Front. Biol. 2010, 5(2): 116–122
DOI 10.1007/s11515-010-0030-9

REVIEW

Establishing cell polarity by the Lgl family proteins

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Abstract The *lethal giant larvae* (*lgl*) gene was first identified more than 30 years ago in *Drosophila* and characterized as a tumor suppressor gene. Studies in budding yeast, flies and mammals all indicate that the evolutionarily conserved Lgl family proteins play an important role in cell polarity. Sro7/77, the yeast Lgl homologues, are important for the establishment and reinforcement of cell polarity through their localized interaction and kinetic activation of the post-Golgi secretion machinery. As for higher eukaryotes, both in epithelial polarity and asymmetric cell division, the role of Lgl protein is deployed by localizing proteins to the membrane in a polarized fashion. In addition, Lgl is transiently required during the establishment phase of polarity, implicating that Lgl functions at strategic time points for proliferation control. Studies in cancer biology provide direct connections between malfunction of Lgl and formation, progression and metastasis of various cancers. Here, we review recent advances in the field, focusing on the function of the Lgl family in cellular polarization.

Keywords asymmetric division, epithelial polarity, Lgl (2), tumor suppressor

1 Discovery of *lgl* family genes as tumor suppressors

The *lethal giant larvae* (*lgl*) gene was first identified more than 30 years ago in *Drosophila*. Although embryogenesis in *Drosophila* lacking *lgl* behaves normal, the mutant larvae suffer from a spectacular overgrowth of the brain and the imaginal discs (Gateff, 1978). Therefore, the mutant phenotype of *lgl* attracted the first attention concerning its role in development, which also gives this gene such a striking name. Following works done on the *lgl* mutants have found that the overgrown tissue shares many of the properties of mammal tumors, including a loss of cell shape and tissue architecture, as well as a failure to differentiation (Bilder, 2004). This phenotype distinguishes *lgl* from many *Drosophila* genes which, when mutated, cause overgrowth without disrupting the architecture of the tissue or the shape and behavior of the overproliferating cells (Humbert et al., 2008). Therefore, together with two other *Drosophila* genes, *lethal discs large* (*dlg*) and *scribble* (*scrib*), *lgl* has been regarded a neoplastic tumor suppressor gene.

Received January 19, 2010; accepted March 3, 2010

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2 Structural and functional conservation of *Lgl* family proteins through species

Over the past 30 years, homologues of *Drosophila lgl* have been characterized in almost all eukaryotic model systems: *SRO7/77* in budding yeast, MO1A10.2a in worms, Penner in Zebrafish, Mgl-1 in mouse, Bgl-1 in bovine, Hug1 in human, Rg1-1 and Tomosyn in rat (Baek, 2004; Zimmermann et al., 2008). Although the average identity is only 30% in sequence, functional analyses gradually indicated that the expression of *Lgl* family genes in higher organisms, namely Mgl-1, Bgl-1, Hug1 and Rg1-1, all rescued yeast *sro7 sro77* double deletion cells. These striking genetic data indicated that Lgl family is highly conserved in function through species. Additionally, Dollar *et al*. reported that loss of *lgl* perturbs epithelial polarity in frog (Dollar et al., 2005). Other similar reverse genetics results also revealed a high degree of functional conservation. For instance, disruption of junction formation was found in zebrafish when Lgl isoform is disturbed (Sonawane, 2005). When the neuronal homologue of *lgl* is knocked out, mice suffer defects in cell polarity and show a terminal phenotype consistent with aberrant asymmetric cell divisions (Klezovitch et al., 2004). Besides genetic evidence, the coding nucleotide sequences of Lgl family members are also shown to form a cluster in a phylogenetic tree, as shown in Fig. 1A (Baek, 2004).

In 2007, the crystal structure of a proteolytic fragment of *S. cerevisiae* Sro7p, spanning residues 61–962 at 2.4 A°

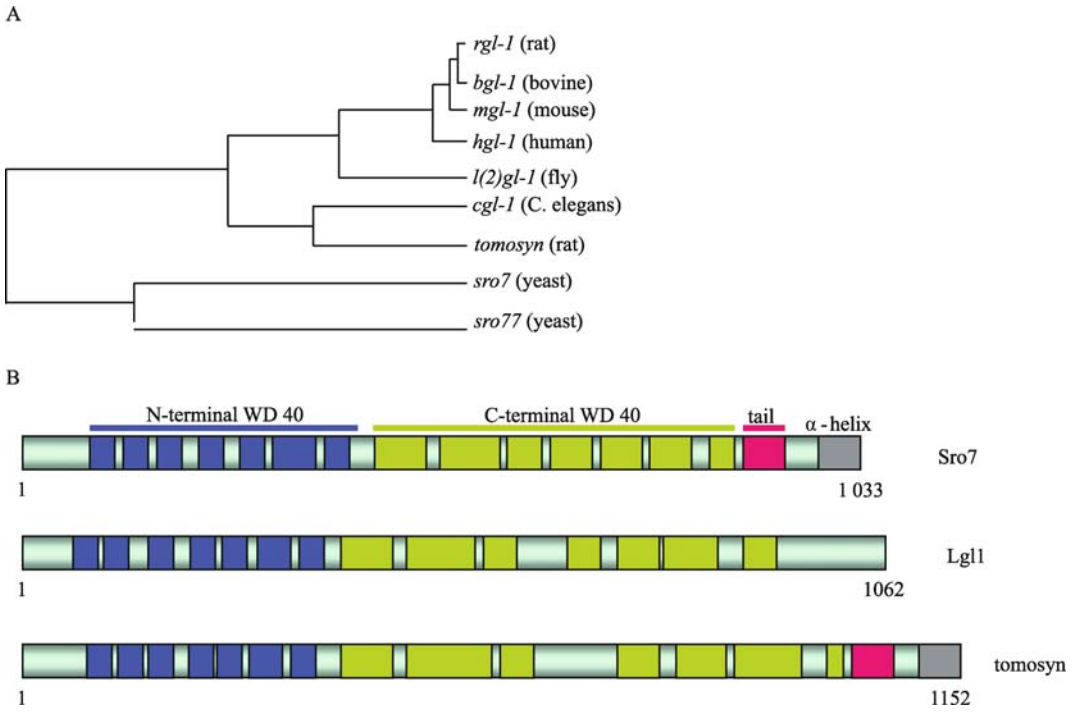

Fig. 1 **A**: Phylogenetic tree of Lgl family products. Subfamily assignments were performed using MegAlign Software from DNAStar (LaserGene) (adapted from Baek, 2004). The *lgl* subfamily includes yeast *Sro7* and *Sro77*, *C. elegans* homologue, fly *l*(*2*)*gl*, human *hugl*, mouse *mgl-1*, bovine *bgl-1*, and rat *rgl-1*. **B**: Schematic of the structure-based sequence alignment of the Lgl family proteins from yeast, mouse and rat. The predicted C-terminal α-helix in Sro7 and the R-SNARE of tomosyn are shown in grey. Dark blue and light green boxes correspond to the WD40 blades as observed structurally.

resolution, was determined (Hattendorf et al., 2007). The structure consists of 14 WD40 repeats spanning almost the entire sequence, followed by a 60-residue tail. The WD40 repeats fold into two seven-bladed β-propeller domains. Sequence alignment of Sro7p with tomosyn, the rat neuronal homologue, and mouse Lgl shows significant conservation in the 14 WD40 repeats and in many elements of the domain interface (Fig. 1B).

Previous studies have indicated that Lgl plays essential roles during the establishment of polarity in epithelial cells and asymmetric neuroblast division (Wirtz-Peitz and Knoblich, 2006; Vasioukhin, 2006), while tomosyn functions in the presynaptic nerve terminal to inhibit priming of synaptic vesicles (Gracheva et al., 2006; McEwen et al., 2006). The common mechanism Sro7p, Lgl and Tomosyn share is to physically interact with Q-SNARE proteins, but with different specificities. Sro7 binds to Sec9 (Lehman et al., 1999), which has both Qb and Qc SNARE motifs, whereas Lgl binds to syntaxin 4, a Qa-SNARE (Musch et al., 2002). Tomosyn has an R-SNARE motif at its carboxy terminus that substitutes for synaptobrevin in the neuronal SNARE complex (Hatsuzawa et al., 2003; Pobbati et al., 2004). Sro7 and Lgl lack this R-SNARE motif, although the 40 amino acids at the extreme C terminus of Sro7 are predicted to form an α-helix of unknown function (Pobbati et al., 2004).

3 The Role of Lgl family for cell polarization

3.1 Asymmetric division *versus* epithelia polarity

Lgl family is shown to play a role in asymmetric cell division. For cells undergoing asymmetric division, it is important that the so-called fate determinants be segregated unequally into only one daughter cell, so that they could promote or repress a particular cell fate in one daughter cell but not the other. In *Drosophila*, for instance, a prominent site of asymmetric cell division is the nascent central nervous system, where the neuroblasts divide in a stem cell-like fashion to give rise to one daughter cell destined for differentiation while its sibling cell retains founder cell identity and continues to divide as neuroblasts. The switch between these two fates is achieved through the asymmetry inheritance of fate determinants (Betschinger and Knoblich, 2004). During interphase, the fate determinants are uniformly distributed in cytoplasm. Upon entry of mitosis, they are recruited into a cortical crescent centered over the basal pole of the dividing cell to be inherited by only one daughter cell. When lacking Lgl, fate determinants in embryo neuroblasts fail to be recruited to the basal cortex and are therefore inherited by both daughter cells (Ohshiro et al., 2000; Peng et al., 2000). Recently, a Chinese group reported that Lgl is required in

the follicle cells for the differentiation of both stalk cells and posterior follicle cells (Li et al., 2008). Loss-of-function mutations in *lgl* cause oocyte mispositioning in the younger one of the fused chambers, due to lack of the stalk. Removal of *lgl* function from the posterior follicle cells using the FLP/FRT system results in loss of the oocyte polarity that is elicited by the failure of those posterior cells to differentiate normally. Similar role of Lgl in morphogenesis has also been reported in other model systems. For example, a recent work in zebrafish indicated that the apical membrane maturation and cellular rosette formation both require Lgl during morphogenesis of the zebrafish lateral line (Hava et al., 2009).

Embryogenesis fails when both maternal and zygotic supplies of Lgl protein are eliminated. However, the conserved mutant phenotype of Lgl family proteins revealed that the role of Lgl is far beyond the angle of developmental biology, especially in cell biology. Studies have shown changes to the shape of epithelial cells when lacking Lgl (Manfruelli et al., 1996). Subsequently, it was indicated that morphology defect of epithelial cells comes from a failure to establish epithelial polarity, which means, to segregate the plasma membrane of epithelial cells into complementary apical and basolateral domains. In *lgl* mutant cells, determinants of apical membrane were found to leak into the basolateral domain, together with a fragmentation of adherent junctions, which are positioned at the interface between the two domains in wild type cells (Bilder et al., 2000). Therefore, the cellular function of Lgl in epithelial cells is to confine the apical membrane determinants to the proper side of the cell. Although there has been a lack of the molecular basis of Lgl interaction with Dlg and Scrib, yet it is speculated that Lgl possesses this function in cooperation with Dlg and Scrib.

3.2 Cellular function of Lgl in budding yeast

Asymmetric cell division and polarization of epithelial cells share a common feature that both processes involve the localization of specific proteins to certain subdomains of the membrane. Similarly, cells with mutations in LGL fail to localize these proteins in both cases. These studies indicated that LGL is required in polarized cells. Further studies in the yeast homologues Sro7p and Sro77p have provided interesting clues as to the molecular mechanism of Lgl function in polarity.

Sro7p were first identified as suppressors of rho3 (an Rho family small GTPase gene) mutant in 1998. Sequence analysis revealed that Sro7 belongs to the Lgl family (Kagami et al., 1998). Sro7p and Sro77p are functionally redundant. There is a cold growth defect when both genes are disrupted in budding yeast. Electronic microscopy analysis reveals an accumulation of post-Golgi secretory vesicles in the double knockout cells (Lehman et al., 1999). This vesicle accumulation phenotype exhibited in *sro7 sro77* double deletion is commonly seen in mutants function in the late stages of secretion. Therefore, it was implicated that the Sro7/77 proteins are involved in exocytosis, the post-Golgi secretion process (Lehman et al., 1999). Exocytosis is a basic membrane traffic event mediated by transport, docking, and fusion of secretory vesicles carrying proteins and lipids to the plasma membrane. Through exocytosis, hormones and neurotransmitters can be released. Also through exocytosis, membrane proteins and lipids can be incorporated into specific domains of plasma membrane for cell surface expansion, cell growth, morphogenesis, and cell migration. For secretory vesicles budding from the Golgi to fuse with the plasma membrane, they must be delivered to the periphery of the cell via cytoskeleton. Then they are docked to specific membrane regions, followed by fusion with the plasma membrane by the action of the SNARE proteins (Chen and Scheller, 2001), which are anchored in membranes of both vesicle and plasma membrane.

Over the recent 10 years, there have been three Sro7/77p direct binding partners identified (Brennwald and Rossi, 2007), as shown in Fig. 2. The plasma membrane t-SNARE protein Sec9p was first found directly binding to Sro7/77p, which, together with their requirement in vesicle fusion, indicates that the Sro7/77p are positive regulators of SNARE activity (Lehman et al., 1999). Although no recognizable enzymatic activity is contained in Sro7/77 sequence, Sro7/77 is speculated to either promote the assembly or the stability of SNARE complexes or by directly participating in SNARE activity. The second study reveals that the yeast Lgl proteins Sro7p and Sro77p directly interact with Exo84p, which is a component of the exocyst complex that is essential for targeting vesicles to specific sites of the plasma membrane for exocytosis. This study also demonstrated a molecular pathway from Rab and Rho GTPases through the exocyst and Lgl to SNAREs, and overexpression of Lgl and t-SNARE (Sso1/2) proteins not only improves exocytosis but also rescues polarity defects in exocyst mutants. Therefore, a possible mechanism is speculated that although Lgl is broadly distributed in the cells, its localized interaction with the exocyst and kinetic activation are important for the establishment and reinforcement of cell polarity (Zhang et al., 2005a). In 2006, another study reported that Sro7p is an effector of the secretory Rab GTPase Sec4p. In addition, they demonstrate the formation of a ternary complex of Sec4-GTP, Sro7p, and the t-SNARE Sec9p.

3.3 Cellular function of Lgl in higher eukaryotes

The role of the yeast Sro7/77 proteins in vesicle trafficking indicates a possible molecular basis by which Lgl functions in higher eukaryotes. Both in epithelial polarity and asymmetric cell division, Lgl functions by localizing proteins to the membrane in a polarized fashion. In budding yeast, the membrane of the bud and that of the mother cell are exactly such two distinguished domains.

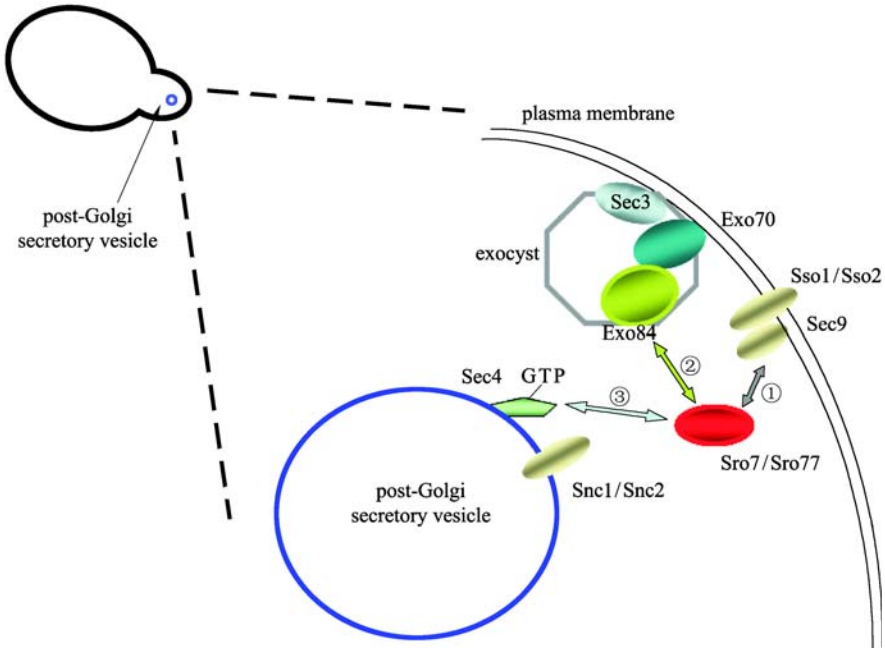

Fig. 2 Possible mechanisms of yeast Lgl function for polarized exocytosis. ①②③ indicate the three direct interactions that Sro7/Sro77, the yeast Lgl proteins, are involved in polarized secretion of post-Golgi secretory vesicles.

Many proteins are confined to the bud and their polarized distribution is dependent on the activity of the secretory apparatus (Jin and Amberg, 2000; Boyd et al., 2004; Zajac et al., 2005). For example, biochemical analysis revealed a pool of the actin cytoskeletal protein Aip3p, which is mostly localized to the bud tip, bound to secretory vesicles. These data imply that the polarized targeting of many proteins is localized by hitchhiking on secretory vesicles as they are delivered to the bud tip (Jin and Amberg, 2000; Zajac et al., 2005). Therefore, it is possible that Lgl functions in the polarized localization of determinant molecules by promoting the targeted fusion of similar carrier vesicles. Consistent with this hypothesis, the *sro7 sro77* null yeast cells indeed exhibit polarity defects, besides secretion defect (Kagami et al., 1998; Gangar et al., 2005). A paradox here is that the Sro7/77 proteins in yeast, as well as Lgl in the neuroblast, are uniformly localized around the cell cortex. How to localize the activity of Lgl is a key question. The interaction between Sro7/77 and Exo84 provides a hypothesis that although Lgl is broadly distributed in the cells, its localized interaction with the exocyst and kinetic activation are important for the establishment and reinforcement of cell polarity (Zhang et al., 2005b). It will be interesting to extend this study to other eukaryotes.

3.3.1 In neuroblasts

As in yeast, localization of Lgl in neuroblasts is mostly around the membrane, and some are also detected in the cytoplasm (Ohshiro et al., 2000). Because Lgl recruits fate determinants to the basal membrane locally, its activity must be restricted to the basal membrane. There are reports showing that Lgl is a substrate for a typical protein kinase C (aPKC) (Betschinger et al., 2003; Yamanaka et al., 2003; Plant et al., 2003), which is part of the Par complex (Wodarz et al., 2000). Localized to the apical cell cortex of neuroblasts, the Par complex initiates an axis of polarity for the recruitment of fate determinants at the opposite side of the cell (Schober et al., 1999; Wodarz, 2002). Phosphorylation of Lgl by aPKC at the apical cortex induces a dissociation of Lgl from the actin cytoskeleton (Betschinger et al., 2005; Tian and Deng, 2008). When a non-phosphorylateable form of Lgl is overexpressed, with the protein not released from the cortex, fate determinants are found mislocalized all around. In the reciprocal experiment, when a dominant active form of aPKC is overexpressed, Lgl fails to be phosphorylated, and fate determinants are all released into the cytoplasm. Therefore, the restricted activity of Lgl to the basal side of the cell is presumably critical for its function in mediating cellular polarization.

These studies in neuroblasts suggested an interesting model of how the activity of Lgl is locally activated: unlike in budding yeast that it is activated where needed, Lgl is repressed in apical region where it is not needed. However, people cannot exclude yet that a positive regulator acts redundantly with the negative regulation by the Par complex to polarize the activity of Lgl.

3.3.2 In epithelial cells

Lgl is reported to be localized to the lateral membrane, the basal of the adherent junctions, and in epithelia of both flies and vertebrates (Bilder et al., 2000; Dollar et al., 2005; Strand et al., 1994; Musch et al., 2002). It turns out that instead of directly recruiting factors in the apical region, Lgl localizes factors to the lateral membrane that repel apical determinants. This is a similar fashion to the Par-1 kinase, which repels the apical determinant Par3 by phosphorylation, followed by removal from the cortex (Benton and Johnston, 2003; Bialucha et al., 2007). However, the cortical recruitment of Par-1 is shown to be independent of Lgl. The current speculation is that Lgl could recruit unidentified factors by a similar mechanism (Wirtz-Peitz and Knoblich, 2006). Characterization of those factors will lead to more discoveries of the mechanism of epithelial polarization. Similar to neuroblasts, the activity of Lgl in epithelial cells is polarized through negative regulation by the Par complex (Grifoni et al., 2007). Again, the contribution of a positive regulator for Lgl cannot be excluded here (Yamanata and Ohno, 2008).

Taken together, these studies revealed the importance of antagonistic interactions between the tumor suppressor LGL and apical polarity regulators such as Crumbs and aPKC. In addition, data from both budding yeast and epithelial cells shed lights on further investigation of the exact molecular basis of the establishment of apical-basal polarity with organized cell-cell junctions and regulation of cell growth in epithelial cells.

3.4 Beyond polarity—the role of Lgl in proliferation control

Like Sro7/77p in yeast, loss of Lgl in mammalian cells does not lead to lethality. But the action of Lgl in cell cycle progression was characterized by some elegant experiments designed to identify the time point of Lgl actions during cell division (Ohshiro et al., 2000; Tanentzapf and Tepass, 2003). Applying a conditional sro7/77 disruption approach, it has been suggested that Sro7/77p in budding yeast preferentially mediate polarized vesicle secretion at early stages of the cell cycle (personal communication). It will be interesting to extend this study in epithelia. Although there is no conclusive answer in higher eukaryotes, yet there is evidence that in both neuroblasts and epithelial cells, Lgl is transiently required during the establishment phase of polarity. This implies that the role of Lgl is not restricted to provide a polarized housekeeping function. Instead, its activity is deployed at strategic time points to localize a set of proteins, which are then maintained by other mechanisms.

4 LGL as a tumor suppressor: tumor formation, progression and metastasis

We have intensively reviewed the role of Lgl proteins in cell polarity and asymmetry division, but as so called tumor suppressors, what is the correlation between their cellular role and tumor inhibition functions? Cell polarity and tissue architecture are intimately linked. In multicellular organisms, the epithelial cells form highly organized tissues specialized not only for protection, but they also achieve secretion and absorption, which require tight regulation of cell polarity and tissue architecture. Disruption of these core processes is a prerequisite feature of epithelial tumors (Roegiers et al., 2009; Feigen and Muthuswamy, 2009). Therefore, proteins controlling cell shape are also responsible for proper localization and assembly of cell–cell junctions and three-dimensional tissue organization. For instance, basolateral junctions are proposed to control epithelial-mesenchymal transition and proliferation crucial for migration and invasion of *Drosophila* ovarian epithelial cells (Zhao et al., 2008). Besides, the extracellular matrix underlying epithelial tissues supports normal tissue architecture and suppresses malignant growth by activation of protective signaling cascades. The polarity pathways could alter the way epithelial cells organize and interact with the tissue microenvironment. Consequently, polarity proteins regulate mammalian cell–cell junctions and cancer pathogenesis. Malfunctions of polarity genes promote aberrant growth and invasion during tumorigenesis.

With emerging evidence from *Drosophila* studies supporting that *lgl* is a tumor suppressor gene with a major function of establishing apical-basal cell polarity (Froldi et al., 2008), studies in cancer biology also reveal direct connection between Lgl and various cancers, especially that the role of Lgl in proliferation control in epithelial tissues is conserved between flies and mammals (PO et al., 2008). In a mouse ocular cancer model, researchers found that both the mislocalization and down-regulation of these proteins may be involved together in ocular carcinogenesis (Vieira et al., 2008). Reduced expression of human homologue of Lgl, Hugl-1, has been reported to be involved in development and progression of human colon cancer, malignant melanoma and endometrial cancer (Tsuruga et al., 2007). To characterize Hugl-1 and to determine the clinical significance of Hugl-1 alterations in hepatocellular carcinoma (HCC), sequence alterations as well as expression of Hugl-1 from 80 HCC specimens and 5 HCC cell lines were analyzed, which revealed that aberrant splicing of Hugl-1 is associated with hepatocellular carcinoma progression (Lu et al., 2009).

In addition, Lgl has been proposed to be a specific biomarker of cell polarity in diagnosis of dysplasia. For example, a recent immunohistochemical study indicated

that another human homologue of Lgl, Lgl2, is lost or aberrantly localized in human gastric dysplasia and adenocarcinoma (Lisovsky et al., 2009). Therefore, Lgl2 may be a potential marker for excluding gastric epithelial dysplasia and adenocarcinoma in diagnostic specimens.

Last but not least, inspired by the more than 30 years of investigation into the Lgl family, more genes have been characterized from *Drosophila* for the integrity of polarized epithelia, in order to address the many remaining questions concerning the full complement and function of the proteins that regulate cell polarity (Froldi et al., 2008). For example, Yurt, Coracle, Neurexin IV and the Na (+), K (+)-ATPase form a novel group of epithelial polarity proteins, complementally to Lgl function (Laprise et al., 2009). The feature of Yrt/Cora group proteins explains the recovery of polarity in embryos lacking the function of the Lgl group of basolateral polarity proteins.

Acknowledgements This work was supported by grants from the National Science Foundation of China (Grant No. 30900720) and Tian Jin Science Foundation (No. 09JCYBJC09000) to Puyue WANG.

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