Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Review

DLG1 (discs, large homolog 1 (Drosophila))

Paola Massimi, Lawrence Banks

International Centre for Genetic Engeneering and Biotechnology (ICGEB), Trieste, Italy (PM, LB)

Published in Atlas Database: May 2009

Online updated version: http://AtlasGeneticsOncology.org/Genes/DLG1ID40333ch3q29.html
DOI: 10.4267/2042/44730

Identity

Other names: DKFZp761P0818; DKFZp781B0426; DLGH1; SAP-97; SAP97; dJ1061C18.1.1; Hdlg

HGNC (Hugo): DLG1

Location: 3q29

DNA/RNA

Description

The DLG1 gene consists of 250,017 bases on the 3q29 locus of chromosome 3 (Azim et al., 1995).

Transcription

The DLG1 gene encodes a 960 amino-acid protein of 100355 Da with several distinct domains. A 1310-bp fragment of the 5' flanking region of the DLG1 gene, corresponding to nucleotide (nt) - 1217/+ 93 contains the promoter sequence plus the consensus-binding sites for the Snail family of transcription factors that repress the expression of some epithelial markers and are up-regulated in a variety of tumours. Snail transcription factors repress the transcriptional activity of the DLG1 promoter (Cavatorta et al., 2008). The carboxyl-terminal 179 aa show strong homology (35.5%) to yeast guanylate kinase (GUK) an enzyme that transfers a phosphate group from ATP to GMP, converting it to GDP, although DLG1 has no enzymatic activity.

DLG1 contains also a 59 aa SH3 (Src homolgy 3) domain, which mainly mediates binding to other proteins. The N terminal half of the molecule contains three copies of the 80-90 aa motif called DHR/GLGF/PDZ (PSD-95, Dlg, ZO-1), which mediate the binding of the protein to the plasma membrane and confers binding to proteins that possess a class I PDZ binding motif (Morais Cabral et al., 1996).

There are two major transcripts of DLG1 gene. One is Discs large homolog 1 isoform 1, which contains an additional exon (99 nucleotides) in the 5' part of the Dlg homology repeats (DHR) domain and lacks an exon in the 3' coding region, resulting in a shorter protein (isoform 1), compared to isoform 2. The second is Discs large homolog 1 isoform 2, which represents the longer transcript and encodes the longer isoform. This second transcript is alternatively spliced with an insertion of 34 nucleo-tides in the region between the SH3 and GUK (isoform 2). Another alternative splice has an inser-tion of 100 nucleotides and the resulting transcript is called Discs large homolog 1 isoform 3.

In conclusion, the protein is regulated by a several different alternative splicing events (Mori et al., 1998) resulting in a number of different combination of spliced variants (which give raise to at least 7 isoforms such as I1I2, I1I3, etc.) (see table), some of which are transcribed in a tissue-specific manner (Lue et al., 1996; McLaughlin et al., 2002).

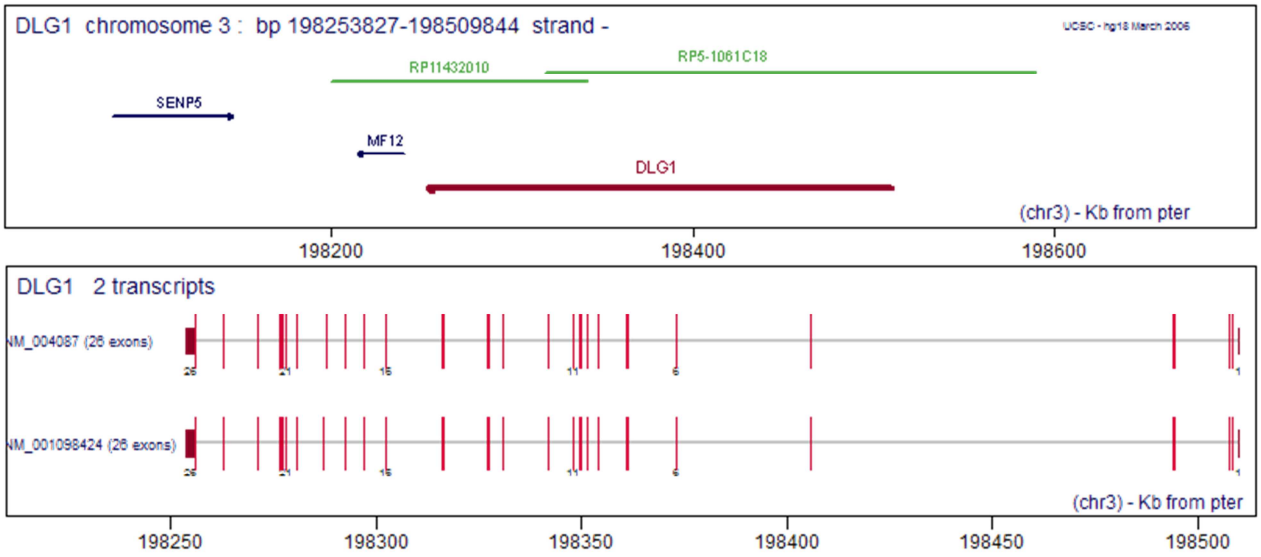
Pseudogene

None.

Protein

Description

The 'discs large' protein, Dlg1, is part of a family of proteins termed MAGUKs (membrane-associated guanylate kinase homologs). MAGUKs are loca-lized at the membrane-cytoskeleton interface, usually at cell-cell junctions, where they appear to have both structural and signaling roles. DLG1 probably exists as an homotetramer.



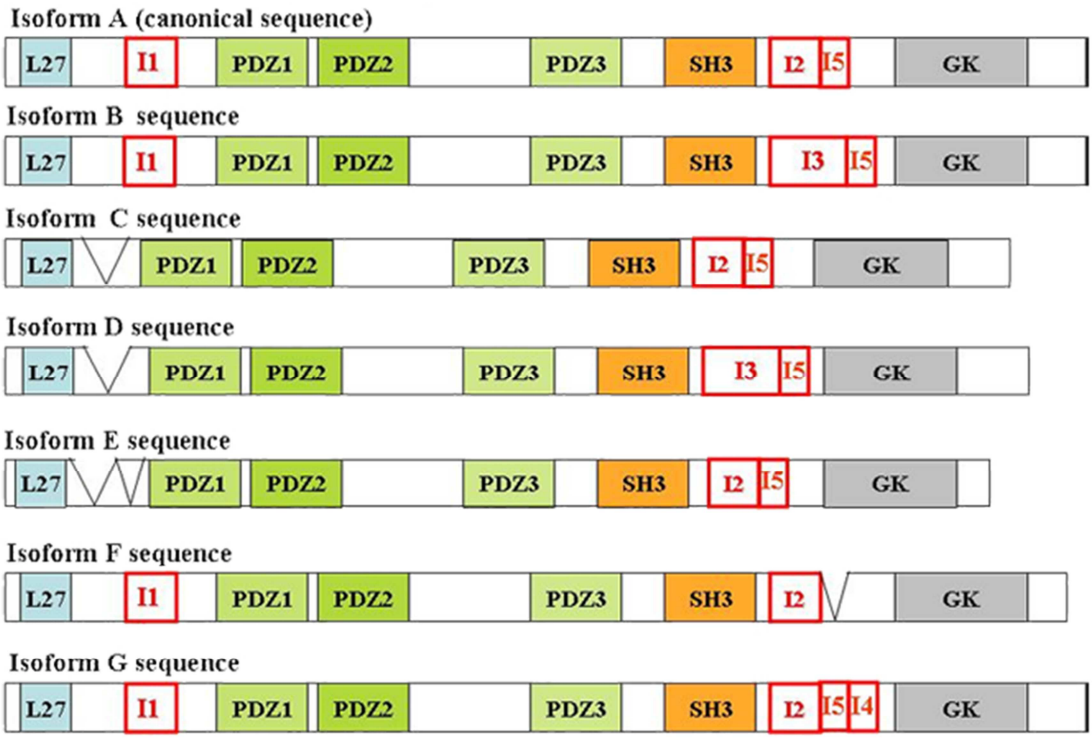


Diagram of DLG1 gene organization and of the two major encoded transcript variants.

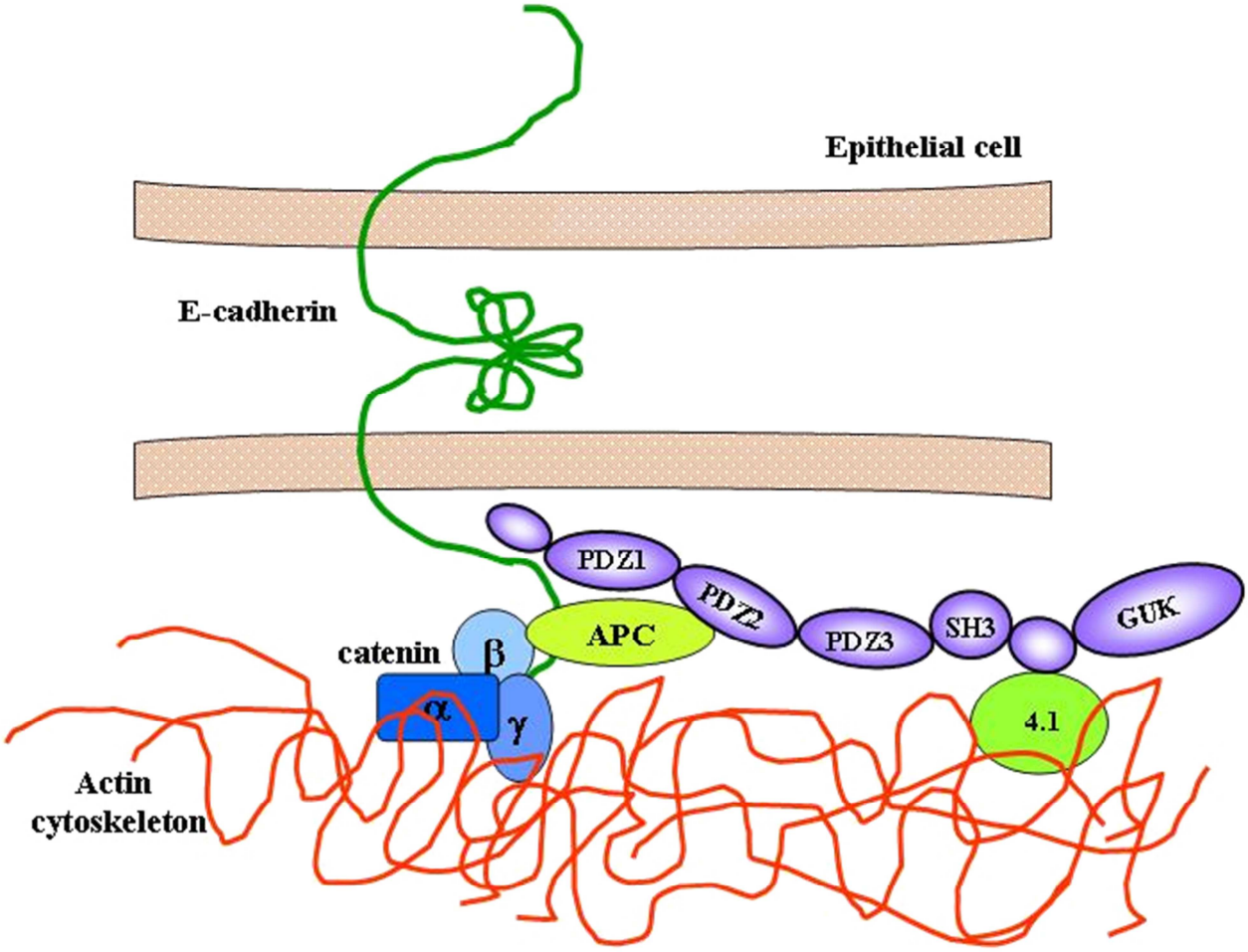


Diagram of the DLG1 protein with its characteristic domains and the main protein-protein interactions at the cell-cell junctions.

Ultrastructural analysis of hDlg by low angle rotary shadow electron microscopy revealed that the full-length hDlg protein as well as its amino-terminal domain exhibits a highly flexible irregular shape. Further evaluation of the self-association state of hDlg using sedimentation equilibrium centrifugation, matrix-assisted laser desorption/ionization mass spectrometry and chemical cross-linking techniques confirmed that the oligomerization site of hDlg is contained within its amino-terminal domain. This is mediated by a unique L27 domain which regulates multimerization of hDlg into dimeric and tetrameric species in solution, and sedimentation velocity experiments demonstrated that the oligomerization domain exists as an elongated tetramer in solution (Marfatia et al., 2000). Thus, the L27 domain regulate DLG1 self-association. The N-terminal alternatively spliced region is capable of binding several SH3 domains and also moderates the level of protein oligomerization.

Specific binding partners are known for each domain of DLG1, and different modes of intramolecular interactions have been proposed that particularly involve the SH3 and GUK domains and the so-called HOOK region located between these two domains.

DLG1 binds to the membrane cytoskeletal 4.1 protein through its C-terminal region (Hanada et al., 2003), via a motif encoded by the alternatively spliced exon located between the SH3 and the C-terminal guanylate kinase-like domains (Isoform I3). The PDZ1-2 modules and the I3 domain associate with the 30-kD NH2-terminal domain of protein 4.1 that is conserved in ezrin/radixin/moesin (ERM) proteins module (Lue et al., 1996; Bonilha and Rodriguez-Boulan, 2001). Indeed SAP97 also interacts with ezrin, an actin-binding protein crucial for morphogenesis of apical microvilli and basolateral infoldings in retinal pigment epithelial (RPE) cells.

Through the PDZ2 domain the protein also interacts with the carboxyl-terminal S/TXV motif of the APC (Adenomatous polyposis coli) tumour suppressor protein and plays an important role in transducing the APC cell cycle blocking signal (Makino et al., 1997; Ishidate et al., 2000; Mimori-Kiyosue et al., 2007). In addition, APC appears to mediate the interaction between DLG1, beta-catenin and the actin cytoskeleton. Beta-catenin is complexed with gamma-catenin and alpha-catenin, through which DLG1 binds to E-cadherin (Reuver et al., 1998). Moreover, the Src

homology domain 2 of the p85/PI3K and hDlg are associated with E-cadherin in a common macromolecular complex in differentiating intestinal cells, and in this way hDlg may be a determinant in E-cadherin-mediated adhesion and signaling in mammalian epithelial cells (Laprise et al., 2004).

DLG1 was demonstrated also to bind with voltage-

gated or Kv K(+) channels through its PDZ domains (Hanada et al., 1997; Tiffany et al., 2000; Eldstrom et al., 2003). The complex formation involves the association of Cav-3 with a segment of SAP97 localized between its PDZ2 and PDZ3 domains. This scaffolding complex can recruit Kv1.5 to form a tripartite complex in which each of the three components interacts with the other two. These interactions between Kv1.5, Cav3 and SAP97 may constitute the nucleation site for the assembly of macromolecular containing potassium channels and thereby regulates cellular potential currents (Folco et al., 2004).

Hanada showed by immunoblot analysis that immunoprecipitates of DLG1 in T lymphocytes contain the Src family tyrosine kinase p56 (lck). Binding analysis demonstrated that LCK interacts with the proline-rich N-terminal domain of DLG1, suggesting that DLG1 may function as a coupler of tyrosine kinase and a voltage-gated potassium channel in T lymphocytes.

The HOOK region of DLG1 is also a specific site for calmodulin binding and interaction of SAP97 to immobilized calmodulin is strictly calcium-depen-dent (Paarmann et al., 2002). The calmodulin seems to regulate the intramolecular interaction between the SH3, HOOK, and GK domains of the protein.

DLG1 also forms multiprotein complexes with CASK, LIN7A, LIN7B, LIN7C, APBA1, and KCNJ12 (Nix et al., 2000; Lee et al., 2002; Leonoudakis et al., 2004) and exists as a tripartite complex composed of DLG1, MPP7 and LIN7 (LIN7A or LIN7C) (Bohl et al., 2007; Stucke et al., 2007). MPP7 dimerized with the LIN7 proteins through its L27C domain. The LIN7/MPP7 dimer then linked to DLG1 though the L27N domain of MPP7. This complex localizes to epithelial adherens junctions in transfected Madin-Darby Canine Kidney cells (MDCK). MPP7 constructs lacking either the PDZ or SH3 domain redistributed MPP7, DLG1, and LIN7 into the soluble cytoplasmic fraction. MPP7 and DLG1 colocalized at the lateral surface of epithelial cells, and they overlapped with markers of adherens junctions and tight junctions. Loss of either DLG1 or MPP7 from epithelial cells resulted in a significant defect in assembly and maintenance of functional tight junctions. The formation of the DLG1-MPP7 complex promotes also epithelial cell polarity.

SAP97 binds two other mLIN-7 binding MAGUK proteins. One of these MAGUK proteins, DLG3, coimmunoprecipitates with SAP97 in lysates from rat brain and transfected MDCK cells. This interaction requires the MRE (MAGUK recruitment) domain of SAP97 and surprisingly, both the L27N and L27 carboxyl-terminal (L27C) domains of DLG3. SAP97 can interact with the MAGUK protein, DLG2, but not the highly related protein, PALS2. The ability of SAP97 to interact with multiple MAGUK proteins is likely to be important for the targeting of specific protein complexes in polarized cells (Karnak et al., 2002).

The kinesin-3 motor protein, GAKIN, is regulated by the direct binding of its protein cargo hDlg. Direct binding of the SH3-I3-GUK module of hDlg to the MAGUK Binding Stalk domain of GAKIN activates the microtubule-stimulated ATPase activity of GAKIN (Hanada et al., 2000; Yamada et al., 2007; Unno et al., 2008).

Using the yeast two-hybrid screening a novel protein from a human cDNA library was isolated as a binding partner of DLG1. This protein is a component of TJs rather than AJs (where DLG1 is normally found), even if it is incorporated into TJs after TJ strands are formed, and therefore it is named Pilt (protein incorporated later into TJs) (Kawabe et al., 2001).

DLG1 is known to interact also with several human virus oncoproteins : HPV E6 (Lee et al., 1997; Kiyono et al.,1997, Gardiol et al., 1999) through its C-terminus and DLG1 PDZ2 domain and as result is subjected to proteasome mediated degradation; HTLV-1 TAX (Suzuki et al., 1999), via the C-terminus of Tax and the PDZ domain of hDLG. Tax prevents the binding of hDLG to APC tumor suppressor gene product, suggesting the mechanism for inhibition of hDLG function; Adenovirus type 9 E4-ORF1 specifically requires endogenous DLG1 to provoke oncogenic activation of phosphatidyl-inositol 3-kinase (PI3K) in cells. E4-ORF1 binding to Dlg1 on ts PDZ domain triggers the resulting complex to translocate to the plasma membrane and, at this site, to promote Ras-mediated PI3K activation, suggesting a surprising oncogenic function for DLG1 in virus-mediated cellular transformation (Frese et al., 2006; Chung et al., 2007).

hDlg also binds the tumor endothelial marker 5 (TEM5), a seven-pass transmembrane protein that is homologous to the B family of G-protein-coupled receptors (GPCRs). The PDZ domains of hDlg bound the C-terminal PDZ-binding motif of TEM5. DLG1 is furthermore able to interact with a novel seven-pass transmembrane protein, which was homologous to TEM5, and was named here a TEM5-like protein (TEM5-like) (Yamamoto et al., 2004).

SAP97/hDlg as a scaffold protein is also targeted to the cytoskeleton by its association with the protein guanylate kinase-associated protein (GKAP), which is part of the postsynaptic scaffold in neuronal cells (Sabio et al., 2005). Moreover, hDlg is believed to

associate with AMPA receptors (AMPARs) containing the GluR1 subunit, but the functional significance of these interactions is partially unclear, even if this interaction seems to be occur early in the secretory pathway, while the receptors are in the endoplasmic reticulum or cis-Golgi (Sans et al., 2001). In light membrane fractions prepared from rat brain, myosin VI and SAP97 form a trimeric complex with the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subunit, GluR1. It is possible that SAP97 may serve as a molecular link between GluR1 and the actin-dependent motor protein myosin VI during the dynamic translocation of AMPA receptors to and from the postsynaptic plasma membrane (Wu et al., 2002).

DLG1 is also able to translocate to the immune synapse and lipid rafts in response to T cell receptor (TCR)/CD28 engagement and LckSH3-mediated interactions with DLG1 control its membrane targeting. TCR/CD28 engagement induces the formation of endogenous Lck-DLG1-Zap70-Wiskott-Aldrich syndrome protein (WASp) complexes in which DLG1 acts to facilitate interactions of Lck with Zap70 and WASp (Round et al., 2005).

Delta 1 acts as a membrane-bound ligand that interacts with the Notch receptor and plays a critical role in cell fate specification. DLG1 binds the Delta 1 C-terminal region, in a PDZ dependent manner. Delta 4 also interacts with DLG1, whereas Jagged1, another Notch ligand, does not (Six et al., 2004).

MARCH 2, which is part of the MARCH family ubiquitin ligases and is implicated in the endosomal trafficking interacts with full-length DLG1 in a PDZ domain dependent manner. Furthermore, MARCH2 co-localized with DLG1 at sites of cell-cell contact (Cao et al., 2008).

SAP97 is a binding partner of the cytoplasmic domain of TACE, which is the Tumour necrosis factor alpha converting enzyme and is the metalloprotease-disintegrin responsible for the ectodomain shedding of several proteins, including tumour necrosis factor alpha. The interaction involved the PDZ3 domain of SAP97 and the extreme C-terminal amino-acid sequence of TACE (Peiretti et al., 2003).

DLG1 is able to interact also with Net 1 which is a nuclear RhoA-specific guanine nucleotide exchange factor. The binding is through the PDZ-binding motif. The ability of oncogenic Net1 to transform cells may be in part related to its ability to sequester tumour suppressor proteins like DLG1 in the cytosol, thereby interfering with their normal cellular function (Garcia-Mata et al., 2007).

DLG1 interacts with the tSNARE syntaxin 4 which is involved in vesicle transport, and this binding may contribute to the correct colocaliation of the other proteins of the Scrib complex: hScribble and Hugl-1 (Massimi et al., 2008).

Expression

DLG1 is widely expressed, with different isoforms displaying different expression profiles (McLaughlin et al., 2002). DLG1 is expressed mainly in epithelial cells and in the nervous system, but is also fond in thymus, bone marrow, T cells, spleen, brain, spinal cord, heart, kidney, lung, liver,

pancreas, prostate (at the protein level).

Localisation

DLG1 is localised at the plasma membrane (Hanada et al., 2000), cell-cell junctions (Lue et al., 1994), at the basolateral plasma membrane (Lue et al., 1996; Mimori et al., 2007). It is also found at the immunological synapse, endoplasmic reticulum, endoplasmic reticulum membrane, postsynaptic density, lateral plasma membrane, neuromuscular junction membrane, raft synapse and the post-synaptic membrane. There is equal expression of the two spliced variants in most human tissues; however, in skeletal muscle the transcript with the 99-bp insertion is predominant, whilst in the brain, the isoform lacking the 99-bp insertion is predominant. In brain there are six different, alternatively spliced transcripts, two of which included a novel, 36-bp, brain-specific exon encoding a peptide bearing significant homology to a portion of rat synapse-associated proteins, SAP97 and PSD95.

Again, the different isoforms of the protein seem to have diverse localisation in the cell. I2 and I3 variants have distinct distributions in epidermal and cervical epithelia. In skin and cervix, I3 variants are found in the cytoplasm. Cytoplasmic localization of I3 variants decreases as cervical keratinocytes differentiate, concomitant with relocalization to the cell periphery. I2 variants are found at the cell periphery of differentiated epidermal and cervical keratinocytes. Nuclear localization of I2 variants is evident in both tissues, with a concentration of nuclear I2 variants in basal and parabasal cervical keratinocytes (Roberts et al., 2007), underlining that different hDlg isoforms play distinct roles at various stages of epithelial differentiation. More-over, upon transient transfection into subconfluent (MDCK) epithelial cells, hDlg-I3 accumulated predominantly at the plasma membrane of cell-cell contact sites, whereas hDlg-I2 distributed in the cytoplasm. The hDlg-I3 but not the hDlg-I2 isoform binds to the FERM (Four.1-Ezrin-Radixin-Moesin) domain of protein 4.1, playing a critical role in recruiting DLG1 to the lateral membrane in epithelial cells (Bonhila et al., 2001; Hanada et al., 2003; Massimi et al., 2003; Wu et al., 2002).

Several different domains of DLG1 contribute to its localisation. Mutation of the SH3 or GUK domain, but not the PDZ domain, results in a re-localization of hDLG to the nucleus and, moreover, DLG1 possess a potential nuclear localization signal in the HOOK domain (Kohu et al., 2002).

It has been reported that the localisation of DLG1 is also dependent on the post-translational modifica-tion of the protein, by phosphorylation occurring post-osmotic shock (Massimi et al., 2006) and also during the cell cycle following CDK phosphoryla-tion (Narayan et al., 2009). Moreover, DLG1 localises dependently from the other proteins involved in the complex at the adherens junctions:

hScribble and Hugl-1 (Massimi et al., 2008).

In addition, CaMKII (calcium/calmodulin-depen-dent protein kinase II) activation led to increased targeting of SAP97 into dendritic spines, whereas CaMKII

inhibition was responsible for SAP97 colocalization in the cell soma with the endoplasm-mic reticulum protein disulfide-isomerase (Mauceri et al., 2004).

Regarding the localisation of the different isoforms, the two main cardiac SAP97 isoforms contains both I3 and I1B inserts and differs by the I1A insert. Both isoforms co-precipitate with hKv1.5 channels, and have different effects on the hKv1.5 current, depending on their capacity to form clusters (Godreau et al., 2003).

In the case of endothelial cells of embryonic liver the expression of TEM5 colocalises with DLG1. This suggest that hDlg localizes at the plasma membrane through TEM5 and TEM5-like proteins and furthermore scaffolds these GPCRs in endothelial cells during tumour angiogenesis and neoangiogenesis (Yamamoto et al., 2004).

Function

DLG1 is an essential multidomain scaffolding protein required for normal development.

It is able to recruits channels (Hanada et al., 1997; Tiffany et al., 2000; Abi-Char et al., 2008), receptors and signaling molecules (Sans et al., 2001; Wuh et al., 2002; Six et al., 2004) to discrete plasma membrane domains in polarized cells. Its main role is played in adherens junctions assembly (Laprise et al., 2004; Bohl et al., 2007; Stucke et al., 2007; Massimi et al., 2008). However DLG1 with the establishment of a multiprotein complexes at cell-cell contacts is also involved in signal transduction (Massimi et al., 2006), cell prolifera-tion (Suzuki et al., 1999; Ishidate et al., 2000; Massimi et al., 2003; Thomas et al., 2005; Frese et al., 2006; Garcia-Mata et al., 2007; Unno et al., 2008), synaptogenesis (Mori et al., 1998; Sans et al., 2001; Mauceri et al., 2004), lymphocyte activation (Hanada et al., 1997; Hanada et al., 2000; Round et al., 2005), cell differentiation (Laprise et al., 2004; Roberts et al., 2007), cell migration (Six et al., 2004) and cellular apical-basal polarity control (Bonilha et al., 2001).

Homology

The four best-characterised mammalian Dlg family members are Dlg1 (hDlg/SAP97), Dlg2 (PSD-93/Chapsyn-110), Dlg3 (NE-Dlg/SAP102) and Dlg4 (PSD-95/SAP90) (Lue et al., 1994; Makno et al., 1997; Brenman et al., 1996; Cho et al., 1992; Humbert et al., 2003). Mammalian Dlg family members display the characteristic MAGUK structural domains found in Drosophila Dlg including the three PDZ domains, a Src homology domain-3 (SH3) and a guanylate kinase-like (GUK) domain. Although most mammalian Dlg homologues were first identified in neuronal tissues, all of these proteins are expressed in a variety of non-neuronal tissues including epithelial and lymphoid cells. Strikingly, localisation studies in all of these tissues are suggestive of a role for mammalian Dlg homologues in polarisation.

Mutations

Note

See paragraphs below.

Germinal

None.

Somatic

There is one report in breast cancer (Fuja et al., 2004).

Implicated in

Epithelial-derived cancers

Note

The mis-localisation of DLG1 is linked to the development of epithelial-derived cancers (Gardiol et al., 2006). In uterine cervical squamous epithelia, prominent localization of hDlg at sites of inter-cellular contact occurs in cells that have left the proliferating basal cell layers and begun maturation. The presence of hDlg at sites of cell-cell contact diminishes, whilst intracellular cytoplasmic levels increase significantly in high-grade, but not low-grade, cervical neoplasias. In invasive squamous cell carcinomas, total cellular hDlg levels are greatly reduced (Watson et al., 2002).

Mammary ductal carcinoma

Note

In humans there is only one report of mutations occuring in Dlg in cancer. In this study somatic mutations were found in three genes (CSNK1 epsilon, encoding the Ser/Thr kinase casein kinase I epsilon, DLG1, and EDD/hHYD, encoding a pro-gestin induced putative ubiquitin-protein ligase) in mammary ductal carcinoma. For CSNK1 epsilon and DLG1, most of the mutations affected highly conserved residues, some were found repetitively in different patients, and no synonymous mutations were found, indicating that the observed mutations were selected in tumours and may be functionally significant (Fuja et al., 2004).

3q29 microdeletion syndrome

Note

Moreover, another report (Willatt et al., 2005) pointed out that the DLG1 and PAK2 genes are deleted in the

3q29 microdeletion syndrome and raised the possibility that loss of one of these genes may contribute to the phenotype since PAK2 and DLG1 are autosomal homologs of 2 X-linked mental retardation genes, PAK3 and DLG3.

Schizophrenia

Note

In addition, DLG1 gene may be a susceptibility factor in male schizophrenics and the modification of the glutamate receptor signalling pathway could be involved in the disease pathophysiology. DLG1 protein levels were decreased to less than half that of the control levels specifically in the prefrontal cortex of schizophrenic patients. In parallel, its binding partner, GluR1, similarly decreased in the same brain region (Toyooka et al., 2002; Sato et al., 2008).

Various cancer

Note

Generally, loss of expression (through diverse mechanisms) is a common feature in many late stages of cancers.

References

Cho KO, Hunt CA, Kennedy MB. The rat brain postsynaptic density fraction contains a homolog of the Drosophila discs-large tumor suppressor protein. Neuron. 1992 Nov;9(5):929-42

Lue RA, Marfatia SM, Branton D, Chishti AH. Cloning and characterization of hdlg: the human homologue of the Drosophila discs large tumor suppressor binds to protein 4.1. Proc Natl Acad Sci U S A. 1994 Oct 11;91(21):9818-22

Azim AC, Knoll JH, Marfatia SM, Peel DJ, Bryant PJ, Chishti AH. DLG1: chromosome location of the closest human homologue of the Drosophila discs large tumor suppressor gene. Genomics. 1995 Dec 10;30(3):613-6

Brenman JE, Christopherson KS, Craven SE, McGee AW, Bredt DS. Cloning and characterization of postsynaptic density 93, a nitric oxide synthase interacting protein. J Neurosci. 1996 Dec 1;16(23):7407-15

Lue RA, Brandin E, Chan EP, Branton D. Two independent domains of hDlg are sufficient for subcellular targeting: the PDZ1-2 conformational unit and an alternatively spliced domain. J Cell Biol. 1996 Nov;135(4):1125-37

Morais Cabral JH, Petosa C, Sutcliffe MJ, Raza S, Byron O, Poy F, Marfatia SM, Chishti AH, Liddington RC. Crystal structure of a PDZ domain. Nature. 1996 Aug 15;382(6592):649-52

Alexander C, Stathakis DG, Lin L, Rahman S, Bryant PJ, Auburger G, Chishti AH. Fine scale mapping places DLG1, the gene encoding hDlg, telomeric to the OPA1 candidate region. Mamm Genome. 1997 Oct;8(10):795-6

Hanada T, Lin L, Chandy KG, Oh SS, Chishti AH. Human homologue of the Drosophila discs large tumor suppressor binds to p56lck tyrosine kinase and Shaker type Kv1.3 potassium channel in T lymphocytes. J Biol Chem. 1997 Oct 24;272(43):26899-904

Kiyono T, Hiraiwa A, Fujita M, Hayashi Y, Akiyama T, Ishibashi M. Binding of high-risk human papillomavirus E6 oncoproteins to the human homologue of the Drosophila discs large tumor suppressor protein. Proc Natl Acad Sci U S A. 1997 Oct 14;94(21):11612-6

Lee SS, Weiss RS, Javier RT. Binding of human virus oncoproteins to hDlg/SAP97, a mammalian homolog of the Drosophila discs large tumor suppressor protein. Proc Natl

Acad Sci U S A. 1997 Jun 24;94(13):6670-5

Makino K, Kuwahara H, Masuko N, Nishiyama Y, Morisaki T, Sasaki J, Nakao M, Kuwano A, Nakata M, Ushio Y, Saya H. Cloning and characterization of NE-dlg: a novel human homolog of the Drosophila discs large (dlg) tumor suppressor protein interacts with the APC protein. Oncogene. 1997 May 22;14(20):2425-33

Mori K, Iwao K, Miyoshi Y, Nakagawara A, Kofu K, Akiyama T, Arita N, Hayakawa T, Nakamura Y. Identification of brain-specific splicing variants of the hDLG1 gene and altered splicing in neuroblastoma cell lines. J Hum Genet. 1998;43(2):123-7

Reuver SM, Garner CC. E-cadherin mediated cell adhesion recruits SAP97 into the cortical cytoskeleton. J Cell Sci. 1998 Apr;111 (Pt 8):1071-80

Wu H, Reuver SM, Kuhlendahl S, Chung WJ, Garner CC. Subcellular targeting and cytoskeletal attachment of SAP97 to the epithelial lateral membrane. J Cell Sci. 1998 Aug;111 (Pt 16):2365-76

Gardiol D, Kühne C, Glaunsinger B, Lee SS, Javier R, Banks L. Oncogenic human papillomavirus E6 proteins target the discs large tumour suppressor for proteasome-mediated degradation. Oncogene. 1999 Sep 30;18(40):5487-96

Suzuki T, Ohsugi Y, Uchida-Toita M, Akiyama T, Yoshida M. Tax oncoprotein of HTLV-1 binds to the human homologue of Drosophila discs large tumor suppressor protein, hDLG, and perturbs its function in cell growth control. Oncogene. 1999 Oct 28;18(44):5967-72

Hanada T, Lin L, Tibaldi EV, Reinherz EL, Chishti AH. GAKIN, a novel kinesin-like protein associates with the human homologue of the Drosophila discs large tumor suppressor in T lymphocytes. J Biol Chem. 2000 Sep 15;275(37):28774-84

Ishidate T, Matsumine A, Toyoshima K, Akiyama T. The APC-hDLG complex negatively regulates cell cycle progression from the G0/G1 to S phase. Oncogene. 2000 Jan 20;19(3):365-72

Marfatia SM, Byron O, Campbell G, Liu SC, Chishti AH. Human homologue of the Drosophila discs large tumor suppressor protein forms an oligomer in solution. Identification of the self-association site. J Biol Chem. 2000 May 5;275(18):13759-70

Nix SL, Chishti AH, Anderson JM, Walther Z. hCASK and hDlg associate in epithelia, and their src homology 3 and guanylate kinase domains participate in both intramolecular and intermolecular interactions. J Biol Chem. 2000 Dec 29;275(52):41192-200

Tiffany AM, Manganas LN, Kim E, Hsueh YP, Sheng M, Trimmer JS. PSD-95 and SAP97 exhibit distinct mechanisms for regulating K(+) channel surface expression and clustering. J Cell Biol. 2000 Jan 10;148(1):147-58

Bonilha VL, Rodriguez-Boulan E. Polarity and developmental regulation of two PDZ proteins in the retinal pigment epithelium. Invest Ophthalmol Vis Sci. 2001 Dec;42(13):3274-82

Kawabe H, Nakanishi H, Asada M, Fukuhara A, Morimoto K, Takeuchi M, Takai Y. Pilt, a novel peripheral membrane protein at tight junctions in epithelial cells. J Biol Chem. 2001 Dec 21;276(51):48350-5

Sans N, Racca C, Petralia RS, Wang YX, McCallum J, Wenthold RJ. Synapse-associated protein 97 selectively associates with a subset of AMPA receptors early in their biosynthetic pathway. J Neurosci. 2001 Oct 1;21(19):7506-16

Karnak D, Lee S, Margolis B. Identification of multiple binding partners for the amino-terminal domain of synapse-associated protein 97. J Biol Chem. 2002 Nov 29;277(48):46730-5

Kohu K, Ogawa F, Akiyama T. The SH3, HOOK and guanylate kinase-like domains of hDLG are important for its cytoplasmic localization. Genes Cells. 2002 Jul;7(7):707-15

Lee S, Fan S, Makarova O, Straight S, Margolis B. A novel and conserved protein-protein interaction domain of mammalian Lin-2/CASK binds and recruits SAP97 to the lateral surface of epithelia. Mol Cell Biol. 2002 Mar;22(6):1778-91

McLaughlin M, Hale R, Ellston D, Gaudet S, Lue RA, Viel A. The distribution and function of alternatively spliced insertions in hDlg. J Biol Chem. 2002 Feb 22;277(8):6406-12

Paarmann I, Spangenberg O, Lavie A, Konrad M. Formation of complexes between Ca2+.calmodulin and the synapse-associated protein SAP97 requires the SH3 domain-guanylate kinase domain-connecting HOOK region. J Biol Chem. 2002 Oct 25;277(43):40832-8

Toyooka K, Iritani S, Makifuchi T, Shirakawa O, Kitamura N, Maeda K, Nakamura R, Niizato K, Watanabe M, Kakita A, Takahashi H, Someya T, Nawa H. Selective reduction of a PDZ protein, SAP-97, in the prefrontal cortex of patients with chronic schizophrenia. J Neurochem. 2002 Nov;83(4):797-806

Watson RA, Rollason TP, Reynolds GM, Murray PG, Banks L, Roberts S. Changes in expression of the human homologue of the Drosophila discs large tumour suppressor protein in high-grade premalignant cervical neoplasias. Carcinogenesis. 2002 Nov;23(11):1791-6

Wu H, Nash JE, Zamorano P, Garner CC. Interaction of SAP97 with minus-end-directed actin motor myosin VI. Implications for AMPA receptor trafficking. J Biol Chem. 2002 Aug 23;277(34):30928-34

Eldstrom J, Choi WS, Steele DF, Fedida D. SAP97 increases Kv1.5 currents through an indirect N-terminal mechanism. FEBS Lett. 2003 Jul 17;547(1-3):205-11

Godreau D, Vranckx R, Maguy A, Goyenvalle C, Hatem SN. Different isoforms of synapse-associated protein, SAP97, are expressed in the heart and have distinct effects on the voltage-gated K+ channel Kv1.5. J Biol Chem. 2003 Nov 21;278(47):47046-52

Hanada T, Takeuchi A, Sondarva G, Chishti AH. Protein 4.1-mediated membrane targeting of human discs large in epithelial cells. J Biol Chem. 2003 Sep 5;278(36):34445-50

Humbert P, Russell S, Richardson H. Dlg, Scribble and Lgl in cell polarity, cell proliferation and cancer. Bioessays. 2003 Jun;25(6):542-53

Massimi P, Gardiol D, Roberts S, Banks L. Redistribution of the discs large tumor suppressor protein during mitosis. Exp Cell Res. 2003 Nov 1;290(2):265-74

Peiretti F, Deprez-Beauclair P, Bonardo B, Aubert H, Juhan-Vague I, Nalbone G. Identification of SAP97 as an intracellular binding partner of TACE. J Cell Sci. 2003 May 15;116(Pt 10):1949-57

Folco EJ, Liu GX, Koren G. Caveolin-3 and SAP97 form a scaffolding protein complex that regulates the voltage-gated potassium channel Kv1.5. Am J Physiol Heart Circ Physiol. 2004 Aug;287(2):H681-90

Fuja TJ, Lin F, Osann KE, Bryant PJ. Somatic mutations and altered expression of the candidate tumor suppressors CSNK1 epsilon, DLG1, and EDD/hHYD in mammary ductal carcinoma. Cancer Res. 2004 Feb 1;64(3):942-51

Laprise P, Viel A, Rivard N. Human homolog of disc-large is required for adherens junction assembly and differentiation of human intestinal epithelial cells. J Biol Chem. 2004 Mar 12;279(11):10157-66

Leonoudakis D, Conti LR, Radeke CM, McGuire LM, Vandenberg CA. A multiprotein trafficking complex composed of SAP97, CASK, Veli, and Mint1 is associated with inward rectifier Kir2 potassium channels. J Biol Chem. 2004 Apr 30;279(18):19051-63

Mauceri D, Cattabeni F, Di Luca M, Gardoni F. Calcium/calmodulin-dependent protein kinase II phosphorylation drives synapse-associated protein 97 into spines. J Biol Chem. 2004 May 28;279(22):23813-21

Six EM, Ndiaye D, Sauer G, Laâbi Y, Athman R, Cumano A, Brou C, Israël A, Logeat F. The notch ligand Delta1 recruits Dlg1 at cell-cell contacts and regulates cell migration. J Biol Chem. 2004 Dec 31;279(53):55818-26

Yamamoto Y, Irie K, Asada M, Mino A, Mandai K, Takai Y. Direct binding of the human homologue of the Drosophila disc large tumor suppressor gene to seven-pass transmembrane proteins, tumor endothelial marker 5 (TEM5), and a novel TEM5-like protein. Oncogene. 2004 May 13;23(22):3889-97

Round JL, Tomassian T, Zhang M, Patel V, Schoenberger SP, Miceli MC. Dlgh1 coordinates actin polymerization, synaptic T cell receptor and lipid raft aggregation, and effector function in T cells. J Exp Med. 2005 Feb 7;201(3):419-30

Sabio G, Arthur JS, Kuma Y, Peggie M, Carr J, Murray-Tait V, Centeno F, Goedert M, Morrice NA, Cuenda A. p38gamma regulates the localisation of SAP97 in the cytoskeleton by modulating its interaction with GKAP. EMBO J. 2005 Mar 23;24(6):1134-45

Thomas M, Massimi P, Navarro C, Borg JP, Banks L. The hScrib/Dlg apico-basal control complex is differentially targeted by HPV-16 and HPV-18 E6 proteins. Oncogene. 2005 Sep 15;24(41):6222-30

Willatt L, Cox J, Barber J, Cabanas ED, Collins A, Donnai D, FitzPatrick DR, Maher E, Martin H, Parnau J, Pindar L, Ramsay J, Shaw-Smith C, Sistermans EA, Tettenborn M, Trump D, de Vries BB, Walker K, Raymond FL. 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. Am J Hum Genet. 2005 Jul;77(1):154-60

Frese KK, Latorre IJ, Chung SH, Caruana G, Bernstein A, Jones SN, Donehower LA, Justice MJ, Garner CC, Javier RT. Oncogenic function for the Dlg1 mammalian homolog of the Drosophila discs-large tumor suppressor. EMBO J. 2006 Mar 22;25(6):1406-17

Gardiol D, Zacchi A, Petrera F, Stanta G, Banks L. Human discs large and scrib are localized at the same regions in colon mucosa and changes in their expression patterns are correlated with loss of tissue architecture during malignant progression. Int J Cancer. 2006 Sep 15;119(6):1285-90

Massimi P, Narayan N, Cuenda A, Banks L. Phosphorylation of the discs large tumour suppressor protein controls its membrane localisation and enhances its susceptibility to HPV E6-induced degradation. Oncogene. 2006 Jul 20;25(31):4276-85

Bohl J, Brimer N, Lyons C, Vande Pol SB. The stardust family protein MPP7 forms a tripartite complex with LIN7 and DLG1 that regulates the stability and localization of DLG1 to cell junctions. J Biol Chem. 2007 Mar 30;282(13):9392-400

Chung SH, Frese KK, Weiss RS, Prasad BV, Javier RT. A new crucial protein interaction element that targets the adenovirus E4-ORF1 oncoprotein to membrane vesicles. J Virol. 2007 May;81(9):4787-97

García-Mata R, Dubash AD, Sharek L, Carr HS, Frost JA, Burridge K. The nuclear RhoA exchange factor Net1 interacts with proteins of the Dlg family, affects their localization, and influences their tumor suppressor activity. Mol Cell Biol. 2007 Dec;27(24):8683-97

Mimori-Kiyosue Y, Matsui C, Sasaki H, Tsukita S. Adenomatous polyposis coli (APC) protein regulates epithelial cell migration and morphogenesis via PDZ domain-based interactions with plasma membranes. Genes Cells. 2007 Feb;12(2):219-33

Roberts S, Calautti E, Vanderweil S, Nguyen HO, Foley A, Baden HP, Viel A. Changes in localization of human discs large (hDlg) during keratinocyte differentiation are [corrected] associated with expression of alternatively spliced hDlg variants. Exp Cell Res. 2007 Jul 15;313(12):2521-30

Stucke VM, Timmerman E, Vandekerckhove J, Gevaert K, Hall A. The MAGUK protein MPP7 binds to the polarity protein hDlg1 and facilitates epithelial tight junction formation. Mol Biol Cell. 2007 May;18(5):1744-55

Yamada KH, Hanada T, Chishti AH. The effector domain of human Dlg tumor suppressor acts as a switch that relieves autoinhibition of kinesin-3 motor GAKIN/KIF13B. Biochemistry. 2007 Sep 4;46(35):10039-45

Abi-Char J, El-Haou S, Balse E, Neyroud N, Vranckx R, Coulombe A, Hatem SN. The anchoring protein SAP97 retains Kv1.5 channels in the plasma membrane of cardiac myocytes. Am J Physiol Heart Circ Physiol. 2008 Apr;294(4):H1851-61

Cao Z, Huett A, Kuballa P, Giallourakis C, Xavier RJ. DLG1 is an anchor for the E3 ligase MARCH2 at sites of cell-cell contact. Cell Signal. 2008 Jan;20(1):73-82

Cavatorta AL, Giri AA, Banks L, Gardiol D. Cloning and functional analysis of the promoter region of the human Disc large gene. Gene. 2008 Nov 15;424(1-2):87-95

Massimi P, Narayan N, Thomas M, Gammoh N, Strand S, Strand D, Banks L. Regulation of the hDlg/hScrib/Hugl-1 tumour suppressor complex. Exp Cell Res. 2008 Nov 1;314(18):3306-17

Sato J, Shimazu D, Yamamoto N, Nishikawa T. An association analysis of synapse-associated protein 97 (SAP97) gene in schizophrenia. J Neural Transm. 2008 Sep;115(9):1355-65

Unno K, Hanada T, Chishti AH. Functional involvement of human discs large tumor suppressor in cytokinesis. Exp Cell Res. 2008 Oct 15;314(17):3118-29

Narayan N, Massimi P, Banks L. CDK phosphorylation of the discs large tumour suppressor controls its localisation and stability. J Cell Sci. 2009 Jan 1;122(Pt 1):65-74

This article should be referenced as such:

Massimi P, Banks L. DLG1 (discs, large homolog 1 (Drosophila)). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(4):368-376.