Review

Apico-basal polarity complex and cancer

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Apico-basal polarity is a cardinal molecular feature of adult eukaryotic epithelial cells and appears to be involved in several key cellular processes including polarized cell migration and maintenance of tissue architecture. Epithelial cell polarity is maintained by three well-conserved polarity complexes, namely, PAR, Crumbs and SCRIB. The location and interaction between the components of these complexes defines distinct structural domains of epithelial cells. Establishment and maintenance of apico-basal polarity is regulated through various conserved cell signalling pathways including TGFβ, Integrin and WNT signalling. Loss of cell polarity is a hallmark for carcinoma, and its underlying molecular mechanism is beginning to emerge from studies on model organisms and cancer cell lines. Moreover, deregulated expression of apico-basal polarity complex components has been reported in human tumours. In this review, we provide an overview of the apico-basal polarity complexes and their regulation, their role in cell migration, and finally their involvement in carcinogenesis.

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1. Importance of polarity in epithelial cells

Cell polarity determines spatial differences in structure, shape and function of the cell. Specific structural polarity in cells includes apico-basal polarity of epithelial cells in adult epithelial tissues, formation of asymmetric cells in early embryonic development, polarity of neurons and polarized cell migration (Martin-Belmonte and Perez-Moreno 2012). Cellular polarity creates morphological and functional asymmetry within an epithelial cell, which is a prerequisite for its function (St Johnston and Ahringer 2010). Structural and functional polarity axis (apico-basal polarity) of epithelial cells is characterized by the presence of two different cell–cell junctions, namely, tight junction (Runkle and Mu 2013) and adherence junction (Ivanov and Naydenov 2013). These two junctions divide the cell and the plasma membrane of epithelial cells into two biochemically and structurally different domains (Sabherwal and Papalopulu 2012). Apical membrane communicates with adjacent cells through tight junctions while baso-lateral membrane comprises structural proteins which give support for the 3D structure of the epithelial tissue (Giepmans and van Ijzendoorn 2009) (figure 1). This asymmetric apico-basal polarity of epithelial cells is regulated through various polarity protein complexes (Shin *et al.* 2006). In addition to apico-basal polarity, epithelial tissue also manifests planar cell polarity, which is a prerequisite for development of various organs during embryonic development (Wallingford 2012). Impairment of planar cell polarity may lead to spina bifidia (Wu *et al.* 2011b) and various congenital heart diseases (Wu *et al.* 2011a). This review, however, will exclusively discuss apico-basal polarity.

Polarity appears to be a fundamental requirement in a wide range of cellular functions. Directional cell migration is an important event during embryonic morphogenesis, tissue repair, regeneration process and carcinoma. The sustained polarity of migrating cells is achieved through regulation of polarity complexes that respond to cues from various chemotactic factors (Ridley *et al.* 2003). A key feature of migrating cell is the presence of transient highly polarized structure in terms of cellular components from the leading to lagging edge. For instance, lamellipodia or filopodia formation at the leading edge requires actin polymerization machinery and interaction of filopodial protein with the extracellular matrix (Ridley *et al.* 2003). Apico-basal polarity is also important for physiological function of epithelial cells: the apical membrane of polarized renal epithelial cell has a more secretory than absorptive role (Sekine *et al.* 2006).

Keywords. Apico-basal polarity; cancer; cell migration; PAR complex

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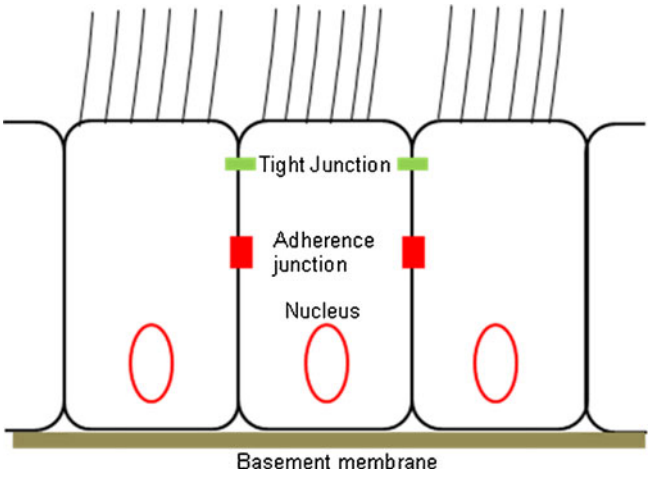

Figure 1. Basic structure of epithelial cells in epithelial tissue

2. Apico-basal polarity complexes

One important molecular determinant of epithelial cell polarity is the polarity complex. Genetic studies on model organism like *Caenorhabditis elegans* and Drosophila in last two decades revealed three major polarity complexes as epithelial cell polarity determinants, namely, (1) 'PAR' (PARtition) complex, (2) SCRIB complex and (3) CRB complex. These polarity complexes are highly conserved from yeast to mammalian cells (Assemat *et al.* 2008).

2.1 *'PAR' complex*

PAR complex is a tri-molecular protein complex localized at the anterior compartment of the cell. The PAR family of proteins was first identified in *C. elegans* during screening of maternal effect lethal mutants for detection of early partition developmental regulated genes (Kemphues *et al.* 1988). These mutants lose apico-basal polarity, which disturbs asymmetric cell division of blastomeres in early gastrulating embryonic cells, leading to the formation of a defective body pattern. Six different mutants were identified and named 'PAR' (for partition) according to their phenotype (PAR1 to PAR6); each may have a different role during early embryonic development (Kemphues *et al.* 1988). PAR1 and PAR4 were shown to have Serine/Threonine kinase activity. PAR1 was demonstrated to be localized to the posterior part of the zygote, while PAR4 exhibited a more uniform distribution. Both PAR1 and PAR4 were shown to be responsible for asymmetric cleavage of zygote to produce daughter cells of different fate (Guo and Kemphues 1996; Watts *et al.* 2000). PAR3 was shown to have asymmetric distribution in zygote and early blastomeres and was suggested to be required for regulating polarity in early embryonic development of *C. elegans* (Etemad-Moghadam *et al.* 1995). Characterization of other *C. elegans* PAR-mutants led to identification of atypical protein kinase C (aPKC) as an interacting partner of PAR3; the two co-localize at the periphery of early blastomeres. *aPKC* mutant studies demonstrated that interaction of PAR3-aPKC was required for asymmetric cell division during early stages of *C. elegans* embryogenesis (Tabuse *et al.* 1998). Three *PAR6* mutants of *C. elegans* exhibited phenotype similar to the *PAR3* mutant (Watts *et al.* 2000). PAR6 co-localization with PAR3 at the anterior periphery of epithelial cells was shown to be dependent upon the activity of PAR3/aPKC complex (Joberty *et al.* 2000). Functional dependence of 'PAR' complex on the small GTPase molecule CDC42 was discovered and a physical interaction of PAR6 with CDC42 was demonstrated in the *C. elegans* embryo (Joberty *et al.* 2000; Gotta *et al.* 2001). Although, this tri-molecular PAR complex was discovered in *C. elegans*, it appears to be conserved from worms to mammals.

Three human homologues of *PAR6* have been identified, namely, *PAR6A* (later renamed as *PAR6α* or *PARD6A*), *PAR6B* (*PAR6β* or *PARD6B*) and *PAR6G* (*PAR6γ* or *PARD6G*) (Noda *et al.* 2001). All three homologues harbour a conserved PDZ domain and a comparatively less conserved CRIB domain (Noda *et al.* 2001). Similarly, two *PAR3* human homologues have been identified, namely, *PAR3A* (or *PAR3α*) and *PAR3B* (or *PAR3β*). *PAR3α* was shown to be involved in tight junction establishment in epithelial cells, but PAR3β lacks aPKC binding domain and is not known to be functionally active at the tight junction (Kohjima *et al.* 2002). PAR3/PAR6/aPKC localization at the tight junction of epithelial cells has been validated (Izumi *et al.* 1998; Lin *et al.* 2000). Interaction of mammalian aPKC with PAR3/PAR6 appears to be an important prerequisite for establishment of cell polarity (Helfrich *et al.* 2007). Taken together, these findings suggest PAR3/aPKC/PAR6 as important components of the polarity complex (Hung and Kemphues 1999; Goldstein and Macara 2007; Assemat *et al.* 2008).

2.2 *SCRIB complex*

SCRIB (a component of SCRIB complex) was first identified in *Drosophila* as a regulator of epithelial cell septate junction. SCRIB was shown to act in combination with lethal giant larvae (LGL) and disc large (DLG) (Bilder *et al.* 2000). SCRIB complex was also shown to have functional interaction with the 'PAR' complex in *Drosophila* as well as in mammals during establishment of polarity in epithelial cells (Benton and St Johnston 2003; Yamanaka *et al.* 2003). SCRIB complex appears to be important for adherence junction integrity and cell–cell contact (Laprise *et al.* 2004) and

may play an important role in the PI3K-mediated regulation of E-cadherin at the adherence junction (Laprise *et al.* 2004).

2.3 *Crumbs (CRB) complex*

The Crumbs complex is a tri-molecular polarity complex conserved from invertebrates to vertebrates. This complex was first identified in *Drosophila* and comprises protein components namely CRB, Sdt and DpatJ/Discs-lost (Bulgakova and Knust 2009). CRB was originally identified in *Drosophila* as a sub-apical localizing factor responsible for formation of normal epithelium and cuticle (Tepass *et al.* 1990; Assemat *et al.* 2008). CRB was shown to be involved in maintenance of zonula adherence junction (equivalent to tight junction of mammalian epthelia) in the apical region of *Drosophila* epithelial cells (Wodarz *et al.* 1995; Klebes and Knust 2000). Stardust (Sdt) was identified as a Crumbs complex component and shown to interact with CRB for maintenance of zonula adherence junction in *Drosophila* epithelial cells (Bachmann *et al.* 2001). Discs-lost was also shown to be a part of the Crumbs complex and appears to be responsible for the establishment and maintenance of embryonic epithelial cell polarity in *Drosophila* (Bhat *et al.* 1999). The CRB mutant exhibited a disorganized epithelium and loss of epithelial cell polarity in *Drosophila* (Tepass *et al.* 1990; Assemat *et al.* 2008). Three human homologues of *Drosophila CRB* (*CRB1*, *CRB2* and *CRB3*) have been identified and characterized as polarity establishment factor in pathological conditions including retinal dystrophy and retinitis pigmentosa (Katoh and Katoh 2004; Richard *et al.* 2006; Chartier *et al.* 2012; Alves *et al.* 2013). Human homologue CRB3 of the Crumbs complex was shown to be involved in regulation of tight junction assembly in the human breast cancer cell line MCF10A (Straight *et al.* 2004). PALS1, human homologue of *Drosophila* Sdt, was identified as an essential component of crumbs complex during establishment of tight junction in human cell lines through interaction with human CRB homologues (Roh *et al.* 2003, 2002; Straight *et al.* 2004). Interestingly, PALS1 was shown to be involved in lymphocyte migration mediated through NFkB (Carvalho *et al.* 2011). PALS1 was also shown to be depleted in retinitis pigmentosa (Park *et al.* 2011). PATJ, the human homologue of DpatJ/Disc-lost, was identified in human epithelial cells and shown to interact with CRB3 and to co-localize at tight junction of CaCo2 cells (Lemmers *et al.* 2002). Tight junction assembly was shown to be affected by depletion of PATJ in MDCK and CaCo2 cells (Adachi *et al.* 2009; Michel *et al.* 2005; Shin *et al.* 2005). PATJ also seems to play a key role in directional migration of MDCK cell mediated through PAR complex (Shin *et al.* 2007).

The three tri-molecular polarity complexes (PAR3/PAR6/aPKC; SCRIB/DLG/LGL; CRB/PALS1/PATJ) appear to be highly conserved through evolution and may play a pivotal role in defining apico-lateral, apical and basolateral domain of epithelial cells. These polarity complexes localize to epithelial cell–cell junctions (tight junction and adherence junction) and provide a central regulatory pathway for the establishment of polarity and epithelial functions (figure 2).

3. Role of 'PAR' complex in cell migration

Cell migration is important in normal physiological conditions (e.g. stem cell migration for renewal of skin and intestinal cell) as well as in various pathological conditions such as invasive carcinoma and metastasis. Cell migration is basically a cyclic process and starts with polarization towards direction of movement in presence of migration-promoting agents. At the leading side of migration, cells form a protrusion either as lamellipodia or filopodia, which helps the migrating cells in binding to extracellular matrix (ECM). Simultaneously, detachment from the lagging side allows the cells to move over the ECM. This protrusive machinery is generated and sustained by the cell cytoskeleton, microtubule organizing centre (MTOC) and Golgi apparatus through a dynamic process of polymerization and depolymerization of actin filaments (Bose and Wrana 2006; Ridley *et al.* 2003). Proteins belonging to the family of small GTPases including RHO, RAC and CDC42 are critical regulators of migration (Charest and Firtel 2007). Activation of CDC42 and RAC are required at the leading edge, where actin and microtubule reorganization takes place for the protrusive activity. In contrast, RHO activity is required more at the rear end, which helps in the induction of actomyosin complex, giving a contractile force for retraction, thus allowing forward movement (Etienne-Manneville 2008).

As discussed in previous sections, polarity complex plays a key role in establishment of epithelial cell polarity. Decades of research has also suggested a fundamental role of these polarity complexes in cell migration. Specifically, interaction of PAR proteins with members of GTPase family suggested their key role during polarization of migrating cells (Aranda *et al.* 2008). The cascade of events regulating cell migration studied in human astrocytes revealed that integrin activation at the leading edge of migrating cell activates and recruits CDC42, PAR6A/aPKC and PAR3 (Joberty *et al.* 2000; Etienne-Manneville and Hall 2001). The activated PAR complex is necessary for activation of downstream targets including the dynein motor protein, required for microtubule and actin polymerization (Etienne-Manneville and Hall 2001; Joberty *et al.* 2000). Further characterization of this cascade led to the discovery of a novel link between PAR complex and WNT signalling. Activated aPKC at the leading edge was shown to phosphorylate glycogen synthase-3β (GSK3β) at the inhibitory site

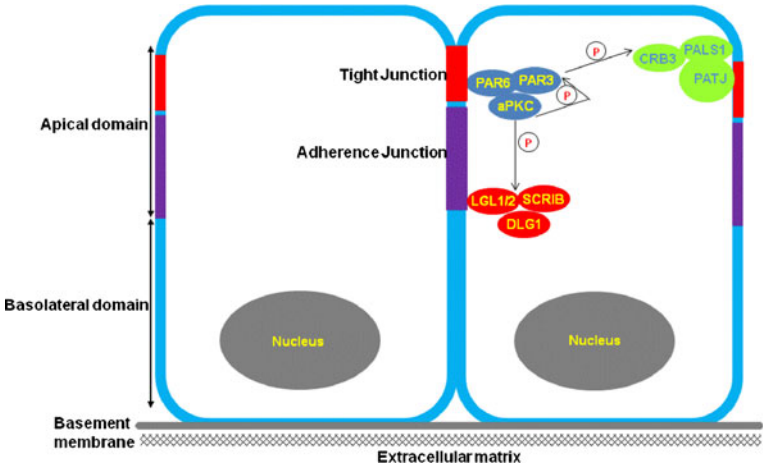

Figure 2. Localization of polarity complex components in a polarized epithelial cell. aPKC of PAR complex phosphorylates and activates PAR3. Activated PAR complex activates CRB3 (Crumbs complex) and LGL1/2 (SCRIB complex). The three activated complexes establish and maintain epithelial cell polarity.

and the inactivated GSK3β was shown to promote clustering of adenomatous polyposis coli (APC) with the plus end of microtubules, thus stabilizing the growing microtubules in migrating cells (Etienne-Manneville and Hall 2003). Also, it has been shown that activated PAR6/aPKC facilitates clustering of the SCRIB complex component DLG1 (a trans-membrane protein). DLG1 clustering facilitates its interaction with APC at the polarized site of migrating cell (Etienne-Manneville *et al.* 2005), ultimately helping in the reorientation of microtubule organizing center (MTOC) towards the leading edge of the migrating cell (Gomes *et al.* 2005).

Activated PAR6/aPKC plays a key role in regulation of RHOA by promoting SMURF1 (an E3 ubiquitin ligase)-mediated degradation of RHOA at the leading end, thus restricting the activity of RHOA to the lagging end, where it induces disorganization of actin cytoskeleton (Wang *et al.* 2003). While PAR6/aPKC complex was shown to regulate leading–lagging polarity and regulate protrusive activity through RHOA degradation mediated by CDC42, PAR3 mediates cell protrusion through interaction with TIAM1 and regulates RAC GTPases activity. Activation of PAR3/TIAM1 (TIAM1 is Rac exchange factor1) complex was demonstrated to be the main event at the leading edge of polarized migrating cells (Chen and Macara 2005; Wang *et al.* 2012). Leading end polarity defects of migrating cells were observed in *TIAM*-knockout cells (Pegtel *et al.* 2007); thus, the 'PAR' complex has emerged as the central cellular machinery for generating leading–lagging polarity axis during cell migration. The process of cell migration, however, is tightly controlled and is regulated by various cellular signalling pathways.

4. Regulation of 'PAR' complex by cellular signalling

As described in previous section, cell migration is a highly regulated cellular mechanism coordinated through polarity complex proteins mainly including the 'PAR' complex. De-regulation of this mechanism leads to various pathological conditions including metastasis. Polarized cell migration requires reorganization of microtubule organizing centre (MTOC) and repositioning of Golgi apparatus between the leading edge and nucleus (Gomes *et al.* 2005). There exist two main signalling pathways that regulate this process mediated by Integrins and TGFβ (Bose and Wrana 2006). Integrins are trans-membrane receptors that bind with extracellular matrix (ECM) (Huttenlocher and Horwitz 2011). Activation of Integrin in focal adhesion complex (protein complex required for cell–ECM adhesion) activates CDC42, which facilitates the activation of aPKC/PAR3/PAR6 complex leading to phosphorylation of inhibitory site of GSK3β, which ultimately blocks phosphorylation of APC. Thus, unphosphorylated APC can bind to growing end of microtubules as described in previous section (figure 3) (Bose and Wrana 2006; Etienne-Manneville and Hall 2001, 2003; Guo and Giancotti 2004).

An important feature of invasive carcinoma cells is the induction of epithelial to mesenchymal transition (EMT) (Nauseef and Henry 2011; Thiery *et al.* 2009). Interestingly, one of the hallmarks of EMT is the loss of polarity, achieved through deregulation of transcription program of polarity related genes (Moreno-Bueno *et al.* 2008). EMT is a complex phenomenon of cellular plasticity and is tightly regulated by various signalling pathways including TGFβ signalling (Xu *et al.* 2009).

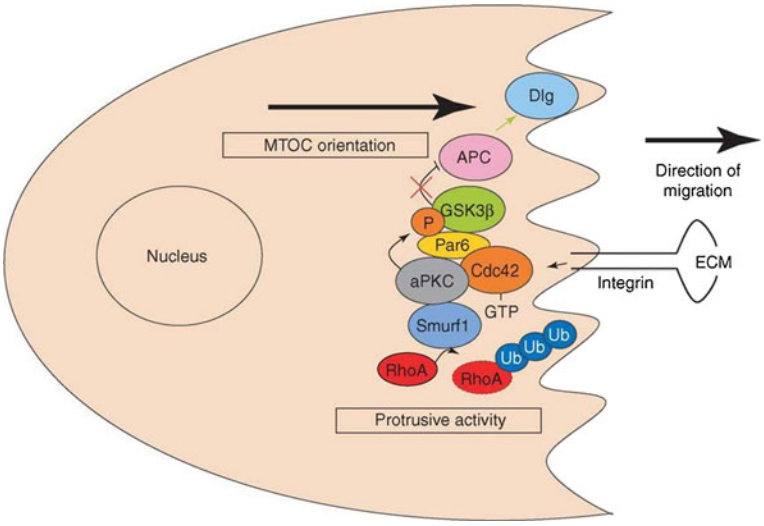

Figure 3. Schematic representation of regulation of cell migration at the leading edge (Bose and Wrana 2006; reproduced with permission from authors and Elsevier publishing group).

Studies have shown that TGFβ signalling may occur through various signalling protein complexes. The canonical pathway acts through SMAD-mediated induction of transcription of mesenchymal-specific genes (Feng and Derynck 2005; Xu *et al.* 2009). In an interesting study, non-canonical TGFβ signalling pathway–mediated EMT regulation was linked to the 'PAR' complex (Bose and Wrana 2006; Ozdamar *et al.* 2005). The study demonstrated that TGFβ activates TβRII; activated TβRII heterodimerizes with TβRI facilitating interaction with PAR6/aPKC, which ultimately recruits and activates E3 ubiquitin ligase SMURF1 to degrade RHOA (Ozdamar *et al.* 2005; Wang *et al.* 2008). As described in the previous section, degradation of RHOA ultimately leads to loss of polarity and induction of EMT (Ozdamar *et al.* 2005, Bose and Wrana 2006). In addition to classical EMT signalling such as Integrin, TGFβ and WNT, small GTPases such as RAS and growth-factor-mediated signalling through PI3K also appears to regulate 'PAR' complex during polarity establishment and cell migration (Etienne-Manneville 2008).

5. Role of apico-basal polarity complex in cancer

Polarity of the epithelium serves as a barrier for tumour formation in epithelial tissue by maintaining tissue organization and 3D architecture. The loss of cell polarity and tissue organization is a hallmark of carcinoma (Royer and Lu 2011). Invasion and metastasis are the major cause of cancer-related morbidity and mortality (Hanahan and Weinberg 2011) and appear to be dependent on EMT. EMT is an important hallmark of carcinoma, where migrating tumour cells recapitulate developmental process of EMT by altering the epithelium structure, disrupting the basal lamina and invading the underlying tissues. Loss of integrity of tight and adherence junctions and loss of polarity are crucial features of EMT. As described in previous sections, cell–cell contact is maintained and regulated by several polarity proteins. These polarity proteins are often targeted by EMT inducers, leading to their altered function, ultimately facilitating cell migration (Martin-Belmonte and Perez-Moreno 2012). EMT-related alterations include overexpression or deregulation of components of polarity complex, mis-localization and deletion or production of altered protein through alternative splicing (Guarino 2007; Etienne-Manneville 2008; Nolan *et al.* 2008). Polarity complexes are emerging as key tumour suppressor complexes in cancer progression. The past two decades of research on polarity complex has provided a wealth of knowledge for a better understanding of advanced stage carcinogenesis. Studies revealed several components of polarity complex (Crumbs, SCRIB and PAR) to be deregulated in carcinogenesis (Rothenberg *et al.* 2010, Martin-Belmonte and Perez-Moreno 2012) (Table 1).

5.1 *Role of SCRIB complex in cancer*

SCRIB complex is well studied with respect to cancer progression. This complex comprises three components (DLG, LGL and SCRIB) first identified in Drosophila and demonstrated to have tumour suppressor function (Gateff 1978; Bilder *et al.* 2000). Neural progenitor cells in Lgl1-knockout mice failed to exit cell division due to loss of polarity and consequent lack of asymmetric division,

Table 1. Alterations of polarity complex proteins in epithelial cell transformation and human cancer

Polarity complex in cancer					
Polarity complex	Component	Alteration	Cancer	Origin	Reference
SCRIB	*SCRIB*	Loss of expression and mis-localization	Cervical cancer	Primary tumour	(Nakagawa *et al.* 2004)
		– do –	Colon cancer	– do –	(Navarro *et al.* 2005)
		– do –	Breast cancer	– do –	(Zhan *et al.* 2008)
	DLG1(Human homologue of *Dlg*)	– do –	Cervical cancer	– do –	(Cavatorta *et al.* 2004)
		Loss of expression	Colon cancer	– do –	(Gardiol *et al.* 2006)
	LGL1 (Human homologue of *Lgl*)	Loss of expression	Colon, breast, ovarian and prostate cancers	– do –	(Schimanski *et al.* 2005; Martin-Belmonte and Perez-Moreno 2012)
		Splice alterations	Hepatocellular carcinoma	Primary tumour and cell line	(Storrs and Silverstein 2007)
	LGL2 (Human homologue of *LGL*)	Loss of expression and mis-localization	Gastric cancer	Primary tumour	
Crumbs	*CRB3*(Human homologue of *CRB*)	Loss of expression	Mouse kidney epithelial cells cells	Mouse model	(Karp *et al.* 2008)
		Mis-localization	Mouse mammary epithelial cells	– do –	(Roh *et al.* 2003)
PAR	$aPKC_{zeta}$	Overexpression	Hepatocellular carcinoma	Primary tumour	(Tsai *et al.* 2000)
		– do –	Bladder, head and neck cancer, breast cancer and PDAC	Primary tumour and cell lines	(Cunliffe *et al.* 2012) (Martin-Belmonte and Perez-Moreno 2012)
	$aPKC_{iota}$	Overexpression and mis-localization	Ovarian cancer, hepatocellular carcinoma, NSLC and PDAC	– do –	(Regala *et al.* 2005;Kojima *et al.* 2008)
	PARD6A	Overexpression	Breast cancer and NSLC	– do –	(Nolan *et al.* 2008)
	PARD6B	Loss of expression	Breast cancer	Primary tumour	(Cunliffe *et al.* 2012)
	PARD3	Deletion and loss of expression	OSCC	– do –	(Zen *et al.* 2009)
		Papilloma formation	Mouse skin cells	Mouse model	(Cavatorta *et al.* 2004)
		Keratoacanthoma formation	– do –	– do –	(Iden *et al.* 2012)

PDAC – pancreatic ductal adenocarcinoma, NSLC – non-small-cell lung carcinoma, OSCC –oesphageal squamous cell carcinoma.

resulting in continuous proliferation, ultimately leading to neonatal death (Klezovitch *et al.* 2004). Mis-localization and reduced expression of SCRIB complex has been observed in the invasive stages of cervical cancer (SCRIB component; Nakagawa *et al.* 2004), colon cancer (SCRIB and DLG components; Gardiol *et al.* 2006), prostate cancer (SCRIB component; Pearson *et al.* 2011) and colorectal cancer (LGL component; Schimanski *et al.* 2005). Loss of expression of SCRIB complex proteins facilitates tumorigenesis in several ways. A correlation of SCRIB loss and elevation of MAPK signalling in the invasive stage of carcinoma has been established in prostate cancer mice model (Pearson *et al.* 2011). SCRIB complex was also demonstrated to be deregulated during c-Myc-mediated tumorigenesis in 3D model of breast cancer (Zhan *et al.* 2008). Studies on a transgenic mouse model of ocular cancer revealed down-regulation of DLG, LGL and SCRIB as a late event in carcinogenesis, indicting their possible role in tumour invasion and metastasis (Vieira *et al.* 2008).

5.2 *Role of crumbs (CRB) complex in cancer*

Human cell line and mouse model studies have shown a potential tumour suppressor role for crumbs complex. Tumorigenic properties such as loss of contact inhibition, loss of apico-basal polarity and disassembly of tight junction in correlation with loss of expression of CRB3 (human homologue of CRB) were identified in a study of CRB3-knockout mouse model (Karp *et al.* 2008). In a breast cancer cell line study, loss of expression of CRB3 along with PALS1 was found to be mediated through ZEB1 and SNAIL (cardinal transcriptional regulators of EMT), suggesting a possible link between classical EMT and polarity regulators (Aigner *et al.* 2007; Whiteman *et al.* 2008). An in vitro human-cell-line-based study revealed PATJ as a target for ubiquitin-mediated degradation through HPV onco protein E6 (Storrs and Silverstein 2007), further suggesting a tumour suppressive role for the Crumbs complex. PALS1 was shown to be important for tight junction maintenance and for providing stability to CRB3 in Crumbs complex through interaction with PATJ (Straight *et al.* 2004). PALS1 has been shown to interact with aPKC, which suggested a link between Crumbs complex and PAR complex in maintenance of tight junction (Straight *et al.* 2004).

5.3 *Functional implication of 'PAR' complex in cancer*

The 'PAR' complex is emerging as both oncogenic as well as tumour suppressive complex in a context-dependent manner during tumorigenesis (Aranda *et al.* 2008). The 'PAR' complex comprises three components, namely, PAR3 (PAR3A and B in mammals), aPKC (aPKClambda, aPKCzeta and aPKCiota in mammals) and PAR6 (PAR6A, B and G in humans). The complex plays a significant role in establishment and maintenance of tight junction in epithelial cells and hence has been shown to be deregulated and targeted during carcinogenesis in several cancers (Aranda *et al.* 2008). Elevated expression and/or mis-localization of aPKC has been observed in non-small-cell lung carcinoma (Regala *et al.* 2005), ovarian carcinoma (Eder *et al.* 2005), hepatocellular carcinoma (Tsai *et al.* 2000), breast carcinoma (Kojima *et al.* 2008) and pancreatic ductal adenocarcinoma (Scotti *et al.* 2010). A study on ovarian carcinoma identified a positive correlation between overexpression of Cyclin E and aPKC, which suggested a possible link between aPKC and cell cycle (Eder *et al.* 2005). PAR3 has been shown to have a possible tumour suppressor function. Significantly reduced expression of PAR3 has been observed in esophageal squamous cell carcinoma (ESCC) and was also shown to have a role in the reestablishment of tight junction in ESCC-derived cell lines (Zen *et al.* 2009). In a study performed on rat epithelial cells, dose-dependent reduction of PAR3 transcript level was identified upon TGFβ (well-established inducer of EMT) treatment and also demonstrated to have positive effect on tight junction assembly (Wang *et al.* 2008).

The human PAR6 family consists of three isoforms, namely, PARD6A, PARD6B and PARD6G, as described above. PAR6 is a central scaffold molecule and interacts directly with PAR3 and CDC42 and activates the formation of tight junction, and its regulatory activity for tight junction assembly is determined by interaction with aPKC (Aranda *et al.* 2008). As mentioned earlier, regulation of tight junction is important to maintain epithelial cell polarity. PAR6 is therefore expected to be deregulated in cancers and targeted by tumour signalling pathways. Par6 was shown to be involved in invasion and metastasis induced by TGF-β in orthotopic mouse models of breast cancer (Viloria-Petit *et al.* 2009). PARD6A overexpression has been detected in breast cancer (Nolan *et al.* 2008; Viloria-Petit *et al.* 2009). Also, PARD6A has been shown to be overexpressed in stromal compartment of non-small-cell lung carcinoma tumour tissues and the elevated expression was well correlated with good prognosis (Al-Saad *et al.* 2008). Moreover, a moderate reduction of PARD6B protein expression was identified in breast tumour tissue and there was a positive correlation between PARD6B protein expression and maintenance of tight junction assembly (Cunliffe *et al.* 2012). Less information is available, however, about expression levels of other isoforms in cancers, and hence the mechanism by which PAR6 isoforms are deregulated is not clearly understood. In a recent study of 3D breast cancer model, ERBB2 (a well-known oncogene in breast cancer) was shown to replace PAR3 in PAR6/PAR3/aPKC complex during in vitro acini formation (Aranda *et al.* 2006). Other studies have suggested a possible oncogenic function for PARD6A (Gunaratne and Di Guglielmo 2013) and possible tumour suppressor function for PARD6B (Cunliffe *et al.* 2012). Interestingly, a localized chromosomal deletion at 18q23 encompassing PARD6G has been observed in several studies including ours (Bashyam *et al.* 2005).

6. Future prospects of apico-basal polarity in cancer research

Studies have revealed an evolutionary conserved mechanism for establishment and maintenance of cell polarity mediated through three conserved polarity protein complexes (PAR6/aPKC/PAR3; CRB/PALS1/PATJ; SCRIB/LGL/DLG). Polarity complex components also appear to be key players in polarized migration of cells. Conserved signalling mechanisms such as TGFβ and Integrin signalling regulate the formation and maintenance of polarity of epithelial cells. Dissolution of tight junction and loss of polarity are a predisposing factor for carcinogenesis. Given the importance of involvement of polarity complex in cell migration and

maintenance of epithelial cell polarity, research in polarity complex regulation during carcinogenesis will be an important step to identify novel and efficient therapeutic targets for cancer treatment. However, restoring lost function of tumour suppressor components in tumours is complex and difficult and will involve evaluation of various approaches.

One hallmark of stem cell (embryonic as well as adult) maintenance is asymmetric cell division; however, the link between cell polarity and asymmetric cell division is largely unexplored. For example, the orientation of mitotic spindle is expected to be different during asymmetric cell division when compared to normal symmetric division of epithelial cells, a phenomenon being explored recently (Bergstralh *et al.* 2013). Transcriptional regulation of establishment of cell polarity in one of the two daughter cells that arise from asymmetric cell division of a stem cell is another area that needs to be studied. The development of mammalian brain is known to be a complex process and polarity complex proteins are expected to be important regulators of growth and differentiation of neuronal and dendritic processes. Several epithelial tumours arising in the brain may also involve deregulation of polarity complex components.

Establishment and maintenance of apico-basal polarity complex is a hallmark of epithelial cells and appears to largely act as a tumour suppressor complex. Despite seminal advances in our understanding of epithelial cell polarity and its importance in carcinogenesis, several important facets remain unanswered. Studies involving knockout animal models for individual polarity complex components as well as mouse models for specific cancers are expected to further our understanding of their pivotal role in tumour suppression.

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