The uncommon retina of the common house mouse

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Unlike most mammals, most cones in house mouse retina express two opsins, one sensitive to UV-light, and another sensitive to middle-wavelengths. Is the mouse unique, having a single cone type that normally expresses two opsins? Or is the mouse a typical mammal having two cone types, but a species wide mutation results in co-expression of two opsins?

Mus musculus, which includes the common house mouse and laboratory mice, has proven surprising in the organization of its retinal cone photoreceptors and in the expression of its visual pigment genes[1,2]. Members of the *Mus* genus appear to be unique in a variety of ways that challenge dogma. Most mammals are dichromats, basing color vision on outputs from two cone types – one sensitive to short-wavelengths or UV light (S–UV cones), and one sensitive to middle-to-long wavelengths (M–L cones)[3]. Typically, the two cone types are intermixed throughout most of the retina, and M–L cones greatly outnumber S–UV cones, for example, humans have 14:1 M–L:S cones[4], and many other species have (relatively) even fewer S cones[2]. To confer dichromatic color vision, the two cone types must have different spectral sensitivities and the neural circuitry to compare their outputs.

The common house mouse has two cone photopigment types, UV and M (Ref. 5), but the organization of cones and the pattern of photopigment expression is atypical for mammals[1]. The first glimpse of the unusual retinal organization came from immunocytochemical analysis of the mouse retina using the Szel antibodies, which recognize cytoplasmically located C-terminal epitopes in each cone opsin[2]. Cones in the ventral half of the retina labeled only with the antibody against UV opsin; cones in the dorsal half labeled with the UV antibody or the M–L antibody. Near the middle of the retina there was a transition zone where some individual cones expressed both UV and M cone opsins. Overall, UV cones were reported to predominate over M–L cones: exactly the reverse of the typical mammal.

Recently, Applebury and co-workers re-visited the mouse retina[1]. Using *in situ* hybridization with probes to known mouse opsin cDNA sequences, and immunocytochemistry with antibodies to extracellular N-terminal peptides of the mouse opsins, they made several new findings. Perhaps the most remarkable was the widespread co-expression of UV and M cone opsins. Co-expression was not limited to a transition zone between dorsal and ventral retina, instead the vast majority of cones co-expressed UV and M opsins. In far dorsal retina, only M opsin was detected in some cones; in middle and ventral retina, only UV opsin was detected in some cones. Two gradients were observed. The frequency of cones expressing UV pigment decreased in a ventral-to-dorsal gradient, and the amount of M opsin protein and mRNA per cell appeared to decrease in a dorsal-to-ventral gradient. These results agree with the electroretinography results of Lyubarsky *et al.*, who reported that in laboratory mice, the cone response to UV light was suppressed by chromatic adaptation to a long-wavelength stimulus[6], a result that is consistent with widespread co-expression of UV and M opsin.

How common is the retinal organization of cone photoreceptors in the common house mouse and does this organization have functional consequences? If all cones uniformly co-expressed UV and M opsin, they would not support color vision. Similarly, less complete mixing of the opsins among the cones would be expected to degrade color vision. However, color vision testing on wild-type mice has not been carried out[7]. Color vision circuits that involve S (or UV) cones are believed to be evolutionarily ancient[8], presumably pre-dating the emergence of mammals. Thus, unless the circuits were specifically lost in a particular line, they should be ubiquitously available to all mammalian orders, including mice, if they have the appropriate photoreceptors to exploit them.

Earlier studies using the Szel antibodies suggested that rabbit and guinea pig also distribute spectral types of cones differently in ventral versus dorsal retina, but much less dramatically than the mouse[2]. Rabbits and guinea pigs differ from mouse in that they have S, not UV, cones[3]. In guinea pig, the retinal region with a high concentration of S cones was not devoid of M cones, as it appeared to be in mouse. Given that there are some similarities in cone photoreceptor distribution between mouse, guinea pig and rabbit, it is reasonable to suggest that very sensitive antibodies, such as those used by Applebury *et al.*[1], would be required to determine whether these species also co-express S and M–L opsins in the majority of cone photoreceptors. The answer to this would shed light on the potential functional consequences of widespread co-expression. That is, if these species exhibit widespread co-expression, this would suggest that some degree of co-expression is not incompatible with color vision. However, the evidence suggests that expression of UV opsin is out of control in the house mouse[1,6]. Mouse is unique in that the electrical response generated in retina, as indexed by the electroretinogram, is dominated by a contribution of the UV pigment[5]. In rabbits and guinea pigs, the S pigments make a minor contribution to the gross electrical potential, similar to what is seen in all other mammals that have been tested[9]. Both guinea pigs and rabbits have dichromatic color vision[3]. As mice have UV cones, and guinea pigs and rabbits have S cones, perhaps some of the differences could be related to the presence of UV versus S cones. However, evidence from other murid rodents indicates that this is not the case.

Three other species of murid rodents have UV cones: Mongolian gerbil (*Meriones unguiculatus*)[10], rat (*Rattus novegicus*)[11] and Siberian hamster (*Phodopus sungoris*)[12]. Color vision studies have not been made with hamsters, and studies in rats were not designed to detect color vision mediated by UV-sensitive cones. Gerbils have dichromatic color vision, although apparently not robust. Antibodies against

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the C termini of human S and M–L opsins were used to examine cone distribution in hamster retinas[12], and the Szel antibodies were used in rat[13] and gerbil[14] retinas. In all three species, the cone types were not spatially segregated. Co-expression studies were not performed on hamster. In rats and gerbils, co-expression of UV and M–L opsin was not observed in adult animals, but was observed transiently during development[2]. Thus, the differences in the distribution of the mouse pigment are apparently not related to it being UV sensitive.

What is the mechanism that underlies the widespread co-expression of UV and M–L opsins in the mouse retina? Applebury *et al.*[1] suggest that mouse simply has one cone type that expresses two different photopigments. Cones in dorsal retina that appear only to express M opsin are suggested to have a mechanism to suppress UV opsin expression. Cells in middle and ventral retina that expressed only UV opsin were questioned as being real, requiring additional studies to confirm. If the mouse truly has one cone type that expresses multiple pigments, then it is surprisingly unique. Although co-expression has been observed in a wide variety of species, including humans[15], it is either limited to developmental stages with little or no co-expression in adults (rats, gerbils, humans), or it is associated with lifestyle changes that accompany metamorphosis or migration (amphibians, reptiles and fish). Observations made in rat provide the foundation for an alternative to the one-cone-type hypothesis. In addition to transient co-expression of UV and M opsin during development, there was a dramatic reduction in S cones in immature compared with mature retina, but there was not a corresponding change in the overall number of cones[2]. This gave rise to the hypothesis that by default, all rat cones initially express UV opsin, and in response to a later developmental switch, most cones stop expressing UV opsin and begin to express M–L opsin. In the adult, there remains a small population of 'true' UV cones that were not programmed to turn on M–L. This is consistent with the observations that S–UV opsin is expressed at earlier developmental time-points than M–L opsin. If a similar mechanism were at work in the mouse, the widespread co-expression of UV and M opsins could be explained by a genetic defect in the switch-off mechanism for UV pigment expression. In this scenario, all mouse cones initially express UV opsin. In response to a later developmental signal, those that would correspond to M–L cones in other species turn on M opsin expression, but fail to turn off UV opsin. This is consistent with results from electrophysiology experiments, which provide evidence that not every cone cell that expresses UV opsin also expresses M opsin[16]. The only observation left unexplained is the presence of a few cells in far dorsal retina that appeared to express only M opsin. However these cells were not examined with the same scrutiny as cones in other retinal locations, and the absence of S opsin in these cells needs to be verified[1].

The fact that co-expression is a genus-wide trait suggests that there might be selective advantage to co-expression – but what it might be escapes us. It presumably would be an impediment to color vision, and ultraviolet light is scattered more than longer wavelengths, which makes it a poor substrate for acute spatial vision. An alternative is that the *Mus* genus went through an evolutionary bottleneck in which the genus was reduced to a very small number of founder animals, all or most of who carried the deleterious mutation in the UV turn-off mechanism. There is precedent for such a species-wide genetic visual defect. For example, several mammalian species, including owl monkey and bush baby, have been found to have monochromatic color vision, and to lack S or UV cones[17]. Similarly, it is hard to think of an advantage conferred by the loss of short wavelength-sensitive cones. In all cases that have been examined genetically, genomic copies of the S or UV pigment genes are present, but they are homozygous for mutations that render the genes or the encoded proteins nonfunctional.

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