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Understanding the Structural and Developmental Aspect of Simple Eye of Drosophila: The Ocelli

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Abstract

Among various photoreceptors present in arthropods Drosophila eye undergoes certain modification to provide high resolution and sensitivity to the animal. Along with the compound eye Drosophila possess three ocelli for its vision, navigation and locomotion purpose. These ocelli are arranged in a triangular manner in between the compound eye. During third instar larvae, from the eye antenna imaginal disc several conserved genes and complex regulatory genetic network help in ocellar patterning. Like compound eye ocelli possess cornea, corneagenous cell, photoreceptor cells (rhabdom). The visual pigment present in ocelli is Rh2 and is responsible for the functioning of ocelli. Although rhabdomere are the photoreceptor organ of the ocelli the arrangement of the rhabdomere in ocelli differs from the compound eye. Interrhabdomereal space which is present between the rhabdomeres of photoreceptor cells are absent in ocelli. The rhabdom is confined only to the apical one-third of the ocelli whereas it expands throughout the length in compound eye. The structural difference present in the compound eye and ocelli enable us to study the functioning of one gene in different photoreceptors within an animal. Thus understanding the mechanism of ocellar development, genes involved in the functioning of ocelli will help us to understand the functioning of various genes in different photoreceptor. The current article summarises the structure, function and genes involved in the development of ocelli.

Keywords: Ocelli; *Drosophila melanogaster*; Orthodenticle; Rhodopsin 2; Ocelli development

Introduction

The eye is the most dominant sensory organ as it provides maximum signal to the brain. Eye mediates photo sensation by recruiting specialised neuronal cells known as photoreceptors [1]. During evolution photoreceptor has undergone modification several times to provide optimum vision to the animals in terms of resolution, distance, light-dark adaptation and colour recognition [2]. No matter how distinguished the structure is, the main function of the photoreceptor is to convert electromagnetic radiation (visible light) into signals for visual transduction [3]. In very primitive animals the photoreceptor organ is a pigment filled cavity, and the function is only to sense the light (distinguish light from dark). With evolution complex structures evolved in the eye for vision and light sensation. Arthropods possess wide variation in compound eye patterning to provide the best fit to the animal under various photic conditions. Arthropod possesses apposition, superposition and neural superposition types of compound eye. Among which neural superposition type of eye is found only in Drosophila. Along with the compound eye, Drosophila further possess extra retinal eyelet and three ocelli for its vision [4,5].

The ocelli of the Drosophila are arranged in the form a triangle between two compound eyes on the vertex of the head. During development ocelli is originated from precursor cells of the eye-antennal imaginal disc of third instar larvae. Among the three ocellus one is median and the remaining is lateral. The lateral ocellus develops from two separate discs, while the median ocellus is a result of combination from the anlagen which is present in each of the two plates [6,7]. Ocelli shares many conserved genes and transcription factors with compound eye in terms of development [6-9]. Furthermore, ocelli is getting special attention because of its association with some parts of largest neurons in insect nervous system which builds a potential scope for researching on neuronal synaptic transmission and its development [10]. The current article summarises the work done regarding structure, function and development of Drosophila ocelli not described in earlier studies.

Function of Ocelli

The Drosophila ocelli are assigned with multiple functions along with perceiving light and estimating the day-night length. It also helps in rearranging the body positioning, orientation towards the light source [11]. If the ocelli is painted artificially in an insect, then the speed of phototaxis decreases [12]. Besides vision and sensitivity, it also affects the functionality of flight. It helps in stable flight by perceiving a field of view coinciding with horizon level [13]. The difference in light sensation by ocelli during a flight inputs information for a fly to maintain a reaction level about its roll axis and pitch. During flight if the fly turns left than there is brightening at right lateral ocellus and vice-versa. Similarly median ocellus brightens when the fly pitches upward [14]. As ocelli tends to follow single sensor hypothesis which mentions that "each ocellus is like an individual optical sensor rather than being comprised with number of individual pixels" [11]. The photoreceptors present in ocelli are highly sensitive towards UV light and thus help in creating a strong contrast between sky and the ground [15]. The ocelli are more sensitive towards light than the compound eyes. In locusts, light signals reaches ganglia within 12ms from ocelli, the transduction latency is faster (twice) than the compound eye [16]. Simple neuronal arrangement (less number of neurotransmitters between effector and detector neurons) [17] and large diameter across

some ocellar interneuron [18] make ocelli's visual transduction faster than the compound eye [19].

Structure of Ocelli

The ocelli are arranged in triangular form in between the compound eyes [20] (Figure 1). Each ocellus is secured by a sole domelike corneal lens (40 µm diameter), below which a thin layer of corneagenous cells, which is followed by around 80 photoreceptor cells (PRCs). Some portion of their axons were seen to be very compacted under an extremely thin layer of corneagenous cells which lies under the corneal lens [21,22]. The corneagen layer is a clear zone of the hypodermis that secretes the lens. A thin layer of pigmented cells encompasses the bunch of PRCs. There were no pigment cells entering among photoreceptor cell bodies in the ocelli. Like compound eyes, the apical layer of ocellar PRCs is extended by tight packed finger-like projections called microvillus which gives rise to rhabdomere.

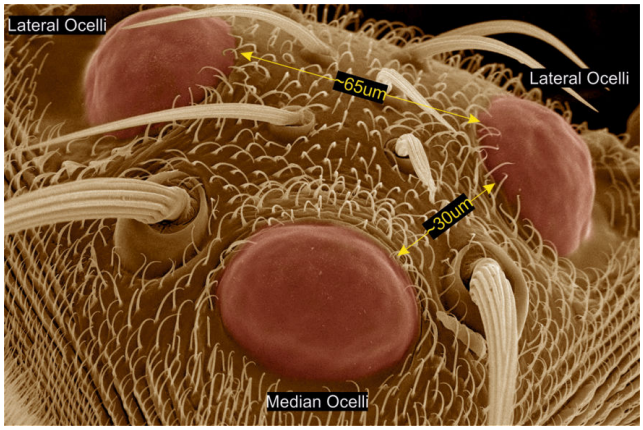

Figure 1: The ocelli from Drosophila: The pseudocolor scanning electron micrograph (SEM) of the ocelli from adult Drosophila showing lateral and median ocellus with approximate distance between the median-lateral and lateral-lateral ocellus.

Rhabdomeres of neighbouring photoreceptor cells were not joined with one another on their distal surfaces. The rhabdomere length does not remain same throughout the ocelli. Rhabdomeres in the middle part of an ocellus were stretched to 7-9 µm and the rhabdomere length decreases towards the periphery [21,23]. PRCs are associated with one another by means of adherens junctions (AJ) also known as belt desmosomes which are located near the apical and proximal part of rhabdomere [21,22]. Furthermore, rhabdomere of the *Drosophila* compound eyes specifically face the neighbouring PRC [21,23] and distinctly separated from one another by intra-rhabdomeral space (IRS), while ocellar rhabdomeres specifically face the neighbouring PRC [21,23]. PRCs from insect eye and ocelli contrast in the rhodopsin expression pattern. The Rh2 expression in ocelli is sensitive to spectrum ranging between 350 nm (UV) and 445 nm (blue) [24]. In case of compound eye each ommatidia has open rhabdom formed of central and peripheral photoreceptor cell. The peripheral PRC expresses Rhodopsin 1 (Rh1) which enables dim light vision and motion detection [25] while the central PRC are for color and polarised light detection. 30% of the ommatidia is of pale type which contains Rhodopsin3 (Rh3, UV sensitive) and Rh5 (blue sensitive) present in R7 and R8 respectively. The rest 70% ommatidia are of yellow type that perceives longer wavelength of UV via Rhodopsin 4 (Rh4) expression in R7 and green sensitive Rhodopsin 6 (Rh6) in R8 [26-28]. Like compound eye, a stalk membrane is also present in the ocelli [24]. Proteins like Crumbs and its partners are expressed in the stalk membrane. More importantly like compound eye, defect in stalk membrane also leads to retinal degeneration in ocelli [24]. Axons which are surrounded by glial cells are seen proximal to the nuclei of rhabdomeres and that axonal cytoplasm have microtubule bundles and membrane-bounded structures like septum (Figure 2) [24]. The structural differences between compound eye and ocellus are summarised in Table 1.

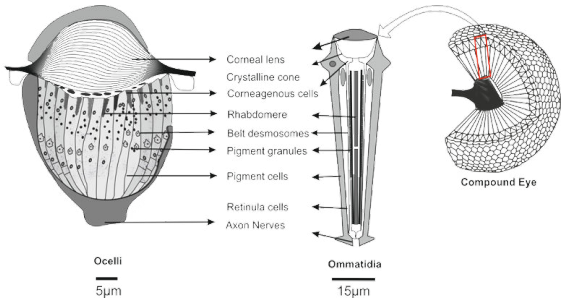

Figure 2: The structure of ocelli and compound eye. (A)The schematic diagram of ocelli and compound eye depicting the arrangement of various cells. Ocelli scheme redrawn from the Chun-Sik Yoon, [66] and ommatidia from Wolff, T. and Ready, D. F. [87].

Characteristic	Compound Eye	Ocelli	References
Structure: cornea lens	~15 µm (length) and ~24 µm (diameter).	~6 µm (length) and 40 µm (diameter).	[24,89-91]
Corneagenous cell	~22 µm (length) and ~20 µm (diameter)	~0.24 µm (length) and ~0.65 µm (diameter).	[66,89,92]
Pigment cells	12	Uncountable	[87,93-95];
Photoreceptor cell	8 (R1-6, R7 and R8)	80	[96,97]
Light sensing unit/ rhabdom	Open rhabdom and it expands throughout the eye; R7, R8 rhabdomere ~1 µm (diameter), R1–6 ~2 µm(diameter); ~85 µm (length).	Spans only the distal portion of the cells. 2 µm (diameter) and 7 µm (length).	[66,92,98-100]
Size of microvilli	1.2-1.5 µm (long) and 50 nm (diameter).	1µm (long) and ~40 nm (diameter).	[24,96]

Visual pigment	Rh1 (R1-6); Rh3 (30% of R7); Rh4 (70% of R7); Rh5 (30% of R8); Rh6 (70% of R8).	Rh2.	[96]
Junction	Septate junction between cone and rhabdom; Adherens Junction between photoreceptor cells.	Junction are found between cornea and cone and between cone and rhabdom; Septate junction in Corneagenous cells.	[17,66,101,102]
Stalk membrane	At the base of rhabdom and crumbs is required for long term stability of rhabdom.	Runs parallel with the rhabdom and crumbs are required for long term stability of rhabdom.	[24,74]
Neuronal wiring	Neural superposition.	Reciprocal synapses in between the receptor terminals and interneurons.	[103]

Table 1: Difference in compound eye and ocelli structure.

Genes regulating the development and maintenance of ocelli

Ocelli share plethora of common genes along with the compound eye although the function varies in both the photoreceptors (Table 2). These genes are expressed in different parts of life starting from larva to adult stage. The genes which are involved in the development are categorised as developmental gene, and the one which are involved in the functioning are classified as functional genes of ocelli.

Name of genes in ocelli	Function in ocelli	Function in Compound eye	References
decapentaplegic	For maintaining ocelli size.	Imaginal disc development and morphogenesis	[58]
eyes absent	Cell specification; inhibits cell death in eye imaginal disc.	Cone cell differentiation.	[78]
sina oculis	Development by activation of Toy gene.	Optic lobe placode formation, eye-antenna disc morphogenesis	[104]
orthodenticle	Ocellus Photoreceptor development.	Essential for rhabdomere biogenesis	[8]
hedgehog	Signalling in ocelli development.	Progression of morphogenetic furrow involved in eye.	[8]
wingless	Regulated by Otd during development of ocelli.	Eye morphogenesis; Positive regulation of eye retinal cell death; eye pigmentation.	[8]
homothorax	Regulate Otd and eyes absent during ocelli development; maintains ocelli size.	Formation of morphogenetic furrow.	[58]
Toy	Important for activation of sine oculis and ocelli formation.	Involved in eye antennal disc; organ development; optic lobe and brain morphogenesis development.	[78]

Table 2: List of important genes involved in Drosophila compound eye and ocelli morphogenesis.

Developmental and signalling genes

Pax6 genes: Pax6 is a widely conserved gene and known to have crucial role in neuronal development [29-31]. It is a transcription factor possessing two DNA binding sites for homeodomain and a paired domain [32]. The latter paired domain has subdomains with a C and N-terminal region. In Drosophila, two homologs of Pax6 are Eyeless (ey) and Twin of eyeless (Toy) [33]. These two homologs share sequence similarity with most holometabolous insects [34]. During evolution ey lost its property of autoregulation while toy share more identity with vertebrate Pax6 and involved in the head formation of fly [34,35]). Toy is the first gene expressed during embryonic stage and plays a role in the development of eye. Besides eye, it is also involved in the development of antenna imaginal disc, parts of brain, optic lobe, ventral nerve cord and ocellar region [34,36]). Null mutants for ey are eyeless with missing eye-antenna imaginal disc [32,37,38]. Similarly, Toy null mutants and Toyhdl (hypomorphic mutants) are headless, even if head forms it is without ocelli [38].

Orthodenticle (Otd): Orthodenticle (otd) is a conserved homeodomain transcription factor involved in determination of eye, antenna and brain of Drosophila. otd expression in eye-antennal imaginal disc is mainly involved in the formation of ocelli, eye and bristles [39]. The conserved homeodomain structure is formed of ~60 aminoacids and acts as a transcriptional regulator involved in cell fate specification of ocelli and CNS (Central Nervous System). The otd null mutation creates affected development in head and segmental patterning [39]. Otd is conserved from invertebrates and vertebrates and play an important role in head formation. From the hypomorphic mutant otduvi (UV light insensitivity) it was further investigated that otd is essential for biogenesis of rhabdomere, causing the activation of rhodopsin's Rh3, Rh5 and Arrestin2 [40,41]. The otduvi mutant results from partial deletion of enhancer region in eye. In 1996's, Royet and Finkelstein reported that otd regulates the combination of hedgehog (hh) and wingless (wg) expression [8,39]. During eye-antenna imaginal disc development otd acts as a target for hedgehog. Later, otd suppresses the expression of wg when it is autoregulated, in turn activates the eya and so expression in ocellar precursor cells. Hence,

otd has a role in eya expression via hh activation in the vertex primordium [8]. In this mutant, Rh7 is affected so the mutant loose sensitivity to UV and gets more attracted towards the visible light. Fatty and malformed rhabdomeres were formed in both compound eye and ocelli [41,42]. Most rhabdomeres appear to be duplicated or disoriented at proximal region as most of them were prematurely terminated. The ocelliless (oc) is otd hypomorphic allele in which the ocelli formation is affected. The role of otd in ocelli is in a dosage dependent manner because partial ocellar phenotype was observed in otd/+ heterozygote. The heterozygote formed from otduvi/oc shows missing ocelli and photoreceptor cells [43].

Optix and sine oculis (so): Sine oculis (so) has an important role in development of larva Bolwig's organ, adult compound eye, optic ganglia and the ocelli [44]. The mutants flies have severe eye defects and if over expressed so produces ectopic eye [37,45]. Drosophila so share similarity with six1/2 of mouse (a homolog of Six3 involved in eye development) [30]. Later optix was found to be the homolog of Six3. The optix is similarly equally involved in the eye development. The so expression is restricted to anterior head region and Bolwig's organ. The so activation starts during the late second instar larval stage in eye disc. The expression of so starts in a gradient manner from anterior to posterior region. so1 is a loss of function mutant with deletion at terminal intron of so gene, non-lethal but they fail to develop compound eye and ocelli. In so3 mutants massive cell death occur and ocelli also gets affected [46]. Homozygous mutation for soD is anti-morphic, gain of function allele mutant produced by point mutation replacement of single amino acid from valine to aspartate at 200 residue position recruits optix co-factor producing a phenotype similar to so1 mutants affecting the compound eye but leaving ocelli unaffected, again they are homozygous lethal [47,48]. Loss of function of optix is not known however its overexpression in imaginal disc of antenna leads to formation of ectopic eye with extra ocelli [49].

Eyes absent (eya): The eya belongs to family of transcriptional co-activator, with one eya in Drosophila and four Eya1-4 from vertebrates [50-52]. The eya is involved in cell specification and inhibits cell death in eye imaginal disc. In second instar larvae, eya expression decreases in a gradient manner from posterior to anterior region. In third instar larvae, eya is expressed in both anterior and posterior morphogenetic furrow and helps in ocelli development [51]. The eya^{3cs} mutant is formed by insertion of roo element in 5' UTR and eya^{4} mutants is formed insertion of I element at 5' UTR. Both (eya^{3cs} and eya^{4}) mutants have reduced eyes with undeveloped ocelli [53].

Homothorax (hth): Homothorax (hth) is involved in embryo patterning and share homology with Meis proto-oncogene with TALE class homeodomain and homeobox related to exd (extradenticle) [54,55]. It has a role in almost every imaginal disc including eye antenna disc, but is ubiquitously expressed at the second instar stage in eye and antenna region [56,57]. In antenna, the expression gets constrained to anterior region of ocelli. During early third instar hth and toy are expressed uniformly throughout ocellar region, which get downregulated during mid and late third instar larvae. hth in association with toy regulates the size of ocelli. hth knockdown creates bigger and fused ocelli [58]. Overexpression of hth produces miniature ocelli without eliminating eya and so expression in ocellar primordium. For a proper ocelli size, the hth must be regulated which is supposedly occurs due to hh signalling pathway and Decapentaplegic (dpp). In the absence of dpp the hh signalling pathway overtakes the role and if hh signalling is inhibited than hth is uniformly expressed inhibiting the eya and so expression.

Defective proventriculus (Dve): Dve is also involved in ocelli development [59]. Dve is expressed in several tissues along with head primordium and causes transcriptional inactivation. In Drosophila eye, Dve is expressed in peripheral photoreceptors (R1-R6) and represses the Rhodopsin Rh3 produced by otd activity in pale type R7 [40,59,60]. Dve acts downstream of otd in vertex primordium and repression of Dve are important for maintenance of hh in order to specify the ocellar region. Dve also represses the frons via type-I feed forward loop of otd and Dve [59].The ocellar specification of Dve occurs via two mechanisms: 1) Dve dependent ocellar specification where late expression of hh, causes Hh induced activation of en and 2) Dve independent ocellar specification in which repression of eyg and wg occurs (Figure 3 and Figure 4) [59].

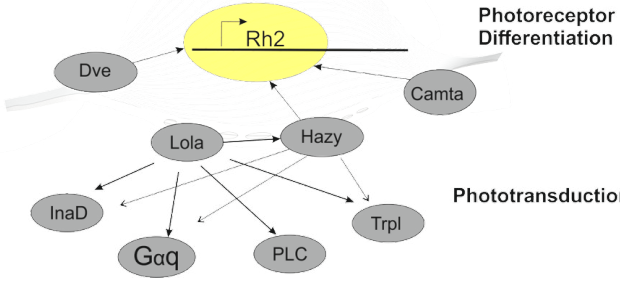

Figure 3: Rh2 expression in ocelli: The ocellar photoreceptor differentiation is mediated by Camta, Lola, Hazy and Dve, which regulates the Rh2 expression. The phototransduction cascade is activated by regulatory genes of Lola and Hazy (The figure based on the published result from Mishra et al. [67]).

Nemo (nmo): The nmo belongs to the family of Nemo-like kinase. It is a conserved gene from invertebrates to vertebrates which regulates cell signalling [61]. It is required in eye development network for positive regulation of eya gene. During eye development nmo is required for planar cell polarity [62]. It is expressed majorly in the eye disc region during second and third instar larval stages and involved in patterning of antenna and ocellar region and in eye specification [62]. After initiating the division of eye antenna disc later, it takes part in patterning of antenna and ocelli. It is ubiquitously co-expressed with ey and eya at the posterior region of the second instar larva. The nmo co-expresses with eya, so and dac (eye specification genes) for further repressing the Hth in ocellar cells. During the third instar larvae stage, the expression is anteriorly restricted and expressed in ocellar primordia. Later nmo is expressed in the morphogenetic furrow (MF) and expressed ubiquitously in the ocelli [63].

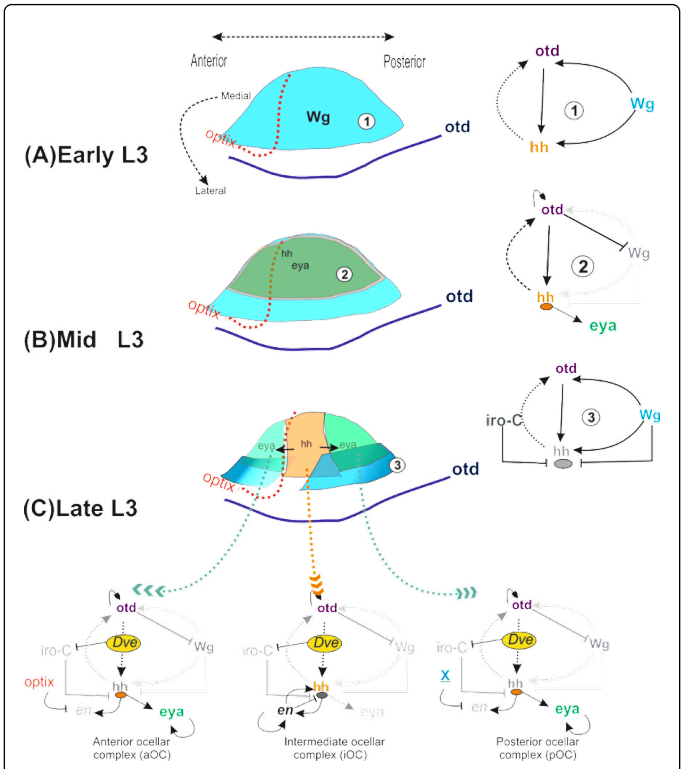

Figure 4: The schematic representation of the patterning in ocelli complex: (A) Early third instar: The wg expression helps initiating the otd expression in the eye disc region later wg and otd turns on transcription of hh. (B) Mid third instar: With the expression initiation of hh, the otd auto regulatory enhancer also gets activated. The high otd level inhibits wg and hh activates its potential target eya required for ocelli formation. (C) Late third instar: The Intermediate ocellar complex (iOC) formed has hh expression confined to the mid region, as hh signalling is maintained by en. The anterior ocellar (aOC) region is formed due to repression of en by optix, similarly, the posterior ocellar (pOC) margin is developed by another en repressor 'X' (similar to optix). The so (not shown) helps in autoregulation of eya in both anterior and posterior ocellar region. (The figure has been adapted from the work of Maria A. Domínguez-Cejudo and Fernando Casares [77].

Functional and structural genes

Crumbs: Crumbs is a conserved transmembrane protein involved in the morphogenesis of the photoreceptor cell of Drosophila compound eye. Crumbs also regulate the development and maintenance of ocelli [24]. Crumbs loss of function affects polarity resulting mishappened Adherens junction (AJ) in ocelli. Like compound eye crumbs is expressed in the stalk membrane the homologous structure to the vertebrate inner segment. Crumbs mutant for ocelli shows more severe phenotype than the compound eye. Like compound eye Crumbs also help to protect the ocelli from light-dependent degeneration. Variation of Crumbs mutant phenotype in both eye and ocelli is striking. The variations may be caused due to the development and architectural difference present in either photoreceptor [24].

Retinal degeneration gene (rdgA and rdgB): The rdgA and rdgB encodes for diacylglycerol kinase and phosphatidylinositol transfer protein respectively in compound eye [64,65]. In adult fly rdgB is localized to sub-rhabdomeric cisternae of compound eyes. Like compound eye rdgB is responsible for formation of membranous structure similar to sub-rhabdomeric cisternae. The characteristic phenotype produced by the rdgB mutants is degenerated photoreceptor. In these mutants, the photoreceptor microvilli are present with failed supply of photoreceptive membrane components. In this mutant of the sub-rhabdomeric cisternae (SRC), the smooth endoplasmic reticulum present below the microvilli is missing which are the initial stages of degeneration of photoreceptor. Hence, in rdgB mutant flies the ocellar sub-rhabdomeric cisternae is affected or not formed. The rhabdomeric microvilli is disintegrated and SRC is absent in the sub rhabdomere region confirming the conserved role of rdgB in both compound eye and ocelli. In both rdgA and rdgB mutants, SRC in ocelli disappeared in the same manner as compound eye hinting that these proteins have activity in ocelli [66].

Rh2 opsin gene: Rh2 encodes the visual pigment present in the ocelli [4]. Being the visual pigment, it also regulates the function of the ocelli. In comparison to compound eye, the functional aspect of ocelli is less studied. The Rh2 opsin is formed of 381 amino acid with seven hydrophobic domains. Rh2 along with other genes help in differentiation of ocellar photoreceptor by regulating the expression of Rh2 [4]. Rh2 has spectral sensitivity between 350-445 nm [23] and have violet pigment type [4,19] (Figure 2).

Lola and camta: Longitudinal lacking (lola) and Calmodulin-binding transcriptional activator (Camta) are two new key players in photoreceptor development [67]. The role of Lola and Camta was established recently in a microarray analysis by Mishra et al. Both the genes are enriched during larval eye and ocelli development [67]. Lola has a POZ (pox virus and zinc finger) domain which helps them in protein binding [68]. Mutation studies revealed its role in neurogenesis and brain dendrite morphogenesis. lola loss causes neuron de-differentiation and tumour formation [69]. In eye, lola makes fate decision of the binary cells and is expressed in photoreceptors for R3, R4 and R7cone cells [70]. How lola plays a role in ocelli development is not fully understood but might have some functional relevance as it is required for conserving rhabdomere morphology and regulating the expression of Hazy and helping the maturation and differentiation of photoreceptor precursor cells in ocelli. Knocking down of lola creates negative Rh2 expression. Similarly, Camta as previously known causes stimulation of dFbxl4 (F-box and leucine-rich-repeat gene 4) affecting fly visibility by deactivation of rhodopsin and G-coupled light receptor rhodopsin [71]. The dCAMTA null mutant flies with full-length dCAMTA has dimerised mutated site with a defective nuclear localization [72]. Microarray analysis indicated the camta presence during ocelli development as it also takes part in rhodopsin formation of adult eye [67].Both genes lola and camta takes part in the regulation of Rh2 expression. In camtates2 (mutant produced by RNAi knockdown in photoreceptors of ocelli) loss of Rh2 expression observed without losing expression of lola or Dve indicating lola acts independently of camta.

Hazy or Pph13: Pph13 stands for PvuII-PstI homology 13 a homeodomain transcription factor, expressed only in photoreceptor cells [42]. It has a role in development of compound eye and ocelli more towards differentiation than speciation of photoreceptor cells. It regulates rhabdomere morphogenesis and help in light detection [42,73]. Pph13 regulates rhodopsin Rh2 and Rh6 genes. It acts on the rhodopsin promoters of Rhodopsin core sequence I (RCSI) binding

site [42]. Pph13 mutant for compound eye have malformed rhabdomere and they cannot initiate phototransduction pathway [73]. Although the functionality of the ocelli is not checked so far, combining the behavioural study the functionality of ocelli questionable at this moment [42,73]. Further study will answer more about the role of hazy in ocelli development and maintenance.

Eyeshut / Spacemaker gene (Eys/Spam): The spacemaker (spam) is a secretory protein found to contain protein motifs present in a polypeptide of 2165 amino-acid [74]. The spam acts as an extracellular protein as it is secreted and localised in inter-rhabdomeral space in between the rhabdomeres. For proper rhabdomere separation in a wildtype Drosophila, the spam needs to diffuse throughout the ommatidia. Unlike Compound eye, the Drosophila ocellar photoreceptors have no inter-rhabdomeral space in between. When spam was specifically overexpressed in ocelli, the inter-rhabdomeral space starts appearing near the rhabdomere region and it get separated, indicating spam has been strongly regulated in the ocellar photoreceptors producing wildtype phenotype [74].

Exit protein of rhodopsin and TRP (XPORT): XPORT is an eye specific secretory pathway membrane protein of Drosophila [75]. It is expressed in compound eye, ocelli and Bolwig's organ. Although it is expressed in Bolwig's organ, loss of function does not affect the Bolwig's organ phenotype in larvae. However, both compound eye and ocelli shows a phenotype in absence of XPORT. Along with connexion and ninaA, it further helps in synthesis of rhodopsin. Mutation in XPORT result faulty accumulation of channel protein TRP and phototransduction protein Rh1 in the secretory pathway of compound eye. Due to defective transporter, the eye undergoes light dependent degeneration. In the xport1 mutant TRP is significantly reduced and its lost expression was also observed in ocelli [67].

Development of Ocelli

The development of the visual organ starts from the third instar larval stage from a dorsal anterior region of eye imaginal disc. From eye-antenna imaginal disc two lateral ocelli are formed from two separate disc and the medial ocellus is a result of fusion of the analgen from two separate discs [7]. Ocelli development is a result of interplay among otd, wg and hh signalling pathways. This interplay results in the patterning from lateral to medial which results in frons, orbital cuticle and ocellar complex [4, 66]. The wnt and Otx family members involved in anterior head patterning of both invertebrates and vertebrates [76] (Figure 5).

Patterning of ocellar region into aOC, iOC and pOC: The patterning of ocelli takes place with certain activation and inactivation of genes at various stages of larva. Due to patterning the ocelli is divided into anterior, intermediate and posterior ocellar complex (Figure. 3). The otd (a member of Otx family) does not take part in the retinal determination network but is solely involved in the formation of the ocelli [76]. During late embryonic stage, all the cells present in the eye-antennal disc expresses eyeless (ey) which later expresses otd. During second instar larva, the otd in disc starts disappearing and confined only to the dorsal anterior region. During third instar larvae otd gets restricted to ocellar primordial cell. The restriction occurs due to Wg and Hh signalling where it is associated with wg expression and hh transcription. Later otd enters autoregulatory loop for its expression [8]. During the mid and late third instar larvae, the ocellar region is subdivided into three regions or domains where hh is transcribed in the mid region and the eya and so is expressed at its adjacent region (anterior and posterior ocellar region) [77] (Figure. 3). The mid ocellar region formation is relied on hh signalling by differential activation of eya and en (engrailed). The activation of en inhibits hh activation which in turn represses the activation of eya causing a clear demarcation of mid ocellar region from the adjacent region that expresses the eya [77]. Transcriptional repressors of Six3/6 optix also play a vital role in maintaining the boundary [77].

Signalling pathway leading ocelli development: The Wg and hh signalling directs the activation of the otd initially. Later, otd is eligible to induce its own expression by autoregulatory feedback loop [8]. In ocelli, primordial cells Toy is considered to be among the primary genes getting expressed initially. The regulation of toy is dependent somehow on otd but its transcriptory regulation is unknown. In otd null mutants, expression of the toy is suppressed but the primordium formation remains unaffected as the expression of eyg is conventional which is an early determinant gene. In toy mutant, the otd expression remains unaffected signifying that toy occurs downstream of otd signalling. The toy and hh causes the onset of eya and so expression independently occurs during the third instar larva. Genes like eya and so expressed in ocelli precursors by the help of toy and hh and its mutations leads to failure in ocelli development. In toy, there is a binding sites at so enhancer region indicating toy to be responsible for activation of so. Toy mutants still show so formation but toy expression also kindles eya expression. As toy cannot activate so in eya mutant background, it implies eya role in so activation. The related pathways for these genes are mentioned (Figure 4). Wg is required for the formation of the otd initially but later otd itself starts repressing the Wg when it achieves its autoregulatory function. Hh expression is positively regulated by otd, hh signalling pathway inhibits conversion of Ci155 to Ci75 which in turn it acts as a transcription factor for eya expression [8].

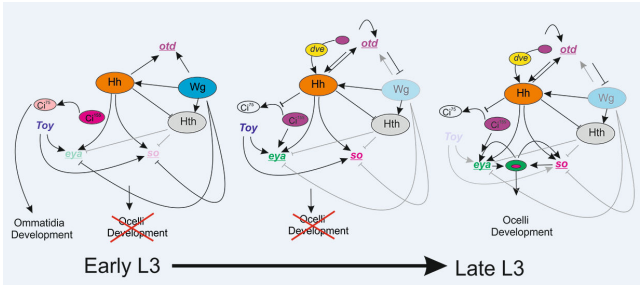

Figure 5: The signalling network for ocelli development: It represents the early and the late L3 stage, where in early L3 the Wg is involved in Hh signalling and otd formation. When otd becomes auto regulatory, it initiates the expression of eya along with toy gene. The eya and so expression later emerges itself being auto regulatory and their product helps in the formation of ocellar region. The self-explanatory pathway is adapted from the ideas of several work of Gehring Walter J, Blanco J. et al., Yorimitsu T. et al., [8,59,88] (The shaded region and lines represents inactive protein or inhibited pathway).

Significance to study this minute photoreceptor

In many aspects, the development and the photo-transduction mechanism of ocelli share similarity with vertebrates. In vertebrates,

Pax6 is a transcription factor involved in oculogenesis [78-80]. Sine oculis, eyes absent and daschund in fly usually share homology with vertebrates suggesting despite different architecture, both invertebrates and vertebrates share similar kind of molecular scaffolds giving significance of Drosophila genetics in studying the eye development in vertebrates. The photoreceptor neurons in eye perceives the light and the cells specialised for transducing the light signals into neuronal information are photoreceptor cells which express the rhodopsins. The rhodopsins that encodes the photosensitive G-coupled receptors (GPCRs) which lead to opening and closing of ion channels initiate the activation of the phototransduction cascade. The genes involved in phototransduction cascade of both compound eye and ocellus are dgq, norpA and arrestin 1 and arrestin 2 [75]. The molecular scaffolds getting activated by the cascade are InaD, Gαq (activates the PLC), along with light sensitive channels Trp and Trpl [67].

In vertebrate, ciliary opsin is present in the retina classified as rod and cone opsin which are required for dim light vision or colour vision respectively. There are many molecules such as rhodopsins, photopsins, piniospsins, neuropsins, melaonopsin, peropsin involved in vertebrate vision [3,81-84]. In ocelli, only a single rhodopsin gene (Rh2) is present in all photoreceptors although involved in activation of InaD, Gαq, PLC and Trpl by regulated expression of Lola and Hazy [85]. The homology of ocellar network and their associated defects (Table 3) in both vertebrates and Drosophila suggest its importance to study this minute photoreceptor. Besides photo sensation, ocelli are also involved in locomotion, flight and orient detection. Reduced phototaxis is observed if the ocelli is missing or if it is painted artificially in Drosophila [12]. A similar observation is found in hive bees, where if the ocelli is painted then in dim light the bee fail to detect the waggle dance of the worker [86]. Further study will answer the functioning of ocelli for other sensory organs.

Drosophila Gene	Homologous gene in Humans	Gene Function in Drosophila	Gene Function in Vertebrates	Mutant phenotype in Vertebrates	References
Eyeless; twin of eyeless	Pax6	Development of eye-antenna imaginal disc development of eye precursors	Lens Placode and optic vesicle formation	Aniridia (humans); Small eye (mouse)	[105,106]
Eyes absent	Eya1	Cell specification in eye; inhibits cell death in eye imaginal disc	Perioptic mesenchyme; Weak lens expression	No eye phenotype in BOR; Cataracts.	[100,107]
Sine oculis	Six3	Development of larva bolwig organ, adult compound eye, optic ganglia and the ocelli	Lens Placode; Optic vesicle	Holoprosencephaly; Microphthalmia	[108]
Optix	Optx2	Development of anterior ocellus	Optic vesicle	Anophthalmia	[109]
Crumbs	CRB1	Morphogenesis of the photoreceptor cell in both eye and ocelli protect photoreceptors from light degeneration	Retina development	Retinitis Pigmentosa	[110]
Orthodenticle	Crx	Eye, antenna and brain determination	Neural retina	Cone-rod dystrophy; Retinitis pigmentosa; Leber congenital amaurosis	[110]
Hedgehog signalling	Sonic - hedgehog signalling	Regulate orthodenticle and eyes absent during ocelli development	Brain ventral midline	Holoprosencephaly	[111,112]
Spacemaker	Eyes shut	Maintains the integrity in ocelli; separates the rhabdomeres in compound eye	Rhabdomere separation; retina formation	Retinitis Pigemntosa	[113]
D-rdg B	H-rdg B	Sub rhabdomeric cisternae in photoreceptor microvilli	Photoreceptor formation	Best disease and Bardet-Biedl syndrome I	[114]
Dve	SATB1(human orthologue)	Specification of ocellar region in Drosophila head	In pathway regulation	Retinoblastoma or cancerous outcome	[115]

Table 3: Genes associated in ocellar complex.

Conclusion

Even after decades of research on vision, still all the genes and molecules regulating the development and function of photoreceptor remains unexplored. Drosophila ocelli involved in photosensation and flight include many complex genetic networks. Understanding the role of these genes will enlighten our idea regarding the development and evolution of the photoreceptor and ultimately will help us to treat various eye related disease. Combined study of ocelli with other sensory organ will help to understand the function of ocelli in other sensory organs as well.

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