Electronegative Low-density Lipoprotein Induces Endothelial DNA Damage and Senescence in vivo

Session Russell Ross Memorial Lectureship in Vascular Biology and Mechanisms of Atherosclerosis

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Author(s) An-sheng Lee , China Medical Univ, Taichung, Taiwan; Wei-Yu Chen, Hua-Chen Chan, China Medical Univ Hosp, Taichung, Taiwan; Ming-Yi Shen, Yu-Chen Wang, China Medical Univ, Taichung, Taiwan; Long-Sheng Lu, Jonathan Lu, Texas Heart Inst, Houston, TX; Tatsuya Sawamura, Natl Cerebral and Cardiovascular Ctr Res Inst, Osaka, Japan; Chu-Huang Chen, Texas Heart Inst, Houston, TX

Background: L5, the most electronegative of the chromatographically resolved low-density lipoprotein (LDL) subfractions (L1-L5), is increased in patients with acute myocardial infarction. L5 can induce both endothelial cell (EC) apoptosis and platelet aggregation via the lectin-like oxidized LDL receptor-1 (LOX-1). To confirm the atherogenicity of L5, we evaluated whether exposure to L5 in vivo induces endothelial DNA damage and senescence_early signs of atherosclerosis.
Methods and Results: We injected C57/BL6 mice with human L5 or L1 (n=4 each; 3 mg/kg/day). At 4 weeks, the aortic endothelium from L5 mice, but not L1 mice, showed strong staining for senescence-associated β-galactosidase (SA-β-Gal). L5 mice also showed LOX-1 overexpression and DNA damage, as indicated by γH2AX-positive nuclear material. Coadministering L5 with N-acetyl-L-cysteine (NAC), which scavenges reactive oxygen species before DNA damage, or caffeine, which blocks ataxia telangiectasia mutated kinase after DNA damage, prevented endothelial senescence. These results were reproducible in cultured human aortic ECs. In *LOX-1*$^{-/-}$ mice (Figure) and human ECs treated with LOX-1 neutralizing antibodies, L5 was ineffective. To assess the in vivo effects of endogenous L5, we fed Golden Syrian hamsters a normal diet (ND) or a high-fat diet (HFD) for 3 months. L5 levels were twofold higher in HFD hamsters than in ND hamsters (n=4 each; $P<0.01$). Positive results for Oil Red O (lipids), SA-β-Gal, LOX-1, and γH2AX were seen in the aortas of HFD hamsters, but not ND hamsters (Figure).
Conclusions: To our knowledge, this is the first study to show that a naturally occurring human LDL subfraction (highly electronegative L5) can induce DNA damage and senescence in arterial endothelium without ex vivo modification. Endogenously produced L5 caused atherogenic effects in hamsters, further suggesting the relevance of L5 in vivo. Future studies should examine whether L5 should be a new target for treatment.

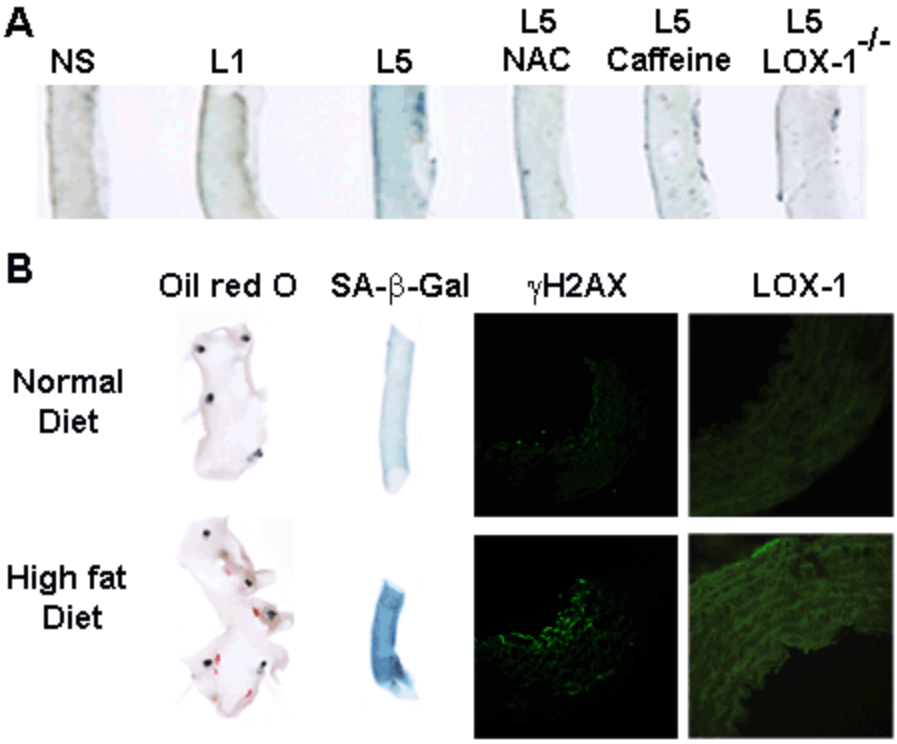

Figure. Atherogenicity of exogenous and endogenous L5. (A) SA-β-Gal staining (blue) in aorta of human L1- and L5-injected mice. (B) Lipid deposition and vascular senescence in hamsters fed a normal or high-fat diet, as determined by Oil Red O and SA-β-Gal staining. Immunohistochemistry was used to detect γH2AX and LOX-1 expression. NS, normal saline; NAC, N-acetyl-L-cysteine; LOX-1, lectin-like oxidized LDL receptor-1; SA-β-Gal, senescence-associated β-galactosidase.

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American Heart Association
7272 Greenville Avenue
Dallas, Texas 75231