
'One Receptor' Rules in Sensory Neurons

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Key Words

Sensory system · Eye · Rhodopsin · *Drosophila* · Exclusion

Abstract

With the recent explosion in the characterization of different sensory systems, a general rule is emerging: only one type of sensory receptor molecule is expressed per receptor neuron. The visual system is no exception and, in most cases, photoreceptors express only one visual pigment per cell. However, the mechanisms underlying the exclusion of sensory receptors are poorly understood. As expression of a given receptor in a given cell is often stochastic, a decision must first be made to express one of the many receptors of the same family (i.e. one particular *rhodopsin*) and this expression must correlate with the silencing of the other receptors. Furthermore, the projection center for the receptors in the brain must be informed of the decision in order to process this information. Although cells can choose from up to hundreds of sensory receptors (e.g. in the olfactory system), they make almost no mistakes. Evidence has recently emerged that the exclusion mechanism involves the sensory receptor molecules themselves. Here, we describe the findings from various systems in mammals and *Drosophila*, and review evidence that in the simple visual system of the fly, rhodopsin molecules play an important role in sensory receptor exclusion.

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Introduction

A common phenomenon in sensory systems is the exclusive expression of a single receptor molecule in a given receptor cell. However, the molecular mechanisms involved in this exclusion process are largely unknown. We will discuss recent progress in our understanding of how the 'single receptor molecule per receptor cell' rule is established. The expression of only one receptor molecule per cell is necessary to prevent sensory overlap in the brain. Once a stimulus has been received, the animal must then respond appropriately. The presence of many receptors in one sensory cell projecting to the brain would complicate the process of determining the appropriate response. We will describe how this rule applies to the visual systems of *Drosophila* and of higher organisms, as well as other sensory systems, despite their differing anatomy and their varying degrees of complexity (more cells, more receptors and more regulations). We will focus on important findings recently described for the *Drosophila* visual system.

Through the Fly Eye

The fly compound eye is composed of approximately 800 individual eyes called ommatidia. Each ommatidium is composed of 20 cells, including 8 photoreceptor cells (PR) named R1–R8 (fig. 1a). Each PR contains a stack of apical microvilli, the rhabdomere, which is filled with a

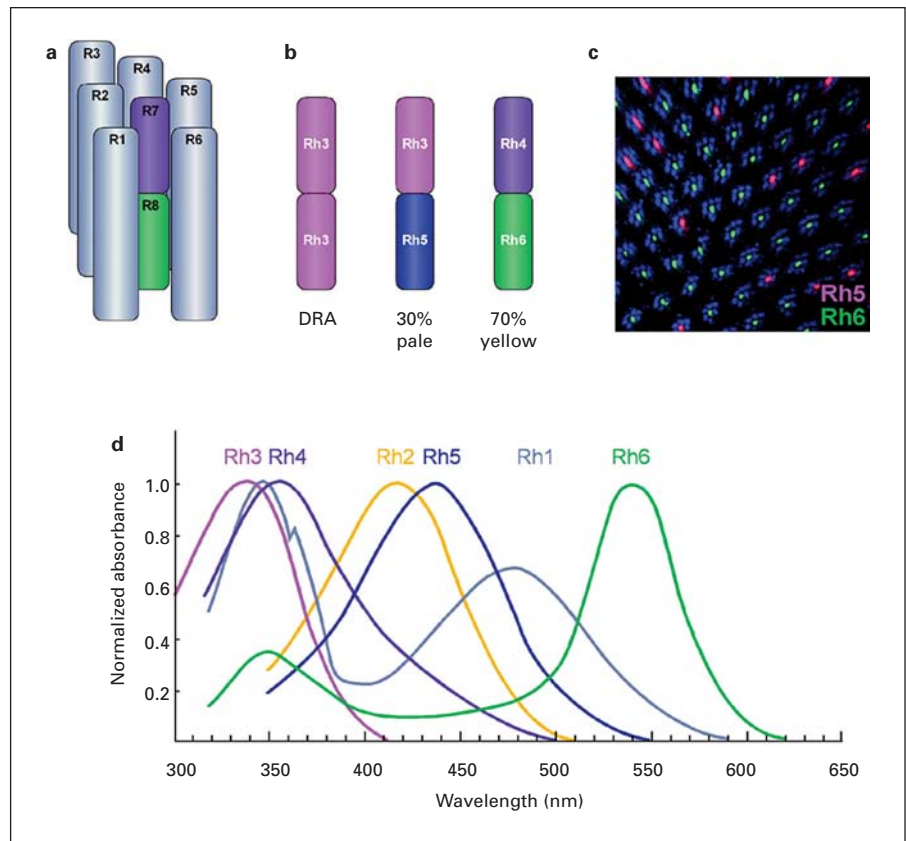


Fig. 1. Organization of the *Drosophila* eye. **a** Schematic representation of one of the ~800 ommatidia that compose the fly eye. Six outer PRs surround R7 and R8 cells located in the center on top of each other, sharing the same light path. **b** The *Drosophila* eye is composed of three different types of ommatidia. In the dorsal most ommatidia, the DRA, both R7 and R8 cells express *rh3* and are involved in measuring the angle of polarized light. The two other subtypes are randomly distributed in the eye. The pale subset comprises 30% of the retina. In this class, R7 cells express *rh3* and R8 cells express *rh5*. In the remaining 70%, the yellow subset, R7 cells express *rh4* while R8 cells express *rh6*. **c** Fluorescent confocal image of an antibody staining on a whole-mounted retina showing Rh5 in red, Rh6 in green and the outer PRs expressing Rh1 in blue. The

outer PRs express always *rh1*, while the inner R8 cells express either *rh5* or *rh6*, in a 30/70% ratio. The PRs always express only one Rh respecting the rule ‘one receptor per cell’. **d** The *Drosophila* genome contains six identified Rhs with absorption maxima ranging from UV to green. Rh1 is the broad absorption Rh most likely involved in motion detection. *rh2* is only expressed in the ocelli located on top of the head and not in the eyes. Rh involved in color vision have a more restricted absorption spectrum. Both R7 rhodopsins are UV sensitive, while the R8 opsins Rh5 and Rh6 are blue and green sensitive, respectively. The absorption maxima are 478 nm (Rh1), 420 nm (Rh2), 345 nm (Rh3), 375 nm (Rh4), 437 nm (Rh5) and 508 nm (Rh6) [9, 13].

photosensitive receptor molecule rhodopsin (Rh) and forms the light-gathering structure of the PR. The rhabdomeres of the 6 outer PRs R1–R6 form an asymmetric trapezoid whose center is occupied by the rhabdomeres of the inner PRs R7 (distal cell) that sits on top of R8 (proximal cell) [1]. Five *rhs* are expressed in the fly eye, each with distinct spectral sensitivities to light (fig. 1). The most abundant Rh in the adult eyes is the broad spectrum Rh1 [2]. Four other Rhs are found in the eye: Rh3 and Rh4 have similar sensitivities in the UV range while Rh5

and Rh6 are maximally sensitive in the visible range; Rh5 is blue-sensitive and Rh6 has its peak of sensitivity in the green (fig. 1) [3–9]. Each of these *rhs* is specifically expressed in particular subsets of PRs: *rh1* in the outer PRs R1–R6, *rh3* and *rh4* in R7 cells and *rh5* and *rh6* in R8 cells (fig. 1b). A sixth *rh*, the short-wavelength-sensitive Rh2 [10, 11] is expressed in the ocelli, a photoreceptive organ on the top of the fly’s head involved in maintaining balance during flight.

The outer and inner PRs represent two overlapping visual systems with different functions: the outer PRs, the equivalent of vertebrate rods, are involved in motion detection and project to the lamina part of the optic lobe; the inner PRs, the equivalent of the vertebrate cones, appear to be involved in color discrimination [1]. The organization of the inner PRs, with R7 in the distal half of the retina and R8 occupying the proximal half underneath, gives the fly the appropriate hardware to discriminate between colors (i.e. to compare the activity of two different pigments). Since the two rhabdomeres share the same visual axis, the different spectral sensitivities of R7 and R8 allow comparison of the wavelength of light [1]. The R7 and R8 axons bypass the lamina and project to two closely apposed layers of the medulla, with the R8 axons projecting just before the R7 terminations. Inputs from R7 and R8 cells are probably compared in this part of the optic lobe [12].

Although all the facets of the fly eye appear to be identical externally, there are clear physiological differences among ommatidia. The main part of the retina consists of a mosaic of two stochastically distributed types of ommatidia. Seventy percent, called the ‘yellow’ type (**y**), have an R7 cell with Rh4 and an R8 cell with Rh6 [3, 6]. The remaining 30% (the ‘pale’ type, **p**) have Rh3 in R7 and Rh5 in R8 (fig. 1). This distribution of Rhs presumably allows color discrimination over a broader range of wavelengths. Although the R7 Rhs (Rh3 and Rh4) are present in two non-overlapping subsets of R7, they have only slightly different absorption spectra in the UV range [13]. However, a blue filtering pigment in **yR7** sharpens the absorption of Rh4 and filters the light that reaches the green-sensitive underlying R8 [1] (fig. 1d). Thus, it is likely that the **p** ommatidia discriminate better over short wavelengths, while the **y** ommatidia discriminate colors extending to the green.

A very specialized region of the eye of many insects, including *Drosophila*, is the dorsal rim area (DRA). The DRA is a row of ommatidia located in the dorsal-most part of the eye. These ommatidia face the sky and detect the vector of polarization of sunlight reflected by the sky, which the fly uses for navigation [14]. Specification of this subclass of ommatidia in a restricted domain of the eye is controlled differently from the rest of the eye. Only in the DRA, R7 as well as R8 cells express the same *rhodopsin*, *rh3* [15] (fig. 1b).

The visual system of the *Drosophila* larva, although different in structure from the adult compound eye, utilizes some of the same Rh proteins. This simple larval visual system is composed of a pair of organs, Bolwig’s

organ (BO), present in the head of the larva. Each BO contains 12 PRs which express one of 2 *rhodopsins*, *rh5* or *rh6*, again in a non-overlapping pattern [Pichaud et al. unpubl. observation]. In flies, BO does not get transformed into the adult compound eye, but it probably persists through metamorphosis and gives rise to extra-retinal PRs known as the ‘Hofbauer-Buchner’ eyelet [16]. One major function of the BO and eyelet is to entrain the circadian clock [17].

How General Is the Rule ‘One Receptor Molecule per Receptor Cell’?

There is no PR that expresses more than one particular Rh gene in the fly. For instance, when R7 expresses stochastically *rh3*, *rh4* is always totally repressed. This is not unique to *Drosophila*, as most known visual systems respect the rule ‘one Rh per cell’. For example, the honeybee (*Apis mellifera*), like *Drosophila*, has compound eyes composed of ~6,000 ommatidia each containing 9 PRs [18]. Recordings from honeybee retinas suggest that there are three types of PRs with different maximal sensitivities [19]. When the bee opsins are expressed and analyzed in a heterologous system, they have absorption maxima that are in perfect agreement with the cellular recordings from the eye supporting the idea that only one opsin is expressed in each PR subtype [20].

The Japanese yellow butterfly *P. xuthus* is also a well-studied model system for color vision. The anatomical organization of the eye is similar to the honeybee eye, having 9 PRs per ommatidium. Intracellular recordings demonstrated the presence of five different receptor cells distributed in different subtypes of ommatidia [21]. Their distribution seems to be random as it is in *Drosophila*, but immunostainings and in situ experiments indicate that some PRs coexpress two opsins [22]. Furthermore, different non-opsin accessory pigments are also present along with Rh. Hence the spectral sensitivity of these PRs depends on both the particular opsin(s) they express, and the particular absorbance of the accessory pigment [23]. Thus, two PRs can express the same opsin, but paired with two different pigments, they will have different absorption maxima [22]. This strategy is not unique to butterflies or even to insects. For example, two cone populations in the chicken retina express the same Rh but contain differently colored oil droplets that change their spectral tuning [24]. Thus, the combination of a Rh and an accessory pigment will determine the spectral sensitivity of the PR. There is no clear biological explanation for

this coexpression, but one can speculate that the expression of more than one pigment tunes the cells to colors that cannot be perceived using a single visual pigment.

The human retina contains rods and cones, which are dedicated to distinct visual tasks. Rods express rod opsin and are involved in image formation under dim light conditions, while the three types of cones express one of the three ‘color’ opsins, blue-, green-, or red-sensitive opsins and are involved in color discrimination [25]. As in *Drosophila*, a single cone PR expresses only one opsin. Besides the rod PRs, the nocturnal mouse has two types of cones, with the UV cones being more abundant ventrally and the green cones being more abundant dorsally. However, these cones also coexpress UV- and green-sensitive opsins at different levels along this regional dorso-ventral gradient [26]. In rats, coexpression of cone opsins is only observed in the ‘transition zone’, while dorsal green cones and ventral UV cones only express one opsin [27]. The loss of exclusive expression, which is incompatible with color vision, is presumably due to the degeneration of the color visual system in these nocturnal animals. In some cases, coexpression of two visual pigments is a mid-step during development. For example, in the human retina, there is a short period of time when cone cells coexpress blue and green or red opsins [28]. While the blue cones initially populate most of the fovea, later on, their number decreases as the green/red cone population increases [28]. This spatio-temporal pattern of expression suggests that cones are first born as blue cones and then switch to either a green or red cone fate. A similar phenomenon has recently been reported for the salmon, which appears to switch its retina from UV to blue sensitivity when its habitat changes from surface to deeper water [29]. Therefore, PRs are usually sensitive to only one peak of wavelength, most often due to the expression of one type of photo pigment per cell. Although there are some exceptions to the rule, these might represent particular adaptations to the environment or a transient stage in development.

Receptor Exclusion in Other Sensory Systems

Odorant receptors (ORs), like Rhs, are G-protein-coupled seven trans-membrane receptors [30, 31]. The ORs generally respect the same rules as the Rhs, in that only one receptor gene is expressed per cell, although the system is much more complex, comprising hundreds of ORs [32]. In the fly, some ORs are expressed in the antenna (the fly’s nose), some in the maxillary palp and some of

them in both areas. No cells expressing more than one particular OR have been identified. However, most of the neurons express an additional receptor (OR83b) that has been postulated to function as a coreceptor [32, 33]. This might be a peculiarity of *Drosophila*. In mice, OR cells generally express only one given OR with a roughly random distribution within a particular zone of the olfactory epithelium [31]. This enables the olfactory system to respond to a vast amount of individual odors. As in the visual system, there are exceptions to the exclusion rule as some cells of the mouse olfactory epithelium express two different ORs [33]. This coexpression might broaden the sensitivity to different odorants, as might coexpression of opsins for colors in butterfly PRs. As it was shown for human opsin genes, recent findings indicate that during development, mice OR cells might coexpress more than one OR [34, 35].

The vomeronasal organ of mammals detects pheromone odorants important for social and sexual behavior. Two receptor families, V1Rs (30–100 receptors) and V2Rs (140 receptors), encode the vomeronasal receptors [36–38]. Although most of the time OR cells express only a single receptor, it has recently been reported that some vomeronasal sensory neurons express more than one of either V1R or V2R receptors. Using antibodies raised to several V2Rs, it was shown that V2Rs are broadly distributed and coexpressed in the same cells as other V2Rs [39]. However, these two subclasses of receptors are never coexpressed in the same cell, indicating that they presumably respond to different odorants.

An extreme exception to the one sensory receptor exclusion rule is the nematode *C. elegans*, where multiple olfactory and chemosensory receptors are expressed in the same receptor cell. Here, the identity of the sensory receptor neuron rather than the receptor repertoire of a single neuron determines the behavior of the animal, allowing it to be either attracted or repulsed by a particular odorant [40]. This was shown by elegant experiments where the diacetyl receptor (ODR-10) that is expressed in the cells that are responsible for attraction was misexpressed in a ‘repulsive’ neuron. The diacetyl receptor then mediated a repulsive response when exposed to diacetyl, indicating that the identity of the neuron is the determinant of the final response [40].

Recent studies have shown that taste receptor cells also detect a single taste modality (sweet, sour, salty, umami, bitter) [41–44]. Detailed expression studies of putative sweet, umami and bitter taste receptors have established that they are expressed in distinct, non-overlapping sets of taste receptor cells. Functional studies have shown that

sweet taste is mediated by a small family of 3 receptors, the T1Rs. The bitter receptors are encoded by the slightly larger family of T2Rs. As there is no coexpression of sweet, umami or bitter receptors in the same taste receptor cell, bitter receptor cells do not respond to sweet or umami stimuli and vice versa [41, 45].

Together, these data indicate that sensory systems share a common characteristic: each sensory cell is sensitive to a given stimulus by expressing only one functional sensory receptor molecule per cell. While in some sensory systems it is sufficient to express only one type of receptor molecule to respond to the environmental stimulus, others need to express a combination of receptors to be able to distinguish among the wide range of stimuli. The expression of a particular receptor or receptor 'set' requires a high degree of regulation. Therefore, efforts trying to understand the precise control of expression of a specific sensory receptor will have a profound impact toward better understanding sensory perception.

Repression of an *rh* Gene by Misexpression of Another

The visual system of *Drosophila* presents a number of advantages to study the mechanisms used by sensory systems to express one particular receptor per cell. In this genetic model system, only 5 Rhs are present in the eye and all have well-characterized promoters. The eye is also very accessible and its optics allows easy in vivo visualization of individual PRs [46]. Until recently, the molecular players responsible for the stochastic choice between γ - (Rh4/Rh6) and ρ -type (Rh3/Rh5) of ommatidia, and for the exclusion and the coordination of *rh* expression between R7 and R8 were not known. However, it was clear that the stochastic choice to become one type of ommatidium was made in R7 cells: in a *sevenless* mutant (which lacks R7 cells), *rh6* expands to nearly all R8 cells. In contrast, the distribution of R7 *rhodopsins* appears unaffected when R8 cells are missing [6, 47]. These results indicate, when an R7- ρ cell chooses to express *rh3*, a signal is sent to the underlying R8 to induce expression of *rh5*. R8 seems to play a passive role in this process and expresses *rh6* by default. Therefore, it has been proposed that Rh4/Rh6 is the default state while Rh3/Rh5 is the acquired state [6, 47].

Recent findings in PR cell specification have shed some light on the process of *rh* expression. The inner R7 and R8 cells are distinguished from the outer PRs (and thus are prevented from expressing *rh1*) by the *spalt* (*sal*)

genes [48]. After acquiring a generic inner default state, R7 and R8 further differentiate into functional R7 and R8 cells. This process appears to occur at least partly by preventing R8 characteristics from being acquired in R7 cells. This function is performed by the homeobox gene *prospero* (*pros*). *pros* is uniquely expressed in R7 cells, and directly represses the expression of R8 *rhodopsins*, *rh5* and *rh6* [49]. In loss-of-function *pros* eyes, the R8 *rhodopsins* are now expanded to subsets of R7 cells. In this genetic background, the immediate question that arises is whether the endogenous R7 *rhs* are coexpressed with R8 *rhs*, or whether the misexpression of R8 *rhs* corresponds to the exclusion of R7 *rhs* from these *pros*⁻ R7 cells: in fact, only few *pros*⁻ R7 cells maintain expression of R7 *rhodopsins*, and these cells never coexpress an R8 *rhodopsin*. R7 *rhodopsin* expression does not appear to be regulated by *Pros* directly, but instead, it seems that their expression is repressed by the presence of the R8 rhodopsin molecules themselves: removing *pros* together with the Rh6 protein (using a *rh6*^[1] mutant) leads to a derepression of *rh4* in *pros*⁻ *rh6*⁻ R7 and coexpression of Rh4 and an *rh6* promoter-lacZ reporter (fig. 2). As coexpression of two functional *rhs* is never observed, this suggests that the Rh proteins themselves play a critical role by somehow repressing each other to achieve the expression of only one sensory receptor per cell. As described below, a similar mechanism has recently been proposed for ORs in mice and suggests an evolutionarily conserved feedback mechanism for ensuring mutual exclusion.

Lessons from Vertebrates

Interesting findings regarding receptor exclusion have emerged from analyzing the genomic structure of the human color visual pigment genes. Trichromacy (blue/green/red) in humans and old-world monkeys seems to have evolved from dichromacy (blue/green) by duplication of the gene encoding the green visual pigments located on the X chromosome. Therefore, the duplicated genes are next to each other in a tandem configuration and have evolved to detect different red or green wavelengths of light. A single locus control region (LCR) lies upstream of both genes and controls the expression of only one of these two genes, presumably by looping and contacting only one of the two promoters (fig. 3c) [50, 51]. Once the LCR has chosen one given promoter, it maintains the mutual exclusive expression of one of the two visual pigments and the cone cell becomes specified as a green or a red cone. Because the cluster is located on the

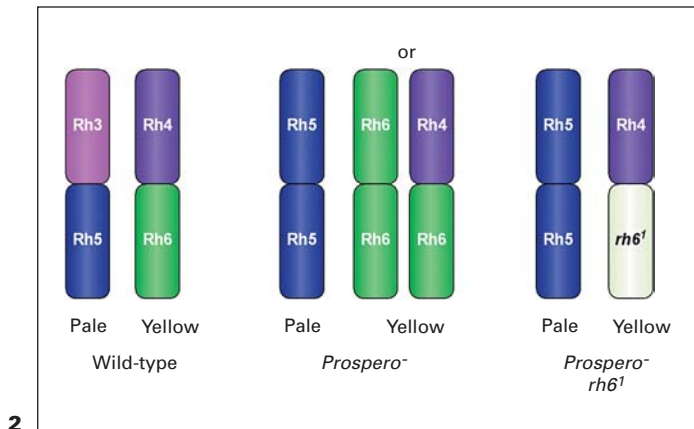
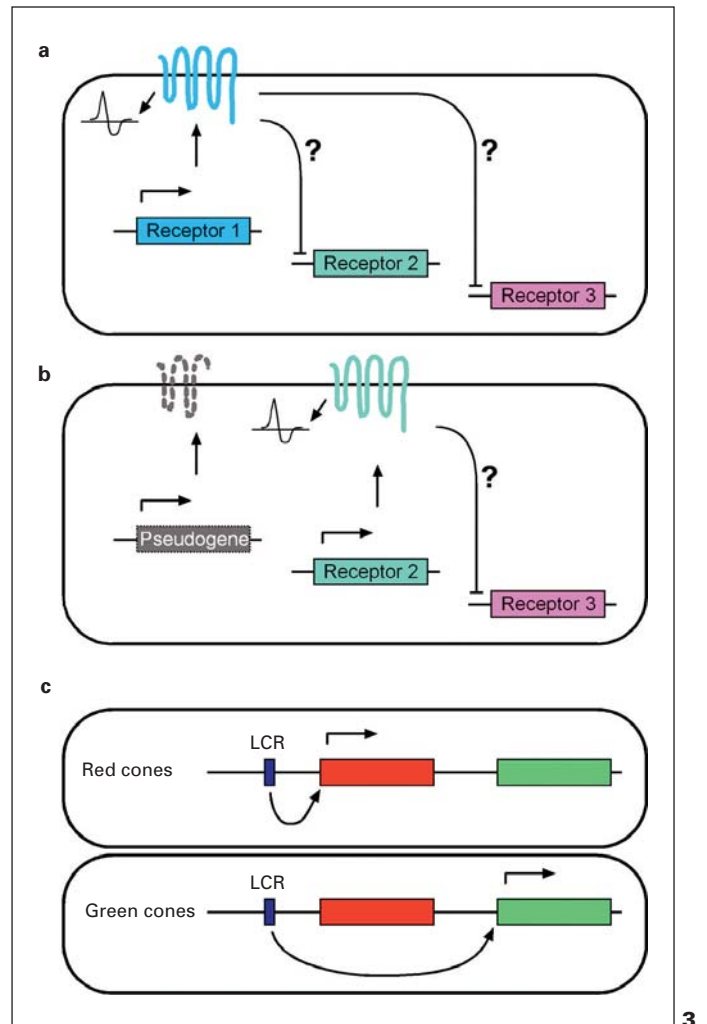


Fig. 2. Mutual exclusion of Rh. In a *prospero*⁻ mutant background, derepression of Rh5 in R7 cells prevents *rh3* expression. Similarly, Rh6 is derepressed in some yR7 and this derepression leads to the repression of *rh4*. In a *prospero*⁻, *rh6*¹¹ double-mutant background, where no functional Rh6 protein is produced, *rh4* is not repressed and is thus coexpressed with a *rh6-lacZ* transgene in yR7.

Fig. 3. Feedback regulation of receptor expression. **a** In a sensory cell, when receptor 1 is chosen for expression, the presence of the protein product is able to prevent the expression of the other two receptors in this cell. The repression is accomplished through an unknown mechanism initiated by the receptor protein, which is distinct from phototransduction or olfactory signal transduction. **b** When a pseudogene (or a reporter gene) is chosen for expression, which does not lead to the expression of a functional receptor protein, another locus (e.g. receptor 2) is recruited for expression. The presence of receptor protein 2 then prevents the further expression of other receptors. **c** An LCR lies upstream of human red and green opsin genes. In a red cone cell the LCR activates the red cone receptor presumably by looping out and contacting the promoter, while in a green cone cell the green receptor is activated.



X chromosome, only one allele is expressed in a given receptor cell.

Along with the aforementioned similarities between the visual and the olfactory systems, a similar LCR region has recently been described upstream of an array of four ORs in mice [52]. As described for the human cone opsins, this region might allow the activation of expression of only one of the genes in the array. Similar to the fly eye, there is also evidence that a functional odorant receptor is required to repress other OR in the array within a particular cell [49, 52, 53]. Together, these studies show that only genes coding for a functional OR are expressed with the ‘single receptor per cell’ rule: genes without a full-length open reading frame (pseudogenes or reporter-only constructs, which do not encode a receptor) are coexpressed with a second receptor, since, when a cell chooses to express this gene, the repression mechanism is not ac-

tivated and an additional gene is chosen, driving expression of a second gene in these cells [52, 53].

These experiments have led to the model in which a positive, stochastic choice is made at the level of the promoter to express a specific receptor. Once this choice has been made, the receptor itself seems to negatively feed back to prevent another choice (fig. 3). This allows sensory information to be decoded at the level of the sensory epithelium. Thus, activation of a sensory cell through its particular receptor leads to an output with a discrete meaning. Understanding how the receptor accomplishes this task is a question that remains to be answered. Many research groups using different sensory systems and model organisms are working not only to understand how a particular sensory receptor is expressed in one cell, but also how its exclusive expression is maintained. As evidences from the visual and olfactory systems indicate,

this mechanism may be more complex than simple transcriptional activation and repression, and appears to involve negative feedback from the proteins themselves. This kind of regulation is used by the immune system when selecting a functional immunoglobulin. In this case, once a functional receptor has been made and expressed at the surface of the cell, signals are sent to the cell via a negative-feedback pathway involving downstream signaling molecules [54].

The signaling cascade initiated by sensory receptors to ensure that a single functional receptor is expressed is distinct from the phototransduction or olfactory transduction pathways. Mutations in the phototransduction pathway do not affect *rh* gene expression in the fly eye [Mazzoni and Desplan, unpubl.]. Similarly, with loss-of-function experiments of critical olfactory signal transduction, components like the G protein G_{off} do not seem to have an effect on OR gene expression [55]. Characterizing

this pathway will answer one of the most fundamental questions in sensory neuron development. Ultimately, it will be important to learn more about how the information gathered at the periphery by the PR is processed and decoded by the brain. Therefore, the challenge for the future is not only to get some insights into the mechanism that coordinates sensory receptor expression and how this unique sensory receptor expression is maintained, but ultimately how these sensory receptor cells communicate the type of sensory input they detect to the brain.

Acknowledgments

The authors would like to thank Justin Blau, Tiffany Cook and Satoko Yamaguchi for helpful discussions and comments on the manuscript. This work was supported by NIH grants ROI-EY13012 to C.D.

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