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Gene Section
Mini Review

MACROD1 (MACRO domain containing 1)

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Identity

Other names: LRP16

HGNC (Hugo): MACROD1

Location: 11q13.1

Local order: Next to OTUB1 and FLRT1.

Note

MACROD1/LRP16 is a member of macro domain protein family, which contains only a stand-alone macro domain functional module at its C-terminus. Through its macro domain module LRP16 binds poly (A), mono (ADP-ribose) or poly (ADP-ribose). LRP16 is an estrogen and androgen-responsive gene. Both estrogen receptor alpha (ERalpha) and androgen receptor (AR) can bind to LRP16 promoter to enhance its transcription. LRP16 also acts as a co-activator of ERalpha, AR, and possible other nuclear receptors, and nuclear factor-kappaB (NF-kappaB) to activate their transcriptional activities. Keratin 18 can associate with LRP16, by which LRP16 was sequestrated in the cytoplasm. In addition, LRP16 can recruit to chromatin when cells were exposed to ironing radiation (IR) by sensing poly (ADP-ribose) synthesized by PARP1, indicating that LRP16 is involved in IR-induced DNA-damage response.

DNA/RNA

Note

MACROD1/LRP16, encoding a 35 kD protein, was originally isolated from human lymphocytes. The proximal region (nt-676 to -24) of the human LRP16 promoter contains a 1/2 estrogen response element (ERE)/Sp1 site and multiple GC-rich elements that confer estrogenic responsiveness and are sufficient for estrogenic action. In the presence of estrogen, ERalpha and Sp1 complex recruits to the LRP16 gene promoter to enhance LRP16 transcription.

Description

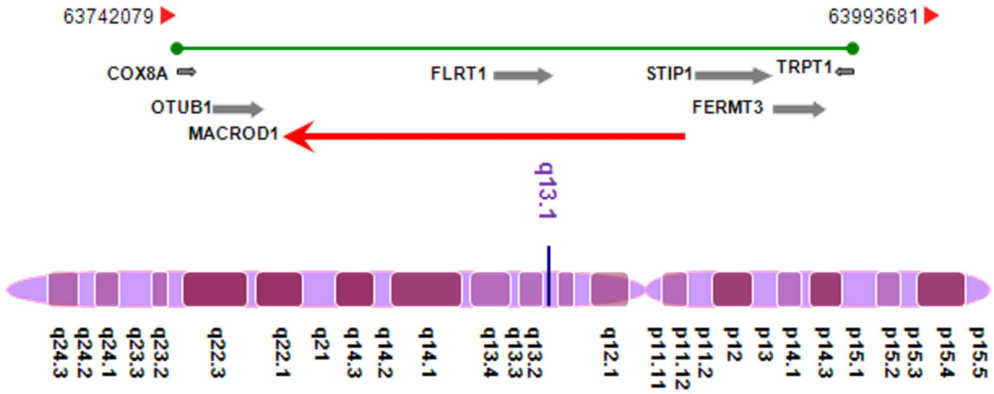
Genomic structure of LRP16: spans 167 kb; 11 exons; ORF: 975 bp.

Transcription

LRP16 mRNA (NM_014067.3) has a size of 1256 bp. Exons: 11; transcript length: 1256 bp; translation length: 325 residues.

Pseudogene

No pseudogenes reported.



Protein

Note

MACROD1/LRP16 contains a single macro domain (Appr-1"-pase_ like). It contains an ADP-ribose-binding pocket through which it can bind mono (ADP-ribose). Moreover, LRP16 also can bind poly (ADP-ribose) and hydrolyze ADP-ribose-1" phosphate to yield ADP-ribose. Therefore, it is reasonable to propose that LRP16 may play an important role in the ADP-ribosylation of proteins, an important post-translational modification which occurs in DNA repair, transcription, chromatin biology, and long-term memory formation.

Description

325 amino acids; 35.505 kDa; containing a single macro domain (from amino acid 141 to 322).

Expression

LRP16 is expressed ubiquitously in nearly all types of tissues and is up-regulated in hormone-dependent cancer cells such as MCF-7 breast cancer cells, Ishikawa endometrial cancer cells, and BG-1 ovarian cancer cells upon estrogenic stimulation. Conversely, estrogen reduces LRP16 expression in estrogen-resistant SKOV-3 ovarian cancer cells. Androgen also up-regulates LRP16 expression in androgen-sensitive prostate cancer cells. In addition, LRP16 is frequently over-expressed in several tumor tissues by comparison with their corresponding normal tissues.

Localisation

Nuclear, cytoplasm and mitochondrion.

Function

1. LRP16 can recruit to DNA-damaged sites through sensing radiation-induced activation of poly-ADP-ribose polymerase-1 (PARP1).
2. LRP16 can interact with both ERalpha and AR to enhance their transcriptional activities.
3. Cytokeratin 18 (K18) can interact with LRP16 through its C-terminal region and sequester LRP16 in the cytoplasm, by which the LRP16 co-activation of ERalpha is inactivated.
4. LRP16 can bind to p65, a component of NF-kappaB, and participates into the NF-kappaB enhanceosome to enhance TNFalpha-induced NF-kappaB activity (our unpublished data).

Homology

- Bos taurus: MACROD1;
- Pan troglodytes: MACROD1;
- Canis lupus familiaris: MACROD1;
- Rattus norvegicus: Macrod1;
- Mus musculus: Macrod1;
- Danio rerio: zgc: 92353;
- Magnaporthe grisea: MGG_09394;
- Neurospora crassa: NCU07925.1.

Implicated in

Prostate cancer

Note

Androgen up-regulates LRP16 expression in both mRNA and protein levels in androgen-sensitive prostate cancer cells such as LNCaP cells, but not in prostate cancer cells without overexpression of LRP16, which significantly stimulates cell growth in the presence of androgen. Reversely, inhibition of the endogenous LRP16 in androgen-sensitive prostate cancer cells markedly diminishes androgen-stimulated cell growth. LRP16 is not only a target of AR in androgen-sensitive prostate cancer cells, but also a coactivator of AR. By the AR-LRP16 feedback pathway, LRP16 may play an important role in the progression of androgen-sensitive prostate cancers.

Estrogen-dependent breast cancer and endometrial cancer

Note

LRP16 is not only a target gene of ERalpha, but also an ERalpha coactivator. LRP16 overexpression significantly promotes MCF-7 cell proliferation. Reversely, knockdown of LRP16 in MCF-7 cells markedly impaired estrogen-stimulated ERalpha activity and cell growth. LRP16 overexpression was observed in more than 30% primary breast cancers.
LRP16 represses E-cadherin (a molecule associated

with cell adhesion and tumor metastasis) expression through antagonizing the binding of ERalpha to the E-cadherin promoter. Inhibition of LRP16 expression in both estrogen-responsive MCF-7 breast cancer and Ishikawa endometrial cancer cells significantly attenuates their invasive capacity.
Collectively, LRP16 may be involved in the progression of estrogen-dependent cancers.

Gastric carcinoma

Note

The expression level of LRP16 in primary gastric carcinoma tissues was significantly higher than that in normal mucosa tissues. In addition, overexpression of LRP16 was positively linked with tumor size, depth of invasion, lymph node metastasis, distant metastasis and TNM stage. Higher expression of LRP16 predicts a poor prognosis of gastric carcinoma patients.

Colorectal carcinoma

Note

The higher expression level of LRP16 was found to be positively associated with the poor differentiation of primary human colorectal carcinomas. In addition, higher expression of LRP16 in primary human colorectal carcinomas was also linked to poor prognosis of patients.

Prognosis

LRP16 overexpression predicts a poor prognosis in several tumors.

t(11;21)(q13;q22) in myelodysplastic syndrome

Hybrid/Mutated gene

A kind of chromosome rearrangement t(11;21)(q13;q22), involved in RUNX1 (also known as AML1) and LRP16, was found in a patient with monocytic leukemia evolving from myelodysplastic syndrome (MDS). The fusion junction of hybrid gene RUNX1-LRP16 has two types, involving either exon 5 or exon 6 of RUNX1 and exon 2 of LRP16. The reciprocal LRP16-RUNX1 chimera is a fusion between exon 1 of LRP16 and exon 7 of RUNX1.

Abnormal protein

Both RUNX1 (exon 5)-LRP16 and RUNX1 (exon 6)-LRP16 retain the RUNT domain (RD) of RUNX1 and the macro domain of LRP16, whereas reciprocal LRP16-RUNX1 retains the transactivation domain (TA) of RUNX1. The formation of fusion protein RUNX1-LRP16 may lead to the inhibition of myeloid differentiation and contributes to leukemia genesis.

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