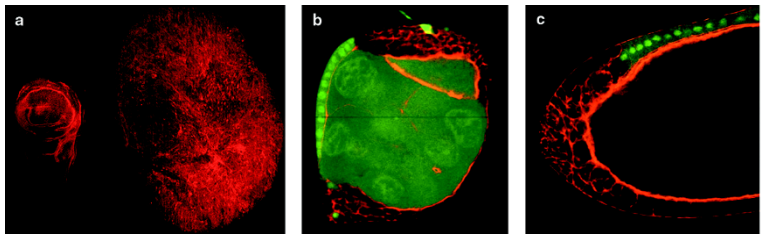
Growth and polarity: the case for Scribble



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The epithelial membranes of any organism consist of cells that have a regular columnar shape and defined apical–basolateral polarity. During carcinogenesis, epithelial cells lose these characteristics, as well as control of cell proliferation, and form disorganized cellular structures that have the potential to develop into metastases. *Drosophila* genetics has always been used to study epithelial morphogenesis and cell proliferation. However, very few genes have been identified that seem ultimately to control both.

Recently, Bilder and Perrimon (*Nature* **403,** 676–680, 2000) reported the isolation of Scribble (Scrib), a member of the LAP (Leucine-rich repeat and PDZ domain) family of proteins (*Nature Cell Biol.* **2,** E114, 2000). Scrib is required to maintain apical–basal polarity, as are the two further LAP proteins recently identified by Borg *et al.* (*Nature Cell Biol.* **2,** 407–414, 2000) and Legouis *et al.* (*Nature Cell Biol.* **2,** 415–422, 2000), although their precise role in this process is unknown.

Bilder *et al.* (*Science* **289,** 113–116, 2000) went on to investigate the mechanism of Scrib's activity. In epithelial cells Scrib co-localizes to the septate junction (the *Drosophila* homologue of the vertebrate tight junction) with Discs-large (Dlg). Dlg is a PDZ-domain protein that functions in cell polarity and as a tumour suppressor. The expression of both Scrib and Dlg overlaps with that of *lethal giants larvae* (Lgl), another known tumour suppressor. Bilder and colleagues conducted a screen to identify other genes that, like *scrib*, are required to maintain the polarity of follicle cells in the *Drosophila* ovary, and identified a new allele of *lgl*, which showed a similar phenotype in follicle cells to that of Scrib mutants.

The authors then returned to embryonic epithelia and noticed that in embyros with mutations in *lgl* or *dlg*, apical–basolateral polarity was altered, in the same way as in *scrib* mutants. Furthermore, they examined another *Drosophila* epithelium, the wing disc, and found that Scrib-mutant cells overproliferated and showed alterations in polarity, similar to those seen for *dlg* and *lgl* mutants (picture **a**). Scrib-mutant follicle-cell clones in the ovary have similar phenotypes (pictures **b** and **c**; absence of green staining shows a Scrib clone), although it is not certain whether this is due to overproliferation.

The similarities in mutant phenotype and the co-localization of each protein led the authors to investigate a link between the three genes in maintaining polarity. Genetic interactions between the three genes, which generate defects in dorsal closure of *Drosophila* embryos, also indicated that these genes act in a common pathway to maintain both polarity and growth. What is this pathway? Looking at the localization of each protein in mutants for the other genes, Bilder and colleagues concluded that Dlg and Srib act in a region called the apical margin of the lateral membrane (ALM) to ensure Lgl is correctly localized. This localization of Lgl is also essential to ensure that both Scrib and Dlg are localised to the ALM.

This leaves us with three proteins, all of which are essential for growth control and maintenance of apical–basolateral polarity, and the localization of which is dependent on the other proteins. How do they elicit their effects to cause such striking and fundamental defects in mutant embryos? Bilder and colleagues speculate on a beautiful model in which Lgl (the yeast homologues of which bind to t-SNAREs, essential players in the secretory pathway) promotes, in a Scrib- and Dlg- dependent manner, fusion of vesicles to the apical membrane; hence cells establish their polarity through vesicle targeting. Growth-factor receptors and cell–cell adhesion molecules are localized to specific apical sites, so their mislocalization in Srib, Lgl or Dlg mutants could lead to the detrimental defects seen in *Drosophila* mutants. As Scrib has a human homologue, it will be exciting to see the influence of these models on cancer research in the years ahead.

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(such as Leu-Ala, but not Ala-Leu). Ubr1 also contains a binding site for a conjugating enzyme partner, and a RING-finger motif that is required for the chemistry of the conjugation reaction, but is dispensible for the binding of type-1 and type-2 substrates. The properties of Ubr1, as elucidated using model substrates, are strikingly conserved in evolution[7]. However, for much of its scientific life, Ubr1 was an enzyme in search of a biological substrate.

A breakthrough came with the finding that mutations in Ubr1 inhibit dipeptide uptake in the yeast *Saccharomyces cerevisiae*[9]. A yeast transcription factor called Cup9 proved to be the relevant substrate[3]. Regulatory molecules such as transcription factors are frequently substrates of the ubiquitin system, for reasons that are easily understood — if a protein turns over rapidly, its steady-state level will be extremely sensitive to changes in the rates of its synthesis and degradation. Cup9 represses the import of peptides by binding to sequences upstream of the *PTR2* gene, which encodes a di/tripeptide transporter. Robust peptide import requires that Cup9 is maintained at a low level through Ubr1-dependent ubiquitination, which leads to the turnover of Cup9 by proteasomes (Fig. 1e). However, the recognition of Cup9 by Ubr1 involves a noncanonical internal degron[3], rather than the Cup9 N terminus.

Turner and colleagues have now linked these apparently disparate substrate-binding properties of Ubr1 in an unexpected and elegant way. They have shown that the turnover of Cup9 in yeast cells is stimulated by dipeptides with type-1 or type-2 N termini, but not by control dipeptides with stabilizing N termini. This N-terminal specificity mimics what would be expected if dipeptides bind to the type-1 and type-2 'substrate' sites of Ubr1 and allosterically activate the ubiquitination of Cup9 that is