Plasminogen and matrix metalloproteinase activation by enzymatically modified low density lipoproteins in monocytes and smooth muscle cells.

Abstract:
Protease activity promotes the progression and rupture of atherosclerotic plaques. LDL has been described to become enzymatically modified within the vessel wall yielding an atherogenic moiety (E-LDL). We studied the effect of E-LDL on the activation of plasminogen and matrix metalloproteinases (MMPs) in monocytes and vascular smooth muscle cells (VSMCs) as well as on MMP activation during cellular interactions. Human monocytes, monocytic MonoMac6 cells and human VSMCs were incubated with human native LDL (n-LDL) or E-LDL for 24 hours. E-LDL in contrast to n-LDL induced substantial activation of the plasminogen activation system as well as of the MMP system in monocytes as measured by enhanced cell surface expression of the urokinase receptor (uPAR), the extracellular matrix metalloproteinase Inducer (EMMPRIN) and the membrane type-1 MMPs (MT1-MMP, MMP-14), as well as by secretion of active uPA, and of MMP-9. Consistently, E-LDL-treated monocytes exhibited increased transmigration through "matrigel", which was specifically abrogated by the MMP inhibitor galardin or the plasmin inhibitor aprotinin. In VSMCs, E-LDL induced MMP-1 and MMP-2 secretion. Moreover, monocyte incubation with supernatants of E-LDL-treated (but not n-LDL-treated)
VSMCs strongly induced MMP-9 in monocytes, which was inhibited by blocking mAb anti-TNF-alpha. Together, enzymatical modification of LDL allows a direct activation of MMP expression in monocytes and VSMCs, and indirectly promotes the induction of paracrine, cytokine-mediated intercellular activation processes. There by, E-LDL may contribute to atheroprosperession, inflammation and plaque rupture.