Unscrambling Color Vision

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Color vision begins when light is absorbed by one of three different visual pigments, located in cone photoreceptor cells of the retinas of humans and some species of monkey. The pigments absorb light at short, middle, or long wavelengths, and the cone photoreceptors containing them are commonly termed blue, green, or red cones. For transmission to the brain, the outputs of the three types of cones are almost immediately recombined to yield signals distributed along two chromatic axes, one describing a range of wavelengths from green to red and the other a range of wavelengths from blue to yellow (yellow is defined as a mixture of green and red). These retinal computations are embodied in the responses of the retinal ganglion cells, neurons with axons that form the optic nerve. A ganglion cell might be excited by stimulation of the red cones and inhibited by stimulation of the green. Such a cell tells the brain how far along the red-green axis the stimulus fell, with high firing rates representing a stimulus containing a lot of red light and low representing a stimulus containing a lot of green light.

In the traditional view, a complicating feature is superimposed on the color-coded responses of the retinal ganglion cells (*1*). For the ganglion cell described above, the region of retina over which red light excites the cell (the cell's receptive field center) is usually smaller than the area over which green light inhibits the cell (the surround). The cell thus ends up with both red-green antagonism and center-surround antagonism, as shown in the left half of the figure. However, there is some evidence (*2*) in favor of an alternative view, in which the surrounds are not chromatically pure—they instead sum the outputs of two or more types of cone (right half of the figure). In this issue of *Science*, Dacey *et al.* (*3*) report experiments that support this alternative view.

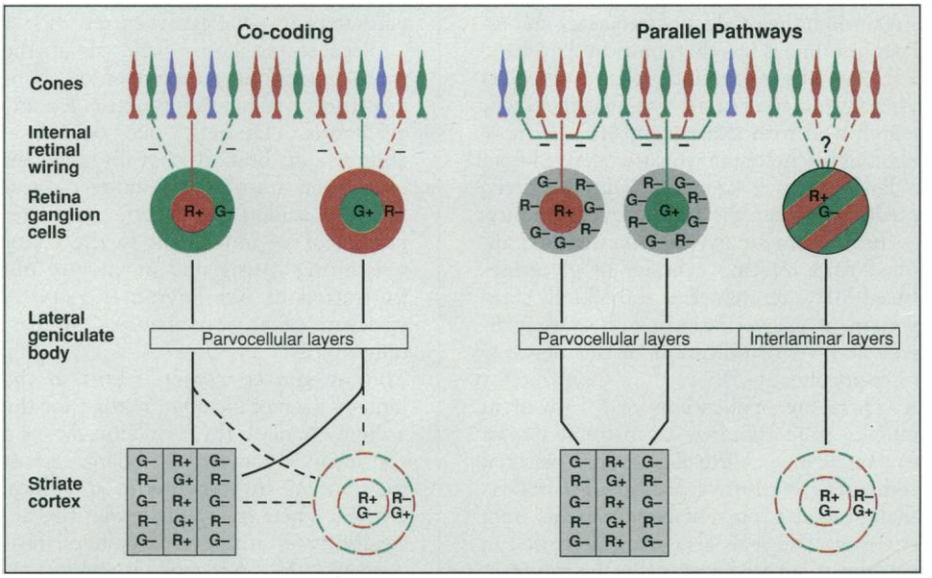
A site where chromatic opponency could be created is the feedback synapse onto cones made by retinal neurons called horizontal cells. If horizontal cells received inputs selectively from a single class of cone, it is easy to imagine how they could create chromatic opponency. And because they have a wide lateral spread, they would create a chromatically pure antagonistic surround at the same time. A few years ago, however, Boycott, Wässle, and colleagues reported that horizontal cells appear to be connected indiscriminately to cones (*4*). Separate physiological studies by Dacheux and Raviola showed that one type of horizontal cell responds to a broad range of wavelengths (*5*). Dacey *et al.* (*3*) have now confirmed these findings using elegant and powerful methods that allow examination of physiological responses and cone connectivity in the same cells.

Dacey and co-workers recorded from horizontal cells in monkey retinas with in vitro fluorescence methods that greatly increase the frequency of successful recordings (*6*, *7*). After each recording was completed, they injected a marker compound that filled the horizontal cell and made visible its contacts with cones. They found that no horizontal cell receives a chromatically pure input. For reasons that are not clear, two subtypes of horizontal cell exist. They are biased in their contacts, one contacting only red and green cones and the other contacting blue cones strongly and the other two weakly. Nevertheless, the main point is that horizontal cells cannot create chromatically pure opponency in the retina's output.

If horizontal cells cannot create chromatic surrounds, where might chromatic surrounds come from? A possibility was that they are created by amacrine cells, the second class of widely spreading neurons in the retina. However, Calkins and Sterling have recently used electron microscopic reconstruction to show that amacrine cells in the primate fovea receive indiscriminate input from all three types of cones (*8*). In sum, apparently definitive anatomical studies provide no evidence for the existence of chromatically pure surrounds.

To see why this issue is important, one needs to think about how the information is used after it leaves the retina. The axons of the retinal ganglion cells synapse upon neurons in the lateral geniculate body, which in turn project to the striate cortex. In the cortex, new types of codings are created. Most striate cortical neurons respond best to oriented stimuli. These neurons are not very color selective. Patches within the striate cortex (called for historical reasons "blobs") contain cells with sophisticated responses to color. Their responses are more than simple replicas of the inputs from the lateral geniculate body. Some of them may have a "double opponent" organization, in which the receptive field's center might be excited by red and inhibited by green and the surround the reverse. Although much remains to be learned about the behavior of these cortical cells, they are likely concerned primarily with transmitting information about color.

There is no doubt that most inputs from the lateral geniculate body to the striate cortex are chromatically selective, at least at the centers of the input cells' receptive fields. If the orientation-selective cortical



Two alternative models for color coding in the visual system. Chromatically pure responses (those that can carry a pure color signal) are indicated in red or green. Responses driven by more than one type of cone are denoted in gray. Pathways known to be of major importance are shown by solid lines. Those that are less certain, or whose importance for color are unknown, are shown by dashed lines. To clarify the issue, the figure shows the pure form of each alternative, but intermediate cases are possible; for example, the outputs of the red and green cones could be transmitted to the brain by co-coding and those of the blue cones (which are phylogenetically older) by a parallel pathway.

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cells are not color selective, color-coded information is thrown away—because all colors are scrambled together when many lateral geniculate cells converge to create an oriented cortical receptive field. Given the usual economy of sensory coding, the idea of throwing away information is horrifying. That conclusion may be avoided by postulating that the color coding inherent in the retinal output is tapped separately to build color-coded responses in the blob regions. This is the possibility shown, in its extreme form, in the left half of the figure. It is labeled co-coding, because a single ganglion cell carries information both about spatial contrast (by means of the center-surround organization) and about color.

An alternative is to postulate that most retinal ganglion cells are not designed to transmit color information at all (*9*, *10*). In this view, again stated here in extreme form, the fact that most retinal ganglion cells carry color information is a byproduct of evolution's relentless search for high visual acuity. In the primate fovea, ganglion cell acuity reaches the maximum possible: Because one ganglion cell is connected to one cone, acuity is limited only by the size and packing density of the cones. Along the way, the centers of ganglion cell receptive fields incidentally acquire color tuning (because a single cone contains only one pigment). However, that information is not used at the cortical level. Instead, a separate channel uses an independent subtype of retinal ganglion cell to code for color. These project, by means of a specialized region of the lateral geniculate body, to the cortical blob regions (*11*).

A ready candidate for the second pathway exists. The ganglion cells discussed above are the garden variety, making up about 80% of all retinal ganglion cells. Among the remaining 20%, a unique anatomical type coding for blue-yellow opponency has recently been conclusively described (*12*). These cells have nonconcentric receptive fields. They are infrequent and have larger fields than the other retinal ganglion cells. Their responses are chromatically opponent—the receptive field consists of a single region in which the cell is excited by blue light and inhibited by yellow. They seem likely to code color. Among other things, acuity for stimuli that are defined only by their color is low, as would necessarily be true if color is coded by a sparse population of cells.

However, the parallel processing model has its own problems. A red-green analog of the specialized blue-yellow ganglion cell has not yet been found. Furthermore, the anatomical evidence denying chromatically pure surrounds is contradicted by some physiologists (*1*, *13*). If the retina takes the trouble to give retinal ganglion cells chromatically pure surrounds (by some unknown mechanism), it seems unlikely that the information would later be discarded. Disagreements also exist about the types of color coding exhibited by cortical neurons (*9*, *14*).

An encouraging thing about Dacey and co-worker's experiment is that their approach can be applied to most retinal neurons. Once a candidate retinal ganglion cell is identified one can relatively easily accumulate a large sample of cells—and each yields both its physiology and its microanatomy. Together with the results of electron microscopic reconstruction, these studies are giving a completeness and precision to our understanding of the retina's color circuitry never before imaginable. And when the color mechanisms of the retina are sorted out, the central mechanisms may also begin to fall into place.

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Lysosomal Degradation of Ubiquitin-Tagged Receptors

Cytosolic proteins destined for degradation by the proteasome are tagged by the addition of the polypeptide ubiquitin (*1*). Proteins located in the plasma membrane can also be ubiquitinated, but because the proteasome has no access to these proteins it has not been clear whether this ubiquitin tag also signals proteasome degradation. A recent paper by Hicke and Riezman in *Cell* (*2*) now indicates that such ubiquitinated membrane proteins are in fact marked for proteolysis—but in vacuoles, the yeast equivalent of the lysosome, not by the proteasome.

There was some indication that one membrane protein, cystic fibrosis transmembrane conductance regulator (CFTR), might be targeted by its ubiquitination for proteasomal degradation, although how this protein might gain access to the cytosolic degradation machinery was unclear. The cell performs quality control of its secretory and membrane proteins before they leave the endoplasmic reticulum and degrades any that are misfolded or incorrectly assembled. During this process, CFTR is polyubiquitinated and degraded by a proteolytic activity similar to that of the proteasome (*3*).

In their new work, Hicke and Riezman (*2*) have now clarified how a protein that cannot be accessed by the proteasome can nevertheless be degraded as a result of its ubiquitination. Ligand-induced ubiquitination of a receptor—one of the yeast mating pheromone receptors—leads to receptor-ligand complex internalization followed by vacuolar degradation. Ligand binding stimulates α-factor receptor (α-FR) internalization and also stimulates ubiquitination of the α-FR cytoplasmic tail. Mutant yeast cells that lack ubiquitin-conjugating enzymes cannot internalize and degrade the receptor in response to added mating pheromone. Cells expressing a mutant receptor that lacks the ubiquitination site bind pheromone but do not ubiquitinate, internalize, or degrade the receptor-ligand complex efficiently. In cells with protease-deficient vacuoles, ubiquitinated α-FR accumulates in the vacuoles but cannot be efficiently degraded, even though the cells contain functional proteasomes. Conversely, cells with defective proteasomes but intact vacuolar protease activity can degrade the ligand-bound, ubiquitinated, and internalized receptor.

Ubiquitination must now be considered a more universal signal for protein degradation: It can trigger either cytosolic degradation by the proteasome or membrane trafficking to the vacuole, where the degradation of protein also occurs.

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