A New Dimension in the Vasculoprotective Function of HDL
Progenitor-Mediated Endothelium Repair

Philippe Lesnik, M. John Chapman

Although the vascular endothelium is a potent antithrombotic, antioxidant, and antiinflammatory barrier, prolonged and repeated exposure to the oxidative stress and chronic inflammation which are intimately associated with cardiovascular risk factors such as hypercholesterolemia, hyperglycemia, hypertension, low shear stress, and smoking ultimately blunts these protective mechanisms. Under these conditions, the endothelium not only becomes dysfunctional, but equally may undergo apoptosis resulting in cellular detachment from the underlying intimal layer. Endothelial dysfunction is a key precocious event in the pathogenesis of atherosclerosis and critically contributes to plaque initiation and progression. Denudation of endothelium is associated with increase in proliferation of vascular smooth muscle cells, enhanced recruitment of monocytes, lipid deposition, and inflammation leading to neointima formation and increased risk of thrombosis. Indeed, thrombi can be formed on denuded endothelial plaque surfaces as well as on apoptotic endothelial cells.1

HDL and Vascular Protection
Atherosclerosis risk is inversely related to circulating levels of high-density lipoprotein-cholesterol (HDL-C). In fact, low HDL-C levels are predictive of elevated cardiovascular risk independently of low-density lipoprotein-cholesterol concentrations. In addition, patients with low HDL-C levels frequently display early-onset atherosclerosis. Based on these observations, prevention trials have been performed with agents such as nicotinic acid and fibrates, which indicate that increase in HDL-C levels may lead to reduction in cardiovascular events. Thus, HDL-C is not only a marker of risk for development of premature CAD, but also a key mediator of vascular health.

Classically, the protective functions of HDL particles have been attributed to their capacity to facilitate cholesterol efflux from peripheral tissues and notably macrophage-fom cells, and to transfer such cholesterol to the liver in the process of reverse cholesterol transport (RCT). Despite detailed knowledge of HDL particle metabolism, the cellular and molecular mechanisms by which HDL and apoAI express atheroprotection remain complex and incompletely understood. For example, the rapidity of expression of the cardioprotective effects of infused HDL particles in both animals and human subjects3,4 may not solely depend on the potential capacity of HDL to deplete cholesterol from macrophage-fom cells. Indeed, HDL may afford protection from vascular disease by exerting additional effects that include antioxidant, antiapoptotic, antithrombotic, antiinflammatory, and vasodilatory functions. HDL antioxidative properties are related to paraoxonase, to LCAT, and to lipoprotein-associated PLA2 activities, as well as to protection of HDL apolipoproteins against oxidative stress; such apolipoproteins include apoA-I, apoA-II, and apoA-IV.5 In an in vivo rabbit model of acute arterial inflammation, antiinflammatory properties of recombinant HDL containing apoAI and phospholipids have been clearly demonstrated. In this model, the antiinflammatory activity of HDL was manifested by reduction in cytokine-mediated expression of adhesion molecules, diminished neutrophil infiltration within the arterial wall, and reduced generation of reactive oxygen species.4

New antiatherogenic roles of HDL are currently emerging, which are related to endothelial cell turnover and function. Indeed one mode of action of HDL on endothelial cells has been recently investigated and demonstrated to provide protection to the endothelium. These HDL may stimulate eNOS activity through binding to SR-BI6 and/or through interaction with the lysophospholipid receptor sphingosine-1-phosphate S1P3.7 Similarly, HDL enhances endothelium- and NO-dependent relaxation in aortas from wild-type but not SR-BI knockout mice.7

Endothelial Progenitor Cells
In both in animal models and in humans, endothelial progenitor cells (EPCs) have been shown to contribute to neovas-
Endothelial progenitor cell–mediated endothelium repair proceeds in several steps that include the tissue mobilization of EPCs, the function and activity of EPCs, the number and half life of EPCs, and the cellular homing/engrafting capacity into the damage/eroded endothelium. Several factors have been implicated in these processes which may have positive or negative impact on vasculoprotection at each step. NO indicates nitric oxide; VEGF, vascular endothelial growth factor; SDF-1, stromal cell-derived factor 1; SR-BI, scavenger receptor type I; ACE, angiotensin converting enzyme.

EPCs and Atherogenesis

In man, studies have clearly established that high circulating EPC levels are associated with attenuated frequency of CAD events,13 and that major risk factors for atherosclerosis (diabetes, hypercholesterolemia, smoking, hypertension) impair the migratory capacity of EPCs.14,15 Equally, factors known to improve endothelial cell dysfunction and NO bioavailability, such as statins,2 angiotensin-converting enzyme inhibitors, estrogens, and physical exercise were found to be potent EPC-mobilizing agents. Consistent with these data, intravenous transfusion of EPCs was observed to reduce neointima formation on arterial injury in animal models16; moreover, mice lacking endothelial NO synthase fail to upregulate matrix metalloproteinase (MMP)-9 and are incapable of EPC mobilization.17 The implication of these findings is that recruitment of EPCs may be impaired in patients with impaired NO bioavailability.

EPC Mobilization and HDL-Induced Endothelial Repair

Although HDL particles afford vascular protection, the underlying mechanisms are incompletely understood. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, the potential effects of HDL on EPC function have been
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further evaluated by the elegant studies of Tso and colleagues. These investigations revealed that on injection of recombinant HDL in murine model of inflammatory deendothelialization, progenitor-mediated endothelial repair is promoted. A in vivo model of endothelial damage was used, in which apoptosis and loss of aortic endothelial cells was induced by lipopolysaccharide (LPS) administration. In this model, Sca-1 progenitor cells repopulated the damaged endothelium and were used as an index of new progenitor engraftment. The origin of Sca-1 cells was not defined in this study, but may originate from several sources including peripheral blood, bone marrow, and the vessel wall itself. The authors excluded upregulation of the Sca-1 marker itself and proliferation of resident endothelial cells as a primary mechanism accounting for the engraftment of Sca-1 cells in damaged aortic tissue. In addition, rHDL led to reduction in circulating levels of progenitor cells thereby arguing for an overall enhancement of progenitor engraftment rather than an increase in progenitor cell bioavailability. We cannot exclude the possibility that HDL may equally constitute a favorable substrate for optimum engraftment and overgrowth of progenitor cells. These highly original data provide convincing evidence that HDL particles play a key role in experimental progenitor mobilization for endothelium repair, and are entirely consistent with a recent study by Seetharam et al demonstrating that HDL/apoAI and SR-BI interaction can promote endothelial monolayer integrity in a model of arterial injury. Indeed, impaired reendothelialization was observed in apolipoprotein A-I knockout mice and SR-BI knockout mice by these investigators (Figure).

In summary, the exciting findings of Tso et al identify a new function of HDL in EPC-mediated arterial repair. These studies equally raise several pertinent questions, not the least of which relate to the potential potency of defined HDL particle subpopulations to promote endothelium repair on the one hand, and to the identification of the specific components of the lipid and protein moieties of HDL particles which account for such vasculoprotective biological activity.

References


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