Cell polarity in development and cancer

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The development of cancer is a multistep process in which the DNA of a single cell accumulates mutations in genes that control essential cellular processes. Loss of cell–cell adhesion and cell polarity is commonly observed in advanced tumours and correlates well with their invasion into adjacent tissues and the formation of metastases. Growing evidence indicates that loss of cell–cell adhesion and cell polarity may also be important in early stages of cancer. The strongest hints in this direction come from studies on tumour suppressor genes in the fruitfly *Drosophila melanogaster*, which have revealed their importance in the control of apical–basal cell polarity.

Most human cancers are derived from epithelial tissues, which are characterized by a specific cellular architecture (Fig. 1). Junctions between neighbouring epithelial cells allow the separation of apical and basolateral membrane domains that vary in protein and lipid content, and the polarity that results is crucial to normal cell function. Important hallmarks of advanced cancerous tumours are the loss of epithelial character from the original tissue and the appearance of more mesenchymal-like cells, especially at the periphery, where the tumour cells are in contact with surrounding stromal cells. Typical of this epithelial–mesenchymal transition (EMT) is the loss of cell–cell adhesion and apical–basal cell polarity as well as the increased motility of tumour cells. Although the importance of EMT for tumour progression is widely accepted (for reviews see refs 1, 2), much less is known about the relationship between cell polarity and early events in carcinogenesis.

Here we discuss how changes in the activities of proteins that regulate polarity may lead to tumour formation and progression. So far, only a small number of proteins have been shown to be crucial for the establishment and maintenance of epithelial tissue architecture. Some of these factors are linked to signalling pathways that had been implicated in the development of cancer for some time. A common feature of these signalling pathways is their ability to regulate apical–basal cell polarity and cell growth simultaneously, frequently by means of independent effector molecules. This suggests that loss of apical–basal cell polarity combined with increased growth can promote cancer.

Many of the genes that control apical–basal polarity in epithelia are also required for the polarization of asymmetrically dividing stem cells. Here we also discuss recent results from *Drosophila* showing that defects in cell polarity or asymmetric division of neural stem cells result in the development of brain tumours. Although it is not known whether similar mechanisms promote the development of cancer in humans, these findings in model organisms will undoubtedly help to establish testable hypotheses.

Loss of E-cadherin: a critical step in the development of cancer

The establishment of cell polarity in epithelia depends on the formation of cell–cell adherens junctions[3]. E-cadherin is a key factor in junction formation (Fig. 1): in addition to providing the physical link between neighbouring cells and intracellular structures, cadherins support the assembly of large signalling complexes[4]. Loss of E-cadherin is implicated in later stages of tumorigenesis and commonly correlates with a more invasive phenotype[5,6]. This loss accompanies EMT and is followed by the loss of intercellular junctions, ultimately leading to cell detachment from epithelial clusters, an important property of metastasizing cells.

Disruption of E-cadherin function in postmitotic intestinal epithelial cells in mice is not sufficient to induce malignant tumours, but it does lead to increased migration and precocious entry into apoptosis[7]. Extending the inhibition of E-cadherin to the proliferating compartment in this tissue causes the development of tumours reminiscent of tumours associated with human inflammatory bowel disease (IBD)[8]. Mutations in *CDH1*, the gene encoding human E-cadherin, are found in more than 50% of stomach cancers, highlighting the importance of E-cadherin as a tumour suppressor gene[9]. In the pancreas, loss of E-cadherin strongly enhances progression from adenoma to carcinoma — an effect that seems directly related to altered cell–cell adhesion[10,11]. However, such disruption of adhesion when E-cadherin function is lost may also affect signalling pathways whose receptors are clustered at sites of cell–cell contacts, including the EGF (epidermal growth factor) receptor and Wnt pathways[12]. A comprehensive coverage of this field is beyond the scope of this review and the reader is referred to some of the excellent recent reviews cited above[4–6].

What can we learn about human cancer from *Drosophila*?

By contrast with mammalian tumours, which usually require a series of consecutive mutations to develop, single-gene mutations are

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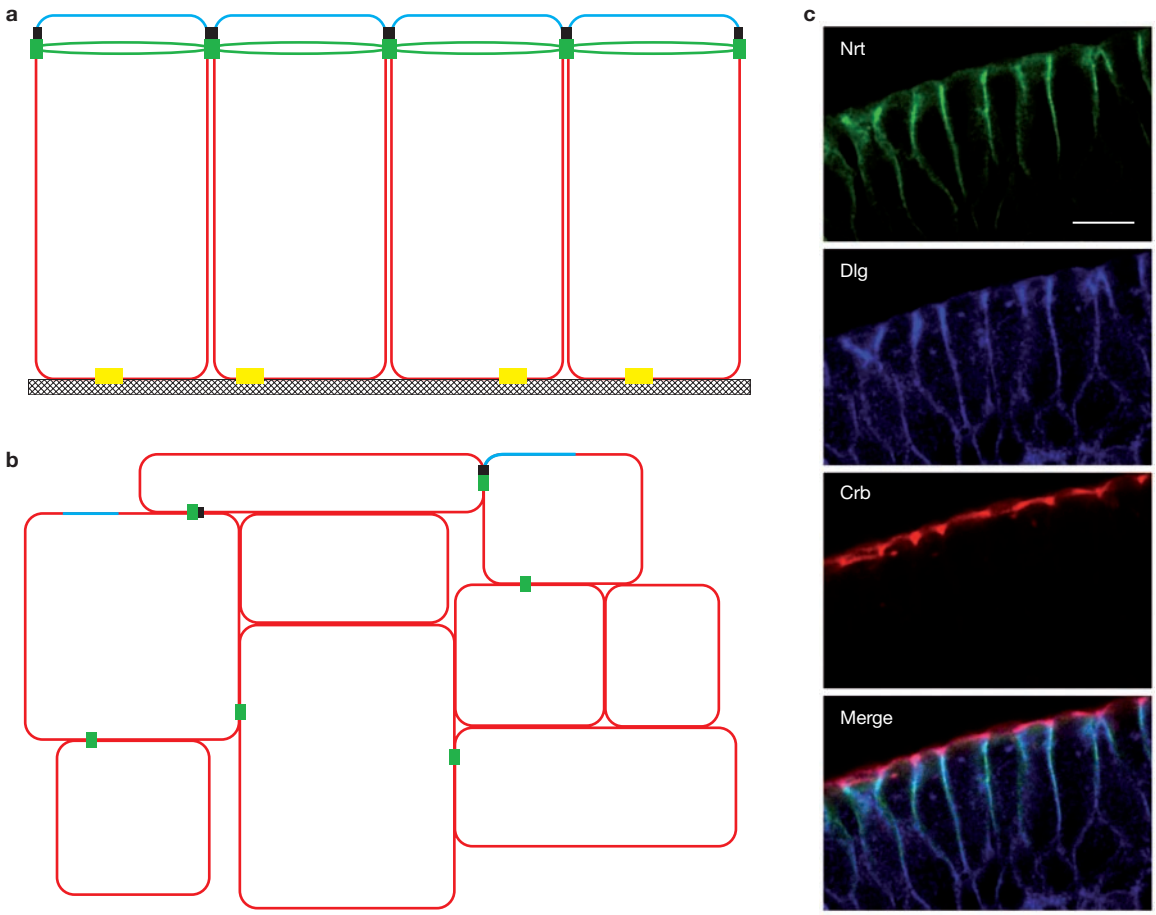

Figure 1 Epithelial polarity and tissue organization are closely linked. (**a**) In a monolayered wild-type epithelium, the apical plasma membrane domain (blue) is separated from the basolateral plasma membrane domain (red) by the tight junction (TJ; black). Cell–cell adhesion is provided by the homophilic binding of cadherins in the zonula adherens (ZA; green), which forms a belt around the apex of each epithelial cell. Cell–substrate adhesion between the cell and the basement membrane (cross-hatched rectangle) is mediated by integrin-rich focal adhesions (yellow). Many of the proteins discussed in this review show a polarized subcellular localization in epithelia. Lgl, Dlg, Scrib and PAR-1 are localized in the cortex underlying the basolateral membrane. E-cadherin is a core component of the ZA. PAR-3, PAR-6, aPKC and Cdc42 are enriched in the TJ. The ErbB2 receptor, integrins and the TGF-β receptors are integral membrane proteins of the basolateral membrane domain. Note that in the wild-type epithelium the cells are homogeneous in size and are arranged in a very orderly fashion. (**b**) Mutations in one of the polarity regulators discussed in the text cause profound changes in cellular architecture. Cells lose apical–basal polarity, disassemble TJs and the ZA, become heterogeneous in shape and size and start to pile up on top of each other. Because cell–cell adhesion is strongly reduced, cells have a tendency to leave the original tissue and invade surrounding tissue. (**c**) The embryonic epidermis of the wild-type fruitfly *Drosophila* serves as a model system for the study of epithelial polarity in a genetically accessible organism. This image shows a confocal optical section labelled with antibodies against Nrt (green), an integral membrane protein of the basolateral membrane, Dlg (blue), which is enriched in the lateral cortex just below the ZA, and Crb (red), an integral membrane protein of the apical plasma membrane domain. Apical is up in all panels. Scale bar represents 10 μm.

sufficient for the formation of tumours in the fruitfly *Drosophila*. The best studied of these genes are the so-called neoplastic tumour suppressors *lethal giant larvae* (*lgl*), *discs large* (*dlg*) and *scribble* (*scrib*)[13–15]. These genes were initially identified in screens for mutations that cause cancerous overgrowth of imaginal discs in *Drosophila* larvae[13,15]. Imaginal discs are epithelia of ectodermal origin that give rise to specific body structures in the adult fly, including wings, legs and eyes. Interestingly, imaginal discs lacking *lgl*, *dlg* or *scrib* not only show massive hyperproliferation but also lose epithelial polarity (Fig. 1). This property distinguishes these neoplastic mutants from hyperplastic mutants, in which cell polarity and tissue architecture are maintained[13,14,16,17]. These findings convincingly showed that *lgl*, *dlg* and *scrib* are key regulators of epithelial polarity, although it is still not clear how they act in this process. The most instructive hints so far have come from genetic epistasis experiments demonstrating an antagonistic relationship between these tumour suppressor genes and polarity regulators acting at the apical junctions of epithelial cells[18–20]. Can the functions of these neoplastic tumour suppressors in cell polarity and cell proliferation be separated? Whereas a construct lacking the two PDZ domains of Dlg causes overproliferation without affecting epithelial polarity[21], a similar analysis of Scrib could not separate these two functions, suggesting that these processes are usually coordinated[22].

Mammalian homologues of *lgl*, *dlg* and *scrib* are functionally conserved and can rescue the mutant phenotypes of the respective *Drosophila* genes *in vivo*[23–25]. Mice lacking Lgl1, one of the two Lgl homologues in mammals, show severe brain dysplasia, accompanied by loss of cell polarity in neuroepithelial cells[26]. Polarity defects in other epi-

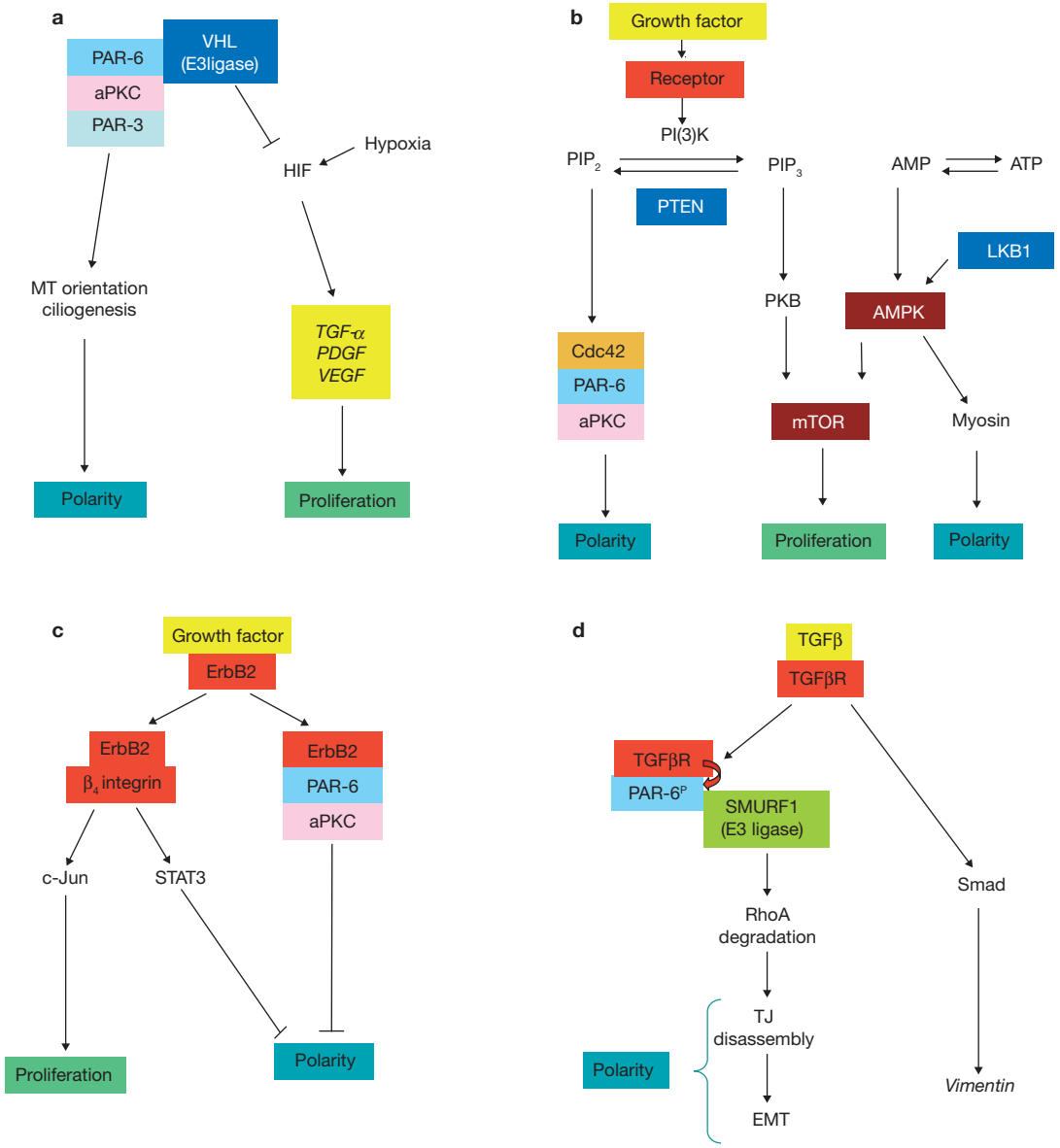

Figure 2 PAR-6 and other members of the PAR–aPKC complex are central components of signalling pathways that control polarity and proliferation. (**a**) The PAR–aPKC complex associates with the von-Hippel–Lindau (VHL) tumour suppressor protein and is required for correct microtubule (MT) orientation during ciliogenesis in kidney epithelial cells. VHL also affects proliferation through degradation of the transcription factor HIF, which is a transcriptional activator of several genes encoding growth factors. (**b**) PTEN controls polarity by regulating the local concentration of the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2), which recruits the PAR–aPKC complex to the plasma membrane. LKB1 regulates polarity by phosphorylating AMPK, which in turn phosphorylates the regulatory light chain of myosin. Both PTEN and AMPK affect the activity of the mTOR kinase, which is a central regulator of cell growth and proliferation. PI(3)K, phosphatidylinositol-3-OH kinase; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PKB, protein kinase B. (**c**) PAR-6 and aPKC bind to the ErbB2 receptor and are required to mediate the effects of ErbB2 on cell polarity. A second signalling pathway downstream of ErbB2 uses β_4 integrin to modulate polarity. In both pathways, polarity and cell proliferation are regulated independently. (**d**) PAR-6 provides a crucial link between the TGF-β receptor and the control of cell polarity. After phosphorylation by the TGF-β receptor, PAR-6 serves as a docking site for the E3 ubiquitin ligase SMURF1, which promotes RhoA degradation, resulting in TJ disassembly and loss of polarity. PAR-6 is not required for other aspects of EMT, for example the SMAD-dependent upregulation of vimentin gene expression. See the text for details of the signalling mechanisms shown here. Tumour suppressors are boxed in dark blue, transmembrane receptors in red, and secreted growth factors in yellow. Protein complexes are represented by attached boxes. The names of genes that are subject to transcriptional regulation by the respective signalling pathway are in italics.

thelia were not detected, probably as a result of functional redundancy. Similarly to their fly counterparts, it remains unclear exactly how these mammalian homologues control cell polarity mechanistically. In MDCK (Madin–Darby canine kidney) cells, mammalian Lgl interacts with the conserved polarity regulators PAR-6 and atypical protein kinase C (aPKC) and is involved in the formation of tight junctions[27,28]. Depleting Scrib from MDCK cells also interferes with the formation of tight junctions and leads to a decrease in E-cadherin levels[29]. Evidence is accumulating that Lgl regulates exocytosis[30,31]. The relationship between exocytosis and cell polarity may not be obvious at first

glance; however, the establishment of plasma membrane polarity and the assembly of junctions at specific locations require the targeted delivery of transmembrane proteins and other membrane components to specific sites through the exocytic pathway[32]. In addition, recent studies have shown that components of the endocytic machinery also seem to function as tumour suppressors in *Drosophila*; however, in this case, the effects on polarity and growth seem to be the altered activation of several signalling pathways, including the Notch and Crumbs pathways (reviewed in ref. 33).

Although the existing data support a role for these mammalian homologues in cell polarity, their contribution to human carcinogenesis is less obvious. Several recent reports show a strong correlation between decreased expression of *lgl*, *dlg* and *scrib* and tumour progression[34–38]. Moreover, a strong correlation between mutations of the Dlg homologue DLG5 and the risk for IBD, a cancer-predisposing condition of the intestinal tract, was discovered by using linkage analysis[39]. In addition, Dlg and Scrib are targeted by the high-risk human papillomavirus (HPV) E6 proteins for ubiquitin-mediated degradation[40–42]. HPV infection is associated with most cases of cervical carcinoma, suggesting that degradation of Dlg and Scrib may contribute to the development of this type of cancer.

Cooperation of Ras with regulators of cell polarity in tumorigenesis

Mutations in the tumour suppressor genes of *Drosophila* are sufficient to cause tumours in imaginal disc epithelia only if the entire animal is homozygous for this mutation. If clones of homozygous mutant cells are induced in imaginal discs of an otherwise heterozygous animal, only few tumours develop; these clones, which exhibit reduced proliferation properties, are eventually eliminated by apoptosis[13,14,43]. The growth disadvantage of these mutant cells can be overcome by simultaneous activation of signalling pathways that promote cell proliferation, such as Ras and Notch[43]. The contribution of Lgl, Dlg and Scrib to the progression and metastasis of tumours induced by a constitutively active form of Ras was tested in *Drosophila* in an experimental system designed to study the interactions between regulators of polarity and proliferation[43,44]. Intriguingly, whereas tumours induced by oncogenic Ras alone never spread, tumours induced by the combined expression of oncogenic Ras with loss of heterozygosity for *lgl*, *dlg* and *scrib* metastasized frequently[44]. In this context, the JNK (c-Jun N-terminal kinase) pathway was essential because mutations in polarity regulators lead to activation of JNK signalling, which causes apoptosis and elimination of the mutant cells, in the absence of oncogenic Ras[43]. However, in the presence of an oncogenic Ras mutation, the JNK pathway cooperates with Ras to promote tumour growth[45,46], possibly through the transcriptional activation of matrix metalloproteases, which are responsible for the degradation of the basement membrane surrounding the primary tumour, an essential step in metastasis[44,47].

The PAR–aPKC complex: multiple links to cancer

In addition to the tumour suppressor genes *lgl*, *dlg* and *scrib*, the screen for mutations that promote the metastasis of Ras-induced tumours uncovered the genes bazooka (*baz)*, stardurst (*sdt*; the *Drosophila* homologue of mammalian PALS1) and *cdc42*. These genes are known to control polarity but do not cause tumours when mutated[3,19,44]. Baz (the *Drosophila* homologue of PAR-3 from *Caenorhabditis elegans* and mammals), the small GTPase Cdc42, PAR-6 and aPKC form the PAR–aPKC complex, which controls polarity in many different cell types throughout the animal kingdom[48,49]. Recent data implicate the PAR–aPKC complex in human carcinogenesis. Gene amplification and elevated constitutive activity of PKC-ι, one of two human aPKC homologues, was detected in ovarian, lung and colon cancer and was correlated with poor prognosis, suggesting that PKC-ι may be an oncogene[50–53]. By using constitutively active and dominant-negative versions of Ras, PKC-ι and Rac, Fields and colleagues showed that PKC-ι functions downstream of Ras and upstream of Rac in cell transformation[51–53]. Not unexpectedly, tumours with elevated levels of aPKC had lost epithelial polarity, which is consistent with the overexpression phenotype of a constitutively active form of aPKC in *Drosophila* epithelia[50].

A recent study showed that the PAR–aPKC complex associates with the tumour suppressor von Hippel–Lindau protein (VHL), which is required for the growth of microtubules during ciliogenesis in kidney cells (Fig. 2a)[54]. VHL, an E3 ubiquitin ligase, targets a variety of proteins for degradation, including hypoxia-inducible factor (HIF) and aPKC[55,56]. Mutations in VHL are responsible for a rare familial cancer syndrome, and inactivation of both wild-type alleles of VHL is also found in sporadic tumours of a similar type[55]. VHL-negative cancer cells lack well-organized adherens and tight junctions, a phenotype that is independent of the role of VHL in controlling HIF levels[57]. The regulation of HIF is nonetheless likely to contribute also to the tumour suppressor function of VHL, because in $VHL^{-/-}$ cells, excess HIF leads to the overexpression of various growth factors, including TGF (transforming growth factor)-α, PDGF (platelet-derived growth factor)-β and VEGF (vascular endothelial growth factor), which may promote overproliferation[55]. Like several other signalling pathways that we discuss below, the VHL tumour suppressor simultaneously affects cell polarity and growth.

The lipid phosphatase PTEN (phosphatase and tensin homologue deleted on chromosome ten) is another frequently mutated tumour suppressor in human cancer that has been predominantly implicated in the control of cell growth and proliferation[58] (Fig. 2b). However, several recent reports have shown that PTEN interacts with components of the PAR–aPKC complex and is also involved in the control of polarity in epithelia, both in mammals and in *Drosophila*[59–61].

During establishment of cell polarity in *Drosophila* and *C. elegans* the PAR–aPKC complex interacts with the serine/threonine protein kinases PAR-1 and PAR-4 (refs 48, 49, 62, 63). Mutations in LKB1, the human homologue of PAR-4, cause the heritable Peutz–Jeghers cancer syndrome (PJS), which is characterized by hamartomas, benign tumours consisting of disorganized differentiated cells in the gastrointestinal tract, and a predisposition to rare types of cancer[64,65]. Conditional activation of LKB1 in mammalian intestinal epithelial cells in culture has demonstrated its role in polarity[66]: cells with activated LKB1 become polarized in the absence of cell–cell and cell–extracellular-matrix contacts, form an actin-rich apical brush border and localize the tight junction component ZO-1 and the adherens junction component p120 in circles around the brush border[66]. Mutations found in *LKB1* alleles of patients with PJS usually do not compromise the kinase activity of LKB1 but impair its ability to induce cell polarization, indicating that loss of, or changes in, polarity may contribute to the phenotypes observed in patients with PJS[67]. It was suggested that the functions of LKB1 in polarity and proliferation are separable, the first targeting the kinase PAR-1 and the latter the AMP-activated protein kinase (AMPK)[64]. However, recent results indicate that *Drosophila* AMPK is also involved in the

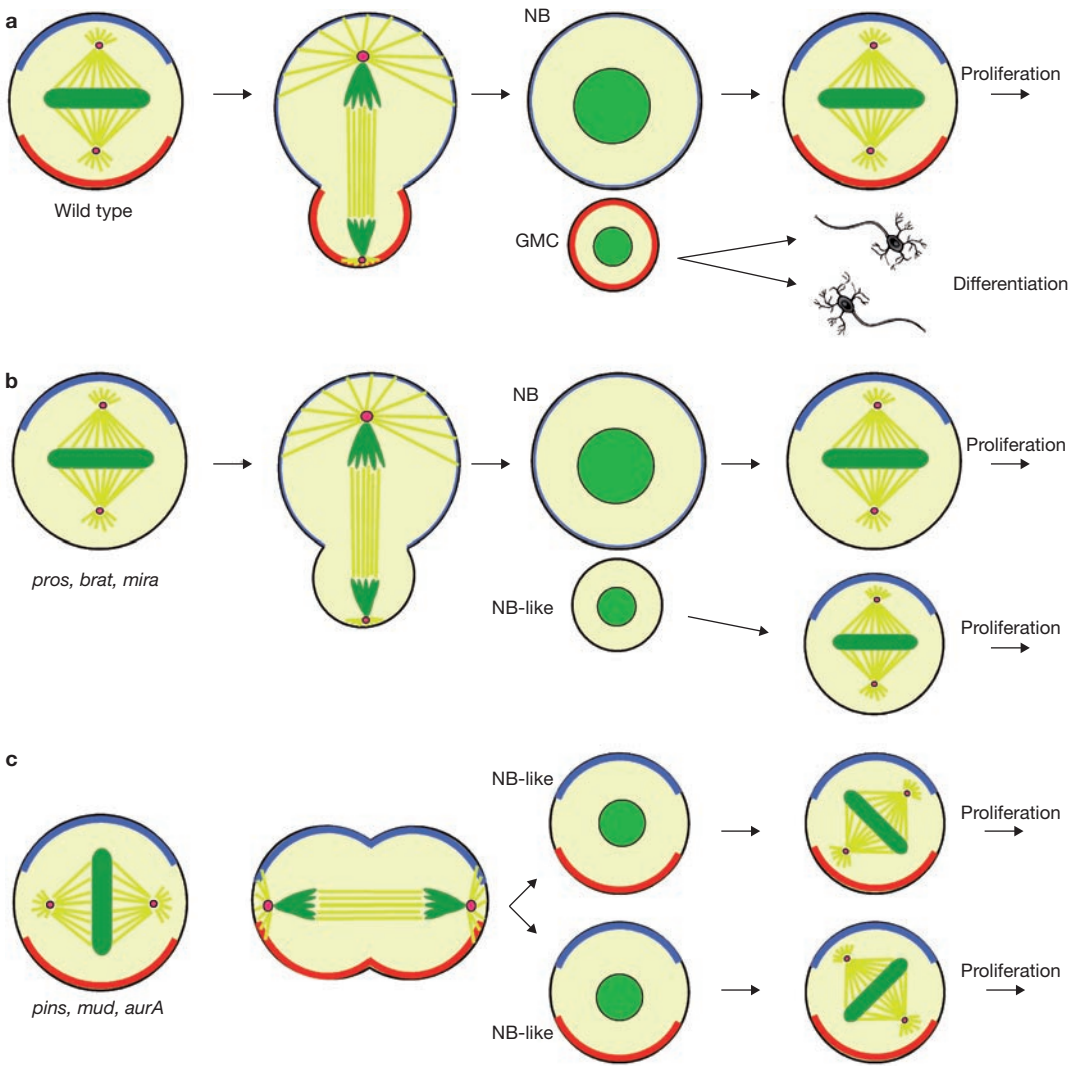

Figure 3 Defects in the asymmetric division of stem cells may lead to the formation of tumours. (**a**) Wild-type larval neuroblasts (NB) of *Drosophila* divide asymmetrically and give rise to another neuroblast and a ganglion mother cell (GMC). The neuroblast continues to divide, whereas the GMC divides only once more and generates a pair of terminally differentiating neurons or glial cells. During division, the PAR–aPKC complex (blue) localizes apically in the NB and segregates exclusively into the new NB in telophase. Cell fate determinants including Prospero (Pros) and Brain tumor (Brat; red) localize basally in the NB and segregate exclusively into the GMC, where they are required for blocking proliferation and for promoting differentiation. (**b**) In larval NBs mutant for *pros*, *brat* or *mira*, the GMC is not specified correctly and behaves similarly to a NB, resulting in excessive cell numbers and a lack of differentiation. (**c**) In larval NBs mutant for genes that control spindle orientation, for example *mushroom body defect* (*mud*), *aurora A* (*aurA*) or *partner of inscuteable* (*pins*), the mitotic spindle is not aligned with the localization of the PAR–aPKC complex and the cell fate determinants, resulting in the abnormal segregation of both. Consequently, none of the daughter cells acquires the correct GMC fate. Daughters fail to differentiate and continue to proliferate. In all panels the mitotic spindle is drawn in yellow, DNA in green and centrosomes are shown by red circles.

control of apical–basal cell polarity under conditions of energetic stress[68,69]. Expression of a phosphomimetic version of AMPK in which the threonine residue targeted by LKB1 phosphorylation is replaced by aspartate rescues polarity defects in the LKB1 mutant, indicating that LKB1 controls cell polarity through the phosphorylation of AMPK[68,69]. One key target for AMPK in this process is the myosin regulatory light chain[68]. Intriguingly, AMPK and PTEN are both linked to the mTOR (mammalian target of rapamycin) signalling pathway, which controls protein synthesis rate and cell growth[64] (Fig. 2b).

Links between growth-factor signalling, cell polarity and cancer

The ErbB2 receptor tyrosine kinase signalling pathway regulates the development of breast epithelium[70]. Overexpression or amplification of ErbB2 is found in 25–30% of breast cancers and is also associated with other epithelial malignancies such as ovary, prostate, pancreas and salivary gland cancer. It was recently discovered that, on activation by its ligand, the ErbB2 receptor binds directly to PAR-6, leading to the recruitment of aPKC to the receptor and the disruption of apical–basal polarity (Fig. 2c)[71]. Expression of a PAR-6 mutant form that still binds to ErbB2 but is unable to recruit aPKC to the complex does not prevent the effect of ErbB2 on cell proliferation but inhibits its effect on polarity, showing that these two functions of ErbB2 are independent[71]. However, the ErbB2-mediated inhibition of apoptosis requires the binding of PAR-6 to the receptor, revealing that polarity and apoptosis are intimately linked[71]. A close connection between polarity and apoptosis has been reported in other contexts, for example when

cells are grown in three-dimensional culture systems on extracellular matrix substrates[72,73].

Independent evidence for two distinct signalling pathways downstream of ErbB2 controlling cell proliferation and polarity was revealed by a study showing the participation of β_4 integrin in ErbB2 signalling (Fig. 2c)[74,75]. This study showed that β_4 integrin binds directly to the ErbB2 receptor and promotes ErbB2-induced proliferation and disruption of polarity. In a cell line expressing a truncated signalling-deficient β_4 integrin, the activation of two downstream targets of ErbB2, namely c-Jun and STAT3 (signal transducers and activators of transcription 3), was strongly reduced. Inhibition of c-Jun led to suppression of proliferation without any effect on polarity. Correspondingly, inhibition of STAT3 partly restored cell polarity in ErbB2-stimulated cells but had no effect on ErbB2-induced cell proliferation[74]. Together, these studies show that ErbB2 affects proliferation and polarity by two independent pathways that both contribute to the malignant phenotype of ErbB2-induced tumours.

TGF-β is a key regulator of EMT and promotes invasion and metastasis in late-stage carcinomas[1,76,77]. A compelling link between TGF-β signalling and cell polarity has recently been uncovered by the finding that TGF-β type I subunit receptor binds directly to the polarity regulator PAR-6 (Fig. 2d)[78] in a ligand-independent manner. Both proteins associate with tight junctions by means of the binding of the type I receptor to the tight-junction component occludin. Upon ligand binding, the TGF-β type II receptor subunit associates with and relocalizes to a complex of the type I receptor with PAR-6[78]. In this tripartite complex, the TGF-β type II receptor phosphorylates PAR-6 at a conserved serine residue. Intriguingly, mutation of this residue to alanine blocks TGF-β-mediated EMT and disassembly of tight junctions[78]. The authors of this landmark study also showed that this phosphorylated residue serves as a docking site for the E3 ubiquitin ligase SMURF1, which is required for the TGF-β-induced degradation of the actin regulator RhoA. Importantly, expression of the non-phosphorylatable mutant version of PAR-6 does not block the SMAD-mediated transcriptional activation of vimentin gene expression, demonstrating that TGF-β-induced disassembly of tight junctions and transcriptional responses are independent, separable events[78].

Together, these findings show clearly that several growth factor signalling pathways relevant for cancer development regulate polarity and growth in a coordinated way. This concept not only applies to ErbB2 and TGF-β, but can also be extended to other signalling pathways. For example, the mTOR signalling pathway receives input from growth factor receptors through phosphatidylinositol-3-OH kinase and PTEN and from sensors measuring the energy status of the cell by means of LKB1 and AMPK. At this point one can only speculate why the coordinate regulation of cell polarity and cell growth is a recurring theme in many signalling pathways related to cancer. Cells organized in epithelial tissues may be subject to growth regulation by the well-known phenomenon of contact inhibition. A prerequisite for contact inhibition is the establishment of intercellular junctions that recruit various growth factor receptors and serve as signalling centres that control growth, proliferation and cell death. Thus, the coordinated regulation of cell polarity, junction formation and cell growth may be a mechanism to keep cell growth in check and prevent uncontrolled proliferation, one hallmark of cancer cells.

Defects in asymmetric stem cell division and cancer

So far we have focused our attention on the consequences of deregulating epithelial polarity for the development and progression of cancer. If the accumulation of mutations in cancer-related genes in a single cell is sufficient for the development of cancer, all cells should be equivalent in their potential to give rise to a tumour. However, growing evidence implicates stem cells as a source of tumours[79–83]. Stem cells are responsible for the continuous renewal of tissues in the adult body, including the blood, the skin and the lining of the gut. Unlike most other cells, stem cells have the unique ability to divide for the lifetime of an organism, rendering them a prominent target for accumulating mutations. In most model systems that have been studied so far, stem cells divide asymmetrically and generate a new stem cell and a daughter cell that has a more restricted developmental potential and gives rise to terminally differentiated progeny. This process is genetically controlled and depends on the establishment of cell polarity in the stem cell. Once polarity has been established, cell fate determinants are localized asymmetrically and after their segregation during mitosis they confer different developmental potential on the daughter cells. Intriguingly, many of the genes that are required for the control of cell polarity in the epithelia discussed above are also essential for the establishment and maintenance of polarity in stem cells[84,85]. Defects in the asymmetric division of stem cells may thus lead to an increase in stem cell number and subsequently to the formation of tumours due to excessive proliferation. This has been recently shown for the stem cells of the fly brain, the larval neuroblasts.

Drosophila larval neuroblasts as a model system for stem-cell-induced tumours

During asymmetric division of neuroblasts, two different daughter cells are generated. The larger daughter cell remains a neuroblast and maintains its stem cell properties, whereas the smaller daughter cell, called the ganglion mother cell (GMC), divides only once more to generate two neurons or glial cells (Fig. 3a). During asymmetric division of neuroblasts, the components of the PAR–aPKC complex and the Pins (Partner of inscuteable)–$G_{\alpha i}$ complex localize to the apical cortex, whereas cell fate determinants such as Prospero, Numb and Brain tumor (Brat) and their adaptor proteins are localized to the basal cortex (Fig. 3a)[84,86]. Loss of function or mislocalization of these polarity regulators or cell fate determinants in larval neuroblasts increases the number of cells with neuroblast-like properties and consequently leads to the formation of brain tumours (Fig. 3b)[87–90]. Why is this so? The asymmetric segregation of the cell fate determinant Prospero to the GMC is required for the transcriptional suppression of neuroblast-specific genes and for the activation of genes that promote neural differentiation[91,92]. Brat functions in a similar way, although at the post-transcriptional level, by inhibiting the translation of the Myc protein, a key regulator of cell growth normally downregulated in the GMC[88].

Brain tumours can be induced by mutations in the genes encoding the cell fate determinants themselves or their adaptor protein Miranda, and in addition by mutations in genes that control spindle orientation in neuroblasts. Neuroblasts mutant for *pins*, *mushroom body defect* (*mud*) or *aurora A* (*aurA*) fail to align the mitotic spindle with the asymmetric localization of cell fate determinants, frequently causing their mis-

segregation into both daughter cells (Fig. 3c)[89,93–97]. Consequently, the GMC fate is not properly established in some daughter cells, causing the formation of ectopic neuroblast-like cells that continue to proliferate and give rise to tumours. Interestingly, the mammalian homologues of Pins (LGN) and Mud (NuMA) directly interact with each other and are also involved in the control of spindle orientation, indicating a conserved function of these proteins[98].

Prospero and Brat act in the GMC. Are there also genes essential for maintaining the stem cell character of the neuroblast? A key determinant in promoting the self-renewal capacity of neuroblasts is aPKC. Larval neuroblasts mutant for *aPKC* stop dividing prematurely and *aPKC* mutant larval brains show reduced numbers of neuroblasts[99,100]. Moreover, expression of a constitutively active, membrane-targeted form of aPKC in larval neuroblasts leads to an enormous increase in neuroblast numbers[99]. Consistent with these results, the increased number of larval neuroblasts in *lgl*, *pins* double mutants and *aurA* mutants correlates with the ectopic localization of aPKC around the entire neuroblast cortex at metaphase[95,97,99].

Can defects in the asymmetric division of stem cells cause cancer in humans?

Whether similar mechanisms are responsible for the development of cancer in humans is unclear at present, but this question opens a fascinating field of research. The human homologue of Aurora A is indeed amplified in many cases of human cancer and is suspected to be an oncogene[101]. As well as controlling spindle orientation, Aurora A has been implicated in the correct segregation of chromosomes during mitosis. Aurora A overexpression can therefore also lead to genomic instability, a hallmark of cancer cells[102]. The involvement of PKC-ι in the development of epithelial cancers has been discussed above. Given its prominent function in self-renewal in *Drosophila* neuroblasts, deregulation of this kinase may also be important in the context of cancer stem cells.

A recent paper demonstrated the importance of asymmetric stem cell divisions for the normal differentiation pattern of the skin. In this case, the proper orientation of the mitotic spindle in dividing stem cells was shown to depend on cadherin-mediated cell–cell adhesion and integrin-mediated cell–extracellular-matrix adhesion[103]. However, whether loss of asymmetry during division in this tissue causes tumours was not determined. In the gut, asymmetric divisions have been proposed to provide a mechanism for the selective protection of the genetic material of stem cells[104,105]. Intriguingly, the most commonly mutated tumour suppressor in colon cancer, APC (adenomatous polyposis coli), has been implicated in controlling the asymmetric division of stem cells in *Drosophila*[106].

Outlook and perspectives

It is unclear at present whether there is a direct causal relationship between loss of cell polarity and tumour initiation in humans, although more advanced tumours usually lack polarity. However, data from *Drosophila* show clearly that loss of polarity and changes in adhesion can be initiating events in tumour formation. These findings in model organisms indicate that slight changes in cell polarity and/or cellular junctions early in tumorigenesis may have escaped detection up to now and should be re-examined more closely with quantitative methods. Animal models that offer researchers the opportunity to inactivate genes involved in polarity in a temporally and spatially controlled manner will be useful in establishing how changes in polarity can direct tumour formation. Beyond doubt is the fact that the loss of apical–basal cell polarity is a hallmark of the most advanced malignant tumours. Thus, interfering with the signalling pathways that promote the loss of epithelial integrity may be one of the most promising avenues in the treatment of advanced tumours to prevent metastasis.

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