Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

LOXL3 (lysyl oxidase-like 3)

Kornelia Molnarne Szauter, Katalin Csiszar

John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii, USA (KMS, KC)

Published in Atlas Database: October 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/LOXL3ID44000ch2p13.html
DOI: 10.4267/2042/44556

Identity

Other names: EC 1.4.3.-, LOXL

HGNC (Hugo): LOXL3

Location: 2p13.3

DNA/RNA

Note

LOXL3 is part of the lysyl oxidase (LOX) family, the members of which are secreted extracellular matrix enzymes. LOXL3 contains a C-terminal region that is conserved in all five isoforms of this copper-dependent amine oxidase family. The domains included within this region are a copper-binding site, lysyl and tyrosine residues that form the lysyltyrosine-quinone cofactor (LTQ) and a cytokine receptor-like domain. The N-terminal region of the full-length LOXL3 contains four SRCR (scavenger receptor cysteine-rich) domains that have high levels of homology with the SRCR domains within LOXL2 and LOXL4, but not with the N-terminal part of LOX or LOXL that do not contain SRCR domains.

Description

The human LOXL3 gene has 14 exons that span more than 21 kb of genomic sequence located on chromosome 2p13.3. The LOXL3 gene has been described to have a 2262 bases (Jourdan-LeSaux et al., 2001) long open reading frame (reported as 2226 bp by Maki et al., 2001) and a 3' UTR of 787 bases.

Transcription

The human LOXL3 cDNA is 3121 bases long. The 3' UTR has three consensus polyadenylation signal sequences. In the 3' UTR there are three AU-rich sequence elements that are usually found within the 3' trailer region of unstable mRNAs.

Alternative splicing was detected in ESTs that appear to represent tissue-specific splice forms of the LOXL3 mRNA. The alternatively spliced LOXL3 mRNA lacks exons 1, 2, 3, and 5 with an exon-intron structure distinct from the full-length LOXL3, and additionally, contains 80 bps in its 5' UTR and 561 bps in its 3'UTR. The protein deduced from this alternative mRNA retains the structural C-terminal elements of a LOX family protein and the fourth SRCR domain at its N-terminus and is predicted to encode a polypeptide of 392 amino acids with a predicted molecular mass of 44 kDa.

In Northern blot analyses of multiple human tissue samples, LOXL3 mRNA was detected at 3.1 kb using PCR-generated (Maki et al., 2001) and at 3.3 kb using EST-derived probes (Jourdan-LeSaux et al., 2001).

Protein

Note

Western blot analysis of HT-1080 cells detected the recombinant cellular and secreted form of the LOXL3 protein as a band of 97 kDa, slightly larger than the predicted overall mass of 83.6 kDa for the recombinant LOXL3, a size difference probably due to cell-type dependent glycosylation.

Description

The predicted LOXL3 protein is 753 (also reported as 754, Jourdan-LeSaux et al., 2001) amino acids long with a 25 amino acid long predicted signal peptide and with a calculated molecular mass of approximately 80.3 kDa. The C-terminal region, (aa. 529-729, Maki et al., 2001) contains the conserved lysyl oxidase domain, including the putative copper binding sequence (aa. 601-611, Maki et al., 2001; 601-612, Jourdan-LeSaux et al., 2001), the lysyl (aa. 634, Maki et al., 2001; 639, Jourdan-LeSaux et al., 2001) and tyrosyl (aa. 689, Maki

et al., 2001; 670, Jourdan-LeSaux et al., 2001) residues that form the lysyltyrosylquinone cofactor, and the cytokine receptor-like motif (aa. 666-727, Jourdan-LeSaux et al., 2001). In the N-terminal region the four scavenger receptor cysteine-rich domains are located at aa. 44-144, 186-281, 307-407, and 417-526 (Jourdan-LeSaux et al., 2001) and a putative nuclear localization signal is at aa. 293-311. The processed LOXL3 polypeptide contains three putative O-glycosylation sites and five potential N-glycosylation sites. There is a putative BMP-1 processing site between amino acid residues 446-448 (Jourdan-LeSaux et al., 2001).

Expression

Tissues: Human LOXL3 mRNA is expressed in leucocytes, in the adult human aorta, neurons, spinal cord, brain, heart, uterus, ovary, testis, prostate, small intestine and spleen. Low mRNA expression was found in the kidney, skeletal muscle and placenta. Expression of the human LOXL3 splice variant mRNA was detected in the kidney, pancreas, spleen and thymus, indicating distinct tissue specificity.
Human LOXL3 protein was detected in the testis, and lung at 44kDa, corresponding to the short spice variant. In the placenta, and colon both the splice product 44 kDa and the full-length 67 kDa LOXL3 were reported.
In mice, LOXL3 protein expression was reported in the tunica media of the adult heart, in aortic smooth muscle cells, and in the cytoplasm of the myocardium. Nuclear localization was detected in the kidney and liver. Cytoplasmic LOXL3 was present in hepatocytes. In the kidney, LOXL3 protein is expressed in the distal and proximal convoluted tubes and the collecting tubes. Strong LOXL3 protein expression was noted in embryonic murine chondrocytes and in skin, epidermis and dermis.
Cell lines: Human LOXL3 mRNA was expressed in the highly invasive breast cancer cell line Hs578T, highly invasive/metastatic human MDA435 cells derived from pleural effusion from a female patient with an infiltrating ductal carcinoma, and human A375P melanoma cell lines. No LOXL3 mRNA expression was detected in MCF7, T47D and MDA MB-231 breast cancer lines.
Murine LOXL3 mRNA was expressed in the C2C12 myoblast cell line, and the highly metastatic HaCa4 squamous cell carcinoma and CarB spindle cell carcinoma cell lines.

Localisation

Nuclear localization was noted in the mouse kidney and liver. In transiently transfected MDKC cells LOXL3 showed perinuclear localization. Cytoplasmic expression was found in the murine myocardium and in hepatocytes. Recombinant LOXL3 protein in human HT-1080 fibrosarcoma cell lines localized both intra- and extracellularly.

Function

LOXL3 likely functions as an amine oxidase, as BetaAPN (Beta-aminopropionitrile) inhibitable enzymatic activity was noted for a recombinant human LOXL3 generated in an E. coli expression system. The recombinant full length LOXL3 showed high catalytic activity towards collagen type I, IV, VIII, X and lower activity against collagen type VI substrates. The splice variant LOXL3 showed highest activity against type IV collagen as a substrate.

Homology

LOXL3 has high level of homology with the C-terminal domains of LOX, LOXL1, LOXL2 and LOXL4 and homology with the four N-terminal SRCR domains within LOXL2 and LOXL4.

Implicated in

Breast cancer

Note
LOXL3 mRNA was expressed in Hs578T highly invasive breast cancer cells, but not in poorly invasive and non-metastatic breast cancer cells MCF7 and T47D.

Disease
Breast cancer invasion.

Epithelial-mesenchymal transition (EMT) - tumor progression

Note
LOXL3 interacts and collaborates with SNAI1 (SNAIL, 20q13.2) to downregulate E-cadherin expression. Overexpression of LOXL3 in MDCK epithelial cells induces an EMT process.

References

Huang Y, Dai J, Tang R, Zhao W, Zhou Z, Wang W, Ying K, Xie Y, Mao Y. Cloning and characterization of a human lysyl oxidase-like 3 gene (hLOXL3). Matrix Biol. 2001 Apr;20(2):153-7

Jourdan-Le Saux C, Tomsche A, Ujfalusi A, Jia L, Csiszar K. Central nervous system, uterus, heart, and leukocyte expression of the LOXL3 gene, encoding a novel lysyl oxidase-like protein. Genomics. 2001 Jun 1;74(2):211-8

Mäki JM, Kivirikko KI. Cloning and characterization of a fourth human lysyl oxidase isoenzyme. Biochem J. 2001 Apr 15;355(Pt 2):381-7

Kirschmann DA, Seftor EA, Fong SF, Nieva DR, Sullivan CM, Edwards EM, Sommer P, Csiszar K, Hendrix MJ. A molecular role for lysyl oxidase in breast cancer invasion. Cancer Res. 2002 Aug 1;62(15):4478-83

Molnar J, Fong KS, He QP, Hayashi K, Kim Y, Fong SF, Fogelgren B, Szauter KM, Mink M, Csiszar K. Structural and functional diversity of lysyl oxidase and the LOX-like proteins. Biochim Biophys Acta. 2003 Apr 11;1647(1-2):220-4

Peinado H, Del Carmen Iglesias-de la Cruz M, Olmeda D, Csiszar K, Fong KS, Vega S, Nieto MA, Cano A, Portillo F. A molecular role for lysyl oxidase-like 2 enzyme in snail regulation and tumor progression. EMBO J. 2005 Oct 5;24(19):3446-58

Lee JE, Kim Y. A tissue-specific variant of the human lysyl oxidase-like protein 3 (LOXL3) functions as an amine oxidase with substrate specificity. J Biol Chem. 2006 Dec 8;281(49):37282-90

Kaku M, Mochida Y, Atsawasuwan P, Parisuthiman D, Yamauchi M. Post-translational modifications of collagen upon BMP-induced osteoblast differentiation. Biochem Biophys Res Commun. 2007 Aug 3;359(3):463-8

This article should be referenced as such:

Szauter KM, Csiszar K. LOXL3 (lysyl oxidase-like 3). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(9):644-646.