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Review

Apicobasal polarity and its role in cancer progression

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Abstract

Appropriate establishment and maintenance of cell polarity is essential for normal development and homeostasis. The vast majority of human cancers originate from epithelial tissues and tumour cell invasion and metastasis are the major cause of mortality in human cancers. Invading cells demonstrate loss of cell polarity, loss of epithelial cell-cell adhesions and tissue disorganisation. We examine the growing evidence linking loss of apicobasal polarity with tumour progression.

Keywords: cancer; epigenetics; epithelial cell polarity; invasion; metastasis.

Introduction

Polarity is a feature possessed by the majority of eukaryotic tissues, which involves a coordinated asymmetric distribution of molecules and organelles within the cells of a tissue (1, 2). This fundamental feature is needed for many essential cellular processes, including asymmetric cell division, cell morphogenesis, cell migration in embryogenesis, the correct transmission of nerve impulses along an axon, the chemotaxis of immune cells and the directional transport of molecules across an epithelial sheet (3).

Although this review will focus specifically on the apicobasal (AB) arrangement in epithelia, we must also acknowledge the presence of other types of polarity, namely planar cell polarity (PCP), which is found perpendicular to the AB axis in epithelial cells, and front-rear (FR) or anterior-posterior (AP) polarity, which is found in migratory cells, neurones and cells undergoing asymmetric division (see Figure 1).

AB polarity is primarily found in epithelial sheets. *In vivo*, these cells arrange into multi- or mono-layered sheets that act as barriers between body compartments. The apical surface commonly faces an organ lumen or the external environment, whereas the basolateral surface interacts with other cells or the extra-cellular matrix (ECM) (4). These cells then traffic the passage of molecules between the two compartments along their AB axis (5).

FR polarity plays a major role in mesenchymal cells, such as fibroblasts and lymphocytes, where it is essential for correct migration. At the leading edge, which is located at the front of the cell, the small RhoGTPases Cdc42 and Rac are activated, resulting in actin polymerisation, which allows the cell to extend forward. In contrast, at the rear of the cell (the uropod) RhoA is activated, causing the contraction of actomyosin fibres. Together, the leading edge and the uropod permit cell movement (6).

Epithelial to mesenchymal transition (EMT) allows for normal tissue remodelling during development (7). Cells undergoing EMT lose epithelial characteristics (such as epithelial cell-cell adhesions and apicobasal polarity) and instead adopt mesenchymal characteristics (such as weak cell-stroma adhesions and front-rear polarity, promoting cell migration). Importantly, the same molecular machinery that is required to create this tissue plasticity appears to be co-opted in invasive carcinoma and is implicated as a key process in cancer progression.

It is important to note that the term 'cell polarity' does not only apply to the organisation of cytoplasmic components, but includes the organisation of cell membrane constituents and protrusions (8, 9). For example, in epithelia the plasma membrane is polarised into distinct apical, lateral and basal domains, each of which have their own defining features (Figure 2). The apical membrane can be characterised by specialisations such as microvilli (10) and the localisation of the Par and Crumbs polarity complexes (3). The margin between the apical and lateral membrane domains is defined by the presence of an adhesive belt, termed the zonula adherens (ZA) (1). The basal and lateral membranes both contain the Scribble polarity protein complex (3), and are distinguished from one another in that the lateral membrane contains adhesive contacts with neighbouring cells, while the basal membrane is in contact with the underlying extra cellular matrix (11). Cell-cell interactions are mediated by adhesion complexes such as E-cadherin-catenin and Nectin-Afadin, while cell-matrix interactions are mediated by proteins such as integrins and dystroglycans (12–14).

Establishment and maintenance of the polarised epithelial phenotype

It is well documented that the establishment of AB polarity in epithelial cells requires the formation of cell-cell and cell-ECM interactions. For example, non-polarised, suspended Madin-Darby canine kidney (MDCK) cells with a random distribution of apical and basal proteins throughout the membrane, can acquire a polarised phenotype through cell-cell contact. This contact triggers the correct segregation of apical and basal proteins to their corresponding domains, as well as the localisation of the tight junction protein, zonula occludens-1 (ZO-1), at the site of cell-cell contact. Furthermore, the

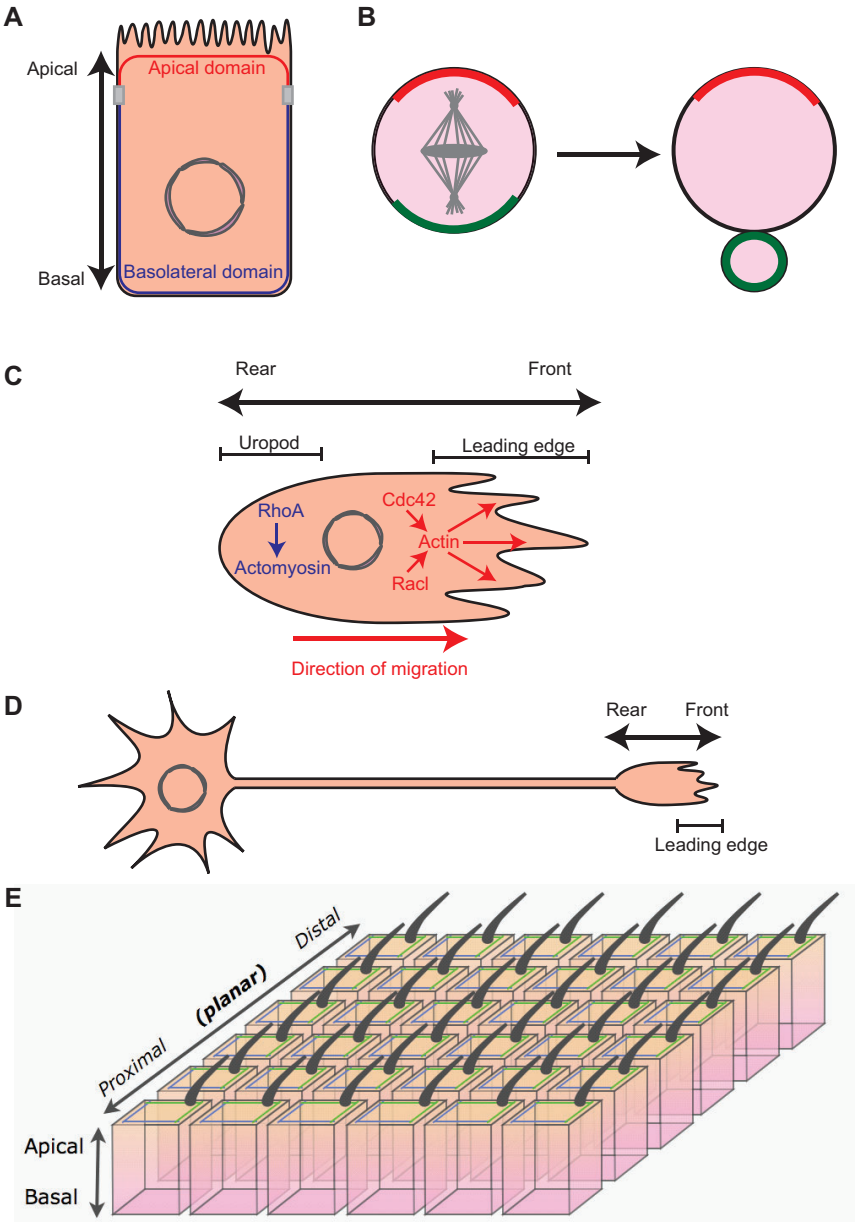

Figure 1 Polarity in different cell types.
(A) Apicobasal polarity is found in epithelia. (B) Apicobasal polarity is also observed in asymmetrically dividing neuroblasts in *Drosophila*. Here, the apically localised Par complex directs the orientation of the mitotic spindle and the basal localisation of cell fate determinants. After mitosis, these cell fate determinants prevent self-renewal and promote differentiation in the daughter cell, while the neuroblast is able to resume cell division. (C,D) Front-rear polarity is found in migrating cells (C) and in the growth cones of developing neurones (D). (E) Planar cell polarity (PCP) provides polarity signals within the plane of the epithelium. It is commonly found in both vertebrate and invertebrate epithelia. For example, PCP is responsible for the correct orientation of bristles and hairs in *Drosophila*, and for the uniform orientation of sensory hair cells in the mammalian auditory sensory organ. Different polarity determinants accumulate at the distal and proximal regions of the cell, thereby providing the positional information required to correctly place the hair.

localisation of ZO-1 can only occur if the cell is also in contact with a substratum, such as the ECM (15).

These cell-cell and cell-substratum interactions provide the spatial information required to redistribute cell surface and cytoplasmic proteins (including polarity proteins and the cytoskeletal networks), allowing them to be re-distributed from a random homogeneous distribution, into a specific and polarised arrangement along the AB axis (16).

The major junctional complexes within epithelial sheets include tight junctions (TJs) and adherens junctions (AJs). TJs form a paracellular diffusion barrier for solutes whereas AJs provide mechanically strong adhesive links between cells and also help define a cell's apicobasal axis within the epithelial sheet. AJs can also form polarised cortical domains in the plane of the epithelium, thereby establishing PCP. The core AJ complex of E-cadherin, α-, β- and p120-catenin is

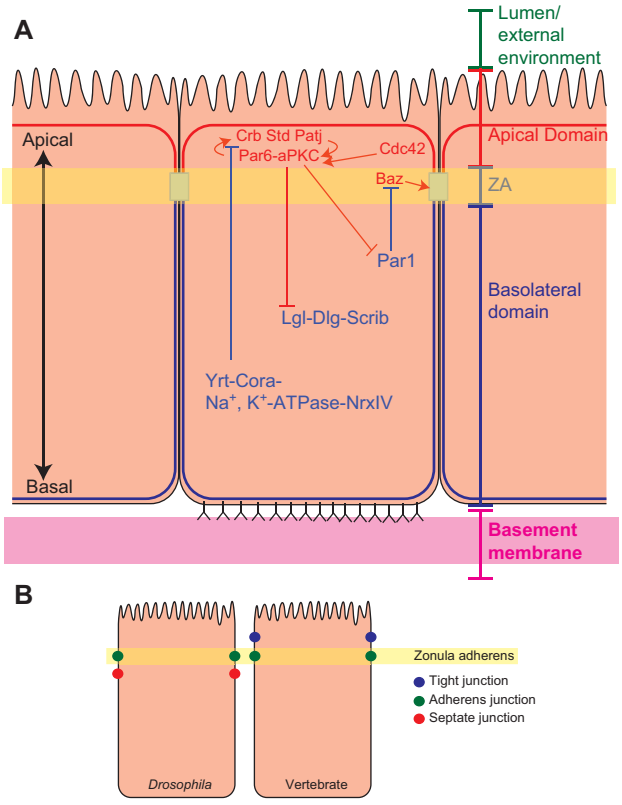

Figure 2 Arrangement of apicobasal polarity proteins and junctions in epithelia.
(A) Apical polarity proteins are highlighted in red; basolateral proteins in blue. The zonula adherens (ZA) separates the apical and basolateral domains and provides an adhesive belt that maintains epithelial integrity. The apical and basolateral polarity proteins act antagonistically to one another, creating zones of mutual exclusion around the ZA, thereby establishing the apicobasal axis of the cell. (B) Epithelial junction organisation in *Drosophila* and vertebrates. The formation of the adherens junction promotes the assembly of the septate junction in *Drosophila* and the tight junction in vertebrates, which differ in terms of their protein composition and their apicobasal positioning, but they both function to provide a paracellular diffusion barrier to the epithelium.

intimately associated with both the actin and microtubule cytoskeletons (Figure 3) and also binds many other proteins, including signalling molecules, providing a hub for protein-protein interactions.

The above junctional complexes are also associated with core polarity protein complex members, which are required to establish and maintain apicobasal polarity. Junctional and polarity complexes are mutually dependant on one another: the positioning, formation and maturation of junctions requires many of these core polarity proteins; conversely apicobasal polarity and the correct positioning of polarity complexes cannot be established without intercellular junctions (12).

Polarity proteins have long been thought of as being organised into several functional modules that were initially discovered in genetic screens in *Caenorhabditis elegans* and *Drosophila melanogaster* (5, 13, 17). Until recently it was thought that three functional modules were required to establish apicobasal polarity (3), however recent work has identified novel polarity modules, as discussed below.

It has long been established in a wide variety of organisms that two highly conserved apical polarity modules localise to and are required to define the apical domain in epithelial cells: namely the Par and Crumbs complexes. Conversely the Scribble complex, together with the kinase Par1, localises to and is restricted to the basolateral domain of the cell. These differentially localised functional modules act antagonistically, creating zones of mutual exclusion around the AJ, thereby establishing the apicobasal axis of the cell.

The Scribble complex localises to the basolateral domain, and consists of Scribble (Scrib), Discs Large (Dlg) and Lethal Giant Larvae (Lgl) (3). Mutations in any of these three genes leads to loss of polarity, disorganisation of the epithelial monolayer, and the formation of neoplastic overgrowths, hence their classification as tumour suppressor genes (18).

The Crumbs complex works antagonistically to the Scribble complex via mechanisms of mutual inhibition, which keeps the localisation of the Crumbs complex in the apical domain, and the localisation of the Scribble complex in the basolateral domain (Figure 2), thus aiding in the establishment and maintenance of apicobasal polarity. This complex consists of the proteins: Crumbs (Crb), PALS1 [whose *Drosophila* homologue is called Stardust (Std)], and PATJ (whose *Drosophila* homologue is Discs Lost) (3).

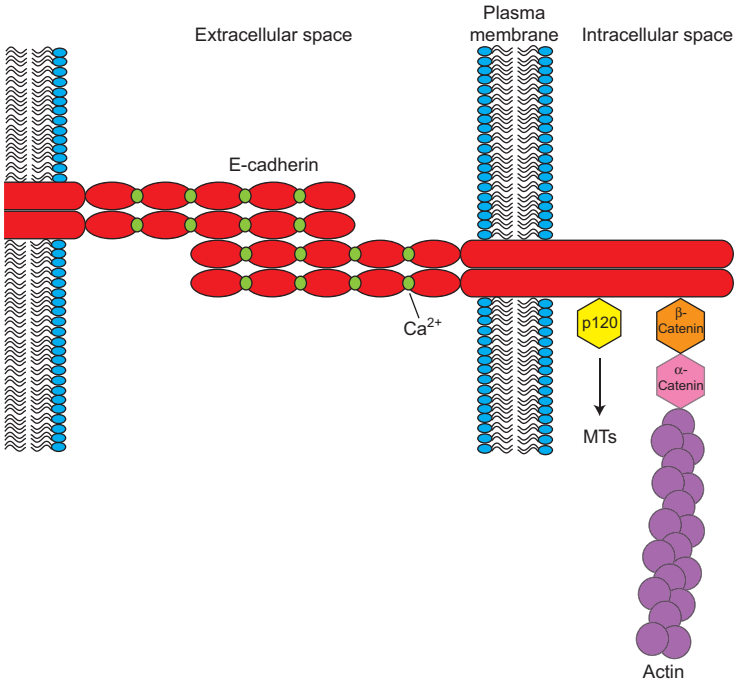

Figure 3 The cadherin-catenin complex.
The cadherin-catenin complex forms the core of the adherens junction. It provides a landmark for the organisation of apicobasal polarity and is a hub for several protein-protein interactions. E-cadherin can dimerise and forms trans-homophilic interactions, forming E-cadherin clusters, thereby providing mechanically strong adhesive links between epithelial cells. Ca^{+} ions are required to stiffen the E-cadherin extracellular domain and are essential for these homophilic interactions. The E-cadherin intracellular domain contains binding sites for both p120 and β-catenin. These catenins connect the adherens junction to the microtubule (MT) and actin cytoskeletons.

The Par complex consists of the scaffolding protein Par-3 [the *Drosophila* homologue is called Bazooka (Baz)], Par-6 and atypical protein kinase C (aPKC) (3). In *Drosophila*, polarity establishment in the first epithelium is known as cellularisation (19) and during this process aPKC and Par6 recruitment to the apical cortex requires Baz and AJs (20). The correct apical localisation of Par6 and aPKC is also known to require the small GTPase Cdc42 (21, 22). However, in somatic clones in a mature epithelium, which possesses an established apicobasal polarity, Par6 and aPKC localisation at the apical cortex is no longer dependant on Baz or even AJs, but is still dependant on Cdc42 function (22). This highlights underlying differences between polarity establishment and its maintenance.

In epithelial cells there is increasing evidence to suggest that Par-3/Baz localises separately from Par-6 and aPKC, which co-localise in the apical domain (23). In epithelia Par-3/Baz is restricted to the apicolateral junction, at the level of the AJs in flies and the tight junctions in vertebrates (20, 24) (Figure 2). This suggests that the Par complex should be viewed less as a physical assembly of its constituent proteins, and more as a transient 'interaction' when in epithelia. In fact, it is now no longer considered feasible to separate apical polarity proteins into distinct Par and Crumbs complexes, as both Par6 and aPKC can interact with the Crumbs complex components PALS1/Std and Crb, both in mammals and *Drosophila* (25–29). Additionally, Crb activity in epithelia requires phosphorylation by aPKC (30). It has also recently been shown in *Drosophila* that Baz binds Std, which is essential for the correct apical recruitment of Std during polarity establishment (31).

The localisation of Baz is very tightly regulated, which is not surprising given its prominent role in promoting apical identity and cell-cell junction formation. Baz segregates from the other two members of the Par complex as it is excluded from the apical domain through one of two mechanisms (Figure 2). The first involves phosphorylation of Baz on serine 980 (S980). The kinase responsible for this phosphorylation is none other than aPKC itself, which binds and phosphorylates Baz, weakening the interaction between the two molecules. Additionally, Baz is prevented from binding to the PDZ domain of Par6 by out-competition, mediated by Crb (23). It has been shown that when overexpressing a Par6-Baz direct fusion transgene, thereby preventing Par6 and Baz dissociation, polarity is disrupted and phenotypes resemble those of a *Drosophila crumbs* mutant (23).

The correct localisation of Bazooka also involves the exclusion of the protein from the basolateral domain. This is achieved via the action of the Scribble complex, which is believed to be involved in the regulation of Par-1, the protein responsible for the phosphorylation of Baz at either S151 or S1085 (32), resulting in its displacement from the membrane within the basolateral domain (33). Therefore Baz localisation is inhibited both apically and basally, restricting its cortical

localisation to the apicolateral border, where it can recruit E-cadherin and β-catenin to the AJ in flies (25) or promote tight junction formation in mammalian epithelia (34).

It is worth noting that in different cell types, such as in the *Drosophila* female germline and in neuroblasts, Baz localises apically, together with aPKC and Par6. Importantly, the Crumbs complex is absent in these cell types, highlighting the important role Crumbs plays in restricting Par-3/Baz localisation in epithelia (35).

In recent years, novel polarity proteins have been identified, and include liver kinase B1 (LKB1) and AMP-activated protein kinase (AMPK), which are required to maintain apicobasal polarity under conditions of energetic stress, resulting in lower cellular ATP levels (36). Additionally, the Yurt/Coracle group (consisting of Yurt, Coracle, the Na^+, K^+-ATPase and Neurexin IV) has been identified in flies (37). This polarity module is functionally similar to the Scribble complex in that it inhibits expansion of the apical domain, in this case via a direct inhibition of Crb, and can recover polarity in fly embryos that are *lgl* mutant (37, 38).

It is important to stress the dynamic nature of polarity signalling, even in relatively stable tissues. For example, cell-cell contacts are constantly being turned over and remodelled, giving an inherent plasticity not only to cell-cell junctions, but to the epithelium as a whole. This plasticity maintains epithelial integrity both in stable epithelia, during processes such as cell division and cell death, and in remodelling epithelia, during complex morphogenetic processes such as cell intercalation (12). Polarity proteins, junctional proteins and cytoskeletal networks are all capable of rapid turnover, highlighting the need to maintain apicobasal polarity through the tight regulation of interdependent polarity signalling pathways.

Polarity genes and cancer progression

The majority of malignant human cancers originate from epithelial tissues that have undergone loss of cellular organisation and tissue invasion. Martin and Jiang (2001) described a correlation between tumour metastasis and a reduction in tight junction integrity (39). Additionally, loss of E-cadherin has been shown to be associated with the metastatic phenotype (40). Both the deregulation of Scribble complex proteins and a loss of cell polarity have been implicated in several types of invasive cancers (41–46). Therefore disruptions to cell-cell adhesion and apicobasal polarity within the epithelium have both been implicated in tumour progression. The core components of the polarity complexes and their interaction partners that have been implicated in human cancers are summarised in Table 1.

There have been several examples in the fly of neoplastic tumour formation resulting from germ-line mutations in individual constituent proteins of the Scribble complex: Scrib, Dlg or Lgl (20, 47). For example, Lgl was first identified in the fly as a tumour suppressor, as when mutated it leads to the formation of neoplastic overgrowths in tissues from *Drosophila* larvae (48). However, work using somatic mutations in *Drosophila* imaginal discs showed that clones mutant for *lgl*, *scrib* or *dlg* are unable become neoplastic in eye imaginal discs and mutant cells are in fact removed from the tissue through cell competition. Mutant cells are eliminated from the tissue through JNK-mediated apoptosis and competition from nearby stromal cells. These mutant clones require cooperating oncogenes in order to develop neoplasia. Additional cooperating oncogenic mutations such as activated *Ras* or *Notch* produce mutant cells that are viable and invasive (49–52).

This work indicates a compensatory effect and multiple-hit model for tumourigenesis that parallels the mammalian system. Importantly, although apical polarity proteins do not cause overgrowth and are not known as tumour suppressors, they have also been shown to be susceptible to neoplastic transformation by activated Ras signalling (49). This suggests that a loss of polarity is key to neoplastic tumour behaviour. However, these experiments also suggest that, although a loss of polarity may be an early event in tumour progression, it is unlikely to be a tumour-initiating event.

Viral oncoproteins and core polarity complex proteins

Several core components of the cell polarity complexes have been implicated in cancer through their interactions with two viral oncoproteins: adenovirus E4-ORF and human papillomavirus (HPV) E6.

Both oncoproteins contain a PDZ domain motif which mediates the interactions with the PDZ domains of cell polarity proteins and induces their degradation through the proteosome pathway; in particular adenovirus E4-ORF targets the degradation of Dlg1, PATJ and Scribble (53), and the HPV E6 oncoprotein targets the degradation of Scribble (53, 54) and Dlg (55). Scrib and Dlg1 bind to human T cell leukaemia virus-1 (HTLV-1) TAX protein via their PDZ domains. This interaction leads to the mislocalisation of Scribble; it also prevents the formation of the Dlg-APC complex in HTLV-1 infected T cells (56, 57) and prevents Dlg-induced cell cycle arrest (57).

Lee et al. demonstrated that E4-ORF1 aberrantly sequesters MUPP1 (a structural paralogue of PATJ) to the cytoplasm, which is targeted for degradation by HPV-18 E6 (58). Mutant viral oncoproteins were unable to bind MUPP1 suggesting that cell proliferation and transformation by viral proteins required inactivation of MUPP1 (58). Finally PATJ was identified as a degradation target of both type 16 and type 18 E6 (59). These studies show that degradation of cell polarity proteins by viral oncoproteins allows disruption of apical-basal polarity and promotion of tumour progression.

Interactions between polarity proteins and the Hippo pathway

The Hippo pathway, originally identified and delineated in *Drosophila*, is an important regulator of cell proliferation and survival. By regulating the transcriptional activator

Table 1 Polarity complex core proteins.

Polarity complex	Proteins in *Drosophila*	Proteins in mammals	Notes	Examples in human cancer	Epigenetic alterations in cancer	Response to decitabine treatment
Partitioning defective (PAR) complex						
Par core components	Partitioning defective -6 (Par6)	PAR6A/C PAR6B PARD/G	Scaffold protein interacts with Cdc42	– PAR6B overexpression in breast cancer cell lines (105) – PAR6 activation correlates with *BRCA1*-associated tumours (106) – PAR6G deletions in lung and adrenal tumours (103)	Unknown	Unknown
	Bazooka (Baz)	PAR3A PAR3B	Scaffold protein interacts with ASPP2 and PTEN	– Reduced in primary oesophageal squamous cell carcinoma cells (15%) and tumours (107) – Deletions in glioblastomas (5%) and head and neck squamous cell carcinoma (9%) (103) – PAR3B deletions in lung and bladder tumours (103)	Unknown	Unknown
	Atypical kinase C (aPKC)	aPKCλ/ι aPKCζ	– Oncogene with kinase activity – Located in sub-apical region	– Over expressed in cancers of the lung (109), pancreas (110), stomach (111), colon (108), oesophagus (119), liver (113), bile duct (114), breast (115), ovarian (120), prostate (112) and brain (121) – Interacts with Par6 to drive cell proliferation in breast cancer cell lines (105)	Unknown	Unknown
PAR complex related proteins	Cdc42	Cdc42	Interacts with Par6	– Interacts with Par6 to drive cell proliferation in breast cancer cell lines (105) – Overexpressed in 61.5% NSCLC (122), 60% colorectal adenocarcinoma (123), melanoma (124), breast cancer (125) and testicular cancer (126)	Cdc42 induces hypermethylation of *ID4* promoter (tumour suppressor gene) (123)	Unknown
	Ankyrin-repeat, SH3-domain and proline-rich-region containing protein (ASPP)	ASPP1 ASPP2	– ASPP2 interacts with Par3 – Transcriptional target of E2F and regulates p53	– Reduced in endometrial endometrioid adenocarcinoma (127) – ASPP1 and ASPP2 reduced in cancer cell lines (68) – ASPP2 mutations in colon cancer (128)	*ASPP1* and *ASPP2* hypermethylation in tumour cell lines with wild-type p53 (68)	Unknown
	Pten	PTEN	Tumour suppressor gene interacts with PAR3	Mutated in 31% glioblastoma cell lines, 100% prostate cancer cell lines, 6% breast cancer cell lines and 17% primary glioblastomas (129)	*PTEN* hypermethylation in gastric cancer (69) and non-small lung cancer (70)	Increased *PTEN* mRNA expression in NSCLC cell lines (70)
	Par4/LKB1	Liver kinase B1, serine threonine kinase 11 (LKB1)	Interacts with PAR1	Inactivated in several sporadic pulmonary, pancreatic and biliary cancers and melanomas (130, 131)	*LKB1* hypermethylation in sporadic colorectal cancer (132)	Unknown

Table 1 (Continued)

Polarity complex	Proteins in *Drosophila*	Proteins in mammals	Notes	Examples in human cancer	Epigenetic alterations in cancer	Response to decitabine treatment
Crumbs (CRB) complex						
CRB core components	Crumbs (Crb)	CRB1 CRB2 CRB3	Located at apical membrane and border between epithelial cells	CRB3 deficiency in immortal baby mouse kidney epithelial cells (116)	Unknown	Unknown
	Stardust (Sdt)	PALS1	Scaffold protein located in cytoplasm Interacts with Lin-7c	Unknown	Unknown	Unknown
	PatJ	PATJ MPDZ/MUPP1	Scaffold protein with multiple PDZ domains – located in cytoplasm	– Large deletions in sarcoma and lymphoma tumours (103) – Degradation target of adenovirus E4-ORF and human papillomavirus E6 (53, 58, 59)	Unknown	Unknown
CRB complex related proteins		Lin-7c	Interacts with PALS1	Lin-7c down-regulation in oral squamous cell carcinoma (72)	*Lin-7c* hypermethylation in oral squamous cell carcinoma (72)	Unknown
Scribble (SCRB) complex						
SCRB core components	Scribble (Scrib)	SCRB	– Neoplastic tumour suppressor gene – Located at basolateral membrane, septate junctions	– Down-regulated in cervical cancer (44), breast cancer (42), colon cancer (95) and lobular carcinomas (43) – Overexpressed in tumours of the colon, bladder, ovary, prostate and uterus (96) – Interacts with TAX in HLTV1 infected T cells (56) – Targeted degradation by adenovirus E4-ORF and HPV E6 (53, 54)	Unknown	Unknown
	Lethal giant larvae (Lgl)	LLGL1 LLGL2	– Neoplastic tumour suppressor gene – Located along lateral membrane	– Reduced or absent in 76% breast cancers, 63% lung cancers, 53% prostate cancers, 50% ovarian cancers and 40% melanomas (97) – Aberrant splice variants in 20–35% hepatocellular carcinoma (99)	Unknown	Unknown
	Discs large (Dlg)	DLG1 DLG2 DLG3 DLG4	– Neoplastic tumour suppressor gene – Located in basolateral domain, septate junctions – Interacts with APC and TAX proteins	– Deletions in lung and cervix tumours (103) – Down-regulated in cervical (41), ovarian (100), gastric (101) and colon cancer (95) – Somatic mutations in mammary ductal carcinoma (45) – Interacts with TAX in HLTV1 infected T cells (57) – Targeted degradation by HPV E6 oncoprotein (55)	Unknown	Unknown
SCRB complex related proteins	Adenomatous polyposis coli (Apc)	APC	Interacts with DLG (104)	– Mutated in colon cancer – Reduced in prostate cancer (71)	*APC* hypermethylation in prostate cancer (71)	Unknown
	Shotgun (Shg)	E-cadherin (CDH1)	– Required for EMT – Interacts with SCRIB	Reduced in prostate cancer (71)	*CDH1* hypermethylation in prostate cancer (71)	Unknown

Yorkie (YAP and TAZ in mammals) the pathway regulates the expression of pro-growth and anti-apoptotic proteins, such as *Myc*, *Inhibitor of Apoptosis 2* (*IAP2*) and *CyclinE* (*CycE*) [for a detailed recent review see (60)]. The Hippo pathway is composed of cell surface upstream regulators, including cell adhesion molecules (Fat and Daschous) and cytoskeleton-binding proteins (Expanded, Merlin); a kinase cascade with two serine-threonine kinases (Hippo and Warts) with regulators (Mats) and adaptors (Salvador); and downstream targets – a transcriptional activator (Yorkie) and its DNA binding partner (Scalloped) (61). This pathway has now been found to be highly conserved in humans [see Figure 4 and (60)].

Several members of the three polarity complexes described previously have been identified as regulators of the Hippo pathway. These interactions are depicted in Figure 4 and components of the Hippo pathway implicated in cancer are described in Table 2. Crumbs has been identified as an upstream regulator of the Hippo pathway as it directly binds to expanded. Perturbation of Crb through depletion, mutation of its FERM-binding site, or overexpression results in a mislocalisation of expanded away from the apical cortex into the basolateral domain, which is likely to deregulate the pathway (62, 63). Overexpression of wild-type Crb causes tissue overgrowth and inactivates the Hippo pathway by targeting expanded for phosphorylation-dependent degradation (62, 64).

Additionally, depletion of Lgl or an overexpression of aPKC results in a co-mislocalisation of Hippo and Ras-associated domain family protein (RASSF) to a basolateral cortical region. RASSF competes with Salvador for Hippo binding and inhibits Hippo activation. When Hippo is inactive, the transcriptional activator Yorkie fails to be phosphorylated, resulting in the upregulation of Hippo pathway target genes (63). The mislocalisation of Hippo can be rescued by the inhibition of aPKC activity in *lgl* mutant cells (63).

Scribble was also found to regulate the interaction of TAZ with the core kinases LATS and MST (human homologues of Yorkie, Warts and Hippo, respectively) in the Hippo pathway of breast cancer cells (65). Scrib mutants showed aPKC-dependant defects in the Hippo pathway of *Drosophila* eye discs, whilst aPKC signalling was sufficient to impair the Hippo pathway independently from JNK activity (66). *Scrib* mutants also demonstrated an upregulation of the Yki target gene *cycE* in imaginal discs of *Drosophila* (50). These studies, highlighting polarity protein – Hippo pathway interactions, provide a direct link between loss of polarity, hyperproliferation and evasion of cell death.

Epigenetic regulation of polarity complex interacting proteins and cancer

Aside from somatic mutations, namely amplifications and deletions, epigenetic modifications in the form of DNA methylation (specifically in promoter regions) and alterations to histone modifications (acetylation, phosphorylation, methylation or ubiquitination of histone tails) can severely alter the transcription of crucial genes required to prevent cancer initiation or cancer progression. DNA methyltransferase (DNMT) enzymes add methyl groups, often to position 5 of cytosine residues found in CpG dinucleotides of vertebrates (67). Changes in DNA methylation in the promoter region can either promote or inhibit gene expression. Examples of promoter hypermethylation are demonstrated in a variety of cancers, specifically for genes which interact with core components of the cell polarity complexes (Tables 1 and 2).

Promoter hypermethylation is a hallmark of silencing gene expression, especially when found alongside inactive histone modifications. Despite the absence of evidence for the epigenetic regulation of core polarity complex proteins, several of their interaction partners show epigenetic alterations in a wide range of cancer types. For example, the down-regulated genes *ASPP2* (68), *PTEN* (69, 70), *APC* (71) and *Lin-7c* (72) display promoter hypermethylation in cancer samples; the protein products of these genes interact with PAR3 (ASPP2 and PTEN), DLG and PALS1, respectively, in normal cells. E-cadherin is also hypermethylated in prostate cancer (71). Numerous members of the Hippo pathway have shown altered epigenetic states in cancers including *MST1* (73), *MST2* (73), LATS1 and LATS2 (73–75), *RASSF1A* (71, 76–78), *RASSF2* (79–83), *RASSF4* (84, 85), *NORE1A* (86–88), *NORE1B* (89) and *RASSF6* (90, 91).

This supports the potential for epigenetic therapies to alter the expression of these genes – such as histone deacetylase inhibitors [like Trichostatin A (TSA)] or nucleoside analogues, which sequester the DNMTs during DNA replication and prevent DNA methylation [for example decitabine (5-aza-2′-deoxycytidine)] (92, 93). Several examples of reversal of gene expression have been documented for hypermethylated genes in cancer following decitabine treatment (see Tables 1 and 2) including *PTEN* in NSCLC cell lines (70), *LATS1* and *LATS2* in astrocytomas (75), *RASSF1A* (77, 78) which induced cell cycle arrest and inhibited cyclin D1 accumulation (94); *RASSF2* (79); *RASSF4* (84, 85); *NORE1A* (86) and *RASSF6* (decitabine plus TSA treatment) (90). The presence of promoter hypermethylation and the epigenetic regulation of gene expression for genes known to interact with core components of the cell polarity complexes highlight a new avenue for further investigation and may provide possible novel targets for cancer therapies.

Polarity proteins implicated in human cancer

The components of the core polarity complexes are essential for maintaining correct cell polarity and tissue architecture integrity. Examples of where these processes are disrupted, either directly or through their interacting proteins, are found in several forms of cancer. Overexpression, mutation or complete loss of these proteins can lead to cancer metastasis, poor patient survival and even define cancer progression. This suggests that the deregulation of polarity protein function does not fall into the simplified categories of oncogenes and tumour suppressors, as both the over-expression and loss of function of individual polarity components can be associated with cancers.

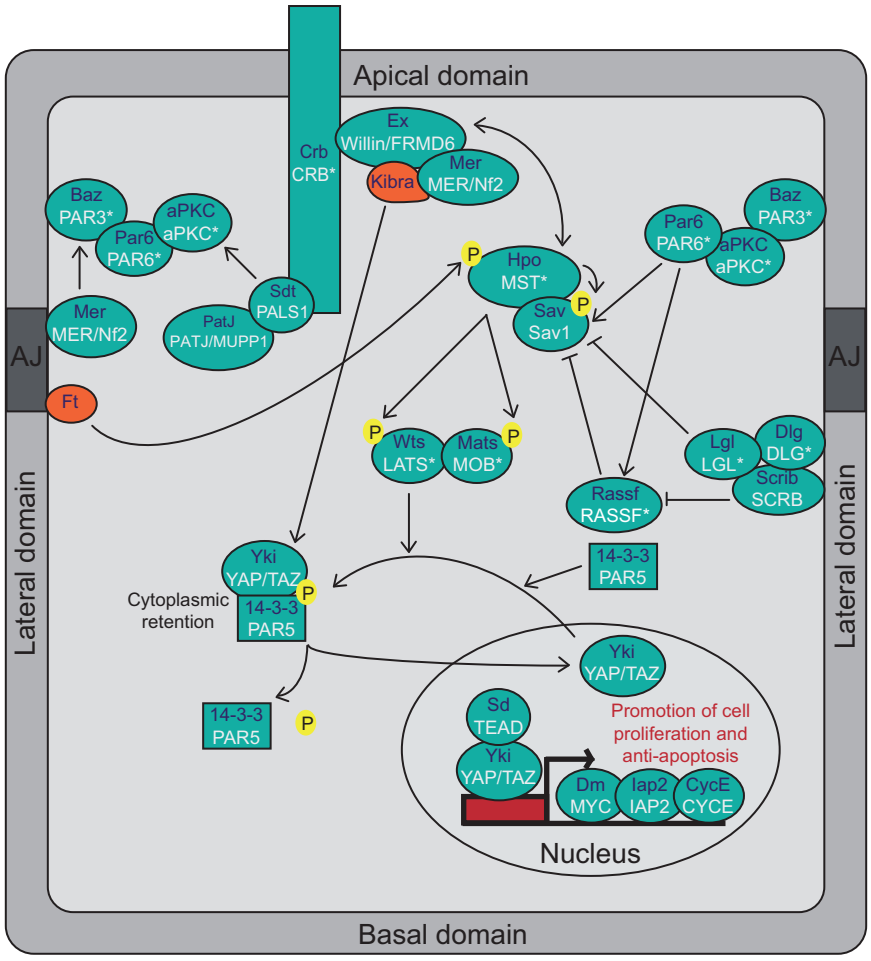

Figure 4 The Hippo pathway.
The Hippo pathway is an essential regulator of cell proliferation and survival in both *Drosophila* and mammals. This function is further regulated by the interactions with components of the core cell polarity complexes, which help define the apical domain (Crumbs and Par complexes) and the basolateral domain (Scribble complex). For abbreviations and the roles of the various proteins please refer to Tables 1 and 2. Ultimately the downstream transcriptional activators of the Hippo pathway (Yorkie in *Drosophila* and YAP/TAZ in mammals) regulate the expression of proteins, which promote growth and prevent apoptosis including Diminutive (Dm), Inhibitor of Apoptosis 2 (Iap2), Cyclin E (CycE) in *Drosophila* and MYC, IAP2 and CYCE in mammals. The components of the Hippo pathway and core cell polarity proteins with homologues in both *Drosophila* and mammals are shown in green, proteins identified only in *Drosophila* are coloured in orange. Phosphorylation is indicated in yellow. *, the presence of several mammalian homologues for the single protein in *Drosophila*; AJ, adherens junction.

The following sections detail current knowledge on how polarity proteins have been implicated in human cancers, and is summarised in Table 1.

Components of the Scribble complex and human cancer

All three components of the Scribble complex have been implicated in several forms of human cancers (Table 1). In cervical cancers, viral oncoprotein HPV E6 targeted degradation of SCRIB led to a dramatic reduction in SCRIB expression during cancer progression (44). Down-regulation and mislocalization of SCRIB promoted transformation of breast mammary epithelial cells and inhibited Myc-induced apoptosis in breast tumours (42). Gardiol et al. found increased alterations to the expression patterns of DLG and SCRIB during tumour progression in colon cancer, while down-regulation of both proteins was associated with lack of epithelial cell polarity and disorganised tissue architecture (95). A reduction of SCRIB has been found in 81% of lobular carcinomas (43), whereas it was surprisingly overexpressed in tumours of the colon, bladder, ovary, prostate and uterus (96).

A reduction or absence of LGL was found in 76% breast cancers, 63% lung cancers, 53% prostate cancers, 50% ovarian cancers and 40% melanomas (97). Schimanski et al. demonstrated reduced expression of LGL1 in 75% colorectal cancer, which correlated with advanced stage and lymph node metastasis (98); in particular LGL1 was reduced or lost in 60% adenomatous polyps and 72% of hepatic metastasis

Table 2 Components and related proteins of the Hippo pathway.

Role in Hippo pathway	Protein in *Drosophila*	Protein in mammals	Notes	Examples in human cancer	Epigenetic alterations in cancer	Response to decitabine treatment
Upstream regulators	Fat (Ft)		Protocadherin	Unknown	Unknown	Unknown
	Crumbs (Crb)	CRB1 CRB2 CRB3	Component of CRB complex, see Table 1	See Table 1	Unknown	Unknown
	Kibra		WW domain-containing protein	Unknown	Unknown	Unknown
	Expanded (Ex)	Willin/ FRMD6	– FERM-domain-containing protein – Positively regulated by CRB	Inhibits cell proliferation in breast cancer cell lines (133)	Unknown	Unknown
	Merlin (Mer)	Merlin/Nf2	– Neurofibromatosis type 2 tumour suppressor – FERM-domain-containing protein	NF2 inactivated in sporadic meningiomas (134) and mesothelioma (135)	*NF2* hypermethylation in meningioma (134)	Unknown
Core complex	Hippo (Hpo)	MST1 MST2	– Ste20-like kinase – Regulated by LGL – Assembly with TAZ regulated by SCRIB in breast cancer cells (65)	– Reduced cytoplasmic MST1 in soft tissue sarcoma (73) and colorectal cancer (136) – Assembly with TAZ regulated by SCRIB in breast cancer cells (65)	Hypermethylation of *MST1* in 37% and *MST2* in 20% of soft tissue sarcomas (73)	Unknown
	Salvador (Sav)	Sav1 (WW45)	WW containing adaptor	Haploinsuffienct *WW45*$^{+/-}$ mice develop liver cancer (137)	Hypomethylation and decrease in H3K9me of retrotransposons in liver (137)	Unknown
	Mats (Mats)	Mps one binder, MOB1 MOB2	Activator of Warts	MOB1 reduced in NSCLC (138)	Unknown	Unknown
	Warts (Wts)	LATS1 LATS2 (Kpm)	– Nuclear Dbf2-related kinase – Assembly with TAZ regulated by SCRIB in breast cancer cells (65)	– LATS1 and LATS2 reduction in breast cancer (74), astrocytomas (75) and soft tissue sarcoma (73) – Assembly with TAZ regulated by SCRIB in breast cancer cells (65)	*LATS1* and *LATS2* hypermethylation in 50–56% breast cancers (74); 60–70% astrocytomas (75); 7% in soft tissue sarcoma (73)	*LATS1* and *LATS2* expression restored in astrocytomas (75)
Downstream targets	Yorkie (Yki)	Yes – associated protein (YAP) TAZ (WWTR1)	– Transcription activator – Affected by LGL and aPKC – Interaction with SCRIB in breast cancer cells (65)	– Activation of YAP or TAZ induces EMT in breast cancer cells and increases invasiveness (139, 140). – Assembly of TAZ with LATS and MST regulated by SCRIB in breast cancer cells (65). – YAP gene amplification in pancreatic cancer (141); increased nuclear YAP expression in hepatocellular carcinoma (142), colonic adenocarcinoma, lung adenocarcinoma and ovarian serous cystadenocarcinoma (143)	Unknown	Unknown
	Scalloped (Sd)	TEAD1-4	Transcriptional factor	Unknown	Unknown	Unknown

Table 2 (Continued)

Role in Hippo pathway	Protein in *Drosophila*	Protein in mammals	Notes	Examples in human cancer	Epigenetic alterations in cancer	Response to decitabine treatment
Other related proteins	Lgl [l(2)gl]	LLGL1 LLGL2	– WD40 repeat containing protein – Part of SCRIB complex – Regulates HPO and RASSF	See Table 1	Unknown	Unknown
	aPKC	aPKCλ/ι aPKCζ	Part of PAR complex; regulates localization of HPO and RASSF	See Table 1	Unknown	Unknown
	Ras association family member (Rassf)	RASSF1A	Competes with Sav for binding Hpo Regulated by LGL	Down-regulated in various cancers (144, 145) including soft tissue sarcoma (76), Ewing sarcoma tumours (77), prostate cancer (71), NSCLC and SCLC (78)	*RASSF1A* hypermethylation in 26% soft tissue sarcoma (76); 68% Ewing sarcoma tumours (77); prostate cancer (71); 30% NSCLC and 100% SCLC and tumours (78)	– Increases *RASSF1A* expression (77, 78) – Induces cell cycle arrest and inhibits cyclin D1 accumulation (94)
		RASSF2	Competes with Sav for binding Hpo Regulated by LGL	Reduced in colorectal cancer cell lines (79), lung tumour cell lines and primary NSCLC tumours (80, 81), gastric cancer (82), and nasopharyngeal carcinoma (83)	– *RASSF2* hypermethylation in colorectal cancer cell lines (79); lung tumour cell lines and primary NSCLC tumours (80, 81); gastric cancer (82); nasopharyngeal carcinoma (83)	Increase *RASSF2* expression (79)
		RASSF4	Competes with Sav for binding Hpo Regulated by LGL	Reduced levels in nasopharyngeal carcinoma cell lines (84), NSLC and SCLC (85), breast, lung, colorectal and kidney tumour cell lines, primary lung and breast tumours (85)	*RASSF4* hypermethylation in 12.5% nasopharyngeal carcinoma cell lines (84); 21% in NSLC and SCLC (85); breast, lung, colorectal and kidney tumour cell lines, primary lung and breast tumours (85)	Restoration of *RASSF4* mRNA (84, 85)
		NORE1A (RASSF5A)	– Competes with Sav for binding Hpo – Regulated by LGL	Reduction in lung, breast, kidney tumour cell lines and primary tumours (86–88)	*NORE1A* hypermethylation in lung, breast, kidney tumour cell lines and primary tumours (86–88)	Restoration of *NORE1A* expression (86)
		NORE1B (RASSF5B)	Competes with Sav for binding Hpo Regulated by LGL	Decreased in hepatocellular carcinomas and hepatocarcinoma cell lines (89)	*NORE1B* hypermethylation in 62% of hepatocellular carcinomas and hepatocarcinoma cell lines (89)	Unknown
		RASSF6	Competes with Sav for binding Hpo Regulated by LGL	Down-regulated in 90% childhood B cell acute lymphocytic leukaemia (ALL) and 40% T cell ALL (90) 30–60% primary tumour tissues from breast, colon, kidney, liver, pancreas, stomach, thyroid gland (91)	*RASSF6* hypermethylation in 90% childhood B cell acute lymphocytic leukaemia (ALL) and 40% T cell ALL (90); 30–60% primary tumour tissues from breast, colon, kidney, liver, pancreas, stomach, thyroid gland (91)	Restored *RASSF6* expression (decitabine + TSA) (90)

originating from colorectal cancer. The presence of aberrant LGL splice variants has also been observed in 20% of hepatocellular carcinoma cell lines and 35% of hepatocellular carcinoma specimens (99).

DLG was also down-regulated in cervical cancer (41) with significant reduction of DLG in invasive cervical (41) and ovarian cancer (DLG4) (100). Additionally microarray analysis showed *Dlg* expression was significantly altered in gastric cancers (101, 102). DLG was found to be mutated in mammary ductal carcinoma (45), and deleted in lung and cervix tumours (103). Finally, DLG1 was found to interact with the PDZ binding motif of APC tumour suppressor protein, implicated in colon cancer (104).

Appropriate expression and regulation of the SCRIB complex is required to maintain cell polarity. The studies outlined above, covering several types of cancer, indicate that deregulation of a single component of the SCRIB complex can aid in loss of tissue architecture and promote cancer progression.

Components of the PAR complex and human cancer

The core components of the PAR complex were either overexpressed (PAR6 or aPKC) or down-regulated (PAR3) in different forms of cancers (Table 1). In particular, PAR6b was overexpressed in breast cancer cell lines where it was found to regulate tumour initiation and progression, specifically promoting proliferation of breast epithelial cells through its interactions with aPKC and Cdc42 (105). PAR6 activation also correlated with BRCA1-associated breast tumours, which have a highly enriched basal subtype associated with EMT and mesenchymal characteristics (106).

In contrast to PAR6 overexpression in cancers, a copy number loss of PAR3 has been observed in 15% of primary oesophageal squamous cell carcinoma cells and expression of PAR3 was significantly reduced in primary oesophageal squamous cell carcinoma tumours (107). A study by Rothenberg et al. showed deletions of *PAR3* in 5% of glioblastomas and 9% of head and neck squamous cell carcinoma (103). The authors also demonstrated deletions of *PAR6G, MPDZ* and *DLG2* in several tumour types (103), as shown in Table 1.

The isoforms of the atypical protein kinase gene are overexpressed in several human cancers, shown in Table 1. aPKCλ/ι activity was required for Ras-mediated transformation, invasion and anchorage-independent growth of intestinal epithelial cells (108). A correlation between aPKCλ/ι overexpression and poor patient survival has been demonstrated in non-small cell lung cancer (NSCLC) (109) and pancreatic cancer (110), where inhibition of aPKCι in pancreatic tumours significantly reduced tumour angiogenesis and metastasis (110). aPKCλ/ι overexpression was a strong prognostic factor for recurrence of gastric adenocarcinoma (111) and prostate cancer (112); whereas expression of aPKCλ/ι has been closely related to pathological differentiation, tumour size, invasion and metastasis of hepatocellular carcinoma (113) and cholangiocarcinoma (cancer of the bile duct) (114).

Additionally, the accumulation of aPKCι in hepatocellular carcinoma (HCC) cytoplasm and nucleolus inhibited the subsequent formation of adherens junctions and/or tight junctions during cell-cell contact (113). aPKCλ/ι overexpression was detected in 80% of breast cancers and apical or cytoplasmic aPKC localisation correlated with tumour pathologic type (115).

The Crumbs complex and human cancer

Despite limited evidence for the misregulation of the Crumbs complex in humans cancers (Table 1), deletions or down-regulation of the core components were common to all examples described. Deficiency of CRB3 in immortal baby mouse kidney epithelial cells showed disruption of tight junction formation, apicobasal polarity and contact-inhibited growth, however reintroduction of *Crb3* expression restored these defects and suppressed migration and metastasis (116). The *Crb3* gene is located at 19p13.3, which also contains several other tumour suppressor genes and is frequently deleted in carcinomas (117). PALS1 interacts with the PDZ domain protein Lin-7C/VELI3/MALS-3 (Lin-7c) (118), which is down-regulated by promoter hypermethylation in oral squamous cell carcinoma (72). Finally, sarcoma and lymphoma tumours showed large deletions of PATJ (103).

Perspectives

This review highlights how the three main core polarity complexes: PAR (PAR6, PAR3/Baz, aPKC), CRB (CRB, PALS1/Sdt, PATJ) and SCRIB (SCRIB, DLG, LGL) are not only crucial for the correct organisation of apicobasal cell polarity in normal epithelia, but are also essential to prevent cancer progression. Disruptions to any of these core components can lead to gross abnormalities in tissue architecture and therefore these proteins play an essential role in maintaining homeostasis and in preventing cancer cell invasion. Several proteins that interact with the core polarity components, including members of the Hippo pathway, have also been implicated in tumourigenesis and cancer progression and demonstrate the diverse range of targets affected by these polarity complexes. Epigenetic regulation of these interacting proteins may highlight potential therapeutic targets for cancers, and demonstrate the potential for epigenetic regulation of cell polarity in normal and cancer tissues.

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