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Mechanisms of photoreceptor patterning in vertebrates and invertebrates

Kayla Viets[#], Kiara Eldred[#], and Robert J Johnston Jr.[#]

Department of Biology, Johns Hopkins University, 3400 N. Charles Street Baltimore, MD 21218-2685 USA

[#] These authors contributed equally to this work.

Abstract

Across the animal kingdom, visual systems have evolved to be uniquely suited to the environments and behavioral patterns of different species. The visual acuity and color perception of organisms depend on the distribution of photoreceptor subtypes within the retina. Retinal mosaics can be organized into three broad categories: stochastic/regionalized, regionalized, and ordered. Here, we describe the retinal mosaics of flies, zebrafish, chickens, mice, and humans and the gene regulatory networks controlling proper photoreceptor specification in each. By drawing parallels in eye development between these divergent species, we identify a set of conserved organizing principles and transcriptional networks that govern photoreceptor subtype differentiation.

Keywords

photoreceptor; retina; mosaic; human; *Homo sapiens*; mouse; *Mus musculus*; fruit fly; *Drosophila melanogaster*; chick; *Gallus gallus domesticus*; zebrafish; *Danio rerio*; regulatory network; eye; color vision; evolution; motion-detecting; color-detecting; cone; rod; inner photoreceptor; outer photoreceptor; stochasticity; regionalization; gene network

Retinas are patterned in stochastic/regionalized, regionalized, and ordered mosaics

Evolution has produced highly tuned opsin proteins that enable organisms to detect wavelengths of light specific to their environments. For instance, humans can differentiate colors most precisely in the yellow to red range of the color spectrum, which corresponds to the colors of ripening fruit(1-3), while flies are sensitive to polarized light, which assists in navigation during flight(4-6). In this review, we describe the patterns of photoreceptor (PR) mosaics and the gene regulatory networks that lead to diverse PR subtype fates across several commonly studied organisms: fruit flies, zebrafish, chickens, mice, and humans. The retinal mosaics of these organisms can be grouped into three classes: stochastic/regionalized,

[#]Corresponding Author. robertjohnston@jhu.edu.

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regionalized, and ordered. These species share numerous similarities in retinal development, revealing surprising conservation in the gene regulatory mechanisms and developmental patterns that form diverse visual systems.

The stochastic/regionalized mosaic of the *Drosophila melanogaster* retina

The *Drosophila melanogaster* (fruit fly) retina is composed of approximately 800 ommatidia (i.e. unit eyes) each of which contains eight PRs, R1-R8 (Fig. 1A2). These PRs can be divided into two groups: the outer PRs, R1-R6, and the inner PRs, R7 and R8. The outer PRs encircle the inner PRs, and the R7 is located above the R8 relative to the apical surface of the retina (Fig. 1A2)(7). A rhabdomere, a series of thousands of microvilli containing a high concentration of photopigment, extends the full length of each PR cell body (Fig. 1A2)(8, 9).

All outer PRs express the motion-detecting photopigment Rhodopsin 1 (Rh1)(Fig. 1A3-A6, A8)(10, 11). Expression of different Rhodopsins in the inner PRs defines four subtypes of ommatidia: **pale** (Fig. 1A3), **yellow** (Fig. 1A4), **dorsal third yellow** (Fig. 1A5), and **dorsal rim** (Fig. 1A6)(4, 12-20). In **pale** ommatidia, **pR7s** express UV-detecting Rhodopsin 3 (Rh3) and **pR8s** express blue-detecting Rhodopsin 5 (Rh5) (Fig. 1A3, A9-A10)(12, 13). In **yellow** ommatidia, **yR7s** express UV-detecting Rhodopsin 4 (Rh4) and **yR8s** express green-detecting Rhodopsin 6 (Rh6)(12, 13) (Fig. 1A4, A9-A10). PRs in the ventral two-thirds of the retina are arranged in a stochastic mosaic: **pale** and **yellow** ommatidia in this region are randomly patterned in a ratio of 35:65(12) (Fig. 1A1 and A7). Specialized ommatidial subtypes occur in the dorsal region of the retina. In the **dorsal third** of the retina, Rh3 is co-expressed with Rh4 in stochastically distributed **yR7s**(4) (Fig. 1A1, A5, A11). **Dorsal rim** ommatidia are found only at the extreme dorsal edge of the retina and express Rh3 in both R7s and R8s (Fig. 1A1, A6, A12)(20).

An ordered array of cones and rods in the retina of *Danio rerio*

As in flies, *Danio rerio* (zebrafish) PRs contain a ciliated region with a high concentration of photopigment (Fig. 1B2)(21, 22). In zebrafish, this region is known as the outer segment and is located at the apical end of the PR (Fig. 1B2). Outer segments connect to the ellipsoid, which refracts light onto the outer segment (Fig. 1B2)(21, 23-26). The ellipsoid is joined to the myoid region, which contracts to extend and retract PRs in response to changes in light (Fig. 1B2)(27-29). Below the myoid lies the cell soma, which contains the nucleus (Fig. 1B2)(21, 23).

Zebrafish retinas contain four PR classes: rods, which express motion-detecting rhodopsin (RH1); short single cones, which express UV opsin (SWS1); long single cones, which express blue opsin (SWS2); and double cone pairs, in which one cone expresses red opsin (LWS) and the other cone expresses green opsin (RH2) (Fig. 1B2)(30-33). Zebrafish PRs are arranged in a repetitive pattern throughout the retina(21). Rows of double cones alternate with rows of interdigitated UV and blue cones (Fig. 1B1, B4). Within double cone rows, each red-green pair is turned 180 degrees with respect to the previous double cone (Fig. 1B1, B4). Each row of double cones is shifted one half cycle with respect to the previous row, so each UV cone is flanked by two green cones and each blue cone is flanked by two

red cones (Fig. 1B1, B4). Rods are interspersed evenly between the rows of cones, forming a square pattern around UV cones (Fig. 1B1, B5)(22, 33-37).

Within this highly ordered mosaic, regionalized expression of two subtypes of LWS (LWS-1 and LWS-2) and four subtypes of RH2 (RH2-1, RH2-2, RH2-3, and RH2-4) in double cones defines distinct areas of the zebrafish retina. In the **inner central/dorsal** area, double cones expressing LWS-2 and RH2-1 are interspersed with double cones expressing LWS-2 and RH2-2 (Fig. 1B3). The **outer central/dorsal** area surrounds the **inner central/dorsal** area, and all double cones in this region express LWS-2 and RH2-2 (Fig. 1B3). The next ring of expression, the **inner periphery/ventral** area, contains double cones expressing LWS-1 and RH2-3 (Fig. 1B3). Finally, double cones in the **outer periphery/ventral** area express LWS-1 and RH2-4 (Fig. 1B3)^(38, 39).

Overlapping regular spacing of PR subtypes forms a semi-random mosaic in the *Gallus gallus domesticus* retina

Similar to zebrafish, the *Gallus gallus domesticus* (chicken) retina contains Rh1-expressing rods, specialized for night vision, and multiple single and double cone types. The four single cone types in the chicken retina are sensitive to red, green, blue, and violet wavelengths of light (expressing LWS, Rh2, SWS2, and SWS1 opsins respectively)(Fig. 1C2)(40, 41). These cone types have been identified chiefly by differently colored oil droplets located between the inner and outer segments, which may act as a filter for specific wavelengths of light, as well as focusing photons onto the outer segment(42-45) (Fig. 1C2). Two morphologically different sets of double cones in chickens are sensitive to long wavelengths of light(46). In the more common double cone pair, both cones have an oil droplet(46, 47) (Fig. 1C2, **Type B**). In the other pair, only the larger (primary) cone contains an oil droplet (Fig. 1C2, **Type A**)(44, 46). These double cones may be specialized for motion detection rather than color vision, as they appear to contain the same photopigments and synapse on one another(3, 48, 49).

Double cones cover about 40% of the chicken retina, with a majority positioned ventrally(43). Green and red single cones each comprise about 20% of total cone cells. Blue and violet cones make up the remaining 12 and 8%, respectively, and are more abundant dorsally(43). Each cone in the chicken retina is positioned at a regular distance from other cones of the same subtype (ex: each red cone is at a specific distance from its neighboring red cone cell)(43). However, the relative positions of different cone cell subtypes (ex: red vs. green) are not regular. Thus, the final retinal pattern in chickens is semi-random (Fig. 1C1, C3, 4D), rather than the perfectly ordered pattern seen in zebrafish (Fig. 1B1)(43).

Chickens and other birds have an avofoate structure, meaning the most central part of the retina is densely packed with cones and lacks rods(40, 50)(**area centralis**, Fig. 1C1). Further from the foveal center, cone packing becomes less dense(43, 45, 51, 52). In addition to the **area centralis**, rod numbers are reduced in a lateral stripe through the center of the retina(40) and in the dorsal retina (**central meridian** and **dorsal rod free zone**, Fig. 1C1). The rod population has a pattern distinct from cones, forming a ventral to dorsal gradient(40) (**dorsal rod free zones**, Fig. 1C1).

Regionalized patterning of cones in the retina of *Mus musculus*

The *Mus musculus* (mouse) retina has fewer PR types than zebrafish and chickens, containing motion-detecting rods that express rhodopsin and three subtypes of color-detecting cones that express S-opsin (UV-detecting), M-opsin (green-detecting), or both S- and M-opsins (Fig. 1D2-D5). These PRs are patterned in a regionalized mosaic, with cones arranged in opposing dorsal to ventral gradients (Fig. 1D1, D6). M-opsin is expressed most highly in the dorsal third, and S-opsin is expressed in the ventral two thirds(53, 54) (Fig. 1D1, D6). In the region in which these opposing gradients meet, single cone cells have varying levels of M- and S-opsin co-expression(54, 55) (Fig. 1D1, D6). A subset of S-opsin expressing cones appears to be stochastically arranged throughout the retina(56) (Fig. 1D1). These cones may be part of a primordial S-cone color system that synapses onto a dedicated population of bipolar cells(57). Rods are evenly interspersed throughout the retina and vastly outnumber cones, making up about 97% of the PR population(58) (Fig. 1D1, D7).

Stochastic/regionalized patterning of cones and rods in the *Homo sapiens* retina

The human retinal mosaic contains four types of PRs: rods for night vision, and blue (S-opsin), red (L-opsin), and green (M-opsin) cones for color and daytime vision(59-63) (Fig. 1E2-E5). Human retinal patterning is mostly random, with a few areas of organization. Similar to chickens, the central area of the human retina is densely packed with cones(64) (Fig. 1E1). This area can be divided into three regions: the **foveola**, the **fovea**, and the **macula** (Fig. 1E1). The **foveola** contains only L- and M-opsin-expressing cones arranged in a stochastic pattern(65, 66) (Fig. 1E1). S-cones become integrated into the mosaic outside the **foveola** within the **fovea** and the **macula** (Fig. 1E1, E6)(67). It is unclear whether the S-cone mosaic is also random(67), or if it is distributed in a lattice pattern, separate from the L/M-cone cell pattern(67-69). Cones in the **foveola** and **fovea** are smaller than those found in the **macula** and in the **posterior pole**(70) (Fig. 1E1). Rods are integrated into the mosaic starting in the **macula** region(67) (Fig. 1E1). The **posterior pole** of the retina is rod-dominated, with a random pattern of L-, M-, and S-cones scattered throughout (71) (Fig. 1E1, E7). One other densely packed cone region exists along the **peripheral rim** of the retina(72) (Fig. 1E1).

L- and M-cones are so similar that until very recently it was almost impossible to distinguish between the two(65, 66, 71, 73-77). It is widely believed that the only difference between L- and M-cones is the opsin expressed. However, evidence from monkeys suggests that the two populations have different numbers of synapses between the cone and the midjet bipolar cell(78). S-cones are easily distinguished by their short, stubby outer segments, while L/M-cones produce long, skinny outer segments(67, 68, 79, 80). S- and L/M-cones also have distinct patterns of connectivity with other retinal cell types(68).

The unique retinal patterning of different organisms has evolved to suit their environments and behaviors

Evolution has optimized stochastic/regionalized, regionalized, and ordered retinal patterns to fit the needs of diverse organisms. For example, regionalization of specialized ommatidia within an overall stochastic mosaic provides the fly with the optimal light-detecting abilities

to respond to its environment. The **dorsal rim** ommatidia detect polarized light to allow proper navigation during flight, while the coexpression of Rh3 and Rh4 in **dorsal third yR7s** may assist in detecting the location of the sun(4-6). The evolutionary advantage of a stochastic rather than patterned distribution of PRs remains unclear. Random placement of **yellow** and **pale** ommatidia that results in similar 65:35 ratios throughout the eye may be the simplest evolutionary mechanism to ensure that all regions of the retina detect multiple wavelengths of light with the same efficiency.

The ordered distribution of zebrafish cones is uniquely suited to its aquatic environment, preventing under- or over-sampling of specific light wavelengths in different areas of the retina(37). The ability to detect such a broad spectrum of light wavelengths may allow the zebrafish to see efficiently when light conditions vary due to water turbidity, seasonal changes, and fluctuations in water microorganism and mineral content(23).

The semi-random mosaic of the chicken retina is tuned to perceive many wavelengths of light with high visual acuity. The chicken's cone-rich retina and densely packed **area centralis**, which also has a greater ganglion cell density (81, 82), likely provides high-acuity color vision in daylight to allow identification of prey and predators. Different bird species display different ratios of cone subtypes. For example, sea birds generally have fewer long-wavelength opsin cones compared to blue and green, possibly because long wavelengths are filtered out by water(44, 83). This implies that genetic mechanisms governing cone subtype specification are highly tunable to the environmental niche that an avian species inhabits.

Because the regionalized mouse retina contains two color-detecting opsins that are mostly separated into the dorsal third and ventral retina, mouse vision is believed to be largely monochromatic. Ventral expression of S-opsin and dorsal expression of M-opsin allows the mouse to maximize sampling of ultraviolet (sky) and terrestrial light sources with the most appropriate PRs. In the center of the retina, where S- and M-opsin expression converges, differing levels of opsin coexpression between neighboring cells may give the mouse dichromatic vision(84, 85).

The random distribution of the three human cone types allows for efficient spectral sampling of the visual field and maximizes contrast sensitivity(1-3). The dense packing of cones in the fovea provides maximal visual acuity in the daylight, and the rod-dominated retina outside of the macula allows for efficient night vision.

The gene-regulatory networks controlling PR specification share functional and sequence-level homologs

The gene-regulatory networks controlling PR specification are extremely complex and in many cases are still being elucidated. Here, we provide simplified networks to highlight the proteins that play conserved roles in PR fate at either the functional or sequence level, focusing mainly on flies, zebrafish, and mice, whose gene-regulatory networks are better characterized than those of chickens and humans. PR differentiation occurs in four basic decision steps (Fig. 2A): 1) PR vs. non-PR fate; 2) Rod vs. cone fate; 3) Cone subtype; and 4) Opsin subtype.

Step 1: PR vs. non-PR fate choice

Step 1 of PR specification involves the expression of factors that distinguish differentiating PRs from other cell fates. In flies, the zinc finger transcription factor Glass plays this role(86) (Fig. 2B, **Step 1**). Vertebrate PR differentiation involves a core set of conserved transcription factors, including Cone-Rod Homeobox (Crx), the Orthodenticle Homeobox proteins (Otx2 and Otx5), and the Retinal homeobox proteins (Rx1, RaxL, Rax)(87-118) (Fig. 2C-E, Sup fig 1, **Step 1**). Species-specific inputs have emerged to regulate these conserved factors. In zebrafish, the Hippo pathway transcriptional activator Yes-associated protein (Yap) represses these core transcription factors (Fig. 2C, **Step 1**), while in mice, the Notch-1 transmembrane receptor plays this role (Fig. 2D, **Step 1**)(119-121). The core PR factors are also activated by species-specific inputs: in zebrafish, the signaling molecule Sonic hedgehog (Shh) and the transcription cofactor Lbh-like activate Rx1 and Otx2, respectively (Fig. 2C, **Step 1**)(87, 122). The network topology between these conserved factors varies between organisms; in mice, Rax activates Otx2(92) (Fig. 2D, **Step 1**), while in zebrafish, no link between Rx1 and Otx2 has been established (Fig. 2C, **Step 1**) (87, 89-92, 100). In both mice and zebrafish, Otx2 likely activates Crx (Fig. 2C-D, **Step 1**)(87, 101). Other regulators complement these core factors: for example, in zebrafish, Crx activates the species-specific Otx homolog Otx5 to drive PR fate (Fig. 2C, **Step 1**)(97-99, 119).

Step 2: Rod vs. cone fate choice

In Step 2, PR precursors select either rod or cone fate. In *Drosophila*, outer PRs (rods) are specified by the presence of the homeodomain protein Defective Proventriculus (Dve), which represses the expression of color-detecting Rhodopsins (Fig. 2B, **Step 2**)(123). In zebrafish, mice, and humans, the bZIP transcription factor Neural retina leucine zipper protein (Nrl) and the orphan nuclear receptor Nuclear Receptor Subfamily 2 Group E Member 3 (Nr2e3) play important roles in rod fate (Fig. 2C-E, **Step 2**)(88, 98, 124-142). Nrl activates Nr2e3 in mice and may play a similar role in humans and zebrafish (Fig. 2C-E, **Step 2**)(143, 144). In zebrafish and possibly chickens, Retinoic acid (RA) signaling is also involved in rod development (Fig. 2C, Sup Fig 1, **Step 2**); in zebrafish, RA signals through the RAR α receptor and possibly the RXR γ receptor to specify rods (Fig. 2C, **Step 2**)(145, 146). Additionally, the growth factor glial cell line-derived neurotrophic factor (GDNF) is expressed specifically in rods in both chickens and mice and may also play a role in zebrafish (Fig. 2-D and Sup Fig 1, **Step 2**)(147-151). Two non-conserved factors, the SUMO-E3 ligase/transcription factor Pias3 and the orphan nuclear receptor Ror β , are also involved in rod fate in mice (Fig. 2D, **Step 2**)(132, 152-154). Recent evolutionary studies suggest that mammalian S-cone and rod PRs may have similar lineages, and may temporally switch from S-cone precursors to rods(155).

In *Drosophila*, the zinc finger transcription factor Spalt (Sal) drives inner PR (“cone”) fate by repressing Dve (Fig. 2B, **Step 2**)(123). In an additional step, not conserved in higher organisms, inner PR “cones” differentiate further into two types: R7s, specified by the homeodomain transcription factor Prospero (Pros) and the transcription factor subunit Nf-yc, and R8s, specified by the zinc finger transcription factor Senseless (Sens)(Fig. 2B, **Step 2**) (156-158).

In zebrafish, the BMP family ligand Gdf6a induces the transcription factor Tbx2b to repress rod fate and allow cone development (Fig. 2C, **Step 2**)(159-161). Tbx2b does not appear to play a conserved role in cone specification; it is involved in dorsal-ventral retinal development in chickens, mice, and humans, but its expression is not restricted to cones(162, 163). In chickens and mice, RA signaling through the Rxr γ receptor may be important for cone fate (Fig. 2D and Sup Fig 1, **Step 2**) (164-167). Additionally, Thr β 2 receptor plays a role in cone specification in chickens, mice, and humans (Fig. 2D-E and Sup Fig 1, **Step 2**) (163, 168-179).

Step 3: Cone subtype choice

In Step 3, cone precursors are specified into subtypes, marked by expression of specific color-detecting opsins. Interestingly, several of the proteins required for cone subtype selection in flies are conserved in vertebrate PRs, though they have been adapted to play different roles. Selection between **yellow** and **pale** ommatidial subtypes in *Drosophila* is based on the stochastic expression of the PAS-bHLH transcription factor Spineless (Ss) in 65% of R7s(180). In **yR7s**, Ss activates expression of Rh4 and Dve, which represses Rh3 (Fig. 2B, **Step 3**)(123, 180). In **pR7s** lacking Ss, Rh4 and Dve are not expressed, leading to activation of Rh3 by Sal and Orthodenticle (Otd), a homolog of vertebrate Crx, Otx2, and Otx5 (Fig. 2B, **Step 3**)(180, 181). Intriguingly, the mammalian homolog of Sal, Sall3, has been conserved at both the sequence and functional levels; it also activates opsins in mice (Fig. 2D, **Step 3**)(182).

In **yR7s**, Ss represses an unknown signal to R8s (Fig. 2B, **Step 3**). In the absence of this signal, the Warts (Wts) serine/threonine kinase is activated, causing repression of the transcriptional coactivator Yorkie (Yki), a homolog of zebrafish Yap, in **yR8s** (Fig. 2B, **Step 3**). Repression of Yki induces activation of Rh6 and loss of Rh5 (Fig. 2B, **Step 3**)(13, 14, 180, 183, 184). In **pR7s**, the unknown signal activates the PH domain-containing protein Melted (Melt), which represses Wts to allow Yki activation and Rh5 expression in **pR8s** (Fig. 2B, **Step 3**)(183, 184). Additionally, Otd acts permissively in **pR8s** to activate Rh5 (Fig. 2B, **Step 3**)(123).

In **dorsal third yR7s**, reduced Ss and Dve levels, combined with activation by the Iroquois complex of transcription factors (IroC), induces co-expression of Rh3 with Rh4 (Fig. 2B, **Step 3**)(4, 123, 185). In the **dorsal rim**, high local concentrations of the diffusible morphogen Wingless (Wg) act with IroC to drive expression of the homeodomain transcription factor Homothorax (Hth) in R7s and R8s (Fig. 2B, **Step 3**, Fig. 3A)(19, 20). Hth represses Ss in R7s and Rh5, Rh6, and Sens in R8s, causing Rh3 expression in R7s and R8s (Fig. 2B, **Step 3**)(19, 20, 186).

In zebrafish, mice, and humans, T3 thyroid hormone signals through the tr β 2/Thr β 2 receptor to drive expression of specific opsins. In zebrafish, T3 activates LWS opsin, in mice, it activates M-opsin and represses S-opsin, and in humans, it may select L/M-opsins over S-opsin (Fig. 2C-E, **Step 3**)(163, 168-179, 187). RA signaling through the RXR γ /RXR γ receptor also controls opsin expression in vertebrates; in zebrafish, RA signaling activates

LWS opsin and represses SWS1 and SWS2 opsins, while in mice, it may repress S-opsin (Fig. 2C-D, **Step 3**)(166, 188, 189).

Since T3 and RA are also involved in earlier steps of PR specification, additional factors likely work with them to specify cone subtypes. In mice, Pias3, BMP, and COUP-TFII work with T3 to activate M-opsin (Fig. 2D, **Step 3**)(152, 170, 190). BMP and COUP-TFII may also assist RA and T3 in repressing mouse S-opsin (Fig. 2D, **Step 3**)(190).

Additional factors have been implicated in vertebrate opsin expression, though it is currently unclear if they are conserved between species. In zebrafish, Gdf6a drives SWS2 expression and works in combination with Tbx2b to activate SWS1 (Fig. 2C, **Step 3**)(159-161).

Additionally, the fish-specific transcription factor Sine oculis homeobox homolog 7 (Six7) drives activation of RH2 (Fig. 2C, **Step 3**)(191). In mice, Shh signaling may activate Sall3, which acts with Ror β to activate S-opsin (Fig. 2D, **Step 3**) (182, 192, 193).

Step 4: Opsin subtype choice

In zebrafish and humans, a final choice further differentiates cone subtypes based on opsin subtype expression (Fig. 2C, E, **Step 4**). Zebrafish red- and green-detecting cones select between multiple LWS and RH2 opsin subtypes, respectively (Fig. 5B)(194-196). RA, potentially acting through RXR γ , directs expression of LWS-1 over LWS-2 (Fig. 5B)(189). Human L/M cones select between the closely related L- and M-opsins (Fig. 5C)(197). In both zebrafish and humans, locus control regions (LCRs) have evolved to regulate opsin subtype choice at the *cis* level (see below; Fig. 5)(194-196).

Functional and sequence-level homology

The proteins controlling PR specification can be divided into three main categories based on their functional and/or sequence-level homology. The first category involves factors that serve similar developmental roles but share no sequence homology (Table 1). A second category includes factors that are conserved on the sequence level but perform unique roles in different organisms (Table 2). The third category contains factors with functional and sequence-level homology (Table 3). In some cases, factors in this category may drive further, species-specific processes in addition to their conserved role.

Gradients of signaling molecules determine regionalized retinal development

In addition to conserved gene-regulatory networks, diverse organisms share a common mechanism for delineating retinal regions, involving gradients of signaling molecules. Two models exist for how such gradients are established. The first, more traditional model suggests that gradients arise from diffusion of signaling molecules from a specific source. This occurs in *Drosophila*, where Wg is secreted from a stripe called the dorsal margin to create a dorsal-to-ventral gradient in the larval eye disc that specifies the location of dorsal rim ommatidia in adults (Fig. 3A)(19, 198).

An alternative “gradient-free” model proposes that enzymes that produce or degrade signaling molecules are expressed in a regionalized pattern, regulating local levels of small molecules to create a gradient throughout the tissue(199). This gradient-free mechanism may establish ventral to dorsal gradients of RA involved in retinal development and patterning in zebrafish, chickens, and mice(40, 145, 146, 170, 188, 200-202). In the developing chicken and mouse retina, the dorsally-expressed aldehyde dehydrogenase AHD2 produces low RA, and the ventrally-expressed aldehyde dehydrogenase V1 produces high RA, creating regional “gradients” of RA in the retina (Fig. 3B-C)(200, 201, 203-205). In the chick, the ventral-to-dorsal gradient of RA mirrors the rod gradient, suggesting that regionalized RA processing enzymes drive gradients of PR subtypes (Fig. 3C)(200, 206, 207). In the mouse, an additional enzyme, the oxidase CYP26, causes RA degradation and a potential breakdown in the gradient in the central retina (Fig. 3B)(200, 208). Together, these conserved patterns delineate different retinal regions during development.

Interestingly, in adult retinas of both chick and mouse, ventral V1 dehydrogenase expression is lost, leaving dorsal AHD2 as the only RA synthesizing enzyme and causing a reversal of the gradient to higher RA levels in the dorsal retina (Fig. 3B-C)(200, 201). In mice, this reversal may promote ventral S-opsin repression after postnatal day 8 by activation of RXR γ (Fig. 3B)(166, 200, 209). In the chicken, it is unclear how this reversal affects PR fate specification (Fig. 3C).

Deiodinases play a similar role in thyroid hormone gradient formation. They are expressed in regionalized areas and/or at different time points in the chick(169), mouse(210, 211), and zebrafish retinas(212-214). In mice, Deiodinase 2 (Dio2), which converts thyroid hormone from the inactive T4 to the active T3 form, is expressed at higher levels in the dorsal retina(210, 215) and likely establishes a T3 gradient(216) (Fig. 3B). High dorsal T3 signaling promotes expression of M-opsin and repression of S-opsin(152, 166, 170, 171, 217) (Fig. 3B). Low T3 signaling in the ventral retina allows expression of S-opsin (Fig. 3B) (170).

Dorsal-ventral BMP gradients and ventral-dorsal Shh gradients in the mouse retina activate M- and S-opsin, respectively, but the sources of these gradients are still unclear (Fig. 3B) (182, 190, 192, 218).

Retinal development proceeds through waves of differentiation

Despite significant differences in morphology, regionalization, and sensitivity between organisms, retinal development in many species involves waves of differentiation. Within the developing fly eye-antennal disc, a wave of differentiation known as the morphogenetic furrow moves from the posterior to the anterior of the retina (Fig. 4A), driven partially by the signaling molecule Hedgehog (Hh) and the bHLH transcription factor Atonal (Ato)(7, 219-223). Undifferentiated PR precursors lie anterior to the furrow, whereas posterior to the furrow, PRs differentiate in a specific order (Fig. 4A)(7, 219). The R8 PR serves as a “founder” cell, recruiting undifferentiated PR precursors and driving their stepwise differentiation into a complete ommatidium via multiple signaling pathways (well-reviewed

in (9, 224-230)). The initial differentiation of R2, R5, R3, and R4 is followed by the second mitotic wave (Fig. 4A), after which R1, R6, and R7 sequentially differentiate(7, 219, 226).

Though separated by over 800 million years of evolution, zebrafish retinal differentiation shares much in common with the processes observed in flies. As in flies, a wave of neural differentiation driven in part by Hedgehog signaling and *ath5*, a zebrafish homolog of Ato, spreads across the developing retina (Fig. 4B)(231, 232). In zebrafish, PRs differentiate from an initial patch(233-235). Cones spread from this patch in a wave resembling an opening fan, with differentiation sweeping from ventral-nasal to dorsal-temporal(21, 233, 234) (Fig. 4B). A mitotic wave follows the initial fan gradient to complete cone differentiation(233, 235). Early-differentiating red cones may act similarly to R8 PRs in *Drosophila*, functioning as “founders” to recruit undifferentiated cone precursors and drive their differentiation(21). While rods are also found initially in the ventral patch, they differentiate separately from cones. Clusters of rod precursors scattered throughout the retina undergo multiple rounds of mitosis before differentiating into rods and migrating to their final positions around UV cones(37, 233, 234, 236).

The chicken retina is similar to the zebrafish in that differentiation begins at a central patch, the area centralis(40, 46, 169). Sequential waves of transcription factor expression emanate from the center to the periphery to drive cell differentiation and retinal patterning (Fig. 4C). First, a wave of cone precursor transcription factors is expressed, including Thrβ2 and Otx2(169). Individual cone subtypes then express opsins in temporal waves. Green and red opsins are expressed first, followed by blue and violet(40) (Fig. 4D). An additional wave of differentiation sweeps linearly across the retina from the ventral to dorsal region to pattern rods (Fig. 4E)(40).

Although mice do not have a fovea, retinal differentiation follows the same central to peripheral pattern that is seen in chickens (Fig. 4C)(237, 238). Generation of different retinal cell types is coincident with temporal waves, and this phenomenon has been used to identify important factors in retinal generation(239).

The developmental pattern of the human and other primate retinas closely resembles the chick and mouse retina, with differentiation following sequential waves emanating from the optic disk, near the fovea, outward(240-242) (Fig. 4C). S-cones are seen first in the foveal area followed by L/M-cones, and later rods outside of the fovea(242, 243). The fetal fovea is not packed as tightly as the adult fovea(64), suggesting that differentiated cones migrate toward the central fovea later in development to create a densely packed array(69, 244, 245).

Looping of DNA elements regulates cone subtypes

Beyond retina-wide signaling gradients and waves of differentiation, conserved mechanisms control retinal development at an individual PR level. Looping of regulatory DNA elements plays a critical role in opsin choice across organisms. In *Drosophila*, DNA looping may regulate the stochastic expression of *ss*, the key determinant of R7 (“cone”) subtype fate. The *ss* locus contains an enhancer, which activates *ss* in 100% of R7s, and two silencers, which randomly repress *ss* in 35% of R7s (Fig. 5A)(246). Because the two silencers are

located at a significant distance from the *ss* promoter, it is likely that they regulate *ss* through a looping-based mechanism. An enticing hypothesis is that the enhancer and silencers compete for looping to the *ss* promoter, resulting in activation or repression of *ss* and regulation of downstream Rhodopsins (Fig. 5A).

In a striking example of convergent evolution between zebrafish and humans, DNA elements known as locus control regions (LCRs) likely regulate opsin expression through looping-based mechanisms. In both cases, ancestral enhancers that regulated the expression of a single opsin gene were adapted in response to an opsin gene duplication(62, 194-196, 247-250).

Zebrafish opsin genes are regulated by two LCRs, one that selects between LWS subtypes and one that selects between RH2 subtypes (Fig. 5B)(194-196). LCR-mediated regulation of opsin subtypes is controlled in a temporal progression(39, 194, 195). RH2-1, RH2-2, and LWS-2 are expressed earliest and are present in the central and dorsal regions of the zebrafish retina, which develop first (Fig. 1B3, Fig. 5B)(39). RH2-3, RH2-4, and LWS-1 are expressed later and thus localize to the later-developing retinal periphery (Fig. 1B3, Fig. 5B) (39).

Human opsin genes are regulated by one LCR that selects between L- and M-opsin expression (Fig. 5C)(251). It is hypothesized that the LCR loops randomly to the promoter of either the L- or M-opsin gene to drive opsin expression(63, 252, 253). Alternatively, the human LCR might activate opsins in a temporal progression, after which L- and M-opsin-expressing cones might migrate to their final, random positions in the human retina(244, 245).

The zebrafish and human LCRs are all about 0.5 kb in size, perhaps reflecting a common sequence length that is required for robust activation of opsin expression (194, 195, 251, 252). Despite their common sizes, the RH2, LWS, and human LCRs have little sequence similarity other than shared binding sites for the transcription factor Crx(194, 195).

Concluding Remarks

Many questions about the gene-regulatory and evolutionary mechanisms governing retinal development remain unanswered (see “Outstanding Questions” box). Further study of PR development and maintenance will provide insight into the evolutionary advantages of different retinal mosaics and uncover additional conserved and species-specific gene-regulatory networks required for retinal patterning. A deeper understanding of these mechanisms may ultimately lead to new treatments for many developmental disorders of the visual system and the development of effective PR regenerative therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Outstanding questions

- What are the functional roles of stochastic/regionalized, regionalized and ordered retinal mosaics?
- What are the missing regulatory nodes controlling photoreceptor fate?
- What are the mechanisms controlling stochastic cell fate specification?
- What signaling or migration mechanisms determine the ordered pattern of photoreceptors in the fish eye?
- How are multiple gradients integrated to dictate regionalized photoreceptor patterns?
- How do functionally homologous gene networks evolve to control similar photoreceptor specification processes?

Trends Box

Retinal mosaics can be organized into three broad categories:
stochastic/regionalized, regionalized, or ordered.

Networks of transcription factors with sequence and/or functional
homologies are utilized to determine photoreceptor fates.

Between diverse species, there are amazing similarities in regulatory
processes including waves of differentiation, gradients of signaling
molecules, and DNA element looping.

Figure 1. Retinas are patterned in stochastic/regionalized, regionalized, and ordered mosaics

- A1)** Schematic of the *Drosophila melanogaster* (fruit fly) PR mosaic (not to scale). D: Dorsal, V: Ventral, A: Anterior, P: Posterior.
- A2)** Schematic of a *Drosophila* ommatidium.
- A3)** Schematic of a pale ommatidium.
- A4)** Schematic of a yellow ommatidium.
- A5)** Schematic of a dorsal third yellow ommatidium.
- A6)** Schematic of a dorsal rim ommatidium.
- A7)** Whole-mount immunostain of a *Drosophila* retina showing the stochastic distribution of ommatidial subtypes.
- A8)** Immunostain showing Rhodopsin 1 (Rh1) expression in the outer PRs.
- A9)** Immunostain showing the stochastic patterning of Rh3 and Rh4 in a section of the *Drosophila* retina.
- A10)** Immunostain showing the stochastic patterning of Rh5 and Rh6 in a section of the *Drosophila* retina.
- A11)** Immunostain of the dorsal third of the *Drosophila* retina, showing coexpression of Rh3 and Rh4 in dorsal third yR7s.
- A12)** Immunostain of the dorsal rim of the *Drosophila* retina, showing expression of Rh3 in R7s and R8s.

B1) Schematic of the *Danio rerio* (zebrafish) PR mosaic (not to scale). D: Dorsal, V: Ventral, A: Anterior, P: Posterior.

B2) Schematic side view of a single unit of the zebrafish retinal pattern.

B3) Schematic showing the overlapping, regionalized expression patterns of zebrafish LWS and RH2 opsin subtypes (not to scale). 1: Inner central/dorsal area, 2: Outer central/dorsal area, 3: Inner periphery/ventral area, 4: Outer periphery/ventral area.

B4) Immunostain of a section of the zebrafish cone mosaic. Reprinted from *Progress in Retinal and Eye Research*, Volume 42, M. Hoon, H. Okawa, L. Della Santina, R.O. Wong, Functional architecture of the retina: Development and disease, Pages 44-84, Copyright (2014), with permission from Elsevier.

B5) Immunostain of a section of the zebrafish rod mosaic. Reprinted from *Developmental Biology*, Volume 258, J.M. Fadool, Development of a rod photoreceptor mosaic revealed in transgenic zebrafish, Pages 277-290, Copyright (2003), with permission from Elsevier.

C1) Schematic of the *Gallus gallus domesticus* (chicken) PR mosaic (not to scale). 1: area centralis, 2: dorsal rod free zone, 3: dorsal rod zone, 4: central meridian, 5: ventral rod rich zone.

C2) The chicken has five different types of cone cells: red, green, blue, violet, and double cones. Type A double cones contain an auxiliary cone lacking an oil droplet. Type B double cones both have oil droplets. Images adapted from Wai *et al.*, 2006 and Santiago Ramon y Cajal, 2000(46, 254).

C3) Light microscope image of oil droplets in the chicken retina. Adapted from Figure 1b from Kram *et al.*, 2010(43).

D1) Schematic of the *Mus musculus* (mouse) PR mosaic (not to scale).

D2-D5) Labeled depiction and immunostaining of mouse PRs. Rods shown in yellow (D2), S-cones in blue (D3), M-cones in green (D4), and S/M-cones in blue/green (D5).

D6) Immunostain of a whole-mount mouse retina. Green: M-opsin. Blue: S-opsin.

D7) Pseudocolored DIC section of whole-mount mouse retina, showing cone and rod distribution. Rods shown in yellow. Blue and green are arbitrarily chosen to represent S- and M-cones, respectively, but each cell could express S-opsin only, M-opsin only, or both S- and M-opsins. Adapted from Jeon *et al.* 1998(58). Copyright 1998, <http://www.jneurosci.org/content/18/21/8936.long>, under Creative Commons Attribution 4.0 International Public License and Disclaimer of Warranties (<http://creativecommons.org/licenses/by/4.0/legalcode>).

E1) Schematic of the *Homo sapiens* (human) PR mosaic (not to scale). 1: foveola, 2: fovea, 3: macula, 4: posterior pole, 5: peripheral rim.

E2-E5) Labeled depiction of human PRs. E2: rod, E3: S-cone, E4: L-cone, E5: M-cone.

E6) Pseudocolored adaptive optics image of the human fovea. Blue: S-cones, Red: L-cones, Green: M-cones. Adapted from Figure 8B of Williams *et al.*, 2011(77). Copyright 2011, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189497/>, DOI 10.1016/j.visres.2011.05.002, under Creative Commons Attribution 4.0 International Public License and Disclaimer of Warranties (<http://creativecommons.org/licenses/by/4.0/legalcode>).

E7) Pseudocolored image of human cones in the posterior pole. Yellow: rods, Blue: S-cones. Red and green are arbitrarily chosen to represent L- and M-cones, respectively, but each cell could be either red or green. Adapted from Curcio *et al.*, 1991(67). Copyright 1991, <http://onlinelibrary.wiley.com/doi/10.1002/cne.903120411/abstract>, DOI 10.1002/cne.903120411,

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Note: In *Danio rerio* and *Mus musculus*, the optic disc is located temporal to the central retina, and in *Gallus gallus domesticus* and *Homo sapiens* retinas, it is located temporal to the foveal center. This area is devoid of photoreceptors and is not represented in the included mosaics.

Figure 2. The gene-regulatory networks controlling PR specification

All gene-regulatory networks have been simplified to emphasize PR factors that are conserved between species. Arrows within gene networks solely represent our current understanding of network relationships and do not imply genetic mechanisms such as direct or indirect transcriptional regulation.

A) The basic steps of PR differentiation, which are largely conserved between organisms.

B) *Drosophila melanogaster*.

C) *Danio rerio*.

D) *Mus musculus*.

E) *Homo sapiens*.

Figure 3. Gradients of signaling molecules determine regionalized retinal development

For A-C, D: dorsal, V: ventral, A: anterior, P: posterior.

A) In *Drosophila*, the diffusible morphogen Wg is expressed in a dorsal patch of the larval eye disc, beginning the signaling cascade leading to expression of Rh3 in the **dorsal rim** in the adult (See Fig. 2B).

B) Gradients of signaling molecules in the mouse retina leading to M (green) and S (blue) opsin expression. Sonic Hedgehog (Shh) is expressed in a ventral to dorsal gradient in both the embryo and the adult. Retinoic acid (RA) is expressed in a ventral to dorsal gradient at

embryonic stages, and is produced by the enzymes V1 (ventral, high enzymatic activity) and AHD2 (dorsal, low enzymatic activity). CYP26 degrades RA in a strip through the middle of the retina. In the adult neither V1 nor CYP26 are expressed, so RA is present in a dorsal to ventral gradient. Thyroid hormone (T3) is present throughout the embryonic retina. In the adult, T3 is present in a dorsal to ventral gradient, presumably governed by the presence of the T3 synthesizing enzyme Dio2. BMP is present in a dorsal to ventral gradient in both the embryonic and adult mouse retina.

C) In the chicken, RA is expressed in a ventral to dorsal gradient at embryonic stages and is produced by V1 and AHD2, as in mice. This mirrors the ventral to dorsal gradient of rods (black) within the chick retina. In the adult, V1 is not expressed, so RA is present in a dorsal to ventral gradient.

Figure 4. Retinal development proceeds through waves of differentiation

For A-E, A: anterior, P: posterior, D: dorsal, V: ventral, N: nasal, T: temporal.

A) In *Drosophila*, waves of differentiation and mitosis move from posterior to anterior.

B) In zebrafish, differentiation proceeds from ventral-nasal to dorsal-temporal in a wave resembling an opening fan.

C) In chickens, mice, and humans, differentiation begins in the center of the retina and expands towards the periphery.

D) Chicken retinal development also involves a temporal wave of cone maturation. Green and red cones are the earliest to mature, followed by blue and violet cones.

E) A ventral-to-dorsal wave of differentiation patterns rods in the chicken retina in a density gradient, excluding the **area centralis**.

Figure 5. Looping of DNA elements regulates cone subtypes

A) In *Drosophila*, looping of regulatory elements may cause activation or repression of *ss*, the key determinant of R7 subtype fate. Sil1: Silencer 1, Enh: Enhancer, Sil2: Silencer 2.

B) RA signaling and LCR looping select between opsin subtypes in zebrafish. Numbers in RH2 box indicate the temporal order of RH2 subtype expression.

C) LCR looping selects between L- and M-opsin for expression in human L/M-cones.

Table 1
PR proteins with functional, but not sequence-level, homology

Function	Fly	Zebrafish	Mouse
PR fate	Glass	Lbh-like	N/A
Rod fate	Dve	N/A	Pias3, Ror β
Cone fate	Pros, Nf-yc, Sens	Tbx2b, Gdf6a	N/A
Opsin choice	Ss, Dve, IroC, Wg, Hth	Gdf6a, Tbx2b, Six7	COUP-TFII, Pias3, BMP, Ror β

Table 2
PR proteins with sequence-level, but not functional, homology

Gene	Fly	Zebrafish	Chicken	Mouse	Human
Otd/Otx2/ Otx5	Opsin choice	PR fate	PR fate	PR fate	Retinal cell fate
Yki/Yap	Opsin choice	PR fate repression	N/A	N/A	N/A
Shh	N/A	PR fate	N/A	Retinal regionalization	N/A

Table 3
PR proteins with functional and sequence-level homology

Gene	Fly	Zebrafish	Chicken	Mouse	Human
Crx	N/A	PR fate	PR fate	PR fate	PR fate
Otx2/Otx5	N/A	PR fate	PR fate	PR fate	N/A
Rx1/RaxL/ Rax	N/A	PR fate	PR fate	PR fate	N/A
Nrl	N/A	Rod fate	N/A	Rod fate	Rod fate
Nr2e3	N/A	Rod fate	N/A	Rod fate	Rod fate
RA	N/A	Rod fate, opsin choice, opsin subtype choice	Rod fate, cone fate	Cone fate, opsin choice	N/A
GDNF	N/A	Rod fate (?)	Rod fate	Rod fate	N/A
Sal/Sall3	Cone fate, opsin choice	N/A	N/A	Opsin choice	N/A
trβ2/Thrβ2	N/A	Opsin choice	Cone fate	Cone fate, opsin choice	Cone fate, opsin choice