DEVELOPMENT

Cellular architects

Architects of any structure know the importance of defining the limits and orientation of a building. The top and bottom must be established and maintained, with interactions between all walls, ceilings and floors closely regulated. Cellular architecture is similarly regulated, with the ceiling (apical), floor (basal) and walls (basolateral) being defined and maintained. Nowhere is this architecture more clearly visualized than in the epithelial cells of *Drosophila melanogaster*. Although many genes that regulate the architecture of these cells have been identified, only now does new work in *Nature Cell Biology* indicate how these individual players might come together as one construction team.

Polarized *Drosophila* epithelial cells contain numerous membrane domains with distinct proteins involved in their maintenance. The *bazooka* group, the *crumbs* group and the *discs-large*/*scribble* group all have precise roles in apical–basal membrane polarity. Formation of a functional zonula adherens (a belt-like adhesion junction which encircles the whole cell) is of primary importance to most epithelial cells, with mutations in all three groups of genes mentioned above affecting this process. By analysing genetic relationships between these three groups, Bilder *et al*. and Tanentzapf and Tepass indicate that these three groups of genes could function co-operatively to order the formation of polarity in an integrated hierarchy.

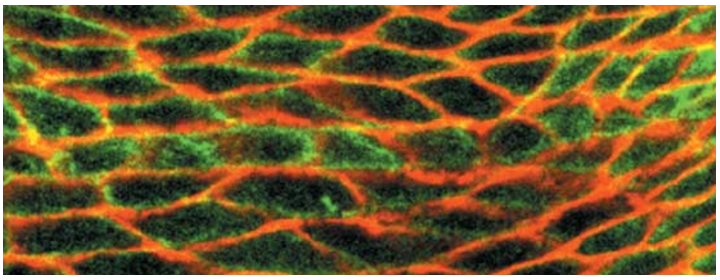
Genetic analysis in *Drosophila* is a powerful tool in understanding how different protein complexes regulate the function of one another. By determining the epistatic relationship of one gene to another, the functional interactions of different protein complexes can be ascertained. By applying this analysis to study the development of apical–basolateral polarity, Bilder *et al.* and Tanentzapf and Tepass tentatively ordered the three groups of genes into a construction network. It seems that the *bazooka* group is the top of the genetic hierarchy and acts to initiate zonula adherens assembly and establish apical polarity. The activity of the Bazooka group is counteracted by the Discs-large group, which is recruited independently to the basolateral membrane and represses the ability of the Bazooka group to induce apical membrane formation, and recruitment of the Crumbs group, in this region. Although the Discs-large group also seems to counteract the activity of the apical-inducing Crumbs group, Bilder *et al.* suggest that the Crumbs group could also act to antagonize the activity of the Discs-large group, creating a complex network of interactions.

Whether these groups of proteins physically interact with one another to generate this network, which regulates polarity and determines zonula adherens formation, is unknown. Yet these three groups resemble the very best in construction expertise as they sensitively balance activity with one another to ensure correct establishment of polarity and cellular architecture.

Sarah Greaves, Senior Editor,
Nature Cell Biology

References and links

ORIGINAL RESEARCH PAPERS Bilder, D. Schober, M. & Perrimon, N. Integrated activity of PDZ protein complexes regulates epithelial polarity. *Nature Cell Biol.* **5**, 53–58 (2003) | Tanentzapf, G. & Tepass, U. Competitive, stage-specific and redundant interactions between the *crumbs*, *lethal giant larvae* and *bazooka* pathways in epithelial polarization. *Nature Cell Biol.* **5**, 46–52 (2003)



STRUCTURE WATCH

It's a wrap!

The Wiskott–Aldrich syndrome protein (WASP) and its homologue N-WASP promote actin polymerization in response to upstream signals, and their importance is highlighted by the Wiskott–Aldrich syndrome (WAS) — an immune disorder that is caused primarily by missense mutations in the Enabled/VASP homology 1 (EVH1) domain of WASP. Although the WASP/N-WASP EVH1 domain has been proposed to bind both phosphoinositides and peptides, these proposals have remained unconfirmed. However, work now published by Lim and colleagues in *Cell* has increased our understanding of both the binding interactions of the WASP/N-WASP EVH1 domain and the effects of WAS-causing mutations.

The authors began by showing that the N-WASP EVH1 domain and other EVH1 domains do not bind phosphatidylinositol-4,5-bisphosphate as was previously thought. They showed, however, that N-WASP EVH1 specifically binds to 25 residues of the WASP-interacting protein (WIP). When they determined the NMR structure of the N-WASP EVH1–WIP complex, they found that, although the overall structure of N-WASP EVH1 was the same as that for other EVH1 domains, N-WASP EVH1 recognizes peptides in a new way. WIP, which is more than double the size of other EVH1 ligands, wraps itself around the EVH1 domain "...like a piece of string around a spool...", and contacts areas of the EVH1-domain surface that are well outside the canonical EVH1 peptide-binding site. This work has therefore identified a new (or hybrid) class of protein–protein interaction, and has also provided insights into how WAS-causing mutations affect the WASP/WIP interaction.

REFERENCE Volkman, B. F. *et al.* Structure of the N-WASP EVH1 domain–WIP complex: insights into the molecular basis of Wiskott–Aldrich syndrome. *Cell* **111**, 565–576 (2002)

The sensitive type

The inner membrane of *Escherichia coli* contains a 'mechanosensitive channel of small conductance' (MscS) that can transport ions (preferably anions) in response to cell-membrane depolarization and stretching. Although there has recently been progress in our understanding of the mechanism of voltage-dependent channel gating, there had been no structural insights. Now, however, in *Science*, Rees and colleagues report the 3.9-Å-resolution crystal structure of 'open' MscS.

They found that MscS forms a homoheptamer, with a transmembrane (TM) region and a large carboxy-terminal cytoplasmic region (the amino terminus of MscS is periplasmic). Each subunit contains three TM helices (TM1–3), and it is the TM3 helices that form the pore. The pore is linked to a large chamber in the cytoplasmic region, and this chamber is linked to the cytoplasm through eight openings. The authors suggest that these openings act as molecular filters to check molecules before they enter the pore.

TM1 and TM2 flank the pore, although they are slightly displaced from it, and Rees and co-workers propose that these flanking helices, with their membrane-embedded arginines, mediate the tension and voltage sensitivities of MscS. Although MscS is probably structurally distinct from other ion channels, the importance of these results lies in the structural organization of MscS, which seems to be relevant to the gating mechanisms of other channels.

REFERENCE Bass, R. B. *et al.* Crystal structure of *Escherichia coli* MscS, a voltage-modulated and mechanosensitive channel. *Science* **298**, 1582–1587 (2002)