SUMMARY
Hemolysis, hemoglobin-oxidation and heme-mediated lipidoxidation in atherosclerotic lesions
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Heme-catalyzed oxidation of low-density lipoprotein (LDL) is one of the relevant mechanisms involved in LDL modification. Oxidized LDL is toxic to vascular endothelium, however, in sublethal dose induces heme oxygenase-1 (HO-1) and ferritin as a defense mechanism. The central importance of this protective system was recently highlighted by the discovery of a child diagnosed with HO-1 deficiency, who exhibited extensive endothelial damage and severe atherosclerosis. We found that both cytotoxicity and expression of heme oxygenase-1 in endothelium strongly correlated to the lipid hydroperoxide content (LOOH) of oxidized LDL. We have discovered novel functions of hydrogen sulfide (H$_2$S), the third endogenous gasotransmitter. H$_2$S delayed heme-mediated oxidation of LDL and decreased the LOOH content of oxidized LDL. H$_2$S can directly protect endothelium against hydrogen peroxide and oxLDL-mediated cytotoxicity. LDL-associated lipid hydroperoxides were found to oxidize ferrohemoglobin to ferrihemoglobin – known to readily release its heme moieties – in a dose-dependent manner. We found elevated cytotoxicity induced by heme-catalyzed oxidation of LDL in immortalized lymphocyte cells derived from the heme oxygenase-1 deficient patient, that might contribute to his vascular disorders. Lipid peroxidation is a key event in the pathogenesis of atherosclerosis while the induction of HO-1 and ferritin provides protection in atherogenesis. We find that oxidation of ferrohemoglobin (FeII) in ruptured advanced lesions occurs generating ferrihemoglobin (FeIII) and via more extensive oxidation ferrylhemoglobin (FeIII/FeIV=O). The protein oxidation markers, dityrosine and crosslinked hemoglobin, accumulate in complicated lesions as hallmarks of the formation of ferrylhemoglobin. Exposure of normal red cells to lipids derived from atheromatous lesions causes hemolysis and oxidation of liberated hemoglobin. In the interactions between hemoglobin and atheroma lipids, hemoglobin and heme promote further lipid oxidation and subsequently endothelial reactions such as upregulation of heme oxygenase-1 and cytotoxicity to endothelium.

Key words: low-density lipoprotein, heme, atherosclerosis