Apoptosis of Vascular Cells by Oxidized LDL

Involvement of Caspases and LOX-1 and Its Implication in Atherosclerotic Plaque Rupture

Noriaki Kume, Toru Kita

Atherosclerotic plaque rupture followed by thrombus formation is a key event in the onset of acute coronary syndrome.1 Apoptotic death of smooth muscle cells in the fibrous cap of the atherosclerotic plaque, in addition to degradation of extracellular matrix proteins by matrix metalloproteinases (MMPs), appears to be involved in atherosclerotic plaque rupture.2 Oxidized LDL (Ox-LDL) has been implicated in the pathogenesis of atherosclerosis and atherosclerotic plaque rupture by promoting lipid accumulation, proinflammatory responses, and apoptotic cell death.2–4 In fact, apoptotic cells are present in atherosclerotic lesions.4,5 These biological effects, including proapoptotic effects, of Ox-LDL appear to be, at least in part, mediated by cell-surface receptors for Ox-LDL.6

Among several different classes of oxidized LDL receptors (also designated scavenger receptors) most of which are expressed mainly by macrophages, lectin-like oxidized LDL receptor-1 (LOX-1) is a type II membrane glycoprotein and expressed by activated vascular endothelial and smooth muscle cells, as well as macrophages.7–10 LOX-1 expression can dynamically be induced by proinflammatory and other pathological stimuli relevant to atherogenesis.11–14 Particularly, LOX-1 is induced by its ligand Ox-LDL,15,16 as well as proinflammatory cytokines,11,12 thus making a positive-feedback loop to enhance the effect of Ox-LDL on vascular cells. Uptake of Ox-LDL through LOX-1 induces reactive oxygen species (ROS), reduces nitric oxide, activates NF-κB,17,18 and thereby upregulates expression of monocyte chemoattractant protein-1 (MCP-1) and MMPs.19–21 LOX-1–dependent uptake of Ox-LDL also induces expression of a proapoptotic factor Bax, downregulates an antiapoptotic factor Bcl-2, and induces apoptosis of cultured vascular smooth muscle cells,15 as well as endothelial cells.16

In human advanced atherosclerotic lesions, but not in normal arterial walls, macrophages and smooth muscle cells in the intima, in addition to vascular endothelial cells, dominantly express LOX-1,22 which is colocalized with Bax.15 In the early stages of atherogenesis, LOX-1 expression is prominent in vascular endothelial cells,22,23 and apoptosis of endothelial cells also are detected, which may be implicated in endothelial dysfunction.4 Thus, evidence has been accumulated to indicate that vascular cell apoptosis is mediated by Ox-LDL and its receptor LOX-1, and it may be crucial for atherosclerotic plaque rupture in the advanced stage, as well as endothelial dysfunction in the early stage.

However, molecular mechanisms involved in cell apoptosis by Ox-LDL and LOX-1 interactions have not been fully understood. In this issue of Circulation Research, Chen et al24 have explored the involvement of caspases and the related molecules, such as Bcl-2 and c-IAP-2, and report that activation of caspase-9 and subsequent activation of caspase-3 are responsible for Ox-LDL–induced apoptosis of cultured vascular endothelial cells through its receptor LOX-1. In addition, release of mitochondrial apoptotic proteins, such as cytochrome c and Smac, was associated with Ox-LDL–induced caspase activation and apoptosis. Because Ox-LDL–induced release of cytochrome c or Smac was blocked by antisense oligonucleotides for LOX-1 but not affected by caspase inhibitors, cytochrome c and Smac appear to be upstream of caspase 9 and caspase 3 or might alternatively be independent of these caspases, although LOX-1 mediates the both pathways.

Chen et al24 have confirmed that caspase 9 is upstream of caspase 325 in the Ox-LDL–induced apoptosis, as shown in cytochrome c–dependent apoptosis by other stimuli.26 In addition, LOX-1–dependent downregulation of Bcl-2 by Ox-LDL is also shown in this study, as shown in cultured vascular smooth muscle cells.15 Bcl-2 appears to be the upstream of cytochrome c and Smac and thus may inhibit their mitochondrial release. Furthermore, c-IAP-1, an inhibitor of caspase activation, has been shown to be downregulated by Ox-LDL, depending on LOX-1, in this study (Figure). LOX-1–dependent downregulation of Bcl-2 and c-IAP-1 may depend on ROS and its downstream signals; however, these points remain to be determined. Because activation of protein kinase C,27 mitogen-activated protein (MAP) kinases,19 and nuclear factor-κB (NF-κB)17 and inhibition of phosphatidylinositol 3-kinase (PI3K)/Akt,27 as well as production of ROS,17 are involved in Ox-LDL and LOX-1–mediated cellular events, roles of these signal transduction cascades and transcription factors in Ox-LDL–induced downregulation of Bcl-2 and c-IAP-1, as well as cell apoptosis, should also be explored. In fact, PI3K/Akt has been implicated in Ox-LDL/LOX-1–induced apoptosis.27,28 In addition, Bax is also the upstream of cytochrome c and Smac release and is upregulated by Ox-LDL–LOX-1 interactions,15 signal transduction cascades, and transcription factors involved in
OX-LDL
↓
↓
LOX-1 ↑ (upregulated expression by Ox-LDL)
↓
↓
Pt3-kinase/Akt ↓ protein kinase C ↑
↓
↓
MAP kinase ↑
↓
↓
NF-κB ↑
↓
stimulated by Bax ↑ ⇒ ↓— blocked by Bel-2 ↓
cytochrome c release ↑, Smac release ↑
↓— blocked by c-IAP-1 ↓—inhibited by Smac ↑
caspase 9 activation ↑
↓— blocked by c-IAP-1 ↓—inhibited by Smac ↑
caspase 3 (CPP32) activation ↑
↓
apoptosis ↑

Molecular cascades involved in apoptosis by Ox-LDL–LOX-1 interactions.

OX-LDL–induced upregulation of Bax should also be examined. More importantly, future studies should be conducted to determine the effect of vascular cell apoptosis in the pathogenesis of atherosclerotic plaque rupture, thrombus formation, and the onset of acute coronary syndrome in humans or suitable animal models in vivo.

References
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_Circ Res._ 2004;94:269-270
doi: 10.1161/01.RES.0000119804.92239.97
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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