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Understanding the Role of Nitric Oxide Synthase 1 in Low-Density Lipoprotein Uptake by Macrophages and Implication in Atherosclerosis Progression

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Abstract : Atherosclerosis is a chronic inflammatory disease characterized by the formation of lipid rich plaque enriched with necrotic core, modified lipid accumulation, smooth muscle cells, endothelial cells, leucocytes and macrophages. Macrophage foam cells play a critical role in the occurrence and development of inflammatory atherosclerotic plaque. Foam cells are the fat-laden macrophages in the initial stage atherosclerotic lesion formation. Foam cells are an indication of plaque build-up, or atherosclerosis, which is commonly associated with increased risk of heart attack and stroke as a result of arterial narrowing and hardening. The mechanisms that drive atherosclerotic plaque progression remain largely unknown. Dissecting the molecular mechanism involved in process of macrophage foam cell formation will help to develop therapeutic interventions for atherosclerosis. To investigate the mechanism, we studied the role of nitric oxide synthase 1(NOS1)-mediated nitric oxide (NO) on low-density lipoprotein (LDL) uptake by bone marrow derived macrophages (BMDM). Using confocal microscopy, we found that incubation of macrophages with NOS1 inhibitor, TRIM (1-(2-Trifluoromethylphenyl) imidazole) or L-NAME (N omega-nitro-L-arginine methyl ester) prior to LDL treatment significantly reduces the LDL uptake by BMDM. Further, addition of NO donor (DEA NONOate) in NOS1 inhibitor treated macrophages recovers the LDL uptake. Our data strongly suggest that NOS1 derived NO regulates LDL uptake by macrophages and foam cell formation. Moreover, we also checked proinflammatory cytokine mRNA expression through real time PCR in BMDM treated with LDL and copper oxidized LDL (OxLDL) in presences and absences of inhibitor. Normal LDL does not evoke cytokine expression whereas OxLDL induced proinflammatory cytokine expression which significantly reduced in presences of NOS1 inhibitor. Rapid NOS-1-derived NO and its stable derivative formation act as signaling agents for inducible NOS-2 expression in endothelial cells, leading to endothelial vascular wall lining disruption and dysfunctioning. This study highlights the role of NOS1 as critical players of foam cell formation and would reveal much about the key molecular proteins involved in atherosclerosis. Thus, targeting NOS1 would be a useful strategy in reducing LDL uptake by macrophages at early stage of disease and hence dampening the atherosclerosis progression.

Keywords : atherosclerosis, NOS1, inflammation, oxidized LDL
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