Photoreceptor morphogenesis and retinal degeneration: lessons from *Drosophila*

Elisabeth Knust

Cells exhibit an amazingly wide range of different forms, and in most cases the shape of a cell is crucial for performing its specific function(s). But how does a cell obtain its particular shape during development, how can the shape be adapted to different environmental conditions, and what are the consequences if morphogenesis is impaired? An ideal cell type to study these questions is the photoreceptor cell, a photosensitive cell present in most metazoa, highly specialised to transform the energy from the light into a visual response. In the last few years, studies in the *Drosophila* eye have led to a considerable increase in understanding of the genetic control of photoreceptor morphogenesis; lessons, which may apply to other cell types as well. Most of the genes involved have been conserved during evolution, and mutations in several of them result in retinal degeneration, both in flies and humans. This makes the fly eye an attractive model to unravel the genetic, molecular and cell biological basis of the mechanisms that prevent retinal dystrophies.

Addresses
Max-Planck-Institute of Molecular Cell Biology and Genetics, Pfotenhauerstr. 108, D-01307 Dresden, Germany

Corresponding author: Knust, Elisabeth (knust@mpi-cbg.de)

The development of *Drosophila* photoreceptor cells

The photoreceptor cells (PRCs) of *Drosophila* develop from the eye imaginal disc, a single layered epithelium, the cells of which exhibit a pronounced apico-basal polarity and are closely connected by the zonula adherens (ZA), an adhesive belt-like structure encircling the apex of the cell. Specification of photoreceptor cells depends on several signalling pathways [1], and ultimately results in the formation of about 800 units, the ommatidia. Each ommatidium is composed of eight PRCs, which are associated with pigment and cone cells, and together form the compound eye of the fly (Figure 1a and b).

During pupal development, PRCs, which are still part of the single-layered epithelium of the imaginal disc, undergo a remarkable cell shape change. During this process, the apical poles of the epithelial cells turn through $90°$, such that the apical membranes of all eight PRCs of each ommatium come to face each other. In addition, the apical membrane becomes subdivided into two distinct regions: the central, most apical part develops into the rhabdomere, a highly pleated array of microvilli, which forms the light-sensing organelle, and the subapical stalk membrane, which connects the rhabdomere with the ZA. The formation of the rhabdomere is associated with a conspicuous deepening of the retina, resulting in an increase in depth from about $20–100 \mu m$ [2]. During this process, the rhabdomeres of the PRCs of one ommatidium, which are initially attached to each other, separate. Concomitantly, a central lumen is formed, into which the rhabdomeres protrude (Figure 2a and b).

One of the prominent features of PRC development is a tremendous increase of the plasma membrane during pupal development, in particular an expansion of the apical surface to accommodate the huge amount of rhodopsin and other components involved in phototransduction. The increase of the apical surface is manifested by the formation of about $50\,000$ microvilli, each of which is $\sim 1.5 \mu m$ in length and only $50\,nm$ wide. Actin filaments, associated with Myosin III, extend the entire length of each microvillus [3]. Any defect in the biogenesis and differentiation of the rhabdomere has an impact on the shape of the whole cell. To dissect this process, several questions can be addressed: (i) What determines apical membrane identity of PRCs and the subdivisions of the apical membrane into stalk and rhabdomere? (ii) Which mechanisms are responsible for the delivery of a huge amount of membrane to allow the formation of the rhabdomere? (iii) How do the rhabdomeres become separated from each other, that is how is the lumen in each ommatidium formed?

Differentiation of the apical membrane of photoreceptor cells

During the first half of pupal development, components marking the apical membrane of PRCs, such as actin or members of the Crumbs-complex, that is Crumbs, Stardust and DPATJ, co-localise apical to the adherens junctions. Specification of the apical membrane depends on *bazooka*, the fly homologue of Par-3 [4]. Bazooka encodes a scaffolding protein with three PDZ-domains and in some cells it can interact with *D*Par-6 and an atypical protein kinase C (*D*aPKC) to form the Par-complex.

Figure 1
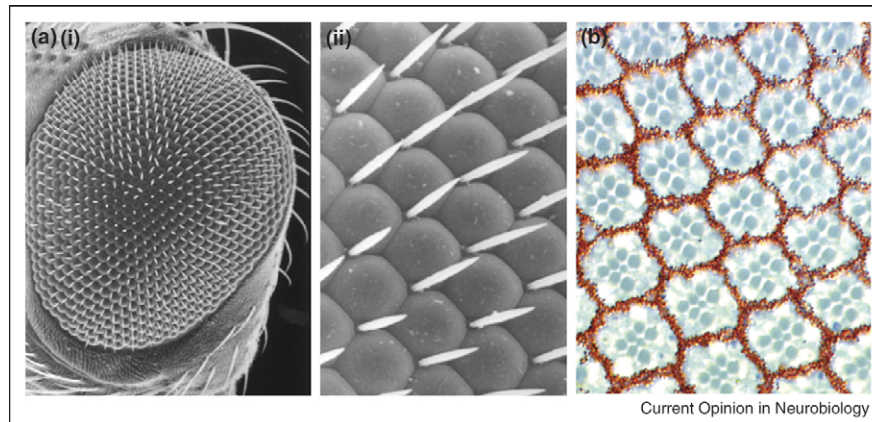
The *Drosophila* compound eye. **(a)** (i) Scanning electronmicrographs of an eye of the adult fly (**a'** higher magnification). The eye is composed of about 800 ommatidia, covered by lenses with a typical hexagonal shape. In every other vertex a bristle is formed. **(b)** A horizontal section through a wildtype eye. In each ommatidium seven photoreceptor cells can be distinguished by their dark rhabdomeres, which are arranged in a stereotype trapezoid pattern. The ommatidia are separated from each other by pigment cells. (Both pictures kindly provided by F. Grawe, Düsseldorf).

Bazooka localises to the ZA in early pupal PRCs, and to the rhabdomere in the second half of pupal development. In ommatidia lacking *bazooka* actin staining is fragmented and randomly positioned. Armadillo, a marker of the ZA, is disrupted and the stalk membrane marker DPATJ is absent or randomised. This points to an essential function of *bazooka* for polarisation of the PRC, and parallels its function in other cell types, such as the embryonic epithelium [5]. In epithelial cells of the follicle, the Ser/Thr-kinase Par-1 is required to exclude Bazooka from the baso-lateral side, thereby restricting it to the apical membrane [6]. In pupal eye discs, Par-1 does not affect apico-basal polarity, but rather seems to have a function in proper elongation of the ZA [7].

Once the apical membrane has been specified, it becomes subdivided into two functional domains, the most apical (rhabdomeric) and the subapical (stalk) domain. This subdivision is initiated at about 50% of pupal development by the segregation of apical markers, so that actin now highlights the most apical part of the membrane, the incipient rhabdomere, and the members of the Crumbs complex demarcate the stalk membrane (Figure 2c). The subdivision requires the recruitment of PTEN, a lipid phosphatase, to the ZA. This is mediated by Bazooka, which can directly interact with PTEN [8$^{••}$,9$^{••}$]. PTEN, in turn, is known to regulate the balance between phosphatidylinositol(3,4,5)-trisphosphate [PtdIns(3,4,5)P$_3$] and PtdIns(4,5)P$_2$ by promoting PtdIns(3,4,5)P$_3$ degradation, and hence has an influence on its controlled accumulation on the entire apical surface. Loss of PTEN from PRCs results in enhanced accumulation of the Ser/Thr kinase Akt1 on the apical surface. As a result, about 50% of PRCs lack the apical membrane, and 20% show split rhabdomeres, in which the interrupted membrane is

positive for stalk-specific components, such as Crumbs or DPATJ [9$^{••}$]. The results indicate that the fine-tuned regulation of phosphoinositide levels is crucial for the proper differentiation of the apical membrane. This seems to be a conserved mechanism, which has been implicated in the migration of *Dictyostelium* cells [10,11] and during polarisation of epithelial cells in culture [12].

After separation of the rhabdomere and the stalk, growth of these two membrane domains, in particular the rhabdomere, takes place. Mutant PRCs lacking the transmembrane protein Crumbs or the scaffolding proteins Stardust or DPATJ show two phenotypic traits: (i) a ~50% reduction in the length of the stalk membrane and (ii) a failure to properly elongate the rhadomere [4,13,14,15$^{••}$]. As demonstrated by the investigation of different *stardust* alleles [15$^{••}$] and a structure-function analysis of *crumbs* (M. Richard and E. Knust, unpublished), these two processes can be functionally separated and are likely to depend on different interacting partners of the complex. In wildtype PRCs, the members of the Crumbs complex form a protein scaffold localised at the stalk membrane, the activity of which must be tightly regulated. This is mediated by Yurt, a FERM (4.1-ezrin-radixin-moesin) protein [16$^{••}$]. Yurt is initially localised at the baso-lateral membrane of developing PRCs, but is recruited to the apical stalk membrane at the end of pupal development, a process that depends on *crumbs*. Yurt can bind via its FERM domain to the cytoplasmic domain of Crumbs, which contains a conserved FERM-binding motif. Loss of *yurt* results in an expansion of the stalk membrane, a phenotype similar to that observed upon overexpression of Crumbs [13] and opposite to that of loss of *crumbs* or *stardust*. *Drosophila yurt* is the orthologue of zebrafish *mosaic eyes*, which is necessary for the normal

Figure 2
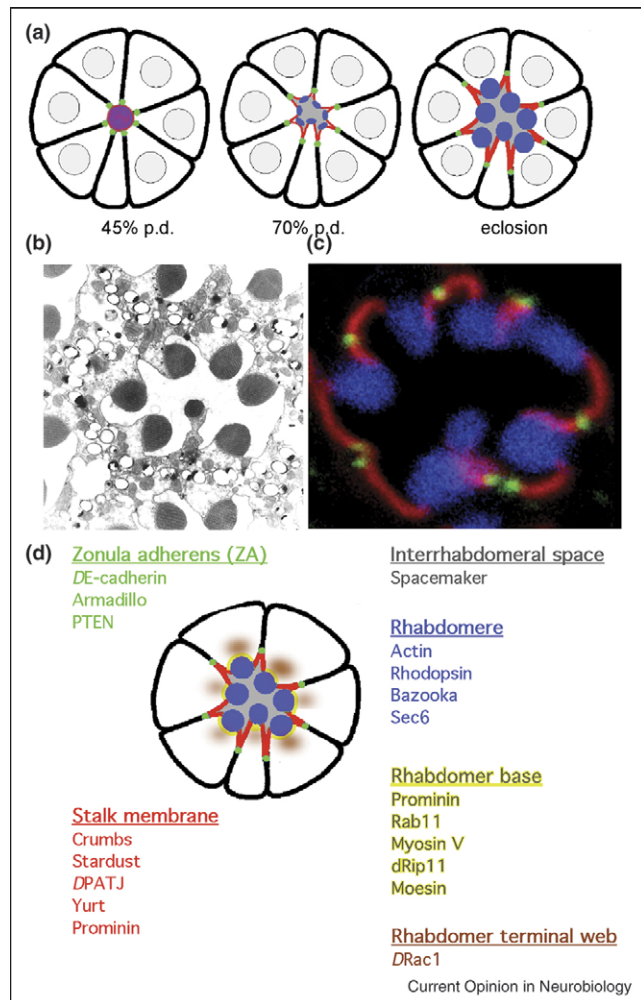
Development and structure of the *Drosophila* compound eye. **(a)** Schematic representation of photoreceptor cells at 45% and 70% pupal development and in the adult. Green: ZA, blue: rhabdomere, red: stalk. In late pupal stages and in the adult eye the rhabdomeres are separated by a central lumen (dark grey), the interrhabdomeral space. **(b)** Cross-section through an ommatidium of an adult wildtype fly. (Kindly provided by F. Grawe, Düsseldorf). **(c)** Optical cross section through an ommatidium of an adult wildtype fly, stained with Armadillo (green), to highlight the ZA, actin (blue) to stain the rhabdomere and Stardust (red) to label the stalk membrane. (Kindly provided by N. A. Bulgakova, Dresden). **(d)** Schematic representation of an adult ommatidium, indicating the different domains discussed in the text. The localisation of the different proteins are indicated by the corresponding colour.

highlights the conserved function of the Crumbs complex and its regulators in the differentiation of apical membranes from flies to vertebrates.

The Crumbs complex is also required for the proper elongation of the rhabdomere [4,13,14,15••,19–21]. Recent results on *stardust* provide evidence that the elongation of the rhabdomere and the length of stalk are independently controlled: one *stardust* allele, sdt^{N5}, which expresses lower amount of proteins, shows a reduced length of the stalk membrane, but normal elongation and shape of the rhabdomeres [15••]. *stardust* encodes scaffolding proteins of the membrane-associated guanylate kinase (MAGUK)-family of proteins. They recruit the transmembrane protein Crumbs and the scaffolding protein DPATJ and *D*Lin-7 into a complex, which is localised at the stalk membrane (Figure 2c).

The cytoskeleton and trafficking control morphogenesis of the rhabdomere

Elongation of the rhabdomere requires an elaborate actin-based cytoskeleton to sustain the constraints acting on the apical pole. The rhabdomere terminal web (RTW) defines the PRC cytoplasmic region next to the base of the rhabdomere. A fusion protein composed of GFP and the actin-binding site of Moesin highlights the RTW as bundled microfilaments that expand from the rhabdomere base deep into the PRC [22]. The RTW is comparable to the terminal web of other epithelia, for example, that of the intestine, underlying the microvilli. One of its organisers is *Drosophila* Rac1 (*D*Rac1), a monomeric GTPase. Expression of a dominant negative form of *D*Rac1 impairs the size and organisation of the rhabdomere and reduces the number of microvilli formed [22]. In addition, the rhabdomere base is not formed. The rhabdomere base (see Figure 2d) is a specialised, highly dynamic region of the rhabdomere adjacent to the cytoplasm [23], and is a site of cytoskeletal organisation and membrane traffic (see below). One of the proteins associated with the rhabdomere base is Moesin, a member of the FERM (4.1-ezrin-radixin-moesin)-protein family. These proteins have been shown to act as cross-linkers between the actin cytoskeleton and the apical plasma membrane, in particular in epithelial cells, and thus play a structural role by anchoring the actin filaments. In PRCs, Moesin is localised to the rhabdomere base immediately adjacent to the base of the rhabdomere. Loss of Moesin severely disrupts the apical organisation of PRCs, including the structure of the membrane cytoskeleton and the microvilli, but does not alter the integrity of the junctions [24].

In addition to its function in dynamic reorganisation of the actin cytoskeleton, the RTW is also the site of intense membrane trafficking. Rhodopsin is abundantly synthesised in PRCs, in particular during the end of pupal development, when the rhabdomere forms. The small GTPase Rab11 localises to the trans-Golgi network and

lamination of the retina [17••]. Zebrafish rod photoreceptors lacking *mosaic eyes* exhibit an expanded outer segment, which is part of the apical membrane and functionally equivalent to the rhabdomere of the fly's eye. As in *Drosophila*, the *mosaic eyes* phenotype is opposite to that of eyes mutant for *crb2a*, one of the zebrafish *crumbs* genes. Similarly, in PRCs lacking *crb2b* function the inner segments, which constitute part of the apical membrane, are significantly shorter [18]. This further

the base of the rhabdomere. Inhibiting Rab11 function results in defects in rhodopsin delivery to the apical membrane and its accumulation in the cytosol [25]. As a consequence morphogenesis of the rhabdomere is impaired, which is consistent with the notion that Rhodopsin, besides its function in light reception, plays an essential structural role during PRC morphogenesis [23]. Rab11 forms a complex with dRip11 (*Drosophila* Rab11 family interacting protein) and myosin V (MyoV). Reducing the function of either of these genes impairs rhodopsin transport to the apical membrane and leads to its accumulation in the cytoplasm. Reduced function of MyoV additionally results in defective apico-basal polarity, manifested by the formation of supernumerary rhabdomeres at the lateral membrane of PRCs. This phenotype has been suggested to be the result of an impaired function of MyoV in pulling post-Golgi secretory vesicles, containing rhodopsin and other proteins, along polarised microfilaments through the apical RTW, thus delivering them to exocytic targeting patches at the base of the rhabdomere [25,26•].

Morphogenesis of rhabdomeres is also compromised in mutant eyes with reduced function of Sec6. Sec6 is a

Table 1

Summary of *Drosophila* proteins discussed in the text

Name of *Drosophila* protein	Structural characteristics	Function in the eye
Spacemaker/Eyes shut	Secreted protein, EGF-like and laminin A G-domain-like repeats	Formation of the interrhabdomeral space
Bazooka	Scaffolding protein with three PDZ-domains	Apico-basal polarity of PRCs
Actin	Cytoskeletal protein	Structure of the cell and the rhabdomere
Rhodopsin	G protein-coupled receptor with seven transmembrane domains	Signal transduction; morphogenesis of rhabdomere
Sec6	Component of the exocyst complex	Transport of rhodopsin
Prominin	Pentaspan membrane glycoprotein	Formation of the interrhabdomeral space
Chaoptin	Transmembrane proteins with leucine-rich repeats	Photoreceptor-specific adhesion molecule
Crumbs	Single-span transmembrane protein, EGF-like and laminin A G-domain-like repeats	Elongation of the PRC/rhabdomere, stalk membrane formation, prevention of light-induced degeneration
Stardust	Scaffolding protein, member of the membrane-assciated guanylate kinase (MAGUK) protein family	
DPATJ	Scaffolding protein, one Lin2/Lin7- (L27)- and four PSD95/Dlg/ZO-1- (PDZ)-domains	
Yurt	FERM/B41-domain	Elongation of rhabdomere and stalk membrane
Prominin	Pentaspan membrane glycoprotein	Formation of the interrhabdomeral space
DE-Cadherin	Transmembrane protein, Cadherin domains	Cell-cell adhesion
Armadillo/β-catenin	Armadillo/beta-catenin-like repeats	Cell-cell adhesion
PTEN	PDZ-binding motif	Controls apical accumulation of lipid PtdIns(3,4,5)P3
Myosin V	Motor protein, ATPase, IQ-domains (calmodulin-binding motifs)	Mediate membrane transport to developing rhabdomeres
Rab11	Monomeric GTPase	
Rip11 (Rab11-interacting protein)	C2-domain	
Moesin	FERM/B41-domain	Assembly of apical membrane cytoskeleton
DRac1	Monomeric GTPase	Organisation of the rhabdomeric microvilli

The colours indicate the major sites where these proteins are localised in the adult eye and refer to those shown in Figure 1d.

component of the exocyst. In late pupal stages and in the adult eye it is co-localised in the rhabdomere together with Sec 5 and Sec8, two other components of the exocyst complex, which has been implicated in apical exocytosis in many different cell types. Strikingly, Sec6 only affects transport of rhodopsin, which is targeted to the most apical region, the rhabdomere, but has no affect on proteins targeted to the subapical stalk or to the basolateral membrane [27].

Formation of the interrhabdomeral space

During pupal development, the apical membranes of the eight PRCs of each ommatidium, which are juxtaposed, are initially in close contact with each other. As pupal development proceeds and the rhabdomeres are formed, they become separated, thus forming a lumen, called the interrhabdomeral space (IRS). Flies mutant in *spacemaker* (*spam*)/*eyes shut* (*eys*) or *prominin* (*prom*) fail to form the IRS, and eyes of adult flies exhibit fused rhabdomeres and lack the central lumen [28••,29••]. *spam* encodes a secreted protein related to the proteoglycans agrin and perlecan, with 14 EGF-like and 4 Laminin G-like domains, and is secreted into the IRS. *prom* encodes a pentaspan membrane glycoprotein, similar to the mammalian prominin, and is localised on the stalk membrane and the apical portions of the microvilli. When expressed in cultured cells, secreted Spam can bind Prom localised on the plasma membrane. Spam and Prom have been suggested to counteract the adhesive forces between rhabdomeres, mediated by the GPI-linked protein Chaoptin, thus allowing the formation of the IRS.

The fly eye as a model for retinal degeneration in human

Most of the genes described above (Table 1), which are required for PRC morphogenesis of the *Drosophila* eye, have mammalian orthologues. Strikingly, some of the genes mentioned are required in the fly to prevent degeneration of PRCs, and perform a similar function in the mammalian eye. For example, loss of *Drosophila crumbs*, DPATJ, *stardust* (some alleles) and *yurt* leads to progressive light-induced PRC degeneration [14,15••,16••,20]. Similarly, mutations in mammalian Crb1 result in retinal degeneration in the mouse and RP12- and LCA-related blindness in human [30–33]. Mice lacking ezrin exhibit a delay in the development of the PRCs. This is because of severe defects in the microvilli of Müller glia cells and cells of the retinal pigment epithelium, both of which are essential for the health of the PRCs [34]. Finally, Prominin-1 (CD133) is associated with plasma membrane protrusions in many mammalian cells, for example, in apical microvilli of epithelial cells and the base of the rod outer segment of the PRC. Mutations in PROMININ-1 cause autosomal recessive retinal degeneration in human [35] and the knockout of mouse prominin-1 results in the complete loss of PRCs in older animals [36].

In addition, mutations in many of the components necessary for the signal transduction itself, such as the light receptor, Rhodopsin, the trimeric G-protein activated by it or components required for signal transduction in the cell, such as phospholipase C, also lead to retinal degeneration in the fly, (see [37••] for a recent review on photo-transduction and retinal degeneration in the fly). In some of the mutants, light-induced degeneration is likely to be caused by the endocytosis of a stable Rhodopsin/arrestin complex. In wildtype eyes, the light-induced signal transduction cascade is turned off by the formation of a complex between metarhodopsin, the activated form of rhodopsin, and arrestin2. The metarhodopsin-arrestin2 complex in turn dissociates upon further modification of its components. In a subset of retinal degeneration mutants, such as *arr2*, *norpA*, *rdgB* or *rdgC*, the metarhodopsin-arrestin2 complex is abnormally stable, and its endocytosis induces apoptosis of the cells by a still unknown mechanism [38,39]. Light-induced retinal degeneration in these mutants can be rescued by feeding larvae with a vitamin A-depleted medium [38,39], which reduces rhodopsin levels by over 95% [40]. Similarly, light-induced retinal degeneration in *crumbs*, *stardust* and *DPATJ* mutant eyes can be rescued by vitamin A depletion [14,15••,20].

The high degree of conservation of genes preventing retinal degeneration in flies and mammals is striking, in particular when considering the differences with respect to the development and the organisation of the eye in flies and mammals as well as the physiological differences during light-induced signal transduction. At the same time they suggest that these genes affect fundamental cell biological processes conserved between arthropods and vertebrates. Using the fly eye as a model will enhance our understanding of the cell biological, genetic and molecular basis of these processes and certainly will have a major impact on understanding the origin of the human diseases resulting from defects in the conserved genes.

Acknowledgements

References and recommended reading

Papers of particular interest, published within the annual period of the review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Kumar JP: **Signalling pathways in *Drosophila* and vertebrate retinal development**. *Nat Rev Genet* 2001, **2**:846-857.

2. Longley RLJ, Ready DF: **Integrins and the development of three-dimensional structure in the *Drosophila* compound eye**. *Dev Biol* 1995, **171**:415-433.

3. Arikawa K, Hicks JL, Williams DS: **Identification of actin filaments in the rhabdomeral microvilli of *Drosophila* photoreceptors**. *J Cell Biol* 1990, **110**:1993-1998.

4. Hong Y, Ackerman L, Jan LY, Jan Y-N: **Distinct roles of Bazooka and Stardust in the specification of *Drosophila* photoreceptor membrane architecture**. *Proc Natl Acad Sci U S A* 2003, **100**:12712-12717.

5. Harris TJC, Peifer M: **The positioning and segregation of apical cues during eoithelial polarity establishment in *Drosophila***. *J Cell Biol* 2005, **170**:813-823.

6. Benton R, St. Johnston D: ***Drosophila* PAR-1 and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells**. *Cell* 2003, **115**:691-704.

7. Nam S-C, Mukhopadhyay B, Choi K-W: **Antagonistic functions of Par-1 kinase and protein phosphatase 2A are required for localisation of Bazooka and photoreceptor morphogenesis in *Drosophila***. *Dev Biol* 2007, **306**:624-635.

8. von Stein W, Ramrath A, Grimm A, Muller-Borg M, Wodarz A:
•• **Direct association of Bazooka/PAR-3 with the lipid phosphatase PTEN reveals a link between the PAR/aPKC complex and phosphoinositide signaling**. *Development* 2005, **132**:1675-1686.

9. Pinal N, Goberdhan DC, Collinson L, Fujita Y, Cox IM, Wilson C,
•• Pichaud F: **Regulated and polarized PtdIns(3,4,5)P3 accumulation is essential for apical membrane morphogenesis in photoreceptor epithelial cells**. *Curr Biol* 2006, **16**:140-149.
The papers 8 and 9 show that in *Drosophila* the lipid phosphatase PTEN is co-localised with Bazooka apically in cells of embryonic epithelia and the follicle epithelium and at the adherens junction in the photoreceptor cells. In these tissues, Bazooka and PTEN localisation coincides with an enrichment of PtdIns(4,5)P$_2$. By contrast, in the developing PRCs, PtdIns(4,5)P$_2$ is excluded from the ZA and strongly enriched at the apical membrane. PTEN directly binds to a portion of Bazooka containing PDZ domains 2 and 3 *in vitro* and *in vivo*. These data are in agreement with results obtained in mammalian cells, where a differential distribution of PtdIns(4,5)P2 and PtdIns(4,5)P$_3$ at the apical and baso-lateral membrane, respectively, are required for proper epithelial polarity (see ref. [12]).

10. Funamoto S, Meili R, Lee S, Parry L, Firtel RA: **Spatial and temporal regulation of 3-phosphoinositides by PI 3-kinase and PTEN mediates chemotaxis**. *Cell* 2002, **109**:601-623.

11. Iijima M, Devreotes PN: **Tumor suppressor PTEN mediates sensing of chemoattractant gradients**. *Curr Biol* 2002, **11**:559-610.

12. Martin-Belmonte F, Gassama A, Datta A, Yu W, Rescher U, Gerke V, Mostov K: **PTEN-mediated apical segregation of phosphoinositides control epithelial morphogenesis through Cdc42**. *Cell* 2007, **128**:383-397.

13. Pellikka M, Tanentzapf G, Pinto M, Smith C, McGlade CJ, Ready DF, Tepass U: **Crumbs, the *Drosophila* homologue of human CRB1/RP12, is essential for photoreceptor morphogenesis**. *Nature* 2002, **416**:143-149.

14. Richard M, Grawe F, Knust E: ***DPATJ* plays a role in retinal morphogenesis and protects against light-dependent degeneration of photoreceptor cells in the *Drosophila* eye**. *Dev Dyn* 2006, **235**:895-907.

15. Berger S, Bulgakova NA, Grawe F, Knust E: **Unravelling the
•• genetic complexity of *Drosophila* stardust during photoreceptor morphogenesis and prevention of light-induced degeneration**. *Genetics* 2007, **176**:2189–2200.
The paper shows that *Drosophila* stardust, encoding a binding partner of Crumbs, and the fly orthologue of mammalian MPP5/Pals1 and zebrafish *nagie oko* is genetically complex. Some mutations only affect epithelial development in the embryo, while others also impair PRC morphogenesis and/or result in light-induced retinal degeneration. This complexity is the result of differential splicing, resulting in tissue-specific expression of different Stardust isoforms. They further suggest that Stardust may be engaged in cell-type specific protein complexes, which may have particular cell biological functions.

16. Laprise P, Beronja S, Silva-Gagliardi NF, Pellikka M, Jensen AM,
•• McGlade CJ, Tepass U: **The FERM protein Yurt is a negative regulatory component of the Crumbs complex that controls epithelial polarity and apical membrane size**. *Dev Cell* 2006, **11**:363-374.

17. Hsu Y-C, Willoughby JJ, Christensen AK, Jensen AM: **Mosaic
•• eyes is a novel component of the Crumbs complex and negatively regulates photoreceptor apical membrane**. *Development* 2006, **133**:4849-4859.
One important apical determinant of epithelial and photoreceptor cells in *Drosophila*, zebrafish, mouse and human is the transmembrane protein Crumbs. In all these cells, Crumbs is restricted to a subapical region, apical to the ZA. Here it organises a protein complex by recruiting the scaffolding protein Stardust/MPP5/Pals1 and DPATJ/PATJ/MUPP1. All Crumbs proteins contain a highly conserved FERM-binding domain. The two papers demonstrate that the *Drosophila* and the zebrafish FERM-protein Yurt/Mosaic Eyes negatively regulates the function of Crumbs. Yurt/Mosaic Eyes can directly bind to Crumbs, and its loss results in an enhanced activity of Crumbs. *Drosophila yurt* mutations can suppress the *crumbs* mutant phenotype in the embryo, but only in those *crumbs* mutants that still obtain some residual *crumbs* function, supporting the view that it mediates its function directly via Crumbs.

18. Omori Y, Malicki J: ***oko meduzy* and related *crumbs* genes are determinants of apical cell features in the vertebrate embryos**. *Curr Biol* 2006, **16**:945-957.

19. Izaddoost S, Nam S-C, Bhat MA, Bellen HJ, Choi K-W: ***Drosophila* Crumbs is a positional cue in photoreceptor adherens junctions and rhabdomeres**. *Nature* 2002, **416**:178-183.

20. Johnson K, Grawe F, Grzeschik N, Knust E: ***Drosophila* Crumbs is required to inhibit light-induced photoreceptor degeneration**. *Curr Biol* 2002, **12**:1675-1680.

21. Nam S-C, Choi K-W: **Domain-specific early and late function of DPATJ in Drosophila photoreceptor cells**. *Dev Dynam* 2006, **235**:1501-1507.

22. Chang H-Y, Ready DF: **Rescue of photoreceptor degeneration in rhodopsin-null Drosophila mutants by activated Rac1**. *Science* 2000, **290**:1978-1980.

23. Kumar JP, Ready DF: **Rhodopsin plays an essential structural role in Drosophila photoreceptor development**. *Development* 1995, **121**:4359-4370.

24. Karagiosis SA, Ready DF: **Moesin contributes an essential structural role in *Drosophila* photoreceptor morphogenesis**. *Development* 2004, **131**:725-732.

25. Satoh AK, O'Tousa J, Ozaki K, Ready DF: **Rab11 mediates post-Golgi trafficking of rhodopsin to the photosensitive apical membrane of *Drosophila* photoreceptors**. *Development* 2005, **132**:1487-1497.

26. Li BX, Satoh AK, Ready DF: **Myosin V, Rab11 and dRip11 direct
•   apical secretion and cellular morphogenesis in *Drosophila* photoreceptor cells**. *J Cell Biol* 2007, **177**:.
The paper shows that *Drosophila* Rab 11 is engaged in the formation of a complex, containing Myosin V and *Drip*, similar as the corresponding proteins do in mammalian cells. This paper underlines the importance of MyoV in polarised membrane transport, which has already been shown for yeast and vertebrate cells.

27. Beronja S, Laprise P, Papoulas O, Pellikka M, Sisson J, Tepass U: **Essential function of *Drosophila* Sec6 in apical exocytosis of epithelial photoreceptor cells**. *J Cell Biol* 2005, **169**:635-646.

28. Zelhof AC, Hardy RW, Becker A, Zuker CS: **Transforming
•• the architecture of compound eyes**. *Nature* 2006, **443**:696-699.

29. Husain N, Pellikka M, Hong H, Klimentova T, Choe K-M,
•• Clandinin TR, Tepass U: **The Agrin/perlecan-related protein Eyes Shut is essential for epithelial lumen formation in the Drosophila retina**. *Dev Cell* 2006, **11**:483-493.
One of the characteristics of the *Drosophila* eye is the formation of an interrhabdomeral lumen to individualise the rhabdomeres. The two papers show that the secretion of Spacemaker/Eyes shut is required for this process, and that Prominin seems to be involved in binding to Spacemake. Interestingly, many insects have eyes with a closed rhabdom, in which the rhabdomeres remain fused and form a single, large photoreceptive structure, which increases the absolute sensitivity at the expense of spatial acuity. Strikingly, the house fly *Musca domestica* and the mosquito *Toxorhynchites amboinensis*, two other Diptera with an open rhabdom, express Spam, while the honeybee *Apis mellifera* and the beetle *Tribolium castaneum*, which develop a closed rhabdome, do not express Spam. In addition, expression of Spam in the *Drosophila* ocellar

photoreceptors, which normally exhibit fused rhabdomeres, results in the formation of an interrhabdomeric lumen. This highlights how the expression of a single gene can influence the morphology of an organ.

30. den Hollander AI, ten Brink JB, de Kok YJ, van Soest S, van den Born LI, van Driel MA, van de Pol DJ, Payne AM, Bhattacharya SS, Kellner U et al.: **Mutations in a human homologue of Drosophila crumbs cause retinitis pigmentosa (RP12)**. *Nat Genet* 1999, **23**:217-221.

31. den Hollander AI, Heckenlively JR, van den Born LI, de Kok YJ, van der Velde-Visser SD, Kellner U, Jurklies B, van Schooneveld MJ, Blankenagel A, Rohrschneider K et al.: **Leber congenital amaurosis and retinitis pigmentosa with Coats-like exudative vasculopathy are associated with mutations in the crumbs homologue 1 (CRB1) gene**. *Am J Hum Genet* 2001, **69**:198-203.

32. Mehalow AK, Kameya S, Smith RS, Hawes NL, Denegre JM, Young JA, Bechtold L, Haider NB, Tepass U, R. HJ et al.: **CRB1 is essential for external limiting membrane integrity and photoreceptor morphogenesis in the mammalian retina**. *Hum Mol Genet* 2003, **12**: 2179–2189.

33. van de Pavert SA, Kantardzhieva A, Malysheva A, Meuleman J, Versteek I, Levelt C, Klooster J, geiger S, Seeliger MW, Rashbass P et al.: **Crumbs homologue 1 is required for maintenance of photoreceptor cell polarization and adhesion during light exposure**. *J Cell Sci* 2004, **117**:4169-4177.

34. Bonilha VL, Rayborn ME, Saotome I, McClatchey AI, Hollyfield JG: **Microvilli defects in retinas of ezrin knockout mice**. *Exp Eye Res* 2006, **82**:720-729.

35. Maw MA, Corbeil D, Koch J, Hellwig A, Wilson-Wheeler JC, Bidges RJ, Kumaramanickavel G, John S, Nancarrow D, Röper K et al.: **A frameshift mutation in prominin (mouse)-like 1 causes human retinal degeneration**. *Hum Mol Genet* 2000, **9**:27-34.

36. Jászai J, Fargeas CA, Florek M, Huttner WB, Corbeil D: **Focus on Molecules: Prominin-1 (CD133)**. *Exp Eye Res* 2006:1-2.

37. Wang T, Montell C: **Phototransduction and retinal degeneration
•• in *Drosophila***. *Pflügers Arch* 2007, **454**:821-847.
This review is an excellent, very detailed overview of the signal transduction mechanism in the *Drosophila* eye, the genes involved and their importance to prevent retinal degeneration.

38. Alloway PG, Howard L, Dolph PJ: **The formation of stable rhodopsin-arrestin complexes induces apoptosis and photoreceptor cell degeneration**. *Neuron* 2000, **28**:129-138.

39. Kiselev A, Socolich M, Vinós J, Hardy RW, Zuker CS, Ranganathan R: **A molecular pathway for light-dependent photoreceptor apoptosis in *Drosophila***. *Neuron* 2000, **28**:139-152.

40. Nichols R, Pak WL: **Characterization of *Drosophila melanogaster* rhodopsin**. *J Biol Chem* 1985, **260**:12670-12674.