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.

See research article http://www.biomedcentral.com/1741-7007/7/62.

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...
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.

**References**

1. Bilder D: Epithelial polarity and proliferation control: links from the Drosophila neoplastic tumor suppressors. *Genes Dev* 2004, 18:1909-1925.
2. Leong GR, Goulding KR, Amin N, Richardson HE, Brumby AM: scribble mutants promote aPKC and JNK-dependent epithelial neoplasia independently of Crumbs. *BMC Biol* 2009, 7:62.
3. Brumby AM, Richardson HE: scribble mutants cooperate with oncogenic Ras or Notch to cause neoplastic overgrowth in Drosophila. *EMBO J* 2003, 22:5769-5779.
4. Gardiol D, Zacchi A, Petrella F, Stanta G, Banks L: Human discs large and scrib are localized at the same regions in colon mucosa and changes in their expression patterns are correlated with loss of tissue architecture during malignant progression. *Int J Cancer* 2006, 119:1285-1290.
5. Thomas M, Massimi P, Navarro C, Borg JP, Banks L: The hScrib/Dlg apico-basal control complex is differentially targeted by HPV-16 and HPV-18 E6 proteins. *Oncogene* 2005, 24:8222-8230.
6. Dow LE, Elsum IA, King CL, Kinross KM, Richardson HE, Humbert PO: Loss of human Scribble cooperates with H-Ras to promote cell invasion through deregulation of MAPK signalling. *Oncogene* 2008, 27:5988-6001.
7. Zhan L, Rosenberg A, Bergami KC, Yu M, Xuan Z, Jaffe AB, Allred C, Muthuswamy SK: Deregulation of scribble promotes mammary tumorigenesis and reveals a role for cell polarity in carcinoma. *Cell* 2008, 135:865-878.
8. Wodarz A, Nathke I: Cell polarity in development and cancer. *Nat Cell Biol* 2007, 9:1016-1024.
9. Eder AM, Sui X, Rosen DG, Nolden LK, Cheng KW, Lahad JP, Kango-Singh M, Lu KH, Warrene CL, Atkinson EN, Bedrosian I, Keyomarsi K, Kuo WL, Gray JW, Yin JC, Liu J, Haldor G, Mills GB: Atypical PKCiota contributes to poor prognosis through loss of apical-basal polarity and cyclin E overexpression in ovarian cancer. *Proc Natl Acad Sci USA* 2005, 102:12519-12524.
10. Osmani N, Vitale N, Borg JP, Etienne-Manneville S: Scrib controls Cdc42 localization and activity to promote cell polarization during astrocyte migration. *Curr Biol* 2006, 16:2395-2405.
11. Dow LE, Kauffman JS, Caddy J, Peterson AS, Jane SMR, Russell SM, Humbert PO: The tumour-suppressor Scribble dictates cell polarity during directed epithelial migration: regulation of Rho GTPase recruitment to the leading edge. *Oncogene* 2007, 26:2272-2282.
12. Igaki T: Correcting developmental errors by apoptosis: lessons from Drosophila JNK signaling. *Apoptosis* 2009, 14:1021-1028.
13. Kim M, Datla A, Brakeman P, Yu W, Mostov KE: Polarity proteins PAR6 and aPKC regulate cell death through GSK-3beta in 3D epithelial morphogenesis. *J Cell Sci* 2007, 120:2309-2317.
14. Uhlirova M, Jasper H, Bohmann D: Non-cell-autonomous induction of tissue overgrowth by JNK/Ras cooperation in a Drosophila tumor model. *Proc Natl Acad Sci USA* 2005, 102:13123-13128.
15. Wagner EF, Nebreda AR: Signal integration by JNK and p38 MAPK pathways in cancer development. *Nat Rev Cancer* 2009, 9:537-549.
16. Forcet C, Etienne-Manneville S, Gaude H, Fournier L, Debilly S, Salmi M, Baas A, Olschwag S, Clevers H, Billaud M: Functional analysis of Peutz-Jeghers mutations reveals that the LKB1 C-terminal region exerts a crucial role in regulating both the AMPK pathway and the cell polarity. *Hum Mol Genet* 2005, 14:1283-1292.