Development of the *Drosophila* compound eye

Patterning of the *Drosophila* eye involves cell-cell interactions

The adult *Drosophila* compound eyes develop from imaginal discs at the anterior end of the embryo (see Fig. 2.6). The *Drosophila* eye is quite different in structure from the vertebrate eye. It is composed of about 800 identical photoreceptor organs called **ommatidia** (singular **ommatidium**) arranged in a hexagonal array of crystalline regularity (Fig. S11.1). Ommatidia in the dorsal and ventral halves of the eye are oriented in opposite directions so that the eye has mirror image symmetry around the equator (red line). Each fully developed ommatidium is made up 20 cells: eight photoreceptor neurons (R1–R8), together with four overlying cone cells (which secrete the lens), and eight additional pigment cells.

The genetic analysis of ommatidium development has provided one of the best model systems for studying the patterning of a small group of cells. An important early finding from lineage analysis was that the pattern of each ommatidium is specified by cell–cell interactions and is not based on cell lineages.

As we saw in Section 10.29, the gene *Pax6* is the master gene for eye development throughout the animal kingdom. The *Drosophila* version of Pax6 is called *eyeless*, as mutations in this gene result in the reduction or complete absence of the compound eye. *eyeless* is expressed in the region of the eye disc anterior to the morphogenetic furrow (see Fig. S11.2). Ectopic expression of the *eyeless* gene in other imaginal discs results in the development of ectopic eyes, and these have been induced in this way in wings, legs, antennae, and halteres. The fine structure of these ectopic eyes is remarkably normal, and distinct ommatidia are present, although they are not connected to the nervous system. It is estimated that some 2000 genes are eventually activated as a result of *eyeless* activity, and all of them are required for eye morphogenesis. The function of *eyeless* in the eye disc may be similar to that of *vestigial* in the wing disc, as it appears to change the interpretation of positional information in discs in which it is ectopically expressed.

The eye develops from the single-layered epithelial sheet of the eye imaginal disc, located at the anterior end of the larva. Specification and patterning of the cells of the ommatidia begins in the middle of the third larval instar. Patterning starts at the posterior of the eye disc and progresses anteriorly, taking about 2 days, during which time the disc grows eight times larger.

One of the earliest events in eye differentiation is the formation of a groove, the morphogenetic furrow, which sweeps across the disc from posterior to anterior in response to a wave of signals that initiate development of ommatidia from the eye disc cells. As the furrow moves across the epithelium from posterior to anterior, clusters of cells that will give rise to the ommatidia, appear behind it, spaced in a hexagonal

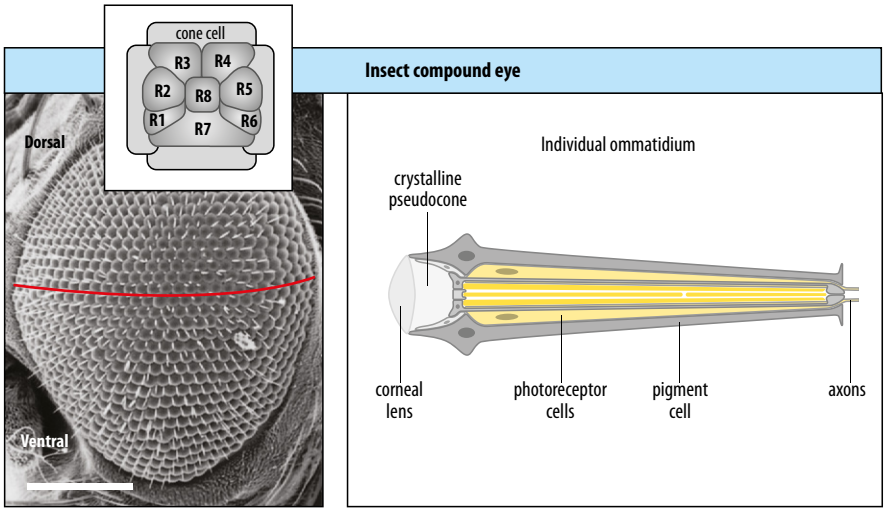

Fig. S11.1 The insect compound eye. Left panel: scanning electron micrograph of the compound eye of adult *Drosophila*. The *Drosophila* compound eye is composed of numerous individual light-sensing structures called ommatidia arranged in a regular array. Ommatidia in the ventral half are oriented in the opposite direction, such that the eye has mirror-image symmetry around the equator (red line). Dorsal is to the top of the photograph and ventral is to the bottom. Scale bar = 50 μm. Right panel: a section through an ommatidium. Each ommatidium has a lens, through which light passes to activate the photoreceptor cells, which are surrounded by pigment cells, and whose axons pass through the optic stalk to the brain.

array (Fig. S11.2). The furrow moves slowly across the disc, at a rate of 2 hours per row of ommatidial clusters. As the morphogenetic furrow moves forward, the cells behind it start to differentiate to form regularly spaced ommatidia. The ommatidia are arranged in rows, with each row half an ommatidium out of register with the previous one. This gives the characteristic hexagonal packing arrangement. The first cells to differentiate are the R8 photoreceptor neurons. These appear as regularly spaced cells in each row, separated from each other by about eight cells. This separation sets the spacing pattern for the ommatidia.

The passage of the morphogenetic furrow is essential for differentiation of the ommatidia, as mutations that block its progress also block the differentiation of new rows of ommatidia, resulting in a fly with abnormally small eyes. Although there are no anterior and posterior compartments in the eye discs, the cells just behind the furrow can be regarded as resembling posterior cells, similar to the situation in the wing-disc posterior compartment (see Section 10.4). They secrete Hedgehog protein, which triggers the expression of *decapentaplegic*, which in turn causes the cells to become competent to form neural tissue. The gene *wingless* also plays a part in eye disc patterning. It is expressed at the lateral edges of the eye disc, and prevents the furrow starting in these regions. We thus see that, even though imaginal discs give rise to very diverse structures, the key signals involved in patterning the leg, wing, and eye are similar, although they have different roles in each case.

Once specified, each R8 cell initiates a cascade of signals that eventually recruits a cluster of 20 cells that form the mature ommatidium. The first cells to be recruited are the prospective photoreceptor cells, which are **sensory neurons**. R2 and R5 differentiate on either side of R8, to form two functionally identical neurons. R3 and R4, which are a slightly different type of photoreceptor, are specified next. All these cells become arranged in a semi-circle with R8 at the center. R1 and R6 differentiate next and almost complete the circle, which is finally closed by the differentiation of R7 adjacent to R8 (see Fig. S11.2).

The clusters then rotate 90°, so that R7 comes to be closest to the equator of the disc and R3 furthest away; rotation is in the opposite direction in the dorsal and ventral halves of the eye. This means that the dorsal and ventral regions of the eye have distinct and different polarities, with ommatidia on the dorsal and ventral sides of the equator having mirror-image symmetry (see Fig. S11.2). The polarization of the ommatidia is yet another example of planar cell polarity (see Section 7.12) and involves a higher level of Frizzled signaling in R3 than in R4.

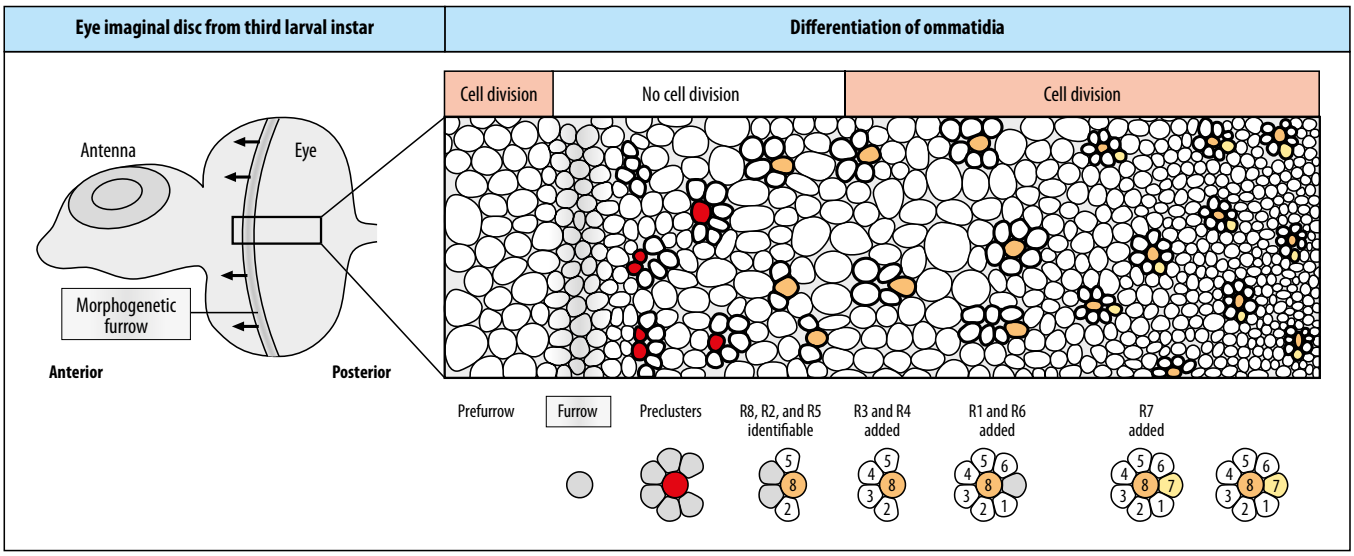

Fig. S11.2 Development of ommatidia in the *Drosophila* compound eye. The compound eye develops from the eye imaginal disc, which is part of a larger disc that also gives rise to an antenna. The morphogenetic furrow develops in the eye disc during the third larval instar and moves across it in a posterior to anterior direction. Ommatidia develop behind the furrow, the photoreceptor neurons being specified in the order shown, R8 developing first and R7 last. The individual ommatidia are regularly spaced in a hexagonal grid pattern. *Illustration after Lawrence, P.*: The Making of a Fly. *Oxford: Blackwell Scientific Publications, 1992.*

The determination of the equator of the eye results from the specification of the dorsal region of the eye disc by members of the *Iroquois* gene complex, which is followed by specification of the equator itself, involving the actions of Notch and its ligands Serrate and Delta, in a similar way to the specification of the dorso-ventral compartment boundary in the wing (see Section 10.5).

The regular spacing of the ommatidia within the eye involves a **lateral inhibition** mechanism that spaces the R8 cells. All cells in the eye disc initially have the capacity to differentiate as R8 cells, and as the morphogenetic furrow passes they start to do so. But some inevitably gain a lead and are thus able to inhibit the differentiation of another R8 cell over a range of around three cell diameters. Cells that will give rise to R8 express the gene *atonal*. Inhibitors of *atonal* that space the R8 cells are the secreted Scabrous protein and Notch. In the eye, cell fate is specified and determined cell by cell, not in groups of cells.

Two proteins crucial in the patterning of an individual ommatidium are the *Drosophila* EGF receptor DER, and its ligand Spitz, a membrane-tethered EGF-like molecule. One model for patterning the ommatidium is based on both EGF receptor activation and the age of the cells (Fig. S11.3). Spitz is produced by the three earliest-specified and most centrally located cells—R8, R2, and R5. It activates the EGF receptor on neighboring cells, and this recruits R3, R4, R1, R6, and R7 to a photoreceptor fate. The responding cells also secrete the protein Argos. This diffuses away and inhibits more distant cells from being activated by Spitz, so that no more cells in the prospective ommatidial cluster develop as photoreceptors. The actual character of each photoreceptor may be determined by the age of the cell, with cells passing through a series of 'states', each representing a potential fate. Other signals are also involved, however. The difference between R3 and R4, for example, involves Notch signaling; the cell with the high level of Notch activity is inhibited from becoming R3, and becomes R4. After the photoreceptors have differentiated, the four lens-producing cone cells develop, and finally the surrounding ring of accessory cells.

The specification of R7 as a photoreceptor cell is one of the best-understood cases of the specification of cell fate on an individual cell basis. It requires expression of

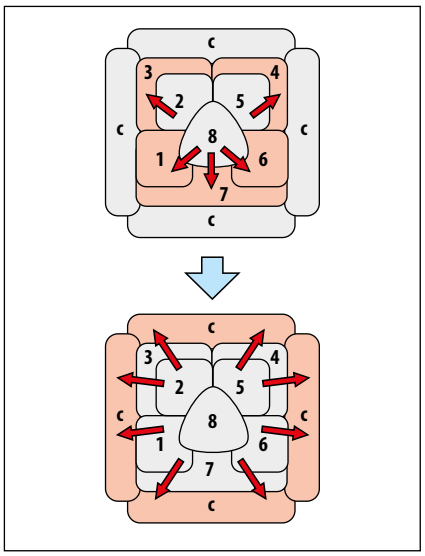

Fig. S11.3 Sequential recruitment of photoreceptors and cone cells during ommatidial development.The three earliest-specified and most centrally located photoreceptor cells—R8, R2, and R5—produce the protein Spitz. It activates the *Drosophila* EGF receptor, DER, on neighboring cells, which recruits R3, R4, R1, R6, and R7 to a photoreceptor fate (top). These then also produce Spitz, which interacts with DER on the prospective cone cells (c) to recruit them to the ommatidium. Once cells are determined they secrete the protein Argos. This diffuses away and inhibits more distant cells from being activated by Spitz, so that no more cells in the prospective ommatidial cluster develop as photoreceptors. *Adapted from Freeman, M.:* ***Cell determination strategies in the Drosophila eye.*** Development *1997,* ***124****: 261-270.*

the gene *sevenless* in the prospective R7 and *bride-of-sevenless* (*boss*) in R8. When either gene is inactivated, the phenotype is the same: R7 does not develop and an extra cone cell is formed. The Sevenless protein is a transmembrane receptor tyrosine kinase, and Boss is its ligand. Sevenless protein is produced not only by R7 but also by other cells in the ommatidium, including lens cells. Thus, expression of Sevenless is a necessary, but not sufficient, condition for R7 specification. Using genetic mosaics it can be shown that for R7 to develop, only R8 need express Boss protein and that this is the signal by which R8 induces R7. Boss is also an integral membrane protein; it is present on the apical surface of the R8 cell, where it makes contact with R7. A second signal for R7 is provided by the R1/R6 pair, which must activate Notch in the R7 cell.

Further reading

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