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Signaling through LRP1: Protection from atherosclerosis and beyond

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Abstract

The low-density lipoprotein receptor-related protein (LRP1) is a multifunctional cell surface receptor that belongs to the LDL receptor (LDLR) gene family and that is widely expressed in several tissues. LRP1 consists of an 85-KDa membrane-bound carboxyl fragment (β chain) and a non-covalently attached 515-KDa (α chain) amino-terminal fragment. Through its extracellular domain, LRP1 binds at least 40 different ligands ranging from lipoprotein and protease inhibitor complex to growth factors and extracellular matrix proteins. LRP-1 has also been shown to interact with scaffolding and signaling proteins via its intracellular domain in a phosphorylation-dependent manner and to function as a co-receptor partnering with other cell surface or integral membrane proteins. LRP-1 is thus implicated in two major physiological processes: endocytosis and regulation of signaling pathways, which are both involved in diverse biological roles including lipid metabolism, cell growth/differentiation processes, degradation of proteases, and tissue invasion. The embryonic lethal phenotype obtained after target disruption of the LRP-1 gene in the mouse highlights the biological importance of this receptor and revealed a critical, but yet undefined role in development. Tissue-specific gene deletion studies also reveal an important contribution of LRP1 in vascular remodeling, foam cell biology, the central nervous system, and in the molecular mechanisms of atherosclerosis.

LRP1 (also known as CD91, or α2macroglobulin receptor, α2MR) is a ubiquitously expressed type 1 transmembrane receptor [1]. The mature form of the receptor is derived from a 600-kDa precursor that is proteolytically processed upon furin cleavage. The processed form of the receptor consists of a carboxyl-terminal β-fragment of 85-kDa, which contains an intracellular and a transmembrane domain. The extracellular portion of the 85 kDa fragment is non-covalently connected to the large amino-terminal 515-kDa α-fragment, which harbors several ligand binding domains that interact with multiple LRP1 ligands (Figure 1) [1,2].

LRP1 is the most multifunctional member of the LDL receptor gene family [3]. It has been implicated in two main biological functions: endocytosis of its numerous ligands and regulation of cell signaling pathways. Through its extracellular domain, LRP1 interacts with at least 40 different ligands ranging from lipoproteins, extracellular matrix glycoproteins,

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protease/inhibitor complexes, viruses, cytokines and growth factors (Table 1). The large variety of ligands LRP1 recognizes reflects the numerous biological functions this evolutionarily ancient receptor has adopted since its inception in the most primitive metazoans. Its ubiquitous expression, the remarkable structural and sequence conservation among species, the absence of any known functional coding mutations of the LRP1 gene in humans, and the lethality of the conventional knockout in mice reveal that LRP1 is indispensible for cellular physiology.

Besides its role in endocytosis [3,4], several studies have shown that LRP1 is essential for multiple signaling pathways. These functions have been described in the vascular wall, in neurons, adipose tissue, and numerous other tissues. In the vascular wall, LRP1 plays a major role in controlling vascular smooth muscle cells (vSMCs) proliferation, and protects against atherosclerosis. Mice lacking LRP1 in vSMCs exhibit hyperplasia of the aortic wall, disruption of the elastic lamina, aortic aneurysm formation and greatly enhanced susceptibility to atherosclerotic lesion development [5]. LRP1-deficient mice fed a high cholesterol diet develop massive foam cell formation within the arterial wall, leading to the complete occlusion of the lumen of the aorta and the mesenteric arteries, and thus the death of the animals from progressive large vessel obstruction. The mechanism by which LRP1 protects against the formation of atherosclerotic lesions is mediated through control of at least two distinct signaling pathways in vSMCs by the receptor: the platelet-derived growth factor BB (PDGF-BB) and the transforming growth factor-β (TGFβ) signaling pathways, which both play major roles during atherosclerosis [5–7]. Excessive smooth muscle hyperplasia of the aorta associated with LRP1-deficiency is accompanied by a major increase in the expression of the PDGF receptor β(PDGFRβ), increased PDGFRβ phosphorylation, and increased phosphorylation of Smad2, a downstream component of the TGFβ pathway that mediates the TGFβ transcriptional response. The PDGF-BB pathway has been previously described as a target of the TGFβ signaling pathway [8–10]. Moreover, LRP1 is identical to the TGFβ receptor (V), a member of the TGFβ receptor superfamily that is expressed together with TGFβ receptor I, II and III at the cell surface [11]. Thus, activation of the TGFβ pathway in the absence of LRP1 can further activate the PDGF-BB signaling pathway, by increasing the expression of PDGFRβ in the arterial wall and thereby promoting atherosclerotic lesion formation.

Macrophage lipoprotein receptors can accelerate progression of atherosclerosis by facilitating uptake of atherogenic particles such as the oxidized lipoproteins [12]. In the particular case of LRP1, deletion of the receptor in macrophages has also been shown to increase atherosclerosis in mice [13]. Transplantation of macrophage LRP1−/− bone marrow into lethally irradiated female LDLR−/− recipient mice resulted in a 40% increase in atherosclerosis [13]. Deletion of LRP1 in macrophages however, did not alter plasma lipid levels or plasma lipoprotein profiles, demonstrating no significant contribution of macrophage LRP1-mediated remnant clearance in influencing plasma lipoprotein levels *in vivo*. LRP1−/− macrophages displayed increased expression of proinflammatory cytokines such as IL-1β, IL-6 and tumor necrosis factor-α expression, and suppression of the pAkt survival pathway [14]. Thus, macrophage LRP1 might protect against atherosclerosis by decreasing inflammation, but also by facilitating efferocytosis, an atheroprotective effect by which apoptotic cells are removed from the lesions by phagocytic cells [13–15].

Since LRP1 in the liver participates in the removal of atherogenic apoE rich lipoproteins from the circulation, its role in that tissue during atherogenesis has also been investigated. Hepatic LRP1 plays a clear protective role in atherogenesis but independent of plasma cholesterol [16]. The mechanism by which hepatic LRP1 affects the development of atherosclerotic lesions is not clear. It might involve clearance of other LRP1 ligands that are related to atherosclerosis such as t-PA or u-PA.

Recently, we have shown that LRP1 is required for normal signaling through a canonical Wnt5a dependent pathway in mouse embryogenic fibroblasts (MEF), and that activation of this pathway prevents intracellular cholesterol accumulation, a prominent and necessary feature of the atherosclerotic lesion formation [17]. LRP1 also regulates LXR-mediated gene transcription and participates in reverse cholesterol transport by controlling cPLA2 activation and ABCA1 expression [18]. LRP1 is further required for lipolysis and for the stimulation of fatty acid synthesis independent of noradrenergic signals, through inhibition of GSK3β and its previously unknown target acetyl-CoA carboxylase (ACC) [17]. LRP1 thus, functions as a physiological integrator of cellular lipid homeostasis with signals that regulate cellular proliferation and vascular wall integrity.

Besides its large contribution to the protection against atherosclerosis, recent work has also shown a role for LRP1 and one of its ligands, tissue plasminogen activator (tPA), in the regulation of vascular tone [19] and the permeability of the blood brain barrier permeability (BBB) [20]. tPA regulates vascular contractility through LRP1 and this is reversed by a physiological tPA inhibitor, plasminogen activator inhibitor 1 (PAI-1). The authors reported that vasoconstriction induced by tPA requires a functional interaction between LRP1 and alpha(v)beta(3) integrin [21]. The mechanism of this interaction and the signaling pathways involved, however, remain unknown. Regulation of BBB permeability is important for neuronal homeostasis and protects the brain against toxins that constantly enter the circulation from the external environment and through the gut. The authors demonstrate that tPA directly induces BBB permeability and that this is blocked by anti-LRP1 antibodies and by the receptor-associated protein (RAP), a chaperone protein that blocks the binding of most of the known LRP1 ligands. These results thus suggest that the tPA-dependent regulation of BBB permeability requires the expression of LRP1 [20].

LRP1 is also playing an important role in the central nervous system (CNS), especially in neurons where it is highly expressed [22,23] and where it interacts with numerous neuronal proteins such as the postsynaptic density protein 95 (PSD-95) and the N-methyl-D-aspartate (NMDA) receptor [24]. In the brain, glutamate is the main excitatory neurotransmitter, which also plays an important role in neuronal cell death in neurodegenerative diseases [25,26]. Moreover, LRP1 has been shown to regulate calcium signaling *in vitro* [27], an important second messenger during glutamate neurotransmission. The active form of α2-macroglobulin (α2M), an LRP1 ligand, inhibits the calcium-dependent NMDA response and the expression of NMDA receptors through a signaling pathway involving LRP1 [28]. Mice lacking LRP1 in neurons exhibit a severe movement disorder, hyperactivity, and premature death [24].

In the lung, a new important role for LRP1 in the course of the inflammatory response has been reported [29]. The authors described that in the absence of LRP1, the surfactant proteins A and D (SP-A et SP-D) bind to the signal inhibitory regulatory protein α (SIRPα). This activates the tyrosine phosphatase SHP-1, blocks Src family kinases and p38 MAP kinases, and thereby inhibits the inflammatory response. By contrast, when LRP1 is expressed, surfactant proteins SP-A and SP-D interact with foreign organisms, apoptotic cells or cell debris, and the presentation of these organisms to LRP1 in macrophages by calreticulin leads to their phagocytosis and inflammatory response in lungs. Interestingly, it has been proposed that adiponectin promotes the uptake of apoptotic debris by peritoneal macrophages via a calreticulin/LRP1 pathway but not through the previously identified adiponectin receptor [30]. Thus, LRP1 is an important component that regulates the initiation of the innate immune response. This function of LRP1 in macrophages is not only important in lung macrophages, but has also implications in other tissues such as the aortas and in clearance of cells that have undergone apoptosis [31] an important physiologic function during development and tissue homoeostasis [32].

As is the case for numerous receptor and membrane proteins, the extracellular domain of LRP1 can be cleaved by cell surface proteases and subsequently released into the extracellular space or the circulation. A circulating form of LRP1 has been found at nM concentration in human plasma [33,34]. This cleaved form of LRP1 contains the α chain of about 515 kDa and a fragment of the β chain (85 kDa) of about 55 kDa, demonstrating that the cleavage occurs close to the plasma membrane [33]. Enzymes that can mediate this cleavage have been identified and include the neuronal BACE1 protease [35] and a hepatic metalloproteinase [33]. The LRP1 soluble form is present in the plasma of mammals, but also in the blood of birds, and reptiles. In most case the physiological meaning of the extracellular cleavage is not certain, but since the soluble form can still bind most of the LRP1 ligands and thereby reduce their endocytosis by cellular LRP1, the soluble fragment may serve to quench extracellular ligand interaction with the cell or regulate their intracellular trafficking.

Several of the mechanisms by which LRP1 controls cell signaling pathways remain unresolved. One potential mechanism involves the cleavage of the transmembrane domain of the LRP1 β chain by regulated intramembraneous proteolysis (RIP). The released fragment (LRP1-ICD) of approximately 12 kDa might thus translocate to the nucleus where it can regulate the transcription of target genes [36]. RIP is a process by which the first step of proteolysis involves an extracellular cleavage event, which is then followed by intramembraneous processing and the release of a, usually small, cytoplasmic fragment that may have functions in the cytoplasm or in the nucleus, including transcriptional regulation [37]. Several proteins including the amyloid precursor protein (APP), Notch, a transmembrane protein that regulates cell fate decision of ES cells during development, the tyrosine kinase receptor ErbB-4 [38], the receptor CD44 [39], sterol regulatory element binding proteins SREBPs [40], ATF6 [41], Ire1[42], and cadherin [43] function through a RIP mechanism. In most cases, the intramembranous cleavage is done by the presenilin (PS)/γ-secretase complex. In the case of LRP1, the intracellular domain can also be released upon proteolytic cleavage by the presenilin (PS)/γ-secretase complex [36]. However, the precise cleavage site and thus the complete sequence of the released fragment remain unknown. Recently, one potential target of the LRP1-ICD has been identified [44]. Lipopolysaccharide (LPS) increases the proteolytic processing of the ectodomain of LRP1, which results in the γ-secretase-dependent release of the LRP1 intracellular domain (ICD) from the plasma membrane and its subsequent translocation to the nucleus, where it interacts with and represses the interferon-γ promoter [44]. The LRP1-ICD fragment contains numerous motifs that have been implicated in numerous signaling pathways: Two NPXY motifs, where the distal motif is contiguous with a YXXL motif, and two dileucine motifs. The YXXL motif is presumably the most important one mediating LRP1 endocytosis [45]. However, both NPXY motifs can bind and interact with numerous cytosolic proteins such as, DAB1, FE65, JIP1, PSD-95, ShcA or CED-6/GULP [6,7,46–50]. *In vitro* studies have shown that the LRP1-ICD can colocalize with the histone acetyl transferase Tip60 in the nucleus [51], which in turn can regulate transcription upon APP cleavage [52,53] suggesting that the LRP1-ICD might be able to regulate the transcriptional activity of the APP-Tip60 complex, and thus have a more general function as a regulator of transcription. In order to dissect the *in vivo* functions of each motifs located in the LRP-ICD, Roebroek and colleagues [54] introduced mutations into the furin cleavage site and into both NPXY motifs located in the cytoplasmic tail of LRP1. Mutation of the NPXY motif of the cytoplasmic domain or in the furin cleavage site caused distinctive liver phenotypes: respectively, either a late fetal destruction of the organ causing perinatal death or a selective enlargement of von-Kupffer cell lysosomes reminiscent of a mild lysosomal storage without an apparent negative effect on animal survival. A mutation of the most distal NPXY motif within the cytoplasmic tail of LRP1 did not exhibit an overt phenotype [54].

In conclusion, LRP1 is a large multifunctional receptor with two main biological functions in multiple ligand endocytosis and in the control and integration of intercellular signaling pathways, which are not required for survival of the cell per se, but essential for the maintenance of basal cellular function and development and survival of the organism. Indicative of its importance, LRP1 is expressed in almost all cells, and there is no known disease-related LRP1 coding mutation that has been described in humans to date. Since it participates in such a large number of physiological activities as a co-receptor and also by interacting with numerous adaptor proteins through its cytoplasmic domain, functional dissection of these mechanisms and identification of further LRP1 partners might open new avenues to the treatment of metabolic diseases such as lipid metabolism and atherosclerosis, but also inflammation, Alzheimer disease and obesity.

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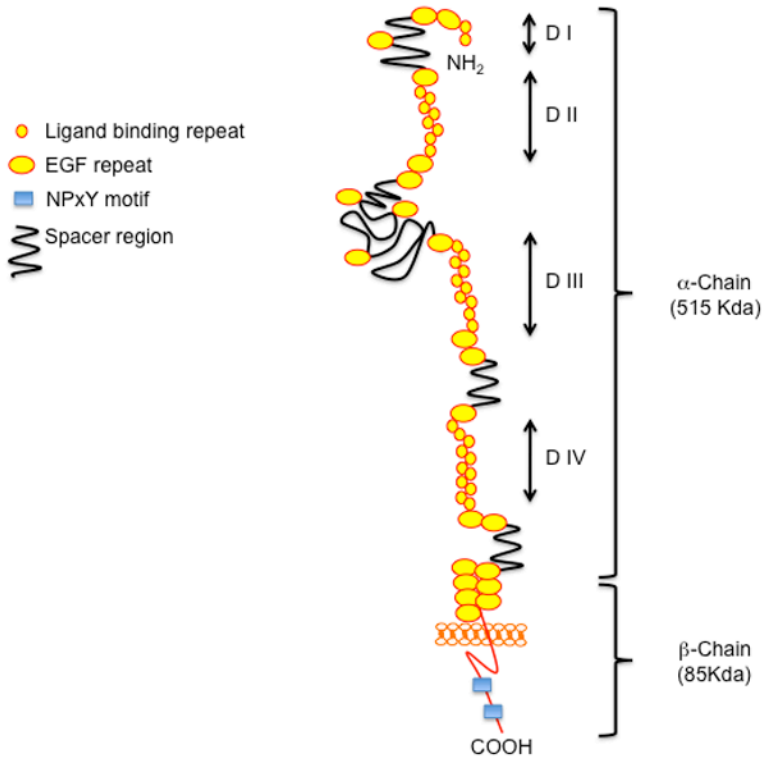

Figure 1.

The low-density lipoprotein receptor-related protein (LRP1). LRP1 is a multifunctional receptors that binds a large spectrum of extracellular and intracellular ligands. The extracellular domain consists of ligand-binding-type repeats organized in four binding domains (DI, DII, DIII, DIV) and epidermal precursor homology domains, which contain YWTD repeats and EGF repeats. The cytoplasmic tail of the receptor is containing cytoplasmic NPxY motifs that mediate protein– protein interactions required for endocytosis as well as for the assembly of scaffold proteins related to signal transduction and trafficking such as Dab1, Fe65, JIP1, omp25, and integrin cytoplasmic domain-associated protein 1.

TABLE 1

LRP1 known ligands

Proteins involved in lipoprotein metabolism
Apolipoprotein E-enriched lipoproteins (chylomicron and VLDL remnants), Lipoprotein lipase (LPL), Hepatic lipase, Sphingolipid activator protein
Proteases and protease/inhibitor complexes
Activated α_2-macroglobulin, α_2-macroglobulin protease complexes, Pregnancy zone protein-protease complexes, Aprotinin, urokinase plasminogen activator (uPA), pro- uPA, plasminogen activator inhibitor (PAI-1), uPA/PAI-1 complexes, tissue-type plasminogen activator (tPA), tPA/PAI-1 complexes, Thrombin/PA-1, Thrombin/anti- thrombin III, Thrombin/protease nexin-1, Thrombin/heparin cofactor II, Neuroserpin, Neuroserpin/tPA complexes, C1s/C1q inhibitor, Protease/protein C inhibitor, Elastase/α_1-anti-trypsin, MMP-9, MMP-13, TSP-2/MMP-2 complexes, Tissue factor pathway inhibitor (TFPI), Factor VIIa/TFPI, Factor VIIIa, Factor IXa, Factor IXa/protease nexin-1, β-amyloid precursor protein
Matrix proteins
Thrombospondin-1, Thrombospondin-2, Fibronectin
Intracellular proteins
Receptor associated protein (RAP), Calreticulin, HIV Tat protein
Growth factors
Platelet-derived growth factor (PDGF), Midkine, Insulin-like growth factor (IGF)- binding protein-3 (IGFBP-3), Connective tissue growth factor (CTGF/CCN2), Transforming growth factor (TGF-β)
Others
Circumsporozoite protein, Lactoferrin, Ricin A, Saposin, Rhinovirus A peptide (monomer), Gentamicin, Polymycin B, Pseudomonas exotoxin A, Complement C3, Collectins (via calreticulin)