Brain, Behavior and Evolution

Brain Behav Evol 2004;64:141–147
DOI: 10.1159/000079743

Eyes: Variety, Development and Evolution

Russell D. Fernald

Neuroscience Program, Stanford University, Stanford, Calif., USA

Key Words
Vertebrate eye · Development · Eye evolution · Eye variety

Abstract
The selective advantages of using light as a source of information are reflected in the diverse types of extant eyes. The physical properties of light restrict how it can be collected and processed, resulting in only eight known optical systems found in animals. Eyes develop through tissue rearrangement and differentiation. Our understanding of the source of genetic information used in developmental programs is growing rapidly and reveals distributions of gene expression with substantial overlap in both time and space. Specific genes and their products are used repeatedly, making causal relationships more difficult to discern. The phenomenon of groups of genes acting together seems to be the rule. Throughout evolution, particular genes have become associated with distinct aspects of eye development, and these suites of genes have been recruited repeatedly as new eyes evolved.

Introduction

Light from the sun has shaped life on earth since biological evolution began some 5 billion years ago. Regular light/dark cycles led to the evolution of circadian rhythms and biological clocks, now known to be ubiquitous among biological organisms. Perhaps because sunlight has been a consistent selective force during biological evolution, it has proven to be the most potent. One important consequence of sunlight striking our planet has been the evolution of eyes for seeing the world. Of approximately 33 animal phyla, about one-third have evolved no specialization for light detection, whereas the remaining two-thirds have either proper eyes or at least a light sensitive organ [Land and Nilsson, 2002].

Scientists have always been fascinated by eyes, wondering about their remarkable variety, their exquisite macroscopic and molecular functioning, their development, and ultimately their evolutionary origin. The growth of our understanding of eyes and vision has been remarkable and we now know details about the variety in eye structure, the morphological sources of ocular tissue, and some of the molecular actors responsible for eye development. We even have some understanding of how eyes might have evolved. This review will present highlights of these topics and some ideas regarding how to think about the issues facing scientists interested in eyes.

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0006–8977/04/0643–0141$21.00/0

Accessible online at:
www.karger.com/bbe

Russell D. Fernald
Department of Biological Sciences, Gilbert Hall
371 Serra Mall, Stanford University
Stanford, CA 94305 (USA)
Tel. +1 650 725 2460, Fax +1 650 723 0881, E-Mail rfernald@stanford.edu

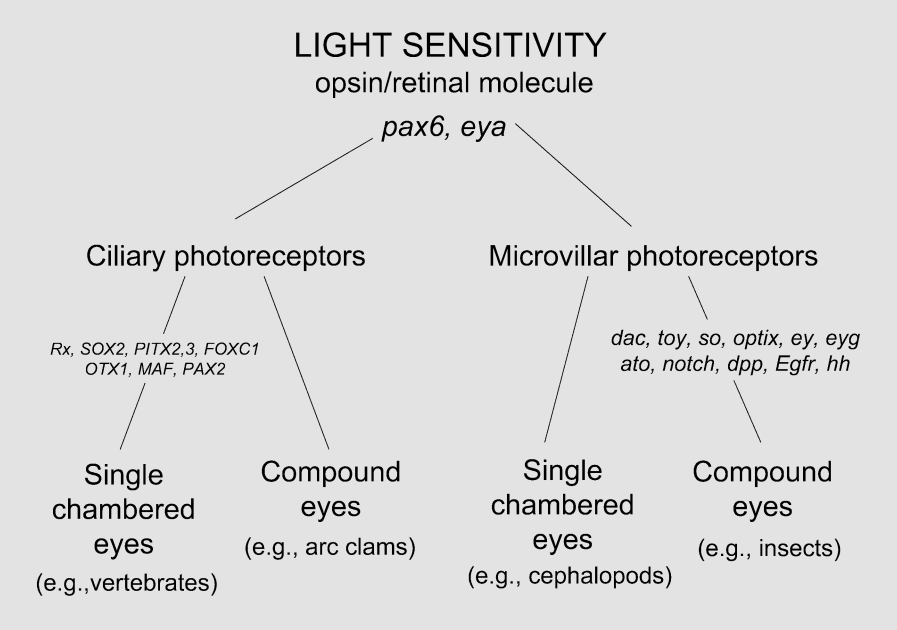

Fig. 1. Schematic illustration of a possible scheme for the evolution of eyes indicating that all eyes share the method of capturing light (opsin) but as different eye types evolved, different suites of genes were recruited for the production of eyes [adapted from Land and Nilsson, 2002, fig. 1.8]. Following the evolution of the opsin/retinal light detection unit, its use appears to have become associated with *pax6* and possibly *eya*. The evolution of ciliary and microvillar photoreceptors each required recruitment of additional genes, some of which have proven to be common to one another. The identification of genes involved is not exhaustive and is based on three reports in the literature [Kumar, 2001; Chow and Lang, 2001; Graw, 2003]. Abbreviations: *ato*, atonal bHLH transcription factor; *dac*, dachshund; *dpp*, decapentaplegic TGF-β secreted morphogen; *Egfr*, receptor tyrosine kinase; *ey*, eyeless homeodomain/paired domain; *eya*, eyes absent; *eyg*, eye gone homeodomain; *FOXC1*, forkhead box gene C1; *hh*, hedgehog secreted morphogen; *MAF*, musculoaponeurotic fibrosarcoma oncogene; *notch*, transmembrane receptor; *optix*, homeodomain/six domain; *OTX1*, orthodenticle homologue 1; *PAX2*, paired box gene 2; *pax6*, paired domain, homeodomain; *Pitx2,3*, paired, like homeodomain transcription factor; *Rx*, retina and anterior neural fold homeobox; *so*, sine oculus homeodomain/six domain; *SOX2*, SRY, box with gene 2; *toy*, twin of eyeless.

Eye Variety

In his landmark book, Walls [1942] provided remarkable insights about all aspects of the vertebrate eye. This 785-page classic has numerous illustrations, many drawn by Walls, that provide details about the range and variety of evolutionary outcomes to be found in vertebrate eyes. Indeed, the variety of eyes is astonishing, reflecting the staggering range of adaptations produced by selective pressures for vision in different habitats. There are several features common to all eyes, however, resulting from constraints on their construction. Because eyes collect and focus light, their structure depends on the physical properties of light, which set limits on the optical features of eyes [see Fernald, 1988; fig. 1]. For example, eyes have evolved to be sensitive to a narrow range of wavelengths, relative to the broad spectrum of energy produced by sunlight. This is likely because early evolution occurred in water, which strongly filters light [Fernald, 1988]. Thus, the essential selective pressure on early organisms was for vision within a limited range of wavelengths. Selection for biochemical mechanisms sensitive to this limited range of wavelengths predisposed the wavelength sensitivity during evolution. Even though many animal species have long since moved onto land where they are exposed to the broader spectrum of electromagnetic radiation from the sun, most animal eyes remain limited to seeing within this narrow band, although insects and some species of fish and birds later evolved additional receptors for ultraviolet light [e.g., Viltala et al., 1995]. The narrow range of wavelength sensitivity is a residual reflection of our aquatic origins and illustrates how early evolutionary solutions persist.

Of the approximately 33 animal phyla, about a third have no specialized organ for detecting light, a third have light-sensitive organs, and the remaining third are ani-

mals with what we would consider eyes [Land and Nilsson, 2002]. Image-forming eyes appeared in six of the 33 extant metazoan phyla (*Cnidaria, Mollusca, Annelida, Onychophora, Arthropoda,* and *Chordata*), and these six contribute about 96% of the known species alive today [Land and Fernald, 1992], suggesting that eyes are, indeed, useful! Existing eyes have many shapes and sizes, reflecting the diverse solutions to the problem of obtaining an image. Eyes can range in size from a fraction of a millimeter to tens of centimeters in diameter. The range of eye types, sizes and locations suggests that they can evolve relatively easily (see below).

Eye optical systems fall into three classes based on their image forming mechanisms: Images formed via shadows, images formed via refraction (e.g., lens and/or cornea), and images formed via reflection. These different optical types were systematically described by Land [1981], who has contributed significantly to our understanding of eyes and, particularly their optical function [e.g., fig. 1.9 in Land and Nilsson, 2002]. The physical laws governing the behavior of light are well known and these fundamentally limit how an eye can be built, whether it produces an image or simply records the direction of incident light. For this reason, similar structures have arisen in distinctly unrelated animals such as fishes and cephalopods. The chambered or camera eyes in these two lineages are similar in a large number of details, despite the fact that their owners are phylogenetically distant [Packard, 1972]. Both evolved spherical lenses to achieve sufficient refractive power, but the inverted retinal layers of fishes (and all vertebrates) are distinctly different from the non-inverted, somewhat simpler retinae of squid. Macroscopically, these eye types and the animals bearing them are not homologous, even though there are homologies at the molecular and developmental levels, which are at the heart of understanding eye evolution.

The greatest variety of eyes exists among invertebrates. These animals have both camera eyes (e.g., *Cephalopods*) and compound eyes. Moreover, invertebrates also have the greatest variety of eyes as regards number and location on a given species. Although vertebrates settled on paired, chambered eyes with lenses, invertebrates species can have multiple, non-paired eyes and eyes in remarkable locations. For example, certain butterflies have light detecting organs located such that darkness signals successful copulation [Arikawa et al., 1996]. In addition, Nilsson and colleagues [Nordström et al., 2003] recently described a visual system in the planula of a box jellyfish, *Tripedalia cystophora*, with eyecups directly connected to motor cilium. In this case, there is no nervous system to process visual information because the eyes are a complete sensory-motor system unto themselves.

Primitive eyes provide information about intensity and possibly the direction of a light source, but more advanced eyes also inform their owners about wavelength and contrast and can, as do human eyes, provide high-resolution images of the illuminated scene using the concentration of receptors in the fovea. The capabilities of eyes as a function of their structure and, hence, the different specificity of their developmental programs, vary greatly. For example, resolution of an image, as measured in subtended degrees differs by about 13-fold among vertebrates and even more between vertebrates and invertebrates. Eagles have the greatest acuity, which is approximately 10,000 fold greater than that found in planaria [Land and Nilsson, 2002]. Similarly, a comparison of relative sensitivities among vertebrates reveals a range of 4×10^5 between highly sensitive deep sea animal vision and human foveal vision [Land and Nilsson, 2002].

Another remarkable adaptation to meet the behavioral needs of animals occurred in the realm of wavelength sensitivity, resulting in what we know as color vision. The selective pressures for evolution of wavelength discrimination appear to have been quite pervasive. Very likely the added value of better contrast discrimination, which increases the likelihood of identifying food, mates and predators, would have been enhanced with chromatic information [e.g., Nagle and Osorio, 1993; Osorio and Vorobyev, 1996]. Indeed, recent work comparing eight primate taxa suggests that trichromatic vision evolved where leaf consumption was critical [Lucas et al., 2003]. In support of this idea, many species of diurnal reptiles and birds have colored retinal filters, composed of oil droplets, which appear to have evolved to increase the number of colors that can be discriminated, suggesting selective pressure for improved color vision [Vorobyev, 2003].

Vertebrate visual pigments (opsins) appeared before eyes [Land and Fernald, 1992] and evolved along at least five lines, diverging from an ancestral type, before teleost fish diverged from other vertebrates [e.g., Hisatomi et al., 1994]. That visual pigments evolved along parallel lines following an ancient divergence is widely accepted, although there are some differences in interpretation [Okano et al., 1992]. Primate photopigments offer examples of recent evolutionary change in these important molecules. For example, Old World monkeys, apes and humans have trichromatic vision, whereas New World monkeys are polymorphic, having dichromatic or trichromatic color vision [Jacobs, 1996]. In this context, *Homo sapiens* may

be unique in the polymorphism found in our color vision system [e.g., Neitz et al., 1996]. This variance in the number and kinds of photopigments in the human retina might reflect the absence of potent selective pressure on color vision. The subtlety of selective pressures on chromatic detection can be found in many species. It is particularly evident in the variation within a single species of bluefin killifish where the relative abundance of cone types depends on whether the animals live in springs or swamps [Fuller et al., 2003]. The novel differential spectral sensitivity in these populations is produced through differential expression of cone classes in the retina, rather than via modification of the spectral tuning of opsin molecules, showing that there are different ways to achieve color detection. More recently, another mechanism for temporal modulation of wavelength sensitivity in cone photoreceptors has been described in Pacific salmon (*Oncorhynchus gorbuscha*). As salmon move from being planctivores living in surface waters where ultraviolet (uv) light is abundant to fish-eating predators in deeper waters where blue-green light prevails, they remodel their uv-sensitive cones with insertion of an opsin that is tuned to blue wavelengths [Cheng and Flamarique, 2004]. A similar mechanism has been previously reported in winter flounder (*Pseudopleuronectes americanus*) in which a single opsin type in juveniles, located in hexagonally arranged single cones, is replaced by three different opsin types in photoreceptors arranged in a square array in the metamorphosed adult [Evans and Fernald, 1993; Evans et al., 1993].

These examples show that animals have evolved eyes with resolution, sensitivity and wavelength sensitivities to match their needs, even as those needs change throughout life. Most of those adaptations are the result of developmental differences as eyes are built during embryogenesis. What is known about eye development and about producing the differences that are so important functionally?

Eye Morphogenesis – What Are the Rules?

Classical experimentation on ocular development focused on vertebrate eyes, which are a specialized extension of the brain. Experimental models were limited to mice and chicks due to their extensive prior exploitation as model organisms. The beautiful images available today make the often subtle but distinctive morphological changes during eye development seem much more obvious than they were when first observed. With scanning electron microscopy and sophisticated methods of timing the state of tissue development, it is possible to watch the production of an eye as it unfolds (e.g., www.med.unc.edu/embryo_images/unit-eye/eye_htms/eye001.htm).

Eyes develop from the prospective forebrain, beginning in the eyefields, which are made up of cells of the anterior neural plate. As the prosencephalon grows, this region moves forward until the optic groove forms, and the neuroectoderm of the groove locally contacts the surface ectoderm, inducing the lens placode. As the placode invaginates to form the lens vesicle, the optic vesicle forms the bilayered optic cup, which ultimately becomes the eye. The interaction between the optic vesicle and the lens placode was identified as the 'organizer of the lens' by Spemann [1924]. The presumptive lens arises from the lens placode, a thickening of the ectoderm in contact with the optic vesicle. Coincident with this change is the onset of expression of proteins that will form the lens. Other structures of the eye are formed by large and small scale tissue movements, caused and accompanied by the expression of tissue-specific genes at that site. The cornea arises from the surface ectoderm over the lens and from migrating mesenchyme derived from the neural crest. Many of the original observations about the role of specific tissue bits in these processes resulted from exquisite embryonic manipulations related to transplantation experiments. For example, Nieuwkoop [1963] identified, among other things, the source tissue essential for the induction of eye production.

With well described macroscopic change in hand, the next challenge is to synthesize the phenomenological, macroscopic morphological observations with molecular explanations of eye development.

Molecular Actors – How Do They Relate to Macroscopic Action?

For eyes, understanding the genetic control of eye construction is particularly important because about half the cases of blindness in children have a genetic basis [Graw, 2003]. The morphological process of eye development has been viewed as a set of steps toward a final tissue arrangement. Underlying this apparently straightforward sequence of large scale events, however, are distributions of gene expression with substantial overlap in both time and space. Gene expression is closely regulated, and specific gene products are used repeatedly, which makes the causal relationships difficult to conceptualize. Nonetheless, progress in characterizing the genes responsible for particular steps in eye development has been reasonably rapid,

as shown in several recent reviews [Harland, 2000; Chow and Lang, 2001; Graw, 2003]. Functions for at least 15 transcription factors and several signaling molecules have been described in human and mice eyes, based on developmental disorders and/or molecular manipulations [e.g., Graw, 2003]. As with other molecular actors, both the transcription factors and signaling molecules are expressed during ocular development and also in a wide range of other tissues. This suggests that the particular combination of expression patterns is important for the proper functioning of these genes in eye development.

As is now well known, the paired box gene 6 (*PAX6*), a member of the family of genes that encode transcription factors with a homeodomain and a paired domain, appears to be important in eye formation across many species. The remarkable demonstration that *PAX6* can induce eyes where they should not be ('ectopic') in *Drosophila* [Halder et al., 1995]. Similar subsequent demonstrations in vertebrates [Chow et al., 1999] led to the suggestion that there might be 'master control genes' responsible for development and differentiation of ocular tissue in many species. Subsequent work has suggested that 'master control gene' is a misnomer, however, as a suite of genes are required, collectively, to initiate eye development, and transcription factors are a necessary part of the initiation process. Moreover, as noted above, the genes in question actually have dynamic spatial and temporal expression during many stages of eye development, in addition to expression for essential purposes in other tissues. Nonetheless, it is remarkable that some of the same genes appear in the context of eye development, despite great evolutionary distance among the owners of the eyes. How this might have occurred is discussed below.

For *Drosophila* eyes, it is now known that a collection of seven genes, encoding transcription factors and two signaling molecules collaborate to make eyes [reviewed in Kumar, 2001]. These nuclear factors (*eyeless [ey], twin of eyeless [toy]* – both of which are *PAX6* homologs, *sine oculus [so], eyes absent [eya], dachshund [dac], eye gone [eyg]* and *optix*) and signaling systems, including the Notch and receptor tyrosine kinase pathways, act via a complex regulatory network that is reasonably well understood [Kumar, 2001; fig. 1]. The master gene hypothesis is not supported, because deletion of any of these genes causes loss or radical reduction in the *Drosophila* compound eye, and, surprisingly, any gene except *sine oculus,* in collaboration with certain signaling molecules, can cause ectopic expression of an eye in a limited set of imaginal discs. This means that the whole troupe is needed to produce a reasonable eye. Why this might be so is suggested by recent work showing that the *eya* gene products are phosphatases, the first case in which a transcription factor can itself dephosphorylate other proteins to fine tune gene expression [Li et al., 2003]. This elegant work demonstrated the details of interactions among *Six1*, *dac* and *eya* in the formation of the kidney, muscle, and inner ear, as well as eyes, suggesting that this suite of genetically interacting proteins has been recruited repeatedly during evolution for organogenesis of different structures.

It is difficult to abandon the heuristic of hierarchical regulatory processes in development originally proposed by Lewis to characterize homeotic properties of bithorax and antennapedia genes, but molecular analysis of eye development shows that this concept may not be useful in this case. Instead, eye development appears to need new ways of thinking about how complex tissues are made and how such organs arose in evolution. The widespread and redundant activities of specific genes during ocular development [e.g., Chauhan et al., 2002; Baumer et al., 2003] suggest that hierarchies, if they exist, are unknown, and the more likely scenario is the orchestrated activity of a suite of molecular actors.

What Does Development Tell Us about the Evolution of Eyes?

Based on paleontological evidence, eyes are thought to have evolved independently in different organisms at least 40 times and possibly as many as 65 times [Salvini-Plawen and Mayr, 1977], confirming their importance to animals. Within arthropods, there is molecular phylogenetic evidence for independent evolutionary origin of ostracod eyes [Oakley and Cunningham, 2002].

As described above, the diversity of eyes confirms their dynamic evolutionary past. Explosive speciation, or the 'Big Bang' of animal evolution happened during the Cambrian [Conway-Morris, 1998], when existing eye types appear to have improved radically, coincident with the onset of carnivory and predation. Many selective forces were likely at work [Fernald, 2000], including perhaps the first instances where light enabled behavioral signals [Parker, 1998], so no predominant selective force can be claimed. The rapidity of eye evolution has always been a question, but, using a simulation, Nilsson and Pelger [1994] suggested that about 2000 sequential changes could produce a typical image-forming eye from a light sensitive patch. With reasonable estimates, this suggests that an eye could evolve in less than half a million years, making the virtual explosion of eyes during the Cambrian

seem plausible [Land and Nilsson, 2002]. After the Cambrian, three phyla emerged: arthropods, mollusks and chordates. Although these groups all use the opsin molecule to capture light, details of the structure and function of their eyes differ considerably.

One of the most interesting developmental differences among extant eyes is the embryonic origin of the different structures in vertebrate and cephalopod eyes [summarized in Nilsson, 1996]. Cephalopod eyes form from an epidermal placode through successive infoldings, whereas vertebrate eyes emerge from the neural plate and induce the overlying epidermis to form the lens as described above. It is also noteworthy that the cephalopod eyes lack a cornea, which is present in all vertebrates whether aquatic or not.

In addition to the differences in embryonic origin, photoreceptor cells divide into either ciliary or microvillar structures to provide the membrane surface for the opsin molecule [Salvini-Plawen and Mayr, 1977]. Microvilli predominate in invertebrates, whereas vertebrate photoreceptors are ciliary. Physiological responses are also quite different, with the microvillous receptors of arthropods and mollusks depolarizing to light, and the ciliary receptors of vertebrates hyperpolarizing to light. In phototransduction, vertebrate photoreceptors exploit cyclic Guanosine 5′-Monophosphate (GMP) as a second messenger system, whereas invertebrates use inositol trisphosphate [Fernald, 2000]. And, even though opsin is the key molecule for detecting light, mechanisms for regeneration (reisomerization) of the chromophore/opsin system are dramatically different among phyla [Gonzalez-Fernandez, 2003].

How Did Eyes Evolve: Independently Recruited Genes?

It seems increasingly evident that as eyes evolved, different functional mechanisms have been generated by recruiting existing gene programs. From genome sequencing we know that there are far fewer genes in organisms than previously thought, so the use and reuse of genes and their products in combinatorial assemblies, as increasingly reported, make sense. In the development of eyes, this seems to be the rule, not the exception. Specifically, in the evolution of eyes (see fig. 1), it seems likely that light sensitivity evolved early in the Cambrian in the form of a proto-opsin molecule in association with the chromophore, retinal. This molecular combination, sensitive to light, became associated with the genes *pax6* [Sheng et al., 1997] and, possibly, *eya* [based on its phosphatase activity; Li et al., 2003]. One can imagine that this combination was recruited and worked well in early evolved eyespots and other light sensing organs. It would not be surprising, for example, to find these genetic players in the recently described eye without a nervous system [Nordström et al., 2003]. As different eye types evolved over time, there was probably repeated recruitment of particular gene groups, not unlike improvisational groups of actors, interacting to produce candidates for selection. The evolutionary fiddling through which various combinations or routines were tried could have led to numerous parallel evolutionary paths for eyes as we now envision (fig. 1). So, the answer to the question of whether eyes evolved from a single prototypical eye (monophyletic), or whether they evolved repeatedly (polyphyletic), may be the wrong question as it depends on the level of comparison [Land and Nilsson, 2002].

Conclusions

It is tempting to imagine that clarity regarding puzzling scientific issues is just around the corner, even though each new level of understanding usually offers a new view of deeper complexities. Or, as Wittgenstein [1953] said: 'We talk of process and states, and leave their nature undecided. Sometime perhaps we will know more about them – we think. But that is just what commits us to a particular way of looking at the matter.' With relation to eye evolution, the particularities of molecular discoveries have focused attention on commonalities across eye types, often causing us to overlook the large differences in eye structures and developmental origins. That opsin is homologous across many different types of eyes does not make those eyes homologous. Rather, at the level of light detection, eyes have converged on a common mechanism. Other functional aspects of the eye, such as the lens, etc., can come from radically different evolutionary and hence embryological sources.

Where and how might progress be expected given our current knowledge? It seems likely that as more genes and their roles are identified we will have a more refined view of eye development and evolution. A better understanding of genes expressed in the development of compound ciliary eyes and microvillar chambered eyes (see fig. 1) would help clarify the gene recruitment processes important for their evolution. Understanding what makes eyes so remarkably different may ultimately be a bigger challenge than discovering what they have in common.

References

Arikawa K, Suyama D, Fujii D (1996) Light on butterfly mating. Nature 382:119.

Baumer N, Marquardt T, Stoykova A, Speiler D, Treichel D, Ashery-Padan R, Gruss P (2003) Retinal pigmented epithelium determination requires the redundant activities of Pax2 and Pax6. Development 130:2903–2925.

Chauhan BK, Reed NA, Yang Y, Cermak L, Reneker L, Duncan MK, Cvekl A (2002) A comparative cDNA microarray analysis reveals a spectrum of genes regulated by Pax6 in mouse lens. Genes to Cells 7:1267–1283.

Cheng CL, Flamarique N (2004) New mechanism for modulating colour vision. Nature 429:279.

Chow RL, Lang RA (2001) Early eye development in vertebrates. Ann Rev Cell Dev Biol 17:255–296.

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

Conway-Morris S (1998) The Crucible of Creation. Oxford UK: Oxford University Press.

Evans BI, Fernald RD (1993) Retinal transformation at metamorphosis in the winter flounder *(Pseudopleuronectes americanus).* Vis Neurosci 10:1055–1064.

Evans BI, Harosi FL, Fernald RD (1993) Photoreceptor spectral absorbance in larval and adult winter flounder (*Pseudopleuronectes americanus*). Vis Neurosci 10:1065–1071.

Fernald RD (1988) Aquatic adaptations in fish eyes. In: Sensory Biology of Aquatic Animals (Atema J, Fay RR, Popper AN, Tavolga WN, eds), pp 185–208. New York: Springer Verlag.

Fernald RD (2000) Evolution of eyes. Curr Opin Neurobiol 10:444–450.

Fuller RC, Fleishman LJ, Leal M, Travis J, Loew E (2003) Intra specific variation in retinal cone distribution in the bluefin killifish, *Lucania goodei*. J Comp Physiol A 189:609–616.

Gonzalez-Fernandez R (2003) Interphotoreceptor retinoid-binding protein: an old gene for new eyes. Vision Res 43:3021–3036.

Graw J (2003) The genetic and molecular basis of congenital eye defects. Nat Rev Gen 4:876–888.

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

Harland R (2000) Neural induction. Curr Opin Gen Dev 10:357–362.

Hisatomi O, Kayada S, Aoki Y, Iwasa T, Tokunaga F (1994) Phylogenetic relationships among vertebrate visual pigments. Vision Res 34:3097–3102.

Jacobs GH (1996) Primate photopigments and primate color vision. Proc Natl Acad Sci USA 93: 577–581.

Kumar JP (2001) Signaling pathways in *Drosophila* and vertebrate retinal development. Nat Rev Gen 2:846–857.

Land MF (1981) Optics and vision in invertebrates. In: Handbook of Sensory Physiology (Autrum H, ed), pp 471–592. Berlin: Springer.

Land MF, Fernald RD (1992) The Evolution of eyes. Ann Rev Neurosci 15:1–29.

Land MF, Nilsson D-E (2002) Animal Eyes. Oxford UK: Oxford University Press.

Li X, Oghi KA, Zhang J, Krones A, Bush KT, Glass CK, Nigam SK, Aggarwal AK, Maas R, Rose DW, Rosenfeld MG (2003) Eya protein phosphatase activity regulate Six1-Dach-Eya transcriptional effects in mammalian organogenesis. Nature 426:247–253.

Lucas PW, Dominy NJ, Riba-Hernandez P, Stoner KE, Yamashita N, Loria-Calderon E, Petersen-Pereira W, Rojas-Duran Y, Salas-Pena R, Solis-Madrigal S, Osorio D, Darvell BW (2003) Evolution and function of routine trichromatic visionin primates. Int J Org Evol 57:2636–2643.

Nagel MG, Osorio D (1993) The tuning of human photopigments may minimize red-green chromatic signals in natural conditions. Proc R Soc Lond B 252:209–213.

Neitz J, Neitz M, Kainz PM (1996) Visual pigment gene structure and the severity of color vision defects. Science 274:801–804.

Nieuwkoop PD (1963) Pattern formation in artificially activated ectoderm *(Rana pipiens* and *Ambystoma punctatum).* Dev Biol 7:255–279.

Nilsson DE (1996) Eye ancestry: old genes for new eyes. Curr Biol 6:39–42.

Nilsson DE, Pelger S (1994) A pessimistic estimate of the time required for an eye to evolve. Proc R Soc Lond B 256:53–58.

Nordström K, Wallen R, Seymour J, Nilsson D-E (2003) A simple visual system without neurons in jellyfish larvae. Proc R Soc Lond B 270: 2349–2354.

Oakley TH, Cunningham CW (2002) Molecular phylogenetic evidence for the independent evolutionary origin of an arthropod compound eye. Proc Natl Acad Sci USA 99:1426–1430.

Okano T, Kojima D, Fukada Y, Shichida Y, Yoshizawa T (1992) Primary structures of chicken cone visual pigments: vertebrate rhodopsins have evolved out of cone visual pigments. Proc Natl Acad Sci 89:5932–5936.

Osorio D, Vorobyev M (1996) Colour vision as an adaptation to frugivory in primates. Proc R Soc Lond B 263:593–599.

Packard A (1972) Cephalopods and fish: the limits of convergence. Bio Rev 47:241–307.

Parker AR (1998) Colour in Burgess Shale animals and the effect of light on evolution in the Cambrian. Proc R Soc Lond B: 265:967–972.

Salvini-Plawen LV, Mayr E (1977) On the evolution of photoreceptors and eyes. Evol Biol 10: 207–263.

Sheng G, Thouvenot E, Schmucker D, Wilson DS, Desplan C (1997) Direct regulation of rhodopsin 1 by Pax-6/eyeless in *Drosophila*: evidence for a conserved function in photoreceptors. Genes Dev 11:1122–1131.

Spemann H (1924) Über Organisatoren in der tierischen Entwicklung. Naturwissenschaften 48: 1092–1094.

Viltala J, Korpimaki E, Palokangas P, Koivula M (1995) Attraction of kestrels to vole scent marks visible in ultraviolet detection. Nature 373:425–427.

Vorobyev M (2003) Coloured oil droplets enhance colour discrimination. Proc R Soc Lond B 270: 1255–1261.

Walls GL (1942) The Vertebrate Eye and Its Adaptive Radiation. Bloomingon Hills: Cranbrook Institute.

Wittgenstein L (1953) Philosophical Investigations. Oxford UK: Basil Blackwell.