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Although the vascular endothelium is a potent anti-thrombotic, 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-fOam 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-fOam cells. Indeed, HDL may afford protection from vascular disease by exerting additional effects that include antioxidant, antiprototic, antithrombotic, antiinflammatory, and vasodilatory functions. HDL antioxidative properties are related to para oxonase, 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-
cularization and reendothelialization, and evidence is accumu-
lating for an essential role of these progenitor cells in en-
dotheial maintenance and repair.

Based on studies in denuded thoracic aortas of rats, Hirsch and colleagues first demonstrated that reendothelialization was more likely attributable to cells migrating over relatively long distances than by replication of local endothelial cells. In addition, under conditions of oxidative stress and ageing, endothelial cells display limited replicative capacity, thereby rendering it unlikely that endothelial cells adjacent to the deendotheliazed area possess optimal capacity for prolifera-
tion and maintenance of the integrity of the endothelial layer throughout life. Additional cellular sources with progenitor capacity and which may facilitate vasculogenesis were iden-
tified by Asahara in 1999. Recent studies further character-
ized these EPCs in terms of surface markers, clonogenic capacity, and tissue origin (for review see reference 10). On recruitment, such EPCs can differentiate into cells that display classical endothelial cell morphology and character-
istics. The initial mechanism of endothelium repair involves mobilization of stem cells to the circulation; such mobiliza-
tion is normally promoted by the release of angiogenic factors (VEGF) in response to tissue injury and is followed by the recruitment of EPCs to the sites of injury (Figure). Little is known of the precise molecular mechanisms of endothelial cell recruitment; they appear however to proceed in three steps: (1) tethering of EPCs by a selectin-dependent pathway, (2) EPC activation by platelets or by the local microenvi-
ronment, resulting in tight cellular adhesion, and (3) the matu-
ration of the arrested EPCs toward a mature phenotype (for review see references 11 and 12).

**EPCs and Atherogenesis**

In man, studies have clearly established that high circulating EPC levels are associated with attenuated frequency of CAD events, and that major risk factors for atherosclerosis (diabetes, hypercholesterolemia, smoking, hypertension) impair the migratory capacity of EPCs. Equally, factors known to improve endothelial cell dysfunction and NO bioavailability, such as statins, 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 models; moreover, mice lacking endothelial NO synthase fail to upregulate matrix metalloproteinase (MMP)-9 and are incap-
able of EPC mobilization. The implication of these find-
ings 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 under-
lying 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.18 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, Sca1 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.19 The authors excluded upregulation of the Sca1 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 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.20 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 al21 demonstrating that HDL/apoAI and SR-BI interaction can promote endothelium 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.5

References