Int J Endocrinol Metab 2003; 1:3-5

The Protective Capacity of Normal High Density Lipoprotein Against Lipid Oxidation

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High density lipoprotein (HDL) acts as a powerful endogenous defense mechanism against atherogenesis. Apolipoprotein A-I is a central component of HDL that, when present, leads to the formation of HDL in vivo. In 1994, Plump et al[1] found that apolipoprotein A-I transgene expression resulted in the reduction of lesion formation in apolipoprotein E knockout mice. Rong and colleagues,[2] using a transplant model, demonstrated, that apolipoprotein A-I transgene expression can significantly change the structure and composition of advanced atherosclerotic plaques. Portions of aorta with advanced lesions were surgically removed from apolipoprotein E knockout mice and transplanted into the aortas of syngeneic mice, maintained on a chow diet. The recipient mice expressing the apolipoprotein A-I transgene had lesions with dramatically different characteristics with an 80% decrease in lesion macrophage areas and 300% increase in smooth muscle cell content. Reis et al,[3] reported a near complete regression of atherosclerotic lesions when portions of aorta with advanced lesions from apolipoprotein E knockout mice on a Western diet were transplanted into the aortas of wild-type mice. Shah et al,[4] found a 40-50% reduction of plaque cholesterol and 29-36% reduction of plaque macrophage content in apolipoprotein E knockout mice, maintained on an atherogenic diet, within 48 hours of injection with a single high dose of recombinant apolipoprotein A-I, indicating that human apolipoprotein A-I can rapidly alter the macrophage and cholesterol content of lesions. Our group found that "seeding molecules", the products of oxidation of linoleic acid and arachidonic acid, essential for the oxidation of LDL by human artery wall cells, can be rapidly removed from LDL and from artery walls cells by human apolipoprotein A-I and synthetic apolipoprotein A-I mimetic peptides.[5,6] We also found that LDL from mice injected with human apolipoprotein A-I became resistant to oxidation by aortic endothelial and smooth muscle cells within 3 to 6 hours of apoA-I injection. Humans infused with human apolipoprotein A-I phospholipid disks were found to have LDL that was resistant to oxidation by artery wall cells within 6 hours of the infusion. With our collaborators, Garber, Anantharamaiah and colleagues, we observed that HDL's ability to inhibit LDL oxidation by human artery wall cells could be restored in mice injected daily with a synthetic class A synthetic peptide

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analogue of apolipoprotein A-I. This analogue also protected the mice from atherosclerosis induced by a high fat, high cholesterol diet.[7]

We have hypothesized that human apolipoprotein A-I could be working to inhibit the oxidation of LDL by preventing the formation and by removing LDL-derived oxidized phospholipids which play roles in stimulating artery wall cells' production of substances promoting monocyte migration, such as monocyte chemoattractant protein (MCP-1), facilitating the conversion of monocytes to macrophages, and macrophage survival,[8] providing an explanation for the studies conducted by Shah et al,[4] and Rong et al,[2] where macrophage content was altered by apolipoprotein A-I. This explanation is further supported in a study conducted by Rong et al,[2] where MCP-1 was reduced in lesions transplanted in mice expressing the human apolipoprotein A-I transgene.

It appears that it can be predicted that the net effect of the transgenic expression of apolipoprotein A-I or the infusion of the recombinant apolipoprotein A-I confers stability to the atherosclerotic lesion.[9] Our group has reported evidence indicating that there is a strong association between the inflammatory response of atherosclerotic lesions and LDL-derived oxidized phospholipids.[10] The inverse relationship between HDL and clinical events is well documented.[11] However, HDL has been described as anti-inflammatory in the basal state and pro-inflammatory during an acute phase response, suggesting that perhaps HDL and LDL-derived oxidized phospholipids are involved in nonspecific innate immunity.[8,10] This hypothesis is further supported by Van Lenten et al, who reported that HDL, during an acute influenza A infection in mice and during elective surgery in humans, did not retain its anti-inflammatory properties.[12,13]

In patients with diabetes, it has been observed that HDL does not have the normal capacity to protect against lipid oxidation. This can be crucial in terms of the protection of lipoproteins against oxidation, and can apply to the oxidation of VLDL, LDL and even to HDL itself.

Reverse cholesterol transport in HDL and lipid oxidation may be linked to the multifactorial regulation of an inflammatory response in atherosclerotic lesions. HDL may play a role in atherosclerotic lesion dynamics and serve as a marker for clinical events. Determination of HDL function and protective capacity may prove to be a valuable predictive test.

References

1. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. Proc Natl Acad Sci U S A 1994; 91: 9607-11.
2. Rong JX, Li J, Reis ED, Choudhury RP, Dansky HM, Elmalem VI, et al. Elevating high-density lipoprotein cholesterol in apolipoprotein E-deficient mice remodels advanced atherosclerotic lesions by decreasing macrophage and increasing smooth muscle cell content. Circulation 2001; 104: 2447-52.
3. Reis ED, Li J, Fayad ZA, Rong JX, Hansoty D, Aguinaldo JG, et al. Dramatic remodeling of advanced atherosclerotic plaques of the apolipoprotein E-deficient mouse in a novel transplantation model. J Vasc Surg 2001; 34: 541-7.
4. Shah PK, Yano J, Reyes O, Chyu KY, Kaul S, Bisgaier CL, et al. High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. Circulation 2001; 103: 3047-50.
5. Navab M, Hama SY, Cooke CJ, Anantharamaiah GM, Chaddha M, Jin L, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. J Lipid Res 2000; 41: 1481-94.
6. Navab M, Hama SY, Anantharamaiah GM, Hassan K, Hough GP, Watson AD, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low

density lipoprotein: steps 2 and 3. J Lipid Res 2000; 41: 1495-1508.
7. Garber DW, Datta G, Chaddha M, Palgunachari MN, Hama SY, Navab M, et al. A new synthetic class A amphipathic peptide analogue protects mice from diet-induced atherosclerosis. J Lipid Res 2001; 42:545-52.
8. Navab M, Berliner JA, Watson AD, Hama SY, Territo MC, Lusis AJ, et al. The Yin and Yang of oxidation in the development of the fatty streak. A review based on the 1994 George Lyman Duff Memorial Lecture. Arterioscler Thromb Vasc Biol 1996; 16:831-42.
9. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001; 104: 365-72.
10. Navab M, Berliner JA, Subbanagounder G, Hama S, Lusis AJ, Castellani LW, et al. HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. Arterioscler Thromb Vasc Biol 2001; 21: 481-8.
11. Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemicheart-disease.,Lancet 1975; 1: 16-9.
12. Van Lenten BJ, Wagner AC, Nayak DP, et al. High-density lipoprotein loses its anti-inflammatory properties during acute influenza A infection. Circulation 2001; 103: 2283-88.
13. Van Lenten BJ, Hama SY, deBeer FC, et al. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. J Clin Invest 1995; 96: 2758-67.