Chapter 10
LOX-1 and Immunity

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Abstract An interesting C-type lectin-like receptor is LOX-1. LOX-1 is a membrane glycoprotein with a cytoplasmic domain, a transmembrane domain, and an oxidized low-density lipoprotein (oxLDL)-binding extracellular lectin-like domain. LOX-1 is involved in a variety of physiological and pathophysiological processes. The LOX-1 receptor is able to mediate the uptake of minimally and maximally oxidized LDL. In addition, LOX-1 plays a role in the phagocytosis of aged and apoptotic cells, the uptake of advanced glycation end products, thrombocyte adhesion, and the interaction between bacterial proteins and endothelial cells in sepsis. It is considered as a therapeutic target in atherosclerosis and cardiovascular disease. Recently, LOX-1 has been described in response to different danger signals, rheumatic diseases, preeclampsia, and bone diseases. This review focuses on the increasing evidence supporting a novel role of LOX-1 in immunity. LOX-1 and other pattern recognition receptors are expressed on the surface of myeloid cells like macrophages, dendritic cells, or neutrophils. They have an important role in the immediate innate immune response and also in the regulation of the adaptive immune response.

Keywords C-type lectin-like receptor • LOX-1 • Lipoprotein • Atherosclerosis • Dendritic cells • Immunity

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10.1 The C-Type Lectin-Like Receptor LOX-1

Lipids are essential for cellular function and metabolism. Lipoproteins are important lipid carriers in the blood stream. An increased plasma level of low-density lipoprotein (LDL) is also a well-known risk factor of metabolic and cardiovascular diseases. Especially under conditions of oxidative stress, LDL can be oxidized (Muller and Morawietz 2009). Classical receptors of maximally oxidized LDL are scavenger receptor A (SR-A), scavenger receptor B (CLA-1/SR-BI), cluster of differentiation (CD) 36 and CD68, and scavenger receptor that binds phosphatidylserine and oxidized lipoprotein (SR-PSOX)/CXC chemokine ligand 16 (CXCL16), while minimally oxidized LDL can interact with, e.g., CD14/toll-like receptor 4 (TLR) 4 (Shashkin et al. 2005).

An interesting novel receptor for oxLDL is the C-type lectin-like oxLDL receptor LOX-1 (Sawamura et al. 1997). LOX-1 is also known as the first member of the CLEC8A family of C-type lectin-like receptors. LOX-1 is a membrane glycoprotein of 50 kDa. The protein has three important functional domains: a short cytoplasmic domain, a transmembrane domain, and an oxLDL-binding extracellular lectin-like domain (Chen et al. 2002). Three LOX-1 homodimers are necessary to bind an oxLDL molecule (Xie et al. 2004). Proteolytic cleavage of the extracellular domain can lead to two almost identical soluble LOX-1 forms (Murase et al. 2000). Whether these soluble forms correlate with the formation of membrane-bound LOX-1 or represent antagonistic forms is under discussion (Mehta et al. 2006; Sawamura et al. 2012).

Several ligands have been described for LOX-1 (Fig. 10.1). The LOX-1 receptor is able to mediate the uptake of minimally and maximally oxidized LDL (Tanigawa et al. 2006). Interestingly, LOX-1 is also involved in the phagocytosis of aged and apoptotic cells (Oka et al. 1998). In addition, a role of LOX-1 in thrombocyte adhesion and in the interaction between bacterial proteins and endothelial cells in sepsis has been described (Chen et al. 2002). LOX-1 could also act as a receptor of advanced glycation end products (AGEs) (Chen et al. 2008). These data suggest a role of LOX-1 in a variety of physiological and pathophysiological processes.

Human LOX-1 is encoded by the oxidized low-density lipoprotein receptor (OLR1) gene. LOX-1 is a single-copy gene located on the short arm of chromosome 12. Genes encoding natural killer cell (NK) receptors (NKG2A, C, D, E, CD94, CD69, and NKR-P1A) are mapped in this chromosomal region as well. LOX-1 is clustered within this "natural killer gene complex" (Aoyama et al. 1999; Yamanaka et al. 1998). The LOX-1 gene has six exons (Yamanaka et al. 1998). The LOX-1 gene structure suggests a relationship between the exon-intron architecture and the resulting protein structure (Yamanaka et al. 1998). Exon 1 encodes a 5′ untranslated region (5′ UTR) and the intracellular cytoplasmic domain. The second exon encodes the transmembrane domain and the third exon the extracellular neck domain. Exons 4–6 encode the carbohydrate recognition lectin-like domain and exon 6 contains the 3′-untranslated region (Yamanaka et al. 1998; Aoyama et al. 1999). The architecture of LOX-1 gene is similar to other C-type lectin

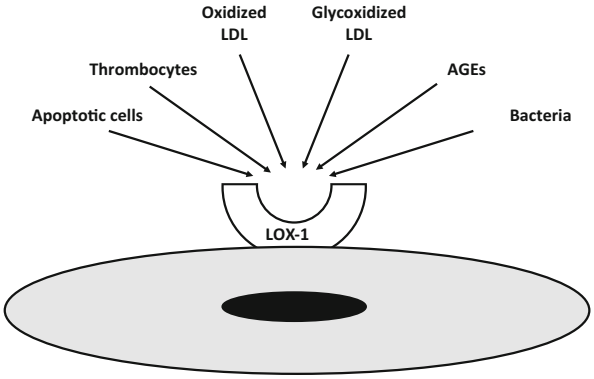

Fig. 10.1 The lectin-like oxLDL receptor LOX-1 mediates the uptake of oxidized or glycoxidized low-density lipoprotein (LDL) and advanced glycation end products (AGEs). In addition, it plays a role in endothelial phagocytosis of aged and apoptotic cells, thrombocyte adhesion, and the interaction between bacterial proteins and endothelial cells in sepsis

receptors expressed on NK cells. The exon-intron junctions in the carbohydrate recognition domain are well conserved between LOX-1 and other NK receptors (Yamanaka et al. 1998). The LOX-1 gene is located 200 kb telomeric of CD94. LOX-1 forms together with CLEC-1/CLEC1A, CLEC-2/CLEC1B, and DECTIN-1 a subfamily of C-type lectin domain receptor genes closely related to the NK receptor genes in the NK complex (Bull et al. 2000; Sobanov et al. 2001). DECTIN-1 shows the highest similarity with LOX-1, whereas CLEC-1/CLEC1A and CLEC-2/CLEC1B are more distantly related (Sobanov et al. 2001). C-type lectin receptors recognize endogenous proteinaceous ligands and are part of detection of virally infected and transformed cells. LOX-1 and other pattern recognition receptors (PRR) are expressed on the surface of myeloid cells like macrophages, dendritic cells (DCs), or neutrophils. PPRs are important for immediate innate immune response and also in regulation of adaptive immune response (Huysamen and Brown 2009; Sattler et al. 2012). Initially, C-type lectin receptors were defined by their carbohydrate-binding function, which is a calcium-dependent mechanism. In later studies, it became obvious that not all of these receptors bind exclusively carbohydrates, sometimes also independent of calcium (Sattler et al. 2012).

LOX-1 is considered to be a therapeutic target in atherosclerosis and cardiovascular disease (Kita 1999; Mehta et al. 2011; Morawietz 2010; Morawietz et al. 1999; Sawamura et al. 2015). Recently, novel roles of LOX-1 have been described in response to different danger signals (Sawamura et al. 2012), rheumatic diseases (Ishikawa et al. 2012), preeclampsia (English et al. 2013; Morton et al. 2012), and bone diseases (Nakayachi et al. 2015). The role of LOX-1 in immunity is less well understood. Therefore, this review article will focus on LOX-1 and immunity.

10.2 LOX-1, Atherosclerosis, and Immunity

The innate immune system is the first line of host defense against different pathogens and comprises eosinophil, neutrophil and basophil granulocytes, mast cells (MCs), monocytes, and macrophages as well as dendritic cells (DCs) and natural killer cells (NKs). These cells trigger inflammatory reactions, which are characteristic for specific diseases. Atherosclerosis is also an inflammatory disease, and innate immune cells are involved in the progression of plaque formation. MCs express PRR which are possible activated by microorganisms and allergens and trigger the release of inflammatory signals that can affect lesion development. Polymorphonuclear leukocytes (PMN) initiate the inflammatory response and are the first line of innate immunity. These cells produce reactive oxygen species (ROS), myeloperoxidase, proteolytic enzymes, and leukotrienes and thereby eliminate microbial pathogens and promote tissue destruction. Most of their functions originate from signal mediated through toll-like receptors (TLR) or C-type lectin receptors. NKs play an important role in response to viruses and tumors. Upon activation by affected cells, perforin-induced cytotoxicity and secretion of pro-inflammatory cytokines increase thus leading to elimination, induction of inflammation, and polarization of adaptive immune response. Production of IFN-γ is thought to be a key mechanism in lesion formation. Monocytes play an important role during progression of atherosclerosis. They mediate the recruitment and adhesion of monocytes to activated endothelial cells. Monocytes are thought to continuously repopulate macrophage or DCs and produce pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. Macrophages derive from monocytes, produce high amounts of ROS and pro-inflammatory cytokines like TNF-α or IL-1β, and participate in Th1 polarization (Chavez-Sanchez et al. 2014). Scavenger receptors (SR-AI/II, CD36, SR-BI, macrosialin/CD68, LOX-1) expressed on macrophages mediate oxLDL uptake and foam cell formation (Xu et al. 2013). DCs are also present in atherosclerotic lesions. During their maturation, they increase MHC molecules, chemokine receptors, and cytokine production and induce different subtypes of $CD4^+$ T cells as well as naive and memory B cells or NK cells (Chavez-Sanchez et al. 2014). LOX-1 expression was found on human monocytes, macrophages, peripheral blood myeloid DC, and B cells, whereas mature $CD83^+$ DCs and T lymphocytes do not express LOX-1 (Delneste et al. 2002; Delneste 2004). Human monocyte-derived macrophages express higher LOX-1 levels than monocytes. LOX-1 expression on primary human monocytes is very low, but differentiation into macrophages increases LOX-1 (Yoshida et al. 1998; Moriwaki et al. 1998). Especially, the role of LOX-1 in monocytes and macrophages was studied intensively in the last years. Several in vitro studies showed an inducible expression of LOX-1 by pro-inflammatory cytokines, which are involved in immune response. Upon recognition of antigen-MHC complexes on the surface of APCs, $CD4^+$ T cells differentiate into effector and regulatory subsets. These cells exert a different cytokine expression profile and belong to the adaptive immune response. Th1 cells mainly secrete IFN-γ, TNF-α, and IL-2, whereas Th2 cells

secrete IL-4. Th1 cells enhance cellular immune response and differentiate from naive T cells in response to IL-12 and IL-18. Differentiation of naive T cells toward Th17 cells, a subpopulation required during fungi and bacterial infections, depends on TGF-β, IL-6, and IL-1β (Ait-Oufella et al. 2014; Lintermans et al. 2014).

Tumor necrosis factor-alpha (TNF-α) and phorbol 12-myristate 13-acetate (PMA) increased LOX-1 expression and oxLDL uptake in endothelial cells (Kume et al. 1998), TNF-α increased LOX-1 expression in macrophages (Moriwaki et al. 1998; Hashizume and Mihara 2012) and vascular smooth muscle cells (Hofnagel et al. 2004). C-reactive protein (CRP), an acute-phase protein associated with progression of cardiovascular outcomes, can actively bind to LOX-1 and thereby activating the complement system via the classical C1q pathway. Blocking of LOX-1 by antibody reduced CRP-induced leukocyte infiltration (Fujita et al. 2011). Several other studies confirmed CRP-induced LOX-1 expression in macrophages (Zhao et al. 2011) and endothelial cells (Li et al. 2004). CRP stimulates oxLDL uptake into endothelial cells, an effect restored by a LOX-1-blocking antibody. LOX-1 expression was also enhanced by interleukin-6 (IL-6) in endothelial cells (Li et al. 2004; Lubrano and Balzan 2013) and transforming growth factor-beta 1 (TGF-β1) in macrophages (Draude and Lorenz 2000; Minami et al. 2000), endothelial cells, and smooth muscle cells (Minami et al. 2000). Several other cytokines are able to induce LOX-1 as well: IL-1α and IL-1β in vascular smooth muscle cells (Hofnagel et al. 2004), IL-4 in macrophages (Higuchi et al. 2001), and IL-18 in TNF-α-activated endothelial cells (Mitsuoka et al. 2009). Histamine is a key player in allergic reactions and is released from dense granules of mast cells and basophiles. Histamine-releasing cells are located in connective tissue, mucosal surface of the lung and the gastrointestinal tract, and dermis of the skin. LOX-1 expression was increased by histamine in monocytes and macrophages, underlining the connection between immune cells in atherogenesis (Higuchi et al. 2001; Tanimoto et al. 2001; Alanne-Kinnunen et al. 2014). Mast cells are histamine-releasing cells, but they also secrete IL-1α, IL-1β, TNF-α, TGF-β, or IFN-γ and link inflammation to atherogenesis. A recently published study underlines a novel role of LOX-1 in macrophages and mast cells. Media captured from activated primary human mast cells induced LOX-1 expression in human monocyte-derived macrophages. Cell culture media of mast cells contained histamine, TNF-α, TGF-β1, and IL-1α. Histamine, TNF-α, and TGF-β1 were able to induce LOX-1 expression also in a synergistic way. However, cellular uptake of oxLDL was not affected by secretory mast cell products. Mast cells neighboring macrophages may stimulate LOX-1 expression and thereby promoting a paracrine modulatory effect on their function. Therefore, LOX-1 could be a novel link between mast cell and macrophages in regulation of innate immune reactions in atherosclerosis (Alanne-Kinnunen et al. 2014). In vitro studies revealed that lipopolysaccharide (LPS) increases LOX-1 expression, augments cellular oxLDL uptake, and promotes foam cell formation. Treatment with an LOX-1 antibody reduced the cellular oxLDL uptake. It seems that LOX-1 promotes cellular oxLDL uptake in activated macrophages and contributes to cardiovascular diseases (Hossain et al. 2015).

A link between LOX-1 and toll-like receptors (TLRs) was also shown in macrophages. TLRs are pattern recognition receptors expressed on macrophages, dendritic cells, or other innate immune cells (Lee et al. 2008). TLRs are signaling receptors, involved in cell activation after contact with pathogens (Jeannin et al. 2005). Activation of TLR9 increased LOX-1 expression in macrophages and enhanced foam cell formation. TLR9 blockade reduced LOX-1 expression and foam cell formation. In contrast, LOX-1 induction and foam cell formation were found after activation of TLR1/2, TLR2, TLR5, and TLR6. TLR4 induced the strongest effect. Therefore, TLRs are able to induce foam cell formation, a mechanism that involves LOX-1 and supports its importance in atherogenesis (Lee et al. 2008).

10.3 LOX-1, Dendritic Cells, and Immunity

Monocytes are able to differentiate into dendritic cells (DCs), a specific subtype of leukocytes. DCs play an important role in the innate and adaptive immune response (Pirillo et al. 2013). Increasing evidence suggests that DCs are involved in the process of atherosclerosis by activating T cells and stimulation of vascular inflammation (Huang et al. 2012). DCs are antigen-presenting cells (APCs). Exogenous antigens are endocytosed by APC and mainly loaded into MHC class II molecules for recognition by $CD4^+$ T cells. In contrast, endogenous antigens are presented by MHC class I molecules to be recognized by $CD8^+$ T cells. Only DCs are able to present exogenous antigens in MHC class I molecules, a process called cross-presentation. In this case, DCs are able to prime both $CD4^+$ and $CD8^+$ T cells for generating cytotoxic T cell responses. The initiation of an immune response by DCs requires the capture and internalization of antigens by endocytotic receptors (Delneste 2004; Delneste et al. 2002). The first reports about a role of LOX-1 in dendritic cell-mediated antigen cross-presentation were published in 2002. This study showed that LOX-1 is a binding structure for heat-shock protein 70 (Hsp70) on DCs. An anti-LOX-1 monoclonal antibody partly prevented binding of Hsp70 to LOX-1 in DCs and macrophages. HSPs are chaperones that control the folding and prevent the aggregation of proteins. Tumor-derived HSPs initiate a protective and tumor-specific cytolytic T cell response (Delneste 2004). HSPs form complexes with non-covalent peptides derived from tumor antigens and bind to DCs and macrophages. The internalization requires mainly scavenger receptors and is followed by co-localization with MHC class I molecules (Delneste 2004). Targeting LOX-1 reduced the Hsp70-induced IL-2 production in vitro, suggesting a role of LOX-1 in antigen cross-presentation in MHC class I molecules. In addition, injection of a LOX-1 antibody triggered an antitumor response in a murine tumor model (Delneste et al. 2002). Further studies addressed the role of HSPs as ligands for LOX-1 in DCs. Hsp60 stimulates intracellular signaling molecules that serve as danger signals of stressed and damaged cells to the innate immune system. Hsp60 interacts with TLR2 and TLR4 and thereby induces a pro-inflammatory

response. Hsp60 binds to LOX-1 and is endocytosed by immature bone marrow-derived DCs. Hsp60 most likely delivers antigens that are incorporated into MHC class I molecules, as measured by an increased IL-2 secretion. Both, uptake and cross-presentation in MHC class I complexes were inhibited by a LOX-1 antibody. Inhibition of LOX-1 also decreased the number of cytotoxic T lymphocytes in response to Hsp65, a protein that elicits protective immunity against tumors (Xie et al. 2010). As described above, LOX-1 is expressed on mature DCs and is upregulated during the maturation process from monocytes to DCs. The best characterized LOX-1 ligand, oxLDL, is taken up by DCs. This process is prevented by a LOX-1-targeting antibody (Nickel et al. 2009; Delneste et al. 2002). OxLDL induces the maturation and differentiation of DC and increases secretion of pro-inflammatory IL-6, decreases anti-inflammatory IL-10, and enhances NF-κB activity in DCs (Nickel et al. 2009). Like oxLDL, angiotensin II (Ang II) is able to stimulate dendritic cell maturation, as measured by an increased CD83 and HLA-DR expression. Cytokines IL-12 and IFN-γ were increased as well. Treatment of DCs with oxLDL or Ang II increased proliferation of T cells. It seems likely that oxLDL increases Ang II secretion in DCs in an autocrine manner. Ang II is one player in oxLDL-induced maturation of DCs. OxLDL and Ang II induced the LOX-1 expression in DCs. AT_1 receptor blocker losartan could restore this. The direct inhibition of LOX-1 by an antibody suppressed oxLDL- and Ang II-induced maturation of DCs. An additional protective effect of losartan as standard therapy in hypertension and heart failure could be the inhibition of LOX-1 (Huang et al. 2012). A recently published study indicates that LOX-1 is also part of the humoral immune response. DCs treated with an anti-LOX-1 antibody (αLOX-1) promoted naive B cell proliferation and differentiation into plasma blasts (PBs) that secrete class-switched immune globulins (Igs). B cells co-cultured with αLOX-1-treated DCs increased their production of IgM, IgG, and IgA, indicating an increased Ig secretion. αLOX-1-treated DCs induced activated B cells to express CCR10. This promotes the migration toward the ligands CCL28 and CCL27. This upregulation in combination with the downregulation of CXCR5 enables PBs to migrate out of the germinal centers toward the mucosal site or to the skin (Joo et al. 2014). To simulate the differentiation of monocytes to DCs in vitro, cells were typically treated with interferon-α (IFN-α). During the differentiation process, LOX-1 levels are high, whereas further treatment with LPS to induce ultimate maturation decreases LOX-1. IFN-α-differentiated DCs internalize apoptotic allogenic lymphocytes and stimulate production of autologous $CD8^+$ T cells. Uptake and proliferative response of $CD8^+$ T cell were prevented by an anti-LOX-1 antibody, suggesting an important role of LOX-1 in both processes. $CD4^+$ T cells were additionally activated, however, to a lesser extent. A greater activation of CD8+ T cells is often seen in HSP-induced activation, also mediated by LOX-1 in IFN-α-differentiated DCs. $CD4^+$ T cells might act as helper cells to induce priming, expansion, and survival of cytotoxic $CD8^+$ T cells. IFN-α-induced LOX-1 expression in DCs and subsequent uptake of apoptotic cells lead to a simultaneous rearrangement of MHC class I and II molecules. An intracellular co-localization of apoptotic cells with MHC class I and II molecules was blocked by an LOX-1 antibody. LOX-1 seems to be an

important player in mediating endocytosis of apoptotic cells into IFN-α-shaped DCs and also in inducing molecules of MHC class I and II complexes. It is still under debate whether this pathway plays mainly beneficial or deleterious effects in cancer or autoimmune diseases (Parlato et al. 2010).

Earlier studies in endothelial cells revealed that LOX-1 mediates binding and phagocytosis of aged red blood cells and apoptotic cells. Phosphatidylserine (PS) is externalized during early steps of apoptosis and is recognized by LOX-1. LOX-1-mediated phagocytosis was inhibited by PS and oxLDL. Under physiological conditions, it might be possible that LOX-1 promotes removal of PS-positive cells to maintain the anticoagulant state of endothelial cells. However, under atherosclerotic conditions with increased oxLDL formation, aged and apoptotic cells remain in the blood stream and can promote thrombotic events (Oka et al. 1998).

First studies revealed that LOX-1 supports the adhesion of Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria to endothelial cells. A monoclonal LOX-1 antibody blocked the binding of both types of bacteria. TNF-α treatment further enhanced the adhesion of *Escherichia coli* to endothelial cells, whereas *Staphylococcus aureus* did not while requiring additional molecules in this setting (Shimaoka et al. 2001). LOX-1 is also part of the recognition of outer membrane protein A (OmpA), a major compound of the outer membrane of Gram-negative *Enterobacteriaceae*. OmpA is a highly conserved moiety for recognition by innate immune receptors. Next to LOX-1 as an endocytotic receptor, toll-like receptor (TLR)-2 is required in the OmpA-induced innate immune response. LOX-1 and TLR2 co-localize and cooperate to trigger subsequent TLR2-mediated cellular responses (Jeannin et al. 2005). Attachment of bacteria to endothelial cells as well as mucosal or epithelial cells is an initial step in bacterial infections. LOX-1 seems to be involved in this process as a cell surface receptor (Jeannin et al. 2005; Shimaoka et al. 2001).

Recently published data underlined the role of LOX-1 in the adhesion of bacterial proteins to macrophages. GroEL is expressed on the surface of common bacteria and is involved in attachment and immune modulation. GroEL in *E. coli* is induced by heat-shock stress and increases phagocytosis by macrophages. LOX-1 facilitates the uptake of *E. coli* in macrophages, mainly by interaction with GroEL. This effect was inhibited by an anti-LOX-1 antibody. Furthermore, GroEL increases LOX-1 expression in macrophages, an effect also seen for other HSPs. Targeting LOX-1 by using a specific antibody increased survival of *E. coli*-induced peritonitis in mice (Zhu et al. 2013).

LOX-1 seems to be involved in the process of endotoxin-induced inflammation as well. Inhibition of LOX-1 could rescue rats from death after LPS treatment. Additionally, leukopenia was reduced by anti-LOX-1 treatment. In a rat model of low-dose endotoxin-induced uveitis, blocking of LOX-1 reduced the number of infiltrated leukocytes and protein exudation. In vivo experiments in retinal blood vessels confirmed that inhibition of LOX-1 decreases the number of rolling leukocytes and increases their velocity. LOX-1 seems to be an adhesion molecule promoting leukocyte recruitment and rolling during endotoxin-induced

inflammation (Honjo et al. 2003). An important role of LOX-1 during sepsis was shown in mice lacking the functional active LOX-1 (LOX-1$^{-/-}$). These animals have substantial higher survival rates after inducing sepsis by cecal ligation and puncture, suggesting that LOX-1 is able to modulate host response. Systemic and lung-specific TNF-α and IL-6 levels were lower in septic LOX-1$^{-/-}$ mice and bacterial clearance as represented by reduced colony forming units (CFU) in peritoneal cavity.

Neutrophils are a subpopulation of leucocytes and play a pivotal role in host defense and during sepsis. Neutrophil migration is impaired during sepsis. LOX-1$^{-/-}$ mice revealed an increased number of neutrophils, less affected chemotaxis, and an improved CXCR2 surface expression which might help to maintain a better neutrophil response. Neutrophils also express higher levels of LOX-1. LPS treatment affects rather LOX-1 surface than total protein expression. The increased neutrophil surface expression during sepsis is modulated by TLR2 and TLR4 (Wu et al. 2011). An association between LOX-1 and TLR2 and TLR4 was shown in monocyte-derived DCs. Activators of TLR2 and TLR4 increased LOX-1 expression. Diesel exhaust particles (DEP) as major air pollutants from diesel cars further enhanced LOX-1 expression. It seems likely that DEP modulate signaling pathways activated by TLR and thereby control SR expression. These data suggest that LOX-1 and other SRs play also a role in DEP-induced lung diseases (Taront et al. 2009).

10.4 Conclusion

In conclusion, the LOX-1 receptor mediates a variety of physiological and pathophysiological processes. LOX-1 could be a therapeutic target in the pathogenesis of atherosclerosis, rheumatic, and bone diseases. Increasing evidence supports a novel role of LOX-1 in dendritic cells and immunity.

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