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The DNA Damage Response Mediates Endothelial Cell Senescence Induced by Electronegative LDL

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Abstract:
Background: The premature senescence of vascular cells may contribute to increased coronary artery disease (CAD) in patients with metabolic syndrome (MetS). Plasma LDL of MetS patients has a high content of L5, the most electronegative and only atherogenic subfraction of chromatographically resolved LDL. We tested the hypothesis that L5 initiates the DNA damage response and triggers senescence of arterial endothelial cells (AECs).
Methods and Results: When human AECs were exposed to L5, L1 (the least electronegative LDL subfraction), or PBS for 5 days, only L5 induced a significant increase in the number of senescence-associated β-galactosidase (SA-β-gal)–positive cells. L5 treatment resulted in increased mitochondrial oxygen consumption and mitochondrial superoxide levels. L5 treatment also initiated the DNA damage response, marked by the presence of nuclear γ-H2AX foci and activation of ATM, Chk2, and p53. DNA damage probably resulted from increased intracellular oxidative stress, as antioxidant N-acetylcysteine (NAC) attenuated L5-induced nuclear γ-H2AX foci formation. Furthermore, activation of the DNA damage response by L5 upregulated p21/WAF1 protein level and decreased telomerase expression and activity, both of which contribute to cellular senescence. Blocking oxidative stress or the subsequent DNA damage response with NAC, caffeine, or siRNA-mediated p53 depletion effectively prevented L5-induced HAEC senescence. Consistent with these findings, intravenous administration of L5 but not L1 (5 mg/kg of each) resulted in nuclear γ-H2AX immunoreactivity, positive SA-β-gal staining, and aortic endothelial atherosclerosis in C57BL/6J mice.
Conclusions: Our data support the hypothesis that exposure of AECs to L5, as seen in MetS, induces intracellular oxidative stress, activates the DNA damage response, and accelerates vascular senescence (Figure). This may provide a potential target for prevention and treatment of CAD in MetS patients.

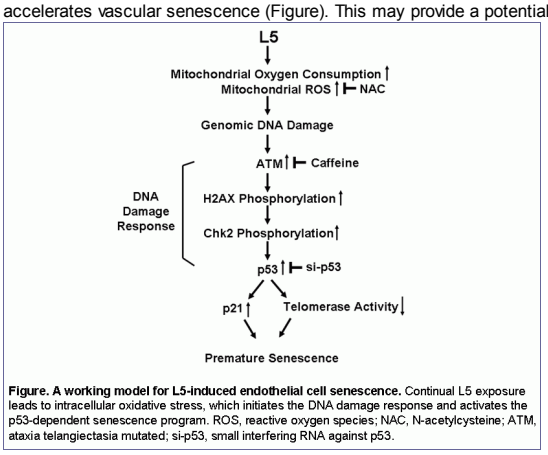

Figure. A working model for L5-induced endothelial cell senescence. Continual L5 exposure leads to intracellular oxidative stress, which initiates the DNA damage response and activates the p53-dependent senescence program. ROS, reactive oxygen species; NAC, N-acetylcysteine; ATM, ataxia telangiectasia mutated; si-p53, small interfering RNA against p53.

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