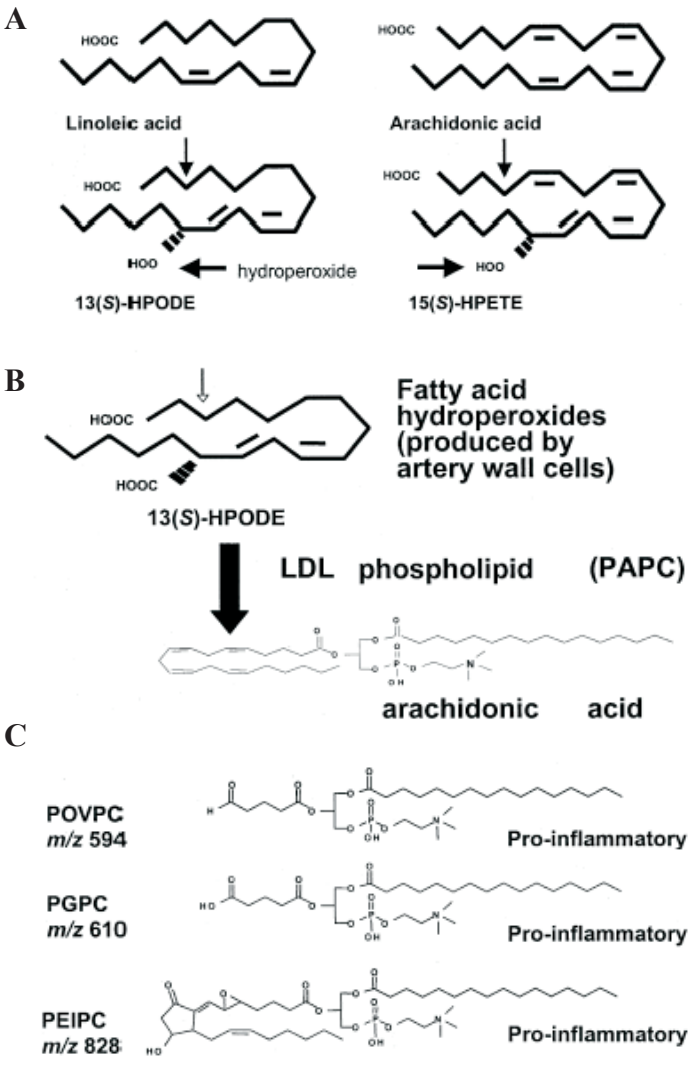

Figure 2. (A) The formation of the fatty acid hydroperoxides 13-hydroperoxyoctadecadienoic acid (HPODE) and 15-hydroperoxyeicosatetraenoic acid (HPETE). **(B)** The action of HPODE on an LDL-derived phospholipid, 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (PAPC). **(C)** Three of the proinflammatory oxidized phospholipids in minimally modified LDL. POVPC, 1-palmitoyl-2-oxovaleryl-sn-glycero-3 phosphorylcholine; PGPC, 1-palmitoyl-2-glutaryl-sn-glycero-3-phosphorylcholine; PEIPC, 1-palmitoyl-2-(5,6-epoxyisoprostane E2)-sn-glycero-3-phosphorylcholine.

enzymes capable of producing proinflammatory, oxidized phospholipids also contribute to the formation of fatty streaks (Figure 3).

Additionally, the enzyme NADPH oxidase may weaken a cell's reducing ability and lead to increased formation of oxidized phospholipids (Sorescu et al., 2001). On the other hand, paraxonase can destroy proinflammatory phospholipids and prevent their formation. Paraxonase knockout mice, for example, have greater incidence of atherosclerosis (Shih et al., 2001; Shih et al., 2000).

Additionally, in epidemiological studies, polymorphisms in the paraxonase gene have been associated with a higher risk of atherosclerosis (Shih et al., 2002).

WHAT MAKES HDL GOOD CHOLESTROL?

A major responsibility of HDL is to transport cholesterol from the periphery to the liver, which excretes excess cholesterol (Zhang et al., 2003; Remaley et al., 2003). HDL also contains enzymes such as paraoxonase (Shih et al., 1998), platelet activating factor, acetylhydrolase (Watson et al., 1995), and lecithin-cholesterol acyltransferase (Forte et al., 2002). These enzymes prevent the formation of or destroy oxidized phospholipids. Additionally, there is accumulating evidence that HDL can reverse LDL oxidation by removing the oxidized phospholipids that make LDL harmful and lead to atherogenesis. Navab and colleagues have shown that in artery cell cultures, HDL, apoA-1, and ApoA-1 mimetic peptides prevented LDL oxidation (Navab et al, 2000). Specifically, an important component of oxidized LDL, lipid hydroperoxides, can be produced via the lipoxygenase pathway. These lipid hydroperoxide levels were reduced by up to 75% if isolated LDL was incubated in the presence of HDL (Navab et al, 2000). Additionally, this HDL-treated LDL, when added to human artery wall cultures, was unable to stimulate monocyte adhesion or monocyte chemotactic activity. Stocker and colleagues demonstrated that these oxidized lipid hydroperoxides are actually carried to the liver by HDL (Bowry et al., 1992). The levels of such oxidized lipids were significantly lower in HDL from mice with mutations that made them resistant to atherosclerosis. This data not only provides evidence for the ability of HDL to remove oxidized lipids from LDL, but it further substantiates the notion that oxidized lipids are responsible for the inflammatory response in atherosclerosis: their removal prevented the monocyte-mediated inflammatory response (Figure 4).

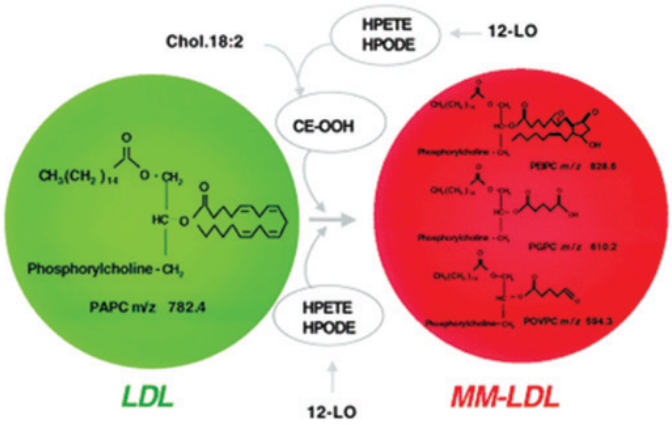

Figure 3. Formation of LDL-derived oxidized phospholipids. LDL contains PAPC that has a mass to ion ratio (m/z) of 782.4. Arachidonic acid is shown in the diagram at the sn-2 position of PAPC. The 12-LO pathway generates HPETE and HPODE, which directly associate with LDL or interact with cholesteryl linoleate (Chol.18:2) to form cholesteryl linoleate hydroperoxide (CE-OOH), which then associates with LDL. Although the diagram depicts CE-OOH as being formed and then associating with LDL, the CE-OOH could also be formed within LDL after HPODE and HPETE are associated with LDL. When a critical concentration of HPETE, HPODE, and CE-OOH is reached in LDL, PAPC is oxidized, forming the pro-inflammatory oxidized phospholipids found in mildly (MM) oxidized LDL. The 3 oxidized phospholipids depicted in MM-LDL are POVPC (m/z 594.3), PGPC (m/z 610.2), and PEIPC (m/z 828.6). See Figure 2 for explanation of abbreviations.

HOW DOES HDL GO BAD?

Given the above data that suggests a protective role for HDL, it could be predicted that HDL and LDL levels would be indicative of atherosclerotic risk. Surprisingly, that is not the case; a significant fraction of individuals who experience coronary artery disease have LDL and HDL levels within the healthy range. One possible explanation is that HDL can go bad. Inflammatory events are associated with acute phase response, which involves an observable elevation in certain acute inflammatory markers. This acute phase response is able to convert protective HDL into inflammatory HDL (Van Lenten et al., 1995) (Figure 5). Inflammatory HDL is unable to exert its protective effects and actually triggers moncoyte chemotactic activity and monocyte adhesion (Ansell et al., 2003). The acute phase response causes a diminished activity of paraoxonase and platelet-activated factor acetylhydrolase associated with HDL and reduces their ability to degrade oxidized phospholipids (Van Lenten et al., 1995). These acute phase responses are temporary. As they subside, HDL reverses its function and becomes protective. However, the acute phase response can become chronic. When it does, HDL continually exerts inflammatory effects and can induce atherosclerosis. How an acute phase response becomes chronic is not fully understood and is beyond the scope of this paper. However, it is important to note that this chronic response can occur in the absence of infection (Ridker, 2002). In addition to these data, there is evidence that if an acute phase response is triggered in hamsters by lipopolysaccharide and the HDL is isolated, this HDL is less capable of contributing to cholesterol efflux from cells (Khovidhunkit et al., 2001).

Interestingly, the ability of HMG-CoA reductase inhibitors to prevent coronary disease does not solely rely on their potential to decrease cholesterol synthesis. These agents may actually prevent atherogenesis by reversing

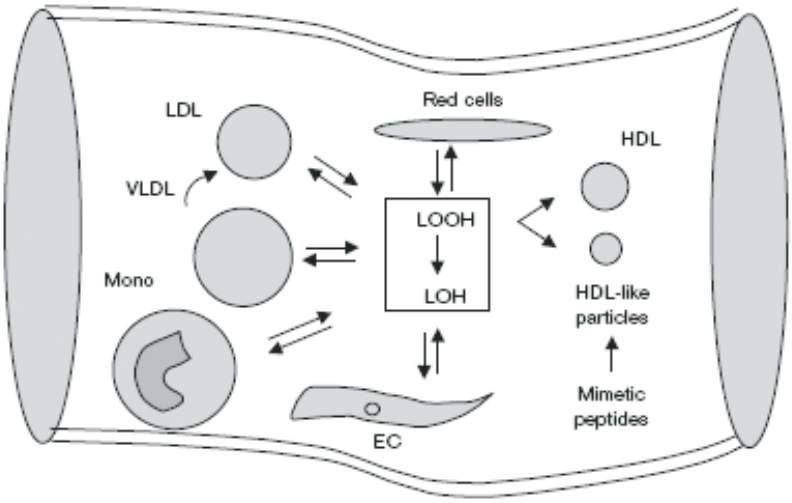

Figure 4. Hypothetical model for the removal of lipid oxidation products by HDL or apoA-I mimetic peptides in the circulation. Lipid oxidation products generated in cells, including endothelial cells (EC), monocytes (Mono) or red cells, or the oxidized lipids associated with VLDL or LDL, may be in equilibrium with those in plasma, and can be picked up by HDL. ApoA-I mimetic peptides that form HDL-like particles appear to act similarly, accepting the oxidized lipids and eliminating them from the circulation. LOH, lipid hydroxides; LOOH, lipid hydroperoxides.

inflammatory HDL's pro-atherosclerotic properties. Under normal conditions, oxidized LDL triggers a baseline level of monocyte chemotactic activity. In the presence of normal HDL, the chemotactic activity of monocytes decreases below the baseline. In the presence of inflammatory HDL, this monocyte chemotactic activity rises above the baseline. Ansell and colleagues studied a group of patients with stable coronary heart disease before and after six weeks of Simvastatin therapy. They found that these patients' HDL was capable of inducing greater than baseline levels of monocyte chemotactic activity before and after therapy. In fact, the HDL's ability to induce this activity decreased after six weeks of treatment with Simvastatin (Ansell et al., 2003).

CONCLUSION

The evidence presented demonstrates that both LDL and HDL undergo specific modifications and outlines the mechanisms responsible for these modifications. The modifications discussed are biochemical in nature, including the oxidation of LDL phospholipids or reduction of the enzymatic activity associated with HDL. However, inflammation and immune function are underlying contributors. In the case of HDL, inflammation is responsible for the decreased activity of antioxidative enzymes; in the case of LDL, immune resistance against sepsis is the driving force for lipid oxidation. Moreover, oxidized LDL serves as a stimulus for monocyte activity, which is an important contributor to atherogenesis. How an acute phase response or chronic inflammation lead to changes in HDL and render it harmful is an interesting question that remains to be elucidated.

FUTURE PERSPECTIVES AND SUMMARY

Understanding the relationship between inflammation and HDL function will be an area of active research in the field of atherosclerosis within the coming years. A more complete understanding could lead to the development of therapeutic approaches involving anti-inflammatory agents capable of preventing the acute phase response to prevent or treat atherosclerosis. Given the strong body of evidence that demonstrates the important role of HDL in preventing lipid oxidation and the downstream monocyte-mediated inflammatory response, HDL molecules or peptides containing domains of HDL that are beneficial may serve as therapeutic agents that can slow atherosclerotic events and augment or even replace our current therapeutic modalities.

Unmodified LDL is taken up by hepatocytes via receptor-mediated endocytosis, whereas oxidized LDL is endocytosed by macrophages. The accumulation of oxidized LDL in the form of cholesteryl esters within the macrophages converts them to foam cells. Foam cells enter the sub-endothelial space and contribute to the formation of atherosclerotic plaques.

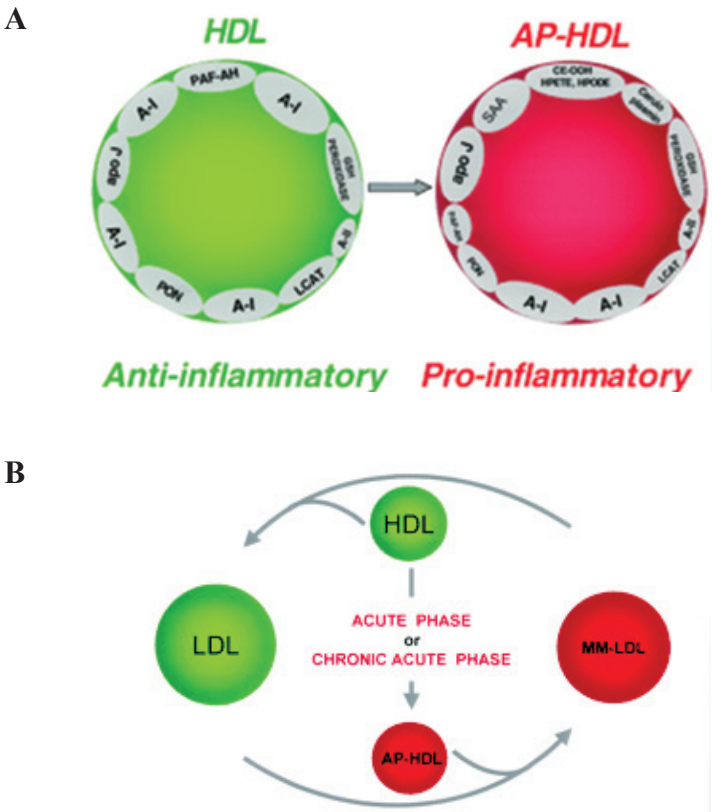

Figure 5. The acute-phase (AP) reaction favors the formation of proinflammatory HDL and mildly oxidized. (A) In the basal state, HDL contains apoA-I and apoJ as well as 4 enzymes, PON, PAF-AH, lecithin:cholesterol acyltransferase (LCAT), and plasma reduced glutathione selenoperoxidase (GSH peroxidase) that can prevent the formation of or inactivate the inflammatory LDL-derived oxidized phospholipids found in mildly oxidized LDL. As a result, in the basal state, HDL may be considered anti-inflammatory. During the acute-phase reaction, A-I may be displaced by the pro-oxidant acute-phase reactant SAA. Another pro-oxidant acute-phase reactant, ceruloplasmin, associates with HDL, as does the anti-oxidant acute phase reactant apoJ. PON, PAF-AH, and LCAT decrease in HDL during the acute-phase reaction, and the lipid hydroperoxides HPETE, HPODE, and cholesteryl linoleate hydroperoxide (CE-OOH) increase in HDL. A-II and GSH peroxidase are shown as unchanged during the acute-phase reaction although there are no data on the latter. The net effect of the changes in HDL during the acute-phase reaction is the production of pro-oxidant, proinflammatory HDL particles (AP-HDL). **(B)** In the basal state, HDL prevents the formation of and inactivates the LDL-derived oxidized phospholipids shown in Figure 1. As a result, HDL favors the maintenance of noninflammatory LDL and the conversion of the proinflammatory, mildly oxidized LDL (MM-LDL) to a noninflammatory state. In contrast, during an acute-phase reaction, AP-HDL favors the conversion of LDL to the proinflammatory MM-LDL. As discussed in the text, the acute-phase reaction can be truly acute, as in the case of a viral infection, or it may become chronic, as in mice that are genetically susceptible to diet-induced atherosclerosis when they are fed an atherogenic diet or in some patients with normal blood lipids and atherosclerosis.

LDL modification involves the addition of reactive oxygen species to the LDL molecule, which in turn oxidizes the LDL. This event is thought to occur within microenvironments in the subendothelial space, which is impermeable to antioxidants. In humans, T15 antibodies form against the phospholipids portion of oxidized LDL molecules. The antigen binding sites of these antibodies also binds to pneumococcal antigens. Therefore, LDL modification may have an evolutionary advantage, because it stimulates the production of antibodies that confer immunity against pneumococcal sepsis.

Based on genetic knockout studies in animals, the lipoxygenase and myeloperoxidase pathways are implicated in the formation of oxidized LDL. Conversely, protective enzymes such as paroxonase can destroy phospholipids that have a proinflammatory role and prevent atherosclerosis.

HDL's protective ability is partially related to the enzyme activity associated with it. HDL contains paraoxonase, platelet activating factor, acetylhydrolase, and lecithin:cholesterol acyltransferase, which prevent the formation of, or destroy, oxidized phospholipids.

When inflammation occurs, the acute phase response leads to the conversion of HDL into a proinflammatory form. If inflammation persists, the acute phase response becomes chronic and leads to the persistence of proinflammatory HDL. This change is central to the process of atherogenesis. HMG-CoA reductase inhibitors are able to reduce the proinflammatory properties of HDL in the setting of chronic

inflammation.

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