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Vascular endothelial cells exposed to oxidized HDL increases LOX-1 destination at the plasma membrane through a mechanism involving ROS/NOX/NF-kB/LOX-1 pathway

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Topic(s):
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Background: Systemic inflammatory diseases are characterized by an increased release of NAD(P)H oxidase (NOX)-derived reactive oxygen species (ROS) and pro-inflammatory cytokines into the circulatory system which generates endothelial cell (EC) dysfunction. As a consequence of this process, circulating lipoproteins such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are converted into its oxidized forms, oxLDL and oxHDL, respectively. LDL and oxLDL are correlated with increased risk of several vascular diseases. In contrast, HDL is a protective factor preventing the development of several vascular diseases. Noteworthy, oxHDL has been linked to several detrimental effects on EC function.

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is the endothelial receptor for oxLDL promoting deleterious effects in EC. Interestingly, some reports have shown that LOX-1 is also the receptor for oxHDL. Considering that LOX-1 is a plasma membrane receptor, its expression must be accompanied with protein destination to the plasma membrane to be able to interact with ligands. Once LOX-1 is activated, an intracellular signalling is elicited generating changes in ECs that promote endothelial dysfunction involving ROS generation, NF-kB activation and pro-inflammatory cytokines secretion.

It has been suggested that oxHDL is also able to increases the expression of LOX-1 on ECs. However, the underlying mechanism involved in the LOX-1 expression and plasma membrane destination induced by oxHDL on ECs and the participation of ROS, NF-kB activation and LOX-1 signalling in this process is unknown.

Purpose: Here we studied whether oxHDL induces changes in LOX-1 expression at the plasma membrane level and investigated the participation of the ROS/NOX/NF-kB/LOX-1 pathway in this process in ECs.

Methods: Human EC line cultures were exposed to HDL and oxHDL in the presence or absence of the inhibitors of ROS, NOX, NF-kB and LOX-1, and LOX-1 expression was measured in the plasma membrane-rich subcellular fraction.

Results: Our results demonstrated that oxHDL, but not the native form HDL, increases LOX-1 expression at the plasma membrane through the activation of LOX-1 receptor. The oxHDL-induced LOX-1 expression increases at the plasma membrane is dependent on the activation of the ROS/NOX/NF-kB/LOX-1 pathway, but is independent on the NF-kB/TNFR/TNFα pathway. Interestingly, simultaneous exposition of TNFα and oxHDL exert a potentiated effect suggesting parallel mechanisms.

Conclusions/discussion: OxHDL increases LOX-1 expression at the plasma membrane through the ROS/NOX/NF-kB/LOX-1 pathway. This mechanism could allow the interaction of this receptor with several ligands enhancing the LOX-1 intracellular signalling in ECs. Furthermore, the potentiated effect of the simultaneous action of oxHDL and pro-inflammatory cytokines could generate a major impact in LOX-1-mediated endothelial dysfunction.
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