Editorial

High-Density Lipoprotein and the Dynamics of Atherosclerotic Lesions

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P lump et al\(^1\) reported in 1994 that the expression of a human transgene for apoA-I, the major apolipoprotein of HDL, in apoE knockout mice dramatically reduced lesion formation. In the present issue of *Circulation*, Rong et al\(^2\) demonstrate that the composition and structure of advanced atherosclerotic plaques can be significantly altered by the expression of this same transgene. Rong and colleagues\(^3\) used a novel transplant model. They fed apoE knockout mice a Western diet for 6 months to generate advanced lesions. Subsequently, they surgically removed portions of the aorta from these mice and transplanted them into the aortas of syngeneic mice on a chow diet, some of which also expressed the transgene for human apoA-I. The recipient mice expressing the human transgene had a 2.5-fold higher HDL cholesterol levels and expressed 130±15 mg/dL of human apoA-I. The non-HDL cholesterol levels were approximately half of those that had been present in the donor mice and were similar, regardless of whether the transgene was expressed or not. Five months later, despite non-HDL cholesterol levels that were half those of the donor mice, there was progression in the transplanted lesions, although there was less progression in the mice expressing the human apoA-I transgene. However, the characteristics of the lesions were dramatically different. The recipients expressing the transgene had a >80% decrease in lesion macrophage area and a >300% increase in smooth muscle cell content, with most of the changes occurring in the superficial subendothelial layer.

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In another study, Reis et al\(^4\) found that transplanting aortic segments from apoE knockout mice on a Western diet with advanced lesions into the aortas of wild-type mice (ie, normal apoE gene and no transgene for human apoA-I; hence, normal HDL and non-HDL cholesterol levels) produced nearly complete regression of the advanced atherosclerotic lesions.

Thus, lesion prevention in apoE knockout mice expressing the human apoA-I transgene\(^1\) and the regression of advanced lesions in aortic segments transplanted into wild-type mice\(^1\) both resulted in almost no lesions. In contrast, the transplantation of aortic segments with advanced lesions into apoE knockout mice expressing the human apoA-I transgene resulted in increased lesion area, but this was due to an increase in lesion smooth muscle cell content that more than offset a decrease in macrophage content.\(^2\) The results of these studies raise 3 questions. (1) What is the role of apoA-I? (2) Are the mechanisms fundamentally different in these models? (3) Do these results have relevance to human disease?

What Is the Role of apoA-I?

Shah and colleagues\(^5\) recently reported that a single high dose (400 mg/kg) of recombinant apoA-I\(_{\text{milano}}\) infused into apoE knockout mice on an atherogenic diet reduced plaque cholesterol by 40% to 50% and reduced plaque macrophage content by 29% to 36% within 48 hours of injection. Although there has been controversy regarding whether apoA-I\(_{\text{milano}}\) is more\(^5\) or less effective\(^6\) than native apoA-I in promoting cholesterol efflux, the data of Shah et al\(^4\) clearly indicate that lesion macrophage and cholesterol content can rapidly change in response to human apoA-I.

Navab and colleagues\(^7\) demonstrated that human apoA-I and synthetic apoA-I mimetic peptides are able to bind cholesterol and phospholipid and can rapidly remove “seeding molecules” from low density lipoproteins (LDL) that are necessary for the oxidation of LDL by human artery wall cells. Furthermore, Navab and colleagues\(^7\) demonstrated that human apoA-I and the apoA-I mimetic peptides could remove seeding molecules from artery wall cells that are also necessary for LDL oxidation. These authors\(^7\) found that injecting human apoA-I (but not human apoA-II, another HDL apolipoprotein) into mice rendered their LDL resistant to oxidation by human artery wall cells within 3 hours of the injection. Infusing apoA-I into humans rendered their LDL resistant to oxidation within 6 hours of the infusion. LDL-derived oxidized phospholipids have been strongly implicated in the inflammatory response that characterizes the macrophage component of atherosclerotic lesions.\(^9\)

Garber and colleagues\(^10\) demonstrated that the daily injection of a synthetic class A amphipathic peptide analogue of apoA-I restored the ability of HDL taken from mice on an atherogenic diet to inhibit LDL oxidation by human artery wall cells and also protected the mice from diet-induced atherosclerosis.

One explanation for the findings of Rong et al\(^2\) and Shah et al\(^4\) with respect to the macrophage component of lesions could be inhibition of LDL oxidation by human apoA-I, with prevention and removal of the LDL-derived oxidized phospholipids that (1) stimulate the artery wall cells to produce the substances necessary for monocyte migration into the artery wall (eg, monocyte chemoattractant protein-1; MCP-1), (2) promote the conversion of monocytes into macrophages, and (3) are necessary for macrophage survival (eg, monocyte...
colony stimulating factor; M-CSF). Consistent with this scenario is the finding by Rong et al \(^2\) that there was a dramatic reduction in MCP-1 in the lesions transplanted into the mice expressing the human apoA-I transgene.

**Are the Mechanisms Fundamentally Different in These Models?**

As noted by Rong et al. \(^2\), it is not clear why there was an increase in smooth muscle cells in the superficial subendothelial layer in the lesions transplanted into apoE knockout mice expressing the transgene but not in the lesions transplanted into wild-type mice. \(^3\) However, in the latter case, the macrophages virtually disappeared from the transplanted aortic segments, whereas in the former, despite the marked reduction in macrophage content, some macrophages remained at the base of the lesions in the vicinity of a lipid core. It may be that the persistence of these macrophages and some of the lipid core at the base of the lesion in the setting of the transgene and a paucity of macrophages in the superficial subendothelial layer favored the migration/proliferation of smooth muscle cells into the subendothelial layer. Thus, although the fundamental mechanisms are probably the same in all of the models, the differences studied may be due to the degree of hyperlipidemia remaining in the transplant model (eg, apoE knockout mouse recipient versus wild-type mouse recipient) and the interactions between the resulting cellular and extracellular components of the lesions.

**Do These Results Have Relevance to Human Disease?**

The net effect of the changes induced by the infusion \(^4\) of recombinant apoA-I \(_{\text{milano}}\), or the expression of the human apoA-I transgene\(^2\) would be predicted to make a more stable lesion. \(^12\) The inverse relationship of HDL levels to clinical events has long been known. \(^13\) However, HDL has also been described as a “chameleon-like” lipoprotein; it is anti-inflammatory in the basal state and pro-inflammatory during an acute phase response. \(^9,11\) It has been hypothesized that LDL-derived oxidized phospholipids and HDL have evolved as components of a system of nonspecific innate immunity. \(^9\)

The work of Shah et al. \(^4\) demonstrates the rapidity of lesion changes induced by changes in HDL. Van Lenten et al. \(^14\) reported that HDL lost its anti-inflammatory properties during acute influenza A infection in mice. Similar changes were seen in humans undergoing elective surgery. \(^15\) It may be that the relative stability of atherosclerotic plaques changes in response to or in parallel with changes in HDL.

Navab et al. \(^16\) recently reported a cell-free assay for detecting HDL that is dysfunctional in preventing the formation and inactivation of oxidized phospholipids. They described a group of 27 patients with angiographically proven atherosclerosis who had perfectly normal lipids, including HDL and LDL, who were not diabetics, who did not smoke, and who were not taking hypolipidemic medications. The HDL from these 27 patients was found to be functionally defective compared with HDL from 31 age- and sex-matched controls, despite the fact that the patients’ plasma HDL cholesterol levels were not different from the controls.

Modulation of the inflammatory components of lesions is surely multifactorial. The roles of reverse cholesterol transport and lipid oxidation are being defined. Perhaps these 2 processes are fundamentally linked. The work of Rong et al. \(^2\) and Shah et al. \(^4\) suggest that HDL and its components may play a major role in atherosclerotic lesion dynamics and, hence, in determining clinical events.

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**References**


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