Review

DLG5 in Cell Polarity Maintenance and Cancer Development

Jie Liu[1], Juan Li[1], Yu Ren[2], Peijun Liu[1]✉

1. Center for Translational Medicine, the First Affiliated Hospital of Xian Jiaotong University College of Medicine;
2. Department of Surgical Oncology, the First Affiliated Hospital of Xian Jiaotong University College of Medicine.

✉ Corresponding author: Peijun Liu, Ph.D.&M.D., Professor, Email: liupeijun@mail.xjtu.edu.cn, Tel: 086-18991232306, Address: 277 Yanta Western Rd., Xi'an, Shaan Xi Province, China, 710061.

Abstract

Failure in establishment and maintenance of epithelial cell polarity contributes to tumorigenesis. Loss of expression and function of cell polarity proteins is directly related to epithelial cell polarity maintenance. The polarity protein discs large homolog 5 (DLG5) belongs to a family of molecular scaffolding proteins called Membrane Associated Guanylate Kinases (MAGUKs). As the other family members, DLG5 contains the multi-PDZ, SH3 and GUK domains. DLG5 has evolved in the same manner as DLG1 and ZO1, two well-studied MAGUKs proteins. Just like DLG1 and ZO1, DLG5 plays a role in cell migration, cell adhesion, precursor cell division, cell proliferation, epithelial cell polarity maintenance, and transmission of extracellular signals to the membrane and cytoskeleton. Since the roles of DLG5 in inflammatory bowel disease (IBD) and Crohn's disease (CD) have been reviewed, here, our review focuses on the roles of DLG5 in epithelial cell polarity maintenance and cancer development.

Key words: DLG5, epithelial cell polarity, EMT, cell proliferation, migration.

Introduction

The establishment and maintenance of epithelial cell polarity is crucial for maintaining epithelial integrity. Epithelial cell polarity maintenance mainly depends on cell polarity complexes and cell adhesion complexes (Table 1). Three major polarity complexes have been identified. The PAR complex, formed by PAR3, PAR6, atypical protein kinase C (aPKC, PKCζ and PKCι in humans) and cell division control protein 42 (CDC42), is required for maintenance of apical-lateral polarity. The crumbs (CRB) complex participates in establishment of the apical membrane and comprises transmembrane protein CRB, cytoplasmic protein PALS1 and PALS1-associated tight junction protein (PATJ). The scribble (SCRIB)-LETHAL (2) giant larvae homologue (LGL)-discs large homologue (DLG) complex (SCRIB-LGL-DLG complex) maintains the basolateral plasma membrane domain [1]. Cell adhesion complexes consist of adherens junctional complexes and tight junctional complexes. Cadherin-catenin and nectin-afadin complexes are two adherens junctional complexes and occur at the core of the adherens junction (AJ) [2]. The tight junctional complexes are composed of zonula occludens (ZO) subfamily, occludin, claudin and junctional adhesion molecules (JAM) [3]. Loss of cell polarity complexes and adhesion complexes lead to failure in maintenance of epithelial cell polarity, inducing epithelial-to-mesenchymal transition (EMT), cell hyperproliferation and enhanced cell invasive potential [4-7].

Membrane Associated Guanylate Kinases (MAGUKs) are a family of proteins that contain multi-PDZ domains, a Src homology 3 (SH3) domain and a guanylate kinase (GUK) domain [8]. According to their different phylogenetic positions and domain architectures, MAGUKs are classified into 10 sub-

types: discs large homolog 1 (DLG1/SAP-97, DLG2-4), calcium/calmodulin-dependent protein kinase (CASK), membrane palmitoylated protein 1 (MPP1, P55), MPP5, MPP2-7, zona occludens (ZO, TJP), DLG5, caspase recruitment domain-containing MAGUK protein (CARMA), voltage-dependent L-type calcium channel β-subunit (CACNB), and membrane-associated guanylate kinase inverted 1-3 (MAGI1-3) [9-11] (Fig. 1, Table 2). MAGUKs act as key scaffolds at cell membranes for protein complexes containing several receptors and various signaling molecules. MAGUKs also play significant roles in cell adhesion and tight junction [12]. DLG1 and ZO1, typical members of MAGUKs, participate in establishment and maintenance of apical-basal polarity of epithelia cells [13]. DLG1, also a component of the SCRIB-LGL-DLG polarity protein complex, functions as a tumor suppressor in mammals [14-16] and affect cell division [17]. ZO1 participates in establishment of the belt-like adherens and tight junctions [18] and its expression decreases in transmigratory cancer cells [19].
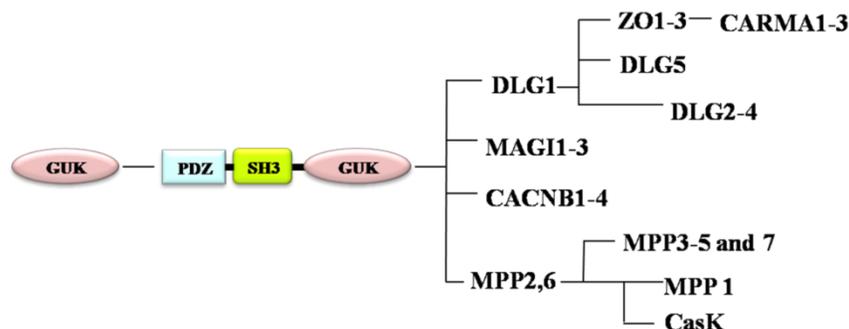

Figure 1. Evolution of MAGUK family.

Table 1. Cell polarity complexes and cell adhesion complexes.

	Complex	Components	Function	Ref.
Cell polarity complexes	PAR complex	PAR3, PAR6, aPKC (PKCζ and PKCι in humans) and CDC42	Maintenance of apical-lateral polarity	[1]
	Crumbs complex	CRB, PALS1 and PATJ	Establishment of the apical plasma membrane	
	SCRIB complex	Scribble, LGL and DLG	Maintenance of the basolateral membrane	
Cell adhesion complexes	Adherens junctional complexes	Cadherin-catenin, nectin-afadin complexes, etc.	Adherens junction	[2]
	Tight junctional complex	ZO subfamily, occludin, claudin and JAM	Tight junction	[3]

Table 2. MAGUKs, their functions and involvement in diseases

Name	Functions	Disease	Ref.
DLG	Maintenance of cell polarity, cell proliferation, migration and adhesion, cell division, synapse formation.	Breast, cervical and clolon cancer, kidney disease and renal failure, schizophrenia, etc.	[23, 33, 59-61]
CASK	Maintenance of cell polarity, progenitor population, synapse formation, cell migration.	Kidney disease and renal failure, nystagmus, Ohtahara syndrome and cerebellar hypoplasia, Pontocerebellar hypoplasia, etc.	[12, 23, 61]
MPP1	Maintenance of cell polarity, invasion, cell division.	Paroxysmal nocturnal haemoglobinuria, idiopathic ataxia, etc.	[62, 63]
MPP5	Maintenance of cell polarity, cell proliferation.	Prostate cancer	[64]
MPP2-7	Maintenance of cell polarity, cell proliferation, synapse formation.	etinal disease, etc.	[23, 65]
ZO	Maintenance of cell polarity, tight junction, cell migration.	Cancer, kidney disease, etc.	[66, 67]
DGL5	Maintenance of cell polarity, cell proliferation, invasion and migration, cell division.	Breast and prostate cancer, Crohn's disease, inflammatory bowel disease, etc.	[20, 22, 46, 49]
CARMA	Cell proliferation, inflammation, apoptosis, and metastasis.	Breast and ovarian cancer, etc.	[68, 69]
CACNB	Calcium- and potassium-channel	Patent ductus arteriosus	[70]
MAGI	Maintenance of cell polarity, invasiveness, synapse formation, apoptosis.	Human hepatocellular carcinoma cells	[23, 71]

DLG5 is a notable member of MAGUKs; it has evolved in the same manner as DLG1 and ZO1. Just like DLG1 and ZO1, DLG5 plays important roles in epithelial cell polarity maintenance, precursor cell division, cell proliferation, cell migration and invasion, and transmission of extracellular signals to the membrane and cytoskeleton. Numerous researchers have focused on the study of the roles of DLG5 in inflammatory bowel disease (IBD) and Crohn's disease (CD) and their findings have been reviewed previously [20]. Here, we will review the functions of DLG5 in epithelial cell polarity maintenance and cancer development.

DLG5 has evolved in the same manner as DLG1 and ZO1

MAGUKs have evolved from a catalytically active GUK encoding gene. PDZ and SH3 domains gradually occur during their evolution. MPP and CACNB are first branched off, followed by the branching-off of DLG, ZO and CARMA subfamilies after duplication of the PDZ domain. DLG5 is formed when an additional PDZ domain is duplicated (Fig. 1) [10]. According to the evolution process of MAGUKs, DLG5, ZO and classical DLG proteins have similar structures. All of them contain a SH3 domain and a GUK domain (Fig. 2). Additionally, DLG5 contains a CARD domain, a DUF domain, a coiled-coil domain, and 4 PDZ domains [21, 22]; DLG1 has an additional L27 domain and 3 PDZ domains; the ZO subfamily has a unique ZU5 domain and 3 PDZ domains [9, 23]. Maintenance of epithelial cell polarity and cell-cell junctions is a characteristic property of PDZ domain-containing proteins. SH3 domain can recognize the proline-rich sequence PXXP of cytoskeletal elements and signaling proteins [24]. The GUK domains of DLG5, DLG1 and ZO1 all contain GMP-binding pockets; however, the GUK domain of DLG1 has

phosphor-peptide-binding modules, which play roles in diverse cellular processes by interacting with proteins, such as mitotic spindle regulatory protein LDN [25]. ZO1 and DLG5 lack residues essential for phosphate recognition in their GUK domain [11]. Studies have revealed that DLG5, DLG1 and ZO1 have similar functions in cell polarity maintenance and cancer development, which we assume may be due to the similarities in their structures.

DLG5 in cell polarity maintenance

DLG5 participates in epithelial polarity maintenance by ensuring delivery of cadherins

DLG5 contains 4-PDZ domains, and therefore, may participate in maintenance of epithelia cell polarity. N-cadherin is a component of the junctional complex and synthesized in Golgi. Newly synthesized N-cadherin quickly binds to β-catenin and is delivered from Golgi to plasma membrane via secretory vesicles. Efficient and targeted delivery of N-cadherin requires a SNARE-dependent fusion of N-cadherin-β-catenin-containing vesicles with AJ proteins [26]. DLG5 interacts with β-catenin [27] and binds to syntaxin 4, a component of t-SNARE complex. Thus, DLG5 acts as a linker between cadherin-catenin-carrying transport vesicles and t-SNARE complex at plasma membrane and promotes targeted delivery of cadherin. Loss of DLG5 will reduce in the level of cell-surface N-cadherin, resulting in mislocalization and disorganization of AJ proteins, subsequent loss of cell polarity, cell adhesion, and ultimately, failure of epithelial maintenance [22]. The above review shows that DLG5 can maintain epithelial cell polarity by interacting with AJ proteins and promoting delivery of N-cadherin to plasma membrane (Fig 3A, B).
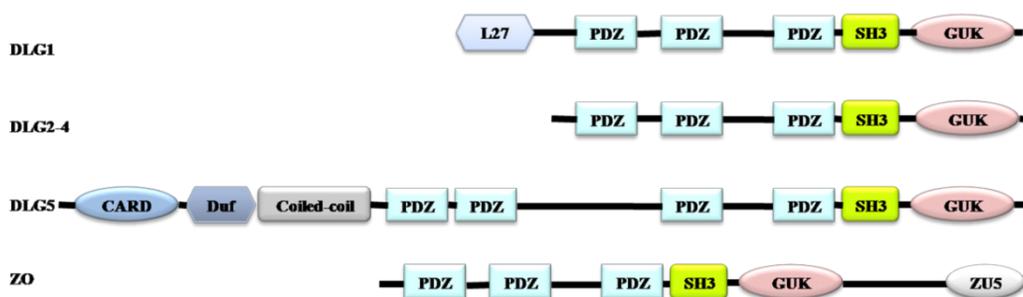

Figure 2. Domain architectures of DLG 1, DLG2-4, DLG5 and ZO. All proteins have the PDZ, SH3 and GUK domains. DLG1 has an additional L27 domain, ZO has a unique ZU5 domain, and DLG5 has a CARD domain, a DUF domain, a Coiled-coil domain, and four PDZ domains.
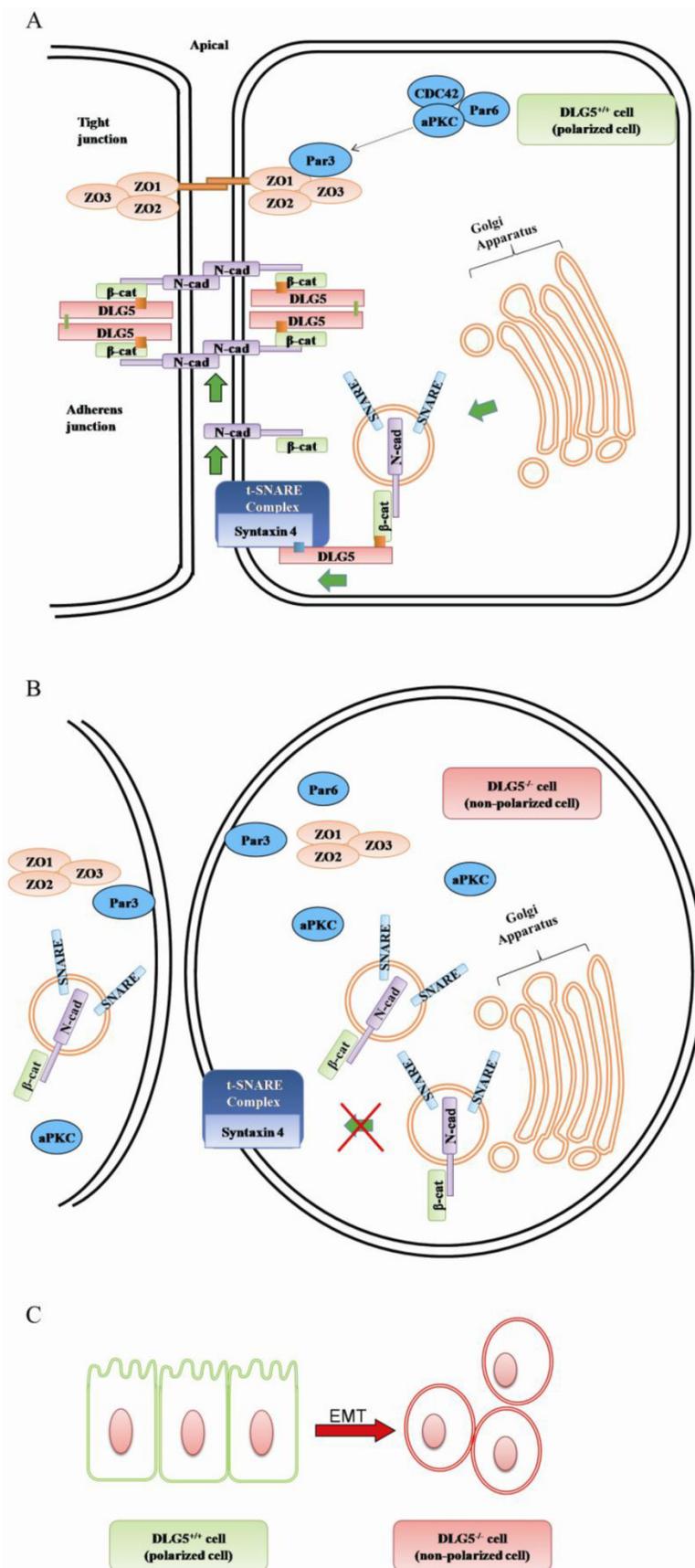
Figure 3. The working model of DLG5 in cell polarity maintenance and cancer development. A. in normal cell (DLG5$^{+/+}$ cell); B in DLG5$^{-/-}$ cell; C. loss of DLG5 induces EMT.

DLG5 stabilizes adherens and tight junction complexes

DLG5 contains a unique coiled-coil domain at the N-terminus. Self-association is an interesting function of coiled-coil domains. Additionally, PDZ3-PDZ4 and SH3-GUK domains of DLG5 also have self-association potential and can bind to the N-terminus of DL5 [22]. The characteristics of the coiled coil, PDZ3-PDZ4 and SH3-GUK domains suggest that DLG5 can self-associate and form a large protein complex containing multiple β-catenin-binding domains. Since DLG5 can interact with N-cadherin and β-catenin of apical junctional adhesion complexes, the protein complex formed by DLG5 oligomerization can scaffold and stabilize cadherin-catenin adhesion complexes at the plasma membrane [22].

The component of the PAR complex, aPKC, is apically localized and participates in maintenance of apical-lateral polarity. aPKC can recruit the PAR3-PAR6 complex from tight junction sites to subapical region; as a result, PAR3 is excluded from tight junction sites, allowing for tight junction formation [28]. ZO1, located on the plasma membrane surface at sites of the cell-cell junction [29], is a well-known organizer for tight junction and notable epithelial marker [30]. ZO1 interacts with ZO2 and ZO3 via their PDZ2 domains to form a tight junctional complex. DLG5 participates in regulation of cell polarity by promoting the apical localization of aPKC [31]. It has been found that aPKC and ZO1 are mislocalized, while PAR3 and remains apically localized in DLG5 knockout mice [22, 31]. Therefore, loss of DLG5 may mislocalize ZO1 by inducing loss of the apically location of aPKC and retention of PAR3 at tight junction, then destabilizes the tight junctional complex, and eventually gives rise to the disorder of the tight junction (Fig 3 A, B). Together, DLG5 maintains epithelial polarity mainly by keeping the stability of tight junction and adherens junction.

DLG5 affects cell division and cell fate via maintenance of apical-basal polarity

DLG1 is a component of the SCRIB-LGL-DLG complex, and it functions to maintain the basal polarity of epithelial cells [32-34]. Another interesting function of DLG1 is that it participates in cell division. DLG1 mediates the cortical protein polarity by regulating the LGL localization, orients the spindles along the apical-basal axis by interacting with Leu-Gly-Asn repeat-enriched protein (LGN) at the GK domain [35-37], and creates intrinsic differences between daughter cells in mitotic neuroblasts [17].

DLG5 shows high homology to DLG1. They both contain 3-PDZ domains, a SH3 domain and a GK domain (Fig. 2). Therefore, DLG5 is also involved in maintenance of the polarity of proteins essential to cell division. Citron kinase (Citk) is highly polarized in neural progenitors and is essential to neurogenic cell division at the ventricular surface of the lateral ventricles in the central nervous system [38]. It has been found that Citk fails to polarize in mitotic neuronal precursors in DLG5 knockout mice, indicating that DLG5 is essential for Citk polarization. Therefore, DLG5 localizes cell divisions to the surface of the lateral ventricles by maintaining the polarity of Citk, which is essential to neurogenic cytokinesis [39]. DLG5 also mediates branching morphogenesis and progenitor differentiation by regulating atypical protein kinase C (aPKC), a component of apical polarity complexes [31]. Taken together, DLG5 and DLG1 can regulate cell division and cell fate via maintenance of apical-basal polarity.

DLG5 in cancer development

Cell polarity is a crucial phenomenon contributing to integrity and development of normal tissues and asymmetrical distribution of proteins. Loss of cell polarity may induce tissue disorganization and contribute to tumorigenesis. In other words, loss of cell polarity is a precondition and hallmark for cancer occurrence and development [40]. Does DLG5, which plays a role in maintenance of epithelial cells polarity, have a role in cancer development? The question will be answered in the following review.

DLG5 is closely correlated with progression of cancer

DLG, ZO1 and ZO2 were first identified as tumor suppressors in *Drosophila* [41]. Human *DLG1* gene often undergoes mutations at conserved positions in mammary ductal carcinomas and its expression reduces in solid tumors [42-44]. Similarly, DLG5 is highly expressed in normal tissues, but its expression is diminished or lost in cancer cell lines [45]. Down-regulation of DLG5 is highly correlated with the stage of tumor [46]. The DLG5 expression is the lowest in basal-type [47] and metaplastic cancer cells [48], which shows epithelial-mesenchymal transitions (EMT) (Fig. 3C), stem cell-like characteristics and poor prognosis. DLG5 is also involved in carcinogenesis [49]. Knockdown of DLG5 induces EMT in cancer cells by affecting the expressions of epithelial/mesenchymal marker proteins, for example, by facilitating the expressions of the mesenchmal markers fibronectin and α-smooth muscle actin and by suppressing the expression of the epithelial marker E-cadherin [50, 51]. Based on the above review, we

speculate that DLG5 may be closely correlated with progression of cancer.

DLG5 inhibits cell proliferation and migration

Sustaining proliferative signaling and activating invasion and metastasis are two recognized hallmarks of cancer [52]. In *Drosophila*, over-proliferation of cancer cells may be the result of mutation in the SH3 domain of DLG [34, 53]. In mammalian cells, overexpression of DLG1 impairs G1-S phase progression and inhibits cell proliferation by DLG1 binding to APC and PTEN [54]. Similarly, DLG5 may suppress cell proliferation by combining with p55 (also a member of MAGUKs containing four internal T/S-X-V motifs at C-terminal) via their PDZ domains to form a complex at the plasma membrane [45]. It has been found that overexpression of DLG5 is involved in pancreatic caricinogenesis by significantly suppressing the growth of pancreatic ductal adenocatcinoma (PDAC) cells [49]. The role of DLG5 in invasion and metastasis has also been reported. In breast cancer, overexpression of DLG5 inhibits cell migration, and knockdown of DLG5 induces cell migration via activation of the ERK signaling pathway [46]. All these reports indicate that DLG5 plays a role in cancer proliferation, migration, and cancer development.

Conclusion and future directions

DLG5 maintains epithelial polarity by ensuring the delivery and stabilization of junctional proteins and interacting with other polarity proteins such as N-cadherin and β-catenin. DLG5 also participates in cell division and cell fate determination.

DLG5 may serve as a tumor suppressor. Knockdown of DLG5 can induce loss of epithelial polarity and promote cancer development, cell proliferation, invasiveness and metastasis. In breast cancer cells, *DLG5* participates in progestin-induced growth inhibition and differentiation and is considered a primary progesterone target gene. This suggests that DLG5 may be used as a target gene in cancer therapy. To validate the role of DLG5 in cancer therapy, the relationship between DLG5 and progesterone receptor (PR) should be investigated [55].

The transforming growth factor-β (TGF-β) can suppress the expression of DLG5 and the reduced expression of DLG5 will enhance EMT induced by TGF-β receptor signaling and promote cancer progression [51]. Meanwhile, DLG5 can interact with TGF-β receptors (TβRs) and promote their degradation [56]. These findings indicate that DLG5 may participate in cancer progression via regulation of the TGF-β receptor signaling pathway. In addition, downregulation of DLG5 is associated with overexpression of YAP (Yes-associated protein), a protein containing PDZ binding domain [46]. YAP has been proved to be an oncogene, whose dephosphorylation may activate the Hippo signal pathway and promote cancer cell proliferation [57, 58]. Based on the above review, new questions arise: Can DLG5 regulate activation of the Hippo signal pathway? Does DLG5 inhibit cancer development via the YAP-Hippo pathway? In-depth research need to be conducted to reveal the role of DLG5 in tumorigenesis as soon as possible.

Together, DLG5 plays important roles in epithelial polarity maintenance and cancer development; it may a potential target for tumor molecular therapy. The DLG5-/- mice may make a significant contribution to research on pathogenesis of cancer and clinical drugs for cancer.

Acknowledgement

Competing Interests

The authors have declared that no competing interest exists.

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