Eye for an Eye: A Comparative Account on Compound Eye of *Drosophila melanogaster* with Vertebrate Eye

Arushi Rai, Sonia Narwal, Harsh Kanodia, and Meghana Tare

Introduction

Eyes, as mentioned by philosopher William Paley, are "miracle of design." Eyes are indeed amazing organs in the animal kingdom, for their ability to provide a unique sense that makes most of the animals stand apart from rest of the living organisms. Although not all kingdoms of life are devoid of visual senses, the ability to connect sense of vision to that of complex nervous system for processing and image formation is unique to the animal kingdom. Diversity of the eyes in the animal kingdom has been attributed to evolution over a large period of time. Based on evidences from fossil records, first eyes appear some 540 million years ago (Parker 2009). There are different kinds of eyes animals possess, which work in different fashions, in order to "sense" the objects, and may be to form an image. Of all diverse life forms, eye of *Drosophila melanogaster* is an example of *eyes; for an eye*; for, it has compound eyes, for sensing, processing and forming the image. For over a century now, *Drosophila melanogaster* eye has provided a new dimension to several different aspects of understanding in the fields of development and several different diseases (Borst 2009). Santiago Ramon y Cajal, a neuroanatomist was the first to notice the similarities between the visual system of vertebrates and that of the insects. He documented a striking similarity between the neuronal circuits that form the major framework of visual system in flies and vertebrates (Cajal and Sanchez 1915). Compound eyes are built as convex structures around the outside of an animal's head, and even though their arrangement looks similar to vertebrate eyes (both sides of head), they are fundamentally different from the concave structure of single chamber eyes (Fig. 1). In spite of this major topological difference, however, the

A. Rai · S. Narwal · H. Kanodia · M. Tare (✉)
Department of Biological Sciences, Birla Institute of Technology and Science, Pilani, Pilani, Rajasthan, India
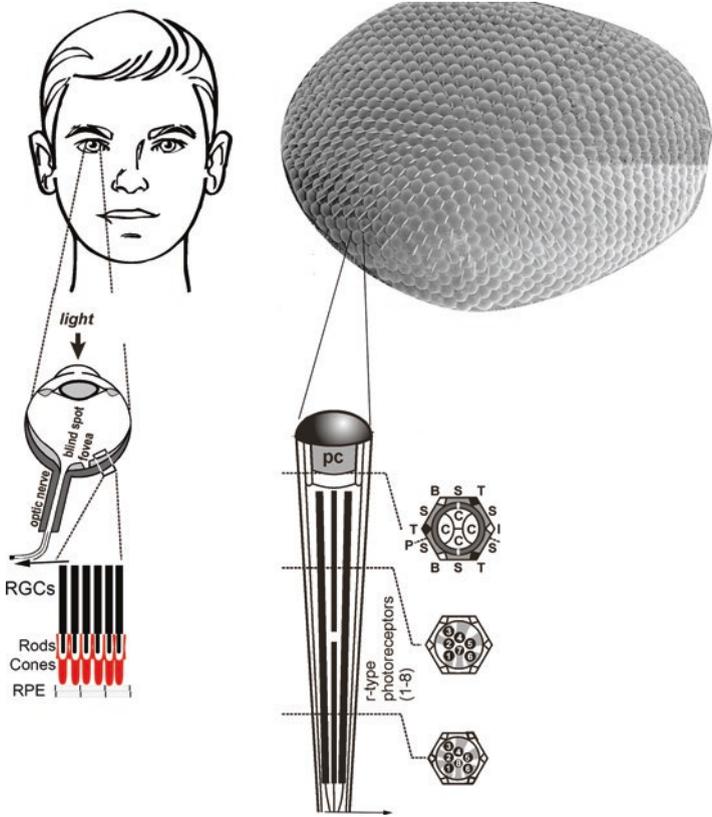e-mail: meghana.tare@pilani-bits.pilani.ac.in

Fig. 1 A vertebrate eye versus *Drosophila melanogaster* eye. Vertebrates have single camera type eyes compared to compound eyes of *Drosophila*. (**a**) In the vertebrate eye, light rays falling are refracted by the cornea (outer protrusion) and lens (oval structure inside) onto PRCs in the neural retina. Cellular arrangement for Retinal Ganglion Cells (RGCs), and rods and cones has been shown in the enlarged portion of the eye. Arrow marks the direction of axons to CNS. (**b**) Compound eye of *Drosophila* is made up of regularly placed facet like structures, each referred to as ommatidium. Each ommatidium appears like a cylindrical structure tapered at the end. Pseudocone (PC), of each ommatidium is secreted by cone cells (C in the section). Eight of the R-type photoreceptor cells (PRCs), labeled as R1–R8. R1–R6 span across the height of the omma-tidium. R7 and R8 lie above and beneath the hexagon. Primary (P), Secondary (S) and Tertiary (T) pigment cells encase the photoreceptor cells and function in absorbing wondering photons. At regular intervals, Bristle (B) cells replace the T cells. Grey areas in the cross sections represent the five of the opsins in image formation. Arrow marks the direction of axons to CNS. (Image adapted from Lewis Held 2017)

jobs of the two kinds of structure are the same: to utilize the incoming light and to develop a sense of vision (Pak 2010; Sanes and Zipursky 2010). For eye is of inter-est to many research fields, in order to stay focused, we compare the anatomy and function while dwelling into events of genesis of the eye in the embryonic stages, and their genetic regulation.

We shall provide the major similarities and differences in the structure, function, and development of the camera type eyes with those of compound eyes of *Drosophila melanogaster* in subsequent sections.

Anatomy of Vertebrate Eye

The arrangement of the eye is extremely intricate as indicated (Fig. 1). The entry of light into the eye is facilitated by the cornea. The cornea is thin and transparent. Its transparency arises from an acellular stroma between a layer of epithelial cells and a layer of endothelial cells. It contains no blood vessels to avoid attenuating the light entering the eyes. The cornea receives nourishment from tears on the outside and aqueous humor on its inner surface. The cornea acting in conjugation with the lens focuses light onto the light detecting cells of the eyes—the photoreceptors. The lens too is highly transparent, an adaptation to maximize the light transmitted into the light-sensitive cells of the eye. The lens allows for its shape to be changed in order to allow accommodation of images at different distances and change the focus of the lens. The lens is held in place by the zonular fibers that extend to ciliary body. The contraction of the ciliary muscles facilitates the change of shape of the lens. The forces of ciliary muscles are conveyed to the lens via the zonular fibers. The contraction of the ciliary muscles releases the tension in the zonular fibers and allows the lens to become more round allowing change in the focal plane of the lens-cornea system. Though the cornea achieves most of the focusing function, it has a fixed focus, thus imparting the important function of accommodation to the lens. The lens unlike the cornea is transparent due to the nature of lens cells that constitute it.

The lens fiber cells lose their nuclei and most of their organelles during differentiation. They have high content of proteins called crystallins which do not scatter light like most other proteins. The crystallins have interestingly shown to be expressed in other cells in the body where they have different functional roles such as enzymatic activity (Piatigorsky and Wistow 1989). The iris regulates the entry of light in through the lens. It can dilate or constrict its opening, thus attenuating the light to different extents. The space anterior to the lens is filled with a fluid known as the aqueous humor which is responsible for maintaining the pressure in this compartment of the eye and gives it its shape. The ciliary bodies secrete the aqueous humor. The aqueous humor leaves the eyes through tiny channels in the periphery of the anterior chamber. Posterior to the lens is the vitreous humor which is a denser fluid gel. It exerts a pressure that keeps in place the retina—which is the neuron rich layer responsible for visual computations and relaying the information regarding the visual field to the higher centers in the brain. The retina is followed by the pigmented epithelium and they line the posterior end of the eye. They are followed by the choroid which is rich in vasculature and supplies the outer retinal cells and the photoreceptors together with the pigmented epithelium with nutrients and facilitates gaseous exchange. The output neurons of the retina project to the brain regions via the optic nerve, which is composed of the axons, called the retinal ganglion cells

(RGCs) of the retina (the output neurons). The outermost coat of the eye is a tough layer known as the sclera, which is a white tissue. The inner retinal cells receive nourishment and gaseous exchange via the repeated branching of retinal artery.

After portraying the anatomical organization of the eye, it becomes important to understand the retina—the most important part for the early processing of the visual scene and encoding it to be processed by higher brain regions. The retina has a vast diversity in constituent cell types (Fig. 1) that all play a role in the computations performed by the retina that maybe categorized on the basis of molecular identity, morphology, and dendritic stratification patterns (Baden et al. 2016; Gollisch and Meister 2010; Masland 2001, 2012). The subtypes of each cell show a regular arrangement—*i.e.*, there exists a region of exclusion around each cell, where other cells of the same subtype are not found. This leads to a mosaic-like arrangement of each non-reducible neuronal cell subtype—a characteristic feature of the retina. These cells help to convert the image perceived in the visual field into parallel streams of information regarding various features of the image. The neurons of the retina are organized in three cellular layers—the ganglion cell layer, the inner nucleate layer, and the outer nucleate layer. There are two synaptic layers—the inner and outer plexiform layers. These synaptic layers show further stratification. There are six major cell types in the vertebrate retina—the photoreceptors, the horizontal cells, the bipolar cells, the amacrine cells, the ganglion cells, and the glial Muller cells. The photoreceptors—rods and cones—receive photostimulation due to the photopigments (opsins) in these cells responding to impinging photons. The opsin proteins are bound to retinal—a form of Vitamin A. The molecule undergoes isomerization upon absorption of photons, the photosensitive reaction that drives a signaling cascade underlying the function of the retina. The photoreceptors project to the outer nucleate layer where they synapse with the horizontal cells and bipolar cells. The photoreceptors use glutamate as a neurotransmitter. Upon impingement by light, the photoreceptors hyperpolarize—their membrane potential decreases. This leads to a reduced secretion of glutamate which effects the bipolar cells and horizontal cells downstream. The bipolar cells show different functional responses to the light responses of the photoreceptors based on the type of glutamate receptors (both ionic and metabotropic) they express—for example, ON bipolar cells express metabotropic mGluR6 which causes reduced depolarization of the bipolar cell membrane upon binding the glutamate, and hence, when light causes lowered glutamate release from the photoreceptor cells, these cells show increased depolarization of membrane and an ON response to increase in light intensity in their receptive fields. The horizontal cells play a role in feedback and modulate the responses of the photoreceptors. The bipolar cells show wide diversity (Tsukamoto and Omi 2013). The bipolar cells then contact ganglion cells in the inner plexiform layer. Here, a divergence of information occurs and various arrangements of these synaptic contacts and interaction and modulation by the amacrine cells allow for a variety of computations. The ganglion cells have over 30–40 types (Baden et al. 2016) and carry parallel information to the brain about the visual scene. The complex interplay of signals from the bipolar, amacrine, and retinal ganglion cells plays an important role in various features detected and encoded by the retinal ganglion cells. Some

instances of these computations include object motion (Baccus et al. 2008), approaching motions (Münch et al. 2009), motion extrapolation amongst other forms of anticipation and adaptations (Chaffiol et al. 2017; Gollisch and Meister 2010; Yao et al. 2018). There are a wide variety of neurotransmitters and receptors involved and they have been implicated in a variety of different functional computations—for instance, dopamine has been implicated in light adaptation of the retina, where the retinal dopamine levels go up with increase in light intensity and seem to be involved in a variety of light adaptive computations that may not be explained by a simple gain control of the retinal cells (Chaffiol et al. 2017; Yao et al. 2018). At the same time, a number of adaptions and functionality of the retina depend on inputs from the brain—retinopetal inputs. This makes it interesting to look at the modulation of signals by various neurotransmitters which are released into the retina by retinopetal neurons in a context-dependent manner. Thus, the mechanism by which the retina computes information cannot be studied independent of these modulating signals.

Anatomy of Drosophila *Eye*

The major structural components in the retina of *Drosophila* are the 750 individual units termed as ommatidia which are precisely organized in the lattice (Fig. 1). Each ommatidium consists of eight R cells which are basically the photoreceptor neurons (R1–R8). The photoreceptors can be categorized it is on the basis of opsins they express: R1–R6 type of photoreceptors expresses Rh1 opsins and controls the motion detection, secondly R7 expresses RH3 or Rh4 opsins which are UV-sensitive and lastly R8 expresses either Rh5 (blue) or Rh6 (green) opsins (Salcedo et al. 1999). The photoreceptor cells direct its visual information towards the **optic lobe**, the primary visual processing center in flies. This optic lobe is composed of four ganglia. First layer is called lamina, beneath it lays the medulla and then the lobula. Mainly in flies, the lobula is further differentiated into lobula and lobula plate (Sinakevitch et al. 2003). The R1–R6 photoreceptors terminate in the first layer lamina while the axons of R7 and R8 end at medulla and hence medulla receives information from the either R7 or R8. In both the R7 and R8 cells, a zinc finger transcription factor called as Sequoia and some N-cadherins are expressed but they majorly control the precise positioning of the axons of photoreceptor R7. Another cell adhesion molecule called Capricious is expressed selectively in R8 cells and regulates the projection of axons of R8 cells (Kulkarni et al. 2016).

The neural circuits are formed of four types of neuronal cells, local neurons or intrinsic neurons, interneurons, photoreceptor axons, and visual projection neurons (VPNs). VPNs connect the optic lobe and the central brain, intrinsic neurons ramify within a single optic ganglion, and interneurons connect more than one ganglion within the optic lobe. Intrinsic neurons, interneurons, and the axons of photoreceptors are oriented in a parallel direction creating a barrel-like structure called the

visual cartridge (Otsuna and Ito 2006). The photoreceptor cells collect information from different point and converge it into these parallel columnar synaptic models. The axon of R1–R6 terminates in the lamina and further directs the motion information to the neurons of lamina (L1–L5) in synaptic units. These synaptic units along with amacrine cells and centrifugal interneurons are termed as laminal cartridge (Meinertzhagen and O'neil 1991). The motion information is further transmitted to the underneath ganglia medulla through the axons of lamina neurons L1–L5 each arborized in the particular medulla layers. Along with the axonal projection of the laminal neurons, the axons of R7 and R8 transmit the color information to the M6 and M3 medulla layers, respectively (Takemura et al. 2008; Morante and Desplan 2008). Hence, the parallel columnar organization of the 750 lamina cartridges and medulla column relays the information in a retinotopic fashion that allows the parallel processing of the visual information from different points.

The fly visual system is made up of different neuronal cell types based on the morphology. It can mainly be categorized into two main classes: the uni-columnar neurons and multi-columnar neurons. The uni-columnar neurons are mainly restricted to one column and its projections extend laterally connecting the neighboring columnar modules. The multi-columnar neurons project in several columnar modules. This parallel relay of information either between the layers or columns optimize the signal-to-noise ratio.

Phototransduction and Image Formation

Compound eyes are apposition kind of eyes where optically isolated ommatidia process the images separately. Apposition eyes are typically optimized for high resolution by "apposing" little overlapping visual fields of neighboring ommatidia based on small apertures and rhabdoms (Fig. 2). Each ommatidium receives light; the light is filtered through the lens situated on the outer surface of the eye. Further, the light passes the crystalline cone structure and then through the pigment cells and finally to the visual cells. Each ommatidium ends with its own nerve fiber which connects it to the common optic nerve. Each ommatidia relay its own information and form a tiny image. All the tiny images from each photoreceptor convalesce to form one visual image (Stavenga et al. 2005).

The camera eye of vertebrates produces an inverted image on the light-sensitive elements that is transmitted to the brain via optic nerves (Fig. 2). (Reviewed in Agi et al. 2014).

The phototransduction compartment, the light-guiding rhabdomere is formed by a stack of some 30,000 microvilli, each containing all the essential elements of the transduction cascade. Several elements of these cascades are common elements found in any phosphoinositol cascade, including the G-protein coupled receptor (rhodopsin), heterotrimeric G-protein (Gq), phospholipase C (PLCβ-4), and two closely related Ca^{2+} channels encoded by the *transient receptor potential* (*trp*) and *trp-like* (*trpl*) genes.
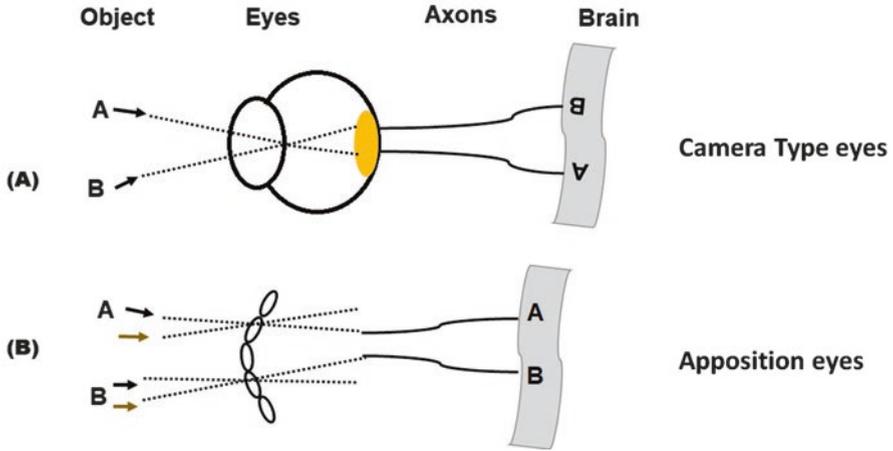
Fig. 2 Comparison of visual systems of vertebrate camera type eyes versus Drosophila apposition eyes. Light paths are shown as *dotted lines*. (**a**) The camera eye of vertebrates produces an inverted image on the light-sensitive elements that is transmitted to the brain via optic nerves. (**b**) Compound eye of *Drosophila* is an apposition type eye, which produces an upright image on the light-sensitive rhabdoms as well as in the first optic neuropil, the lamina. Image formed by individual ommatidium of the compound eye is an inverted image and only contributes a single pixel to the final image that is not further resolved. (Image adapted from Agi et al. 2014)

Development of Eye

The similarities and differences in compound eye of *Drosophila* versus camera type eye of vertebrates are due to the major differences and similarities of those hailed from embryonic or the developmental stages. Events at different developmental stages are tightly governed by the conserved genetic and molecular mechanisms which are common to both vertebrate and *Drosophila* eye development.

If it is only about developing an organ, such as an eye, both compound and camera type, what would be required? Assembly of cells, which will eventually differentiate into specialized structures of lens, retina, cornea, photoreceptors, rods, cones, pigment cells, accessory cells, and their neuronal connections to brain. Interestingly, for eye organogenesis, the classical processes of specification, determination, and differentiation follow the same processes for both flies and vertebrates.

Development of eye in both *Drosophila* and vertebrates begins at early embryonic stages. It is a fascinating process of converting a layer of cells into a three-dimensional functional organ involving axial patterning, followed by proliferation and differentiation. A pioneering research in the field of generation of axes during eye development has indicated that default *Drosophila* eye primordium is ventral, over which dorsal field is specified as the fly enters and proceeds to larval stages (Singh and Choi 2003; Singh et al. 2006, 2012, 2019). Once the dorsal-ventral axes are specified by specific axial patterning genes, cell proliferation is signaled.

Interestingly, these initial events are similar in the development of vertebrate eye as well, described below.

The early stages of vertebrate eye development have been revealed by several embryology experiments, which describe the morphological development of the early eye begins at embryonic day 8.5 (E 8.5), involving formation of an optic vesicle. The optic vesicle contacts head ectoderm to induce thickening of ectoderm forming lens placode. The lens placode invaginates and separates from surrounding ectoderm to form lens vesicle, while optic vesicle folds on itself inward, forming the optic cup. The lens vesicle cells eventually differentiate into lens structures, while optic cup cells form the neural and pigmented layers of the retina (Pei and Rhodin 1970; reviewed in Grainger 1992).

Drosophila eye primordium is ectodermal in origin, which is set aside as a group of only a few number of cells during embryonic stages. Studies have confirmed that the compound eye of *Drosophila* develops from population of embryonic primordial cells which converge to form anterior head segments, and develop into eye imaginal discs as early as first larval instar stage (Haynie and Bryant 1986; Jürgens et al. 1986; Green et al. 1993; Younossi-Hartenstein et al. 1993; Namba and Minden 1999; Chang et al. 2001; Huang et al. 2017). Imaginal discs are sac-like monolayer epithelial structures which form the blue prints for the adult organs in the *Drosophila*. The eye imaginal disc is a compound disc, which eventually differentiates into eye, antenna, and the head structures (Fig. 3) (Weismann 1864; Vogt and Anderson 1964; Gehring 1967; Ouweneel 1970; Baker et al. 1978; Haynie and Bryant 1986). During the first and second instar larval stages, eye disc cells divide almost homogeneously
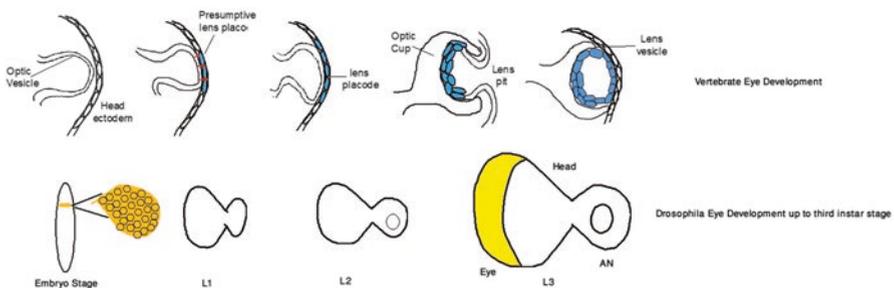

Fig. 3 Stages of eye development in vertebrates compared to *Drosophila*. (**a**) Eye development begins at embryonic day 8.5 in mouse. The optic vesicle forms a pouch like structure of the forebrain in the beginning, and contacts the head ectoderm on E9.0. Signals (indicated by red arrows), from optic vesicles induce formation of lens placode by E9.5. At E10.0, a few cells of lens placode (blue) invaginate to form a lens pit, whereas, optic vesicle forms an optic cup. The lens vesicle detaches itself from the ectoderm and invagination of lens pit gets completed by E10.5 to form the lens. Hereafter, the differentiation of the optic cup continues to form neural and pigmented epithelial layers of the retina. (**b**) Eye primordial cells are specified by ectodermal cells at an early embryonic stage. These cells proliferate in first and second instar larval stages (L1 and L2) to make a differentiated third instar (L3) eye antennal imaginal disc, which is a larval blue print for the adult eye, antenna and the head cuticle. The portion in yellow in L3 eye disc indicates the differentiated photoreceptor neurons which are separated from antenna and head through morphogenetic furrow (curved line)

and symmetrically by mitosis and imaginal disc grows bigger in size. However, at the end of second instar, or early third instar larval stage, mitotic divisions become asymmetric, for differentiation to begin. A stripe of *atonal* expression to recognize the R8 cells (*Math 5* in vertebrates) determines the apical constriction in posterior cells of the eye disc which appears like a furrow and moves towards the anterior of the eye disc. The stripe of *atonal* expression defining R8 cells, or the morphogenetic furrow (MF) rather moves like a Mexican wave in the football crowd (described by Jarman 2000). As the MF moves anterior, cells just ahead of it enter G1 arrest and stop proliferating. As cells are released from the furrow, they exit the cell cycle and begin differentiating as the R8, R2/R5/R3/R4 photoreceptor neurons of the precluster. A small subset will undergo a final round of mitosis (the second mitotic wave) before following their sister cells out of the cell cycle and into the ommatidium as the R1/R6/R7 photoreceptors, lens secreting cone cells, and optically insulating pigment cells (Ready et al. 1976; Wolff and Ready 1991; reviewed by Kumar 2018). A fully grown third instar eye disc (Fig. 3) contains antenna, head cuticle blue prints, in addition to differentiated photoreceptor neurons. This monolayer epithelial layer undergoes further changes into pupal stages, which include developing lenses, establishing neuronal connection with the brain, and acquiring pigments to appear a three-dimensional compound eye. After 36 h of pupariation, extra cells between the ommatidia are removed via apoptosis to form the regularly placed hexagonal facets.

It is intriguing that movement of MF in the *Drosophila* eye disc is required not only for differentiation, but also for regularly spaced photoreceptors; and is indeed similar to movements which occur in some of the vertebrates as well. The Mexican wave-like movement has also been demonstrated during eye development in zebrafish. Neurogenesis begins in optic cup epithelium, closer to optic stalk and then spreads outwards like a wave, which is controlled by *atonal* homolog *ath5*.

Genetic Regulation of Eye Development

The highly organized process of eye development is regulated by complex interplay of genetic networks. The advancements in the field of developmental genetics continue to demonstrate a high degree of genetic and molecular conservation during organogenesis of the eye, or oculogenesis between *Drosophila* and vertebrates. Many of the regulators of eye development were identified in *Drosophila* by gain-of-function and/or loss-of-function experiments before they were identified and characterized in vertebrate models. Molecular identities began to shine between two systems when *Pax6,* a member of Paired box family of transcription factor was found to be expressed initially in head ectoderm and optic vesicle, and then became restricted to lens placode ectoderm (Walther and Gruss 1991; Grindley et al. 1995). Despite the distinct morphological differences between the fly and vertebrate eyes, *Pax6* homologs, *eyeless* (*ey*) (Quiring et al. 1994) and *twin of eyeless* (*toy*) (Czerny et al. 1999) provide identity to the eye primordium. Out of two, *toy* is more similar

to Pax6 and acts upstream to *ey*. Both *Pax6* and *ey/toy* are capable of inducing ectopic eyes in most of the tissues upon overexpression and their mutations result in aniridia in mouse, and no eye phenotypes in flies (Ton et al. 1991; Glaser et al. 1992; Collinson et al. 2000; Quinn et al. 1996; Prosser and van Heyningen 1998; Quiring et al. 1994; Czerny et al. 1999; Halder et al. 1995). Several research labs have demonstrated that both *ey* and *toy* are expressed in other non-optic tissues as well, and therefore require other genes to induce the differentiation of the eye. Ectopic induction of ey can induce eye formation in the presence of *decapentaplegic* (*dpp*), a TGF-β family of growth factors (Heberlein et al. 1993; Chen et al. 1999). In addition to *ey* and *dpp*, other genes which are required for eye development are *Eyes absent* (*Eya*) (Bonini et al. 1993), *sine oculis (so)* (Cheyette et al. 1994), and *dachshund (dac)* (Mardon et al. 1994). Their vertebrate homologs are EYA 1/EYA2 (Zimmerman et al. 1997), Optix 2/Six 3 (Zuber et al. 1999), and Dach, respectively (Heanue et al. 1999; Ohto et al. 1999). These genes act in concert to aid in eye development (Fig. 4), and their mutations have been shown to cause defects in the eye development/visual impairment. Table 1 summarizes the comparative account on the genes involved in early events for eye development in *Drosophila* and vertebrates. It is noteworthy that genetic regulation is further accompanied by signaling events which are also conserved in vertebrates and *Drosophila*. For example, for differentiation of the eye primordium, downstream to *ey* additional signal from decapentaplegic pathway feeds in to initiate *eya* and *so*, which is actually a homolog of Bone Morphogenetic Protein-4/7 (BMP) in vertebrates. However, the difference between flies and vertebrates is, BMPs act in concert with *Pax-6* to induce lens placode, which eventually initiates the process of differentiation by inducing *Eya* and *Six-3/Optx-2* (reviewed by Chen et al. 1999).

Even though the initial events of the eye organogenesis are homologous in flies and vertebrates, the structural and anatomical differences (those discussed in previous sections) arise due to extremely complicated genetic networks, controlled by signaling events which are different in terms of spatiotemporal profiles, yet are governed similarly in the later stages of development which lead to formation of a three-dimensional eye.

Signaling aspect of cell–cell communication plays a major role in both vertebrate and *Drosophila* eye development. *Drosophila* equivalents of TGF-β, Sonic

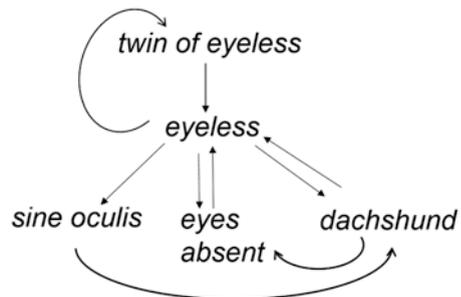**Fig. 4** Genetic regulation of eye development in *Drosophila*

Table 1 A comparative account of genes involved in retinal development in *Drosophila* and vertebrates (homologous domains of respective products have also been mentioned)

Genes	Vertebrates	*Drosophila melangoster*
Pax 6	Expressed in broad domain of head ectoderm and optical vesicle (Grindley et al. 1995).	*Pax 6* homolog *ey* (*eyeless*) restricted expression in cells anterior to morphogenetic furrow in a third instar imaginal disc (Quiring et al. 1994). *Pax 6* homolog *toy* (*twin of eyeless*) acts upstream of *ey* (Czerny et al. 1999). More orthologous to *Pax 6* due to a conserved C-terminal transcription activation domain.
Eyes Absent	*Eya1* expressed in retinal pigment epithelium and optic nerve. Knockout of this gene cause severe optic abnormalities, cataracts (Azuma et al. 2000). *Eya2* expressed in neural retina, sclera and optic nerve sheath. *Eya3* expressed in the branchial arches and CNS, but lacks cranial placode expression (Xu et al. 1997). *Eya4* expressed primarily in the craniofacial mesenchyme, the dermamyotome and the limb (Borsani et al. 1999).	*Eya* shares a highly conserved 271 amino acid regions at the C-terminus of the protein with the four homologs (Xu et al. 1997).
Dachshund	Human –*DACH*. They have a homologous conserved domain called Dachbox –N and –C. -expressed in eye, limb, brain, neural tube, dorsal root ganglia, rib primordia and genital eminence (Hammond et al. 1998; Kozmik et al. 1999).	*Dac* also contains the Dachbox which is homologous to the *Ski* and *Sno* family of oncogene-related proteins (Caubit et al. 1999).
Bmp	*Bmp4* and the *Bmp7* gene co-express with *Pax6* in regulating eye formation and maintain lens placode development (Wawersik et al. 1999).	*dpp* (*decapentaplegic*) a member of the TGF-β family of growth factors co-expresses with *ey* (Chen et al. 1998).
Six family	**Six 3**- member of six gene family are expressed in in-vaginating lens vesicle and developing retina. Mutations in this gene lead to microphthalmia and holoprosencephaly (Wallis et al. 1999).	**So** (*Sine oculis*) have a conserved homeodomain and a stretch of 110 amino acids 5'to the homeodomain like six gene family (Ohto et al. 2002). *Eyeless* stimulates the expression of both *so* and *eya* gene (Halder et al. 1998).
Optx	*Optx2/six 6/six9:* Expressed only in optical vesicle and lens placode. It act as a fate determinant of retinal precursor cells that forms retinal neurons and photoreceptors (Toy et al. 1998). Humans- deletion of this gene lead to bilateral anophthalmia (Gallardo et al. 1999).	*Optx* gene- it is a true ortholog of *six3* gene and *optx2* gene. Expressed in early development of eye primordia and head (Toy et al. 1998).

Hedgehog, JNK, JAK STAT, EGFR, and Notch pathways have been widely studied in eye development as early as axes determination until sculpting the final organ shape (Greenwood and Struhl 1999; Roessler et al. 1996) (Fig. 4).

Concluding Remarks

Eye development is vast and has been studied widely to understand the processes of organogenesis and physiology by more researchers than we can think of. In the entire past century, the developmental biologists have elucidated basic framework of eye organogenesis in early and later stages, to understand the regulation and execution of these processes. With this framework aided with newer technologies such as 5D light sheet microscopy, newer forms of genetic manipulation techniques, and genome projects in *Drosophila* as well as vertebrate models, a converge understanding of regulators of eye development is being paved, which will aid the pre-existing knowledge to extrapolate the analogies between the two.

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