Seminars in Cell and Developmental Biology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Shaping an optical dome: The size and shape of the insect compound eye

Franck Pichaud [a,*], Fernando Casares [b,*]

[a] MRC Laboratory for Molecular Cell Biology (LMCB), University College London, WC1E 6BT London, United Kingdom
[b] CABD-Centro Andaluz de Biología del Desarrollo, CSIC-Universidad Pablo de Olavide, ES-41013 Seville, Spain

A B S T R A C T

The insect compound eye is the most abundant eye architecture on earth. It comes in a wide variety of shapes and sizes, which are exquisitely adapted to specific ecosystems. Here, we explore the organisational principles and pathways, from molecular to tissular, that underpin the building of this organ and highlight why it is an excellent model system to investigate the relationship between genes and tissue form. The compound eye offers wide fields of view, high sensitivity in motion detection and infinite depth of field. It is made of an array of visual units called ommatidia, which are precisely tiled in 3D to shape the retinal tissue as a dome-like structure. The eye starts off as a 2D epithelium, and it acquires its 3D organisation as ommatidia get into shape. Each ommatidium is made of a complement of retinal cells, including light-detecting photoreceptors and lens-secreting cells. The lens cells generate the typical hexagonal facet lens that lies atop the photoreceptors so that the eye surface consists of a quasi-crystalline array of these hexagonal facet-lenses. This array is curved to various degree, depending on the size and shape of the eye, and on the region of the retina. This curvature sets the resolution and visual field of the eye and is determined by *i)* the number and size of the facet lens – large ommatidial lenses can be used to generate flat, higher resolution areas, while smaller facets allow for stronger curvature of the eye, and *ii)* precise control of the inter facet-lens angle, which determines the optical axis of the each ommatidium. In this review we discuss how combinatorial variation in eye primordium shape, ommatidial number, facet lens size and inter facet-lens angle underpins the wide variety of insect eye shapes, and we explore what is known about the mechanisms that might control these parameters.

1. Introduction

Evolving sensory systems capable of detecting and interpreting odours, sounds and light is arguably one of the most important steps in animal evolution. The olfactory, auditory, and visual systems have all evolved specific morphological features and 3D tissue organisation, which are suited for their function. For the eye, and across species, there is a set of common key constraints that need to be met to generate a functional eye. The resolution of an eye ultimately depends on how finely "pixelated" the image it generates is [1]. Two major eye types exist: the camera-like eye, where a surface slit or a lens focuses light onto the photoreceptor in the neural retina, and the compound eye, which is made of adjacent unit eyes, called ommatidia, each coming with its own dioptric apparatus and core set of photoreceptor cells (Fig. 1A) [2]. While in camera type eyes each photoreceptor (R) cell represents a pixel, in most compound eyes each pixel is contributed by one ommatidium. Compound eyes are typical of Crustacea and Hexapoda (including insects) but are also present in other arthropods, such in Myriapoda or the chelicerate *Limulus* [3,4], and therefore represent the most abundant eye type in nature. In these eyes, each ommatidium is formed by three types of cellular elements arranged in a slender cylinder: the R cells, at the centre; the screening pigment cells around the R cells; and the cells secreting the dioptric apparatus, formed by two elements: the cuticular lens and the pseudocone, which are deposited on top of the R cells [5,6]. The dioptric apparatus focuses light onto the core R cells in each ommatidium. In most arthropods, R cells juxtapose their heavily folded apical membranes (called "rhabdomeres") to form a common central light gathering structure called rhabdom, which bear the photopigments, called Rhodopsin. In this case, all R cells in one ommatidium work as a single light detecting unit. The situation is more complex in Diptera (i.e. flies). Here, the rhabdomeres of each R cell is detached from its neighbours, and individual rhabdomeres are arranged around a central luminal space – the inter-rhabdomeric space [5]. This type of open rhabdom arrangement, allows for each R cell within an ommatidium to see a different part of the visual space (Fig. 1A). Thanks to the wiring of the R axons as they reach the optic lobe, where visual information is processed, R cells from adjacent ommatidia that focus on the same point in space project their axons to the same optical synaptic column [7]. This neural architecture allows for sharp vision and increased sensitivity. Critically, it relies on the perfect arrangement of ommatidia and ommatidial cells: the compound eye of flies is a precision optical device, in which the lenses form an hexagonal lattice, which maximises occupancy (although there are lenses of different shapes, such as squares) on a dome-shaped convex surface (Fig. 1A-C).

* Corresponding authors.
E-mail addresses: f.pichauf@ucl.ac.uk (F. Pichaud), fcasfer@upo.es (F. Casares).

https://doi.org/10.1016/j.semcdb.2021.11.002
Received 21 July 2021; Received in revised form 2 November 2021; Accepted 4 November 2021

Please cite this article as: Franck Pichaud, Fernando Casares, *Seminars in Cell and Developmental Biology*, https://doi.org/10.1016/j.semcdb.2021.11.002

Therefore, animals equipped with compound eyes see a pixelated world, and the geometry or "shape" of this convex eye is critical for function. The optical performance of the compound eye depends, by and large, on the density of ommatidia (higher density increases resolution), facet size (larger facets allow higher sensitivity) and curvature (with higher curvature permitting a broader field of view). These parameters not only vary from species to species, but also within a single eye, sometimes with areas of higher and lower resolution/sensitivity (for further discussion of compound eye optics, see [1,4]). The type of Rhodopsin expressed in R cells determines the wavelength sensitivity of each ommatidium to detect light's colour and vector of polarisation [8,9].

Most of what we have learned of how the compound eye develops its curved, convex shape comes from studies in the fruit fly *Drosophila melanogaster*. *Drosophila* is a holometabolous insect, living through a larva and an adult form, which are connected through metamorphosis. Although some other groups of insect have a life cycle in which larval and adult stages are more similar to one another (hemimetabolous insects), the general mode of eye development seems to be largely conserved across insects [3] and, therefore, we expect that the general principles underlying the development and shaping of the compound eye can be derived from *Drosophila* studies.

The eye of *Drosophila melanogaster* has been a particularly useful model to study how cells work together to assemble a multicellular unit, the ommatidium, during tissue patterning. However, understanding how the eye is built has often been reduced to understanding cell specification and movement in the 2D plane of the tissue. This approach has revealed that ommatidia can differ in photoreceptor content, depending on the type of Rhodopsin they express [9,10]. It has also revealed how retinal cells work together to assemble the ommatidium and determine its size and shape [11,12]. The ommatidium is a modular unit, and is well suited for studying how different cell types work together to generate a functional organ at different scales: cells, tissue units and whole tissue. For instance, in flies and other insects the dorsal-most rows of ommatidia are specifically adapted for detecting polarised light, which is used for navigation [13]. In many fly species, the eyes of males are enlarged dorsally at the expense of head cuticle. This expansion is thought to enable higher spatial resolution in this part of the eye, which is used to locate sexual partners for in-flight mating - the so-called "love-spot" [14]. For example, in some hoverfly species, this male-specific dorsal extension is made by addition of more ommatidia. In some tabanids, though, the love spot is generated by enlarging the facet size of the dorsal ommatidia (Fig. 1D).

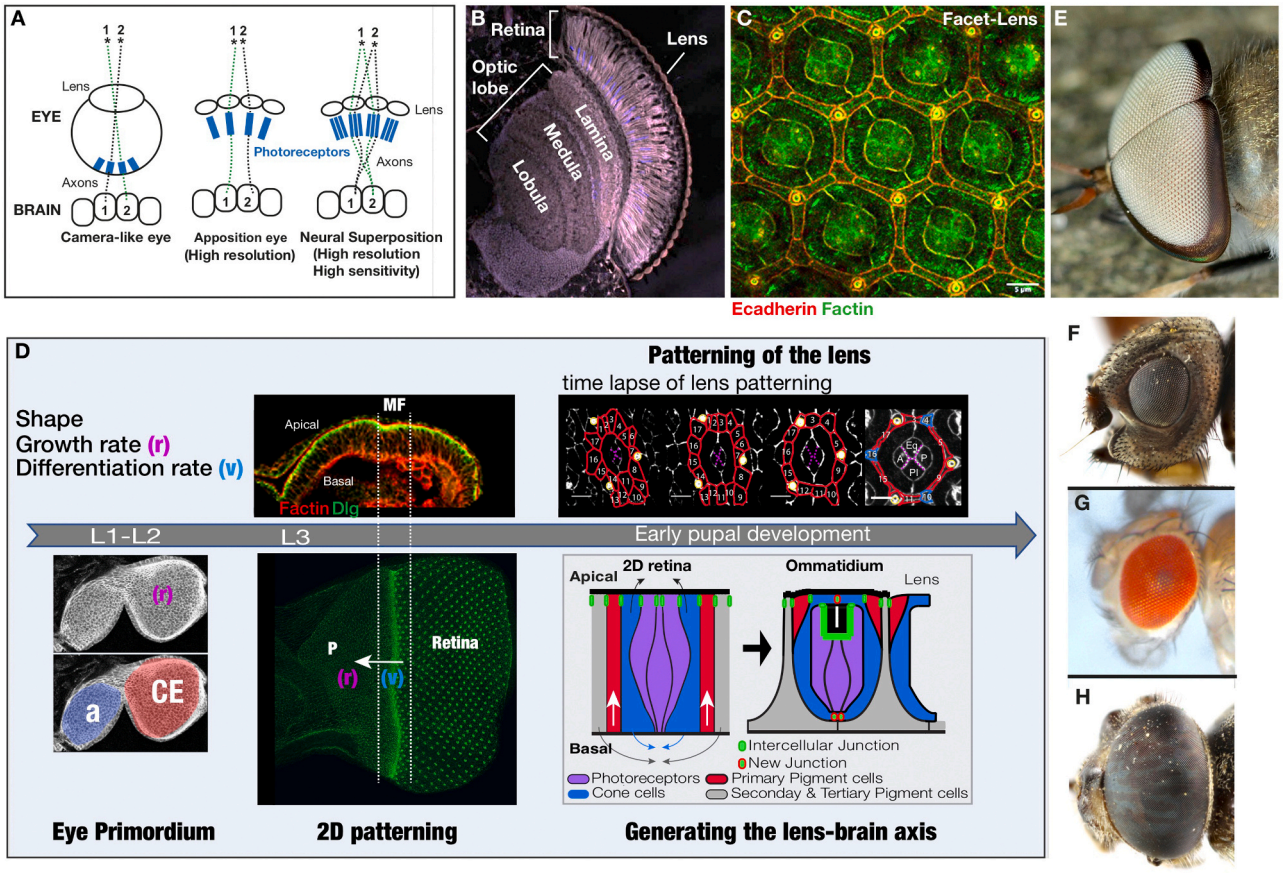

Fig. 1. Building a compound eye. (A) Schematic representation of different types of eyes, camera-like, apposition and superposition (Dipteran) eyes. (B) A cryosection through the eye of *Drosophila* showing the retina, which includes R8 cells expressing the UV-sensitive rhodopsin 5 (blue). (C) On-face view of the surface lens of the pupal eye of *Drosophila*, at a stage where patterning of the lens is complete. Ecadherin (red) and F-actin (green). (D) Developmental time-line of eye development in *Drosophila*, showing key stages relevant for 3D pattering of the eye. From left to right, confocal image of an eye (CE) antenna (a) disc at the L1-L2 stage. In L3, the eye tissue is patterned as the Morphogenetic Furrow (MF) sweeps across the disc from the posterior to the anterior pole. As the animal enters pupation, the 2D retina undergoes remodelling so that the cone cells (blue) move on top of the photoreceptors. This correlates with a 90° rotation of the photoreceptors (purple) apical-basal polarity axis. Lens formation also involves the primary pigment cells (red) translocating to the tissue surface and eventually detaching from the basement membrane. Stills of a time lapse movie of lens patterning shows how cells interact to pattern the ommatidium as a supracellular hexagonal structure. (E-H) Pictures of fly eyes that differ in their shape, size area and that show regionalisation in their facet lens size- (E) the eye of a Tabanid male fly shows a dorsal anterior region of low curvature with large facets ("love spot", light brown) and a lateral-posterior region of higher curvature with smaller facets (dark brown region). Image courtesy of Stephen A. Marshall. (F) *Baeopterus robustus* male (Natural History Museum (NHM) London specimen code: 010401386); (G) *Drosophila melanogaster* male (H); *Hermetia illucens* female (Natural History Museum (NHM) London specimen code: 013435435).

Eye development in *Drosophila* proceeds in two phases, one in 2D and another in 3D (Fig. 1E). During the 2D phase, which takes place during the last larval stage and the early pupa, the development of the eye unfolds in a flat monolayered epithelium. During the 2D phase the eye primordium grows in size, thanks to the proliferation of its progenitor cells. Simultaneously, cell differentiation takes place by progressive and patterned recruitment of progenitor into the different cell types that compose the ommatidia. The balance between growth and differentiation, together with the geometry of the epithelium will determine to a great extent the size and shape of the final eye. Then, the 2D epithelium is remodelled into a 3D organ during later pupal stages.

Understanding how the ommatidium is assembled clearly helps understanding how the eye is built. However, it falls short of explaining how the eye is shaped in 3D. For this, we need to consider tissue level regulations and ask, what mechanisms control the size and shape of the retinal primordium? What pathways set the number of ommatidial cells? And, what induces bending of the retina to generate its dome-like shape? Addressing these questions is broadly relevant for our understanding of the pathways that shape all organs. In what follows we will describe what is known (and what is still not known) about the processes we have just highlighted, basing our discussion on what is known in *Drosophila*.

2. Shaping the compound eye, one ommatidium at a time

Drosophila melanogaster is one of the most popular invertebrate model systems: its genetics allows for manipulating cells in space and time, while it is possible to image them as they work together to generate tissues. Using this animal system has allowed to establish the pathways that ***i)*** specify the eye primordium, ***ii)*** control the growth of the primordium, and ***iii)*** induce ommatidia development. Together, these three aspects of early eye development set the stage for determining the size and shape of the eye.

2.1. The 2D phase: size and shape blueprints

The eye develops from a flat epithelial sac (Fig. 1E) that gives rise to most structures of the fly head: the so-called eye-antennal imaginal disc. The eye-antennal imaginal disc invaginates during late embryogenesis to lay adjacent to the neuroblasts that will develop to form the optic lobes [15,16]. During the early stages of development, in the larva, the eye-antennal imaginal disc will grow, and two major regions will be specified within it: the anterior antennal domain and the posterior eye domain [17,18](Fig. 1D). Within the disc, each of the two layers comprises cells of distinct cellular morphotype: One layer is a pseudostratified columnar epithelium, and is known as "main epithelium" as it gives rise to the adult head structures, including the eye. The other layer, called peripodial epithelium, is composed by squamous cells and serves an ancillary role, providing signals to the main epithelium during development [19,20]. The peripodial epithelium participates in the "eversion" of the disc during pupation, a phenomenon by which the apical side of the epithelium, which faces the sac's lumen during larval development, turns "inside-out" to end up facing "outside" after metamorphosis.

2.2. Eye primordium specification, growth and differentiation

Eye differentiation starts at the beginning of the third and last larval stage. Up to this point, the eye progenitor cells have been increasing the size of the primordium through cell proliferation. Differentiation is triggered at the posterior margin of the eye primordium. Once initiated, differentiation proceeds as a wave that sweeps across the primordium from posterior to anterior. As cells differentiate behind the wavefront (which is visible morphologically as an epithelial furrow, called "morphogenetic furrow" – Fig. 1E), they exit the cell cycle. Therefore, growth terminates when all progenitor cells have been recruited by the wavefront [21]. In this context, recent work, using modelling and quantification of developing eyes, has revealed that the final morphology of the eye depends on the precise interplay of a number of variables: the size and shape of the primordium at the time of differentiation start (beginning of L3), the rate at which progenitor cells proliferate, and the speed at which the morphogenetic furrow moves [22–24].

Before the onset of differentiation, during the L1 and L2 larval stages, three important processes take place. Firstly, the eye primordium is defined in the posterior region of the disc by the coexpression of transcription factors, including the Pax6 genes *eyeless (ey)* and *twin of eyeless (toy)* and the Six2 gene *sine oculis (so)* which jointly define the "eye" identity of the eye progenitor cells. Secondly, the eye primordium region is shaped as an approximately elliptical domain, at least in *Drosophila*. Third, the size of the eye primordium increases through the proliferation of the eye progenitor cells (reviewed in [15,16,25]).

Differentiation of the retinal cells, which is preceded by a halt in the cell cycle, is triggered by the Hedgehog (Hh) signalling molecule that is produced by cells adjacent to the eye primordium, which diffuses anteriorly into the eye primordium region of the disc. Hh signalling also induces the apical constriction in the morphogenetic furrow, which marks the onset of retinal cell differentiation [26,27]. R cell differentiation starts with the expression of the bHLH proneural transcription factor *atonal (ato)* [28] and ommatidia formation is initiated with the singling out of regularly spaced ato+ R8 cells. Each R8 cell will act as "ommatidial founder" cell by signalling to its neighbours to initiate recruitment of the remaining ommatidial cells, starting with the other seven R cells [29]. R cells express Hh themselves, which leads to the induction of more R cells [30]. In this manner, a feed-forward loop is established, which induces movement of the morphogenetic furrow. As cells exit the cell cycle behind the furrow to initiate their differentiation, growth of the eye primordium continues as long as there are proliferative progenitors ahead of it, and ends when the differentiation wave reaches the anterior pole exhausting the progenitor cell pool, at which point the eye has accrued all its ommatidia within an epithelial domain of a defined shape. Since ommatidia do not exchange neighbours, this developmental stage directly determines the final shape of the eye when the epithelium morphs into a 3D dome.

The relevant size, that of the primordium at the onset of differentiation, can vary depending upon the size of the primordium when it is set aside within the eye-antenna imaginal disc and on the progenitor cell proliferation rate. As mentioned above, one of the genes responsible for defining the eye primordium within the disc is *ey*. Work by Ramaekers et al. [31] showed how temporal differences as to when *ey* transcription is restricted to the prospective eye domain explains the eye size differences (i.e. differences in number of ommatidia) between *D. melanogaster* and the related species *D. pseudobscura,* and even between strains of *D. melanogaster* showing size differences. An earlier determination of the eye primordium results in a longer proliferation time for progenitor cells such that, at the onset of differentiation, the eye progenitor field is larger [31]. However, the shape of this primordium may play a role as well [32]. For example, for primordia of equal cell number, the differentiation wave will have to travel a shorter distance in narrower primordia to reach its anterior pole, in principle leading to a differently sized and shaped eye. However, to our knowledge, no study has investigated how the shape of the primordium is set or whether there is any further specific control of tissue shape during its ensuing development in L3.

More is known on the mechanisms regulating the proliferation rate of the retinal progenitors, and the differentiation velocity. Progenitors are maintained in a proliferative state by the combined action of several transcription factors: the Meis-family transcription factor *homothorax (hth)* and the zinc-finger paralogues *teashirt (tsh)* and *tiptop (tio)* [33–35]. These transcription factors seem to act as partners of the Hippo pathway nuclear transducer, *yorkie* (Yki), which is involved in cell proliferation and survival control [36]. In addition, progenitor proliferation is stimulated by the activity of the Notch signalling pathway both directly and indirectly through the Notch-induced activation of the

cytokine *Unpaired (Upd/os)* [37–44].

Part of the regulatory functions exerted by the differentiation wave is the production of signals that repress the progenitor-specific transcription factors, such that their repression is concomitant with the activation of *ato* [33,45,46]. The other important variable is differentiation speed: that is, the velocity at which the differentiation wave sweeps across the epithelium. This speed ultimately depends on how fast the Hh-receiving progenitor cells differentiate into R cells and become Hh-producing themselves. The Hh signalling exerts several functions during eye differentiation. In addition to inducing a proneural fate in eye progenitors, Hh is required for the stalling of the cell cycle through the transcriptional activation of dacapo/p21, a cyclin inhibitor [47]. Also, Hh produced by the R cells induces expression of Bone Morphogenetic Protein 2 (Dpp in flies), and both signalling pathways contribute in inducing the apical constriction, apicobasal contraction and basal nuclear migration of receiving cells [26,27] which result in the characteristic furrowing of the wavefront [48]. However, Hh signalling is transient. It peaks at the morphogenetic furrow but behind it, signalling declines. This decline allows cells to exit their "furrow" state and start differentiating. Mechanistically, this is mediated by delayed negative feedback: high Hh signalling results in the transcriptional activation of the SPOP homologue *Roadkill (Rdx)*. Rdx drives a Cullin-3-mediated degradation of the nuclear transducer of the Hh signalling pathway, the Gli transcription factor Cubitus interruptus (Ci) [49,50], reduces the activity of the pathway. In addition, the speed at which Hh signalling peaks and then declines is itself regulated by a Hh-target gene, *dachshund (dac)* [51]. *dac* encodes for a nuclear factor that favours the accumulation of the activator form of Ci, CiA. By doing so, Dac accelerates Hh signalling, inducing a shaper activation-deactivation signalling dynamics. This fact explains that in *dac*-mutant cells, eye differentiation still occurs, but a slower pace [52]. Therefore, the speed at which the differentiation wave moves might be subject to regulated variation, depending on the species and even sex in a species. Variations in the speed of furrow propagation are expected to have an impact on the final size and shape of the eye primordium at the end of L3. This is because it determines the number of ommatidia that can be generated while also setting the time that is available for the eye primordium to continue growing – as Hh signalling is responsible for inducing the cell cycle exit and differentiation of progenitor cells.

2.3. Recruiting retinal cells to assemble the ommatidium

During pupation, further critical changes in ommatidial organisation take place. But before getting to this stage, it is important to briefly review two additional processes occurring during L3. Ommatidial cell differentiation and assembly, and control of ommatidial cell size.

Immediately behind the morphogenetic furrow, the expression of *ato,* which was uniform anterior to it, becomes restricted to regularly-spaced cells, a restriction that is mediated by Notch signalling. Each of these *ato*-expressing cells will become R8 photoreceptors which act as founder cells of each ommatidium, initiating the recruitment, by short-range intercellular signalling through the EGF receptor and Notch pathways, of the remaining cell complement that will form the ommatidium [11]. These include the other 7 R cells (R1–7), four cone cells and two primary pigment cells. Secondary and tertiary pigment cells are shared among adjacent ommatidia to form the hexagonal lattice of the eye. In addition, mechanosensory bristle complex cells are specified that are also shared among ommatidia.

R8 first recruits R2 and 5, and next R3 and 4 among surrounding cells. At this point, a wave of mitoses is induced that provides for extra cells to assemble the ommatidia [53]. The specification of all R cells then occurs during L3 while that of the remaining cell types extends into the early pupal life of the animal. The mechanisms of spacing and specification of R8 cells progresses, as the differentiation wave moves forward, through a templating mechanism, in which the position of the R8 singled out in a cell row mark the position of the next R8 that will be recruited [54]. Therefore, there are as many ommatidia as R8 cells are specified. Since R8 cells are directly recruited among progenitors, the size of an eye (measured as the number of ommatidia it comprises) reflect the amount of growth attained by its progenitors.

We mentioned earlier that one important optical property of the ommatidium is its light sensitivity, something that depends on the diameter of its lenses (cornea plus pseudocone). It is not clear whether larger lenses are the result of the cells secreting more lens material or the result of ommatidial cells being larger. In some eyes with extreme differences in facet-lens area (such as some robber flies, [55]), larger lenses cover wider and taller ommatidia, and vice versa, suggesting a proportional increase in size of all component cells. Although the eyes of robber flies and of some male tabanids (See Fig. 2) are examples of large differences in facet-lens area and thickness, many species show a heterogeneous distribution of facet-lens sizes across the eye even if not so striking. This is even the case in *Drosophila melanogaster* and related species [56,57]. How these patterns of facet-lens size are regulated is currently unknown, although recent work indicates that temporal differences in the time of the transcription factor *otd* expression in ommatidial cells might contribute to these differences [58]. Usually, large facet-lenses are displayed on less curved regions of the eye's dome. This makes for regions of both high sensitivity (i.e. high quantum catch) and resolution. It is possible that large facets-lenses result in less curved surfaces if the interommatidial angle is constant regardless of the ommatidial size, but this has not been studied systematically.

3. A fluid to solid jamming transition marks the onset of 3D tissue morphogenesis?

Building the ommatidium requires ***i)*** cells to remodel their size, shape and polarity to generate the distal (lens) – proximal (brain) axis of the retina, ***ii)*** the culling of cells to refine the interommatidial lattice while, ***iii)*** the remaining cells to move in the plane of the lens to acquire their niche.

This transition from a disordered to an ordered epithelium prefigures the onset of retinal tissue curvature, and we would argue here promotes this curvature. As the animal enters pupation, the core clusters of R cells are formed, and they are surrounded by an excess of interommatidial cells which undergo neighbour exchange [59,60]. At this stage the tissue appears fluid-like in that, cells move relative to each other. However, once all retinal cells have acquired their position in the tissue at around 45 h after puparium formation, these supracellular units pack tightly as a hexagonal array. Life imaging of pupal discs show the "fluid-like" movements of the epithelia surrounding the eye epithelium, while this latter is dragged along as what seems to be a stiffer epithelium (MovieS1). Therefore, the transition from a disordered epithelium to a supracellularly ordered one could result in a tissue "jamming" with a concomitant transition from a fluid to a flexible solid state [61,62]. This hypothetical state transition deserves experimental testing. But this seems like a necessary change in the physical properties of the eye. After this stage, the retina curves as a dome and it is likely this morphing is dependent on specific mechanical properties of the tissue.

3.1. Giving the eye a third dimension – evolving the lens-to-brain-axis of the eye

The mature retina is a partially stratified tissue where the bulk of the soma of the corneal lens lie above the photoreceptors to collect light and focus it onto the rhabdomeres of the R cells (Figs. 1B, 1E). In this 3D tissue organisation, the 1° pigment cells have detached from the basement membrane to relocate their whole volume in the surface lens. The cone and 2°/3° pigment cells, which are also part of the lens each extend towards the floor of the retina to remain attached to the basement membrane. The R cells are located at the core of the ommatidium [5,63]. This complex 3D tissue reorganisation is induced as the cone cells move outside the 2D plane of the retinal tissue to close on top of the R cells.

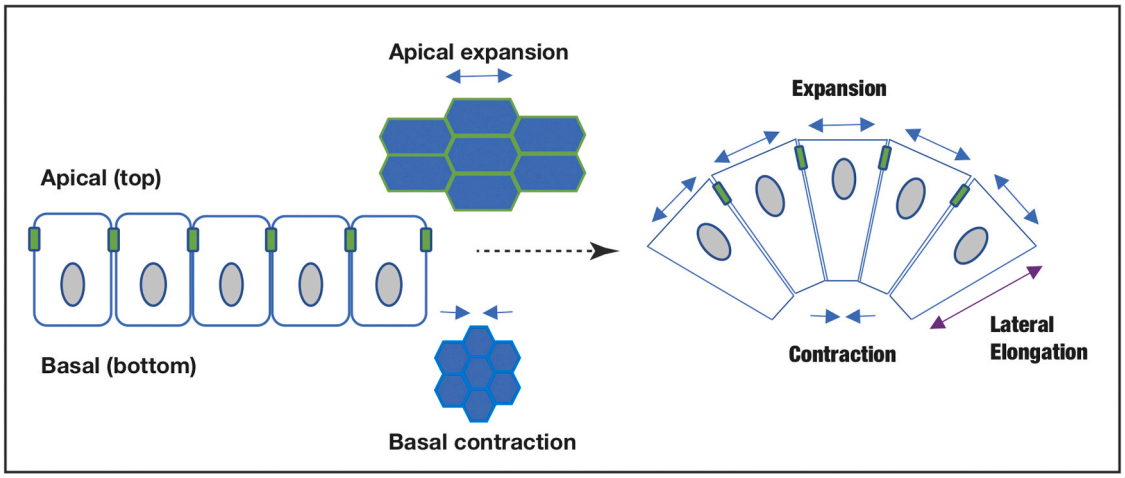

Fig. 2. Possible mechanism if retinal tissue bending. Depiction of how a 2D monolayered epithelium might transform into a dome-shape tissue. In this example, translocation of cells volume towards the surface lens leads to an expansion of this surface. As cells undergo lengthening – same rate of lengthening across the tissue – this surface expansion would be predicted to induce bending the cells can lead to convex bending of the tissue. In this example, basal contraction reinforces this bending by amplifying lens surface expansion.

What triggers and directs this movement is not known. However, it correlates with polarity remodelling of the R cells. This polarity remodelling step is such that the apical (top) – basal (bottom) axis of the R cells rotates by 90º, as the apical membrane of these cells, involute within the plane of the epithelium, towards the centre of the ommatidium [5,64,65] (Fig. 1E). This way, the apical membranes of the R cells become aligned with the optical axis of the incident light. The R cells are mechanically coupled to the cone cells as they share adherens junctions with them [66]. Therefore, it is possible that their polarity remodelling of the R cells promotes lens formation by pulling onto the cone cells to bringing them closer. Alternatively, the cone cells could move above the photoreceptors through a process of cell-on-cell migration. Concomitant with this process, a mechanism must then exist that promotes cone-cone interaction, so these cells close on top of the photoreceptors by establishing new intercellular junctions (Fig. 1E). What pathway(s) promote formation of these junctions to seal the lens is not known. How different cell types interact to induce a 3D tissue organisation, like that of the retina, is a fascinating problem in biology, and the cone-cell/photoreceptor interaction in lens formation is a great example of cell interaction in 3D tissue morphogenesis.

R cell polarity remodelling also generates a new axis in the eye: the proximal (brain) – distal (lens) axis of the retina. In *Drosophila*, ommatidial cells elongate approximately 4-fold along this axis, to reach 100 μm in length, giving the retina its thickness. What controls the length of the retinal cells and therefore the thickness of the retina is not known. Interestingly, ommatidial length can vary across the eye. In addition, ommatidia at the centre of the eye are longer than those located at its margin, indicating that a gradient of ommatidial length is set during development [5].

3.2. *Establishing a highly ordered tissue organisation*

As the ommatidial cells work together to pattern the lens, a programme of cell death is initiated that eliminates surplus cells that have failed to be incorporated in any ommatidium. This generates the typical hexagonal array that forms as the interommatidial secondary (2º) and tertiary (3º) pigment cells get into shape and position within the ommatidium (Fig. 1E). This step of programmed cell death has been characterised in detail in *Drosophila*. It is a highly regulated process, and it ensures that ommatidia are optically insulated from each other [67,68].

In the newly formed lens, there can be up to 12–14 interommatidial cells that surround an ommatidium. The final hexagonal lattice consists of 9 cells, and therefore 3–4 of them are eliminated to set the hexagonal cell lattice [63]. Genetic experiments have revealed that this programmed cell death step depends on the balance between the survival-promoting EGFr–Ras signalling pathway and death inducing Wingless and Notch pathways [69–71]. During this step, the cone cells are thought to secrete the EGFr-ligand that activates this pathway in flanking interommatidial cells, thus preventing their death. Those interommatidial cells that are not in contact with the 1º pigment cells do not activate EGFr and are eliminated. This way, the number of interommatidial cells scales with the size of the 1º pigment cells.

Concomitantly with this cell death programme, specification of the 2º/3º pigment cells includes movement of these cells in the plane of the lens as well as changes in their shape [60]. At this stage the tissue appears fluid (MovieS1). Once it is complete, the position of the 2º/3º pigment cells within the ommatidium is stereotypical and these cells acquire their position around the 1º pigment cells by maximising their adhesion with them. This preferential adhesion between the 2º/3º and 1º pigment cells is mediated by the Nephrin-like adhesion receptors Roughest and Hibris [72]. In this system, Roughest in the interommatidial cells binds to Hibris *in trans*, expressed in the 1º pigment cells to maximise adhesion among them. Roughest-Roughest adhesion is not favoured, and this limits the length of the junction between the 2º and 3º cells, which also contributes to shaping the apical perimeter of these cells (Fig. 1C and time lapse in Fig. 1D). This preferential adhesion system is also used to precisely position the central cone cells within the ommatidium and is therefore a key pathway of ommatidium patterning [73]. In addition, the contractile actomyosin cytoskeleton is also essential for ommatidial cell morphogenesis. Pulsatile actomyosin meshworks are present at the apical pole of all lens cells, which are connected to the cell perimeter. These power cell deformation, and thus drive the cell shape changes that underpin morphogenesis of the lens cells [73,74]. Together, preferential adhesion between ommatidial cells and the cell-intrinsic contractile meshworks enable the cell-type specific positioning and morphogenesis programmes of ommatidial cells. Once cells are into place and have acquired their shape, the apical surface of the ommatidium is shaped as a supracellular hexagon. Cells are no longer moving and, as we mentioned above, the tissue ~~as~~ appears to be in jammed state – the organisation of the lens is set.

4. Generating a dome-like shaped retina

As the hexagonal lattice of the lens is formed and photoreceptors begin to elongate, the retina also starts to become curved. Very little is

known of the principles and pathways that control curvature of the compound eye. However, many tissues are bent, or present folds and much progress has been made in our understanding of the pathways that promote these tissue deformations [75–77]. From these studies we can envisage a number of mechanisms capable of inducing retinal tissue curvature, including ***i)*** differential tissue surface expansion or contraction), ***ii)*** external forces, such as forces exerted by the tissue surrounding the eye (i.e. head capsule), or ***iii)*** a combination of these processes.

Whether fluid-like to jammed/solid state transition of the retinal tissue directly influences curvature is not clear. However, as the lens is secreted, at around mid-pupal development [63,78], the external curvature of the eye is set. Therefore, the mechanisms acting on the retina to induce its curvature must operate before a solid lens is generated.

4.1. Inducing tissue curvature through scaling a tissue surface

One possible mechanism to induce tissue curvature is differential changes in areas, such that one of the surfaces of the tissue expands while the other surface does not, or follows the opposite trend and contract. For example, cell apical constriction drives fold formation and, in some cases, cell ingression in multiple tissues, as seen during lens placode pit formation during vertebrate eye development. Similarly, basal cell contraction has been involved in shaping tissue in flies [79], and also bending of the optic cup in vertebrates [80,81]. While basal contraction has been much less studied than apical constriction, it is thought to be powered by a contractile actomyosin cytoskeleton that largely remains to be characterised in detail. However, this basal contraction machineries largely remains to be studied in detail in epithelial cells. Conversely, cell area relaxation and expansion can also induce tissue curvature, as for example reported during fold formation in the *Drosophila* wing primordium (i.e. wing disc) [82].

In *Drosophila*, retinal tissue bending occurs relatively early on during eye development, in the wake of lens patterning, before any substantial proximal-distal cell elongation has taken place [83]. Lens patterning also involves a significant expansion of the apical area of all lens cells [74], as the cone and primary pigment cells translocate their volume toward the lens. In theory, this apical surface expansion could contribute to inducing retinal tissue bending. However, this idea has not been tested yet, by for example preventing apical translocation of retinal cells as the lens develops (Fig. 2). In addition, the basal tissue surface contracts, but this contraction begins after patterning of the lens and secretion of the cornea [5], arguing it might not be the main driver of tissue curvature. However, this largely remains to be investigated in sufficient detail. Theoretically, varying the degree of apical surface expansion and basal contraction could act as a relatively simple mechanisms to determine eye shapes by setting the radius of curvature of the eye, which in turn sets the interommatidial angles to define the optical axis of each ommatidium. Since eye curvature is often non-uniform (that is, there are regions which are more curved than others), these tissue changes should be ultimately linked to the system of genetic coordinates that set the dorsal-ventral and anterior-posterior axes. These axes are set during larval development while the eye primordium is still a monolayer. Which genetic determinants are establishing the “curvature map” and how these are linked to the actual morphogenetic machinery are important questions to be pursued. As we discussed earlier, when considering eye curvature, one needs to consider variation in facet-lens area. At fixed interommatidial angle across the eye, regions of large facet-lens area will be flatter, generating high resolution regions in the eye. A fixed interommatidial angle across the eye is however not obligatory and therefore, combination of local variation in interommatidial angles and facet-lens area is often at play.

4.2. Alternative mechanisms of tissue curvature

In addition to cell intrinsic mechanisms driving tissue surface expansion or contraction, external mechanical regulation might also promote retinal tissue bending. Enormous hydrostatic pressure is present in the pupae where the eye develops, and this inside-out pressure applied on the retina might also contribute to inducing tissue curvature through mechanical regulation. It is also interesting to note that the optic lobe, which lies adjacent to the retina is shaped as a sphere (Fig. 1B). As the brain and optic lobe grow it is also possible that it applies pressure onto the retinal tissue, or serves as a “cast”, and contributes to inducing curvature. While these ideas remain to be tested, it is also important to note that ectopic eyes that can be induced on the antenna or legs tend to be curved, where there is no optic lobes underneath, suggesting most of the retinal curvature programme is intrinsic to the retinal tissue.

Boundary regulation, coming from the tissue that surrounds the retina (the head capsule), might also play a role in retinal tissue curvature. In vertebrates, the cells flanking the optic cup undergo lateral contraction and this applies mechanical tension onto the cup that has been shown to amplify curvature on the cup [84]. In the *Drosophila* eye, lateral constriction might explain why ommatidia at the periphery of the retina end up shorter than at the centre of the tissue. Establishing exactly when and how this length gradient is established would help clarifying its possible role in enhancing retinal tissue curvature.

5. Conclusion

The making of a compound eye starts with setting the size and 2D shape of the eye primordium. Patterning follows with the number of ommatidia being directly linked to the number of progenitor cells, and thus the size of the eye primordium. As we’ve discussed here, the pace of the differentiation wave will also influence the shaping of the retina, as a slow pace will allow for more proliferation of the retinal progenitor cells.

A key phase in shaping the eye in 3D unfolds during the pupal life of the animal. This follows a step of tissue jamming, which prevents any further movement of cells in the plane of the lens. Whether and how exactly this might contribute to inducing 3D organisation of the eye is not known and will be interesting to test in the eye. Jamming of epithelial tissue has been recognised in a number of circumstances, in health and disease, but its influence in inducing 3D tissue organisation, including curvature has not been explored.

Finally, while we begin to know how the size to the early eye primordium is set, we know very little of the mechanisms and pathways that shape it. The 2D eye primordium serves as a template to the 3D mature eye, and it will be important to figure out which pathways, be it biochemical or mechanical set its shape. All these are important questions of biology, with ramification running well beyond the relatively simple compound eye of insects. Identifying the pathways that shape the eye will continue to a have broad repercussion for our understanding of tissue morphogenesis and organogenesis at large.

Conflicts of interests

None.

Acknowledgements

Work in the Pichaud lab is funded by grants for the MRC (MC_UU_12018/3), the BBSRC (BB/R000697) and the Royal Society grant (Award #181274), and benefited from MRC core funding to the LMCB, covering access to microscopy. (MC_12266B). Work in the Casares lab is funded by PGC2018-093704-B-I00, BFU2016-81887-REDT, BFU2017-90869-REDT, and MDM-2016-0687, from MINECO (Ministerio de Ciencia e Innovación (Spain)) and FEDER (European Regional Development Fund (Spain)).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semcdb.2021.11.002.

References

[1] K. Kirschfeld, The resolution of Lens and compound eyes, in: Z. Zettler, R. Weiler (Eds.), Neural Principles in Vision, Springer-Verlag, Berlin Heilderberg, Germany, 1976, pp. 354–370.
[2] D.E. Nilsson, From cornea to retinal image in invertebrate eyes, Trends Neurosci. 13 (2) (1990) 55–64.
[3] S. Harzsch, G. Hafner, Evolution of eye development in arthropods: phylogenetic aspects, Arthropod Struct. Dev. 35 (4) (2006) 319–340.
[4] M.F. Land, D.E. Nilsson, Animal Eyes, Oxford University Press, Oxford, UK, 2021.
[5] D.F. Ready, Drosophila compound eye morphogenesis: Blind mechanical engineers? in: K. Moses (Ed.), Results and Problems in Cell Differentiation Springer-Verlag, Berlin Heildelderg New York, 2002, pp. 191–204.
[6] A.L. Stahl, M. Charlton-Perkins, E.K. Buschbeck, T.A. Cook, The cuticular nature of corneal lenses in Drosophila melanogaster, Dev. Genes Evol. 227 (4) (2017) 271–278.
[7] E. Agi, M. Langen, S.J. Altschuler, L.F. Wu, T. Zimmermann, P.R. Hiesinger, The evolution and development of neural superposition, J. Neurogenet. 28 (3–4) (2014) 216–232.
[8] F. Pichaud, C. Desplan, Evolution of color vision, in: K. Moses (Ed.), Drosophila Eye Development, Springer, Berlin, Heidelberg, 2002, pp. 135–149.
[9] F. Lebhardt, C. Desplan, Retinal perception and ecological significance of color vision in insects, Curr. Opin. Insect Sci. 24 (2017) 75–83.
[10] H. Ebadi, M. Perry, K. Short, K. Klemm, C. Desplan, P.F. Stadler, A. Mehta, Patterning the insect eye: From stochastic to deterministic mechanisms, PLoS Comput. Biol. 14 (11) (2018), e1006363.
[11] R.I. Johnson, Hexagonal patterning of the Drosophila eye, Dev. Biol. 478 (2021) 173–182.
[12] F. Pichaud, Transcriptional regulation of tissue organization and cell morphogenesis: the fly retina as a case study, Dev. Biol. 385 (2) (2014) 168–178.
[13] T.F. Mathejczyk, M.F. Wernet, Sensing polarized light in insects. Oxford Research Encyclopedia, 2017, pp. 1–32.
[14] M.W. Perry, C. Desplan, Love spots, Curr. Biol. 26 (12) (2016) R484–R485.
[15] F.A.I. Casares, Fast and furious 800. The retinal determination gene network in drosophila, in: B.P. Castelli-Gair, J. Hombría (Eds.), Organogenetic Gene Networks, Springer, 2016, pp. 95–124.
[16] T.L. Davis I. Rebay. Master regulators in development: Views from the Drosophila retinaldetermination and mammalian pluripotency gene networks Dev Biol 421 2 2017 93 107.
[17] J.P. Kumar, K. Moses, EGF receptor and Notch signaling act upstream of Eyeless/Pax6 to control eye specification, Cell 104 (5) (2001) 687–697.
[18] C.W. Wang, Y.H. Sun, Segregation of eye and antenna fates maintained by mutual antagonism in Drosophila, Development 139 (18) (2012) 3413–3421.
[19] M.C. Gibson, G. Schubiger, Peripodial cells regulate proliferation and patterning of Drosophila imaginal discs, Cell 103 (2) (2000) 343–350.
[20] L.R. Baker, B.M. Weasner, A. Nagel, S.D. Neuman, A. Bashirullah, J.P. Kumar, Eyeless/Pax6 initiates eye formation non-autonomously from the peripodial epithelium, Development 145 (15) (2018).
[21] J.E. Treisman, Retinal differentiation in Drosophila, Wiley Inter. Rev. Dev. Biol. 2 (4) (2013) 545–557.
[22] J. Vollmer, P. Fried, M. Sanchez-Aragon, C.S. Lopes, F. Casares, D. Iber, A quantitative analysis of growth control in the Drosophila eye disc, Development 143 (9) (2016) 1482–1490.
[23] P. Fried, M. Sanchez-Aragon, D. Aguilar-Hidalgo, B. Lehtinen, F. Casares, D. Iber, A Model of the Spatio-temporal Dynamics of Drosophila Eye Disc Development, PLoS Comput. Biol. 12 (9) (2016), e1005052.
[24] F. Casares, A.P. McGregor, The evolution and development of eye size in flies, Wiley Interdiscip. Rev. Dev. Biol. 10 (2) (2021), e380.
[25] N.E. Baker, L.C. Firth, Retinal determination genes function along with cell-cell signals to regulate Drosophila eye development: examples of multi-layered regulation by master regulators, Bioessays 33 (7) (2011) 538–546.
[26] D. Corrigall, R.F. Walther, L. Rodriguez, P. Fichelson, F. Pichaud, Hedgehog signaling is a principal inducer of Myosin-II-driven cell ingression in Drosophila epithelia, Dev. Cell 13 (5) (2007) 730–742.
[27] L.M. Escudero, M. Bischoff, M. Freeman, Myosin II regulates complex cellular arrangement and epithelial architecture in Drosophila, Dev. Cell 13 (5) (2007) 717–729.
[28] M. Dominguez, Dual role for Hedgehog in the regulation of the proneural gene atonal during ommatidia development, Development 126 (11) (1999) 2345–2353.
[29] J.P. Kumar, Building an ommatidium one cell at a time, Dev. Dyn. 241 (1) (2012) 136–149.
[30] E.M. Rogers, C.A. Brennan, N.T. Mortimer, S. Cook, A.R. Morris, K. Moses, Pointed regulates an eye-specific transcriptional enhancer in the Drosophila hedgehog gene, which is required for the movement of the morphogenetic furrow, Development 132 (21) (2005) 4833–4843.
[31] A. Ramaekers, A. Claeys, M. Kapun, E. Mouchel-Vielh, D. Potier, S. Weinberger, N. Grillenzoni, D. Dardalhon-Cumenal, J. Yan, R. Wolf, T. Flatt, E. Buchner, B. A. Hassan, Altering the temporal regulation of one transcription factor drives evolutionary trade-offs between head sensory organs, Dev. Cell 50 (6) (2019) 780–792 e7.
[32] F.J. Lobo-Cabrera, T. Navarro, A. Iannini, F. Casares, A. Cuetos, Quantitative relationships between growth, differentiation, and shape that control drosophila eye development and its variationquantitative relationships between growth, differentiation, and shape that control drosophila eye development and its variation, Front. Cell Dev. Biol. July(Evolut. Dev. Biol.) 9 (2021).
[33] J. Bessa, B. Gebelein, F. Pichaud, F. Casares, R.S. Mann, Combinatorial control of Drosophila eye development by eyeless, homothorax, and teashirt, Genes Dev. 16 (18) (2002) 2415–2427.
[34] R.R. Datta, B.P. Weasner, J.P. Kumar, A dissection of the teashirt and tiptop genes reveals a novel mechanism for regulating transcription factor activity, Dev. Biol. 360 (2) (2011) 391–402.
[35] M. Neto, M. Naval-Sanchez, D. Potier, P.S. Pereira, D. Geerts, S. Aerts, F. Casares, Nuclear receptors connect progenitor transcription factors to cell cycle control, Sci. Rep. 7 (1) (2017) 4845.
[36] H.W. Peng, M. Slattery, R.S. Mann, Transcription factor choice in the Hippo signaling pathway: homothorax and yorkie regulation of the microRNA bantam in the progenitor domain of the Drosophila eye imaginal disc, Genes Dev. 23 (19) (2009) 2307–2319.
[37] K.L. Kenyon, S.S. Ranade, J. Curtiss, M. Mlodzik, F. Pignoni, Coordinating proliferation and tissue specification to promote regional identity in the Drosophila head, Dev. Cell 5 (3) (2003) 403–414.
[38] M. Dominguez, J.F. de Celis, A dorsal/ventral boundary established by Notch controls growth and polarity in the Drosophila eye, Nature 396 (6708) (1998) 276–278.
[39] V. Papayannopoulos, A. Tomlinson, V.M. Panin, C. Rauskolb, K.D. Irvine, Dorsal-ventral signaling in the Drosophila eye, Science 281 (5385) (1998) 2031–2034.
[40] F.J. Gutierrez-Avino, D. Ferres-Marco, M. Dominguez, The position and function of the Notch-mediated eye growth organizer: the roles of JAK/STAT and four-jointed, EMBO Rep. 10 (9) (2009) 1051–1058.
[41] E.A. Bach, S. Vincent, M.P. Zeidler, N. Perrimon, A sensitized genetic screen to identify novel regulators and components of the Drosophila janus kinase/signal transducer and activator of transcription pathway, Genetics 165 (3) (2003) 1149–1166.
[42] J. Vollmer, P. Fried, D. Aguilar-Hidalgo, M. Sanchez-Aragon, A. Iannini, F. Casares, D. Iber, Growth control in the Drosophila eye disc by the cytokine Unpaired, Development 144 (5) (2017) 837–843.
[43] J.L. Chao, Y.C. Tsai, S.J. Chiu, Y.H. Sun, Localized Notch signal acts through eyg and upd to promote global growth in Drosophila eye, Development 131 (16) (2004) 3839–3847.
[44] E.C. Richardson, F. Pichaud, Crumbs is required to achieve proper organ size control during Drosophila head development, Development 137 (4) (2010) 641–650.
[45] C.S. Lopes, F. Casares, hth maintains the pool of eye progenitors and its downregulation by Dpp and Hh couples retinal fate acquisition with cell cycle exit, Dev. Biol. 339 (1) (2010) 78–88.
[46] L.C. Firth, N.E. Baker, Retinal determination genes as targets and possible effectors of extracellular signals, Dev. Biol. 327 (2) (2009) 366–375.
[47] J.C. de Nooij, M.A. Letendre, I.K. Hariharan, A cyclin-dependent kinase inhibitor, Dacapo, is necessary for timely exit from the cell cycle during Drosophila embryogenesis, Cell 87 (7) (1996) 1237–1247.
[48] D.F. Ready, T.E. Hanson, S. Benzer, Development of the Drosophila retina, a neurocrystalline lattice, Dev. Biol. 53 (2) (1976) 217–240.
[49] D. Kent, E.W. Bush, J.E. Hooper, Roadkill attenuates Hedgehog responses through degradation of Cubitus interruptus, Development 133 (10) (2006) 2001–2010.
[50] Q. Zhang, L. Zhang, B. Wang, C.Y. Ou, C.T. Chien, J. Jiang, A hedgehog-induced BTB protein modulates hedgehog signaling by degrading Ci/Gli transcription factor, Dev. Cell 10 (6) (2006) 719–729.
[51] G. Mardon, N.M. Solomon, G.M. Rubin, dachshund encodes a nuclear protein required for normal eye and leg development in Drosophila, Development 120 (12) (1994) 3473–3486.
[52] C. Bras-Pereira, D. Potier, J. Jacobs, S. Aerts, F. Casares, F. Janody, dachshund Potentiates Hedgehog Signaling during Drosophila Retinogenesis, PLoS Genet. 12 (7) (2016), e1006204.
[53] T. Wolff, D.F. Ready, The beginning of pattern formation in the Drosophila compound eye: the morphogenetic furrow and the second mitotic wave, Development 113 (3) (1991) 841–850.
[54] D.K. Lubensky, M.W. Pennington, B.I. Shraiman, N.E. Baker, A dynamical model of ommatidial crystal formation, Proc. Natl. Acad. Sci. USA 108 (27) (2011) 11145–11150.
[55] T.J. Wardill, S.T. Fabian, A.C. Pettigrew, D.G. Stavenga, K. Nordstrom, P. T. Gonzalez-Bellido, A. Novel, Interception strategy in a miniature robber fly with extreme visual acuity, Curr. Biol. 27 (6) (2017) 854–859.
[56] N. Posnien, C. Hopfen, M. Hilbrant, M. Ramos-Womack, S. Murat, A. Schonauer, S. L. Herbert, M.D. Nunes, S. Arif, C.J. Breuker, C. Schlotterer, P. Mitteroecker, A. P. McGregor, Evolution of eye morphology and rhodopsin expression in the Drosophila melanogaster species subgroup, PLoS One 7 (5) (2012), e37346.
[57] S. Kim, J.J. Cassidy, B. Yang, R.W. Carthew, S. Hilgenfeldt, Hexagonal patterning of the insect compound eye: facet area variation, defects, and disorder, Biophys. J. 111 (12) (2016) 2735–2746.
[58] E.B. Montserrat Torres-Oliva, Alexandra D. Buffry, V. Maike Kittelmann, Lauren Sumner-Rooney, Pedro Gaspar, Georg C. Bullinger, Genoveva Guerrero, Fernando Casares, Saad Arif, ProfileNico Posnien, Maria D.S. Nunes, Alistair P. McGregor, Isabel Almudi, Differences in orthodenticle expression promote ommatidial size variation between Drosophila species, bioRxiv (2021).

[59] F. Robertson, N. Pinal, P. Fichelson, F. Pichaud, Atonal and EGFR signalling orchestrate rok- and Drak-dependent adherens junction remodelling during ommatidia morphogenesis, Development 139 (18) (2012) 3432–3441.
[60] D.E. Larson, Z. Liberman, R.L. Cagan, Cellular behavior in the developing Drosophila pupal retina, Mech. Dev. 125 (3–4) (2008) 223–232.
[61] E. Lawson-Keister, M.L. Manning, Jamming and arrest of cell motion in biological tissues, arXiv 2102 (2021) 11255.
[62] N.I. Petridou, C.P. Heisenberg, Tissue rheology in embryonic organization, EMBO J. 38 (20) (2019), e102497.
[63] R.L. Cagan, D.F. Ready, The emergence of order in the Drosophila pupal retina, Dev. Biol. 136 (2) (1989) 346–362.
[64] F. Nunes de Almeida, R.F. Walther, M.T. Presse, E. Vlassaks, F. Pichaud, Cdc42 defines apical identity and regulates epithelial morphogenesis by promoting apical recruitment of Par6-aPKC and Crumbs, Development 146 (15) (2019).
[65] R.F. Walther, F. Pichaud, Crumbs/DaPKC-dependent apical exclusion of Bazooka promotes photoreceptor polarity remodeling, Curr. Biol. 20 (12) (2010) 1065–1074.
[66] U. Tepass, K.P. Harris, Adherens junctions in Drosophila retinal morphogenesis, Trends Cell Biol. 17 (1) (2007) 26–35.
[67] T. Wolff, D.F. Ready, Cell death in normal and rough eye mutants of Drosophila, Development 113 (3) (1991) 825–839.
[68] C.B. Brachmann, R.L. Cagan, Patterning the fly eye: the role of apoptosis, Trends Genet. 19 (2) (2003) 91–96.
[69] D.T. Miller, R.L. Cagan, Local induction of patterning and programmed cell death in the developing Drosophila retina, Development 125 (12) (1998) 2327–2335.
[70] J. Cordero, O. Jassim, S. Bao, R. Cagan, A role for wingless in an early pupal cell death event that contributes to patterning the Drosophila eye, Mech. Dev. 121 (12) (2004) 1523–1530.
[71] R. Hays, C. Craig, R. Cagan, Programmed death in eye development, Results Probl. Cell Differ. 37 (2002) 169–189.
[72] S. Bao, R. Cagan, Preferential adhesion mediated by Hibris and Roughest regulates morphogenesis and patterning in the Drosophila eye, Dev. Cell 8 (6) (2005) 925–935.
[73] L. Blackie, M. Tozluoglu, M. Trylinski, R.F. Walther, F. Schweisguth, Y. Mao, F. Pichaud, A combination of Notch signaling, preferential adhesion and endocytosis induces a slow mode of cell intercalation in the Drosophila retina, Development 148 (10) (2021).
[74] L. Blackie, R.F. Walther, M.F. Staddon, S. Banerjee, F. Pichaud, Cell-type-specific mechanical response and myosin dynamics during retinal lens development in Drosophila, Mol. Biol. Cell 31 (13) (2020) 1355–1369.
[75] T. Lecuit, P.F. Lenne, Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis, Nat. Rev. Mol. Cell Biol. 8 (8) (2007) 633–644.
[76] E.J. Pearl, J. Li, J.B. Green, Cellular systems for epithelial invagination, Philos. Trans. R. Soc. Lond. B Biol. Sci. 372 (1720) 2017.
[77] M. Denk-Lobnig, A.C. Martin, Divergent and combinatorial mechanical strategies that promote epithelial folding during morphogenesis, Curr. Opin. Genet. Dev. 63 (2020) 24–29.
[78] D.F. T.a.R. Wolff, Pattern formation in the Drosophila retina, in: C.S.H. Press (Ed.), The Development of Drosophila melanogaster, Cold Spring Harbor, NY, 1993, pp. 1277–1325.
[79] L. He, X. Wang, H.L. Tang, D.J. Montell, Tissue elongation requires oscillating contractions of a basal actomyosin network, Nat. Cell Biol. 12 (12) (2010) 1133–1142.
[80] M. Nicolas-Perez, F. Kuchling, J. Letelier, R. Polvillo, J. Wittbrodt, J.R. Martinez-Morales, Analysis of cellular behavior and cytoskeletal dynamics reveal a constriction mechanism driving optic cup morphogenesis, Elife 5 (2016).
[81] J.R. Martinez-Morales, M. Rembold, K. Greger, J.C. Simpson, K.E. Brown, R. Quiring, R. Pepperkok, M.D. Martin-Bermudo, H. Himmelbauer, J. Wittbrodt, ojoplano-mediated basal constriction is essential for optic cup morphogenesis, Development 136 (13) (2009) 2165–2175.
[82] L. Sui, S. Alt, M. Weigert, N. Dye, S. Eaton, F. Jug, E.W. Myers, F. Julicher, G. Salbreux, C. Dahmann, Differential lateral and basal tension drive folding of Drosophila wing discs through two distinct mechanisms, Nat. Commun. 9 (1) (2018) 4620.
[83] R.L. Longley Jr., D.F. Ready, Integrins and the development of three-dimensional structure in the Drosophila compound eye, Dev. Biol. 171 (2) (1995) 415–433.
[84] S. Okuda, N. Takata, Y. Hasegawa, M. Kawada, Y. Inoue, T. Adachi, Y. Sasai, M. Eiraku, Strain-triggered mechanical feedback in self-organizing optic-cup morphogenesis, Sci. Adv. 4 (11) (2018) eaau1354.
[85] P. Fichelson, A. Brigui, F. Pichaud, Orthodenticle and Kruppel homolog 1 regulate Drosophila photoreceptor maturation, Proc. Natl. Acad. Sci. USA 109 (20) (2012) 7893–7898.