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Review

LOX-1 and atherosclerotic-related diseases

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ABSTRACT

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), a scavenger receptor of oxidized low-density lipoprotein (ox-LDL) found in various cells, plays a crucial role in the formation and progression of atherosclerotic plaques. Animal studies have suggested that LOX-1 mediates the balance between internalization and degeneration of endothelial cells, thereby contributing to various steps in the atherosclerotic process, from initiation to plaque rupture. Under pathological conditions, the extracellular domain of membrane bound LOX-1 can be largely proteolytically cleaved into a soluble form (sLOX-1), which is proportional and linked to the LOX-1 expression level. Circulating levels of sLOX-1 are regarded as a risk biomarker for plaque rupture and acute coronary syndrome (ACS). Recently, studies have shown that sLOX-1 is also elevated in patients with acute stroke and can be a predictive biomarker for acute stroke. With the discovery of the vital role of LOX-1 in atherosclerosis, there is growing focus on the influence of LOX-1 in atherosclerotic-related diseases, including coronary arterial disease(CAD), stroke, and other cardiovascular events. Genetic polymorphisms of LOX-1 have been investigated and have been found to modulate the risk of these diseases. Most polymorphisms have been found to be risk factors, except for the splicing isoform LOXIN. This review concludes with a discussion of the potential future applications of LOX-1 for atherosclerotic-related diseases.

1. Introduction

Endothelial dysfunction together with modified lipid deposition are the main causes of atherosclerosis initiation. ox-LDL plays an important role in triggering fatty streak formation through the interaction with LOX-1. LOX-1 is the major contributor to ox-LDL uptake, internalization, and degradation in various cells. This promotes plaque formation and triggers disease progression via several mechanisms, including the induction of endothelial cell activation and dysfunction, the transformation of macrophages into foam cells, and smooth muscle cell (SMC) migration and proliferation [1]. A series of studies have demonstrated that oxidative stress can promote LDL-cholesterol oxidation to form ox-LDL [2]. This leads to the up-regulated expression of cellular LOX-1. The interaction between ox-LDL and LOX-1 leads to an increase in the production of reactive oxygen species, aggravating oxidative stress and causing the formation of more ox-LDL. Thus, the key to blocking this positive circulatory loop is to prevent high expression of LOX-1.

LOX-1 is a 50 kd transmembrane glycoprotein that belongs structurally to the C-type lectin family and is expressed in vascular endothelium and vascular-rich organs. It was first cloned in bovine aortic endothelial cells and is important in receptor mediated binding, internalization, and degeneration of ox-LDL [3]. Human LOX-1 contains 273 amino acid residues encoded by the lectin-like oxidized low density lipoprotein receptor 1 (OLR1) gene, a single copy gene located in the p12.3–p13.2 region of human chromosome 12 [4]. It is divided into an N-terminal cytoplasmic domain, a transmembrane domain, an extracellular stalk region (which mediates receptor oligomerization), and a C-type lectin-like extracellular domain (which is responsible for binding with ligands) [5]. The integrity of the extracellular domain is necessary for LOX-1 to interact with ligands and has also been shown to be highly conserved in other species [6]. Endothelial cells were the first cells identified to express LOX-1 as major scavenger receptors of ox-LDL; however, monocytes/macrophages, SMCs, platelets, fibroblasts, cardiomyocytes, and neurons have also been found to express LOX-1 [2]. Further, studies on the ligands of LOX-1 have revealed a diverse range of ligands other than ox-LDL, including bacteria, C-reactive protein (CRP), activated platelets, and apoptotic cells [7]. Furthermore, LDL could promote the prognosis of atherosclerosis by upregulating the expression of angiotensin II receptor type I, which further regulates the induction of LOX-1 [8,9]. The basal cellular expression of LOX-1 is low, but can be rapidly evoked by proinflammatory cytokines , vasoconstrictors and advanced glycation end products. In turn, activation of

*Abbreviations:*ARD, atherosclerotic-related diseases

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LOX-1 induces a state of oxidative stress, leading to further oxidation of native LDL cholesterol and promotion of the progression of endothelial dysfunction. Cellular LOX-1 expression is also elevated in patients with risk factors for atherosclerosis, including those with hypertension, diabetes, hypercholesterolemia, and cigarette smoking [1].

2. Novel contributors to atherosclerotic-related diseases

Similar to LOX-1, the basal circulating levels of sLOX-1 are very low, but can be rapidly elevated under pathological conditions; this can promote plaque instability. It is well-known that sLOX-1 levels are a predictor of coronary plaque vulnerability; significantly elevated sLOX-1 levels appear to be more sensitive to the presence of acute coronary syndrome (ACS) without myocardial necrosis, as compared to traditional markers such as troponin T (TnT) and CRP [10]. sLOX-1 is also related to the prognosis of myocardial infarction (MI); recurrent MI and long-term all-cause mortality are higher among those with high sLOX-1 levels (sLOX-1 level $>$ 71 pg/ml) compared to those with low sLOX-1 levels (sLOX-1 level $\leq$ 71 pg/ml) [11]. Higher levels of sLOX-1 have also been observed in patients with a coronary slow flow pattern compared to a normal coronary flow pattern [12]. sLOX-1 is the soluble form of LOX-1 which is cleaved in the NECK domain. The NECK domain is stabilized with a coiled-coil heptad repeat motif structure in its normal state; however, mobile inter-helix space increases the susceptibility of the NECK domain to proteolytic cleavage [13]. Activation of both tumor necrosis factor-α converting enzyme (TACE) and ROS are reported to play a role in the cleavage and release of sLOX-1 induced by CRP [14]. The exact molecular mechanism of LOX-1 cleavage remains unclear; future research is needed to elucidate the underlying molecular mechanisms.

A novel assay for the atherogenic effects of modified LDL has been developed. This assay measures the LOX-1 ligand containing apoB (LAB) using recombinant LOX-1 and monoclonal anti-apolipoprotein B antibodies, instead of one specific antigenic determinant; thus, this assay provides a more comprehensive measure of modified LDL concentration. In a study of 992 community-dwelling Japanese men, Okamura et al. [15] found that the forth LAB quartile (842 μm) had the highest risk of increased carotid intima-media thickness (IMT) compared to the first quartile (797 μm). This difference was observed even after adjusting for confounding risk factors; however, after further adjustment for total cholesterol, this difference was no longer statistically significant. Thus, it is difficult to identify whether LAB alone has an effect on carotid thickness. A positive effect of hyperlipidemia on LAB activity has already been established and high levels of LAB activity are associated with hypercholesterolemia.

It is very difficult to quantitatively evaluate LOX-1 expression levels; therefore, a LOX-1 index has been proposed as another biochemical maker to directly and simply evaluate the activation of LOX-1. The LOX-1 index is acquired by multiplying the plasma concentration of sLOX-1 with that of LAB. Inoue et al. [16] performed a cohort study of 2437 residents and followed them up over an 11 year period to explore the relationships between the LOX-1 index and both coronary heart disease (CAD) and stroke. A novel assay was used, with either recombinant LOX-1 and monoclonal anti–apoB antibodies or with two monoclonal antibodies against LOX-1. The results revealed that the participants in the top quartile of the serum LOX-1 index had twice the risk for CAD and three times the risk of stroke, as compared to the bottom quartile, after adjusting for confounding risk factors. Thus, the LOX-1 index may be a novel diagnostic and prognostic marker for atherosclerotic-related events. sLOX-1 is primarily a predictor of ACS but not chronic coronary diseases. Therefore, we propose that the LOX-1 index may be a chronic maker for predicting susceptibility to CAD; however, sLOX-1 may be an acute maker for the occurrence of deterioration of cardiovascular disease or even life-threatening plaque rupture.

Electronegative L5-LDL has been shown to promote vascular inflammation through its interaction with LOX-1. Plasma L5 has been found to be elevated in ST-elevation MI, together with increased levels of inflammatory cytokine IL-1β. Elevated L5 induces activation of caspase-1 and NF-κB in macrophages via the LOX-1 signaling pathway. Recently, Shen et al. [17] demonstrated that the plasma L5 level of ischemia stroke patients was higher than that of healthy patients; ischemic stroke patients also exhibited platelet activation and increased LOX-1 expression in platelets and macrophages. As the mild ox-LDL of the LDL subfraction, L5-LDL can promote platelet activities to release the amyloid β (Aβ) peptide via the LOX-1/IκB kinase 2 (IKK2) signal axis; thus, L5 and Aβ synergistically participate in the progression of ischemic stroke [17]. However, it is not clear whether LOX-1 directly recognizes Aβ to increase risk of stroke. This article also suggested that L5 may be a candidate therapy target for treatment. Given that many biomarkers have been identified, it is crucial to explore their maximal practical value and the relationship between each biomarker and disease. All biomarkers have advantages and shortcomings. Gaining maximum value from biomarkers will improve the diagnostic rate of disease.

3. LOX-1 mediates effects in CAD

3.1. LOX-1 interacts with risk factors of CAD

CAD is the primary critical cardiovascular event caused by coronary artery luminal obstructions and atherosclerotic plaque cracks associated with atherosclerosis. Many animal and human studies have shown that LOX-1 expression can be up-regulated by well-known coronary risk factors, including hypertension, hyperlipidemia, and diabetes mellitus. Furthermore, relationships between LOX-1 and other risk factors, including sex, smoking, and alcohol consumption, have been reported. The morbidity of CAD in males is higher than in premenopausal females; this suggests a role of the sex hormones, with androgen acting as a protective factor. It is speculated that high levels of androgen may reduce LOX-1 expression. Further, in a rabbit CAD model where rabbits were fed a cholesterol-rich diet, testosterone replacement was shown to reduce LOX-1 expression at the transcription and translation level, inhibiting the development of atherosclerosis [18]. Oxidative stress is the main mechanism underlying the inflammation of blood vessels induced by smoking. The intensity of cigarette smoking and the concentration of expired carbon monoxide has been demonstrated to correlate with elevated LOX-1 expression, as evaluated by increased serum sLOX-1 and high-sensitivity CRP (hs-CRP) levels. However, this study lacked a non-smoking control group [26]. Nonetheless, the evidence suggests that LOX-1 plays a role in smoking-induced inflammation and acts through an interaction with oxidative stress. Another study reported that the LOX-1 index significantly decreased from baseline to three months after the onset of smoking cessation therapy; correlations between the LOX-1 index and smoking-related factors, such as hs-CRP level, LDL-C level, and expired CO concentration, were also identified after adjusting for sex [19].

The relationship between oxidative stress and the inflammatory reaction has been implicated in the formation and progression of CAD. Growing evidence has demonstrated that the activity of cellular LOX-1 plays an important role in oxidative stress-induced cardiomyocyte necrosis and apoptosis. LOX-1 expression can be elevated by multiple stimuli, including oxidative stress and inflammatory cytokines and chemokines. In turn, activated LOX-1 can aggravate the state of oxidative stress through decreasing the release of nitric oxide and promoting the release of the superoxide anion [20]. LOX-1 gene knockout or the administration of an anti-LOX-1 antibody can inhibit ischemic-reperfusion injury in the brain and heart. Further, many drugs can inhibit LOX-1 expression through other signaling pathways to attenuate the damage associated with oxidative stress [21]. ox-LDL contributes to the development of endothelial dysfunction and apoptosis of vascular cells via overexpression of LOX-1 in endothelial cells; this effect can be

increased by overproduction of ROS [22]. LOX-1 as scavenger receptor can mediate the proatherogenic effect of several risk factors. Recent studies have suggested that L5 level is elevated in MI. Furthermore, L5-LDL can induce inflammation factor 1 beta via LOX-1 in macrophages and endothelial cells. However, the LOX-1 signaling pathway is not the only; other signals are still recovered and there is a complementary relationship between physiological function and pathogenic function. However, we still do not know the physiological function of the low level of LOX-1 under basal expression. If it is not involved in normal processes, and is only a potential pathogenic risk factor, knockout of the OLR1 gene maybe the most efficient method to protect the vascular system from the interaction between LOX-1 and the risk factors for atherosclerosis.

3.2. LOX-1 polymorphisms have been found in coronary disease

OLR1 gene polymorphisms, such as the coding gene of LOX-1, have been examined in many patients with CAD and their influence on CAD susceptibility has been investigated. Seven SNP polymorphisms have been identified in the OLR1 gene, including one coding located in G501C of exon 4 and another six non-coding polymorphisms within intron 4, intron 5, and the 3′UTR; these have been shown to be associated with increased susceptibility to CAD, especially in MI. Trabetti and his team [23] demonstrated that OLR1 G501C, which encodes a K167 N substitution, can increase the number of obstructed vessels and incidence of MI. Paquette et al. [24] studied 665 special adult patients who were genetically confirmed to have familial hypercholesterolemia (FH) and explored the connection between the OLR1 rs11053646 variant and CAD risk. This study concluded that carrying the C allele is associated with an increased risk of CAD in younger patients with FH as well as in smokers. On the other hand, the six non-coding SNPs comprise a complete linkage disequilibrium (LD) block and this LD block within the SNPs was shown to exhibit a strong association with MI, especially with respect to 3′UTR188C > T [25]. However, the correlations between 3′UTR188C > T and both coronary artery stenosis and MI were not replicated in a cohort study of an Italian sample [26]. In another study, a mate analysis of all published related studies on G501C and 3′UTR188C > T suggested that variants of both are associated with CAD as low penetrant risk factors [27].

Several studies have demonstrated that some intronic SNPs are linked to susceptibility to MI through regulation of the expression of a new functional protective splicing isoform of the OLR1 gene called LOXIN [28]. LOXIN, a new isoform lacking exon 5, is responsible for the functional region involved in ligand binding. It interacts with full-length LOX-1 to form LOX-1 oligomers and reduces the appearance of LOX-1 receptors in the plasma membrane, thereby mediating a marked impairment in ox-LDL binding and uptake. LOXIN has been found to be a protective factor for LOX-1-induced atherosclerosis associated with CAD. However, Cappelletti and colleagues [29] did not find any correlation between LOXIN and severity or prognostic localization of CAD on the left main and/or proximal left anterior descending artery; there was also no significant association between coronary risk factors and the OLR1 polymorphism. It remains unclear whether the OLR1 gene can be considered a biomarker risk factor for MI.

The primary studies on the OLR1 gene polymorphisms associated with cardiovascular disease are listed in Table 1.

3.3. sLOX-1 as a biomarker for CAD

SLOX-1, the soluble form of LOX-1 found in circulating blood, reflects the expression level of the membrane-bound receptor and can be up-regulated by inflammatory stimuli. Hayashida et al. [10] first reported that sLOX-1 significantly increased before the onset of acute coronary syndrome (ACS) and peak sLOX-1 values were observed before peak TnT values were observed, reflecting instability of the atherosclerotic plaques rather than myocardial cell damage. These findings suggest that sLOX-1 is more sensitive to early diagnosis before plaque rupture, as compared to TnT or hs-CRP. Similarly, Kume et al. [32] reported that the area under the receiver-operating characteristic curve for sLOX-1 had higher diagnostic sensitivity and specificity for ACS, compared to that of TnT and heart-type fatty acid binding protein (H-FABP). In another study, clear increases in sLOX-1 levels were observed in recurrent ACS compared with a group of patients not relapsing, while there was no difference in TnT and hs-CRP [33] between the groups. Thus, sLOX-1was not only able to detect ACS in those whose TnT levels were not significantly elevated, but sLOX-1 levels were also associated with prognosis after ACS. Taken together, these data suggest that the combination of TnT and sLOX-1 can be used to evaluate the diagnostic accuracy of ACS. Serum sLOX-1 level can reveal the severity of ACS; patients with ST elevation or plaque rupture have higher sLOX-1 levels than those without. Further, sLOX-1 levels can indirectly reflect the lesion site; LAD lesions producing damage in the proximal or middle segments are associated with higher sLOX-1 levels than lesions in the distal segment.

Aside from ACS, sLOX-1 levels are also associated with stable CAD; sLOX-1 levels can be used to evaluate the severity of stable CAD. Serum sLOX-1 levels were found to be higher in stable CAD patients with complex lesions compared to those with a single lesion, and sLOX-1 levels were found to be independent predictors of lesion complexity [34]. Percutaneous coronary intervention-related periprocedural myocardial infarction (PCI-RPMI) is the main adverse outcome associated with PCI therapy for stable CAD; thus, it is important to evaluate whether or when PCI therapy should be used in a stable CAD patient. Balin et al. [35] examined 214 consecutive stable patients undergoing elective NSV-PCI to explore the relationship between sLOX-1 levels and PCI-RPMI, which was confirmed as elevated CK levels of at least three times the upper limit of the normal value range accompanied by elevation of CK-MB and TnT. The authors found that sLOX-1 levels were significantly higher in PCI-RPMI(+) than PCI-RPMI(−) patients and were positively correlated with CK, CK-MB, and TnT. These findings indicate that the higher the sLOX-1 level, the greater the likelihood of PCI-RPMI. sLOX-1 may help to identify risk of periprocedural MI before therapeutic strategies for stable CAD are implemented.

Table 1
The association of OLR1 gene polymorphisms with cardiovascular diseases.

Marker	Disease	References
K167 N	CAD with FH	Paquette [24]
K167 N G/G	Obstructed vessels	Trabetti et al. [23]
3′UTR(C > T	AMI	Mango et al. [25]
3′UTR(C > T)	CAD	Cheng [30]
LOXIN	Protective against AMI	Mango [31]
IVS4–14 A > G	No association with CAD	Cappelletti [29]

4. LOX-1 mediates effects in stroke

4.1. LOX-1 interacts with risk factors for stroke

Stroke is one of the leading causes of long-term acquired disability and death around the world. It is characterized by inefficient blood flow support caused by arterial obstruction or hemorrhage. Unlike MI, which is often caused by atherosclerosis affecting coronary arteries, there are many complicated risk factors associated with stroke due to the many varieties of stoke. At the most basic level, stroke can be divided into two types: hemorrhagic and ischemic stroke. Hypertension is the important risk factor for hemorrhagic stroke. Dyslipidemia causes atherosclerosis of intracranial blood vessels. LOX-1 can be activated by angiotensin II (AngII) via its typeIreceptor (AT1R) to regulate blood pressure. AngII induced hypertension was found to be significantly attenuated in LOX-1 deletion mice infused with Ang IIfor four weeks [36]. However, there was no clear correlation between LOX-1 expression levels and degree of

sharply fluctuating blood pressure, as the main cause of brain hemorrhage. LOX-1 participates in the pathogenesis of neuron apoptosis evoked by hypertension [37]. Further, LOX-1 was identified to interact with immune activities and oxidative stress in the brain tissue of mice with AngII induced hypertension [38]. Hypertension also can promote the overexpression of endothelial cellular LOX-1. There are no direct studies of LOX-1 in hemorrhagic stroke; however, a single study examined the association between elevated LOX-1 expression under subarachnoid hemorrhage. This study found that overexpression of LOX-1 may increase the incidence of vasospasm [39].

Overexpression of LOX-1 driven by traffic-generated air pollution was shown to aggravate inflammatory and oxidative stress during brain microvascular dysfunction in ApoE knockout mice [40]. Furthermore, administration of LOX-1 antibody treatment was also found to attenuate expression of MMP and lipid peroxidation. In another study [41], high expression of LOX-1 in the foci of affected cerebral vasculature was observed after inhalation exposure to traffic-generated air pollutants in a high-fat diet animal model of stoke; this was similar to what has been observed with the ox-LDL scavenger receptor CD-36. The affected cerebral vasculature was found to exhibit increased inflammatory MMP-9 activity and oxidative stress together with increased blood brain barrier permeability.

4.2. LOX-1 polymorphisms found in stroke

In contrast to the large body of research on OLR1 gene polymorphisms in cardiovascular disease, there is little research on OLR1 in stroke, and studies to date are restricted to east Asian ethnicities. Recently, Guo et al. [42] demonstrated that the LOX-1 gene rs1050283 polymorphism was associated with atherosclerotic cerebral infarction susceptibility; patients with the rs1050283 T allele had higher expression levels of LOX-1 and higher serum concentrations of sLOX-1. However, the earlier study by Liu et al. [43] reported no significant association between 3'-UTR-C188T and cerebral infarction. It is the G501C variant of OLR1 that may be associated with susceptibility to cerebral infarction among the northern Chinese Han population. Even after adjusting for confounding risk factors associated with cerebral infarction, this relationship remained. This assertion is supported by a meta-analysis of 1898 cases and 2119 controls; this study found that the C allele of G501C increases the risk of stoke [44]. Finally, another study reported that ischemic stroke patients with the G allele recover better than those with the C allele when examined six months after discharge from hospital; however, this study reported no difference between genotypes with respect to ischemic stroke severity at admission [45].

The LOXIN splicing isoform appears to be protective for MI. LOXIN, which is the LOX-1 isoform lacking domain interaction with ox-LDL, is regulated by the polymorphisms of the OLR1 gene within the linkage disequilibrium block, including intron 4 IVS4–14, IVS4–73, and IVS4–27. Vietri et al. [46] studied 43 patients with ischemic cerebrovascular disease and 69 healthy controls; they analyzed the IVS4–14 A/G and IVS4–73C/T SNP polymorphisms and found that the patients with G homozygosity for the IVS4–14 polymorphism and T homozygosity for the IVS4–73 polymorphism had an increased risk of cardiovascular disease. They also found that the A allele was responsible for the expression of the LOXIN protein and the G allele determined expression of the LOX-1 protein, indicating that LOXIN may play a protective role in the pathogenesis of ischemic cerebrovascular disease. Considering that the increased risk of CAD associated with OLR1 SNPs was not observed in a large population cohort (~13,000 individuals) in the ARIC study [47], the association between LOXIN and cerebrovascular disease should be further explored in studies with large sample sizes. Further, to more clearly explore the effect of SNPs of the OLR1 gene, genetic background, environmental factors, and ethnic variation should be considered.

The associations between OLR1 gene polymorphisms and cerebrovascular diseases are listed in Table 2.

Table 2
The association of OLR1 gene polymorphisms with cerebrovascular diseases.

Marker	Disease	Reference
rs11053646	Ischemic stroke	Zhang et al. [45]
rs11053646	Carotid plaque	Wang et al. [48]
IVS4–14 A/G	ICVD	Vietri et al. [46]
IVS4–73C/T	ICVD	Vietri et al. [46]
rs1050283	Atherosclerotic cerebral infarction	Guo et al. [42]

4.3. sLOX-1 as predictive maker for stroke

In emergent state ACS, serum sLOX-1 largely increases and is potentially useful as a diagnostic biomarker for ACS, together with TnT and CRP. Therefore, we predict that sLOX-1 can be used as a predictive biomarker for future emergent state stroke. The literature suggests that the impact and predictive effect of sLOX-1 on stroke events depends on the type of stroke. Yokota et al. [49] investigated 377 patients with stroke and healthy controls matched on age and sex. They examined serum sLOX-1 with ELISA using two monoclonal antibodies against LOX-1. The findings revealed that median serum sLOX-1 levels in patients with atherothrombotic cerebral infarction were significantly higher than those in controls: 641 vs. 496 ng/l($p = 0.02$), while there was no difference between sLOX-1 levels in other subtypes of stroke, such as cardioembolic stroke and lacunar infarction. Furthermore, this study also analyzed differences in sLOX-1 levels between patients with acute stroke and controls. Ischemic stroke patients had higher sLOX-1 levels than controls: 526 vs. 486 ng/l ($p = 0.009$) and intracerebral hemorrhage patients had higher levels than controls: 720 vs. 513 ng/l ($p < 0.001$). These findings indicate that high levels of sLOX-1 can predict acute stroke events.

Similarly, in another study, serum sLOX-1 levels were found to be significantly elevated in patients with large-artery atherosclerotic (LAA) ischemic stroke [50]. This study also found that serum sLOX-1 levels were lower in stroke patients with good nervous functional outcome compared to those with poor nervous functional outcome, and sLOX-1 levels were negatively correlated with modified Rankin Scale scores. Skarpengland et al. [51] reported that patients with acute ischemic stroke and transient ischemic stroke caused by either carotid atherosclerosis or atrial fibrillation had comparable elevated sLOX-1 levels; the elevated sLOX-1 levels were independent of the time since relevant cerebral ischemic symptoms and were prolonged for at least three months. As sLOX-1 levels in ACS were observed to reach peak values within one day of admission, sLOX-1 levels may be an early predictive biomarker for ACS. It is likely that the utility of sLOX-1 levels as a predictive biomarker for stoke will depend not only on the degree of elevation but also on the time that the peak sLOX-1 value occurs. sLOX-1 levels may be elevated in the presence of acute stroke, independent of the etiology, but whether they are elevated in patients with stroke during a retrospective cohort study appears to depend on the stroke subtype. In other words, elevated sLOX-1 levels in stroke caused by atherosclerosis may last longer than elevated sLOX-1 levels in other stroke subtypes; therefore, sLOX-1 levels may be used to distinguish atherosclerotic stoke from other subtypes.

5. LOX-1 mediates effects in other cardiovascular events

Atherosclerosis is associated with hypertension, although there is a still significant debate as to whether hypertension is the cause or the result of atherosclerosis. Ding et al. reported that LOX-1 knockout mice exhibited less of an increase in blood pressure than wild-type mice under control infusion of Ang II. At the same time, the experimental group showed less expression of NADPH oxidase and less activation of P38 MAPK, nuclear factor-KB, autophagy-related proteins, and TLR4, implying an association between LOX-1 and both redox signals and immune activation in hypertension [38]. LOX-1 has also been

implicated in the pathogenesis of hypoxic pulmonary hypertension in mouse models; differentiation of pulmonary arterial smooth muscle cells (PASMCs) and pulmonary vascular remodeling were both accompanied by overexpression of LOX-1 and this pathogenic effect was weakened by either LOX-1 siRNA knockdown or antibodies directed against LOX-1 [52]. Further, LOX-1 was found to be overexpressed in the pathogenesis of chronic hypoxia pulmonary hypertension and right ventricular hypertrophy, accompanied by an increase in NADPH oxidases (NOX); LOX-1 knockout was found to attenuate h9c2 hypertrophy through decreasing production of NOX2/4 and ROS [53].

Several studies have suggested that LOX-1 may participate in the process of cardiac damage associated with hypertension, and sLOX-1 levels are suggested to be related to the ejection function of the left heart. sLOX-1 levels have been shown to be higher in essential hypertension with left ventricular hypertrophy (LVH) than in essential hypertension without LVH, and SNP polymorphisms of the LOX-1 gene (G501C) together with sLOX-1 levels may be used to predict the development of LVH in hypertension [54]. In patients with ischemic cardiomyopathy, sLOX-1 levels are higher in patients with left ventricular systolic heart failure than in patients without it, and sLOX-1 levels are negatively correlated with left ventricular ejection fraction [55]. LOX-1 deletion can not only inhibit AngII-induced cardiac remodeling, but can also attenuate cardiac remodeling evoked by chronic ischemia through decreasing collagen accumulation and the response to AngII in mouse models [56].

High LOX-1 activity has been observed in many atherosclerotic diseases, except for non-coronary arterial diseases. High circulating blood sLOX-1 levels had been reported to occur in early stage AAD. Patients with AAD have much higher sLOX-1 levels and lower TnT levels than patients with non-ST elevation ACS; therefore, the combination of sLOX-1 and TnT can distinguish between AAD and non-ST elevation ACS [57]. Further, type 2 diabetes patients with peripheral arterial disease (PAD) have been shown to have higher sLOX-1 levels compared to those without PAD, and sLOX-1 levels were negatively correlated with ankle-brachial index (ABI), a noninvasive measure for evaluation of blood flow in the lower extremities [58].

6. Conclusion

In summary, the scavenger receptor LOX-1 is an important signal factor in the progression of atherosclerotic disease and its complications. Multiple studies have reported that the interaction between LOX-1 down signals and oxidative stress signals participates in ox-LDL-induced atherosclerosis. Several risk factors can up-regulate the expression of LOX-1 and elevate serum sLOX-1; in turn, activated LOX-1 can promote inflammatory factors and activate oxidative stress, aggravating the pathogenesis of related diseases. LOX-1 gene knockout or the administration of an anti-LOX-1 antibody can prevent the progress of atherosclerosis through inhibit the binding of the inflammatory factors to LOX-1 [59]. Furthermore, many drugs can attenuate the damage caused by atherosclerosis associated inflammation response by inhibiting LOX-1 expression [60].LOX-1 may be a potential novel target to prevent atherosclerotic plaques, from formation to rupture. Genetic studies have revealed that the G501C SNP of the OLR1 gene, which encodes the domain structure of cellular LOX-1, is the most potent risk SNP for CAD and ischemic stroke; further studies with large sample sizes are required to identify other potential risk SNPs. The LOXIN isoform, as a protective against LOX-1-induced damage, may also be a potential target for treating atherosclerotic-related diseases [61]. However , The association between the OLR1 gene and stroke has not been well established, and needs further investigations.

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