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LOX-1 and Angiotensin Receptors, and Their Interplay

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Abstract The renin-angiotensin system (RAS) plays an important role in regulating blood pressure, water-salt balance and the pathogenesis of cardiovascular diseases. Angiotensin II (Ang II) is the physiologically active mediator and mediates the main pathophysiological actions in RAS. Ang II exerts the effects by activating its receptors, primarily type 1 (AT1R) and type 2 (AT2R). Most of the known pathophysiological effects of Ang II are mediated by AT1R activation. The precise physiological function of AT2R is still not clear. Generally, AT2R is considered to oppose the effects of AT1R. Lectin-like oxidized low-density lipoprotein scavenger receptor-1 (LOX-1) is one of the major receptors responsible for binding, internalizing and degrading ox-LDL. The activation of LOX-1 has been known to be related to many pathophysiological events, including endothelial dysfunction and injury, fibroblast growth, and vascular smooth muscle cell hypertrophy. Many of these alterations are present in atherosclerosis, hypertension, and myocardial ischemia and remodeling. A growing body of evidence suggests the existence of a cross-talk between LOX-1 and Ang II receptors. Their interplays are embodied in the reciprocal regulation of their expression and activity. Their interplays are involved in a series of signals. Recent studies suggests that reactive oxygen species (ROS), nitric oxide (NO), protein kinase C (PKC) and mitogen activated protein kinases (MAPKs) are important signals responsible for their cross-talk. This paper reviews these aspects of dyslipidemia and RAS activation.

Key words LOX-1·AT1 receptor (AT1R) · AT2 receptor (AT2R) · Reactive oxygen species · Atherosclerosis · Hypertension

Abbreviations

ACE2	angiotensin converting enzyme-2
Ang II	angiotensin II
AP-1	activating protein-1
ARBs	AT1R blockers
AT1R	angiotensin II type 1 receptor
AT2R	angiotensin II type 2 receptor
BK	bradykinin
cGKI	cGMP kinase inhibitor
cGMP	cyclic guanosine monophosphate
CNS	central nervous system
eNOS	endothelial nitric oxide synthase
ERK	extracellular regulated kinase
FAK	focal adhesion kinase
GPCRs	G-protein-coupled receptor superfamily
HCAECs	human coronary endothelial cells
IC3	intracellular loop 3
iNOS	inducible nitric oxide synthase
JAK	januse kinase
JNK	c-jun-NH2-terminal kinase
KO	knockout
LDLR	low-density lipoprotein receptor
LOX-1	lectin-like oxidized low-density lipoprotein scavenger receptor-1
MAPK	mitogen activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MEF-2	myocyte enhancing factor-2

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MI	myocardial infarction
MMPs	matrix metalloproteinases
NADPH	nicotinamide adenine dinucleotide phosphate
NF-κB	necrosis factor-kappa B
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
Nox-4	NADPH oxidase 4
OLR1	oxidized low-density lipoprotein receptor 1
ox-LDL	oxidized low-density lipoprotein
PAK	p21-activated kinase
PI3K	phosphatidylinositol-3 kinase
PKB	protein kinase B
PKC	protein kinase C
PLC	phospholipase C
PMSF	phenylmethyl sulfonylfuoride
PTK	protein tyrosine kinase
RAS	renin-angiotesion system
ROS	reactive oxygen species
SBP	systolic blood pressure
SHR	spontaneously hypertensive rat
sLOX-1	small lectin-like oxidized low-density lipoprotein scavenger receptor-1
Sp1	specificity Protein 1
STAT3	signal transducer and activator of transcription 3
TYK	tyrosine kinase
VSMCs	vascular smooth muscle cells

Introduction

Dyslipidemia and hypertension are two powerful risk factors leading to cardiovascular diseases, and are often co-exist [1]. Angiotensin II (Ang II) and its receptors are a major physiological regulator for electrolyte-fluid balance, blood pressure, secretion of aldosterone, cell proliferation, angiogenesis, inflammation and tissue remodeling, and play a central role in the pathophysiology of hypertension, myocardial infarction (MI), myocardial remodeling after MI, ischemic stroke, congestive heart failure, and atherogenesis [2–7]. Lectin-like oxidized low-density lipoprotein scavenger receptor-1 (LOX-1) is an important membrane receptor that mediates uptake and internalization of oxidized low density lipoprotein (ox-LDL). Increasing evidence suggests that there is a cross-talk between renin-angiotensin system (RAS), via Ang II type 1 receptor (AT1R) and ox-LDL via LOX-1, in atherogenesis and probably other disease states [8–10].

Ang II exerts its effects by activating its receptors, primarily AT1R and AT2R, which mediate most of functions of RAS. Both receptors belong to the members of a G-protein-coupled receptor superfamily (GPCRs) and play their role via activation of G protein-mediated signaling pathway [11–13]. The functions of AT1R and AT2R are different; generally, AT1R is viewed to mediate most of the molecular and cellular actions of Ang II, and AT2R is thought to oppose AT1R function.

LOX-1, as an important scavenger of ox-LDL, has a strong ability in binding, internalizing and degrading ox-LDL in many cell types, such as endothelial cells, monocytes and macrophages as well as platelets [14–16]. LOX-1 activation via ox-LDL is now thought to play a key role in the pathogenesis of atherosclerosis. Ox-LDL causes endothelial dysfunction and injury and its accumulation leads to early atherosclerotic lesion development [16, 17]. Recently, a cross-talk between LOX-1 and AT1R has been reported by several groups [10, 18–22]. Dyslipidemia up-regulates and activates AT1R, and RAS activation in turn up-regulates and activates LOX-1, and then facilitates uptake of ox-LDL into endothelial cells. Whether there is a cross-talk between LOX-1 and AT2R is still not clear.

LOX-1 receptor: its signaling and function

LOX-1, also known as oxidized low-density lipoprotein receptor 1 (OLR1), was first identified and cloned by Sawamura and his colleagues in endothelial cells. Subsequent studies revealed that it is also expressed on reticulocytes, eosinophils, monocytes, platelets, cardiomyocytes and vascular smooth muscle cells (VSMCs), and in renal, pulmonary and neuronal tissues [23–25]. LOX-1 gene is a single-copy gene and located on p12.3-p13.2 region of human chromosome 12 and encodes a 273 amino acid protein [26]. The expression of LOX-1 gene is regulated through the cyclic AMP signaling pathway. In general, the expression of LOX-1 gene and protein is minimal under physiological conditions, but is accentuated by diverse stimuli such as endothelin-1, Ang II, high glucose concentration and phorbol ester, and in several pathological conditions such as hyperlipidemia, diabetes mellitus, hypertension, MI, atherosclerosis and chronic renal failure [27–34].

Structurally, LOX-1 is a 50-kDa type II transmembrane glycoprotein with a typical C-type lectin structure at the extracellular C-terminus that belongs to the class E scavenger receptor subfamily of the C-type lectin family. In cell membranes, LOX-1 exists as covalently-linked dimers and multimers and can further associate into non-covalently-linked oligomers [26]. It binds carbohydrates in a Ca^{2+}-dependent manner, and is comprised of four domains: a short N-terminal cytoplasmic domain, a single transmembrane domain; a short 'neck' or stalk region and a C-type lectin-like fold. Mutagenesis studies have revealed that the lectin domain is the functional domain that recognizes the LOX-1 ligand [35]. The C-terminal end residues and several

conserved positively charged residues spanning the lectin domain are essential for ox-LDL binding [35, 36].LOX-1 can be cleaved and transformed into a 187-residue, 35 kDa soluble protein known as sLOX-1[35].

The large loop between the third and fourth cysteine and C-terminal end residues is responsible for binding ox-LDL [37]. Ox-LDL binding to LOX-1 activates a series of signals. The most important intracellular signaling mediated by LOX-1 is activation of protein kinase C (PKC). Activation of PKC can further activate the subsequent signals including p38 mitogen activated protein kinase (MAPK), p42/44 MAPK, nuclear factor-kappaB (NF-κB), p21-activated kinase (PAK), nuclear translocation of the transcription factor (Nrf2) and activating protein-1 (AP-1) [37–43]. Activation of c-jun-NH2-terminal kinase (JNK) and Src kinases, phosphoinositide 3-kinase (PI3K)/Akt, and protein tyrosine kinase (PTK) also play important roles in LOX-1 signaling. In addition, LOX-1 activation has been observed to trigger inflammatory reaction through PKC-CD40/CD40L signaling pathway [42]. The activation of above-mentioned signaling molecules in turn induces LOX-1 expression, and enhances its activity. It is has been reported that activation of PKC, p-p38MAPK, p42/44 MAPK, JNK, NF-κB, AP-1and Nrf2 increases LOX-1 expression in human VSMCs and macrophages, and inhibitions of these signals significantly decreases LOX-1 expression and activity [41, 43].

An increasing body of evidence indicates that ROS is also a key signaling molecule in LOX-1-mediated signaling pathways, and the expression of ROS and LOX-1 have a strong inter-twined relationships. Some studies show that an increase in ROS generation can up-regulate LOX-1 expression, and others show that LOX-1 activation up-regulates NADPH oxidase subunits ($p47^{phox}$, $p40^{phox}$, $p22^{phox}$, $gp91^{phox}$) and Rac1, and induces generation of large amounts of ROS. These observations suggest a positive feedback loop between ROS and LOX-1 [19, 44, 45]. As an important secondary messenger, ROS plays a key role in many cellular events including cell proliferation, apoptosis, hypertrophy and inflammation. Indeed, ox-LDL-LOX-1-NADPH oxidase-ROS-MAPKs-NF-κB pathway is also the basic signaling pathway in these events.

The binding of ox-LDL to LOX-1 initiates further LOX-1 generation and activation. LOX-1 activation has been known to mediate numerous physiological and pathological actions including cell apoptosis, proliferation and differentiation, increase of iNOS, MCP-1, MMP-1, ROS production, expression of adhesion molecules and inflammatory cytokines, decrease of eNOS and NO release, and to participate in or to be related to the pathogenesis and progress of some diseases such as atherosclerosis, ischemic stroke, acute coronary syndrome, chronic renal failure, MI, hypertension, obesity, hyperlipidemia, aging, diabetic nephropathy, acute lung inflammation and injury, rheumatoid arthritis, osteoarthritis (Table 1) [34, 37, 41, 44–55]. Apart from the recognition of ox-LDL, LOX-1 also recognizes other antigens such as the aged or apoptotic cells, activated leucocytes and platelets and bacteria, and mediates immune reaction and inflammation [45, 56]. For example, Lee et al. reported that LOX-1 activates the NF-κB-mediated inflammatory signaling and up-regulates IL-6 and IL-8, and adhesive molecules [44].

AT1 receptor: its signaling and function

AT1R is the most important Ang II receptor subtype in adults, and is widely expressed in endothelial cells, VSMCs, monocytes, cardiomyocytes, fibroblasts, and in many adult tissues including blood vessels, hearts, brain, lung, kidney liver and placenta (Table 1) [57, 58]. AT1R expression is affected by many factors, including Ang II, ox-LDL, oxidative stress, chronic hypoxia, high glucose, shear stress, and various transcriptional factors such as Sp1, Sp3, myocyte enhancing factor-2 (MEF-2), peroxisome proliferator-activated receptor-γ (PPAR-γ) and NF-κB. AT1R expression is up-regulated in many pathological conditions such as atherosclerosis, hypertension, MI, myocardial hypertrophy, chronic heart failure, diabetic nephropathy, cancers, and inflammation [59].

AT1R gene has been cloned in humans, mice, rats, rabbits, pigs, dogs, turkeys and frogs [60]. Human AT1R gene resides on chromosome 3q21-3q25, and encodes a 359 amino acids protein with a 41 kD molecular mass [58, 60, 61]. Rat AT1R gene has two different isoforms AT1Ra and AT1Rb that are localized to rat chromosome 17 and chromosome 12, respectively. The mouse AT1R gene is mapped on mouse chromosome 12 [62, 63]. In humans, AT1R gene consists of five exons and three introns [64, 65]. In rat, AT1Ra has four exons, with the coding sequence located on the third exon, and rat AT1Rb has only three exons, with the coding sequence encoded in the third exon [2, 66, 67]. Rat AT1Ra and AT1Rb are expressed in different levels in different tissues [65]. AT1Ra, AT1Rb and mouse AT1R genes also encode a protein of 359 amino acids [2]. There is 60% homology between the non-mammalian receptors and 95% homology among human AT1R, mouse AT1R, rat AT1Ra and rat AT1Rb [60]. They have the similar ligand binding abilities and signal transduction properties.

Structurally, AT1R is a seven trans-membrane protein with an extracellular N-terminus followed by seven a-helical transmembrane-spanning domains, which are connected by three extracellular and three intracellular loops, and ended as a intracellular C-terminal domain [2]. The C-terminus is rich in serine, threonine and tyrosine residues that are the phosphorylation sites of PKC [2].

Table 1 Distribution, functions, signaling and the correlated diseases of LOX-1, AT1R and AT2R

		LOX-1	AT1R	AT2R
Distribution	Cell types	Endothelial cells, VSMCs, reticulocytes, eosinophils, monocytes, macrophages, platelets, cardiomyocytes, chondrocytes, hepatocytes, adipocytes, dendritic cells,	Cardiomyocytes, endothelial cells, VSMCs, monocytes, fibroblasts, neurons, embryonic stem cells, intestinal epithelial cells, T lymphocytes, podocytes	Cardiomyocytes, endothelial cells, VSMCs and adipocytes in a low level; fibroblasts and embryonic stem cells in a higher level
	Tissues	Blood vessels, heart, adipose tissue, liver, kidney, lung, neuronal tissues	Heart, blood vessels, kidney, liver, lung, brain, gastric mucosa, adrenal gland, ovine, placenta	Widely distributed in fetal tissues, low expression in gastric mucosa, adrenal gland, heart, kidney ovine after birth, upregulated in pathophysiolical caodition such as heart failure
Function		ox-LDL metabolism, pro-atherogenesis, pro-apoptosis, pro-proliferation and pro-differentiation, reduction of NO release, increase of ROS production, upregulation of MCP-1, MMP-1, iNOS and adhesion molecules, dowregulation of eNOS, proinflammatory cytokine release, induction of inflammation, collagen secretion	Vasoconstriction, angiogenesis, water and sodium intake, renal sodium retention, aldosterone release, increase of blood pressure, pro-proliferation, pro-apoptosis (except tumor cells), increase of ROS production, upregulation of MCP-1, MMP-1, and adhesion molecules, induction of fibrosis, inflammation and myocardial remodeling	Pro-apoptosis, anti-growth? function at fetation, anti-inflammation? vasodilation, inhibition of renin biosynthesis, anti-hypertrophy? induction of NO release, inhibition of collagen secretion
Signaling	Main signaling molecules	ox-LDL, NADPH oxidase, ROS, Protein kinases, MAPKs,NF-κB, AP-1, JNK, Akt	Ang II, PLC, Protein kinases, Ca^{2+},NADPH oxidase, ROS, Rho and Rac, PI3K, JNK, MAPKs, Akt	Ang II, Ca^{2+}/calmodulin, iNOS, eNOS, cGMP, NO, ERK, MAPK, STAT3
	Main signaling pathway	Ox-LDL-LOX-1-PKC-NADPH oxidase-ROS-MAPKs-NF-κB pathway	Ang II-AT1R-G12-Rho/Rac-ROS-MAPKs NF-κB pathway; Ang II-AT1R-Gq- Ca^{2+}/PKC-PI3K-Akt pathway;	Ang II-AT2R/BK-NO-cGMP pathway
Correlated diseases		Atheroslerosis, endothelial dysfunction, ischemic stroke, acute coronary syndrome, MI, hyper-lipidemia, hypertension, aging, chlamydia pneumoniae infection, chronic renal failure, obesity, diabetes, diabetic nephropathy, acute lung inflammation and injury, autoimmune diseases (rheumatoid arthritis, osteoarthritis) ?	Hypertension, atherosclerosis, MI, myocardial hypertrophy, ischemic stroke, chronic heart failure, diabetic nephropathy, cancers panencephalitis, autoimmune diseases (chronic glomerulopathies, rheumatoid arthritis, uveoretinitis, multiple scerosis and cirrhosis), pulmonary tuberculosis	(anti-) hypertension, (anti-) atherosclerosis, (anti-) MI (cardioprotective effects), inhibition of neointimal hyperplasia of blood vessels, inhibition of pancreatic carcinoma grafts, chronic renal failure, pulmonary tuberculosis, diabetes, obesity

Wang et al. demonstrated that the third intracellular loop (IC3) of AT1R is the most important domain for AT1R coupling to Gq protein, and the N-terminal and C-terminal portions of IC3 to be important for AT1R signaling, through which AT1R activates phospholipase C (PLC) [13].

AT1R-mediated signaling is divided into two groups: G protein-dependent and G-protein-independent signaling pathways [68]. The transduction of AT1R-mediated signals is mainly via several plasma membrane effector systems; Gq/11, G12/13, and Gi/o [60, 69]. AT1R coupling to Gq/11 proteins mainly mediates inositol phosphate/Ca^{2+} and the activation of PKC, coupling to Gi/o proteins mainly inhibits adenylyl cyclase in some target tissues, and coupling to G12/13 proteins mainly mediate the activation of PLC and Rho kinases (Figure 1) [70].

PLC activation promotes the hydrolyzation of membrane lipid phosphoinositol-4,5-bisphosphate (PIP_2) into inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), which then causes an increase of cytosolic Ca^{2+} concentration $[Ca^{2+}]_i$ and the activation of PKC [71, 72]. The sustained increase of $[Ca^{2+}]_i$ in cardiomyocytes induces the activation of calmodulin (CaM)-dependent protein phosphatase 2B, and then up-regulates the expression of atrial natriuretic peptide (ANP), β-myosin heavy chain (β-MHC) and α-skeletal muscle (α-SKA), which cause the cardiac hypertrophy [73, 74]. The activation of Rho kinase signaling regulates a series of cellular functions including cell-matrix formation, cytoskeleton remodeling, cell-cell adhesion, cell migration, and cytokinesis. Moreover, Rho kinase and Rac activation increases the generation of ROS through the activation of NADPH oxidases [73, 75]. It has been reported that AT1R mediates ROS generation in Rho- and Rac-dependent manner in rat neonatal cardiomyocytes [76]. In addition, the increase in ROS generation can further activate Rho/Rho kinase signaling (Figure 1) [75].

ROS serve as important secondary messengers in G12/13- and Gq/11-mediated signaling pathways. A series of studies have documented that AT1R activation can further activate MAPKs, a step that requires ROS generation and activation [76, 77]. A selective inhibition of G12/13 can significantly decrease ROS generation and the activation of p38 MAPK, P42/44 MAPK and JNK [76]. Therefore, Ang II-AT1R-G12/13-Rho/Rac-ROS-JNK/p38MAPK pathway is a primary pathway in AT1R-mediated signaling (Figure 1). MAPKs are most important signals in AT1R signaling. AT1R activation phosphorylates other kinases and transcription factors that regulate various cellular activities such as cell proliferation and differentiation, and cell survival and apoptosis (Figure 1) [60].

The serine/threonine kinase Akt is another important signaling molecule in AT1R signaling [78]. Akt, also known as protein kinase B (PKB) is one of the downstream targets of PI3 Kinase (PI3K). It is known that AT1R coupling to Gq proteins will lead to the increase of $[Ca^{2+}]_i$ and the activation of PKC, then activate PI3K that further activate Akt and NF-κB [79, 80]. Ang II-AT1R–Gq–Ca^{2+}/PKC-PI3K-Akt pathway is another important pathway in AT1R-mediated signaling (Figure 1). The activation of this

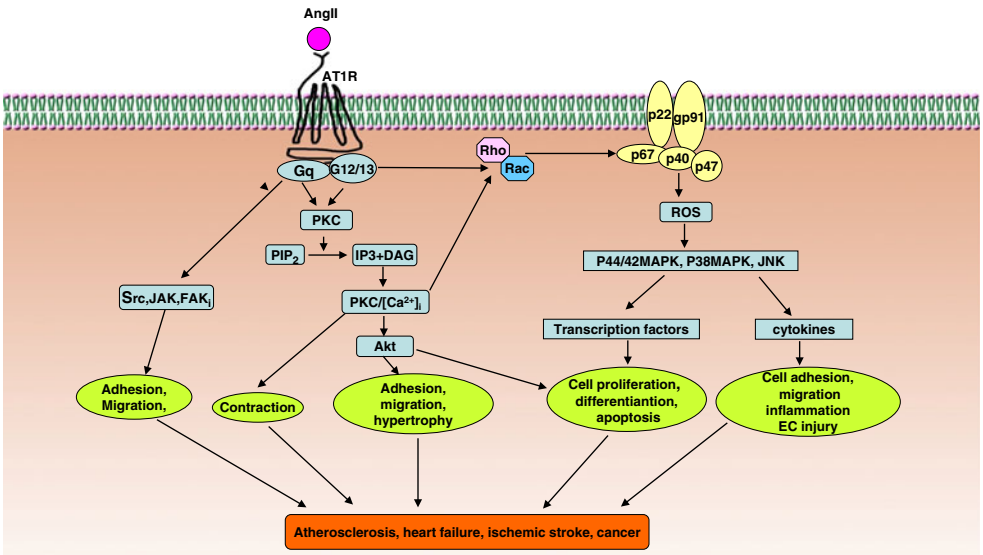

Fig. 1 Summary of AT1R signaling and functions

pathway also plays a key role in mediating signals for cell proliferation and differentiation, cell survival and apoptosis, and glucose metabolism, as well as is often linked to many diseases including cardiac hypertrophy, heart failure, ischemic stroke, diabetes, inflammation and cancers [68, 81–83]. AT1R coupling with Gq proteins also mediates the activations of Src kinases, Janus kinases (JAK), and focal adhesion kinases (FAK).

AT1R has been observed to play its pathophysiological role in cardiovascular, renal, neuronal, endocrine, hepatic, adrenal gland, ovarian, placental and other target cells, and regulate water and sodium intake, renal sodium retention, blood pressure, aldosterone release, cell proliferation and apoptosis, fibrosis, inflammation, and renal function (Table 1). It is also known that AT1R activation participates in or is related to the pathogenesis and progress of hypertension, atherosclerosis, MI, myocardial hypertrophy, ischemic stroke, chronic heart failure, diabetic nephropathy, caners and inflammations (Table 1).

The main role of AT1R is to regulate systemic blood pressure and water-salt balance. It is well known that Ang II causes vasoconstriction of blood vessels through AT1R activation, which lead to the increase of systemic blood pressure. Long time activation of AT1R is one of the main reasons for sustained hypertension. In kidney, AT1R regulates blood pressure through regulating renal glomerular filtration rate, and renal tube fluid and sodium re-absorption, and keeps water-salt balance [84, 85]. Aldosterone, produced following AT1R activation in the adrenal glands, is another important factor in determination of systemic blood pressure and the pathogenesis of hypertension. Higher level of aldosterone leads to increased sodium and water re-absorption [86]. Aldosterone also induces ROS generation, which further leads to endothelial dysfunction [87]. The endothelial dysfunction accelerates the progression of hypertension. Moreover, ROS, especially Nox2 and Nox4, regulate systemic blood pressure through their signaling in the central nervous system [88].

Recently, there has been much interest in the role of AT1R in cell apoptosis. Increasing evidence suggests that Ang II and AT1R activation mediate apoptosis in human coronary artery endothelial cells [89], rat pancreatic acinar cells [90], rat hearts [91] and the cultured rat cardiac fibroblasts [92]. The activation of PLC/PKC pathway is responsible for AT1R-mediated cell apoptosis [89, 92]. But, studies in tumor cell lines suggest that AT1R activation stimulates tumor growth and inhibits cell apoptosis in most solid cancers. It has been reported that AT1R activation suppresses adriamycin-induced MCF-7 cell apoptosis [93]; and blockade of AT1R with losartan increases the expression of p53, p21, p27 and Bax, decreases the expression of Bcl2 and Bxl-xl, and triggers apoptosis in human pancreatic cancer cells [94]. The inhibitory effects of AT1R on cancer cell apoptosis were also observed in other tumors such as osteosarcoma [95], gastric cancer [96] and bladder cancer [97], In addition to tumor cells, Yin et al. showed AT1R activation inhibits the marrow-derived endothelial progenitor cell apoptosis [98]. These reports suggest that increase in eNOS and activation of PI3K/Akt pathway are responsible for the anti-apoptotic effects of AT1R activation [93, 98].

Accumulating evidence suggests that AT1R activation promotes the secretion of inflammatory cytokines such as IL-6 and monocyte chemoattractant protein-1 (MCP-1), and initiates inflammatory response. Several reports have revealed that AT1R expression is up-regulated in human disease states [99] and animal models with inflammation [100] or activated cultured cells [101]. Sakkurai et al. showed that AT1R activation is involved in the progression of chronic pancreatitis [102]. In these studies, treatment with AT1R blockers (ARBs) significantly prevented the development of chronic inflammation and fibrosis in pancreas [102]. ARBs are used to treat several disease states characterized by inflammation such as chronic renal inflammation [103].

AT1R are also expressed in central nervous system-resident cells and cause the inflammation [100]. AT1R activation has also been implicated in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis, uveoretinitis and multiple sclerosis. Treatment with ARBs decreases the expression of CCL2, CCL3, and CXCL10, CCL2-induced migration of antigen-presenting cells, which is beneficial in these disease states [104, 105]. Recent studies have demonstrated that treatments with ARBs suppress autoreactive TH1 and TH17 cells and promotes antigen-specific CD4+FoxP3+ regulatory T cells (Treg cells) [106].

AT2 receptor: its signaling and function

Like AT1R, AT2R also belongs to a seven transmembrane receptor superfamily, and plays its role via the activation of G protein-mediated signaling pathway [12, 107]. Both receptors share about 34% amino-acid sequence homology, but they have similar affinity for Ang II and function collaboratively [13]. AT2R is thought to be associated with the development of fetal organs [108]. It is expressed highly only in the fetal tissues, and its expression decreases very soon after birth [109]. In the healthy adults, AT2R has been localized to heart, kidney, brain, ovine, brain, uterus, adrenal gland, pancreas, retina, skin, and both endothelial cells and VSMCs, but only at a very low level (Figure 1) [107, 110–117]. AT2R, however, is up-regulated in pathological conditions, such as MI, diabetic nephropathy, ischemia-reperfusion injury and inflammation, and the

tissues retain the capability to re-express AT1R without age limit (Table 1) [118–122].

Human AT2R gene is located on X chromosome, and encodes a protein of 363 amino acids [123]. Structurally, AT2R is also a seven trans-membrane protein with the transmembrane hydrophobic domain, and the extracellular intracellular domains. The homology between AT2R and AT1R is located in the transmembrane domains [124]. The third extracellular loop and seventh transmembrane spanning domain have been identified to be the major determinants for the binding of AT2R ligands and mainly responsible for AT2R signaling [124].

Although AT2R also couples to G-protein and signal through Gq and Gi proteins, its signaling pathways are markedly different from those associated with AT1R. The most important signaling molecule are cyclic guanine 3′,5′-monophosphate (cGMP), nitric oxide, and bradykinin (Table 1) [125]. Bradykinin and cGMP/nitric oxide signaling pathway following AT2R activation was first described by Siragy and Carey [126, 127], and demonstrated by further in vivo and in vitro studies [128–131]. AT2R stimulation also activates protein phosphatases, and thus dephosphorylate and inactivate MAPKs including ERK1/2, JUK and p38, which inhibits AT1R signaling pathways (Figure 2) [125]. AT2R stimulation also enhances PLA2 activity and promotes arachidonic acid release, and thus activates lipid signaling pathways [125, 132]. Long term stimulation of AT2R has been shown to induce ceramide generation, which leads to the activation of stress kinases and caspases and induction of cell apoptosis [133, 134]. Several studies suggest that the activation or/and up-regulation of AT2R up-regulates and activates iNOS and nNOS, which promote cell apoptosis [135, 136].

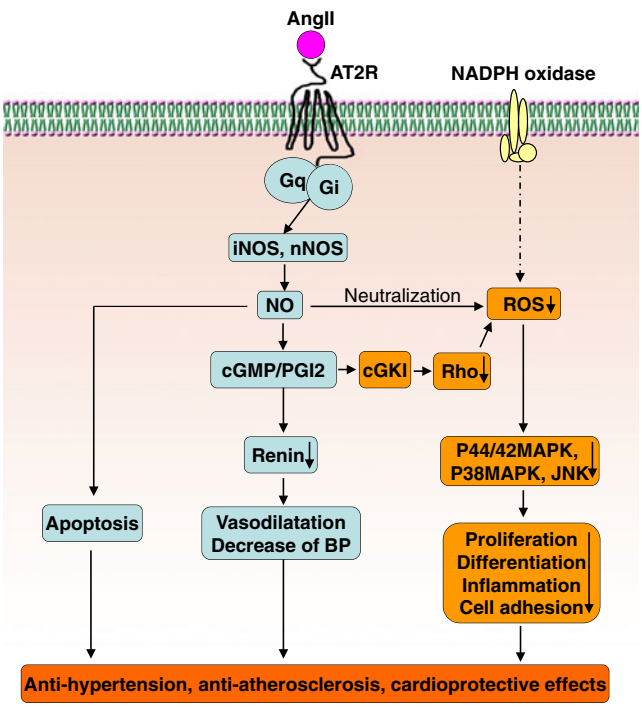

Fig. 2 Summary of AT2R signaling and functions

Although much work has been done on the biology of AT2R, its precise physiological function is still not clear. Currently, it is known that AT2R has functions in mediating vasodilation, cell migration, hypertrophy, proliferation, and fibrosis [119, 125]. The role of AT2R in the development of the hypertension is still not well understood. Generally, AT2R is viewed to participate in the regulation of blood pressure and oppose AT1R's effects on blood pressure, and thus may have a salutary role in hypertension [137]. Selective stimulation of AT2R by circulating Ang II has been demonstrated to lower blood pressure in both salt-restricted rats and renal wrap hypertensive rats [138, 139]. Several studies suggest that AT2R ligand CGP42112 has the function to lower blood pressure in conscious rats, and induce vasodilation in its own right in the perfused rat mesenteric artery [140, 141]. Hannan et al. reported that AT2R mediates vasodilation in rat uterine artery; and showed that the AT2R blocker PD123319 has no effect on the maximum contractile response to Ang II, but functions to enhance the potency of Ang II in the uterine artery [142]. Siragy et al. used AT2R KO mice to directly define the role of AT2R activation in blood pressure in response to the physiological increases of Ang II or the infusion of exogenous Ang II [143, 144]. They found that AT2R KO mice had an elevated baseline systolic blood pressure, and sustained hypersensitivity of blood pressure and sodium excretion to Ang II [143, 144]. Bradykinin and cGMP levels and NO production were also lower in AT2R KO mice than those in wild-type mice in response to dietary sodium restriction or exogenous Ang II [143]. These findings strongly suggest that AT2R plays a counterregulatory protective role in blood pressure regulation via bradykinin and NO against the antinatriuretic and pressor actions of Ang II [143]. Lacking AT2R would lead to vascular and renal hypersensitivity to Ang II, including sustained antinatriuresis and hypertension [143]. Other studies have suggested that AT2R mediates vasorelaxation in a variety of locations, including mesenteric, renal, coronary, cerebral and uterine vascular beds via stimulation of NO/cGMP/bradykinin signaling pathways. In the central nervous system, AT2R activation increase NO and facilitates neuronal potassium current, evoke sympatho-inhibition [145, 146].

AT2R activation is believed to oppose the actions of AT1R, but sometimes, it also has synergistic effects with AT1R. The classic example of synergistic effect is cell apoptosis, seen in several cell lines, including fibroblasts, neurons, vascular smooth muscle cells, endothelial cells and some cancer cells [147, 148]. However, the pro-apoptotic effect of AT2R in cardiomyocytes remains controversial.

For example, Qi et al. reported that the overexpression of AT2R in neonatal cardiomyocytes through recombinant adenovirus transduction can significantly increase cell apoptosis [149]. Other studies, however, showed that the increased AT2R expression does not affect cardiomyocyte apoptosis [131]. Kong et al. even suggested that Ang II does not have a significant effect on cardiomyocyte apoptosis [150]. These variable effects probably reflect effect of AT2R on different cell types from different animals of different ages used in these studies. The methods used in these studies to increase AT2R expression were also different.

Crosstalk between AT1 and AT2 receptors

AT1R and AT2R, as two major receptors of Ang II, play fundamental roles of RAS activation. Increasing evidence suggests that cross-talk between AT1R and AT2R may exist in the cardiovascular and other systems. It is known that up-regulation of AT1R increases AT2R expression. Some in vivo studies showed that the overexpression of AT1R was followed by an up-regulated AT2R expression in patho-physiological conditions. Our recent studies also show that AT1R overexpression is associated with increased expression of endogenous AT2R expression in cultured HL-1 cardiomyocytes. But, there are studies that suggest that inhibition of AT1R activity would upregulate AT2R expression. For example, Jugdutt et al reported that ARBs valsartan and irbesartan each significantly up-regulated the expression of AT2R protein in mongrel dogs subjected to ischemia-reperfusion injury [151].

The role of AT2R expression in modulating AT1R expression is controversial. Some in vivo and in vitro studies suggested that AT2R overexpression could decrease endogenous AT1R expression. Jin et al. reported that overexpression of AT2R decreased AT1Ra expression at both mRNA and protein levels in the presence or absence of Ang II after transfection with AT2R gene in cultured rat vascular smooth muscle cells [152]. These authors thought that up-regulation of endogenous AT1Ra was mediated by the bradykinin/NO pathway in a ligand-independent manner, because AT2R overexpression also increased the expression of bradykinin and inducible NO, and bradykinin B2 receptor antagonist HOE-140 and NO synthase inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME) inhibited the decreases of AT1Ra in the AT2R-overexpressed rat vascular smooth muscle cells [152]. However, a subsequent study by this group showed that AT2R overexpression only affected endogenous AT1R expression in the vascular smooth muscle cells from Wistar-Kyoto rats; but not from the spontaneously hypertensive rats [153]. This finding suggests that the effect of AT2R overexpression may occur in the physiological condition. However, work by our and other groups also indicates that AT2R over-expression in mice via AAV-mediated gene transfer does not affect the expression of endogenous AT1R [154, 155]. Recently, Zhu et al. reported that AT2R overexpression via AAV-mediated transfer at lower titers (40 and 80 MOIs) had no effect on endogenous AT1R expression, but when the transfer titers were increased to 160MOIs, AT2R overexpression increased endogenous AT1R expression, but this may have been a non-specific response [131]. Matavelli et al. also observed that AT2R activation did not affect AT1R mRNA expression, but it did influence AT2R protein synthesis and degradation [156].

Cross-talk between AT1R and AT2R is also embodied in their roles in the pathogenesis of several disease states. Several reports suggest the balance and interplay between AT1R and AT2R is an important factor that determines the process of disease states such as atherosclerosis, MI and myocardial remodeling [157, 158]. As mentioned earlier, both AT1R and AT2R may be up-regulated in the same pathologic state [159]. ROS is an important ‘signal bridge’ between AT1R and AT2R in some pathologic states, such as atherosclerosis. It is known that AT1R activation promotes the progression of atherogenesis through the up-regulation of NADPH subunits and increase of ROS generation; however, AT2R activation promote NO generation that has the function to remove ROS (Figure 2). In this sense, AT2R over-expression may be a physiologic mechanism to counter the effects of AT1R over-expression.

Human studies and animal experiments have suggested that ARBs play their pharmacological action through increase in AT2R expression. The up-regulation and activation of AT2R mediated by AT1R blockade has been shown in several studies [151, 160]. Voros et al. showed that the use of losartan and AT2R overexpression have very similar effects in limiting fibrosis and attenuating left ventricular remodeling in post-MI remodeling in mice [158]. A number of studies have shown that the cardio-protective functions of ARBs could be abolished by simultaneous treatment with AT2R inhibitor PD123319 and its key signaling molecule bradykinin inhibitor HOE-140, NO inhibitors L-ANME or N^{G}-mono-methyl-L-arginine, or PKC inhibitor chelerythrine [161–164]. These findings also suggest that ARBs’ benefits are partially derived from the up-regulation and activation of AT2R, and the up-regulation of AT2R mediated by AT1R inhibition is through activation of the bradykinin/nitric oxide/cGMP pathway. Except for the reported AT2R involvement in AT1R may reverse the beneficial effects of AT1R blockers and increase AT1R expression [165–167].

Several lines of evidence suggest that AT2R is an antagonist of AT1R, and the signaling pathway associated with AT1R can be blocked by AT2R activation [168]. It has been known for some time that AT1R activation has pro-fibrotic effects in the pathological tissues and ARBs can

decrease fibrosis [169–171]. Several studies have shown that AT2R activation reduces collagen synthesis and inhibits the growth of cardiac fibroblasts. Tsutsumi et al. showed that AT2R expression was increased in the failing human hearts with interstitial fibrosis and the persistence of AT2R in the fibroblasts exerted an inhibitory effect on fibrosis [172]. Ohkubo et al. observed that the expression of both AT1R and AT2R was higher in the fibrotic area than in the normal area, and PD123319 could inhibit AT2R's effect on fibrosis and enhance Ang II-stimulated increase in net collagenous protein after 44-weeks of PD123319 treatment [173]. Varagic et al. showed that AT2R inhibitor PD123319 could fully reverse valsartan-induced reductions in cardiac fibrosis and cause a small reversal of losartan-induced antihypertensive effect in SHR [165, 174].On the other hand, some studies have shown that activation and up-regulation of AT2R causes fibrosis. For example, Mifune et al. reported that overexpression of AT2R and AT2R agonist CGP42212A both stimulated collagen synthesis in a dose- and time-dependent manner in cultured smooth muscle cells.

Cross-talk between AT1R and AT2R in regulating kidney disease remains controversial. Some in vivo and in vitro studies showed that AT1R and AT2R both are up-regulated in the kidney during inflammation and are involved in fibrotic response [156, 175]. For example, Matavelli reported that both AT1R and AT2R expressions increased in the clipped rat kidneys within 4 days of induction of renal ischemia [156]. In addition to the kidney, Okada et al. observed that AT1R and AT2R both were increased in the splenocytes exposed to inflammatory stimulation (10 ng/ml lipopolysaccharide) [176]. Recently, we have observed AT1R and AT2R both increased in kidneys of chronically ischemic mice heart. Ruiz-Orteqa et al. suggested that the combined blockade of AT1R and AT2R is necessary to completely abolish renal inflammation [177]. However, Clayton et al. suggested that the expression of AT1R was increased by 67% and the expression of AT2R was decreased by 87% in rabbits with chronic heart failure [178]. Similar alterations were observed in spontaneously hypertensive rats by Landgraf et al, who observed that the expression of AT1R was increased by 126% and that of AT2R decreased by 66% in the kidneys of 4-week-old SHR [179]. Some reports suggest that ARBs attenuate inflammation in kidney diseases via AT2R activation and through a feedback activation mechanism described earlier [180]. There have been other reports suggesting that AT1R protein expression is up-regulated in the kidney with progressive injury that could be countered by simultaneous losartan administration, however, the expression of AT2R was unchanged in the kidney and was not affected by losartan administration [181]. Sullivan et al. investigated AT1R and AT2R expression and function in uterine arterial endothelium in the non-pregnant and pregnant states. They found that both AT1R and AT2R expression and the AT1R/AT2R ratio were increased through the extracellular signal-regulated kinase (ERK) pathway in uterine artery endothelium and vascular smooth muscle in the pregnant states [182]. The author also believed that the net effect of pregnancy was mediated through a complex AT1R-AT2R interaction.

Cross-talk between LOX-1 and AT1 receptors

Accumulating evidence supports the concept of interplay between LOX-1 and AT1R. Moraweietz et al. reported that Ang II increases the expression of the LOX-1 gene and the uptake of ox-LDL in Ang II-treated human umbilical vein endothelial cells [22]. Similar responses were also observed in the coronary artery endothelial cells in our laboratory, and in monocytes, macrophages and human vascular smooth muscle cells by other groups [155, 183–185]. Several in vitro studies showed that the Ang II response varied in a dose-dependent manner, and could be completely blocked by AT1R blocker losartan, but not by PD123319 [39, 185]. This suggests that the effect of Ang II is mediated by AT1R, and not by AT2R, activation. Hayek et al. also found that losartan inhibits the cellular uptake of ox-LDL in the human monocyte-derived macrophages from hypercholesterolemic patients via blockade of AT1R [28]. Other in vivo studies showed that losartan can effectively inhibit the upregulation of LOX-1 in animal models [29, 32]. Chen et al. found that losartan could decrease LOX-1 expression at genomic level in aortas of rabbits on high cholesterol diet [32]. Further confirmation came from the observations of Ge et al. who showed that losartan could down-regulate the LOX-1 expression in endothelium and neointima of autologous vein grafts of the hypercholesterolemic rabbits, and inhibit the vein grafts atherosclerosis development [29]. Recently, Kizawa et al. reported that Ang II also induces LOX-1 expression in patients with the obstructive sleep apnoea [186].

Several studies have suggested that hypercholesterolemia, especially increase in LDL-cholesterol, regulates AT1R expression. Nickenig et al. reported that 12-hour incubation with 100 μg/ml LDL causes about 2.5-fold of the up-regulation of AT1R mRNA and protein levels in cultured smooth muscle cells isolated from rat aortas, and this phenomenon was further enhanced by additional Ang II [186]. Their work also demonstrated that only ox-LDL had the effect to up-regulate AT1R mRNA expression, yet native-LDL did not affect AT1R mRNA level in cultured smooth muscle cells [187]. Thus, the up-regulation of AT1R was mainly secondary to the formation of ox-LDL in hyperlipidemia. Recent work from our laboratory showed that AT1R expression was markedly up-regulated by ox-

LDL stimulation, and the expression level of AT1R paralleled LOX-1 expression [19]. Subsequent in vivo studies demonstrated that AT1R expression was increased in animal models with high plasma cholesterol. Yang et al. reported that high levels of serum cholesterol led to a several-fold increased expression of total Ang II receptors in the aortic intima of hypercholesterolemic rabbits [188]. Their work further demonstrated the increase of total Ang II receptors was mainly coming from the increase of AT1R expression. AT1R predominantly expressed in the smooth muscle layers in the hyperlipidemic states. Maczerwski et al. also showed that AT1R was also up-regulated 8 weeks after MI, and could be further increased by hypercholesterolemia and restored to baseline levels by atorvastatin [189].

There is increasing evidence that, ROS plays an important role in the interplay between LOX-1 and AT1R. This process is in an NADPH oxidase-dependent manner and is mediated by ROS generation [19, 190, 191]. It has been known that Ang II induces the generation of oxidative stress and ROS via AT1R transcription. Pendergrass et al. showed that 1 nM Ang II could increase intra-nuclear ROS generation, while the AT1R antagonist losartan or the NADPH oxidase (NOX) inhibitor DPI abolished the increase in ROS [192]. The up-regulation of LOX-1 also stimulates ROS generation, and then enhances AT1R expression and activity. Sakamoto et al. showed that LOX-1 increase ROS generation was through the activation of Akt/eNOS and Ca^{2+} signaling pathways [191]. Work done in our laboratory demonstrated that AT1R and LOX-1 inhibition attenuate Ang II-mediated oxidant stress and the expression of NADPH oxidase ($p40^{phox}$ and $gp91^{phox}$ subunits) [19]. Our work further demonstrated that low concentrations of ox-LDL and Ang II induce capillary formation from endothelial cell through ROS dependent pathway, and this effect can be inhibited by apocynin (NADPH oxidase inhibitor) [38, 190]. Other studies also showed that the inhibition of the NADPH oxidase activity attenuates the expression of AT1R and LOX-1 [193, 194].

Apart from NADPH oxidase and ROS, there are other factors that influence the interplay between AT1R and LOX-1, for example, angiotensin-converting enzyme 2 (ACE2) and MAPKs. A recent study showed that ACE2 plays an important role in regulating the expression of LOX-1 and AT1R simultaneously [195]. The overexpression of ACE2 in the abdominal aorta significantly lowers the expression of LOX-1 and AT1R at the same time; nonetheless, these authors believe that the final role of ACE2 on the expression of LOX-1 and AT1R is mediated through regulation of ROS [196]. This information, along with previous observations, strongly suggest that NADPH oxidase and ROS are an important "signal bridge" in the interplay between AT1R and LOX-1. Moreover, AT1R and LOX-1 activations both activate MAPKs through the ROS-induced PKC activation [19, 37, 77, 89]. The activation of ROS-PKC-MAPKs signaling pathway play an important role in the interplay between LOX-1 and AT1R.

Studies thus far have indicated that LOX-1 and AT1R coordinate in the pathogenesis and development of several diseases, e.g. atherosclerosis. It has been known that both receptors participate in the formation and progression of atherosclerotic lesions, and contribute to macrophage cholesterol accumulation, and their up-regulation and/or activation are hallmark of early atherogenesis. Previous studies have shown that AT1R and LOX-1 were the up-regulated and activated simultaneously in hyperlipidemic animal models [50, 188, 197]. Activation of both receptors stimulates atherogenesis through induction of ROS generation and inflammation [197].

Cross-talk between LOX-1 and AT2 receptor

It is not clear if there is a cross-talk between LOX-1 and AT2R. Recent studies have given a hint that there are some relationships between LOX-1 and AT2R, and that LOX-1 acts in coordination with AT2R in certain pathological conditions, such as hyperlipidemia, atherogenesis, hypertension, MI, ischemic stroke, inflammation and some cancers (Table 1).

Some in vitro studies showed that LOX-1 expression level and its activity did not affect AT2R expression and activity, and vise-versa. Li et al reported that upregulation of LOX-1 could be prevented by inhibition of AT1R using losartan in cultured endothelial cells, but not PD123319 [185]. Watanabe et al. indicated that the increase of LOX-1 expression and its activity by ox-LDL stimulation did not affect AT2R expression [109]. These studies suggested no cross-regulatory effects between LOX-1 and AT2R in cultured endothelial cells and cardiomyocytes. In physiological conditions, AT2R is often expressed at a very low level in the cardiovascular system, including endothelial cells and cardiomyocytes, which may limit the cross-regulation between AT2R and LOX-1.

Hu et al. recently found that AT2R overexpression could inhibit LOX-1 expression [155]. They induced AT2R overexpression in homozygous LDLR- KO mice by using recombinant adeno-associated virus type-2 (AAV) carrying AT2R cDNA (AAV/AT2R) transduction, and then examined the expression of LOX-1, eNOS and HO-1. Their results showed that LOX-1 expression was dramatically increased in the LDLR KO mice compared with that in the wild-type mice. AT2R overexpression could efficiently prevent the enhancement of LOX-1 expression caused by hyperlipidemia. And, atherogenesis in the aorta was also reduced by AT2R overexpression by about 50% compared with the

LDLR KO animals given the empty vector. This work suggested that a cross-talk may exist between LOX-1 and AT2R in some pathological conditions. The upregulation of AT2R in pathological conditions may be the prerequisite of interplay of LOX-1 and AT2R.

The cross-talk between LOX-1 and AT2R may be important in their role in the evolution of diseases such as atherosclerosis. Both receptors regulate the process of atherogenesis and modulate atherosclerotic lesions evolution. Atherogenesis involves lipid accumulation, especially ox-LDL [198]. LOX-1, a scavenger receptor of ox-LDL, plays pro-atherogenic effects; whereas, AT2R plays an anti-atherosclerotic effect [199]. The balance between LOX-1 and AT2R may determine the extent of atherosclerosis. Several studies have reported that both LOX-1 and ox-LDL are elevated in atherosclerotic plaque [46, 155, 200]. Recently, Dandapat et al. showed that AT2R overexpression could decrease collagen accumulation and the expression and activity of MMPs in atherosclerotic plaques [201]. It is known that collagen accumulation in the arteries is one of the determinants of the formation of atherosclerotic intima [202]. Collagen type I has been thought to be an important characteristic ofthe atherosclerotic plaque, and other subtypes of collagen are also critical components of the atherosclerotic lesion [203–205]. It has been demonstrated that LOX-1 has the potential to promote the accumulation of collagen [198, 206]. Hu et al. found that LOX-1 deletion could decrease collagen accumulation in atherosclerotic plaques in LDLR KO mice, which was related to MMP activity and redox-sensitive signaling. LOX-1 deletion could normalize the expression and activity of MMPs compared with LDLR KO mice in which the expression and activity of MMP2 and MMP9 was found to be increased near 100%. These authors also found that $p47^{phox}$, p22phox, $gp91^{phox}$, and Nox-4 subunits of NADPH oxidase were markedly increased in the LDLR KO mice, and these subunits of NADPH oxidase and ROS generation were reduced by LOX-1 deletion in the LDLR KO mice. Further studies by this group showed that the LOX-1 and related $TGF\beta_1$ expression regulated collagen accumulation [14]. These authors found that $TGF\beta_1$-mediated collagen formation in fibroblasts was a critical role of LOX-1, which is involved in NADPH oxidase activation and increased ROS generation. On the other hand, AT2R activation functions to decrease ROS levels through increase in NO generation, which can neutralize ROS (Figure 2) [98, 207]. Collagen formation and accumulation in arteries and atherosclerotic plaques may involve an interplay of LOX-1 and AT2R; however, this remains to be shown in well-designed experiments.

The pathogenesis of atherosclerosis also involves an ongoing inflammatory response [208]. Ox-LDL retained in the intima, can induce the expression of adhesive molecules, chemokines, pro-inflammatory cytokines, and other mediators of inflammation in macrophages and vascular wall cell, all of which initiate the immune response and promote the progression of atherosclerotic lesions [196]. Several studies have suggested that AT2R inhibits atherosclerotic lesion development by decreasing systemic and local inflammation [44, 122]. The effects of both receptors on the inflammatory process may modify the process of the formation of atherosclerotic plaques. There are other cross-function, such as cell apoptosis and proliferation, regulation of blood pressure, fibrosis, between LOX-1 and AT2R that may influence a variety of disease states [209–211].

Clinical implications

Drugs acting on the RAS, such as renin inhibitors, angiotensin converting enzyme inhibitors, AT1R blockers and aldosterone antagonists, are often used in a vast array of disease states, including atherosclerosis, hypertension, myocardial ischemia, progression of renal disease and congestive heart failure. LOX-1 over-expression is being identified as a potential target of therapy in these disease states. The discovery of the concept of mutually facilitating cross-talk between LOX-1 and AT1R suggests that combination of therapies designed to block RAS and LOX-1 may be more useful than those that affect only one pathway. The role of AT2R in human disease states is beginning to be recognized, but not clearly defined as yet. It is possible that the definition of the precise role of AT2R might lead to development of drugs that target AT2R expression, and their use either alone or with therapies targeted at AT1R and LOX-1.

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