Evolution of eyes

Russell D Fernald

Seeing is important for most species and it has been a key selective advantage throughout evolution. Consequently, there is a remarkable diversity among types of eyes. Animals have converged on eight optical solutions for collecting and focusing light; in contrast, all eyes share the same molecular strategy for absorbing photons. Recent studies have identified similarities in the genetic information that is used in the development of eyes, leading to the hypothesis that distinctly different eye types might have had a monophyletic origin. Across many species, there is a remarkable continuity of the developmental genes that participate in the construction of similar – but not necessarily homologous – eyes.

Addresses
Program in Neuroscience, Stanford University, Stanford, CA 94305-2130, USA; e-mail: russ@psych.stanford.edu

Current Opinion in Neurobiology 2000, **10**:444–450

0959-4388/00/$ – see front matter

Introduction

Light has probably been the most profound selective force to act during biological evolution. The 10^{15} sunrises and sunsets that have taken place since life began have led to the evolution of eyes which use light for vision and for other purposes including navigation and timing. Although eyes occur in a variety of shapes, sizes, optical designs and locations on the body, they all provide similar information about wavelength and intensity to their owners. How did this happen?

Logically, eyes might be either monophyletic, having evolved from a single progenitor, or polyphyletic, having arisen more than once during evolution. In their seminal paper of 1977, Salvini-Plawen and Mayr [1] compared overall structure, photoreceptor types, developmental origins of eye tissue, position of receptor axons and other anatomical markers among eyes. Based on this analysis, they concluded that eyes evolved not once but at least 40 different times, and possibly many more (reviewed in [2]). Recently, the 'multiple-origins' hypothesis based on morphological evidence has been challenged by results from molecular experiments. Specifically, Gehring and Ikeo [3•] propose that because a single, well conserved 'master' gene, *Pax*-6 (paired homeobox-6), can initiate eye construction in diverse species, eyes must have arisen from a single ancestor. Did eyes appear many times in the course of evolution making them polyphyletic, as claimed by Salvini-Plawen and Mayr [1], or have all eyes 'descended' directly from a common, primitive form, making them monophyletic, as claimed by Gehring and Ikeo [3•]? And why does this matter?

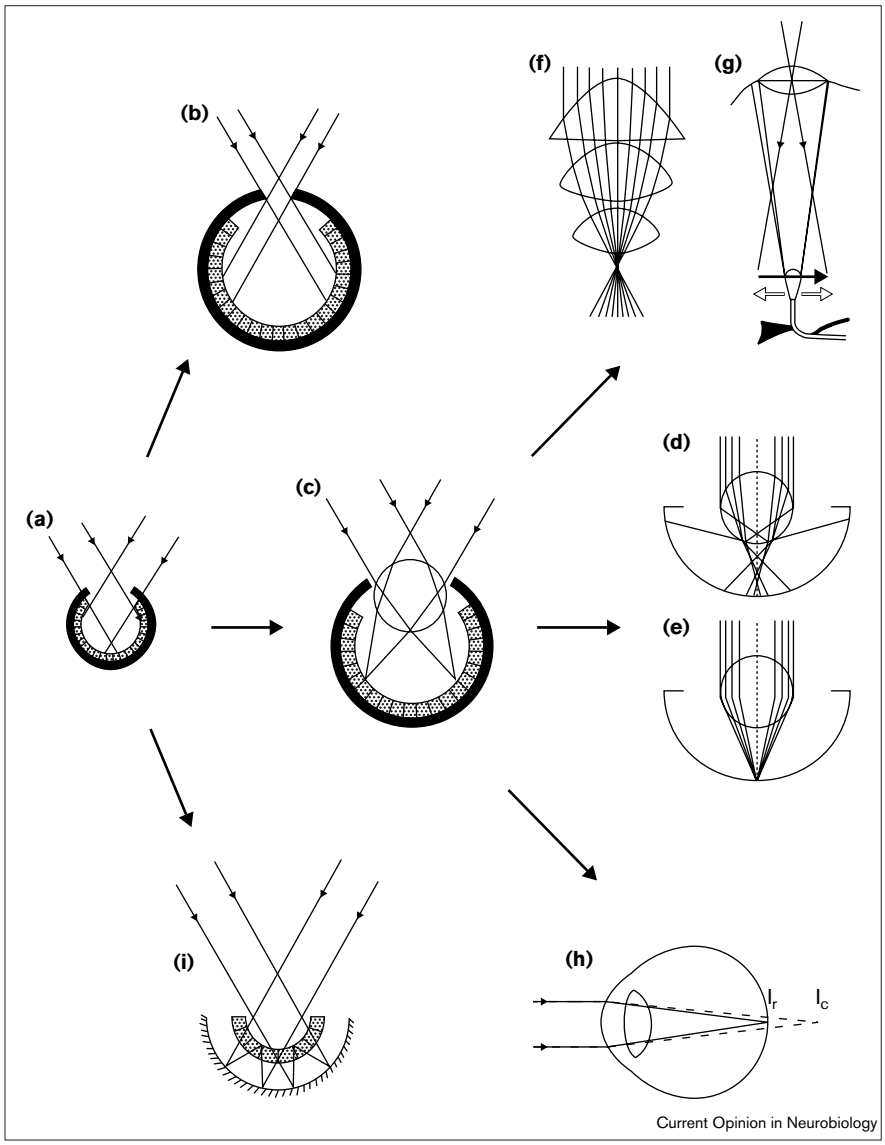
Here I will review current thinking and recent evidence pertinent to the evolution of eyes. I will discuss the striking similarities and differences among eye types found in diverse species and their evolutionary implications. The striking conservation of opsins across phylogeny will be contrasted with the equally striking non-conservation of lens proteins. It appears that as eyes evolved, they always used opsins to collect photons but whatever tissues were at hand to refract light. The recent discovery that many of the genes responsible for the development of the eye are conserved across species will be discussed and the evidence for evolutionary continuity examined. Finally, the question of whether eyes have evolved once or many times will be discussed.

Similarities and differences among eye types

By the time of the Cambrian, eyes were present in the form of very simple eyecups, useful for detecting light but not for processing directional information [4]. Although the causes are unknown, explosive speciation or the 'Big Bang' of animal evolution happened during the Cambrian [5]. Existing eye types improved radically, coincident with the appearance of carnivory and predation. Parker [6] has proposed that eye evolution may have been accelerated by the emergence of light as a behavioral signal. He has examined species collected from the Burgess Shale, which is located in Yoho National Park in the Canadian Rocky Mountains and contains an exceptional collection of fossils from the mid Cambrian age (approximately 550 million years ago). Discovered in 1909, it contains a wide diversity of fossil invertebrates that are beautifully preserved. Parker suggests that regularities on the rough body surfaces of some Burgess Shale species (*Wiwaxia corrugata*, *Canadia spinosa*, and *Marrella splendens*) could have acted as diffraction gratings. Under incident light, these tiny creatures would have reflected an iridescent rainbow of metallic colors, just as the back of a compact disc shimmers because its grooves diffract light into its constituent colors. Parker speculates that the iridescence, flashing from spiny appendages, may have deterred predators, possibly becoming the first visual signal among metazoans. The idea that rapid evolution in eyes during the Cambrian was influenced by visual signals is appealing. However, because many selective forces must have been at work simultaneously [5,7•], the relative importance of light as a behavioral signal is impossible to assess directly.

Eyes collect light through an aperture and focus it with a lens onto photoreceptor cells specialized to convert photons into neural signals. Some eyes exist without pupils and even without lenses (*Nautilus*), but, by definition, all eyes require specialized phototransducing cells. Three phyla emerged from the Cambrian with functional eyes: mollusks, arthropods and chordates.

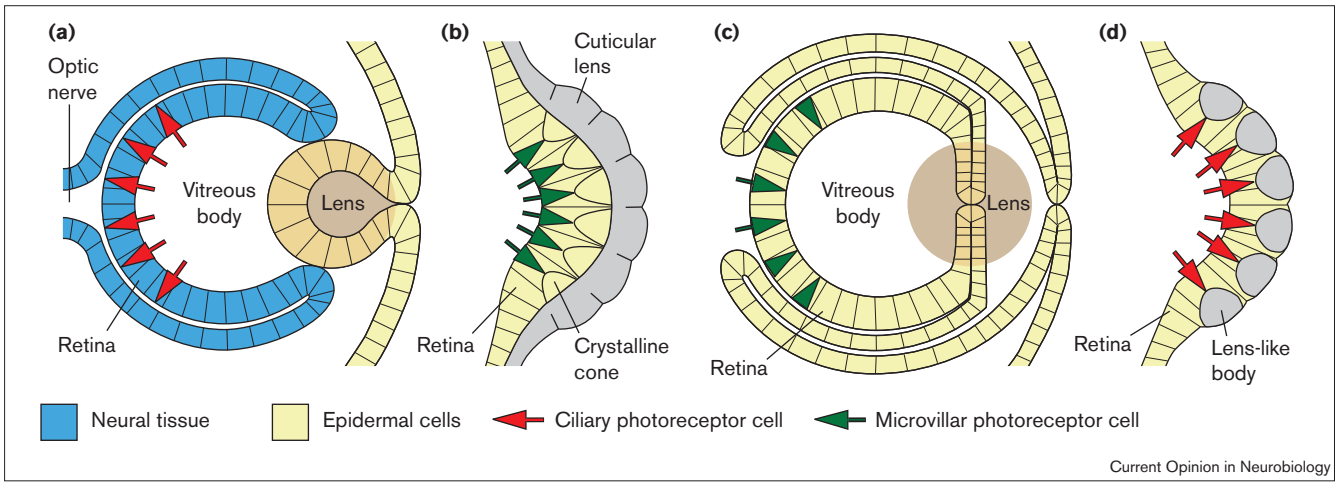
Figure 1



The likely evolution of single-chambered eyes. Arrows indicate functional developments, not specific evolutionary pathways. **(a)** Pit eye, common throughout the lower phyla. **(b)** Pinhole of *Haliotis* or *Nautilus*. **(c)** Eye with a lens. **(d)** Eye with homogeneous lens, showing failure to focus. **(e)** Eye with lens having a gradient of refractive index. **(f)** Multiple lens eye of male *Pontella*. **(g)** Two-lens eye of *Copilia*; solid arrow shows image position, open arrows show movement of the second lens. **(h)** Terrestrial eye of *Homo sapiens* with cornea and lens. Ic, image formed by cornea alone; Ir, final image on the retina. **(i)** Mirror eye of the scallop *Pecten*. From [2].

These lines produced essentially eight optical solutions to seeing (Figure 1); two of these solutions appear in chordates, and one solution, namely using a gradient of refractive index to produce a lens, is shared with other animals living underwater [2]. In many details of their structure and function, eyes of these three phyletic groups differ substantially. For example, photoreceptor cells divide into two basic types, those with cilia and those with microvilli, both of which provide large membrane surfaces to hold opsin, the phototransducing molecule [1]. Microvillar photoreceptors predominate in invertebrate animals whereas all vertebrate photoreceptors are ciliary. These photoreceptor types also differ in their physiological responses. Microvillous receptors of arthropods and mollusks depolarize in response to light, meaning that photon absorptions open Na^+ channels. Ciliary receptors of vertebrates, in contrast, hyperpolarize in response to light by closing Na^+ channels. Vertebrates and invertebrates also differ in their mechanisms of phototransduction. Vertebrate photoreceptors use cyclic GMP as a second messenger system, whereas invertebrates use inositol trisphosphate. The reisomerization of the photopigment is also different in these eye types. Finally, the structures of the two major chambered eyes, those of vertebrates and cephalopods, arise from distinctly different parts of the embryo. The cephalopod eye forms from an epidermal placode through successive infoldings, whereas the vertebrate eye emerges from the neural plate and induces the overlying epidermis to form the lens (Figure 2). The cephalopod eye also lacks a cornea, which is present in all vertebrates. The striking diversity in structure, function and development of extant eyes supports their polyphyletic origin [8].

Figure 2



Building plans of four types of eye. **(a)** A vertebrate eye. **(b)** An arthropod compound eye. **(c)** A cephalopod lens-eye. **(d)** A compound eye in polychaete tube-worms and arcoid clams. Note that the construction of eyes varies considerably. For example, in chordates, photoreceptor cells differentiate from the central nervous system, whereas cephalopod and arthropod eyes differentiate from the epidermis. In addition, the retina is inverse (e.g. photoreceptors are at the back of the eye) in vertebrates and everse (e.g. photoreceptors are at the front of the eye) in cephalopods [31].

Opsins are homologous across phylogeny

All existing eyes use a vitamin-A-based visual pigment comprising a chromophore and an apoprotein, opsin, that has a history even more ancient than eyes. Genetic analysis has shown that all opsins are homologous, derived from a common ancestor. Even though this is not the only way to detect light, as is evident from the ubiquitous distribution of cryptochromes in plants and animals [9], it has proven irresistible for use in eyes. Is this not support for a monophyletic origin of eyes? Possibly, but consider that opsin is homologous with numerous other seven-transmembrane-domain G-protein-coupled receptors — most famously those responsible for olfaction [10] — yet there is no claim that organs for vision and olfaction are homologous.

The ancestral light-absorbing opsin molecule diverged 350–400 million years ago into four cone families, providing chromatic distinctions. Later, a rod opsin family emerged, subserving vision in low light [11]. This is evident from analysis of the opsins in teleost fish, reptiles and birds. Mammals, on the other hand, have rod-dominated vision and only recently (35 million years ago) re-evolved color vision based on three visual pigments through gene duplication [12••].

In animals today, the number of different opsins expressed in an eye ranges from 2 to 12, governing, in principle, the number of different wavelengths that can be discriminated. Teleost fish, reptiles and birds all have genera with rods and four spectral classes of cone, enabling trichromatic vision.

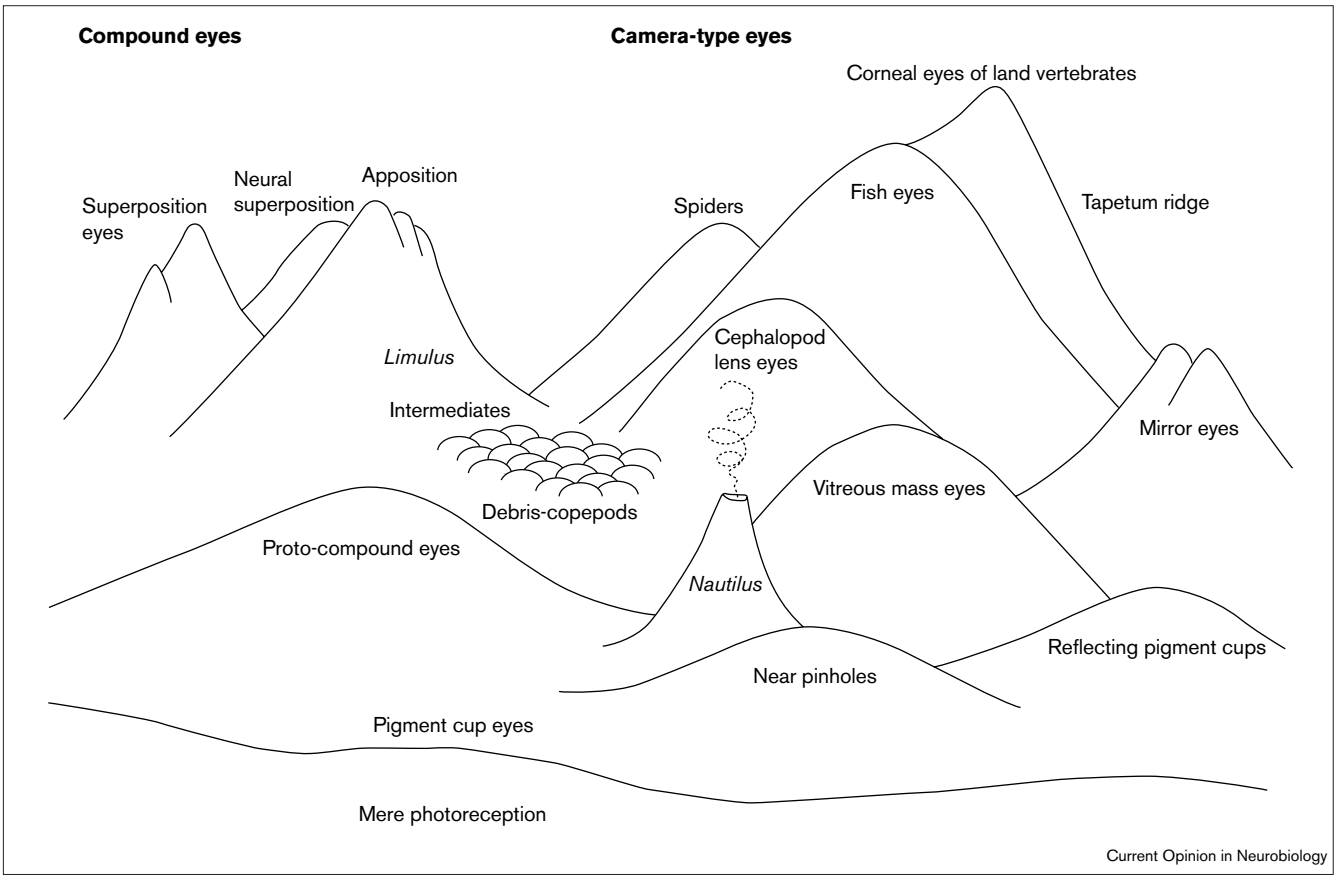
The ability to distinguish different wavelengths requires that each type of photoreceptor contain a particular opsin/chromophore combination. Recently, Wang *et al.* [13••] discovered how the locus control region ensures that particular opsins are expressed in particular cone types — a prerequisite for the evolution of trichromatic vision [14].

The peak sensitivity of cone photoreceptors in most species is tuned to environmentally important wavelengths reflecting the chromatic landscape. This principle was recently demonstrated for the coelacanth (lobe finned fish) *Latimeria chalumnae* [15]. Even the visually blind subterranean mole rat appears to have evolved an opsin with a wavelength sensitivity that is ideal for setting its circadian rhythm [16].

Lens proteins are not homologous, but the strategy for making lenses is

Does the composition of lenses yield insight about how eyes evolved? In vertebrates, lenses are formed from modified epithelial cells and contain high concentrations of soluble proteins, known as ‘crystallins’ because of their organized packing. In contrast, in invertebrates, the lens proteins are secreted by specialized cells of the eye. Recently, lenses of mitochondrial origin have been found in the two pairs of eyes of the parasite *Neoheterocotyle rhinobatidis* [17]. Despite their distinct cellular origins, for a lens to function optically its constituent proteins must be distributed to produce a radial gradient of refractive index that is low at the edge of the lens and high in the center (see [2,18]). This gradient of refractive index is essential for vision in animals living in water and has been adopted by vertebrates and invertebrates alike. Most remarkably, cephalopods assemble their spherical lens from two distinct embryological sources, yet manage to produce the required gradient of refractive index [19].

Figure 3



A possible landscape of eye evolution created by Mike Land. Height represents optical quality and the ground plane evolutionary distance. Land writes that "Climbing the hills is straightforward but going from one hill top to another is near impossible." From [42].

The ten or so crystallin proteins were thought until recently to be unique to lens tissue and hence to have evolved for this function. Alpha and beta–gamma crystallins are specialized lens proteins in vertebrates, related to heat-shock protein and schistosome egg antigen, respectively. However, the remaining vertebrate lens proteins are a non-conserved, diverse group used as enzymes elsewhere in the body. Surprisingly, most of these taxon-specific lens proteins are actually products of the same genes that produce the enzymes. For example, in crocodiles and some bird species, the glycolytic enzyme lactate dehydrogenase B is a major protein in the lens [20]. One gene coding for a protein with two entirely different functions has been termed 'gene sharing' [21] and may be a prelude to gene duplication. This molecular opportunism is so effective that it has also been used both in cephalopods [22] and in *Drosophila* [23].

The evolution of lenses depended on generating a relatively large amount of refractile protein at the front of the eye, assembled to produce a specific gradient of concentration so that the lens can focus light. The common cellular strategy of constructing lenses from a variety of different proteins seems to be a convergent evolutionary solution for which proteins whose synthesis proved easy to regulate may have been selected. The exquisite gradient of the refractive index, corresponding to a gradient of protein concentration that evolved convergently in vertebrates and invertebrates alike, resulted because it is the only way to making an optically useful lens.

Conservation of developmental programs for making eyes

It is becoming increasingly clear that analogous developmental processes in very different species are controlled by homologous genes, particularly the homeotic genes. In an important set of experiments, Gehring and co-workers showed first that *eyeless*, a gene known to be important for eye development in *Drosophila*, was a homolog of *Small eye* (*Sey* or *Pax*-6) in the mouse and of *Aniridia* in humans [24]. These homologous genes encode a transcription factor with both a paired domain and a homeodomain. Subsequently, Halder *et al.* [25] demonstrated that targeted expression of *eyeless* could induce ectopic eyes in *Drosophila*, as could targeted expression of mouse *Pax*-6. This remarkable finding led Halder *et al.* to anoint *Pax*-6

a 'master control gene' for eye development. The concept of master control genes [26] implies a linear hierarchy of genes whose expression specifies construction of an organ system. That a single gene could trigger construction of an animal's eye led to the recent proposal that eyes are monophyletic [3•]. Clearly, all evidence points to strong conservation of *Pax*-6 (and its promoters; [27]) over evolutionary time. However, the contention that this confirms a monophyletic origin of eyes warrants closer examination.

First, there is a strong suggestion that *Pax*-6 is autoregulatory, as are many transcription factors. Given this, do experimentally expressed *Pax*-6 genes from other species act directly to produce an eye in *Drosophila* or do they instead activate the native *ey* genes to produce eyes? Could insertion of a mouse *Pax*-6 gene rescue eye development in *Drosophilia* with an *ey*-null background? If so, then a necessary role for *Pax*-6 in eye ontogeny would seem more likely. Second, several additional genes have been shown to induce ectopic eyes in *Drosophila*, including *sine oculus* (*so*), *dachshund* (*dac*), and *teashirt* (*tsh*) [28] as well as the second *Pax*-6 gene, *toy* [29]. As the complete suite of homologous genes has been reported in mouse [30], it will be interesting to see if other homeotic genes can generate eyes. Is only one of these genes in charge of making eyes or can they serve as substitutes for one another? Third, there are many animals with no eyes that nevertheless express *Pax*-6 or its homologues (cnidarian corals, *C. elegans*; [31]). Clearly *Pax*-6 plays other roles in these species, primarily in head formation. Fourth, *Pax*-6 does not just organize eye development, but appears at numerous other expression sites. It is expressed during neural tube development, in the olfactory epithelium, and in several other brain sites including the spinal cord, cerebellum [32] and cerebral cortex [33]. Moreover, it has been found to be essential for activation of proglucagon gene transcription in both the pancreas and intestine [34,35]. Consistent with the role of *Pax*-6 in anterior body axis determination, misexpression of *Pax*-6 has been shown to produce axial defects but no ocular phenotype in *Xenopus* [36]. Recently, however, Chow *et al.* [37] have reported success in generating ectopic *Xenopus* eyes through *Pax*-6 misexpression. Finally, other genes in vertebrates are clearly upstream in the controlling pathways for eye development, making it difficult to label a single gene as the 'master'. For example, Fang *et al.* [38] found in a direct developing amphibian *Eleutherodactylus coqui* that *Xenopus laevis noggin* RNA can induce ectopic heads with eyes.

Taken together, these data suggest that neither *Pax*-6 nor any other gene exerts a master control of eye development across phylogeny. Genetic control of eye construction is staggeringly complex and it seems more likely that an interactive 'gene network' regulates development of all complex organs, including the eye [28]. Indeed, at least one genetic network implicated in eye development also controls myogenesis using an expanded collection of genes [39]. Because *Pax*-6 existed before eyes [31], like other developmentally important genes, it may have been recruited for the formation of eyes, just as was opsin and possibly some of the specific lens constituents as the selective pressure demanded.

Are all eyes homologous?

Not unexpectedly, the parallels in the developmental genetics of several structures including hearts, body segments and appendages raise the same set of issues about homology between structures separated by significant evolutionary distances. Tabin *et al.* [40•] in an insightful analysis conclude that, for appendages, there has been continuity of the genetic information that regulates the development of similar but nonhomologous structures.

Homology implies an hypothesis about the evolutionary origins of a trait or structure. Many kinds of evidence, including the expression of genes, can provide useful evidence. But it is not possible to infer the phylogeny of a structure such as the eye from a single character whether it is an optical system [41] or a gene sequence. Understanding the origins of eyes will require more data from the fossil record and a more complete analysis of the genetic regulatory circuits that control the development and function of eyes (Figure 3).

While the similarity of eye structures is a fascinating topic, a deeper question is not how similar developmental programs of eye structures are, but rather what causes their remarkable differences. What distinguishes the ontogenesis of apposition and superposition compound eyes? What regulates the construction of eyes with mirror optics as compared to those with lens optics? How are receptor axons instructed to emerge from the front of the eyecup (inverse) in vertebrates as opposed to the back of the eyecup (everse) in cephalopods? As we learn about fundamental similarities among eyes, we also need to discover the developmental programs responsible for producing profoundly different eye phenotypes. We need to learn how many genes, including *Pax*-6, it takes to make an eye and why, if they use many of the same developmental genes, the eyes of *Drosophila*, mouse and cephalopod are so different.

Conclusions

Clearly different tissues have been recruited to build lenses and retinas across the phyla. The inexorable physical constraints imposed by the properties of light have led to the repeated use of gradients of refractive index to make lenses, even though the lenses themselves are made from very different proteins in different species. In the case of lenses, as eyes evolved, they used the proteins available in the organism to produce lenses. In contrast, the mechanism for absorbing photons, the opsin–chromophore combination, has been conserved across phylogeny. So, one part of the eye relies on homologous proteins and another does not. Recently, the discovery of

conservation of many of the genes used during ontogeny of the eye, particularly *Pax*-6, has led to the proposal that all eyes are monophyletic — that is, they arose from an 'Ur' eye. However, our current level of understanding of the genetic control of eye development does not support this conclusion. Instead, there appears to be a continuity of genetic information that regulates the development of similar but nonhomologous eyes. How similar developmental programs produce such radically different eyes remains unknown.

Acknowledgements

I thank Pat Bateson, Anne Fernald, Kim Hoke, David Kingsley, Mike Land, Rex Robison, Matt Scott, Cliff Tabin and Graeme Wistow for thoughtful discussions and comments. Supported by National Institutes of Health EY 05051.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Salvini-Plawen LV, Mayr E: **On the evolution of photoreceptors and eyes.** *Evol Biol* 1997, **10**:207-263.

2. Land MF, Fernald RD: **The evolution of eyes.** *Annu Rev Neurosci* 1992, **15**:1-29.

3. • Gehring WJ, Ikeo K: **Pax 6: mastering eye morphogenesis and eye evolution.** *Trends Genet* 1999, **15**:371-377.
This is a review of several papers by various laboratories making the case for monophyletic origin of eyes based on the conservation of *Pax*-6.

4. Land MF: **The evolution of eyes.** *Proc Berlin Brandenberg Acad Sci* 2000, in press.

5. Conway-Morris S: *The Crucible of Creation*. Oxford: Oxford University Press; 1998.

6. Parker AR: **Colour in Burgess Shale animals and the effect of light on evolution in the Cambrian.** *Proc R Soc Lond B Biol Sci* 1998, **265**:967-972.

7. • Culler TS, Becker TA, Muller RA, Renne PR: **Lunar impact history from $^{40}Ar/^{39}Ar$ dating of glass spherules.** *Science* 2000, **287**:1785-1788.
This study suggests that the evolutionary Big Bang was triggered by cosmic debris. Analysis of impacts from cosmic debris shows an increase roughly coincident with the 'Cambrian explosion' of complex life on earth. The authors suggest that the increased debris influx may have simulated the rate of biotic diversity.

8. Fernald RD: **The evolution of eyes.** *Brain Behav Evol* 1997, **50**:253-259.

9. Cashmore AR, Jarillo JA, Wu YJ, Liu D: **Cryptochromes: blue light receptors for plants and animals.** *Science* 1999, **284**:760-765.

10. Buck L, Axel R: **A novel multigene family may encode odorant receptors; a molecular basis for odor recognition.** *Cell* 1991, **65:**175-188.

11. Bowmaker JK: **Evolution of colour vision in vertebrates.** *Eye* 1998, **12**:541-547.

12. •• Nathans J: **The evolution and physiology of human color vision: insights from molecular genetic studies of visual pigments.** *Neuron* 1999, **24**:299-312.
This insightful article draws together molecular and psychophysical data that bear on the selective forces leading to the evolution of trichromatic vision. Many aspects of visual processing, including the mechanisms underlying spatial and chromatic structures in the retina, are discussed clearly.

13. •• Wang Y, Smallwood PM, Cowan M, Blesh D, Lawler A, Nathans J: **Mutually exclusive expression of human red and green visual pigment-reporter transgenes occurs at high frequency in murine cone photoreceptors.** *Proc Natl Acad Sci USA* 1999, **96**:5251-5256.
A necessary condition for color vision is that individual photoreceptors respond to a restricted range of wavelengths. This is achieved in visual systems by having each photoreceptor type express a single type of opsin. This paper examines the molecular mechanism through which mutually exclusive expression of red and green opsin pigments can be achieved. This elegant paper describes how this may occur by identifying the necessary relationship between the locus control region and the pigment gene promoters.

14. Mollon JD: **Color vision: opsins and options.** *Proc Natl Acad Sci USA* 1999, **96**:4743-4745.

15. Yokoyama S, Zhang H, Radlwimmer GB, Blow NS: **Adaptive evolution of color vision of the Comoran coelacanth (*Latimeria chalumnae*).** *Proc Natl Acad Sci USA* 1999, **96**:6279-6284.

16. David-Gray ZK, Cooper HM, Janssen JW, Nevo E, Foster RG: **Spectral tuning of a circadian photopigment in a subterranean 'blind' mammal (Spalax ehrenbergi).** *FEBS Lett* 1999, **461**:343-347.

17. Rohde K, Watson NA, Chisholm LA: **Ultrastructure of the eyes of the larva of Neoheterocotyle rhinobatidis (Platyhelminthes, Monopisthocotylea), and phylogenetic implications.** *Int J Parasitol* 1999, **29**:511-519.

18. Kröger RHH, Campbell MCW, Fernald RD, Wagner H-J: **Multifocal lenses compensate for chromatic defocus in vertebrate eyes.** *J Comp Physiol [A]* 1999, **184**:361-369.

19. Jagger WS, Sands PJ: **A wide-angle gradient index optical model of the crystalline lens and eye of the octopus.** *Vision Res* 1999, **39**:2841-2852.

20. Wistow G, Piatigorski J: **Lens crystallins: the evolution and expression of proteins for a highly specialized tissue.** *Annu Rev Biochem* 1988, **57**:479-504.

21. Wistow G: **Lens crystallins gene recruitment and evolutionary dynamism.** *Trends Biochem Sci* 1993, **18**:301-306.

22. Tomarev SI, Zinovieva RD: **Squid major lens polypeptides are homologous to glutathione S-transferase subunits.** *Nature* 1988, **336**:86-88.

23. Janssens H, Gehring WJ: **Isolation and characterization of drosocrystallin; a lens crystallin gene of *Drosophila melanogaster*.** *Dev Biol* 1999, **207**:204-214.

24. Quiring R, Walldorf U, Kloter U, Gehring W: **Homology of the *eyeless* gene of *Drosophila* to the *small eye* gene in mice and *aniridia* in humans.** *Science* 1994, **265**:785-789.

25. Halder G, Callaerts P, Gehring WJ: **Induction of ectopic eyes by targeted expression of the *eyeless* gene in *Drosophila*.** *Science* 1995, **267**:1788-1792.

26. Lewis EB: **Clusters of master control genes regulate the development of higher organisms.** *J Am Med Assoc* 1992, **267**:1524-1531.

27. Xu P-X, Zhang X, Heaney S, Yoon A, Michelson AM, Maas RL: **Regulation of *Pax6* expression is conserved between mice and flies.** *Development* 1999, **126**:383-395.

28. Pan D, Rubin GM: **Targeted expression of *teashirt* induces ectopic eyes in *Drosophila*.** *Proc Natl Acad Sci USA* 1998, **95**:15508-15512.

29. Czerny T, Halder G, Kloter U, Souabni A, Gehring WJ, Busslinger M: **Twin of eyeless, a second Pax-6 gene of *Drosophila*, acts upstream of eyeless in the control of eye development.** *Mol Cell* 1999, **3**:297-307.

30. Davis RJ, Shen WP, Heanue TA, Mardon G: **Mouse Dach; a homologue of *Drosophila* dachshund is expressed in the developing retina, brain and limbs.** *Dev Gen Evol* 1999, **209**:526-536.

31. Nilsson DE: **Eye ancestry: old genes for new eyes.** *Curr Biol* 1996, **6**:39-42.

32. Engelkamp D, Rashbass P, Seawright A, van Heyningen V: **Role of Pax-6 in development of the cerebellar system.** *Development* 1999, **126**:3585-3596.

33. Götz M, Stoykova A, Gruss P: ***Pax6* controls radial glia differentiation in the cerebral cortex.** *Neuron* 1998, **21**:1031-1044.

34. St-Onge L, Sosa-Pineda B, Chowdhury K, Mansouri A, Gruss P: **Pax6 is required for differentiation of glucagon-producing alpha-cells in mouse pancreas.** *Nature* 1997, **387**:406-409.

35. Hill ME, Asa SL, Drucker DJ: **Essential requirement for *Pax*-6 in control of enteroendocrine proglucagon gene transcription.** *Mol Endocrinol* 1999, **13**:1474-1486.

36. Hirsch N, Harris WA: ***Xenopus Pax6* and retinal development.** *J Neurobiol* 1997, **32**:45-61.

37. Chow RL, Altmann CR, Lang RA, Hemmati-Brivanlou A: ***Pax-6* induces ectopic eyes in a vertebrate.** *Development* 1999, **126**:4213-4222.

38. Fang H, Marikawa Y, Elinson RP: **Ectopic expression of *Xenopus* noggin RNA induces complete secondary body axes in embryos of the direct developing frog *Eleutherodactylus coqui*.** *Dev Genes Evol* 2000, **210**:21-27.

39. Heanue TA, Reshef R, Davis RJ, Mardon G, Oliver G, Tomarev S, Lassar AB, Tabin CJ: **Synergistic regulation of vertebrate development by *Dach2*, *Eya2*, and *Six1*, homologs of genes required for *Drosophila* eye formation.** *Genes Devel* 1999, **13**:3231-3243.

40. • Tabin CJ, Carroll SB, Panganiban G: **Out on a limb: parallels in vertebrate and invertebrate limb patterning and the origin of appendages.** *Amer Zool* 1999, **39**:650-663.
A thoughtful discussion of the issues related to homology at the molecular level.

41. Gaten E: **Optics and phylogeny: is there an insight? The evolution of superposition eyes in the Decapoda (Crustacea).** *Contrib Zool* 1998, **67**:223-235.

42. Dawkins R: *Climbing Mount Improbable*. New York: Norton; 1996.