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Sensory Systems: Seeing the World in a New Light

Most terminally differentiated sensory neurons express a single sensory receptor molecule. A *Drosophila* photoreceptor organ breaks this rule by switching to expressing a different type of Rhodopsin as it metamorphoses from larva to adult.

Kerstin Hofmeyer and Jessica E. Treisman

In order to recognize specific stimuli, sensory cells must contain specific receptors. Maximum specificity is achieved when each cell expresses only a single receptor, a rule that has been shown to hold true for a variety of sensory systems in both vertebrates and invertebrates [1,2]. For example, in the mouse olfactory system each individual olfactory neuron expresses only one of approximately 1500 odorant receptor genes [1]. Similarly, the majority of photoreceptor neurons in the *Drosophila melanogaster* retina express only one of five different types of Rhodopsin [2].

Deviations from this rule may occur in organisms with a small number of sensory cells. For instance, individual chemosensory neurons in *Caenorhabditis elegans* express a large number of independently functional receptors [3]. The activation of each of these receptors by distinct stimuli thus elicits the same behavioral response, allowing broad sensitivity but low discriminatory power. Some butterfly photoreceptors similarly broaden their absorption spectra by expressing more than one opsin [4]. Alternatively, receptor coexpression can simply reflect the requirement for two receptors to function together to detect a single stimulus. In the olfactory system of several insect species, each stimulus-specific odorant receptor pairs up with a ubiquitous co-receptor that may influence receptor trafficking or sensitivity [5]. These and other previously reported exceptions to the 'one neuron — one receptor' rule involve the concurrent coexpression of multiple receptors in a single cell. A recent paper by Sprecher and Desplan [6] describes a different kind of exception to the rule. These authors show serial expression of two distinct Rhodopsin receptors in a single photoreceptor neuron at consecutive stages of the life cycle.

In addition to a complex eye responsible for image analysis, many organisms possess extra-ocular photosensory organs that coordinate behavior in response to light. One such organ in *Drosophila* is the Hofbauer-Buchner eyelet, a group of four photoreceptors located between the retina and the optic lobes. These photoreceptors express the green-sensitive Rhodopsin 6 (Rh6) and contribute to circadian clock entrainment in the adult [7]. The eyelet arises during metamorphosis by transformation of the larval Bolwig's organ, a cluster of 12 photoreceptors which mediates light avoidance behavior as well as clock entrainment [7,8]. Bolwig's organ develops in the embryo from four primary founder neurons, which recruit eight secondary photoreceptors by producing a ligand for the epidermal growth factor receptor [9]. At larval stages, the primary cells express the blue-sensitive Rhodopsin 5 (Rh5) under the control of the transcription factors Spalt (Sal) and Orthodenticle (Otd), while secondary photoreceptors express Rh6 driven by the nuclear receptor Seven-up (Svp) [10].

Persistent Rh6 expression in the adult eyelet led to the assumption that it was derived from the Rh6-positive population of secondary larval photoreceptors. Sprecher and Desplan [6], however, now demonstrate that the Rh6-positive photoreceptors of the adult eyelet instead derive from the Rh5-expressing larval photoreceptors, which switch expression of Rhodopsin subtypes during metamorphosis [6]. Previously, tracking the two subpopulations of larval photoreceptors was complicated by the loss of expression of most photoreceptor markers during early pupal stages [7]. Sprecher and Desplan [6] solved this problem by using two different approaches to permanently label the Rh5-expressing larval photoreceptors. They used the *rh5* promoter to drive either excision of a stop cassette separating a ubiquitous promoter from a reporter, or expression of a fluorescently tagged histone that becomes stably incorporated into chromatin. These techniques allowed them to show that the four primary photoreceptors survive metamorphosis, repress *rh5* and activate *rh6* expression. These cells continue to express Sal, suggesting that they have specifically altered their *rhodopsin* expression rather than changing their fate. In contrast, the secondary larval photoreceptors do not persist until the adult stage (Figure 1). Consistent with this interpretation, the adult eyelet was absent when pro-apoptotic genes were expressed exclusively in larval Rh5-positive neurons, and contained additional Rh6-positive neurons when larval Rh6-expressing cells were protected from apoptosis by expression of p35 [6]. Interestingly, the cell-autonomous effects of these manipulations suggest that the two cell populations develop independently through metamorphosis.

What signals could trigger this switch in sensory specificity? Its timing, which

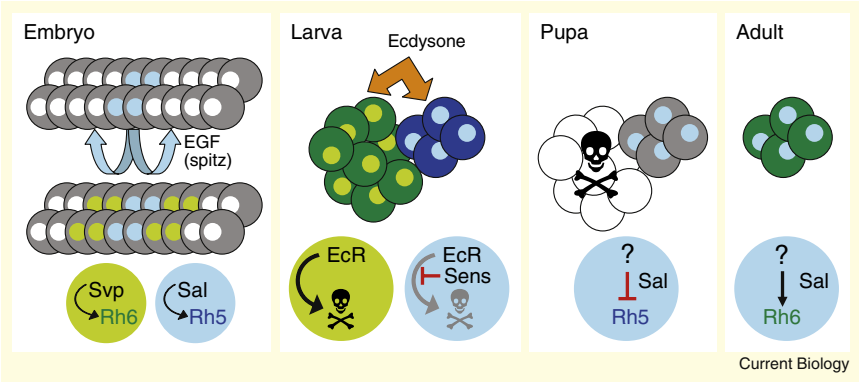

Figure 1. A switch in Rhodopsin expression in *Drosophila* photoreceptors.

In the embryo, primary precursors expressing Sal (light blue nucleus) signal through the EGFR to recruit secondary precursors expressing Svp (light green nucleus). These two transcription factors activate larval expression of *rh5* (dark blue cytoplasm) and *rh6* (dark green cytoplasm), respectively. In late larval development, ecdysone signaling leads to death of the Rh6-expressing cells at the pupal stage, while Rh5-expressing cells are protected by the activity of Sens. Unknown transcription factors downstream of ecdysone lead to *rh5* repression and *rh6* activation in these photoreceptor cells.

coincides with metamorphosis, made the hormone ecdysone a likely candidate. Sprecher and Desplan [6] used both dominant negative and RNAi approaches in combination with *rh5* or *rh6* promoters to remove the function of the nuclear ecdysone receptor (EcR) in either subtype. They found that, in the absence of EcR function, the eyelet photoreceptors maintained their larval characteristics: The Rh6-expressing cells survived, and the Rh5-expressing cells continued to express exclusively Rh5 [6]. However, EcR is unlikely to act directly on *rh5* or *rh6* expression, as neither promoter contains a consensus EcR binding site, and EcR signals to these cells only early in pupal development and is not required at later stages to maintain Rh6 expression [6]. Interestingly, the adult eyelet neither acquires expression of the positive *rh6* regulator Svp, nor does it lose expression of the negative *rh6* regulator Otd, which has been shown to act directly on the *rh6* promoter [11]. Otd-mediated *rh6* repression must, therefore, be somehow alleviated in the adult eyelet.

One critical factor present in larval Rh5-positive photoreceptors is the zinc-finger transcription factor Senseless (Sens). Ectopic expression of Sens in the Rh6-expressing photoreceptor cells allowed them to survive metamorphosis, suggesting that Sens normally protects the Rh5-expressing cells from ecdysone-induced apoptosis [6]. However, the authors did not provide loss-of-function data assaying the role of Sens in the Rhodopsin switch. Sens would be a good candidate for this activity because its function can be modulated from repression to activation by interactions with other transcription factors [12]; in fact, it is capable of activating the *rh6* promoter *in vitro* in combination with Otd [13] and can turn on *rh6* when misexpressed in outer photoreceptors in the adult eye [14]. However, both Sens and Otd are present prior to ecdysone signaling, suggesting that an additional ecdysone-induced factor must contribute to *rh6* activation and *rh5* repression. The zinc-finger transcription factor Krüppel-homolog 1 (Kr-h1), which acts downstream of EcR in mushroom body neurons [15], or the Broad complex of zinc finger transcription factors, which mediate EcR-induced dendritic remodeling of motor neurons [16], might be interesting possibilities to investigate. It is surprising that despite their relatively small regulatory regions [11], *rh5* and *rh6* appear to be regulated by three different mechanisms, involving Svp, Sal and Otd in the larval photoreceptor organ [10], Sal, Otd and signaling from R7 to R8 photoreceptors through the transducers Warts and Melted in the adult eye [14,17], and a novel set of unidentified factors in the eyelet [6].

A better understanding of the functional relevance of this switch in spectral sensitivity will require behavioral analysis of animals that fail to switch their Rhodopsin type. It is possible that the ancestral Bolwig's organ consisted of only the primary Rh5-expressing photoreceptors, and that the switch predates the evolutionary addition of secondary photoreceptors. Enabling the adult eyelet to detect light of longer wavelengths by altering the specificity of the primary cells during pupal development may have been an adaptation to its more sheltered position below the retina. Salmonoid fish, for instance, undergo a similar adaptive switch of cone opsin type as they age from planktivores dwelling in ultraviolet light-rich surface waters to fish-eating predators in deeper waters, where visibility is restricted to blue–green light [18]. Serial expression of multiple receptors is likely to be restricted to neurons that persist through several developmental stages and must adjust to changing sensory requirements.

In addition to switching *rhodopsin* expression, the larval photoreceptors alter their pattern of connectivity to clock neurons as they transform into the eyelet [6]. Similar changes occur in other parts of the nervous system during insect metamorphosis: Many larval neurons die, while others extensively remodel their dendrites and synaptic connections or alter their neurotransmitter expression or electrophysiological properties [19,20]. Replacement of a sensory receptor may be an extreme example of the developmental plasticity that allows cells to be used for novel purposes at different stages of the life cycle. Perhaps further investigation of amphibian metamorphosis, developmental changes in habitat or hormonally induced maturation processes will yield examples of similar changes in neuronal properties during vertebrate development.

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Cytokinesis: A New Lipid Aboard the Raft

Several components of membrane rafts play a critical role in cytokinesis. A recent paper reports a new lipid component of these rafts required for proper cell division.

Lea M. Alford and David R. Burgess

Over the last twenty years, the view that membrane lipids are mere passive players in cellular processes such as cytokinesis has been challenged as researchers have recognized that certain specific lipids cluster within biological membranes forming domains that have been dubbed 'rafts' [1]. The characterization and functional analyses of such rafts has become a priority in membrane biology; they have been implicated in a number of processes in eukaryotic cells, including cell division. A recent *Current Biology* paper by Szafer-Glusman *et al.* [2] reports evidence that a distinct lipid type, very-long-chain fatty acids, play an essential role, not only in furrow ingression and cytokinesis, but also in proper formation of the central spindle.

In the late 1980s, Simons and colleagues [3] demonstrated the functional importance of lipid microdomains for protein sorting within polarized epithelial cells; since then, several biologically relevant functions of rafts have been identified. For example, membrane rafts play a role in T cell activation by recruiting signaling proteins and cytoskeletal components to the synapse [4]. Byfield *et al.* [5] showed, by cholesterol depletion, that membrane rafts are required to stabilized the interaction between the membrane and F-actin in aortic endothelial cells. Similarly, in fission yeast, maintenance of the actomyosin ring that mediates cell division, and its attachment to the membrane, have been found to be dependent on sterol-rich membrane domains [6,7]. Interaction between the cytoskeleton and plasma-membrane lipids has been demonstrated in many cell types, suggesting that such interactions are generally important and evolutionarily conserved.

In addition to these biological processes, several components of lipid microdomains, such as phosphatidylinositol (4,5) bisphosphate (PIP_2), phospholipase Cγ (PLCγ), sphingolipids and Src kinase family members, have not only been found at the cleavage furrow, but also shown to play functional roles in cell division [8–12]. In cells where PIP_2 is indispensable for cleavage furrow stability and cytokinesis [10], it has been shown to act at the furrow in adhesion of the contractile ring to the plasma membrane [12].

Lipid signaling proteins also appear to be locally regulated in the furrow membrane. The lipid phosphatase PTEN and PI 3-kinase regulate the spatial distribution of phosphatidylinositol (3,4,5) tri-phosphate (PIP_3), which in turn regulates cytokinesis [13]. The p85 regulatory subunit of PI 3-kinase controls localization of the GTPase Cdc42 to the cleavage furrow, where its activity is necessary for actin remodeling during cytokinesis [14]. The involvement of membrane lipids in cell division is also demonstrated by the effects of disrupting phosphatidylethanolamine, PIP5 kinase or PIP_2 at the cell surface [15]: in each case, cytokinesis is compromised because the component has an essential role in the dynamic structure of the contractile ring and membrane remodeling. Thus, the interaction of specific membrane lipid domains, or rafts, in the furrow with the cytoskeleton has been shown to be crucial for the completion of cell division.

Following these observations, Szafer-Glusman *et al.* [2] used a genetic approach to disrupt elongation of very-long-chain fatty acids in *Drosophila*