

Low-density lipoprotein receptor-related protein in metalloproteinase-mediated pathologies: recent insights

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Abstract: Low-density lipoprotein receptor-related protein (LRP)-1, LRP-1b, LRP-2, LRP-5, and LRP-6 mediate the endocytosis of metalloproteinases and inhibitors and/or promote the expression of metalloproteinases. These properties confer important and complex roles in the development of pathologies related to an intense proteolytic degradation of the cellular microenvironment. The cell surface levels of the identified endocytic receptors, LRP-1, LRP-1b, and LRP-2, are themselves regulated by metalloproteinases. The released extra- and intracellular domains may also exert functions in these pathologies.

Keywords: LRP, MMP, ADAM, ADAMTS

Introduction

Pathologies related to metalloproteinase activities represent an important part of biomedical research, yielding about 20,000 citations in PubMed. To understand the molecular mechanisms by which metalloproteinases mediate these pathologies represents the most important and exciting challenge for the development of new therapeutic strategies. In addition to regulation at both the expression and secretion levels, metalloproteinases can be further controlled.¹ Thus, metalloproteinases are generally synthesized as inactive proenzymes and must be activated to be proteolytically efficient. Once activated, the metalloproteinases are inhibited by broad spectrum or specific inhibitors. An additional and efficient mechanism of control of metalloproteinases is the endocytic clearance mediated by members of the low-density lipoprotein (LDL) receptor (LDLR) family, LDLR-related proteins (LRPs). In addition to their endocytic activities, some of them exhibit signaling properties that can modulate the expression of some metalloproteinases.

After a brief description of the LDLR family, we focus this review on the LDLR family members involved in the regulation of metalloproteinase activity and/or expression, their role in the development of pathologies associated to metalloproteinase activities, and their own regulation by a shedding process mediated by metalloproteinases.

General features of the LDLR family

The LDLR family consists of membrane receptors involved in the endocytosis of a variety of ligands, most of which are lipoproteins.² In humans, this family includes LDLR,³ VLDLR,⁴ LRP-1,⁵ LRP-1b,⁶ glycoprotein 330 (gp330)/megalin/LRP-2,⁷ LRP-3 (closely resembles ST7/LRP-12),^{8,9} MEGF7/LRP-4,¹⁰ LRP-5,¹¹

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LRP-6,¹² LRP-7,¹³ apoER2/LRP-8,¹⁴ LRP-9,¹⁵ LRP-10,¹⁶ and sorLA/LR11.¹⁷ They are type I membrane proteins that contain a single transmembrane-spanning domain with the exception of LRP-4, which is a type II membrane protein.¹⁰ They all share additional common modules characteristic of the LDLR family (epidermal growth factor [EGF] repeats, LDLR ligand-binding repeats, cytoplasmic domain) and exhibit both endocytic and signaling properties¹⁸ (Figure 1).

Members of the LDLR family regulate metalloproteinase activity

Until now, only LRP-1, LRP-1b, LRP-2, LRP-5, and LRP-6 have been demonstrated to regulate the level of metalloproteinases or their inhibitors, either by endocytosing them or by modulating their expression.

Regulation of metalloproteinase activity by endocytosis

Among the five members of the LDLR family that modulate metalloproteinase activity, only LRP-1, LRP-2, and LRP-1b mediate endocytosis of metalloproteinases or their inhibitors.

LRP-1

LRP-1, previously identified as an α_2 -macroglobulin receptor,¹⁹ is the first member of the protein family related to LDLR.²⁰ It is synthesized as a 600 kDa single-chain protein cleaved by a furin-like protease in the trans-Golgi compartment into a 515 kDa α -chain and an 85 kDa β -chain that remain noncovalently associated. The extracellular α chain harbors four LDLR ligand-binding repeats that interact with about 40 ligands, whereas the transmembrane β -chain contains an extracellular portion, a transmembrane domain, and a short cytoplasmic tail that includes two NPxY motifs for triggering endocytosis and recruiting adaptor and signaling proteins.²¹

LRP-1 regulates extracellular proteolytic activities by mediating the endocytic clearance of all active proteinases (including metalloproteinases) bound to the pan-proteinase inhibitor α_2 -macroglobulin.¹⁹ More specifically, LRP-1 endocytoses members of the matrix metalloproteinase (MMP) family, MMP-2, MMP-9, and MMP-13, and members of the adamalysin-like metalloproteinase with thrombospondin (TSP) motifs (ADAMTS) family, ADAMTS-4 and ADAMTS-5.²² In addition, it also endocytoses members of the tissue inhibitor of metalloproteinases (TIMP) family, TIMP-1, TIMP-2, and TIMP-3.²²

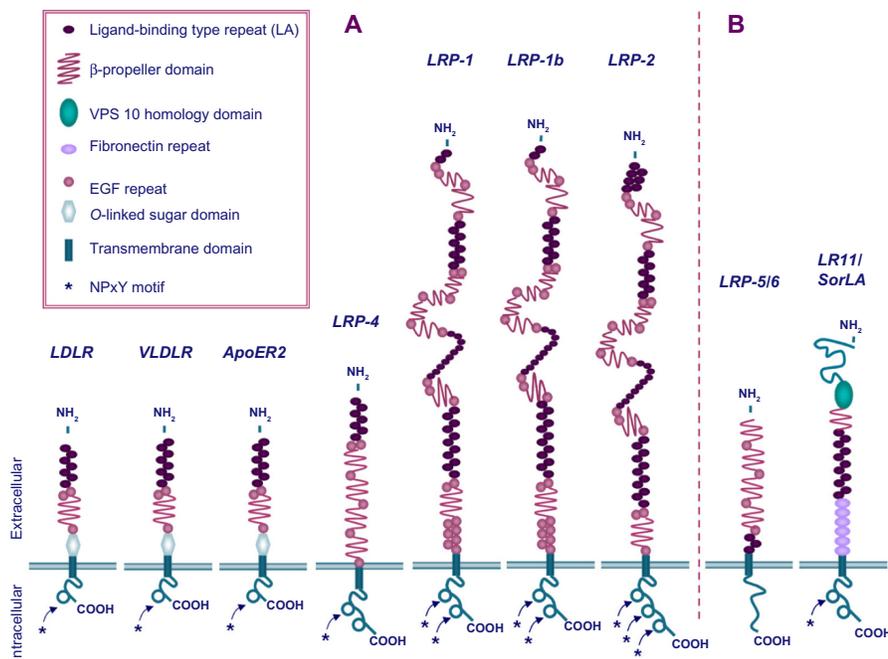


Figure 1 The low-density lipoprotein (LDL) receptor gene family.

Notes: (A) The core of the LDL receptor family consists of the LDL receptor (LDLR), VLDL receptor (VLDLR), apolipoprotein E receptor 2 (ApoER-2), LRP-4 (multiple epidermal growth factor containing protein 7; MEGF7), LRP-1, LRP-1b, and LRP-2 (megalin). The extracellular domains consist of arrays of ligand-binding type repeats, always followed by epidermal growth factor precursor homology domains. All receptors are anchored in the plasma membrane by a single membrane-spanning segment and contain a short cytoplasmic tail. (B) Distantly related receptors LRP-5 and LRP-6, which do not contain NPxY motifs in their cytoplasmic tail, and LR11/SorLA, which harbors a VPS10 homology domain and six fibronectin repeats.

Abbreviation: VLDL, very low-density lipoprotein.

MMP-2, MMP-9, and MMP-13

MMP-13 was the first metalloproteinase identified as ligand of LRP-1.²³ This was based on the observation that the parathyroid hormone promotes clearance of rat collagenase (the ortholog of human collagenase-3 or MMP-13) from the culture medium conditioned by rat osteosarcoma cells.²⁴ MMP-13 endocytosis is a two-step process of binding and internalization that requires both an unidentified 170 kDa coreceptor and LRP-1²³ (Figure 2). The endocytosis of MMP-2 involves a preliminary association with a soluble partner, TSP-2,²⁵ or TIMP-2,²⁶ followed by recruitment by a membrane heparan sulfate proteoglycan for a MMP-2/TSP-2 complex or an unidentified coreceptor for MMP-2/TIMP-2. In contrast, endocytosis of MMP-9, whether complexed to TIMP-1²⁷ or not,²⁸ results from a direct binding to LRP-1.

ADAMTS-4 and ADAMTS-5

ADAMTS-4 and ADAMTS-5 are considered major metalloproteinases that degrade the proteoglycan aggrecan in cartilage.²⁹ They are both endocytosed by LRP-1 expressed by chondrocytes.^{30,31} The rate of endocytosis of ADAMTS-4 is slower than that of ADAMTS-5. Such a difference is explained by a 13-fold lower affinity of ADAMTS-4 for LRP-1 compared with that of ADAMTS-5.

TIMP-1, TIMP-2, and TIMP-3

TIMP-1 was first identified as an LRP-1 ligand only as a complex with MMP-9.²⁷ However, using recombinant TIMP-1, we recently showed by surface plasmon resonance analysis that free TIMP-1 interacts directly with LRP-1 with high affinity.³² As with TIMP-1, TIMP-2, either as a complex with MMP-2 or as a free form, binds to and is internalized

by LRP-1.²⁶ The third member of the TIMP family, TIMP-3, has also been identified as an LRP-1 ligand.^{33,34}

LRP-2

Another important and multifunctional member of the family is LRP-2 (also known as megalin and gp330). LRP-2 has a molecular mass of approximately 600 kDa and contains 36 cysteine-rich ligand-binding domains, 16 EGF repeats, and 40 YWTD repeats in the extracellular domain.⁷ As with LRP-1, LRP-2 harbors four clusters of ligand-binding domains, allowing binding and internalization of a variety of ligands including proteinase/inhibitor complexes, vitamin/vitamin binding protein complexes, hormones, and lipoproteins.³⁵ LRP-2 has in particular been recognized as a new functional endocytic receptor for MMP-9 clearance.²⁸ This receptor is expressed at the apical surface of epithelial cells, with the main site of expression being the proximal renal tubule, where LRP-2 functions as the major scavenger receptor.

LRP-1b

LRP-1b, initially referred to as LRP-DIT (deleted in tumor), is a candidate tumor suppressor.⁶ LRP-1b and LRP-1 share several common features. Along with LRP-2, they are the largest known members of the LDL receptor family, with molecular masses around 600 kDa. Furthermore, both have four putative extracellular ligand-binding domains that are separated by clusters of EGF precursor repeats and propeller regions. The number and arrangement of these repeats are similar in both LRP-1 and LRP-1b, but LRP-1b contains one additional ligand-binding repeat in the ligand-binding domain IV, as well as an additional 33-amino acid sequence

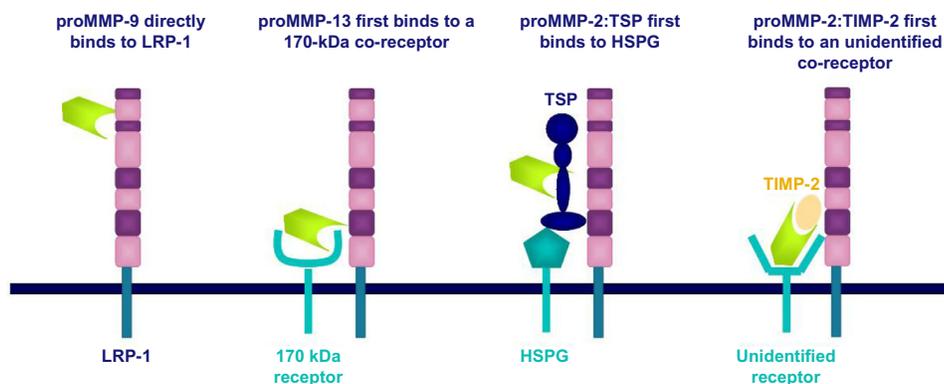


Figure 2 Different mechanisms of low-density lipoprotein receptor-related protein 1 (LRP-1)-mediated clearance of matrix metalloproteinases (MMPs).

Notes: The more straightforward mechanism is the direct association of proMMP-9 with LRP-1. ProMMP-13 first binds to an unidentified 170 kDa cell surface coreceptor before LRP-1-mediated endocytosis. LRP-1-mediated clearance of proMMP-2 involves two different coreceptors: if bound to thrombospondin (TSP), proMMP-2 first associates with an unknown cell surface heparan sulfate proteoglycan (HSPG) before interaction with LRP-1, and when complexed with TIMP-2, proMMP-2 first binds to an unidentified coreceptor.

within its cytoplasmic tail. Although LRP-1 is found in all tissues, LRP-1b expression appears to be more limited, with preferential localization in brain, thyroid, and salivary glands. The function of LRP-1b is still largely unknown, but LRP-1b has several ligands common to LRP-1, including complexes of urokinase plasminogen activator/plasminogen activator inhibitor type 1. Furthermore, LRP-1b inactivation in thyroid cancer cells modifies the tumor microenvironment that promotes cell growth and invasive capacity. Restoration of LRP-1b impairs both *in vitro* and *in vivo* tumor growth, inhibits cell invasion, and leads to a reduction of MMP-2 in the conditioned medium without a difference in MMP-2 messenger (mRNA) levels.³⁶ This data clearly indicates that LRP-1b mediates the endocytic clearance of MMP-2.

Regulation of metalloproteinase activities through signaling function of members of the LDLR family

In addition to its endocytic functions, LRP-1 also modulates metalloproteinase activity through signaling functions. Similarly, LRP-5 and LRP-6 appear to be associated with the modulation of metalloproteinase expression.

LRP-1

In addition to its endocytic function, LRP-1 also modulates metalloproteinase expression through its signaling function. Thus, binding of the serine protease tissue-type plasminogen activator to LRP-1 induces tyrosine phosphorylation of the β -chain cytoplasmic part and triggers intracellular signal transduction to induce MMP-9 expression in renal interstitial fibroblasts.³⁷ Such an MMP-9 upregulation by tissue-type plasminogen activator binding to LRP-1 has also been demonstrated in brain, both in cell culture and *in vivo*.³⁸ Rather surprisingly, binding of the serine protease inhibitor protease nexin-1 to LRP-1 stimulates extracellular signal-regulated kinase activation that results in increased MMP-9 mRNA levels in mammary tumor cells.³⁹ In addition, LRP-1 silencing impeded glioblastoma cell migration and invasion by inhibiting MMP-2 and MMP-9 expression through a decreased level of phosphorylated extracellular signal-regulated kinase.⁴⁰

LRP-5

LRP-5 exhibits the modules characteristic of the LDLR family. However, it has a unique organization of EGF and LDLR repeats, suggesting LRP-5 could represent a new category of the LDLR family (Figure 1).¹¹ LRP-5 has been shown to be specifically required for Wnt/ β -catenin signaling.⁴¹

Interestingly, Wnt/LRP-5 interactions have been demonstrated to modulate the expression of various metalloproteinases, including MMP-2,⁴² MMP-3,⁴³ MMP-13,⁴⁴ and MMP-14.⁴²

LRP-6

LRP-6 displays a pattern of four EGF and three LDLR repeats in the extracellular domain comparable with those of LRP-5, and consequently, it can be classified in the same new class of the LDLR family as LRP-5.¹² As with LRP-5, LRP-6 interacts with Wnt.⁴⁵ Transgenic mice overexpressing LRP-6 in mammary epithelial cells exhibit significant Wnt activation and upregulation of the expression of several MMPs, including MMP-2, MMP-3, MMP-7, MMP-9, MMP-13, and MMP-14.⁴⁶ In contrast, another study revealed that the heterozygous loss-of-function mutation in LRP-6 gene in mice leads to less β -catenin signaling within articular cartilage and increased degenerative joint disease after ligament and meniscus injury associated with increased MMP-3 and MMP-13 expression.⁴⁷

Effect of metalloproteinase regulation by members of the LDLR family on pathologies Focus on LRP-1

As reviewed earlier, members of the LDLR family can, either positively or negatively, regulate metalloproteinase activity through their endocytic and/or signaling properties. Moreover, these receptors may themselves affect pathologies independent of metalloproteinase regulation.^{20,48} It is thus rather difficult to estimate their exact contribution in the development of metalloproteinase-mediated pathologies. As a consequence, this section is focused on the endocytic and signaling receptor LRP-1 through some examples selected among the main metalloproteinases-related pathologies.

Neurological disorders

Alzheimer's disease is a neurodegenerative disorder leading to dementia. The prevailing view of Alzheimer's disease pathogenesis posits that accumulation of amyloid- β peptide (A β), particularly A β 42, is the central event triggering neurodegeneration.⁴⁹ It has been postulated that the development of amyloid plaques in AD may result from an imbalance between the generation and clearance of the A β . The amyloid precursor protein (APP) can be cleaved by metalloproteinases, precluding the production of A β or contributing to the degradation of the neurotoxic peptide.⁵⁰ Evidence suggests that metalloproteinases, and in particular MMPs and ADAMs, may process APP or A β .⁵¹ Among them, MMP-9 and ADAM-10

cleave the A β sequence in its middle, and this not only precludes its formation but also generates the secreted product sAPP α that possesses neurotrophic and neuroprotective properties.^{52,53} In addition, MMP-9 and MMP-2 can proteolytically degrade the fibrillary forms of A β 40 and 42.⁵¹ However, such neuroprotective properties can be counterbalanced by TIMPs, particularly TIMP-1, which is largely produced by astrocytes surrounding the amyloid plaques.⁵⁴ MMP-2 and MMP-9, as well as TIMP-1, TIMP-2, and TIMP-3, are all LRP-1 ligands (see preceding text). Moreover, TIMP-1 binding to LRP-1 expressed at the surface of neurons greatly impairs neurite growth, a hallmark of neurodegenerative disorders.³² From the point of view of metalloproteinase regulation, the role of LRP-1 in the development of Alzheimer's disease remains difficult to understand.

Cancer

Cancer progression is largely associated with the metalloproteinase-mediated breakdown of the extracellular matrix surrounding cancer cells.⁵⁵ Thus, LRP-1 could act as a true tumor repressor by regulating metalloproteinase activity (as detailed above in the paragraph "Members of the LDLR family regulate metalloproteinase activity/Regulation of metalloproteinase activity by endocytosis/LRP-1"). In this sense, decreased expression of LRP-1 has been associated with tumor progression in numerous cancer types.⁵⁶⁻⁵⁹ By reducing MMP-2 levels in the microvasculature, LRP-1 improves the antiangiogenic activity of TSP-2 in a murine glioma model.⁶⁰ In contrast, human malignant astrocytomas exhibit an increased LRP-1 expression.⁶¹ As pointed out earlier with regard to neurological disorders, the anticancer effect of LRP-1 related to its capacity of endocytosing metalloproteinases may be counterbalanced by its capacity to endocytose their inhibitors or by its protumor signaling properties. Thus, LRP-1 mediates MMP-2 and/or MMP-9 expression by tumor cells on various stimuli.³⁷⁻⁴⁰ In addition, LRP-1, whose expression is increased by hypoxia,⁶² regulates cancer cell survival and metastasis development.⁶³ Finally, LRP-1 may promote tumor cell invasion both by regulating cytoskeleton organization and adhesive complex turnover⁶⁴ and by internalizing the adhesion receptor CD44.⁶⁵

These opposite effects observed in vitro or in animal models also occur in humans, apparently depending on the organs. Thus, the *T* allele of the C766T polymorphism in the LRP-1 gene has been associated with an increased risk for breast cancer development.⁶⁶ LRP-1 overexpression has been also found in the highly aggressive Her-2/neu overexpressing and in triple-negative breast carcinomas.⁶⁷ In contrast, LRP-1

expression in stromal cells is associated with a favorable outcome in lung cancer.⁶⁸

Other metalloproteinase-mediated pathologies

Vascular pathological conditions, such as atherosclerosis and aortic aneurysms, are characterized by intense metalloproteinase activities.⁶⁹ MMP-2 and MMP-9 actively participate in the development of aneurysms⁷⁰ through their capacity of degrading elastin, a main component of the elastic fibers in vascular walls.⁷¹ Interestingly, binding of activated α_2 -macroglobulin to LRP-1 increases MMP-9 expression by macrophages.⁷² The main metalloproteinases involved in cartilage matrix degradation in osteoarthritis are MMP-13, for collagen degradation, and ADAMTS-4 and ADAMTS-5, for aggrecan degradation.⁷³

LRP-1: angel or devil?

As illustrated earlier, LRP-1 may exert a protective effect by inhibiting the excess of extracellular metalloproteinases (eg, MMP-2 and MMP-9 in vascular pathologies and MMP-13, ADAMTS-4, and ADAMTS-5 in osteoarthritis). LRP-1 also exerts deleterious effects by eliminating metalloproteinase inhibitors (TIMP-1, TIMP-2, and TIMP-3). The signaling function exerted by LRP-1 further adds a supplemental level of difficulty for understanding the actual effect of this receptor in metalloproteinases-mediated pathologies.

Metalloproteinases regulate members of the LDLR family by shedding their ectodomain

The members of the LDLR family that regulate metalloproteinase activities by endocytic process, that is, LRP-1, LRP-1b, and LRP-2, are themselves controlled by metalloproteinases, which shed their ectodomain (ECD).

LRP-1

The presence of soluble LRP-1 ECD was first reported in human plasma.⁷⁴ Further characterization of LRP-1 ECD in human choriocarcinoma cells revealed that soluble LRP-1 α -chain copurified with a truncated 55-kDa β -chain, corresponding to the predicted molecular weight of the extracellular portion of the β -chain, meaning that LRP-1 shedding occurs by proteolytic cleavage close to the junction between the extracellular and the transmembrane domains.⁷⁵ A metalloproteinase was responsible for LRP-1 ECD shedding in this model. A recent study reported the presence of soluble LRP-1 ECD in human brain tissue and cerebrospinal fluid.⁷⁶ In this study,

LRP-1 shedding was regulated by ADAM-10 and ADAM-17. We previously provided evidence that LRP-1 ECD shedding occurred in cultures of human endometrial explants.⁷⁷ We also characterized MT1-MMP and ADAM-12 as new sheddases of LRP-1 in the human fibrosarcoma HT1080 cell line.⁷⁸

As with numerous transmembrane receptors, such as Notch,⁷⁹ LRP-1 undergoes regulated intramembrane proteolysis. This sequential proteolytic process involves preliminary ECD shedding. This generates a substrate for a second protease system, generally a γ -secretase presenilin, which cleaves within the transmembrane domain and releases the intracellular domain (ICD) (Figure 3).

We also showed that the cholesterol content of plasma membrane was involved in the shedding of the ECD of LRP-1 and could influence its endocytic properties.⁷⁸

LRP-1b and LRP-2

In contrast to LRP-1, only a few data concerning the regulation of cell surface expression by shedding are available for LRP-1b and LRP-2. Thus, by using specific metalloproteinase inhibitors, Liu et al showed that LRP-1b ECD was shed by ADAM-17.⁸⁰

Immuno-ultrastructural studies revealed two forms of LRP-2 in the brush border of kidney proximal tubules.⁸¹ One of these forms, which lacked its cytoplasmic domain, was associated with the microvillar surface. These observations, which strongly suggested that LRP-2 can be proteolytically processed, were confirmed by in vitro studies demonstrating the shedding of LRP-2 ECD by unidentified metalloproteinases in an opossum kidney proximal tubule cell line.⁸²

Effect of shedding on metalloproteinase-mediated pathologies

Increased LRP-1 shedding from human lung fibroblasts impairs endocytosis of MMP-2 and MMP-9, and thus might contribute to lung tissue destruction in acute respiratory distress syndrome.⁸³ We similarly reported that the inhibition of LRP-1 shedding improves MMP-2 and MMP-9 clearance in cultures of human endometrial explants and may help prevent the occurrence of abnormal uterine bleeding.⁷⁷ Importantly, LRP-1 ECD retains ligand-binding capacity and acts as a decoy receptor.⁸⁴ Thus, the addition of LRP-1 ECD to cultured rat hepatocytes resulted in the inhibition of tissue-type plasminogen activator clearance.⁷⁴ We recently

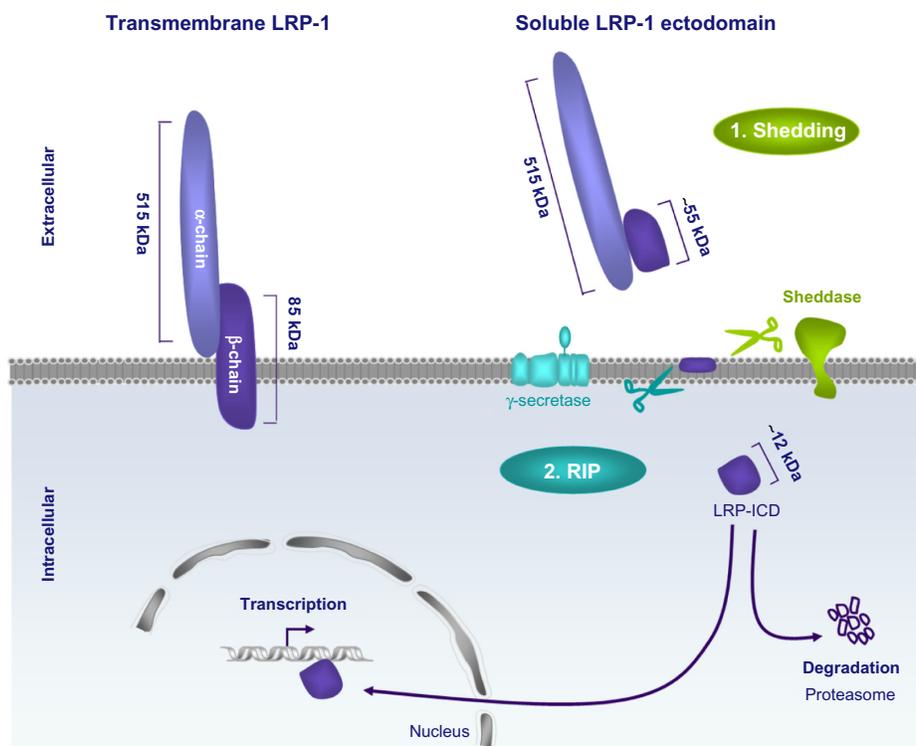


Figure 3 Low-density receptor-related protein 1 (LRP-1) ectodomain shedding and regulated intramembrane proteolysis.

Notes: LRP-1 undergoes a cleavage by a proteolytic enzyme in the extracellular domain of its β -chain, leading to the release of its ectodomain. After this shedding, LRP-1 undergoes a γ -secretase-dependent intramembrane cleavage of the 25 kDa membrane-bound β chain, leading to the release of the intracellular domain (LRP-ICD), a fragment of approximately 12 kDa. This process, called regulated intramembrane proteolysis (RIP), may in some cases be coupled with nuclear signaling, as previously reported for Notch and amyloid precursor protein.

demonstrated that TIMP-3 bound to LRP-1 ECD became resistant to endocytosis and retained its inhibitory activity against metalloproteinases.³⁴ Although no experimental data exist concerning the binding of metalloproteinases; of their inhibitors TIMP-1 and TIMP-2 to LRP-1 ECD; or of MMP-9 to LRP-2 ECD and the preservation of their activities, it is tempting to attribute to these ECDs a role in the development of pathologies associated with excessive inflammation. In this sense, LRP-1 ECD levels are increased in the plasma of patients with rheumatoid arthritis and osteoarthritis.⁸⁵ In addition, the increased levels of LRP-1 ECD in the cerebrospinal fluid of old individuals suggest that LRP-1 shedding during aging could contribute to the pathogenesis of Alzheimer's disease.⁷⁶

The ICD generated by shedding of Notch translocates to the nucleus for regulating transcription of target genes.⁸⁶ In vitro studies showed that similar to Notch ICD, LRP-1 ICD is translocated to the nucleus.⁸⁷ It has been described as impairing the transcriptional activity of APP, Fe65, and Tip60 complex.⁸⁸ In neurons, LRP-1 ICD translocation to the nucleus leads to apoptotic cell death in ischemic conditions.⁸⁹ In macrophages, LRP-1 ICD represses the interferon- γ promoter and limits the inflammatory response.⁹⁰ Blocking of LRP-1b ICD release impedes the ability of LRP-1b to suppress anchorage-independent growth in a cell line derived from a human central nervous system tumor.⁸⁰

These data highlight putative roles exerted by ECD and ICD from members of the LDLR family in the development of metalloproteinase-mediated pathologies.

Conclusion

After presenting the different members of the LDLR family involved in the regulation of metalloproteinase activities, we focused this review on LRP-1 and its involvement in the main metalloproteinase-mediated pathologies that are Alzheimer's disease, cancer, vascular diseases, and osteoarthritis. By coupling endocytosis with cell signaling, LRP-1 appears to be an efficient cell surface receptor that allows a rapid answer to a modification of the cell microenvironment.

Understanding the pathways regulated by LRP-1 in the metalloproteinase-mediated pathologies represents an important challenge for providing adequate responses to patients.

Acknowledgments

We thank Dr Charlotte Selvais for her help in preparing figures. HE is supported by the Université de Reims Champagne-Ardenne and the Centre National de la Recher-

che Scientifique, France. EM is supported by the Université catholique de Louvain.

Disclosure

The authors report no conflicts of interest in this work.

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