

# Gene Section

## Review

### DLC1 (deleted in liver cancer 1)

Frankie Chi Fat Ko, Irene Oi-Lin Ng, Judy Wai Ping Yam

Department of Pathology, University Pathology Building, Queen Mary Hospital, Pokfulam, Hong Kong, China (FCFK, IOLN, JWPY)

Published in Atlas Database: May 2010

Online updated version : <http://AtlasGeneticsOncology.org/Genes/DLC1ID40328ch8p22.html>

DOI: 10.4267/2042/44958

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2011 Atlas of Genetics and Cytogenetics in Oncology and Haematology

#### Identity

**Other names:** ARHGAP7, FLJ21120, HP, STARD12, p122-RhoGAP

**HGNC (Hugo):** DLC1

**Location:** 8p22

#### DNA/RNA

##### Note

GeneLoc location for GC08M012985:

Start: 12940872 bp from pter,

End: 13372395 bp from pter,

Size: 475895 bases,

Orientation: minus strand.

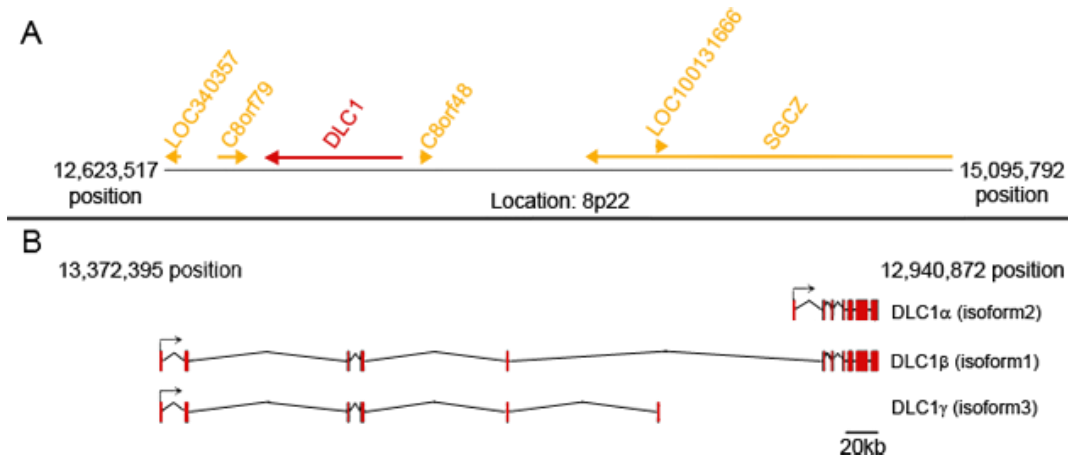
#### Description

DLC1 was first isolated from human hepatocellular carcinoma (HCC) by PCR-based subtractive hybridization method in 1998 (Yuan et al., 1998). It maps to human chromosome 8p21.3-22, a region recurrently deleted in HCC and other solid tumors. Several isoforms of DLC1 have been found, namely DLC1alpha (isoform 2), DLC1beta (isoform 1) and DLC1gamma (isoform 3). DLC1alpha, DLC1beta and DLC1gamma contain 15 exons, 19 exons and 6 exons respectively.

#### Transcription

Transcript size:

DLC1alpha: 6044 bp (NM\_006094),



**Genomic organization of human DLC1.** (A) Schematic diagram illustrating chromosomal location of human DLC1 at 8p22. Arrow underneath the gene symbol indicates the orientation of transcription. LOC340357, hypothetical transcript; C8orf79/C8orf48, chromosome 8 open reading frame 79/48; LOC100131565, pseudo eIF4-like; SGCZ, Sacroglycan, zeta. (B) Genomic organization of human DLC1 locus. Coding (filled boxes) and non-coding (horizontal lines) regions are shown. Arrow represents the position of the transcriptional start site.

DLC1beta: 7445 bp (NM\_182643),  
DLC1gamma: 1975 bp (NM\_024767).

Among the three DLC1 isoforms, DLC1alpha represents the predominant isoform. It has a unique 5' untranslated region and a transcript size of 6044 bp. DLC1beta has the longest transcript size of 7445 bp. It contains a total of 19 exons including exons 2 to 14 of DLC1alpha and another 5 exons upstream of the transcriptional start site of DLC1alpha. DLC1gamma is the shortest isoform with a transcript size of 1975 bp. It shares the first 5 exons with DLC1gamma and has a unique exon 6.

CpG islands have been reported to be found in -387 to +502 and +554 to +765 of DLC1alpha promoter. In this region, 11 SP1 and 4 GCF transcription factor binding sites (-162 to +67) have also been documented (Yuan et al., 2003). Genomic deletions and promoter hypermethylation are responsible for the underexpression of DLC1 not only in HCC but in various cancer cells and tissues (Wong et al., 2003; Durkin et al., 2007a). DLC1beta and gamma share the same promoter region and are formed by alternative splicing at the 3' end. One potential AP-1 site has been reported to be localized at -134 position in DLC1beta and gamma promoter region. The absence of CpG island in DLC1beta and gamma promoter region suggests that their expressions are less likely to be transcriptionally regulated by epigenetic alterations.

## Protein

### Note

Protein size:

DLC1alpha: 1091 amino acids; 122 kDa,

DLC1beta: 1528 amino acids,

DLC1gamma: 498 amino acids.

### Description

DLC1alpha and beta are structurally similar containing SAM, RhoGAP and START domains. DLC1alpha encodes a 1091-amino acid protein with a predicted molecular weight of 122 kDa. Comparing with DLC1alpha, DLC1beta possesses a longer N-terminal region. It encodes a protein of 1529 amino acids. DLC1gamma is the smallest isoform of DLC1 with only 498 amino acids and has no functional domains. It shares the N-terminal region with DLC1beta isoform.

Functional domains:

**SAM** (Sterile Alpha Motif)

Interpro: IPR001660; SAM

Pfam: PF07647; SAM\_2

PROSITE: PS50105; SAM\_DOMAIN

**RhoGAP** (RhoGTPase Activating Protein)

Interpro: IPR000198; RhoGAP

Pfam: PF00620; RhoGAP

PROSITE: PS50238; RHO GAP

SMART: SM00324; RhoGAP

**START** (STERoidogenic Acute Regulatory related lipid Transfer)

Interpro: IPR002913; START\_lipid\_bd

Pfam: PF01852; START

PROSITE: PS50848; START

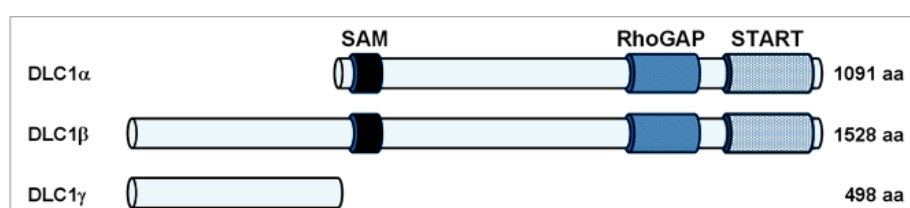
SMART: SM00234; START

### Expression

Northern blot analysis showed that DLC1 is ubiquitously expressed in normal human tissues with high abundance in lung and ovary (Yuan et al., 1998). Quantitative PCR analysis showed that DLC1alpha is the dominant isoform in all human tissues examined, except in heart tissue whereas DLC1beta is the most abundant isoform in the heart. Among all the normal tissues examined, DLC1alpha is relatively abundant in the lung and ovary. Besides, it is moderately expressed in the thyroid, spleen, intestine and kidney, and least expressed in the adrenal gland, liver and pancreas. DLC1gamma is rarely detectable in tissues. Although DLC1 was first identified as a putative tumor suppressor gene in HCC, accumulating studies have supported that DLC1 is involved in various human cancers. Frequent underexpression of DLC1 has been detected in a wide range of tumor tissues and cancer cell lines. Both genomic deletions and epigenetic silencing are responsible for the underexpression of DLC1.

### Localisation

Subcellular localization of ectopically expressed DLC1 was first reported to be present in the cytoplasm of HCC cell lines, Focus and 7703K (Zhou et al., 2003). DLC1 was later reported to be colocalized with vinculin when expressed in cells (Yam et al., 2006). DLC1 has been reported to interact with tensin proteins at focal adhesions. Focal adhesion localization is crucial to the tumor suppression activity of DLC1 (Liao et al., 2007; Qian et al., 2007; Chan et al., 2009).



**Schematic representation of DLC1 protein.** DLC1 is a multiple-domain protein including sterile alpha motif (SAM), Rho GTPase activating protein (RhoGAP) and StAR-related lipid transfer (START) domains.

It is also intriguing to note the presence of nuclear localization signal (NLS) and nuclear export sequences (NES) in DLC1. It is reported that the presence of a basic residues rich motif in DLC1 resembling the NLS is responsible for the nucleocytoplasmic shuttling of DLC1 (Yuan et al., 2007). It has been shown that activated protein kinase C (PKC) and protein kinase D (PKD) stimulate the association between DLC1 and 14-3-3 proteins. The enhanced association blocks DLC1 nucleocytoplasmic shuttling and inhibits the RhoGAP activity of DLC1 (Scholz et al., 2009).

### Function

Since the identification of DLC1 in 1998, accumulating studies have well characterized DLC1 as a bona fide tumor suppressor not only in HCC, but in diverse human cancers (Liao and Lo, 2008). DLC1 encodes a protein containing three major functional domains, namely, sterile alpha motif (SAM) at the N-terminus, and RhoGAP and steroidogenic acute regulatory (StAR)-related lipid transfer (START) domains at the C-terminus. RhoGAP activity has been demonstrated to be critical for the biological activities of DLC1. It possesses selective activity towards RhoA, RhoB and RhoC and less towards CDC42 but not Rac1 (Wong et al., 2003; Healy et al., 2008). Abrogation of Rho/ROCK-mediated cytoskeleton reorganization by DLC1 has been shown to be RhoGAP dependent (Wong et al., 2008). DLC1 RhoGAP defective mutant failed to inhibit stress fiber formation in HCC cells (Wong et al., 2005).

The tumor and metastasis suppressive effects of DLC1 have been well characterized by ectopic expression of DLC1 in various cancer cell lines. Extensive studies have shown that the RhoGAP activity is crucial to the biological activities of DLC1. Introduction of DLC1 into cancer cell lines has been shown to suppress cell proliferation (Ng et al., 2000), inhibit cell migration and invasion (Wong et al., 2005; Qian et al., 2007), and induce apoptosis (Zhou et al., 2004). Moreover, restoration of DLC1 expression has been shown to inhibit metastasis of cancer cells in mouse model (Goodison et al., 2005). Functional data about the loss of DLC1 in HCC tumorigenesis was first demonstrated in a mouse model using a liver-specific, short-hairpin RNA-mediated DLC1 knockdown approach (Xue et al., 2008). In p53 null; c-myc-transduced mouse hepatoblasts, RNAi knockdown of DLC1 could promote *in vivo* tumorigenicity of cells. Apart from RhoGAP activity, proper focal adhesion localization and interaction with tensin proteins have been demonstrated to play important roles in the biological activities of DLC1 (Yam et al., 2006; Liao et al., 2007; Qian et al., 2007; Chan et al., 2009). Other proteins including caveolin-1 (Yam et al., 2006), p120RasGAP (Yang et al., 2009) and 14-3-3 (Scholz et al., 2009) protein have also been identified as interacting partners of DLC1 with functional implications. Using knockout mouse model, DLC1 has been shown to be crucial to

the early embryonic development of mouse (Durkin et al., 2005). DLC1<sup>-/-</sup> embryos are embryonic lethal while DLC1<sup>+/-</sup> mouse is phenotypically normal. Mouse embryonic fibroblasts isolated from DLC1 deficient mice displayed altered cytoskeletal organization and focal adhesions.

### Regulation

DLC1 is widely expressed in normal human tissues, but it is frequently underexpressed in HCC and other cancers. Heterozygous deletion and promoter hypermethylation of DLC1 are commonly found in about 30-50% of cases in various human cancers (Yuan et al., 2003a). Although DLC1 expression and activity have been well documented to be regulated at the transcriptional level, recent studies about the regulation of RhoGAP activity, interacting potentials and subcellular localization of DLC1 have pointed to an essential regulatory role by the central region of DLC1. In the central focal adhesion targeting region of DLC1, somatic mutations of DLC1 have been first detected in human prostate cancers (Liao et al., 2008). These mutations impaired the RhoGAP activity of DLC1. Crucial residues in the central region have also been shown to be responsible for proper focal adhesion localization and interacting with tensin proteins (Chan et al., 2009; Liao et al., 2007). Mutation at these crucial residues caused DLC1 to lose its focal adhesion localization and tumor suppressive activity. More importantly, the central region has been subjected to post-translational modifications. Scholz et al. have suggested that PKD-mediated DLC1 phosphorylation stimulates the association between DLC1 and 14-3-3 proteins. Enhanced association blocks DLC1 nucleocytoplasmic shuttling and inhibits the RhoGAP activity of DLC1 (Scholz et al., 2009). Moreover, identification of rat homolog of DLC1, p122RhoGAP as the substrate of Akt has provided insights into other potential regulatory pathways of DLC1 (Hers et al., 2006). However, the functional significance Akt phosphorylation in p122RhoGAP and its relevance in human DLC1 have not been investigated.

### Homology

DLC family members (DLC1, DLC2 and DLC3) are structurally conserved with high sequence homology (Durkin et al., 2007b). DLC2 localizes at human chromosome 13q12.3 while DLC3 maps to human chromosome Xq13. DLC1 shares 58% and 44% amino acid identities with DLC2 and DLC3 respectively.

## Mutations

### Note

Somatic mutations of DLC1 have been reported to be rarely found in HCC, colorectal and ovarian cancers (Wilson et al., 2000; Park et al., 2003). Until recently, DLC1 mutations have been reported in colorectal and prostate cancers (Liao et al., 2008). Mutational analysis

of human genomic and cDNA has been performed in nucleotide sequence encoding the focal adhesion targeting region (201-500 amino acids) of DLC1.

### **Somatic**

(Reference sequence: NM\_006094)

Colorectal cancer (N=37)

1243 G->T (S308I) - (1/37) 2.7%

1279 G->T (S320I) - (1/37) 2.7%

1333 AC->TA (Y338L) - (1/37) 2.7%

1336 T->A (L339\*) - (1/37) 2.7%

Prostate cancer (N=28)

1189 C->T (P290L) - (2/28) 7.1%

1222 C->A (T301K) - (1/28) 3.6%

1243 G->T (S308I) - (3/28) 10.7%

1249 C->A (S310\*) - (1/28) 3.6%

The nonsense mutations (S310\* and L339\*) resulted in truncated DLC1 proteins with the loss of intact focal adhesion targeting region, RhoGAP and START domains. These truncated proteins are nonfunctional. Colony formation assay revealed that both T301K and S308I mutants displayed significant reduction in growth suppression activities. In addition, RhoGAP activity was downregulated in the two mutants as well.

## **Implicated in**

### **Hepatocellular carcinoma**

#### **Note**

DLC1 was isolated from human HCC by PCR-based subtractive hybridization method in 1998 (Yuan et al., 1998). It was mapped to chromosome 8p21.3-22, a region suspected to harbor tumor suppressor genes and recurrently deleted in HCC and other solid tumors. DLC1 gene is widely expressed in normal human tissues, but it is frequently underexpressed in primary HCCs ranging from 20-68% and in half of the HCC cell lines examined (Ng et al., 2000; Wong et al., 2003; Ko et al., 2010). It has been reported that epigenetic silencing is responsible for DLC1 underexpression. Hypermethylation of DLC1 promoter has been detected in both HCC tissues and cell lines. Apart from promoter hypermethylation, homozygous deletion of DLC1 gene was detected. Frequent allelic loss of DLC1 locus was observed in primary HCCs and HCC cell lines (Ng et al., 2000; Wong et al., 2003). However, somatic mutation of DLC1 gene was not detected (Park et al., 2003). Introduction of DLC1 into HCC cell lines suppressed growth, migration, invasion and in vivo tumorigenicity (Ng et al., 2000; Zhou et al., 2004; Wong et al., 2005). DLC1 also induced apoptosis when ectopically expressed in HCC cell lines (Zhou et al., 2004). Expression of DLC1 in HCC cells negatively regulated Rho/ROCK/MLC2 pathway and induced disassembly of actin fibers and focal adhesions (Wong et al., 2008). In another study, DLC1 has been shown to downregulate expressions of osteopontin and matrix metalloproteinase-9 in HCC cells (Zhou et al., 2008).

### **Breast cancer**

#### **Note**

Reduced or absence of DLC1 mRNA level was detected in up to 76% of breast cancer tissues and 70% of breast cancer cell lines (Plaumann et al., 2003; Yuan et al., 2003b; Ullmannova et al., 2006; Seng et al., 2007). Genomic deletion was detected in 40% of primary breast tumors (Yuan et al., 2003b) and promoter hypermethylation was detected in breast cancer cell lines (Yuan et al., 2003a). Transfection of DLC1 into breast cancer cells led to significant inhibition of cell growth, reduction of colony formation and suppression of in vivo tumorigenicity (Yuan et al., 2003b). Combined knockdown of PTEN and DLC1 expressions enhanced breast cancer cell migration (Heering et al., 2009). In addition, restoration of DLC1 in metastatic breast cancer cells resulted in the reduced migration and invasion potentials in vitro and inhibited metastasis in vivo (Goodison et al., 2005).

### **Lung cancer**

#### **Note**

Using a cancer profiling array containing tumor and normal tissue samples derived from cancer patients, a study revealed that DLC1 mRNA level was downregulated in 90% of lung cancer tissues (Ullmannova et al., 2006). Yuan et al. also reported that DLC1 mRNA expression was decreased or absent in 95% of human primary non-small cell lung carcinoma (NSCLC) and 58% of NSCLC cell lines (Yuan et al., 2004). Silencing of DLC1 has been attributed to aberrant methylation of DLC1 promoter. When DLC1 was expressed in NSCLC cell line in which DLC1 was not expressed, cell proliferation, colony formation and in vivo tumorigenicity were greatly reduced. In addition, DLC1 has been shown to suppress anchorage independent growth and invasion of NSCLC cells (Healy et al., 2008).

### **Ovarian cancer**

#### **Note**

DLC1 mRNA level has been reported to be suppressed in 79% of ovarian cancer tissues (Ullmannova et al., 2006). DLC1 has also been reported as one of the genes to be upregulated by progesterone in ovarian cancer cell line (Syed et al., 2005). Introduction of DLC1 in ovarian cancer cells resulted in growth inhibition and enhancement of caspase-3 activity. In addition, DLC1 also abrogated soft agar colony formation and invasion of ovarian cancer cells.

### **Kidney cancer**

#### **Note**

DLC1 underexpression was detected in 75% of kidney tumor tissues (Ullmannova et al., 2006). In another study, it is reported that high levels of DLC1 mRNA and protein expression were observed in 90% of normal renal tissues. DLC1 expression level in primary tumors



with metastases was significantly lower than that in cases without metastases. DLC1 underexpression was significantly correlated with the advanced histological grade and stage (Zhang et al., 2009a). Overexpression of DLC1 in renal cell carcinoma cells resulted in dramatic growth inhibition and ability to form tumor in nude mice. The inhibitory activity was associated with the induction of apoptosis and cell cycle arrest (Zhang et al., 2009b). Conversely, suppression of DLC1 expression was associated with higher proliferative activity. Besides, reintroduction of DLC1 inhibited cell migration and induced dephosphorylation of focal adhesion kinase.

### **Colon cancer**

#### **Note**

Downregulation of DLC1 mRNA expression was detected in 43% of colon cancer tissues (Ullmannova et al., 2006) and 70% of colon cancer cell lines examined (Yuan et al., 2003a). Mutational analysis of genomic DNA from normal and colon cancer patients revealed that no mutation was found in normal samples while 4 mutations were detected in cancer samples (Liao et al., 2008). Reintroduction of DLC1 expression in HT29 cells significantly inhibited proliferation and migration potentials of cells. Flow cytometry revealed that DLC1 induced apoptosis and cell cycle arrest in cells (Wu et al., 2009). Using a complementary approach, silencing of DLC1 in LoVo colon cancer cells resulted in enhanced cell growth and migration (Jin et al., 2008).

### **Gastric cancer**

#### **Note**

Ullmannova et al. reported that DLC1 mRNA was downregulated in 41% of gastric cancer tissues (Ullmannova et al., 2006). In another study, Kim et al. reported that DLC1 mRNA expression was lost in 7 out of 9 human gastric cancer cell lines (Kim et al., 2003). In 5 of these DLC1 nonexpressing gastric cancer cell lines, DLC1 promoter was methylated. DLC1 mRNA expression could be restored by the addition of 5-aza-2'-deoxycytidine (5-Aza-dC). In addition, the study also revealed that 30% of primary gastric cancers showed methylation of DLC1 CpG island.

### **Prostate cancer**

#### **Note**

Underexpression or loss of DLC1 mRNA was detected in prostate carcinomas and cell lines and benign prostatic hyperplasias (Yuan et al., 2003a; Guan et al., 2006). Absence of DLC1 protein was also detected in prostate carcinomas and benign prostatic hyperplasias. Promoter methylation and genomic deletion were identified in prostate carcinomas. DLC1 methylation was significantly correlated with the age of prostate cancer patients and with prostate-specific antigen in benign prostatic hyperplasia patients. In 3 prostate cancer cell lines with low DLC1 expression, addition of cells with inhibitors of DNA methyltransferase or

histone deacetylase induced reexpression of DLC1 level. In addition, several missense and nonsense mutations within the central focal adhesion targeting region of DLC1 were detected in cDNAs of prostate cancer patients (Liao et al., 2008). Adenovirus-mediated expression of DLC1 in prostate cancer cells inhibited cell proliferation, anchorage-independent growth, invasion in vitro and tumorigenicity in nude mice. In addition, DLC1 also induced cell cycle arrest. Rho activation and actin stress fiber formation were also suppressed by DLC1 (Guan et al., 2008).

### **Nasopharyngeal carcinoma (NPC)**

#### **Note**

Silencing of DLC1 was detected in 91% of nasopharyngeal carcinoma cell lines examined (Seng et al., 2007). Although no genomic deletion of DLC1 was detected in NPC, hemizygous deletion was observed in some NPC cell lines. DLC1 promoter was frequently methylated in NPC cancer cell lines and 89% of primary tumors. In 2 NPC cell lines, 5-Aza-dC treatment caused reexpression of DLC1 level and decrease in methylated alleles of DLC1.

### **Esophageal carcinoma**

#### **Note**

DLC1 underexpression was detected in 40% of esophageal carcinoma cell lines examined (Seng et al., 2007). In the same study, analysis of DLC1 promoter region revealed that 51% of esophageal carcinomas were methylated and none of the normal esophageal tissues displayed methylation. Ectopic expression of DLC1 in esophageal carcinoma cells showed significant inhibition in colony formation.

### **Cervical cancer**

#### **Note**

About 63% of cervical cancer cell lines examined showed underexpression of DLC1 (Seng et al., 2007). DLC1 promoter was methylated in 87% of primary cervical carcinomas.

## **References**

- Yuan BZ, Miller MJ, Keck CL, Zimonjic DB, Thorgeirsson SS, Popescu NC. Cloning, characterization, and chromosomal localization of a gene frequently deleted in human liver cancer (DLC-1) homologous to rat RhoGAP. *Cancer Res.* 1998 May 15;58(10):2196-9
- Ng IO, Liang ZD, Cao L, Lee TK. DLC-1 is deleted in primary hepatocellular carcinoma and exerts inhibitory effects on the proliferation of hepatoma cell lines with deleted DLC-1. *Cancer Res.* 2000 Dec 1;60(23):6581-4
- Wilson PJ, McGlinn E, Marsh A, Evans T, Arnold J, Wright K, Biden K, Young J, Wainwright B, Wicking C, Chenevix-Trench G. Sequence variants of DLC1 in colorectal and ovarian tumours. *Hum Mutat.* 2000;15(2):156-65
- Kim TY, Jong HS, Song SH, Dimtchev A, Jeong SJ, Lee JW, Kim TY, Kim NK, Jung M, Bang YJ. Transcriptional silencing of the DLC-1 tumor suppressor gene by epigenetic mechanism in gastric cancer cells. *Oncogene.* 2003 Jun 19;22(25):3943-51

- Park SW, Durkin ME, Thorgeirsson SS, Popescu NC. DNA variants of DLC-1, a candidate tumor suppressor gene in human hepatocellular carcinoma. *Int J Oncol.* 2003 Jul;23(1):133-7
- Plaumann M, Seitz S, Frege R, Estevez-Schwarz L, Scherneck S. Analysis of DLC-1 expression in human breast cancer. *J Cancer Res Clin Oncol.* 2003 Jun;129(6):349-54
- Wong CM, Lee JM, Ching YP, Jin DY, Ng IO. Genetic and epigenetic alterations of DLC-1 gene in hepatocellular carcinoma. *Cancer Res.* 2003 Nov 15;63(22):7646-51
- Yuan BZ, Durkin ME, Popescu NC. Promoter hypermethylation of DLC-1, a candidate tumor suppressor gene, in several common human cancers. *Cancer Genet Cytogenet.* 2003 Jan 15;140(2):113-7
- Yuan BZ, Zhou X, Durkin ME, Zimonjic DB, Gumundsdottir K, Eyfjord JE, Thorgeirsson SS, Popescu NC. DLC-1 gene inhibits human breast cancer cell growth and in vivo tumorigenicity. *Oncogene.* 2003 Jan 23;22(3):445-50
- Yuan BZ, Jefferson AM, Baldwin KT, Thorgeirsson SS, Popescu NC, Reynolds SH. DLC-1 operates as a tumor suppressor gene in human non-small cell lung carcinomas. *Oncogene.* 2004 Feb 19;23(7):1405-11
- Zhou X, Thorgeirsson SS, Popescu NC. Restoration of DLC-1 gene expression induces apoptosis and inhibits both cell growth and tumorigenicity in human hepatocellular carcinoma cells. *Oncogene.* 2004 Feb 12;23(6):1308-13
- Durkin ME, Avner MR, Huh CG, Yuan BZ, Thorgeirsson SS, Popescu NC. DLC-1, a Rho GTPase-activating protein with tumor suppressor function, is essential for embryonic development. *FEBS Lett.* 2005 Feb 14;579(5):1191-6
- Goodison S, Yuan J, Sloan D, Kim R, Li C, Popescu NC, Urquidí V. The RhoGAP protein DLC-1 functions as a metastasis suppressor in breast cancer cells. *Cancer Res.* 2005 Jul 15;65(14):6042-53
- Wong CM, Yam JW, Ching YP, Yau TO, Leung TH, Jin DY, Ng IO. Rho GTPase-activating protein deleted in liver cancer suppresses cell proliferation and invasion in hepatocellular carcinoma. *Cancer Res.* 2005 Oct 1;65(19):8861-8
- Guan M, Zhou X, Soultz N, Spandidos DA, Popescu NC. Aberrant methylation and deacetylation of deleted in liver cancer-1 gene in prostate cancer: potential clinical applications. *Clin Cancer Res.* 2006 Mar 1;12(5):1412-9
- Hers I, Wherlock M, Homma Y, Yagisawa H, Tavaré JM. Identification of p122RhoGAP (deleted in liver cancer-1) Serine 322 as a substrate for protein kinase B and ribosomal S6 kinase in insulin-stimulated cells. *J Biol Chem.* 2006 Feb 24;281(8):4762-70
- Ullmannova V, Popescu NC. Expression profile of the tumor suppressor genes DLC-1 and DLC-2 in solid tumors. *Int J Oncol.* 2006 Nov;29(5):1127-32
- Yam JW, Ko FC, Chan CY, Jin DY, Ng IO. Interaction of deleted in liver cancer 1 with tensin2 in caveolae and implications in tumor suppression. *Cancer Res.* 2006 Sep 1;66(17):8367-72
- Durkin ME, Ullmannova V, Guan M, Popescu NC. Deleted in liver cancer 3 (DLC-3), a novel Rho GTPase-activating protein, is downregulated in cancer and inhibits tumor cell growth. *Oncogene.* 2007 Jul 5;26(31):4580-9
- Durkin ME, Yuan BZ, Zhou X, Zimonjic DB, Lowy DR, Thorgeirsson SS, Popescu NC. DLC-1: a Rho GTPase-activating protein and tumour suppressor. *J Cell Mol Med.* 2007 Sep-Oct;11(5):1185-207
- Liao YC, Si L, deVere White RW, Lo SH. The phosphotyrosine-independent interaction of DLC-1 and the SH2 domain of cten regulates focal adhesion localization and growth suppression activity of DLC-1. *J Cell Biol.* 2007 Jan 1;176(1):43-9
- Qian X, Li G, Asmussen HK, Asnagli L, Vass WC, Braverman R, Yamada KM, Popescu NC, Papageorge AG, Lowy DR. Oncogenic inhibition by a deleted in liver cancer gene requires cooperation between tensin binding and Rho-specific GTPase-activating protein activities. *Proc Natl Acad Sci U S A.* 2007 May 22;104(21):9012-7
- Seng TJ, Low JS, Li H, Cui Y, Goh HK, Wong ML, Srivastava G, Sidransky D, Califano J, Steenbergen RD, Rha SY, Tan J, Hsieh WS, Ambinder RF, Lin X, Chan AT, Tao Q. The major 8p22 tumor suppressor DLC1 is frequently silenced by methylation in both endemic and sporadic nasopharyngeal, esophageal, and cervical carcinomas, and inhibits tumor cell colony formation. *Oncogene.* 2007 Feb 8;26(6):934-44
- Yuan BZ, Jefferson AM, Millecchia L, Popescu NC, Reynolds SH. Morphological changes and nuclear translocation of DLC1 tumor suppressor protein precede apoptosis in human non-small cell lung carcinoma cells. *Exp Cell Res.* 2007 Nov 1;313(18):3868-80
- Guan M, Tripathi V, Zhou X, Popescu NC. Adenovirus-mediated restoration of expression of the tumor suppressor gene DLC1 inhibits the proliferation and tumorigenicity of aggressive, androgen-independent human prostate cancer cell lines: prospects for gene therapy. *Cancer Gene Ther.* 2008 Jun;15(6):371-81
- Healy KD, Hodgson L, Kim TY, Shutes A, Maddileti S, Juliano RL, Hahn KM, Harden TK, Bang YJ, Der CJ. DLC-1 suppresses non-small cell lung cancer growth and invasion by RhoGAP-dependent and independent mechanisms. *Mol Carcinog.* 2008 May;47(5):326-37
- Jin Y, Tian X, Shang Y, Huang P. Inhibition of DLC-1 gene expression by RNA interference in the colon cancer LoVo cell line. *Oncol Rep.* 2008 Mar;19(3):669-74
- Liao YC, Lo SH. Deleted in liver cancer-1 (DLC-1): a tumor suppressor not just for liver. *Int J Biochem Cell Biol.* 2008;40(5):843-7
- Liao YC, Shih YP, Lo SH. Mutations in the focal adhesion targeting region of deleted in liver cancer-1 attenuate their expression and function. *Cancer Res.* 2008 Oct 1;68(19):7718-22
- Wong CC, Wong CM, Ko FC, Chan LK, Ching YP, Yam JW, Ng IO. Deleted in liver cancer 1 (DLC1) negatively regulates Rho/ROCK/MLC pathway in hepatocellular carcinoma. *PLoS One.* 2008 Jul 23;3(7):e2779
- Xue W, Krasnitz A, Lucito R, Sordella R, Vanaelst L, Cordon-Cardo C, Singer S, Kuehnel F, Wigler M, Powers S, Zender L, Lowe SW. DLC1 is a chromosome 8p tumor suppressor whose loss promotes hepatocellular carcinoma. *Genes Dev.* 2008 Jun 1;22(11):1439-44
- Zhou X, Zimonjic DB, Park SW, Yang XY, Durkin ME, Popescu NC. DLC1 suppresses distant dissemination of human hepatocellular carcinoma cells in nude mice through reduction of RhoA GTPase activity, actin cytoskeletal disruption and down-regulation of genes involved in metastasis. *Int J Oncol.* 2008 Jun;32(6):1285-91
- Chan LK, Ko FC, Ng IO, Yam JW. Deleted in liver cancer 1 (DLC1) utilizes a novel binding site for Tensin2 PTB domain interaction and is required for tumor-suppressive function. *PLoS One.* 2009;4(5):e5572

Heering J, Erlmann P, Olayioye MA. Simultaneous loss of the DLC1 and PTEN tumor suppressors enhances breast cancer cell migration. *Exp Cell Res*. 2009 Sep 10;315(15):2505-14

Scholz RP, Regner J, Theil A, Erlmann P, Holeiter G, Jähne R, Schmid S, Hausser A, Olayioye MA. DLC1 interacts with 14-3-3 proteins to inhibit RhoGAP activity and block nucleocytoplasmic shuttling. *J Cell Sci*. 2009 Jan 1;122(Pt 1):92-102

Wu PP, Jin YL, Shang YF, Jin Z, Wu P, Huang PL. Restoration of DLC1 gene inhibits proliferation and migration of human colon cancer HT29 cells. *Ann Clin Lab Sci*. 2009 Summer;39(3):263-9

Yang XY, Guan M, Vigil D, Der CJ, Lowy DR, Popescu NC. p120Ras-GAP binds the DLC1 Rho-GAP tumor suppressor protein and inhibits its RhoA GTPase and growth-suppressing activities. *Oncogene*. 2009 Mar 19;28(11):1401-9

Zhang T, Zheng J, Jiang N, Wang G, Shi Q, Liu C, Lu Y. Overexpression of DLC-1 induces cell apoptosis and proliferation inhibition in the renal cell carcinoma. *Cancer Lett*. 2009 Sep 28;283(1):59-67

Zhang T, Zheng J, Liu C, Lu Y. Expression of DLC-1 in clear cell renal cell carcinoma: prognostic significance for progression and metastasis. *Urol Int*. 2009;82(4):380-7

Ko FC, Yeung YS, Wong CM, Chan LK, Poon RT, Ng IO, Yam JW. Deleted in liver cancer 1 isoforms are distinctly expressed in human tissues, functionally different and under differential transcriptional regulation in hepatocellular carcinoma. *Liver Int*. 2010 Jan;30(1):139-48

---

*This article should be referenced as such:*

Ko FCF, Ng IOL, Yam JWP. DLC1 (deleted in liver cancer 1). *Atlas Genet Cytogenet Oncol Haematol*. 2011; 15(2):141-147.

---