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Review

Eye evolution at high resolution: The neuron as a unit of homology

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ABSTRACT

Based on differences in morphology, photoreceptor-type usage and lens composition it has been proposed that complex eyes have evolved independently many times. The remarkable observation that different eye types rely on a conserved network of genes (including *Pax6/eyeless*) for their formation has led to the revised proposal that disparate complex eye types have evolved from a shared and simpler prototype. Did this ancestral eye already contain the neural circuitry required for image processing? And what were the evolutionary events that led to the formation of complex visual systems, such as those found in vertebrates and insects? The recent identification of unexpected cell-type homologies between neurons in the vertebrate and *Drosophila* visual systems has led to two proposed models for the evolution of complex visual systems from a simple prototype. The first, as an extension of the finding that the neurons of the vertebrate retina share homologies with both insect (rhabdomeric) and vertebrate (ciliary) photoreceptor cell types, suggests that the vertebrate retina is a composite structure, made up of neurons that have evolved from two spatially separate ancestral photoreceptor populations. The second model, based largely on the conserved role for the *Vsx* homeobox genes in photoreceptor-target neuron development, suggests that the last common ancestor of vertebrates and flies already possessed a relatively sophisticated visual system that contained a mixture of rhabdomeric and ciliary photoreceptors as well as their first- and second-order target neurons. The vertebrate retina and fly visual system would have subsequently evolved by elaborating on this ancestral neural circuit. Here we present evidence for these two cell-type homology-based models and discuss their implications.

Evolving eyes

The evolution of the eye has been a subject of controversy dating back to Charles Darwin's *The Origin of Species* (Darwin, 1859). Debate initially focused on whether an organ as complex as the eye could arise from a series of accrued random mutations. Darwin devoted an entire chapter to 'Difficulties of the Theory' in which he conceded that 'organs of extreme perfection and complication' such as the eye were problematic (though he went on to posit that if graded and increasingly complex functional variations were shown to exist, then the eye too could be the product of natural selection). It is now generally accepted that the eyes of extant animals are a product of natural selection and modern debate has focused on the eye's phylogenetic origins. The traditional view has held that visual systems have evolved multiple times, an assertion that is supported by the existence of eyes with different morphologies, photoreceptor types and lens compositions (Nilsson, 2004). This view has been revised due to the surprising observation that morphologically disparate visual systems rely on a conserved network of genes for their formation (Gehring, 2005). These genetic similarities imply that all eyes have evolved from a shared ancestral prototype.

In this review, we first survey the different types of animal eyes and summarize the data supporting the argument that complex eyes have evolved many times from a simple prototype. We then focus on two recent contributions to our understanding of visual system evolution that stem from the identification of unexpected cell-type homologies between neurons in the vertebrate and *Drosophila* visual systems. The first study proposes that the rhabdomeric photoreceptors of the fly eye are ancestrally related to the ganglion cells of the vertebrate retina and suggests that the vertebrate eye is a composite structure made up of cell types located in distinct regions of the ancestral bilaterian brain (Arendt et al., 2004). In contrast, the second study suggests that homologies exist between the progenitor cells, photoreceptor-target neurons and projection neurons of the vertebrate retina and fly optic lobe, and supports the argument that the visual systems of complex eyes evolved from an ancestral visual circuit that already contained photoreceptors and their target neurons (Erclik et al., 2008).

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Animal eyes

Morphological eye types

One encounters a great diversity of photoreceptive organs among the extant animal groups. *Simple eyes* consist of individual or small clusters of photoreceptors, typically accompanied by pigment cells and/or lens-forming cells (Arendt, 2003). These primitive structures enable the animal to sense light vs. dark, and the direction of incident light, but do not allow for the formation of images. In contrast, *complex eyes* are able to form images (Land, 2005). They are comprised of large arrays of photoreceptors, pigment cells and lens cells and fall into two mutually exclusive classes: single-chambered and compound (Figs. 1A–D). Single-chambered eyes can be further divided into three types based on the mechanism employed for the collection of light. In their simplest form, as found in the pinhole eyes of the cephalopod *Nautilus*, they consist of a pigmented pit that relies on shadows to form an image (Land, 2005). More elaborate variations contain a lens to focus light (vertebrates and squids) or a mirror to reflect it (scallops). In contrast, compound eyes, as found in insects and crustaceans, employ a fundamentally different design. They are made up of ommatidial facets, each of which is a 'mini-eye' containing a group of photoreceptors and, in most cases, a lens.

Photoreceptor cell types

The photoreceptors that comprise simple and complex eyes predominantly belong to one of two types – rhabdomeric or ciliary – based on the mechanism used to maximize light sensitivity (Arendt, 2003). Rhabdomeric photoreceptors, such as those found in the insect compound eye, fold the apical membrane into microvilli for the storage of photopigment whereas ciliary photoreceptors, such as those found in the vertebrate retina, fold the membrane of a modified cilium. These two photoreceptor types differ in at least four additional ways: (1) they employ distinct phototransduction cascades. Ciliary photoreceptors use cyclic GMP as a second messenger system whereas rhabdomeric receptors employ inositol triphosphate. (2) The opsin photopigments and proteins involved in receptor function and response attenuation, while related, belong to distinct classes specific to each photoreceptor type. (3) The two receptors have opposite physiological responses to stimulation. Ciliary photoreceptors hyperpolarize in response to light while rhabdomeric receptors depolarize. (4) Only ciliary photoreceptors express the *Retinal homeobox* (*Rx*) transcription factor (Arendt et al., 2004).

Many animal taxa contain both the ciliary and rhabdomeric photoreceptor cell types. This has been demonstrated for basal deuterostomes (ascidians and cephalochordates; Lacalli, 2001) and

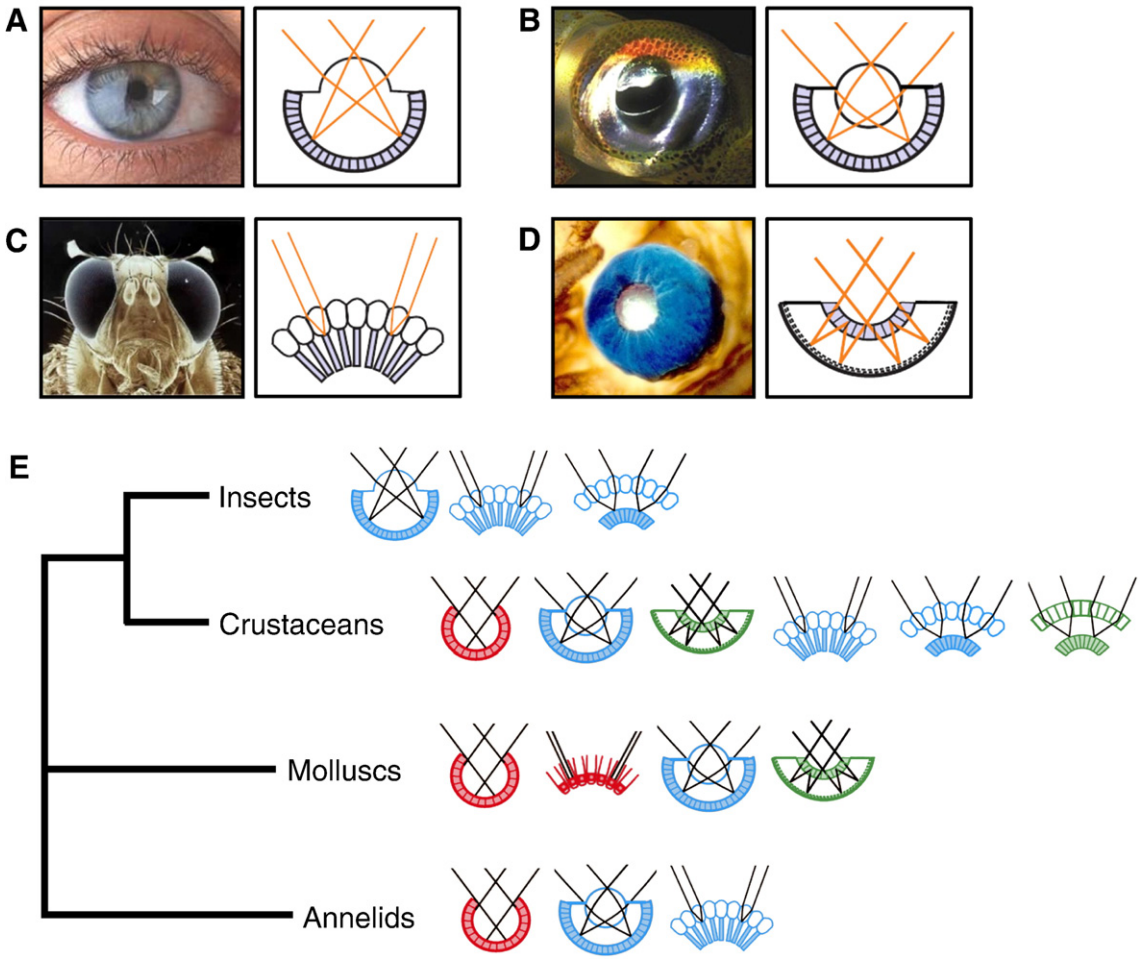

Fig. 1. Complex animal eye types and their phylogenetic distribution. (A–D) Four types of complex animal eyes. Neural structures are shown in purple. Orange lines depict how incoming light rays are imaged. (A) A vertebrate single-chambered eye with corneal optics (human). (B) A cephalopod single-chambered eye with a spherical lens (squid). The remarkable similarity seen between the single-chambered lens eyes of vertebrates and cephalopods serves as a textbook example of convergent evolution. (C) An insect apposition compound eye. (D) A single-chambered eye with a reflecting concave mirror (scallop). Schematic outlines of eye types adapted, with permission, from Land (2005). (E) Complex eye types found in selected branches of the protostome clade. Note the presence of multiple eye types in each branch, and of similar types in distant branches. The color of the outline for each eye type reflects the image forming mechanism employed; red is for shadows, blue for refraction (lenses and corneas) and green for reflection (mirrors). Adapted from Treisman (2004). (Sources for photographs: (B) Wikipedia; (C) Wikipedia; (D) Maria del Pilar Gomez/Boston University.)

lophotrochozoans (e.g., annelids and platyhelminths; Arendt et al., 2004; Morris et al., 2007; Purschke et al., 2006; Sopott-Ehlers et al., 2001). The presence of both ciliary and rhabdomeric photoreceptors in the same animal suggests that both cell types already existed in the bilaterian ancestor, if not earlier.

Complex eyes have evolved many times

The presence of disparate eye types in the same branch of the evolutionary tree, and of similar eye types in distant branches, suggests that complex eyes have evolved many (up to 65) times (Fig. 1E) (Salvini-Plawen and Mayr, 1977; Treisman, 2004). The laws of physics would then have ensured that they converged onto a small number of optical solutions (Fernald, 2004). A textbook example of convergent evolution is the remarkable similarity seen between the single-chambered lens eyes of cephalopods and vertebrates. While these eyes represent nearly identical optical designs, the fundamental differences in their developmental origin and photoreceptor-type usage (see below) make it highly improbable that they are derived from a common ancestral single-chambered eye (Nilsson, 2004).

Further support for the argument that complex eyes have evolved multiple times comes from the observation that most complex eyes contain either rhabdomeric or ciliary photoreceptors, but not both. For example, the compound eyes of insects use rhabdomeric photoreceptors whereas the compound eyes of arc clams use ciliary photoreceptors. Similarly, the single-chambered eye of vertebrates contains ciliary receptors whereas the receptors in the single-chambered eye of the squid are rhabdomeric (Nilsson, 2004).

A final argument for the independent evolution of complex eyes stems from the molecular composition of lens cells in disparate eye types. The eyes of vertebrates, insects and cephalopods use a similar strategy to focus light, a lens with a refractive index gradient (Fernald, 2000). The gradient is made up of high concentrations of a refractive protein at the centre of the lens and low concentrations in the periphery. Despite this shared mechanism, the proteins used to build the gradient are unrelated in these organisms (Fernald, 2000). This observation, together with the fact that these lenses are derived from different embryonic tissues, suggests that the lenses of vertebrates, insects and cephalopods have evolved independently and are an impressive example of convergent evolution.

Complex eyes have likely evolved from a simple ancestral prototype

The remarkable discovery that the homeobox gene *Pax6* acts as a 'master control gene' for eye morphogenesis in flies and vertebrates has led to the proposal that complex animal eyes are monophyletic in origin (Gehring, 2005). Several observations indicate that *Pax6* and its *Drosophila* homolog, *eyeless* (*ey*), play a conserved role in eye formation: (1) *Pax6*/*ey* is broadly expressed in the developing eyes of mice and flies. (2) *Pax6*/*ey* loss-of-function mutations in humans, mice and flies result in the absence of eyes. (3) Ectopic expression of *Pax6* or *ey* leads to ectopic eye formation in flies and vertebrates (Figs. 2A and B). *Pax6* homologs are also expressed in the early developing eyes of cephalopods, planarians, nemertines and polychaetes (Arendt, 2003), suggesting that perhaps all animal eyes are derived from a *Pax6*-dependent ancestral eye.

Conservation of the genetic pathway required for eye formation extends beyond *Pax6*: many of the genes required for *Drosophila* eye specification have orthologs that are expressed in the developing vertebrate eye (Fig. 2C) (Donner and Maas, 2004; Kumar, 2008). The strongest case for conserved activity, outside of *Pax6*, lies with the *Six*-family genes, *Six3* and *Six6*, vertebrate orthologs of *optix* (Gallardo et al., 1999; Jean et al., 1999; Oliver et al., 1995; Wallis et al., 1999). The *Six3,6*/*optix* genes are expressed in the early developing vertebrate and *Drosophila* eyes; their loss-of-function mutations result in the absence of eyes; and their misexpression can induce ectopic eye structures in flies and vertebrates (Donner and Maas, 2004). Like *Pax6*, conservation of *Six* function in eye development may extend beyond flies and vertebrates as *six1/2* homologs are expressed in the eyes of polychaetes and of planaria, where they are required for eye regeneration (Arendt et al., 2002; Pineda et al., 2000).

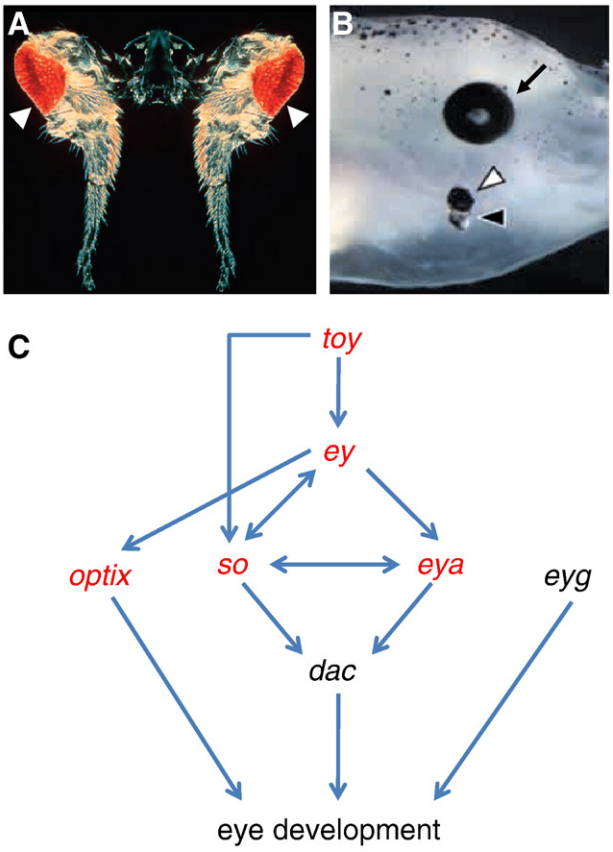

Fig. 2. Conservation in the genetic pathway that regulates eye formation in flies and vertebrates. (A and B) Misexpression of *Pax6* family members is sufficient to induce ectopic eye structures in flies and frogs. (A) *Drosophila*: ectopic eyes on the legs of an adult (arrowheads) induced by the targeted misexpression of the fly *Pax6* homolog, *twin of eyeless* (from Gehring, 2005). (B) *Xenopus*: ectopic eye in an embryo injected with *Pax6* RNA. Side view of a stage 48 embryo. Arrow denotes endogenous eye. Arrowheads mark the ectopic eye cup (white arrowhead) and lens (black arrowhead) (Chow et al., 1999). (C) Simplified version of the gene regulatory network controlling eye specification in *Drosophila*. For a more detailed summary see Kumar (2008). The nuclear factors depicted in this circuit are both necessary and sufficient for eye determination in the fly. The homologs of genes highlighted in red are also required for eye development in vertebrates. Note that the *Rx* gene, which sits atop the genetic cascade for eye specification in vertebrates, is not required for fly eye development. *toy*, *twin of eyeless*; *ey*, *eyeless*; *so*, *sine oculis*; *eya*, *eyes absent*; *dac*, *dachshund*; *eyg*, *eyegone*.

Topological similarities in the embryonic position of the eye field further support the argument that the eyes of vertebrates and flies share a common origin. The embryonic anlagen of various *Drosophila* anterior neural structures (including the eyes) are laid out in a manner that strongly resembles the topology of the vertebrate embryonic brain/eye field (Arendt and Nubler-Jung, 1996; Chang et al., 2001; Hartenstein and Reh, 2002). Furthermore, homologies exist between several regulatory molecules that pattern the anterior neuroectoderm of the early vertebrate and insect embryos: the *Otx*/*otd* and *Tlx*/*tll* homeobox genes are expressed in the anterior neuroectoderm; the Hox genes are excluded from this region; and the *Six*/*so* genes define the eye field (Arendt and Nubler-Jung, 1996; Hartenstein and Reh, 2002).

The requirement for *Pax6* and other shared regulatory genes in morphologically disparate eyes suggests that all eyes evolved from a

common ancestral prototype. It has been proposed that this prototype eye would have been very simple, containing only a photoreceptor to detect light and a shading pigment cell to determine its direction of incidence, thus enabling phototaxis (Gehring and Ikeo, 1999). Simple two-celled eyes such as these can be found in extant organisms such as planarians and some polychaete larvae (Arendt and Wittbrodt, 2001). Complex eyes would then have evolved from this prototype. The observation that *Pax6* directly activates the expression of opsin and pigment cell fate genes in flies and mice suggests that the terminal differentiation genes in the prototype eye were under direct *Pax6* control (Baumer et al., 2003; Kozmik, 2005; Martinez-Morales et al., 2004; Sheng et al., 1997). As eyes evolved, genes then would have become intercalated between *Pax6* and its downstream targets (Gehring and Ikeo, 1999), thus explaining how *Pax6* has remained at the top of the eye-forming genetic cascade in eyes that have assumed radically different morphologies.

It is worth noting however, that while these genetic similarities are compelling, significant differences exist between the genetic cascades that direct vertebrate and fly eye formation. For example, the *dachshund* gene plays a central role in fly eye specification, but does not have an important role in vertebrate eye formation (Davis et al., 2001; Mardon et al., 1994). Even more strikingly, the homeobox gene *Rx* sits atop the genetic cascade for eye specification in vertebrates, but *Drosophila* eye development is *Rx*-independent (Bailey et al., 2004; Davis et al., 2003). These data have led to the hypothesis that the observed conservation in the genetic pathways that regulate eye formation in vertebrates and insects is a product of the independent recruitment of gene cassettes that are commonly used during organogenesis (Fernald, 2006).

In addition to the similarities in the genetic cascade required for eye specification, vertebrates and flies employ a surprisingly comparable strategy to pattern their retinas. In *Drosophila*, the third instar eye imaginal disc is patterned by the morphogenetic furrow, a wave of differentiation, driven by Hedgehog signaling, that sweeps across the eye disc from posterior to anterior (Kumar, 2001). Immediately behind the furrow, retinal differentiation begins with the specification of regularly spaced photoreceptor founder cells. Remarkably, the zebrafish retina is also patterned by a wave of Sonic hedgehog-driven differentiation that results in a regular array of founder cells (in this case ganglion cells rather than photoreceptors) (Neumann and Nuesslein-Volhard, 2000). Furthermore, in both systems, the founder cells require the activity of the proneural gene *atonal* for their differentiation and require the down-regulation of *Pax6* expression (Pichaud et al., 2001).

Does the use of a common mechanism for the patterning of the retina in flies and vertebrates suggest that this mechanism existed in the ancestral eye? As stated above, it is generally accepted that the Urbilaterian eye would most likely have been very simple, containing only a few photoreceptors and pigment cells (Arendt and Wittbrodt, 2001). This simple eye would seem to have had little use for a Hedgehog-based patterning mechanism during its development. Thus, the use of Hedgehog for the patterning of vertebrate and fly eyes is most likely an example of convergent evolution brought about by a conserved role for Hedgehog in patterning fields of cells at many times, and in many different tissues, during development (Pichaud et al., 2001).

In summary, the requirement for *Pax6* and other shared regulatory genes in morphologically disparate eyes suggests that all eyes evolved from a simple ancestral prototype. But what were the neural components of the ancestral eye and how did this eye interact with the primitive nervous system? And what were the evolutionary steps that led to the formation of different types of complex visual systems? The remainder of this review will focus on recent genetic and developmental data pertaining to these questions. To set the stage for this analysis, we will first provide a brief overview of two complex visual systems: the vertebrate retina and insect compound eye/optic lobe.

The vertebrate and insect visual systems

The vertebrate neuroretina

The neurons of the vertebrate eye are located in the retina — a thin, laminated structure that lines the back of the eye (Wassle, 2004). Retinal neurons are responsible for the detection of light, processing of the visual signal and its transmission to the brain. Neuroanatomical studies, initiated by Santiago Ramon y Cajal more than 100 years ago, have revealed that the retina contains five classes of neuron (Fig. 3A). Rod and cone *photoreceptors* detect light and convert it into a neural signal (Wassle, 2004). *Bipolar cells* act as the bridge for all visual information in the retina; they make direct synapses with the upstream photoreceptors and downstream amacrine and ganglion cells (Masland, 2001a). *Ganglion cells* are the output neurons of the retina. Their dendrites collect visual information from bipolar and amacrine cells and their axons transmit this information along the optic nerve to the visual centers of the brain (mainly the lateral geniculate nucleus). One rare ganglion cell type of particular interest is the melanopsin-expressing ganglion cell. This cell is intrinsically light sensitive, is required for circadian clock entrainment and has recently been proposed to share homology with invertebrate rhabdomeric photoreceptors (see below) (Arendt et al., 2004). Melanopsin-positive ganglion cells differ from all other ganglion cells by their projection to brainstem nuclei controlling circadian rhythms (suprachiasmatic nucleus) and pupillary reflexes (Berson, 2007). The signals between the three major neuronal classes of the retina are modulated by *horizontal* and *amacrine cells*. The complexity of neural processing in the retina is highlighted by the observation that its five neuronal classes are composed of between 50 and 100 distinct cell types (Masland, 2001b; Wassle, 2004).

The neurons of the retina develop from a pool of proliferating and multipotent neuroepithelial cells known as retinal progenitor cells (Livesey and Cepko, 2001). A suite of transcription factors – mainly of the homeodomain and Basic helix–loop–helix classes – has been identified as regulators of retinal neuron specification and/or early differentiation (Burmeister et al., 1996; Chow et al., 2004; Dyer et al., 2003; Freund et al., 1997; Fujitani et al., 2006; Furukawa et al., 1997; Li et al., 2004; Mu and Klein, 2004; Ohtoshi et al., 2004).

The Drosophila visual system

The neural components of the adult *Drosophila* visual system comprise two major structures: the compound eyes and the underlying optic lobes, the latter of which are located in the brain (Fig. 3B) (Meinertzhagen and Hanson, 1993). In the compound eye, photoreceptors convert light into a visual signal. Within the optic lobe, the visual signal received from the photoreceptors undergoes complex processing before it is transmitted to the higher-order centers of the brain.

The compound eye is composed of approximately 800 ommatidia, each containing eight photoreceptors (designated R1 through R8) that can be assigned to two broad categories based on their position within the ommatidium (Cook, 2003). The outer photoreceptors, R1–R6, are required for motion detection (Heisenberg and Buchner, 1977; Yamaguchi et al., 2008) while the inner photoreceptors, R7 and R8, participate in color, UV and polarized light detection and orientation behavior (Gao et al., 2008; Menne and Spatz, 1977; Rister et al., 2007; Wernet and Desplan, 2004). Consistent with these functional differences, the inner and outer photoreceptors project to distinct regions in the optic lobe. R1–R6 project to the first optic ganglion, the lamina, whereas R7 and R8 extend their axons through the lamina and synapse in distinct layers of the second optic ganglion, the medulla (Morante and Desplan, 2004).

The optic lobe can be divided into four distinct neuronal compartments: the aforementioned lamina and medulla, and the

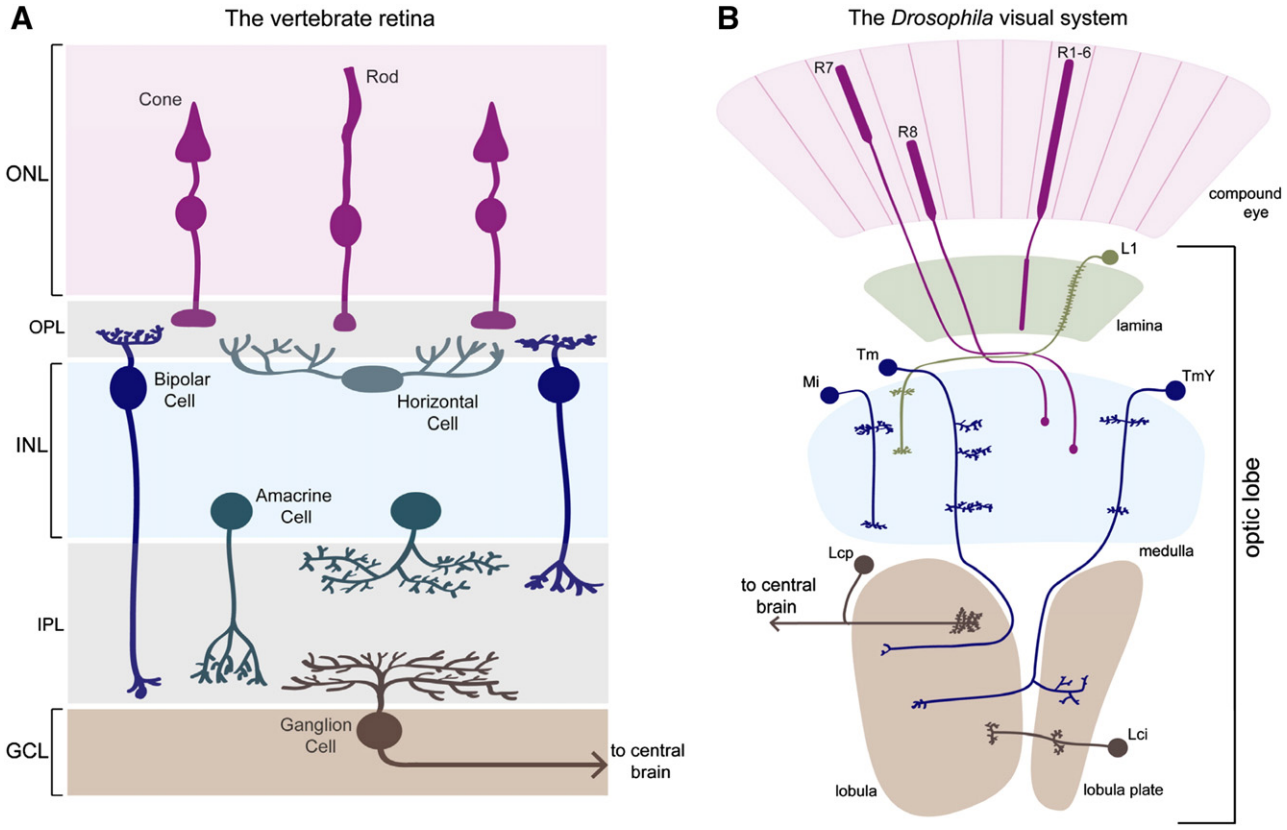

Fig. 3. Neuronal cell types found in the vertebrate and *Drosophila* visual systems. (A) The vertebrate retina is composed of six neural cell types: cone and rod photoreceptors, horizontal cells, bipolar cells, amacrine cells and ganglion cells. The total number of subtypes found within each neuronal class is greater than what is depicted in this schematic; for example the mammalian retina can contain up to 50 distinct subtypes of amacrine cell. Synaptic contacts are limited to the OPL (outer plexiform layer) and IPL (inner plexiform layer). Cell bodies are found in the ONL (outer nuclear layer), INL (inner nuclear layer) and GCL (ganglion cell layer). (B) The *Drosophila* visual system is made up of the compound eye and the underlying optic lobe. Only a subset of the ~125 optic lobe neuronal cell types is shown here; for a more comprehensive review see Fischbach and Dittrich (1989). Depicted neurons are chosen to illustrate the flow of visual information from the compound eye to the central brain. R1–6, outer photoreceptors; R7 and R8, inner photoreceptors; L1, lamina monopolar neuron 1; Tm and TmY, transmedullary neurons; Mi, medulla intrinsic neuron; Lcp, lobula complex projection neuron; Lci, lobula complex intrinsic neuron. Vertebrate retinal neuron morphologies are adapted from Masland (2001a). *Drosophila* optic lobe neuron morphologies are adapted from Fischbach and Dittrich (1989). The color-coding shows the hypothesized evolutionary relationships between the layers of the two visual systems as predicted by Model 2 (see text and Fig. 5).

lobula and lobula plate (which together make up the lobula complex) (Meinertzhagen and Hanson, 1993). The *lamina* consists of visual sampling units called cartridges and acts as the initial processing centre for the motion-detection pathway (Rister et al., 2007). Each cartridge receives contributions from the processes of ~10 neurons (including the outer photoreceptors, R1–R6) and six of these neurons, together with R7 and R8, project to distinct layers in the distal medulla.

The *medulla* acts as a bridge for all visual signals and is thus responsible for the processing of both color- and motion-detection information (Gao et al., 2008; Rister et al., 2007). The majority of the over 60 distinct medullary cell types can be placed into one of two classes: transmedullary and local neurons (Fischbach and Dittrich, 1989; Morante and Desplan, 2008). Transmedullary neurons, a subset of which is directly targeted by R7 and R8, project from the medulla to the lobula complex. In contrast, the processes of local neurons are restricted to within the medulla neuropil, where they likely function to modulate the output of the transmedullary neurons.

The *lobula complex* is responsible for the transmission of the signals received from the medulla to the higher-order visual processing centers of the brain (mainly the ventrolateral protocerebrum) (Otsuna and Ito, 2006). The complex is mainly composed of neurons that either project to the central brain (projection neurons) or make local connections restricted to the lobula and lobula plate (intrinsic neurons).

The neurons of the compound eye and optic lobe develop from three distinct epithelial structures in the larva: the eye imaginal disc generates the photoreceptors of the compound eye (Cook, 2003); the outer optic anlagen generates the lamina and distal medulla; and the inner optic anlagen gives rise to the proximal medulla and the lobula complex (Hofbauer and Campos-Ortega, 1990; Nassif et al., 2003). Whereas the genetic control of cell-type specification has been intensively studied in the eye disc, very little is known about the regulatory genes required for the specification of the ~125 different optic lobe neuronal cell types.

Retracing the evolutionary history of the vertebrate and fly visual systems: a search for neuronal cell-type homology

How did the vertebrate and insect visual systems, found at the end of evolutionarily distant phylogenetic branches, evolve from the supposedly simple visual system of the bilaterian ancestor? And what can a comparison of these two complex visual systems tell us about the nature of the ancestral eye? The recent identification of unexpected cell-type homologies between neurons in the vertebrate and *Drosophila* visual systems has shed light on these questions. Before we review these homology-based models we must first define cell-type homology. Evidence has shown that the genes that control the specification and early differentiation of a cell type are more likely to be conserved across evolution than genes that are required for earlier patterning or later terminal differentiation events (Allan et al., 2005; Arendt, 2003; Shirasaki and Pfaff, 2002; Wagner, 2007). Therefore a key criterion for cell-type homology between visual system neurons is a reliance on orthologous transcription factors for

their specification and early differentiation. Additional considerations may include shared developmental origins (do the neurons derive from similar tissues or progenitor cell populations?), connectivity (do the neurons occupy similar locations in their circuits?), and effector gene expression. It is important to note that there is no need for homologous neurons to have any morphological similarities since neural morphology can be quite plastic, even between neurons that are known to be homologous. For example, the lamina L4 monopolar neurons of flies and bees are considered homologous despite very different morphologies (Fischbach and Dittrich, 1989).

Based on the above criteria, multiple cell-type homologies have recently been identified between neurons in the vertebrate and *Drosophila* visual systems. These homologies have led to two proposed models that outline the state of the ancestral visual system and the evolutionary events that led to the formation of the more complex vertebrate and insect visual circuits. In the following sections we will summarize these models and discuss their implications for visual system evolution.

Model 1: The vertebrate retina is a composite structure made up of cell types derived from two spatially distinct ancestral photoreceptor populations

Model 1 suggests that vertebrate retinal ganglion cells and insect rhabdomeric photoreceptors are ancestrally related (Arendt, 2003; Arendt et al., 2004). Consistent with this hypothesis, both cell types: (a) express and/or require the activity of the transcription factors *Pax6/eyeless*, *Math5/atonal* and *BarH/barH1* during their development; (b) express ancestrally related photopigments, *r-opsin* in rhabdomeric photoreceptors and, surprisingly, *melanopsin*, in a subset of retinal ganglion cells; (c) employ similar phototransduction cascades downstream of these opsins (Isoldi et al., 2005); and (d) extend a long axon that targets the brain. One could additionally argue that the timing of specification for these cell types is similar since retinal ganglion cells and rhabdomeric photoreceptors are the first cell types to be generated by the Hedgehog-driven moving waves that pattern the neuroretina and eye disc (Pichaud et al., 2001).

The proposed homology between retinal ganglion cells and rhabdomeric photoreceptors, taken together with the observation that, in basal bilaterians such as *Platynereis*, ciliary and rhabdomeric photoreceptors are located in different regions of the brain, has led to the following model for bilaterian eye evolution (Fig. 4) (Arendt, 2003; Arendt et al., 2004). The fly eye evolved directly from the population of rhabdomeric photoreceptors found in the eye of Urbilateria, whereas the vertebrate eye evolved from both the ciliary and rhabdomeric populations of photoreceptors located in the Urbilaterian brain. In the evolutionary line leading to vertebrates, the ciliary photoreceptors directly gave rise to the rods and cones while the rhabdomeric photoreceptors that had populated the ancestral eye were recruited into the evolving retina where they became ganglion cells. This model thus suggests that the vertebrate eye is a composite structure made up of both ciliary and rhabdomeric photoreceptive cells derived from independent regions of the ancestral brain. The model also challenges the argument that the complex eyes of vertebrates and insects are derived from a common ancestral eye.

It has further been proposed that homology to the rhabdomeric photoreceptors extends beyond the retinal ganglion cells to include the amacrine and horizontal cells (Arendt, 2003). A subset of these cell types, like rhabdomeric photoreceptors and ganglion cells, expresses *Pax6* and *melanopsin*. Additionally, amacrine cells, horizontal cells and rhabdomeric photoreceptors express the homeobox gene *Prox1/prospero* (the expression of *Prox1* would have been lost in the ganglion cells). What then is the evolutionary history of the fifth major class of retinal neuron, the bipolar cell? It has been suggested that bipolar cells may be derived from ciliary photoreceptors; these

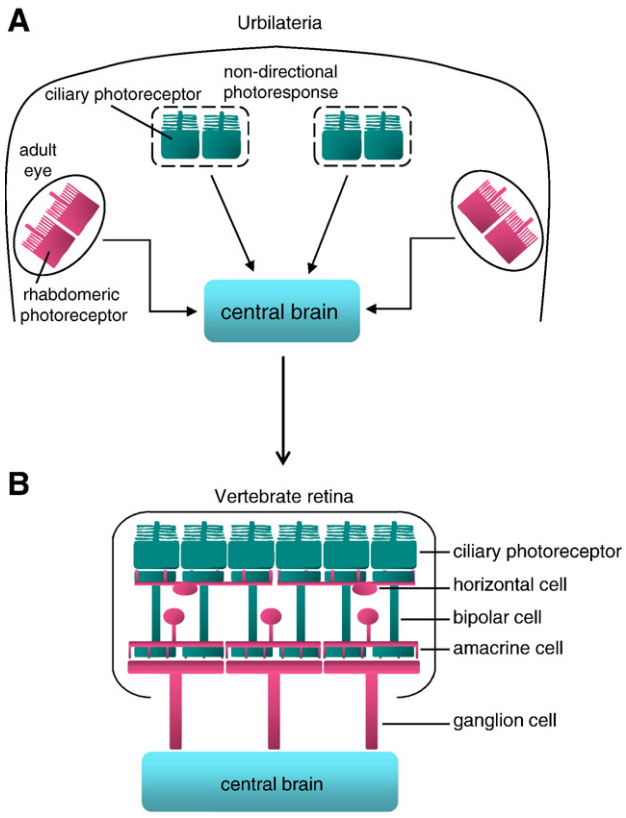

Fig. 4. Model for the origin of the vertebrate retina from spatially distinct ancestral photoreceptor populations. (A) Urbilateria contained two types of photoreceptor; rhabdomeric receptors in its eye and ciliary receptors in its brain (which likely mediated a non-directional photoresponse). The arthropod eye evolved directly from this ancestral eye, whereas the vertebrate eye evolved from the population of ciliary photoreceptors located in the brain. Schematic shapes of ciliary and rhabdomeric photoreceptors adapted from Arendt and Wittbrodt (2001). (B) The vertebrate retina is a composite structure made up of cell types derived from ciliary and rhabdomeric photoreceptors. The ganglion, amacrine and horizontal cells of the retina are ancestrally related to the rhabdomeric photoreceptors of the Urbilaterian eye whereas the bipolar cells evolved from the ciliary photoreceptors (see text for details).

cell types share several structural and molecular similarities, including expression of the *Otx5b* homeobox gene and the *recoverin* effector gene (Arendt, 2008; Lamb et al., 2007; Viczian et al., 2003).

Thus, all retinal neuronal cell types may have evolved from rhabdomeric and ciliary photoreceptors (Fig. 4B). In the earliest version of the vertebrate retina, ciliary photoreceptors might have synapsed directly onto ganglion cell-like projection neurons (of rhabdomeric origin) (Lamb et al., 2007). Subsequently, these two cell types diversified to give rise to the bipolar, amacrine and horizontal cells. The nascent cell types could have intercalated between the photoreceptors and ganglion cells, resulting in a three-layered retina with increased processing power. Support for this model comes from the observation that in the retina of the hagfish, a primitive chordate, photoreceptors synapse directly onto ganglion cells (Holmberg, 1977).

Model 2: The vertebrate retina and *Drosophila* visual system evolved from a shared ancestral eye that already contained photoreceptors and their target neurons

A second model for bilaterian visual system evolution is based on evidence that suggests that the first- and second-order interneurons located in the vertebrate retina and the *Drosophila* optic lobe are evolutionarily related (Erclik et al., 2008; Hartenstein and Reh, 2002). Cell-type homology analyses suggest that:

Retinal bipolar cells are homologous to optic lobe transmedullary neurons

Several pieces of evidence are consistent with the hypothesis that vertebrate retinal bipolar cells and the transmedullary neurons of the *Drosophila* optic lobe are evolutionarily related. Both cell types: act as a bridge for visual information, synapsing with photoreceptors and the projection neurons that target the brain (Fischbach and Dittrich, 1989; Gao et al., 2008; Wassle, 2004); develop from a *Chx10/dVsx*-dependent pool of neuroprogenitor cells (Erclik et al., 2008); and express the *Chx10/dVsx* (Erclik et al., 2008) and *Lhx(3/4)/apterous* (Elshatory et al., 2007) homeobox genes throughout their development and in the adult.

In *C. elegans*, the homologs of the *Vsx* and *Lhx* genes, *ceh-10* and *ttx-3* respectively, are required for the development of the AIY interneuron, which is directly targeted by the AFD thermosensory neuron (Altun-Gultekin et al., 2001; Svendsen and McGhee, 1995; Wenick and Hobert, 2004). While the AFD neuron is thermosensitive in *C. elegans*, several pieces of evidence suggest that it may have evolved from a photoreceptor (Svendsen and McGhee, 1995): the AFD neuron shares morphological similarities with rhabdomeric photoreceptors (Burr, 1985); AFD specification requires the activity of the *ttx-1* gene, whose homologs *otd* and *Otx* are required for photoreceptor differentiation in flies and vertebrates (Satterlee et al., 2001); and the photoreceptor of the light sensitive marine nematode *Onchcolaimus vesicarius* is located in roughly the same position as the AFD cell in *C. elegans* (Burr and Burr, 1975). The above data support the intriguing possibility that the worm AFD-AIY thermosensory circuit is ancestrally related to the photosensory circuits of flies and vertebrates. Of note however, a group of photosensory neurons has recently been identified in *C. elegans* (Ward et al., 2008). While these neurons share molecular similarities with vertebrate ciliary photoreceptors, they do not target the AIY interneuron.

Ganglion cells are homologous to the projection neurons of the lobula complex

Homology between the neural circuitry of the vertebrate retina and fly optic lobe may extend to the ganglion cells and lobula complex projection neurons. Both cell types: receive synaptic input directly from photoreceptor-target neurons and project to higher-order visual processing centers in the brain (Masland, 2001a; Otsuna and Ito, 2006); and sequentially express the homeodomain proteins Math5/ATONAL and Brn3b/ACJ6 during their development (Erclik et al., 2008; Mu and Klein, 2004).

Retinal progenitor cells are homologous to outer optic lobe progenitor cells

Vertebrate retinal progenitor cells and the progenitors of the fly outer optic anlagen may represent ancestrally related cell types. Both progenitor types: require the *Chx10/dVsx* genes for their proliferation (Erclik et al., 2008); and first undergo symmetric and then, later, switch to asymmetric divisions to generate photoreceptor-target neurons (Egger et al., 2007; Livesey and Cepko, 2001). However, it is important to note that a key difference between these progenitor populations is that the retinal progenitor cells give rise to all the neurons of the retina, whereas the progenitors of the outer optic anlagen do not generate the photoreceptors of the compound eye or the neurons of the lobula complex.

Based on these cell-type homologies, the following model has been proposed to describe the evolution of bilaterian visual systems (Erclik et al., 2008) (Fig. 5). (1) The last common ancestor of flies and vertebrates possessed a simple basiepithelial brain that contained both ciliary and rhabdomeric photoreceptors, as well as specialized visual target neurons. These formed a visual network that processed/

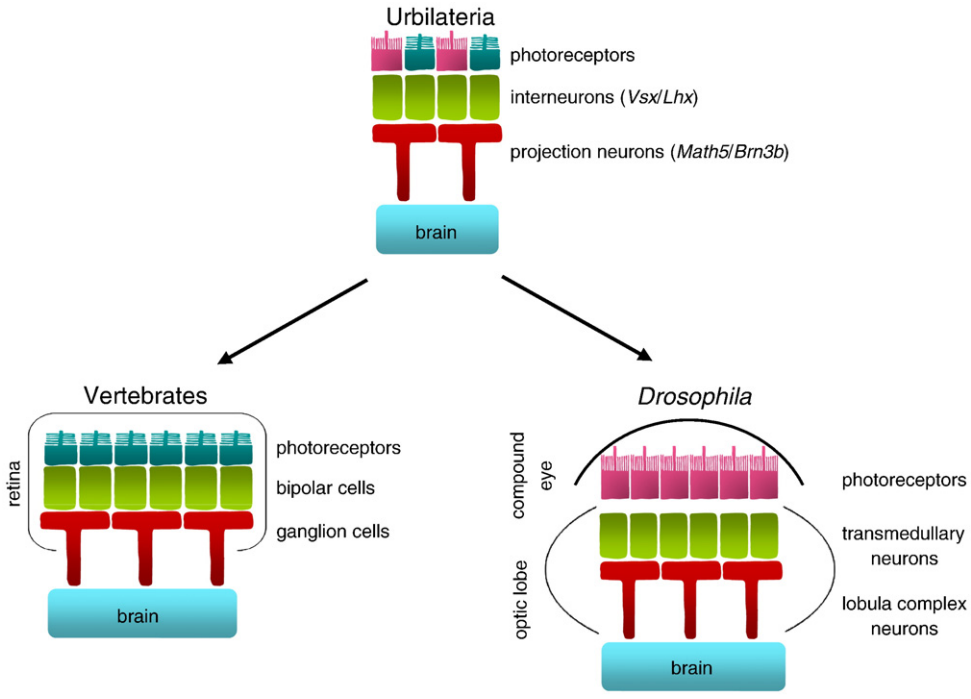

Fig. 5. Model for the origin of the vertebrate and fly visual systems from a shared ancestral eye that already contained photoreceptors and their target neurons. Urbilateria contained ciliary (blue) and rhabdomeric (pink) photoreceptors that targeted *Vsx*- and *Lhx*-positive interneurons. These neurons synapsed onto *Math5*- and *Brn3b*-positive projection neurons that targeted the motor centers of the brain. In the evolutionary line leading to vertebrates, the rhabdomeric photoreceptors were lost and the ciliary photoreceptors and their targets developed together in the retina. In the line leading to arthropods, the ciliary photoreceptors were lost and the progenitors for the rhabdomeric photoreceptors and the deeper neuronal layers were separated during development. Consequently, photoreceptors are located in the compound eye whereas their neuronal targets are found in the optic lobe. Modified, with permission, from Erclik et al. (2008).

relayed information to the motor centers of the brain. The photoreceptors and their target neurons developed from progenitor cells dependent on the *Vsx* genes for their proliferation. The presence of multiple downstream interneurons in this visual network suggests that in addition to serving simple functions, such as phototaxis, the ancestral eye may have already possessed the capability to perform basic visual processing tasks, including contrast enhancement by lateral inhibition, adaptation to different light levels or the integration of signals from multiple photoreceptors. (2) In the evolutionary line leading to vertebrates, the basiepithelial brain invaginated and became the (anterior) neural tube. Subsequently, ciliary photoreceptors and their neuronal targets everted from the neural tube to form the retina. The rhabdomeric photoreceptors may have become incorporated into the deeper layers of the retina as a subset of melanopsin-expressing ganglion cells (as proposed by Arendt et al.) or have been lost altogether. (3) In the line leading to arthropods, the brain did not invaginate. Instead, the progenitors for the central nervous system split at an early stage from the neuroectoderm, taking with them the progenitors of the visual target neurons, which evolved into the optic lobe. The progenitors of the rhabdomeric photoreceptors and other specialized cells (such as pigment and lens) remained in the ectoderm and evolved into the compound eye. The ciliary photoreceptors were lost from the evolving eye.

A number of observations on the structure and development of the visual system in extant invertebrates support this view of visual system evolution. For example, basal lophotrochozoa (polychaete annelids, macrostomid platyhelminths) and ecdysozoa (e.g., tardigrada) have simple eyes (rhabdomeric, ciliary or both) that are typically embedded in the brain (Greven, 2007; Lacalli, 1982; Morris et al., 2007; Purschke et al., 2006). This may reflect a condition that is structurally/developmentally close to that hypothesized in the bilaterian ancestor. Similarly, protochordates (ascidians, amphioxus) possess simple eyes that form part of the anterior neural tube and include both rhabdomeric and ciliary photoreceptors (Lacalli, 2001). The ciliary frontal eye in the cerebral vesicle of Amphioxus and the photolith in the sensory vesicle of ascidian larvae, along with surrounding (not yet characterized) visual target neurons may represent the evolutionary forerunners of what later everted as the neuroretina in vertebrates. It will be informative to assay for the expression of *Vsx* homologs in the simple brains of basal lophotrochozoa and deuterostomia, to establish whether the correlation of Vsx expression with primary visual target neurons holds up in these systems as well.

Conclusions and outlook

Morphological and genetic considerations suggest that complex eyes have evolved multiple times from a shared ancestral prototype. Recent studies that have identified potential homologies among the neurons that comprise the vertebrate and *Drosophila* visual systems have led to two contrasting models for how bilaterian visual systems have evolved. The first proposes that the vertebrate retina is a composite structure; made up of ganglion, amacrine and horizontal cells – that are ancestrally related to rhabdomeric photoreceptors – and bipolar cells, which derived from ciliary photoreceptors. The second model suggests that the last common ancestor of flies and vertebrates already contained an eye with both ciliary and rhabdomeric photoreceptor cells as well as their target neurons, and that these neuronal populations are ancestrally related to the photoreceptors and first- and second-order interneurons found in the insect and vertebrate visual systems.

It is worth mentioning that these two models are not mutually exclusive. As mentioned above, the rhabdomeric photoreceptors of the ancestral eye may have given rise to specialized ganglion cells in both models. Furthermore, the first-order interneurons of the ancestral visual system (as proposed by Erclik et al.) may have been the product of earlier photoreceptor duplication and functional segregation events (as proposed by Arendt and others for bipolar cells).

In the future, the identification of additional genes that are required for the development of visual system neurons will provide added substrates for comparative analyses. It will also be important to extend these analyses to the functional level. For example, *Brn3b* is required for retinal ganglion cell axon extension (Mu and Klein, 2004). Is the fly *Brn3b* homolog, *acj6*, required for axon extension by the lobula complex projection neurons? Future studies should also aim to extend the cell-type homology approach to organisms other than vertebrates and arthropods, including those that model Urbilateria such as the aforementioned ragworm, *Platynereis,* and the flatworm, *Macrostomum* (Morris et al., 2004). The expression of *Vsx*, *Lhx*, *Math5* and *Brn3* homologs in the photoreceptor-target and projection neurons of these organisms would strongly support the model that the neural circuits required for vision in flies and vertebrates are ancestrally related. In contrast, the observation that photoreceptors directly synapse onto projection neurons in some basal eye types (as shown in the hagfish) would support the proposal that the ancestral vertebrate retina was composed of ciliary photoreceptors and projection neurons of rhabdomeric origin. Further support for this model would also come from the identification of projection neurons that possess rhabdomeric morphology.

It is expected that future experiments designed to determine which of the above models (if either) is correct will contribute significantly to our understanding of visual system evolution.

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