

Gene Section

Mini Review

STARD13 (star-related lipid transfer (START) domain containing 13)

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Identity

Hugo: STARD13

Other names: DLC2 (Deleted in Liver Cancer 2);
FLJ37385; GT650

Location: 13q13.3

DNA/RNA

Note: GeneLoc location for GC13M032575: Start: 32,575,307bp from pter; End: 32,757,892; Size: 182,585; Orientation: minus strand.

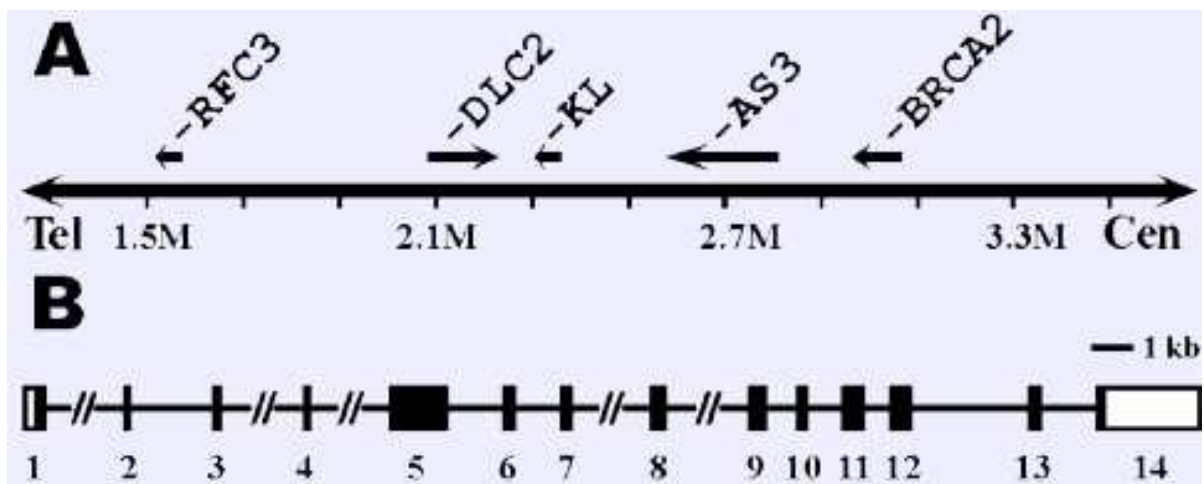
Description

DLC2 was identified due to striking sequence homology to DLC1. It localizes to a small region of 13q12.3, which is a locus frequently deleted in hepatocellular carcinoma (HCC) as well as in other

cancers. Physical mapping of DLC2 in human genome revealed that it is in close proximity to the BRCA2 locus and flanked by microsatellite markers D13S171 and D13S267. The human DLC2 gene spans a region of 182 kb and contains 14 coding exons.

Transcription

The mRNA of DLC2 is 5886 bp long with an open reading frame of 3342 bp. Using bioinformatic analysis, 4 isoforms of DLC2, namely, DLC2alpha (5886 bp), DLC2beta (5810 bp), DLC2gamma (5784 bp), and DLC2delta (943 bp) have been identified. These 4 isoforms are generated by alternative splicing of the 5' end of the transcript. Northern blot analysis detected 7.2- and 4.2-kb DLC2 transcripts in all tissues examined, with the highest expression in heart, skeletal muscle, kidney, and pancreas.



Genomic characterization of human DLC2. (A) chromosomal map location of human DLC2 at 13q 12.3. Arrows underneath the gene symbols indicate the orientation of transcription. RFC3, replication factor C subunit 3; KL, Klotho; AS3, androgen shutoff 3; BRCA2, breast cancer 2, early onset; Tel, telomeric; Cen, centromeric. (B) genomic organization of human DLC2 locus. Non-coding (open boxes) and coding (filled boxes) are shown. (Ching YP, et al. J Biol Chem 2003).

Protein

Description

DLC2alpha encodes a 1113-amino acid protein which has a calculated molecular mass of 125 kD. DLC2 contains an N-terminal sterile alpha motif (SAM) domain for protein-protein interactions, followed by an ATP/GTP-binding motif, a GTPase-activating protein (GAP) domain, and a C-terminal STAR-related lipid transfer (START) domain. The 4 isoforms of DLC2, DLC2alpha, DLC2beta, DLC2gamma, and DLC2delta, encode proteins of 1113, 1105, 995, and 135 amino acids, respectively. DLC2alpha and DLC2beta encode a protein containing three functional domains, SAM, RhoGAP and START domains. DLC2alpha and DLC2beta differ by only a few N-terminal amino acids. DLC2gamma contains the RhoGAP and START domains, but lacks the N-terminal SAM domain, whereas DLC2delta contains only the SAM domain. Co-immunoprecipitation assay of ectopically expressed DLC2 in cells revealed that DLC1 forms homodimers in vivo and the region 160-672 residues is responsible for the interaction.

Expression

DLC2 is ubiquitously expressed in human tissues and is more abundant in heart, skeletal muscle, kidney and pancreas.

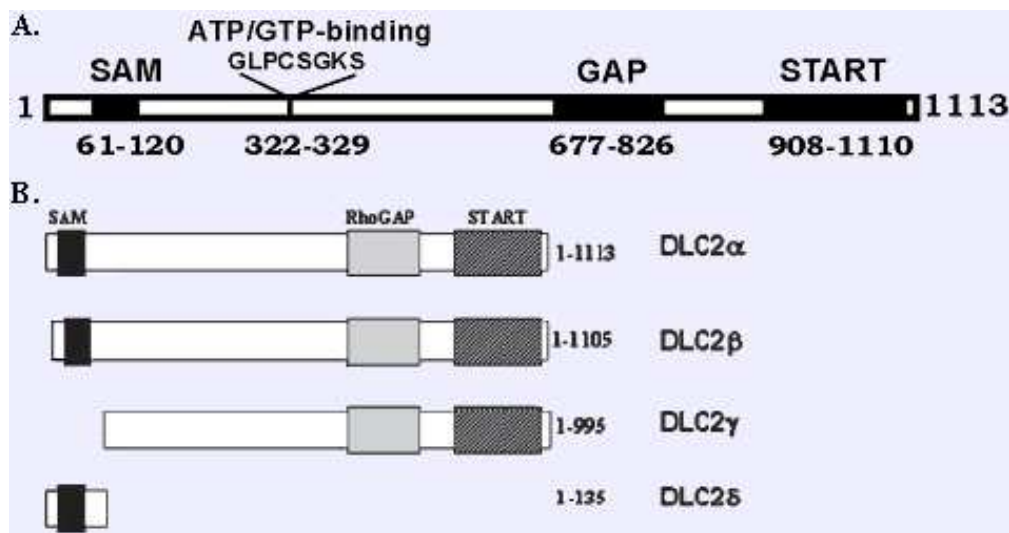
Localisation

DLC2alpha, DLC2beta and DLC2gamma are predominantly localized in the cytoplasm in mouse

fibroblast and human HCC cells. Cellular fractionation and immunofluorescence microscopy revealed that DLC2 localizes to cytoplasmic speckles overlapping with mitochondria and in structures in close proximity to lipid droplets. The START domain of DLC2 has been demonstrated to be responsible for mitochondria targeting of DLC2.

Function

DLC2 has been implicated to be a tumor suppressor protein. DLC2 has growth suppressive and anti-metastatic effects on HCC cell line, HepG2 and breast cancer cell line, MCF7. The RhoGAP domain has been demonstrated to be responsible for its biological functions and the RhoGAP activity has been demonstrated in vitro and in vivo. Recombinant DLC2 showed GAP activity specific for small GTPases, RhoA and Cdc42. Using GST-Rhotekin pull down assay, in vivo RhoA activity has been shown to be negatively regulated by DLC2. However, in cells transfected with DLC2 RhoGAP mutant, the in vivo RhoA activity remained unchanged. Moreover, DLC2 inactivates RhoA activity via its RhoGAP domain and leads to the inhibition of actin stress fiber formation. Ectopic expression of DLC2 changed mouse fibroblast morphology from angular and spindle-shaped to round-shaped with dendritic cellular protrusions. Cells express DLC2 RhoGAP mutants did not exhibit morphological change and the actin stress fiber formation in these cells is unaffected. Introduction of human DLC2 into mouse fibroblasts suppressed Ras signaling and Ras-induced cellular transformation in a GAP-dependent manner. Overexpression of DLC2 also



A. DLC2 is a multifunctional protein. Diagram of protein domains in DLC2. SAM, sterile alpha motif; ATP/GTP binding, ATP/GTP-binding site motif A; GAP, RhoGAP domain; START, StAR-related lipid transfer domain. (Ching YP, et al. J Biol Chem 2003).

B. Functional domains of the DLC2 isoforms. DLC2alpha and DLC2beta each contains a SAM, a RhoGAP, and a START domain, but they differ in their N-terminal sequence. The difference in the amino acid sequence was located at the first 60 aa in DLC2alpha and the first 52 aa in DLC2beta. DLC2gamma contains a RhoGAP and a START domain. DLC2delta only contains a SAM domain. (Leung TH, et al. Proc Nat Acad Sci USA. 2005).

suppressed cell proliferation, motility and anchorage-independent growth in human hepatoma cells.

Collectively, down regulation of RhoA activity in HCC cell line by DLC2 resulted in change of cell morphology, migration rate, proliferation rate and transforming ability.

Several proteins were identified as interacting partners of DLC2 by yeast two-hybrid screening. These proteins include SWI/SNF, alpha-tubulin, HMG CoA reductase, and TAX1 binding protein (TAX1BP1).

Homology

DLC family members: DLC1 is located at chromosome 8p22; DLC3 is located at chromosome Xq13; DLC2 shares 51% and 52% amino acid identities with DLC1 and DLC3, respectively.

Implicated in

Cancer

Note: DLC2, with its RhoGAP domain, is able to inhibit the activity of RhoA, which is believed to play a significant role in cell transformation in many cancer types. Down regulation of DLC2 mRNA expression has been reported in various types of cancer including liver, breast, lung, ovarian, renal, uterine, gastric, colon and rectal tumors.

DLC2 localizes to a small region of 13q12.3 commonly deleted in HCC. DLC2 is flanked by microsatellite markers D13S171 and D13S267. Loss of heterozygosity on these two markers is frequently found in HCC. Allelic losses at markers D13S171 and D13S267 are detected in 33.3% and 40.7% of the informative cases, respectively. RT-PCR analysis of DLC2 mRNA in 45 HCC samples revealed that 17.8% of the cases showed significant underexpression (more than 2-fold) of DLC2 mRNA when compared with the corresponding non-tumorous liver tissues from the same patients.

Studies in human cancers have suggested that small GTPases of the Rho family are critically involved tumorigenesis. Suppression of RhoA activity may be able to reverse the transformation phenotype in cancers. RhoGAP activity of DLC2 has been demonstrated both in vitro and in vivo. Anchorage-independent growth of cancer cells is a hallmark of cellular transformation. Stable expression of DLC2 in liver cancer cell line

effectively abolished the anchorage-independent growth ability of the cells. This indicated that DLC2 is capable of reducing the transforming phenotype and supports the view that DLC2 is a functional tumor suppressor.

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