Oxidized LDL inhibit protective autophagy and induce apoptotic cell death in bovine cultured endothelial cells: role of oxidative stress and LOX-1.

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Oxidized-low density lipoproteins (oxyLDL) are strong inducers of endothelial dysfunction. In particular, oxyLDL causes overproduction of reactive oxygen species, inflammatory processes and finally apoptotic cell death. Lectin-like oxyLDL scavenger receptor-1 (LOX-1) is responsible for binding, internalizing and degrading oxyLDL. We studied the role of LOX-1 in balance between apoptotic cell death and protective autophagy in injured endothelial cells.

OxyLDL caused apoptotic cell death in bovine aortic endothelial cells (BAEC) in a concentration-dependent manner through a mechanism involving free radical overproduction, as confirmed by pretreatment with N-acetylcysteine or S-nitroso-N-acetylpenicilammine which prevented endothelial cell death. In particular, oxyLDL early caused a time-dependent LOX-1-mediated dephosphorylation of eNOS impairing its activity. This event was followed by iNOS and caspase-3 over-expression observed after incubation with higher concentrations of oxyLDL. Increasing iNOS and caspase-3, in turn, were accompanied by decreasing levels of Beclin-1, an important effector of protective autophagy and a direct caspase substrate that, after cleavage, contributes to the mitochondrial release of pro-apoptotic factors. Silencing LOX-1, autophagy was restored as demonstrated by modulated expression of LC3-II, another marker of autophagic process.

Altogether these results show that OxyLDL internalization is accompanied by an imbalanced oxidative state of endothelial cells characterized by an early impairment of eNOS activity, an over-production of free radicals and, finally, to apoptotic cell death. These events are mediated by LOX-1 activation able to inhibit autophagy; indeed, the inhibition of molecular mechanisms induced by LOX-1, restores protective autophagy. We can conclude that, under oxidative stress, LOX-1 has a key role in mediating the switch between apoptosis and autophagy of endothelial cells during the early stages of atherosclerosis.