[文章编号] 1007-3949(2010)18-07-0577-05

• literature Review •

"Ox-LDL-LOX-1-ROS" Signaling Pathway Involvement in Foam Cell Formation

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[KEY WORDS] Atherosclerosis; Oxidized Low Density Lipoprotein; Lectin-like Oxidized Low Density Lipoprotein Receptor-1; Reactive Oxygen Species; Foam Cell Formation

[ABSTRACT] Atherosclerosis is a multifactorial chronic vascular inflammatory disease characterized by lipid deposition and even lipid plaque formation in the vascular intima. Macrophage cholesterol accumulation and foam cell formation are the hallmarks of early atherogenesis. However, the underlying mechanisms of foam cell formation are not fully elucidated. Herein, we hypothesize that the signaling model composed of the oxidized low density lipoprotein (ox-LDL), the lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) and the reactive oxygen species (ROS) plays an important role in foam cell formation. In this model, ox-LDL is the activating factor, LOX-1, the main ox-LDL receptor expressed in endothelial cells, acts as a signal transducer while the ROS, a direct product of ox-LDL binding with LOX-1, is regarded as a catalyst and an inducer.

1 Introduction

Since Witztum proposed the hypothesis of oxidized low-density lipoprotein (ox-LDL) as the major cause of atherosclerosis[1], the potential role of ox-LDL in atherogenesis was extensively studied. Accumulated evidence strongly suggested the pivotal role of ox-LDL, the mixture of heterogeneously modified particles of low-density lipoprotein (LDL), in endothelial activation, injury and dysfunction in the first step of atherosclerosis[2]. Although the behavior and metabolism of ox-LDL in vivo is poorly understood, the mechanism by which LDL is oxidized is not clear, and the modified structures of ox-LDL are not yet fully elucidated, ox-LDL is confirmed as a well-known risk marker for cardiovascular diseases[3]. A tremendous number of studies revealed that ox-LDL could induce numerous atherogenic effects, which were comprehensively summarized and updated[3-5]. In the past few decades, several cell-surface receptors for ox-LDL such as class A scavenger receptor (SR-A), class B scavenger receptors such as CD36 and SR-BI, type D scavenger receptor (lectin-like oxidized LDL receptor-1, LOX-1) and FEEL-1/FEEL-2 have been identified, and their structure, ligand specificity, regulation, and function have been thoroughly investigated[6-8].

Though quite a few of endothelial scavenger receptors for ox-LDL have been discovered, LOX-1 has been identified as the main ox-LDL receptor that is present primarily in endothelial cells[9] and as the principal receptor that mediates the action of ox-LDL in the vascular walls[8]. LOX-1 was first discovered by using a complementary DNA expression library derived from bovine aortic endothelial cells (BAEC)[9]. It is a 50-kDa type Ⅱ membrane protein that structurally belongs to the C-type lectin family[10]. Studies about the expression pattern of LOX-1 in human tissues revealed that LOX-1 is highly expressed in vivo in blood-vessel-abundant places such as placenta, lung, marrow and spinal cord, moderately expressed in hippocampi, testicle, large arteries and slightly expressed in heart, skeleton muscle, ovary, etc[11]. Furthermore, its expression could be regulated by many factors including chemicals, inflammatory cytokines, oxidized stress, pathological conditions and physical action[12]. LOX-1 exhibits multiple binding activities to quite a few of ligands including ox-LDL, advanced glycation end products (AGEs)[13, 14], Gram-positive and Gram-negative bacteria[15], aged red blood cells and apoptotic cells[16]. Since endothelial activation and dysfunction induced by ox-LDL is one of the key steps in the initiation of atherosclerosis, as the main receptor for ox-LDL in endothelial cells, the potential role of LOX-1 in atherosclerosis was gradually recognized[10, 17-21]. Therefore, LOX-1 was speculated as a promising therapeutic target for atherosclerosis[22].

The standard method of preparing ox-LDL in vitro by co-in-

[收稿日期] 2009-12-24 [修回日期] 2010-04-23
[Acknowledgement] This study was supported by the Research Fund of the University of Macau (UL016/09-Y2/CMS/WYT01/ICMS) and Macao Science and Technology Development Fund (049/2005/A-R1 and 029/2007/A2).

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cubation of LDL with copper sulfate has been consistently questioned and few mechanisms about the ox-LDL formation in vivo were proposed[23]. In view of the state of heightened oxidative stress in atherosclerosis[24], the speculation that part of LDL in the plasma could be directly oxidized by ROS is reasonable and tenable. Recent study also demonstrated that LDL could be oxidatively modified by stimulated platelets-derived ROS by collagen via GP91(phox)[25].

Reactive oxygen species (ROS), referred to free radicals sometimes, is a variety of small molecules with one unpaired electron derived from the metabolism of molecular oxygen. It includes a series of very small and highly reactive molecules such as hydroxyl radical (·OH), superoxide anion ($O^{2\cdot-}$), hydrogen peroxide (H_2O_2), and singlet oxygen etc[26]. Under physiological conditions, the deleterious effects of ROS are minimized by antioxidant defense mechanisms, which prevent its formation in excess and act as scavengers or repair the damage. However, uncontrolled ROS production results in a deleterious state called oxidative stress, which has been implicated in the pathogenesis of atherosclerosis[27, 28]. The direct consequence of LOX-1 activation by ox-LDL is the quick production of a large amount of intracellular ROS[29, 30]. The close relationship among ox-LDL, LOX-1, and ROS make us to speculate an "ox-LDL-LOX-1-ROS" model involvement in foam cell formation.

2 Hypothesis

As known to all, foam cell formation resulted from uncontrolled intracellular lipid droplets accumulation in macrophages and/or vascular smooth muscle cells is the hallmark of early atherosclerosis. The mechanisms underlying foam cell formation have been extensively studied for more than a decade and several theories have been proposed. Curtiss et al suggested that platelets contributed to foam cell formation by inducing macrophage cholesteryl ester[31]. While Daub et al emphasized the role of adherent platelets in foam cell formation[32] and Siegel-Axel et al concluded that platelet lipoprotein interplay triggered formation of foam cells[33]. Aviram proposed that LDL-platelet interaction under oxidative stress induced foam cell formation[34]. Bobryshev summarized the role of monocyte recruitment and foam cell formation in atherosclerosis[35]. Botham et al explained the foam cell formation from chylomicron remnants point of view[36]. Furthermore, there is also evidence supporting the role of oxidative stress in foam cell formation[37-39]. However, none of these hypotheses could interpret the complicated process of foam cell formation in detail. In this manuscript, we proposed that "ox-LDL-LOX-1-ROS" signaling pathway plays an important role in foam cells formation and atherogenesis. In this model, ox-LDL is an activating factor, LOX-1 acts as a signal transducer while ROS is regarded as a catalyst and an inducer (Fig. 1.).

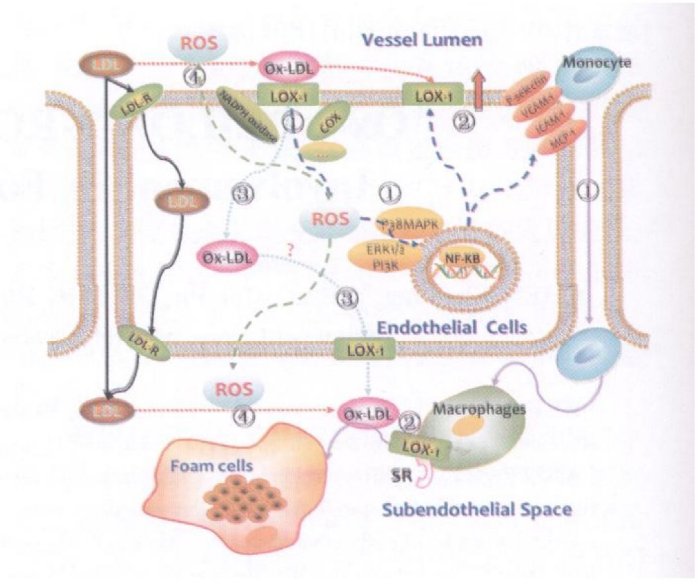

Figure 1. "ox-LDL-LOX-1-ROS" signaling pathway promotes foam cells formation through several pathways.

The binding of ox-LDL to LOX-1 induced quick formation of intracellular ROS mediated by NADPH oxidase and/or COX, which activates NF-κB through p-38MAPK/ERK1/2/PI3K pathways resulting in enhanced expression of ICAM-1, VCAM-1, MCP-1, P-selectin, etc, assisting monocyte adhesion to endothelial cells and infiltration into subendothelial space. ④ Ox-LDL induced LOX-1 expression both in endothelial cells and macrophages, facilitating ox-LDL endocytosis. ⑷ LOX-1 might also serve as ox-LDL transporter to ship ox-LDL from vascular lumen to subendothelial space. ROS mediates oxidative modification LDL in vascular lumen and subendothelial space. LDL, low density lipoprotein; LDL-R, low density lipoprotein receptor; Ox-LDL, oxidized low density lipoprotein; LOX-1, lectin-like oxidized LDL receptor-1; COX, cycloxygenase; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; ICAM-1, intercellular cell adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; SR, scavenger receptor.

3 Potential evidence for hypothesis

This model is dissected into several interrelated parts and discussed as below.

3.1 ox-LDL increased LOX-1 expression

The plasma ox-LDL, together with some other cytokines such as TNF-α, IL-1α, etc induced endothelial cells LOX-1 expression in vascular wall[9, 40, 41], which was mediated by ROS formation resulting in the activation of nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK)[30, 42, 43]. The increased LOX-1 expression could be activated by ox-LDL again, which might contribute to further up-regulation of LOX-1 expression. This seems to be a vicious cycle. Beside, the activation of LOX-1 by ox-LDL also mediated the elevated expression of vascular cell adhesion molecule 1 (VCAM-1), intercellular cell adhesion molecule 1 (ICAM-1), monocyte chemoat-

tractant protein 1 (MCP-1), and P and E-selectin leading to monocyte attachment and activation[19, 22], which facilitated the adhesion and migration of monocyte to cross the endothelium[44-46].

3.2 LOX-1 mediated endocytosis of ox-LDL

It is interesting to note that ox-LDL could be acted as both the ligand and inducer for LOX-1. As described above, there are quiet a few ligands for LOX-1, but ox-LDL is the most favorite ligand for LOX-1 with high affinity and ox-LDL uptaken is mediated by LOX-1 in endothelial cells[9, 47, 48]. However, the fate of ox-LDL after endocytosis is not clear especially in activated or injured endothelial cells. Could LOX-1 be acted as an ox-LDL transporter, which transfer ox-LDL from the vascular lumen to the subendothelial space?

3.3 Ox-LDL binding to LOX-1 resulted in intracellular ROS production

The first event confirmed at present after the binding of ox-LDL to LOX-1 is the quick intracellular ROS production, which could be observed at 30s after ox-LDL treatment in endothelial cells in vitro[29]. Secondly, ROS resulted in the activation of NF-κB and eventually affected the expression of LOX-1, ICAM-1, VCAM-1 and so on. Thirdly, some kinds of ROS could cross the endothelial membrane and reach the vessel lumen and the subendothelial space, where the oxidative modification of LDL might be happened. Therefore, LOX-1 mediated ROS formation could take part in LDL modification both in the vascular lumen and in the subendothelial space. In addition, the production of ROS also reduced the bioavailability of nitric oxide (NO) by formation of peroxynitrite, which would dramatically inhibit endothelium-dependent relaxation of vascular wall. There are some enzymes involved in ROS production in endothelial cells such as cycloxygenase (COX), lipoxidase (LOX), xanthine oxidase (XO), and NADPH oxidase. Our previous study confirmed that NADPH oxidase, LOX, and COX might be involved in this process[49].

3.4 Expression of LOX-1 in vascular smooth muscle cells and macrophages

Generally speaking, vascular smooth muscle cells (VSMC) and macrophages are the two major sources of foam cell. Expression of LOX-1 in VSMC was observed both in vitro and in vivo[10, 41, 50, 51], and could be regulated by lovastatin[52], transforming growth factor-beta 1(TGF-β1)[53], cytokines such as IL-1α, IL-1β and TNF-α[50], Heparin-binding EGF-like growth factor (HB-EGF)[54], angiotensin II[55], etc. Similarly, regulated expression of LOX-1 in macrophages was also documented[40, 56-59]. The exact role of enhanced expression of LOX-1 in atherogenesis was not clear, but be possibly involved in ox-LDL accumulation in VSMC[60]. Quite a few of scavenger receptors for ox-LDL have been identified in macrophages and involved in lipid accumulation in macrophages[61, 62]. LOX-1 mediated ox-LDL uptake might not play a crucial role in the progression of macrophages to foam cells[63]. However, recent findings also put insight into the role of LOX-1 in the initial of foam cell formation: LOX-1 augments ox-LDL uptake by lysoPC-stimulated murine macrophages[64] and combines Nox1 regulating TLR9-mediated foam cell formation[65].

These steps might happen in order during foam cells formation. However, in most cases, they could be happened at the same time. Of course, the detailed mechanisms still need further study to elucidate.

4 Scientific implication

The potential role of oxidative stress in the formation of atherosclerosis and foam cell formation has been extensively investigated[66-68] and the beneficial effect of anti-oxidant in atherosclerosis therapy was also confirmed by clinical observations[69, 70]. However, the mechanism of oxidative stress formation and its role in the initial of foam cell formation and atherogenesis were not fully understood. In this study, we proposed a signaling model composed of ox-LDL, LOX-1 and ROS involved in the development of atherosclerosis. The "ox-LDL-LOX-1-ROS" signaling pathway might promote foam cell formation by increasing adhesion molecular expression leading to facilitate monocyte migration to subendothelial space, by oxidizing native LDL both in the vessel lumen and subendothelial space to form ox-LDL, and by activating and injuring endothelial cells to initiate the first step of atherogenesis. According to this model, interference of ox-LDL-LOX-1 interactions by pharmacological inhibitors or other methods might provide new therapeutic potentials for clinical practice in atherosclerosis prevention and treatment.

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(此文编辑 李小玲)

“氧化型低密度脂蛋白—凝集素样氧化型低密度脂蛋白受体 1—活性氧”信号通路参与泡沫细胞的形成

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[关键词] 动脉粥样硬化；氧化型低密度脂蛋白；凝集素样氧化型低密度脂蛋白受体 1；活性氧；泡沫细胞形成

[摘 要] 动脉粥样硬化是多因素引起的，以动脉壁内脂质的沉积甚至粥样斑块的形成为特征的慢性血管炎症性疾病。巨噬细胞内胆固醇的堆积和泡沫细胞的形成是早期动脉粥样硬化形成的标志。然而，泡沫细胞形成的确切机制尚未完全阐明。于此，我们推测氧化型低密度脂蛋白(oxidized low density lipoprotein, ox-LDL)，凝集素样氧化型低密度脂蛋白受体 1(lectin-like oxidized low density lipoprotein receptor-1, LOX-1)和活性氧(reactive oxygen species, ROS)组成了一个促进泡沫细胞形成的“信号通路”，在泡沫细胞的形成乃至诱导动脉粥样硬化发生中起始动作用。在这一通路中，氧化型低密度脂蛋白，这种经过氧化修饰的低密度脂蛋白，是“激活子”；凝集素样氧化型低密度脂蛋白受体 1，作为内皮细胞上的氧化型低密度脂蛋白的主要受体是信号“转导子”；活性氧，这氧化型低密度脂蛋白与凝集素样氧化型低密度脂蛋白受体 1结合后的直接产物是“催化子”和“诱导剂”。

[中图分类号] R363 [文献标识码] A

[基金项目] 澳门大学研究基金(UL016/09-Y2/CMSAWYT01/ICMS)和澳门科学技术发展基金(049/2005/A-R1 and 029/2007/A2).

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