Lipoprotein Effects on the Vessel Wall

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Accumulation of lipids within the arterial wall is a distinguishing characteristic of the atherosclerotic lesion and is seen in virtually all stages of plaque development. This process is directly correlated with the serum level of some lipids, especially cholesterol, LDL, and other lipoprotein particles. In contrast, an increased serum level of HDL is protective against plaque formation. Evidence has steadily accumulated showing that HDL acts as a “sink” for cholesterol, presumably removing it from tissue. In any discussion of trafficking of materials between blood and the arterial wall, the endothelium must be considered pivotal because of its critical location at the junction between blood and blood vessel. Penetration of lipoproteins into the arterial wall has been shown both quantitatively and qualitatively in experimental animal models. Areas of lipid accumulation appear at localized sites along the arterial lumen in these animal models, consistent with the focal nature of plaque development in humans. The mechanism for the predilection of some localized areas to accumulate plaque has been under debate for a considerable time and is likely multifactorial. In some instances, this process seems related to a focal transient loosening of the tight association between adjoining endothelial cells (ECs). In these areas, there may be easy access to underlying vascular tissue. However, because such gaps appear only occasionally, it is likely that some ECs are actively involved in the accumulation of lipids. These topics are at the center of the study by Rutledge et al described in this issue of Circulation Research.

In the present study, VLDL was fluorescently labeled and perfused into rat arteries. Attachment of VLDL at the arterial surface was modest, but with the addition of lipoprotein lipase and subsequent VLDL lipolysis, there was accumulation of lipids in the arterial wall in focal areas, or “lakes.” After addition of HDL, the lipid-lake accumulation was ameliorated. It seems that HDL acts by both interfering with endothelial permeability and increasing lipid removal rate from the arterial wall. The implication of the former observation is that the permeability of endothelium can be modified by its milieu, and of the latter is that HDL is actively involved in the removal of lipids from tissue. The study provides ex vivo evidence of the ability of HDL to remove lipids from a cellular deposition site and confirms in vitro reports gathered from cell culture studies. The study is particularly important because the site modified by HDL is the arterial wall.

The hypothesis that atherosclerotic progression can be reduced by either improving the barrier function of the arterial wall or modifying blood lipoprotein concentration is the basis of a great deal of current preventative research. Risk factors for atherosclerosis, such as hypertension, smoking, mechanical injury, dense LDL, and genetic predisposition, may affect the barrier function of the arterial wall, predisposing to atherosclerosis. The study by Rutledge et al focuses on the modifications of VLDL by lipoprotein lipase and HDL and their influence on the arterial wall and endothelial function.

The concept that alteration in EC function may play a pivotal role in the pathobiology of atherogenesis has been the subject of numerous investigations. Consequently, many of the responses of these cells to stimuli, both physiological and nonphysiological, have begun to provide a mechanistic motif for understanding intracellular EC reaction pathways. With the current hypothesis of atherosclerotic plaque formation centering on the roles of circulating lipoproteins, an understanding of how these lipoproteins affect EC function has begun to emerge. Such studies may not only convey insight into the pathogenesis of plaque formation but also provide important therapeutic implications.

Triglyceride-rich lipoproteins, including VLDL, chylomicrons, and their remnants, are acknowledged as cardiovascular disease risk factors, and studies have implicated VLDL pathogenically in atherosclerosis. For example, triglyceride-rich remnants have been shown to impair vasorelaxation, and plasma triglyceride levels show a direct correlation with plasminogen activator inhibitor (PAI-1) levels. Incubation of ECs with VLDL induces the synthesis of PAI-1. Because elevated PAI-1 levels may interfere with fibrinolysis and therefore predispose to excessive thrombosis, high-serum VLDL levels may play a role in the development of thrombotic disorders and cardiovascular disease. Hence, investigations have been carried out to understand the mechanism of this effect. Studies using HepG2 cells have investigated the intracellular signaling pathway induced by VLDL exposure. VLDL seems to induce protein kinase C activity, resulting in activation of mitogen-activated protein kinase. Studies carried out in ECs indicate that VLDL can also induce nuclear factor-κB (NF-κB), a transcription factor that has been shown to play an important role in the phenotypic modulation of ECs to a proinflammatory condition. When rats were infused with VLDL, there ensued an increase in expression of RelA, a component of NF-κB, and an induction of cell adhesion molecules in the arterial endothelium. Thus, evidence is accumulating that VLDL directly affects the
endothelium, which may help explain why VLDL is proatherogenic.

HDL seems to protect against plaque formation. This observation has been documented in both experimental animal studies and human epidemiological investigations. Animal studies describe protection against the development of lipid deposits when HDL is abundant in the plasma. Rutledge et al.2 provide an additional demonstration of the effectiveness of HDL in protecting against plaque formation by showing that HDL can remove lipid buildup from the vessel. Cell culture studies have examined the salutary effect of this lipoprotein on the endothelium. To understand the potential cellular effect of HDL as a vascular protective agent, ECs were incubated with HDL during exposure to a potent inducer of EC dysfunction, tumor necrosis factor-α (TNF-α).7 HDL inhibited TNF-α-induced expression of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular cell adhesion molecule-1 (ICAM-1). TNF-α is a well-recognized activator of ECs and seems to have its primary effect in upregulating adhesion molecule expression by induction of NF-κB. However, the ability of HDL to moderate the TNF-α effect on ECs may be caused by enhancement of Cox-2 expression. By inducing this enzyme, ECs exposed to HDL produce an abundance of prostacyclin, which is recognized for its ability to inhibit leukocyte function. Thus, HDL can modulate a potent activator of ECs and TNF-α; and interestingly, the mechanism seems to be independent of the transcriptional regulation of NF-κB.

LDL has been shown to have a strong correlation with atherosclerotic vascular disease. How LDL is handled by the blood vessel is a major concern for understanding arterial wall plaque development. Elevated LDL levels are associated with a lack of vasorelaxation. With a rapid decrease in the serum level of LDL using apheresis, vascular reactivity in humans can be restored rapidly. The endothelial response to LDL has been examined using cell culture. The EC phenotype can be modulated by LDL, especially when the concentrations of LDL in the culture medium are similar to those identified with the development of atherosclerosis.

LDL has numerous effects on the endothelium, including effects on PAI-1, arachidonate metabolism, and induction of adhesion molecule expression. Of particular interest to the inflammatory component of plaque development is the upregulation of both ICAM-1 and VCAM-1. In examining the mechanism underlying this modulation, it has been determined that exposure of ECs to LDL causes the rapid activation of Ras. Ras activation leads to induction of the signaling cascade that activates JNK and the expression of AP-1, which in turn can upregulate ICAM-1. In contrast to VLDL-induced signaling, NF-κB seems to have little, if any, role in the induction of adhesion molecule formation by LDL. Indeed, LDL is the only physiological substance known to behave in this fashion. Recent studies have pursued this finding and indicate that most of this activation resides in the free-cholesterol component of LDL. If this is the case, it can be hypothesized that cholesterol is a biologically active molecule carried by LDL, which initiates cellular activation. One of the implications of this notion is the likelihood not only that LDL and serum cholesterol are risk factors for developing atherosclerosis, but also that lipids can act directly as atherogenic factors. Hence, our ability to comprehensively understand the varying roles of lipoproteins as they affect the arterial vasculature has major ramifications for understanding and controlling atherosclerosis.

References


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