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Minireview

Scribble at the crossroads

Sandrine Etienne-Manneville

Address: Institut Pasteur, Cell Polarity and Migration Group and CNRS URA 2582, 25 rue du Dr Roux, 75724 Paris cedex 15, France.
Email: sandrine.etienne-manneville@pasteur.fr

Abstract
Although proteins involved in determining apical-basal cell polarity have been directly linked to tumorigenesis, their precise roles in this process remain unclear. A recent report in *BMC Biology* clarifies the signaling pathways that control cell polarity, proliferation and apoptosis downstream of the tumor suppressor and apical-basal polarity determinant Scribble.

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As the signaling networks that control cell polarity are deciphered, it is clear that some of the main regulators of epithelial apical-basal polarity are also involved in tumorigenesis. This is hardly surprising. As loss of polarity and tissue architecture is a common feature of carcinomas, we might expect that regulation of cell polarity would be altered at some stage of tumor development. But whether loss of cell polarity on its own is sufficient for tumor formation is debatable. A more general question is whether polarity proteins contribute to tumorigenesis directly through disruption of their polarizing functions, or whether their involvement in tumorigenesis is due to their roles in the signaling pathways that independently control cell division, cell apoptosis and cell polarity?

In *Drosophila*, the genes *scribble* (*Scrib* in mammals), *discs large* (*Dlg*) and *lethal giant larvae* (*Lgl*) act together to regulate epithelial cell apico-basal polarity and also act as tumor suppressor genes [1]. Scribble encodes a multidomain scaffold protein of the LAP (LRR and PDZ) family and is therefore likely to be involved in several distinct signaling pathways. A single mutation in *scribble* can induce loss of apical-basal polarity and massive hyperproliferation of the imaginal discs, demonstrating a role for Scribble in the regulation of both polarity and cell proliferation. In a recent paper in *BMC Biology*, Anthony Brumby and colleagues (Leong *et al.* [2]) provide further insights into the role of polarity proteins in tumorigenesis. They have characterized two distinct signaling pathways downstream of Scribble in *Drosophila*, one of which controls both cell polarity and cell proliferation, whereas the other leads to apoptosis.

Polarity proteins and cancer

In *Drosophila*, homozygous *scribble* mutant clones in an otherwise heterozygous animal develop relatively few tumors, which are eliminated by apoptosis, and simultaneous oncogenic mutations involving Ras or Notch are required to promote hyperproliferation and metastasis [3]. In humans, a correlation between reduced Scrib expression and malignant progression has been reported in colon cancer [4]. In addition, Scrib is targeted for ubiquitin-mediated degradation by high-risk human papillomavirus (HPV) E6 proteins [5], suggesting that Scrib degradation contributes to the development of HPV-induced cervical carcinoma. However, as in *Drosophila*, it seems that additional oncogenic mutations are needed to drive tumorigenesis in humans [6,7].

In addition to Scrib, Lgl and Dlg, several other major regulators of cell polarity have been shown to be involved in cancer progression [8]. In particular, the atypical protein kinase C (aPKC) PKCι may function as an oncoprotein in humans, as high levels of aPKC lead to both cell hyperproliferation and loss of epithelial apical-basal polarity [9] (Figure 1). This raises the question of how polarity proteins are linked to the regulation of cell proliferation and tumorigenesis and whether this relationship involves the signaling pathways that control cell polarity?

Polarity and cell proliferation

The original genetic studies performed in *Drosophila* showed that Scribble functions in a complex with Dlg and Lgl to promote basolateral membrane identity. Two other protein complexes - the Bazooka (Par3 in mammals) complex, which also includes Par6 and aPKC, and the Crumbs complex of Crumbs, Stardust and Patj - define the apical surface (see [1] and references therein). The relationship between these three complexes lies at the heart of epithelial cell polarity. aPKC seems to be a critical linking factor, as it mediates the phosphorylation of both Par3 and Crumbs to control their apical localization. Conversely, the Crumbs complex activates aPKC and prevents the Scribble complex forming in the apical part of the cell. The mechanism underlying this remains obscure, but it might be due to phosphorylation

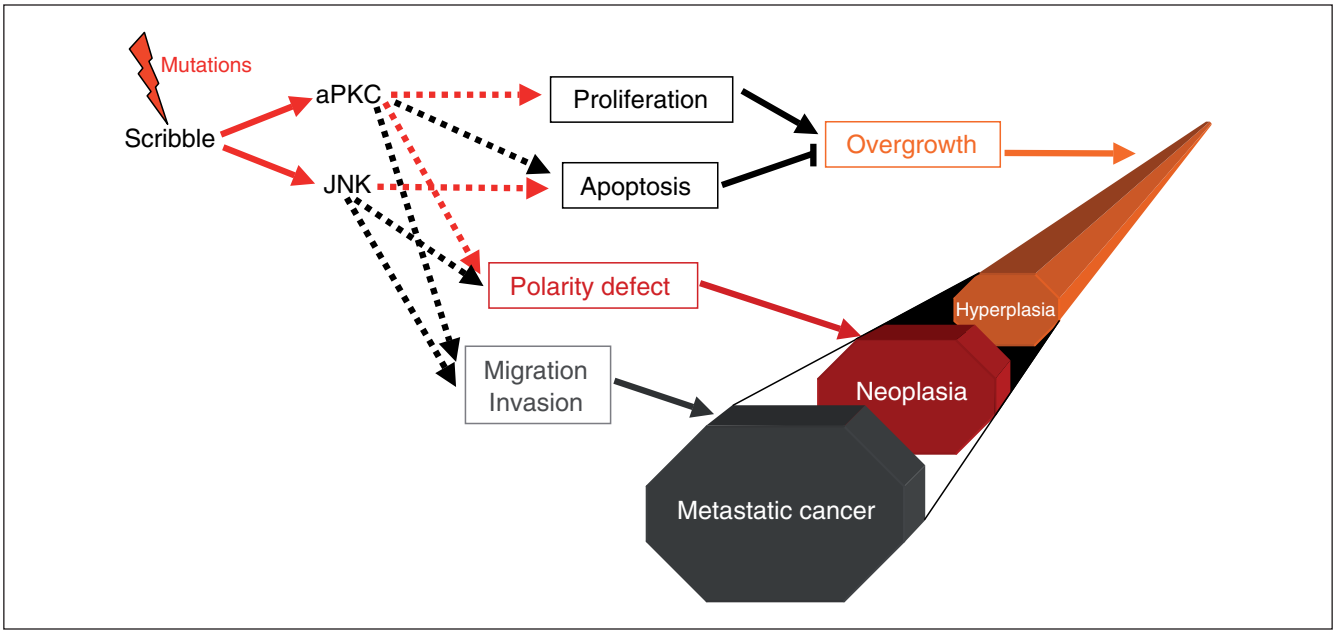

Figure 1

Complex interplay between oncogenic pathways. Changes in tumor malignancy from hyperplasia to metastatic cancer result from the accumulation of numerous alterations of normal cellular functions. Cell polarity, cell proliferation and apoptosis are key targets of neoplastic mutations. Proteins such as Scribble, aPKC or JNK (see text) can simultaneously participate in several signaling pathways (dotted arrows) controlling these different cell functions. Consequently, changes in their activity are likely to have dramatic effects on tumor progression. In the case of Scribble, mutations lead to loss of cell polarity, to increased cell proliferation and to the induction of pro-apoptotic pathways via a subset of these intertwined signaling cascades (highlighted in red).

of Lg1 by aPKC. Reciprocally, Scribble has also been shown to act upstream of aPKC to dictate cell polarity in the directed migration of mammalian astrocytes and epithelial cells [10,11].

The antagonism between aPKC and the Scribble complex in the regulation of cell polarity is reflected by the opposing effects of aPKC and Scribble in tumor development. Whereas *scribble* acts as a tumor suppressor gene, oncogenic functions have been attributed to PKCι in humans [9]. Leong *et al.* [2] now show that in *Drosophila*, overexpression of a membrane-targeted aPKC mimics the *scribble* mutant phenotype. Normal cell morphology was obtained when a dominant-negative aPKC was expressed in *scribble* mutant cells. This aPKC function does not involve regulation of the Crumbs complex, as a null mutation in Crumbs did not compensate for the effects of the *scribble* mutations on cell polarity and proliferation [2]. This study clearly highlights the role of aPKC in mediating Scribble function in both polarity and cell proliferation and it is tempting to speculate that aPKC is also involved in overgrowth and in the polarity defects observed in wing discs following Crumbs overexpression. Their results suggest that the functions of Scribble in cell polarity and cell proliferation cannot be separated.

Polarity and overgrowth

In the absence of additional oncogenic mutations, *scribble* mutant clones display defects in cell polarity and show increased cell proliferation but do not overgrow. Growth control results from the regulation of both cell proliferation and apoptosis (Figure 1). In *Drosophila*, signaling via the fly version of the mammalian Jun-N-terminal kinase (JNK) pathway induces apoptosis, which eliminates developmentally aberrant cells from a tissue [12]. In line with this, JNK is activated in the *scribble* mutant cells investigated by Leong *et al.* and limits tumor growth by promoting apoptosis [2,3].

Interestingly, the Par6-aPKC polarity complex can inhibit apoptosis in polarized mammalian epithelial cells in culture [13], and conversely, pro-apoptotic JNK is also a major component of the WNT-regulated planar cell polarity pathway in mammals, suggesting that polarity and apoptosis may use common signaling pathways (Figure 1). However, in *Drosophila*, Leong *et al.* [2] find that inhibition of aPKC does not prevent JNK-mediated cell death of *scribble* mutant cells, and that expression of dominant-negative JNK does not rescue the effects of *scribble* mutations on cell proliferation and polarity. Thus, cell proliferation and polarity on the one hand, and apoptosis on the other, are controlled by two distinct

signaling pathways downstream of Scribble (Figure 1). The relationship of Scribble to the JNK-dependent pro-apoptotic pathway is likely to be indirect; this pathway may be triggered by altered cell-cell junctions or tissue disorganization and may also involve autocrine or paracrine stimulation of cells by the cytokine tumor necrosis factor.

One puzzling observation from this and other studies in *Drosophila* is that although JNK is pro-apoptotic, it is also required for the neoplastic overgrowth observed in *scribble* mutants expressing the additional oncogenic signals induced by mutant Ras, Notch, Stardust or Crumbs [2,14]. Whether these oncogenic signals modulate JNK activation levels and alter its function, or whether they control other transcriptional regulators that may divert JNK signals, remains unclear. In mammals, two JNK proteins (JNK1 and JNK2) are expressed, and they seem to have opposing tumor-suppressive and tumor-promoting activities [15]. The observations in *Drosophila* may therefore reflect a limitation of this model system, in which a single JNK can both restrain and enable overgrowth.

Loss of polarity and tumorigenesis

The study by Leong *et al*. [2] indicates that the effects of Scribble on cell polarity and cell proliferation in *Drosophila* involve the same aPKC-dependent and JNK-independent pathway, and it is not yet possible to distinguish separate mechanisms regulating cell polarity and proliferation. In humans, the protein kinase LKB1 acts as a polarity protein and a tumor suppressor. Causal mutations in the carboxy-terminal domain of LKB1 in people with the cancer-prone Peutz-Jeghers syndrome do not affect cell proliferation but strongly alter cell polarity [16], suggesting that polarity and proliferation result from distinct pathways. Loss of polarity in epithelial cells is, however, bound to alter their response to mitogenic signals. Could loss of polarity be a first step towards overproliferation and tumorigenesis? The intimate link between cell polarity and cell proliferation remains unclear, and further investigation of the signaling pathways controlling these two essential properties of functional epithelial tissues should lead to a better understanding of the multiple steps leading to cancer.

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