An Apolipoprotein A-I Mimetic Works Best in the Presence of Apolipoprotein A-I

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Ou et al. report that an apolipoprotein A-I (apoA-I) mimetic peptide, D-4F, reduced wall thickness and improved vasoreactivity in the femoral artery (internal diameter 180 to 240 μm) in low-density lipoprotein (LDL) receptor–null mice on a Western diet. If the mice also lacked apoA-I, D-4F improved vasoreactivity but it did not reduce wall thickness. The authors concluded that apoA-I or some critical threshold of high-density lipoprotein (HDL)-cholesterol was required for maximum effectiveness of D-4F.1

In previous studies these authors reported that LDL caused endothelial nitric oxide synthase to produce more superoxide anion relative to nitric oxide and the balance between nitric oxide and superoxide anion was restored by the apoA-I mimetic peptide, D-4F.2 In vivo 4F improved vasoreactivity in LDL receptor null mice fed a Western diet and in a mouse model of sickle cell disease.3 Both of these mouse models were wild-type for apoA-I.3

4F is an 18-aa peptide that has no sequence homology with apoA-I but forms a class A amphipathic helix and mimics the lipid binding properties of apoA-I.4 Oral administration of 4F synthesized from all D-amino acids (D-4F) has been shown to dramatically reduce atherosclerosis in mouse models with wild-type apoA-I.4 Oral D-4F synergized with pravastatin to increase HDL-cholesterol,4 and rendered HDL antiinflammatory.4 The inflammatory properties of HDL appear to be inversely correlated with the ability of HDL to promote cholesterol efflux from macrophages (ie, antiinflammatory HDL is better able to promote cholesterol efflux).5

Ou et al. reported that treatment with D-4F reduced the association of myeloperoxidase (MPO) with apoA-I in vivo (but not in vitro) and decreased 3-nitrotyrosine content of apoA-I without altering plasma MPO levels. Nitric oxide–derived oxidants (as measured by nitrotyrosine levels) were significantly higher in patients with coronary heart disease (CHD) than in patients without CHD, and statin therapy significantly reduced nitrotyrosine levels, with a magnitude similar to the reductions in total cholesterol and LDL particle number but independent of alterations in C-reactive protein (CRP).6

ApoA-I in human atheroma and in human serum is a selective target for MPO-catalyzed nitration and chlorination.11 As a result of these oxidative alterations of apoA-I there was a marked decrease in the ability of the modified apoA-I to promote cholesterol efflux from macrophages via the ATP binding cassette (ABC) A1 pathway.11 Specific tyrosine residues in apoA-I were altered by MPO-mediated nitration and chlorination and resulted in decreased lipid binding and a decrease in ABCA1-dependent cholesterol efflux from macrophages.12 However, recombinant apoA-I without tyrosine residues was equally susceptible to dose-dependent MPO-mediated loss of ABCA1-dependent cholesterol acceptor activity and loss of lipid binding activity, indicating that nitro- and chlorotyrosine residues were a marker of MPO modification of apoA-I but were not responsible for the loss of function.13

Tyrosine modification in human atherosclerotic intima was 6-fold higher than in circulating HDL and MPO epitopes colocalized with nitrotyrosine.14 HDL from CHD patients contained twice as much 3-nitrotyrosine as did HDL from healthy subjects.14 MPO was identified as a component of lesion HDL, suggesting that MPO and HDL directly interact in atherosclerotic lesions.15

Because D-4F treatment restored vasodilation in both the presence and absence of apoA-I but failed to render HDL antiinflammatory and failed to reduce the thickness of the femoral artery in the absence of apoA-I, it was concluded that either the presence of apoA-I or some critical level of HDL-cholesterol was required for D-4F to reduce vessel wall thickness.1 The work of Moore et al.16 indicates that apoA-I inhibits atherosclerosis by promoting macrophage reverse cholesterol transport and HDL antiinflammatory function independent of HDL-cholesterol levels, and thus suggests that the absence of apoA-I was responsible for the findings of Ou et al with regard

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to vessel wall thickness and HDL inflammatory properties. The ability of D-4F to restore the balance between nitric oxide and superoxide anion production and restore vasoreactivity in the absence of apoA-I suggests that different mechanisms may be involved.

Both native apoA-I and 4F have been reported to have multiple antiinflammatory effects. Kruger et al reported that D-4F induced vascular heme oxygenase-1 and extracellular superoxide dismutase resulting in decreased endothelial cell sloughing with improved vascular reactivity in a rat model of diabetes. Gupta et al recently reported that 4F (but not scrambled 4F) inhibited the inflammatory responses of endothelial cells exposed to bacterial lipopolysaccharide (LPS) or lipid A (the major lipid component of LPS) by reducing LPS binding to its plasma carrier molecule and to endothelial cells. Van Lenten et al found that D-4F treatment of LDL receptor null mice nasally infected with influenza A virus resulted in decreased lung viral titers, inflammation, and cytokine expression, and decreased macrophage traffic into arteries. D-4F treatment of human type II pneumocytes infected with influenza A virus in vitro reduced viral titers and reduced the secretion of proinflammatory oxidized phospholipids without altering the secretion of nonoxidized phospholipids. Caspase activation and cytokine secretion were also dramatically reduced by D-4F treatment.

Thus, both 4F and native apoA-I have multiple antiinflammatory properties. Because D-4F is not likely to interact with mammalian proteins, its various activities are likely dependent on its lipid binding properties. The demonstration by Ou et al that native apoA-I is required for some of its biologic actions is fascinating and presents new opportunities for understanding the mechanism of action of both native apoA-I and apoA-I mimetic peptides.

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References


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