

Gene Section

Review

LRP1B (low density lipoprotein receptor-related protein 1B)

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Abstract

Review on LRP1B, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: LRP-DIT, LRPDIT

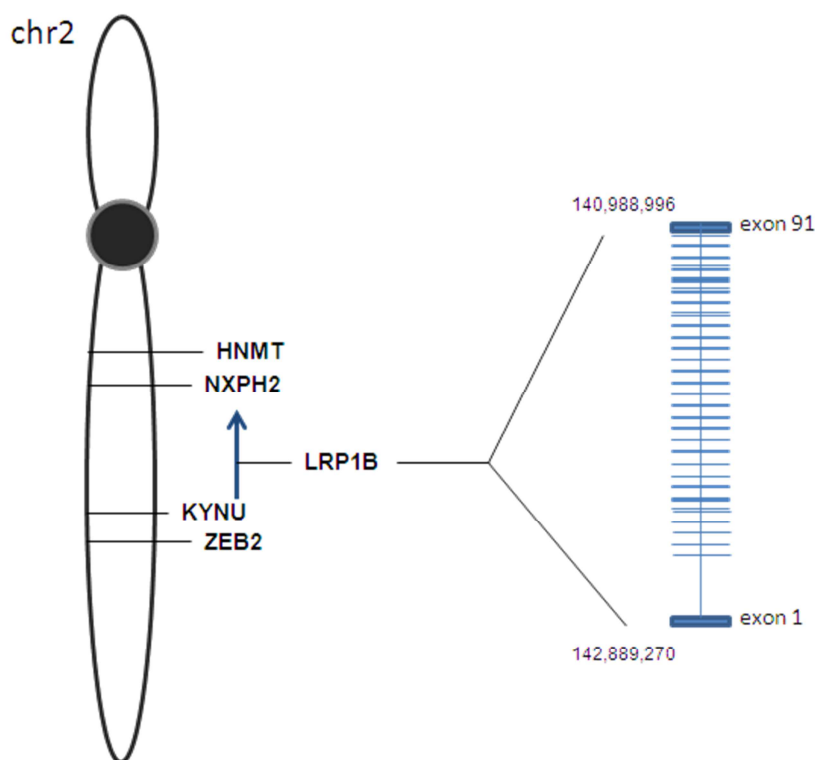
HGNC (Hugo): LRP1B

Location: 2q22.1

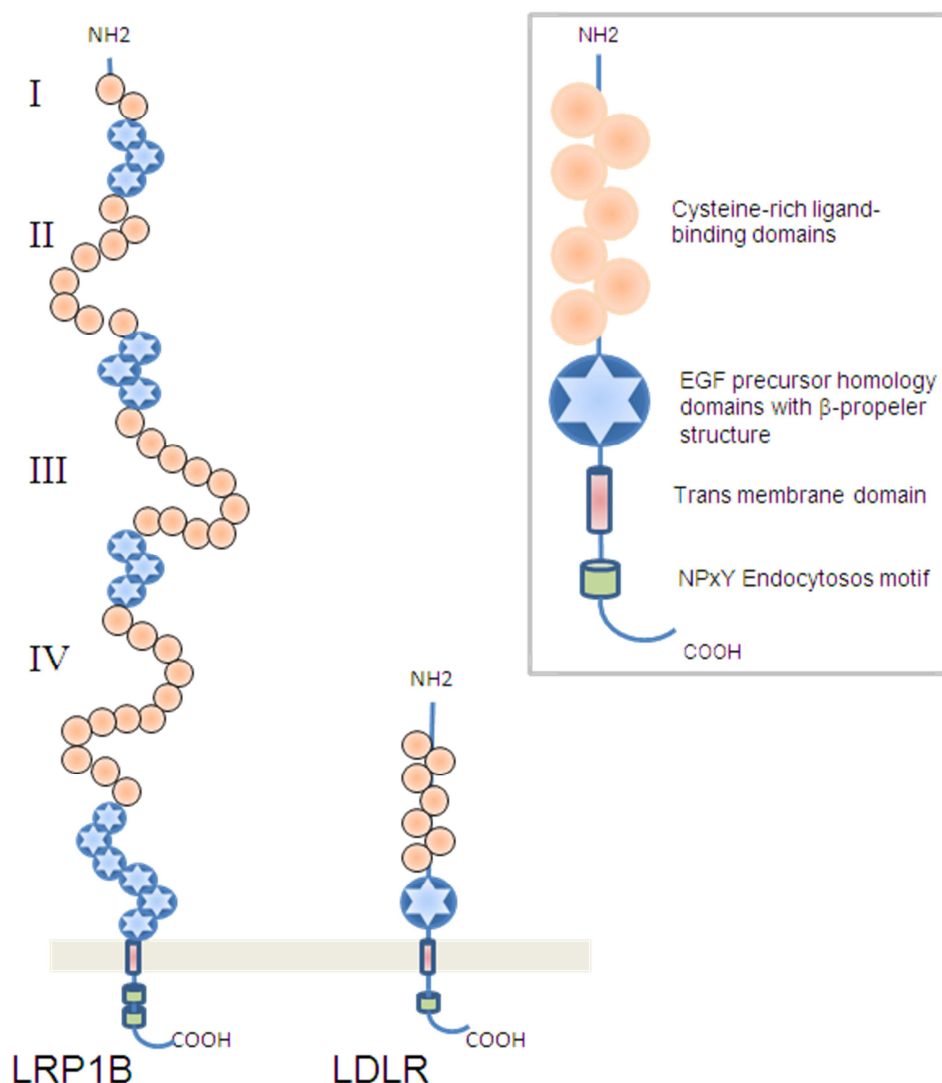
Local order: Centromere ... - HNMT - SPOPL - NXPH2 - **LRP1B** - KYNU - ARHGAP15 - GTDC1 - ZEB - ... qter

Note

LRP1B is encoded in the long arm of chromosome 2, from the minus strand.



Mapping diagram.



Protein diagram. LRP1B is composed of modular domains, namely extracellular cysteine ligand-binding repeats (CRs) and epidermal growth factor precursor-like domains with β -propeller structure, single pass transmembrane region and cytoplasmic domains with endocytosis NPXY motifs that are nonetheless homologous to other LDL Receptor Family members, for which the prototypic member is the LDL Receptor. The specificity in LRP1B structure comes from the number and organization of these modules.

The transmembrane domain of LRP1B is separated from domain IV and by a cassette of six epidermal growth factor-like precursor repeats. The cytoplasmic tail of LRP1B contains two NPXY motifs. Between these two, there is a unique insertion of 33 amino acid residues contributed by exon 90 (Willnow et al., 1999).

Expression

LRP1B is expressed at higher levels in the central nervous system, thyroid, skeletal muscle and testis. In other organs lower expression levels are detected (Haas et al., 2011).

Localisation

LRP1B expression localizes to the cell membrane as well as to several categories of membrane vesicles involved in intracellular traffic. Proteomic analysis has also detected LRP1B in extracellular vesicles, namely as a component of exosomes (Looze et al., 2009).

Soluble LRP1B ectodomains may be released to the extracellular milieu through the action of shedases and exert anchorage independent functions (Dietrich et al., 2010).

Function

The modular protein domains of Lipoprotein Receptors (LRs) account for three important properties. First, individual LRs have been shown to recognize multiple (more than 30) structurally unrelated extracellular ligands, that include lipoprotein complexes but also many other categories of molecules. Second, LRs are capable of engaging endocytosis, resulting in clearance of their ligands from the extracellular milieu. Third, LRs can associate with other membrane bound receptors, such as integrins and receptor tyrosine kinases, and with intracellular signaling molecules. The classical roles of LRPs are to act as scavenger receptors

in the clearance of a myriad of extracellular ligands from the pericellular environment (Herz and Strickland, 2001; May et al., 2007). The best studied ligands of LRs include lipoprotein complexes and proteinase/proteinase inhibitor complexes, such as $\alpha 2$ macroglobulin and members of the urokinase Plasminogen Activating (uPA) system (uPA, uPAR and PAI-1) (Herz et al., 1992; Nykjaer et al., 1992).

LRP1B functions at the extracellular and cell membrane levels:

In order to characterize LRP1B ligands, immobilized recombinant extracellular sub-domains of LRP1B have been used as decoys to perform affinity chromatography using brain lysates (Liu et al., 2001) or in serum (Haas et al., 2011) as a source of potential physiological ligands. Using this strategy, LRP1B has been previously found to bind lipoproteins and ligands of the uPA system (Liu et al., 2001; Li et al., 2002; Knisely et al., 2007). Also several serum proteins, including fibrinogen and apoE-carrying lipoproteins showed affinity to LRP1B extracellular regions (Haas et al., 2011).

It should nevertheless be noted that these approaches inherently under-estimate the full impact of LRP1B activity since, in the former study (Liu et al., 2001), the proteome which has been interrogated was derived from brain-lysate fractions, rather than the extracellular proteome which shares the physiological milieu with LRP1B. In the latter study (Haas et al., 2011), the use of serum restricts candidate ligands to systemic circulating factors and neglects local factors that may play a role in the tissue microenvironment. Evidence that LRP1B activity may, directly or indirectly, modulate the abundance of multiple extracellular factors comes from the analysis of conditioned media from LRP1B overexpressing cells, relative to their parental counterparts. Conditioned media from cells overexpressing LRP1B shows a reduction in the amounts of MMP2 as well as other metalloproteinases, growth factors, cytokines and angiogenic factors, indicating that LRP1B impacts the overall extracellular proteome (Prazeres et al., 2011).

It is thus expected that LRP1B, in analogy with other LRs, can display a myriad of additional extracellular ligands that impact the physiology in the extracellular microenvironment.

LRP1B ligands also include the cellular prion protein (Taylor and Hooper, 2007; Lu et al., 2010).

At the membrane level, LRP1B has been shown to modulate the localization of Urokinase and PDGF receptors (Tanaga et al., 2004) and to retain beta-amyloid precursor protein at the cell surface and reducing amyloid-beta peptide production (Cam et al., 2004).

Intracellular LRP1B partners:

Six interacting partners of the LRP1B cytoplasmic region have been identified by yeast two-hybrid screen and immunoprecipitation.

One of the partners, PICK1 recognizes the C-terminus of LRP1B and inhibits phosphorylation of LRP1B by PKC alpha (Shiroshima et al., 2009). The output of these interactions in terms of signaling pathways activated in consequence of LRP1B activity remains unexplored.

Proteolytic release of LRP1B domains:

LRP1B ectodomains resulting from proteolytic shedding of the extracellular region can be found in the soluble form (Dietrich et al., 2010).

LRP1B has also been shown to undergo regulated intra-membrane proteolysis in a gamma-secretase-dependent manner, releasing an intracellular domain (ICD) that then translocates to the nucleus (Liu et al., 2007).

The functions of the ICD in the nucleus are unknown.

Functions associated with heterologous ligands:

LRP1B may also act as a receptor for heterologous biomolecules such as the *Pseudomonas* exotoxin (Pastrana et al., 2005) and, most interestingly, for certain drugs, putting emphasis on the role of endocytosis in cellular drug uptake (Chung and Wasan, 2004).

In accordance with this, reduced uptake of liposomes by LRP1B may underlie the mechanism of acquired resistance to liposomal doxorubicin chemotherapy in high-grade serous ovarian cancers that display LRP1B deletion (Cowin et al., 2012).

Homology

LRP1B is a member of the LDL receptor family which is composed of seven receptors structurally homologous to the LDL receptor, the prototypic gene of familial hypercholesterolemia (Hobbs et al., 1992).

These receptors, commonly known as lipoprotein receptors (LRs), include the LDL receptor, very low density lipoprotein (VLDL) receptor, apoE receptor 2, multiple epidermal growth factor-like domains 7 (MEGF7), glycoprotein 330 (gp330/megalin/LRP2), LRP1 and LRP1B. In addition, the family includes members that are more distantly related, such as LRP5, LRP6 and SorLa/LRP11.

The close similarity in protein domain structure between LRPs strongly suggests that Lipoprotein Receptors may share a comparable spectrum of ligands.

Nevertheless, this deduction may not be straightforward.

For instance, LRP1B ligands of the uPA system were found to overlap those of LRP1, its closest related member (Liu et al., 2001).

However, distinct properties are displayed by LRP1B since, in contrast to LRP1, cells expressing LRP1B display a substantially slower rate of uPA/PAI-1 complex internalization (Knisely et al., 2007), which impairs the regeneration of free uPAR on the cell surface and correlates with a diminished rate of cell migration (Liu et al., 2001; Li et al., 2002). This

emphasizes that the functions of LRs may be overlapping and yet distinct as a result of their ligand spectrum and kinetics of endocytosis (Liu et al., 2001).

Mutations

Germinal

No germline LRP1B mutations have been characterized.

Somatic

The LRP1B gene was originally isolated by positional cloning on the basis of homozygous deletions (HD) detected in human lung cancer cell lines (Kohno et al., 2010; Liu et al., 2000a; Liu et al., 2000b). In a genomic-wide screen, LRP1B was reported amongst the top 10 most significantly deleted genes across 3312 human cancer specimens (Beroukhi et al., 2010).

Mapping of focal deletions found in these cancer specimens are published at <http://www.broadinstitute.org/tumorscape/pages/portalHome.jsf>. In individual studies of specific tumor types, LRP1B deletions have been reproducibly been observed in lung (Nagayama et al., 2007; Kohno et al., 2010), esophagus (Sonoda et al., 2004), oral (Cengiz et al., 2007), breast (Kadota et al., 2010), renal (Langbein et al., 2002; Ni et al., 2013), neural (Roversi et al., 2006; Yin et al., 2009), thyroid (Prazeres et al., 2011) and ovarian cancer (Chung and Wasan, 2004).

Aside from deletions, LRP1B point mutations have been reported in a significant percentages of lung cancer (Ding et al., 2008) as well as in the sequencing of genomes derived from melanoma (Nikolaev et al., 2011) and triple negative breast cancer (Craig et al., 2013).

Implicated in

Cancer, across types

Note

The diversity of biological ligands underlies the role of LRs in multiple pathologic processes, that include atherosclerosis (Tanaga et al., 2004; Seki et al., 2005) Alzheimer's disease (Jaeger and Pietrzik, 2008; Lillis et al., 2008; Wagner and Pietrzik, 2012) and cancer, the focus of this description below.

LRP1B, a member of the low-density lipoprotein (LDL) receptor family, was identified as a putative tumor suppressor. The down-expression of LRP1B was observed in multiple primary cancers.

Oncogenesis

The "signature" of LRP1B inactivation is archetypal of a tumor suppressor gene and reflects selection towards bi-allelic inactivation and complete abrogation of the gene function.

In tumors, one can observe that multiple inactivation hits, of structural and regulatory nature, have taken place, on both alleles through diverse combinations of

events such as genetic deletions (observable by homozygous deletion), accompanied by epigenetic silencing (DNA methylation), or sometimes by microRNA overexpression (Prazeres et al., 2011).

The role of LRP1B as a tumor suppressor may result from modulation of cell migration and invasive capacity, through regulation of the urokinase plasminogen system (Liu et al., 2001). Cells expressing LRP1B display a substantially slower rate of uPA/PAI-1 complex internalization (Knisely et al., 2007) which impairs the regeneration of unoccupied uPAR on the cell surface and correlates with a diminished rate of cell migration (Li et al., 2002; Tanaga et al., 2004). Aside from members of the plasminogen system, LRP1B expression has been shown to deplete the extracellular medium of MMP2 and other factors (Prazeres et al., 2011). These results support the hypothesis that LRP1B endocytosis may (directly or indirectly) constrain the abundance of critical factors in the tumor microenvironment.

Lung cancer

Note

Nagayama, Kohno et al. (2007) have described that homozygous deletions (HD) was searched for in 43 lung cancer cell lines. The gene LRP1B was also included among the genes. Fifty-one homozygous deletions regions containing 113 genes were identified. The LRP1B was the third most frequent targets of HD. All eight HD segments at the LRP1B gene locus detected in that study included its coding exons, consistent with previous reports (Liu et al., 2000a; Sonoda et al., 2004). At present, the pathogenic significance of LRP1B deletions is unclear; however, frequent HD in these loci indicates that the inactivation of this gene has major roles in the development of lung cancer. LRP1B was mapped at the fragile sites, FRA2F, FRA3B, and FRA16D, and had been found homozygously deleted in a subset of lung cancers (Liu et al., 2000a; Zöchbauer-Müller et al., 2000; Paige et al., 2001; Fabbri et al., 2005; Smith et al., 2006).

Kohno, Otsuka et al. (2010) have verified homozygous deletions in 176 genes. They consisted of 171 protein-encoding genes and five miRNA genes. These 176 genes were located in 45 regions on 17 chromosomes. They included known tumor suppressor genes, as well as candidate tumor suppressor genes shown to be hemizygously or homozygously deleted in several types of human cancers, such as LRP1B (Sonoda et al., 2004).

Esophageal carcinoma

Note

The expression of LRP1B mRNA is frequently lost in esophageal squamous cell carcinoma (ESCs) as a consequence of either homozygous deletions or DNA methylation and the re-expression of this gene inhibits growth of ESC cells. These two types of events affecting the LRP1B gene may be useful as novel

diagnostic markers for ESC because of their high frequencies, although it remains unclear whether precancerous lesions of this tumor contain either of those alterations. The apparent multiplicity of tumor-suppressing activities of LRP1B, however, suggests that this molecule might be a useful starting point for development of novel therapeutic strategies (Sonoda et al., 2004).

Oral carcinoma

Note

Genome-wide LOH analysis demonstrated high LOH ratio of 2q21-23 region by using the markers D2S1334 and D2S1399 in head and neck cancer (Beder et al., 2003). So far no other study showed frequent LOH of this region in oral cancer, but it has been suggested that at least one tumor suppressor gene exists at 2q21-24 and involves in the carcinogenesis of various cancers including oral carcinoma. One candidate gene could be LRP1B, which has already been proposed to function as a tumor suppressor (Cengiz et al., 2007).

Breast cancer

Note

Kadota, Yang et al. (2010) have observed intragenic deletions within several genes which potentially function as breast cancer tumor suppressor loci. These included deletions which disrupted LRP1B in MCF10CA1h and MCF10CA1a cell lines.

Renal cancer

Prognosis

In urothelial cancer, only 8% of cases with Grade 1 and none with Grade 2 tumors showed loss of heterozygosity at the LRP1B gene, whereas 49% of the Grade 3 cases had allelic loss at the LRP1B genomic region, which can be taken to indicate that alteration of the LRP1B gene region is associated with high grade of urothelial cancer (Langbein et al., 2002).

Oncogenesis

Ni, Hu et al. (2013) have investigated the expression of LRP1B in Renal cell cancer (RCC) and its function on cell migration.

They found that LRP1B mRNA was widely expressed in the normal renal tubular epithelial cells, but it was frequently down-expressed in RCC tissues and cell lines.

The depletion of LRP1B increased the anchorage-independent growth, cell migration and invasion in vitro. Moreover, the expression and activation of Rho family members, actin cytoskeletons and focal adhesions complex (FAC) were also affected, indicating that down-expression of LRP1B led to the increase of cell migration and invasion, which is possibly mediated by actin cytoskeleton remodeling, and expressional alteration of FAC components. At the same time, they also found that silencing of LRP1B obviously occurred in T1 of TNM. The result suggests that silencing of LRP1B is an early event in RCC.

Their observation provided an insight into the potential contribution of LRP1B to tumorigenesis, and that LRP1B may be explored as a molecular target in RCC therapy by regulated epigenetic activation means.

These functional specificities in cell spreading, migration and invasion strongly validated that LRP1B may function as a tumor suppressor, and exert opposite effects to LRP1 on cell transformation and malignant progression.

Glioma

Note

Data analysis of full-coverage chromosome 19 highlighted two main regions of copynumber gain, never described before in gliomas, at 19p13.11 and 19q13.13-13.2.

Genomic hotspot detection facilitated the identification of small intervals resulting in positional candidate genes such as LRP1B (2q22.3) for losses, and other for gains.

These data increase the current knowledge about cryptic genetic changes in gliomas and may facilitate the further identification of novel genetic elements, which may provide us with molecular tools for the improved diagnostics and therapeutic decision-making in these tumors (Roversi et al., 2006).

LRP1B has been found frequently mutated in glioblastoma (GBM) (Roversi et al., 2006). A novel internal deletion of LRP1B was discovered in the U118 GBM cell line and four GBM samples. Nucleotide sequencing of the LRP1B gene from U118 cells showed loss of exons 3 to 18 and an early stop codon, suggesting that the protein was no longer functional. This data suggest that LRP1B acts as a tumor suppressor gene in glioma cells and is aberrant in GBM (Yin et al., 2009).

Thyroid cancer

Note

In non-medullary thyroid cancer, LRP1B under-expression is significantly lower in highly aggressive undifferentiated thyroid tumors (Prazeres et al., 2011).

LRP1B expression levels are significantly associated with vascular invasion in follicular thyroid cancer (Prazeres et al., 2011).

Oncogenesis

Prazeres, Torres et al. (2011) have shown that LRP1B inactivation (by chromosomal, epigenetic and microRNA (miR)-mediated mechanisms) resulted in changes to the tumor environment that confer cancer cells an increased growth and invasive capacity.

Restoration of LRP1B impaired in vitro and in vivo tumor growth, inhibited cell invasion and led to a reduction of matrix metalloproteinase 2 in the extracellular medium.

This emphasized the role of an endocytic receptor acting as a tumor suppressor by modulating the extracellular environment composition in a way that constrains the invasive behavior of the cancer cells.

Ovarian cancer

Prognosis

LRP1B binds to fibrinogen and apoE-containing ligands (Haas et al., 2011) and importantly, several studies have suggested that LDL receptor family members are involved in uptake of anionic liposomes and drugs (Chung and Wasan, 2004; Lakkaraju et al., 2002).

Due to high degree of intratumoral heterogeneity and the large number of chemotherapeutic agents commonly used in the relapse setting in high-grade serous cancer (HGSC) patients, the most common subtype of ovarian cancer, it is likely that there will be multiple mechanisms of acquired resistance. It was described that the deletion or downregulation of the lipid transporter LRP1B emerged as a significant correlate of acquired resistance. Functional studies showed that reducing LRP1B expression was sufficient to reduce the sensitivity of HGSC cell lines to liposomal doxorubicin, but not to doxorubicin, whereas LRP1B overexpression was sufficient to increase sensitivity to liposomal doxorubicin. These data indicates that LRP1B loss contributes to the emergence of resistance to chemotherapy, specifically to liposomal doxorubicin (Cowin et al., 2012).

In conclusion, in high-grade serous ovarian cancers, LRP1B deletion is associated with worse prognosis as a result of acquired chemotherapy resistance to liposomal doxorubicin (Cowin et al., 2012).

Alzheimer's disease

Note

Initially, LDL receptor gene family was of high interest due to its key function in cholesterol/apolipoprotein E (ApoE) uptake, with the e4 allele of ApoE as the strongest genetic risk factor for late-onset Alzheimer's disease (AD).

In a review, Jaeger and Pietrzik (2008) have highlighted the involvement of different lipoprotein receptors in AD. Their functional implications reach from mediating amyloid precursor protein (APP) internalization, as LRP1B, intracellular trafficking, A β clearance out of the brain (LRP1) to an involvement in ApoE/cholesterol metabolism. These findings implicate an important role for lipoprotein receptors in the underlying mechanisms leading to the development of AD. These mechanisms will give way to new therapeutic strategies for the treatment of neurodegenerative diseases via interference with the role of lipoprotein receptors.

Atherosclerosis

Note

Seki, Bujo et al. (2005) have characterized the functions of three groups of cultured smooth muscle cells (SMCs) with different origins in atherosclerotic arteries, in order to know a functional significance of LRP1B in the increased migration of SMCs. The

results strongly suggest that LRP1B plays a role in the regulation of migration activity of SMCs through the modification of PDGF signals in the process of atherosclerosis.

Tanaga, Bujo et al. (2004) have described that LRP1B modulates the catabolism of uPAR and PDGFR, affecting the migration of smooth muscle cells (SMCs). This functional characterization of LRP1B opens novel avenues for elucidating the (patho)physiological significance of SMC migration in atheromatous plaques.

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