

Gene Section

Review

DLG1 (discs, large homolog 1 (Drosophila))

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Abstract

The human homologue of Drosophila disc large tumor suppressor protein (hDlg) also known as synapse-associated protein 97, is a scaffold protein, a member of the membrane-associated guanylate kinase family. It is one of the proteins known to act cooperatively in regulating cell polarity and proliferation, suggesting an important connection between epithelial organization and cellular growth control. An abnormal expression of hDlg has been reported in several cancer types. This protein may have a role in cell junction formation, signal transduction, cell proliferation, synaptogenesis and lymphocyte activation.

Keywords

Polarity, cell junctions, tumour progression

Identity

HGNC (Hugo): DLG1

Location: 3q29

Other names: SAP97, DKFZp761P0818, DKFZp781B0426DLGH1, dJ1061C18.1.1, Hdlg

DNA/RNA

Description

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

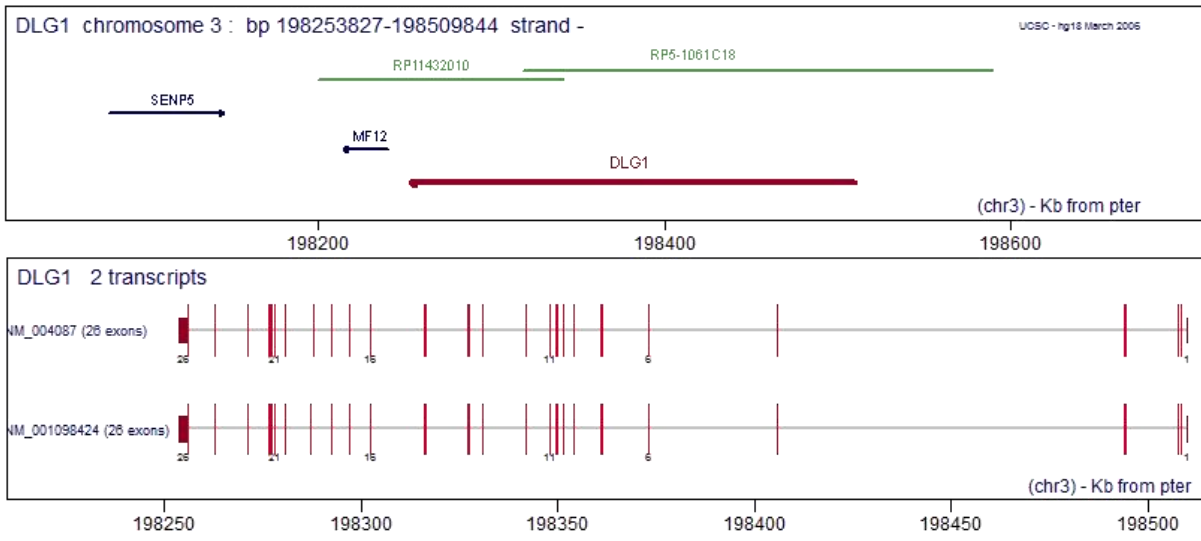
Transcription

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 homology 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).

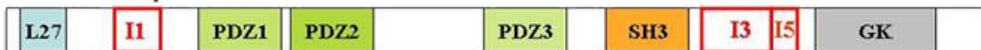
There are two major transcripts of DLG1 gene. One is Discs large homolog 1 isoform 1, which contains an additional exon (99 nucleotides) in the 5' part of the Dlg homology repeats (DHR) domain and lacks an exon in the 3' coding region, resulting in a shorter protein (isoform 1), compared to isoform 2. 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 nucleotides in the region between the SH3 and GUK (isoform 2)



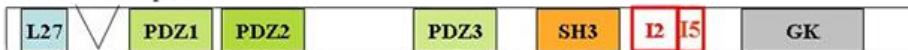
Isoform A (canonical sequence)



Isoform B sequence



Isoform C sequence



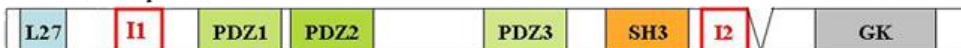
Isoform D sequence



Isoform E sequence



Isoform F sequence



Isoform G sequence



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

Another alternative splice has an insertion 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 localized 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. 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.

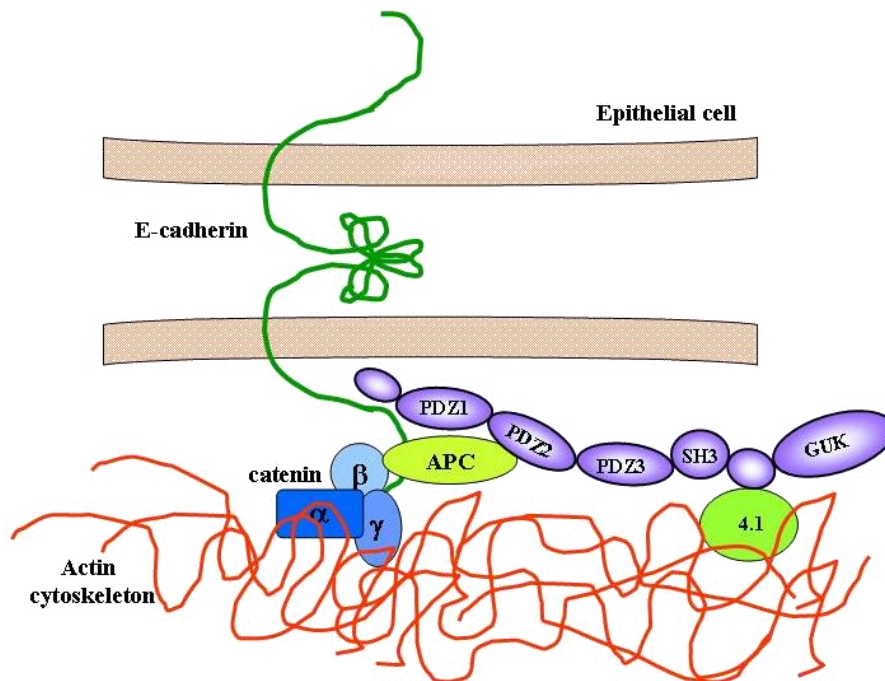


Diagram of the DLG1 protein with its characteristic domains and the main protein-protein interactions at the cell-cell junctions

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). Recent studies report that APC can bind to all the three PDZ domains from hDlG, whereas PTEN mainly binds to PDZ-2/hDlG. This indicates the existence of overlapping, but distinct PDZ-domain recognition patterns by APC and PTEN. Furthermore, a ternary complex formed by APC, PTEN, and hDlG has been detected, suggesting that hDlG may serve as a platform to bring in proximity APC and PTEN tumor suppressor activities, which may be relevant in oncogenesis (Sotelo et al. 2012). 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-dependent (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 through 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 phosphatidylinositol 3-kinase (PI3K) in cells. E4-ORF1 binding to Dlg1 on its 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).

Moreover, phosphatidylinositol 3-kinases are one class of signaling molecules reported to regulate adherens junction and to be activated by adherens junction assembly . While the exact molecular mechanisms involved are not clear, data indicate that one of the earliest events likely involves c-Src which is rapidly activated by E-cadherin-mediated cellular aggregation and may facilitate the recruitment and activation of PI3K to E-cadherin-containing complexes. Beta-catenin, gamma-catenin and hDlg which are present at cell-cell adhesions can act as docking proteins for PI3K (Rivard N. 2009).

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 (AMPA) containing the GluR1 subunit, but the functional significance of these interactions is partially unclear, even if this interaction seems to 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 colocalization of the other proteins of the Scrib complex: hScribble and Hugl-1 (Massimi et al., 2008).

Osmotic stress triggers hDlg degradation through a mechanism different from the one mediated by proteasomes, and hDlg is also a caspase substrate during the apoptotic process, although its proteolysis may not be implicated in the progression of early apoptosis (Inesta-Vaquera FA et al. 2009).

In response to hyperosmotic stress, p38 β also regulates formation of complexes between hDlg and the nuclear protein polypyrimidine tract-binding protein-associated-splicing factor (PSF). Following osmotic shock, p38 β in the cell nucleus increases its association with nuclear hDlg, thereby causing dissociation of hDlg-PSF complexes. Moreover, hDlg and PSF bind different RNAs; in response to osmotic shock, p38 β causes hDlg-PSF and hDlg-RNA dissociation independently of its kinase activity, affecting mRNA processing and/or gene transcription (Sabio et al. 2010). Moreover, the exposure of cells to osmotic shock induces the hyperphosphorylation of Dlg and its concomitant accumulation within the cell membrane at sites of cell contact, a process that requires an intact actin filament network. In addition, hyperphosphorylation of Dlg also renders it more susceptible to degradation induced by the HPV-18 E6 oncoprotein (Massimi et al.2006).

Also the ERK5 pathway is reported to mediate hDlg cell cycle dependent phosphorylation. This is likely to have important implications in the correct timely mitotic entry and mitosis progression (Inesta-Vaquera et al. 2010).

Using the yeast two-hybrid system to screen a human aorta cDNA library, mitogen-activated protein/extracellular signal-responsive kinase (ERK) kinase (MEK)2, a member of the ERK cascade it was identified as an hDlg binding partner. Site-directed mutagenesis showed a major involvement of the PSD-95, disc-large, ZO-1 domain-2 of hDlg and the C-terminal sequence RTAV of MEK2 in this interaction. hDlg acts as a MEK2-specific scaffold protein for the ERK signaling pathway differentially tuning MEK1/MEK2 signaling and cell responses (Maiga et al. 2011). Both proteins localize also to a sub-structure of the midbody, the midbody ring (Massimi et al. 2003; Gaudet et al. 2011).

Using a proteomic approach it has been shown that a strong interacting partner of hDlg is the RhoG-specific guanine nucleotide exchange factor SGEF. The interaction between hDlg1 and SGEF involves both PDZ and SH3 domain recognition, and directly contributes to the regulation of SGEF's cellular localization and activity. Consistent with this, hDlg

is a strong enhancer of RhoG activity, which occurs in an SGEF-dependent manner and directly contributes to the invasive capacity of HPV-16 and HPV-18 transformed tumour cells displaying a distinct oncogenic function in the context of HPV induced malignancy (Krishna Subbaiah et al. 2012). Loss of gap junctional communication correlated with relocalization of Cx43 to the cytoplasm late in tumorigenesis. A similar pattern of altered expression for the hDlg was found in cervical tumour cells, with partial co-localization of Cx43 and hDlg in an endosomal/lysosomal compartment. Relocalization of these proteins is not due to a general disruption of cell membrane integrity or Cx targeting. Cx43 (via its C-terminus) and hDlg interact directly in vitro and can form a complex in cells. This novel interaction requires the N- and C-termini of hDlg (Macdonald et al. 2012).

The components of the Scrib/Dlg tumour suppressor complex have complementary roles in *Drosophila* and loss of both proteins is a common event in many different human tumours. In human keratinocytes the removal of hScrib greatly reduces cell-cell contact and cell-matrix interactions, and promotes an invasive phenotype. Conversely, in cells lacking hDlg1 cell-cell contacts are maintained and there are decreases in both cell growth and invasion (Massimi et al. 2012).

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 found 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 postsynaptic membrane. In human vascular tissues, hDlg is highly expressed in smooth muscle cells (VSMCs) and in these cells associates with the endoplasmic reticulum and microtubules (Maiga et al. 2011). 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. Moreover, 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 modification of the protein, by phosphorylation occurring post-osmotic shock (Massimi et al., 2006; Remy et al. 2010) and also during the cell cycle following CDK phosphorylation (Narayan et al., 2009). Nuclear forms of Dlg phosphorylated on its CDK phospho-acceptor sites (S158 and S442) has enhanced susceptibility to E6-induced degradation (Narayan et al. 2009; Nagasaka et al. 2013). 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-dependent 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 endoplasmic 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 suggests 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 recruit 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 proliferation (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

See paragraphs below.

Implicated in

Epithelial-derived cancers

The mis-localisation of DLG1 is linked to the development of epithelial-derived cancers (Gardioli et al., 2006).

In uterine cervical squamous epithelia, prominent localization of hDlg at sites of intercellular 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; Vazquez-Ulloa et al., 2011).

Mammary ductal carcinoma

In humans there is only one report of mutations occurring 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 progesterin 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

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

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

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

Malignant fibrous histiocytoma

The patients with a weak or negative expression of hDlg had a significantly shorter metastasis-free survival rate and disease-free survival rate in comparison with those with a strong or moderate expression. The patients have a significantly shorter overall survival rate. A reduced expression of hDlg protein is an independent negative prognostic factor for MFH (Niimi et al. 2010).

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