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Eye evolution: a question of genetic promiscuity

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Animal eyes have long served as a classical example of independent origin followed by convergence of structures onto a few different solutions. During the past decade this view has been challenged by the discovery of shared developmental regulatory genes. The *Pax6* gene in particular is almost universally employed for eye formation in bilaterian animals, despite widely different embryological origins. The resulting controversy on the multiple or single origins of animal eyes has gradually been sharpened by continuing discoveries of further general similarities in the genetic regulatory circuits of eye development. Recent work on gene expression in specified cell types, together with comparative studies of developmental genes in cnidarians, now show some promise to a solution of the controversy.

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Abbreviations
Ma million years

Introduction

The most interesting parts of eye evolution happened just before and during the Cambrian explosion (543–520 million years [Ma] ago), when essentially modern types of animal appear for the first time [1••]. Fossils from before the Cambrian (>543 Ma) show no obvious traces of bilaterians, but cnidarians appear to have been abundant in the preceding 30 Ma [1••,2–5]. Genetic dating of phylogenetic divergences indicates that the major branches of Bilateria separated 100–300 Ma before the Cambrian explosion, and that Cnidaria was split off even earlier [6–9]. As the first animal communities with long range predators, which require swift mobility and vision, appear as a product of the Cambrian explosion [1••, 10–12], it is likely that cnidarians and the major branches of bilaterians existed before a need for simple photoreception turned into a need for real eyes.

All eyes, irrespective of their degree of sophistication, require a few fundamental building blocks, such as photoreceptor cells and screening pigment. The way photoreceptor cells and pigment shields are arranged, and whether there are any refracting or any reflecting optical elements involved depend on the type of eye and the amount of information it is supposed to provide [11]. Interestingly, the light sensitivity of photoreceptor cells is not exclusively useful in eyes — it is a widespread sensory modality present in nearly all forms of life, including animals, plants, fungi, unicellular eukaryotes, and prokaryotes [13]. The unique innovation in early animals was the assembly of photoreceptive cells and other structures to provide eyes. In terms of sensory information this was a giant leap from simple monitoring of ambient light intensities to pictorial information of immense potential for mobile organisms [10]. Evolution of photoreceptor cells is thus a separate process that must have largely preceded eye evolution.

An answer to the question of whether eyes evolved once or many times crucially depends on whether or not all eyes share a common type of photoreceptor cell that can believably be traced back to a prototypic eye in an ancestral species [14]. Here, I initially discuss such early events in eye evolution, and then continue to the origin of more elaborate eyes. Finally, I focus on the particularly difficult problems of homologies in cell specification, and demonstrate how recent advances are beginning to reveal the faint contours of an evolutionary history where evidence from physiology, embryology, and developmental genetics are assessed together.

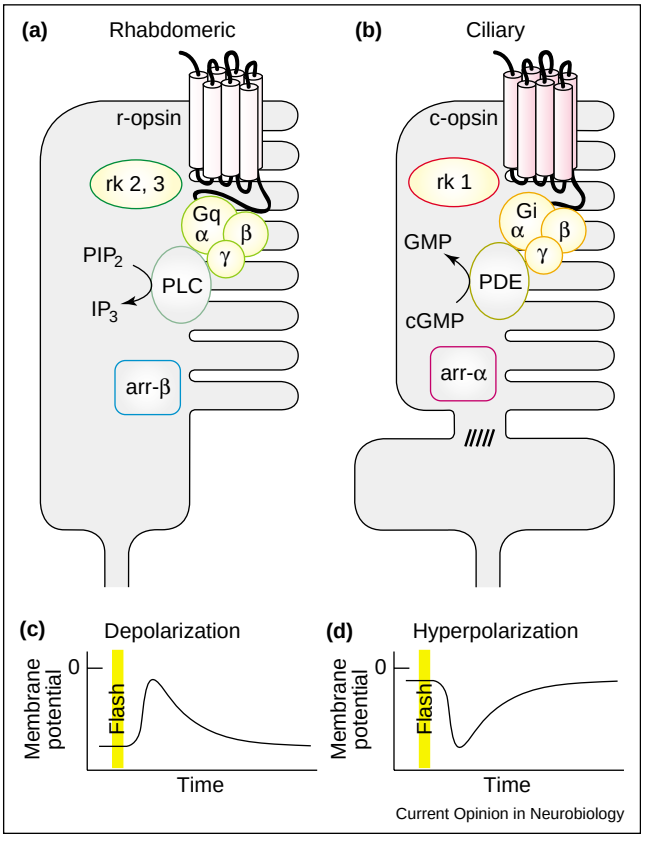
Evolution of visual pigments and photoreceptor cells

Light is an important cue to many forms of life, and light sensitive pigments exist in nearly all branches of living organisms, from bacteria to man [13]. Different flavoproteins, including cryptochromes, phototropins, and photoactivated adenyl cyclase, act as photopigments in unicellular algae [15]. Cryptochromes are also known for their role in insects and vertebrates, in which they are involved in control of the biological clock [16–20]. To date, none of the flavoproteins are known to be linked to a transduction cascade for generation of a receptor potential. The other large group of photopigments is the retinal-binding opsins, known for their role in bacteria, unicellular algae, and animals [21,22]. These are membrane bound proteins with seven trans-membrane (7-TM) regions, and they belong to the same family as most chemoreceptor proteins. It is possible that chemoreception preceded photoreception in this protein family.

In animal sensory cells and neurons this family of receptor proteins is coupled to a transduction machinery for generating a receptor potential, and the 7-TM receptor proteins are commonly referred to as G-protein coupled receptors. Photopigments known to be involved in animal vision are exclusively of the opsin family, but there are also several types of opsin involved in extraocular photoreception in animals [23–27].

There are many different cell types containing photopigments in animals, and many more are probably yet to be discovered. The most obvious photoreceptor cells in animals are those involved in vision, because they contain conspicuous membrane specializations in the form of microvilli or modified cilia [28]. The visual demand for fast response and sensitivity over narrow angles requires these large concentrations of photopigment, whereas cells that only signal slow changes of ambient intensity can work without such specializations. Animal visual cells come in two main varieties, one with specialized cilia and one with specialized microvilli (forming rhabdoms) [28]. Vertebrate eyes have ciliary receptors and the majority of invertebrate eyes have rhabdomeric receptors. Molecular comparisons of the opsins indicate an ancient dichotomy between the ciliary and the rhabdomeric types [14]. The two major classes of opsins are neatly distributed in each of the two receptor-types. The transduction machinery also differs between ciliary and rhabdomeric receptors. Each of the two receptor types has its own subgroup of G-proteins and different transduction cascades, which involve phosphodiesterase and hyperpolarizing responses in ciliary receptors, and phospholipase C and depolarizing responses in rhabdomeric receptors (Figure 1; [14]). The ancestral difference between the two types is further strengthened by general differences in the way the response is terminated [14]. Exceptions to this strict division in photoreceptor types are the mantle eyes of clams, which in many respects seem to represent a third class [14]. Cnidarian photoreceptors are generally of the ciliary type but it is yet unknown if they comply fully with the bilaterian ciliary type.

Figure 1

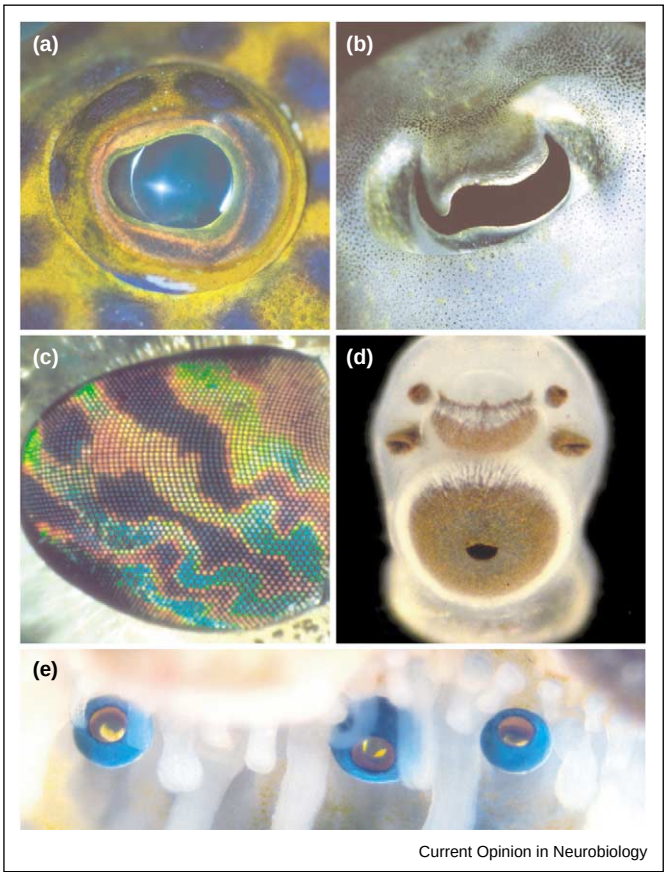


Two types of photoreceptor cell coexist in the major branches of Bilateria: **(a)** the rhabdomeric type and **(b)** the ciliary type. The photopigment and proteins of the transduction cascade are consistently paralogous between the two receptor-types, which suggests that the common ancestor to all Bilateria possessed both types. The photopigments (r-opsin and c-opsin) absorb light by means of a bound retinal chromophore. After receiving a photon, the opsins activate a G-protein (Gq and Gi) composed of three subunits (α, β, γ). In rhabdomeric photoreceptors the G-protein activates a phospholipase enzyme (PLC) turning PIP_2 (phosphatidyl inositol diphosphate) into IP_3 (inositol triphosphate), **(c)** which eventually leads to a depolarization of the membrane potential. The ciliary receptor instead contains a phosphodiesterase (PDE), which turns cGMP (cyclic guanosine monophosphate) into GMP (guanosine monophosphate), **(d)** which finally leads to hyperpolarization of the cell. Also the arrestins (arr-b and arr-a), and rhodopsin kinases (rk 2, 3 and rk 1), which terminate the response, are paralogous proteins in the two receptor-types. Compilation of data from Arendt and Wittbrodt [14].

Eyes and their components

The classical view of eye evolution is one of multiple origin and astonishing convergences onto a few optical types of eye (Figure 2; [10,11,29,30]). The vertebrate and cephalopod eyes have been a particularly celebrated example of how functional constraints can channel different origins into almost indistinguishable optical designs. The reason for assuming different origin has been that different tissues contribute to form eyes in different animal groups. Cephalopod eyes, for instance, are ontogenetically formed entirely by a series of invaginations of the lateral head ectoderm, whereas the vertebrate retina and pigment epithelium develop from the neural ectoderm of the brain vesicle, which induces the lateral head ectoderm to form the lens [10]. Arthropod compound eyes are formed from the same tissue as that in cephalopods, but the ontogeny is radically different, resulting in an array of ommatidia [10]. The prominent eyes in clams are not cephalic structures at all, but develop from the mantle-edge epithelium, and could exist in parallel with reduced cephalic eyes [31]. Photoreceptor cells are rhabdomeric in arthropod compound eyes and cephalopod camera eyes, but ciliary in vertebrate eyes and the mantle eyes of clams [10,14]. The proteins (crystallines) forming animal lenses are different

Figure 2



Animal eyes might appear extremely diverse, but they all belong to a small number of optical types. The illustrations show **(a)** a vertebrate camera-type eye (coral cod), **(b)** a cephalopod camera-type eye (cuttlefish), **(c)** an insect compound eye (horse fly), **(d)** a box jellyfish rhopalium with both camera type eyes and pigment-pit eyes, and **(e)** a row of concave mirror eyes of a clam (scallop). The insect and cephalopod eyes both have rhabdomeric photoreceptors and develop from the lateral head ectoderm, but the optical designs are so different that there can be no functional intermediates. Their last common ancestor can at most have had a pair of simple pit eyes with rhabdomeric receptors. Present day vertebrate eyes show many signs of an independent origin. The vertebrate eye has ciliary photoreceptors and an unusual embryology that could possibly be explained by an ancestor that lost or never had vision, but retained photoreceptors. Although both ciliary and rhabdomeric photoreceptors exist in all major branches of Bilateria, it is most often the rhabdomeric type that has been incorporated into eyes. Jellyfish eyes, along with those of vertebrates, belong to the relatively rare examples of eyes with ciliary receptors, but there is yet insufficient information to say if jellyfish photoreceptors are in every respect homologous to bilaterian ciliary receptors. The mantle eyes of clams are non-cephalic and likely to be new acquisitions. Their ciliary photoreceptors could form a third class, displaying a mixture of components possibly co-opted from other types of photoreceptor and chemoreceptor [14,31].

and unrelated in vertebrates, cephalopods, and clams, clearly indicating independent origin of the lenses [32,33].

Comparative physiology versus developmental genetics

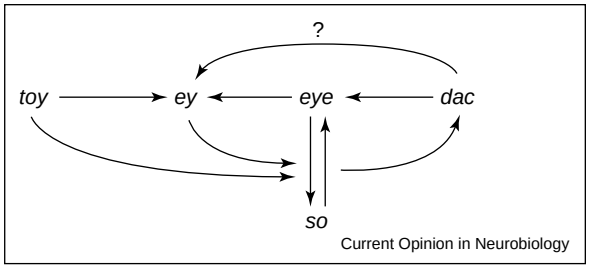
Based on fundamental differences in eye ontogeny and the consistent differences between ciliary and rhabdomeric systems, the impressive optical design of eyes seems to have evolved multiple times independently, but from only a few ancient types of photoreceptor cell. An earlier morphological investigation [28] even suggested that eyes evolved independently between 40 and 65 times, but this was probably taken to be an exaggeration by most visual physiologists. These views might seem incompatible with the discovery that eye formation in Bilateria is almost universally initiated by a transcription factor from a family of conserved homologous genes, now generally termed *Pax6* [34–36]. Naturally, this led to the suggestion that all eyes date back to a common ancestor with a prototypic eye formed by related genetic pathways [35]. But the accumulated evidence for multiple origins of eyes could not be so easily discarded, leading to the now decade-long controversy on how eyes evolved. However, there is no reason to exaggerate the depth of the controversy because it is partly semantic. The proposed prototypic eye is simple, with only one photoreceptor cell and one pigment cell [35]. To most

visual physiologists, this is not an eye; just as a muscle cell and an osteocyte is not a leg. Visual physiologists and developmental geneticists alike will still have to agree that the optical design of cephalopod and vertebrate eyes remains an impressive case of convergent evolution.

The core of the controversy is more fundamental and rests on the fact that homologous developmental genes generate paralogous photodetection systems. The differences between rhabdomeric and ciliary photoreceptor cells are profound, as described above, but the general homology in eye developmental genetics seems equally profound. It is not just *Pax6* genes that are shared in eye development. An entire regulatory circuit involving the genes *Pax6*, *Six* (*sine oculis* gene; vertebrate), *Eya* (*eyes absent* gene; vertebrate), and *Dach (dachshund* gene; vertebrate*)* with largely overlapping expression patterns in vertebrate eye development has a counterpart in *Drosophila* eye development with the homologous set of genes *ey/toy* (*eyeless/twin of eyeless* gene; *Drosophila*), *so* (*sine oculis* gene; *Drosophila*), *eya* (*eyes absent* gene; *Drosophila*), and *dac* (*dachshund* gene; *Drosophila*) (Figure 3; [37–40,41•,42]). After these genes have determined the eye field, a self-propagating wave is set up by short range signaling from homologous genes in zebrafish (*Shh; Sonic hedgehog*) and *Drosophila* (*hh; hedgehog*) [43–46]. This wave of *Shh/hh* signaling moves across the eye field to activate the proneural gene *Atonal* and turn off *Pax6*. In both zebrafish and *Drosophila* the result is a regular array of founder cells from which the mosaic of retinal cells differentiate [43].

From these striking similarities it might seem that vertebrate and insect eyes must date back to a rather advanced ancestral eye. But picking out only the similarities can be deceptive. The waves of *hh* or *Shh* expression are different in important details. In *Drosophila*, *hh* is necessary for neurogenesis and eye formation, whereas in zebrafish, *Shh* is mainly responsible for the regular spacing of ganglion cells, but not necessary for eye formation. In vertebrates other than zebrafish, such as *Xenopus*, mouse, and chicken, the effects of *Shh* signalling differ markedly from those in *Drosophila* and zebrafish [46]. There are notable differences also in the roles of *Pax6*, *Six*, *Eye*, and *Dach* in the various species in which they have been investigated [47–50]. The proposed role of *Pax6* as 'a master control gene' for eye development [34,35] can be dismissed, because neither in vertebrates nor in *Drosophila* are the first stages of eye development prevented by *Pax6* null mutants [48,51], and eyes in planarians form completely even when *Pax6* is inactivated [49,50]. Eye developmental genes in general are also involved in development of the nervous system, other sensory modalities, and even outside the sensory/nervous system [52,53]. Similar complications are encountered in the role of *Hox* genes in axial patterning [54,55,56•], which indicates that homologies of developmental genes need not correspond entirely with morphological homologies. An interesting aspect that deserves further study is the difference in genetic regulatory circuits between larval and adult eyes in animals with metamorphosis, or between first formed and regenerated eyes in animals with such abilities.

Figure 3



Genetic regulatory network for eye development in *Drosophila* (Redrawn from Gehring [36]). At this resolution the network is the same in vertebrates and involves homologous genes.

Before Bilateria

Cnidarians offer an interesting comparison because they have fewer classes of *Pax* genes than found in Bilateria. Apparently, a duplication of *Pax* genes occurred in ancestral Bilateria, and *Pax6* is a product of this duplication [57]. Thus, bilaterian *Pax* gene classes 2/5/8 and 4/6 are both thought to correspond to a single class, *PaxB*, in cnidarians [57,58••]. Although most cnidarians are eyeless, the medusa stage of a few species has lens eyes of surprising sophistication. Of these, the hydrozoan *Cladonema* and the cubozoan *Tripedalia* both express *PaxB* in their eyes [57,58••]. Cubozoans are unique in having pigmented photoreceptors in the larval stage [59•], and *Tripedalia* larvae do express *PaxB* [58••]. As the polyp stage is believed to be ancestral in Cnidaria [60,61], and polyps never have eyes, the connection between eyes and *Pax* genes might be independent from that in Bilateria. Anthozoans, which have no medusa stage, still have a complete cnidarian set of *Pax* genes [62]. Even sponges, which have neither eyes nor a nervous system, do have at least one copy of a *Pax* gene [63]. The pattern that gradually appears is that the degrees of conservation and homology become gradually lower from developmental genes through regulatory networks to ontogenetic processes. Information from developmental genetics will thus have to be interpreted with caution in evolutionary discussions.

Cell-type homologies

Recent attempts to reconcile the seemingly incompatible data from comparative visual physiology and developmental genetics have highlighted the complexity of the question. In an exemplary study, Arendt and Wittbrodt [14] have compiled both classical data and new molecular data, concentrating on possible homologies and divergences in photoreceptor cells throughout the animal

kingdom. The result is a proposed early divergence into a few photoreceptor types, and an early formation of simple eyes from which modern sophisticated eyes developed independently in the various phyla. In a subsequent study, Arendt [64••] emphasizes the importance of tracking homologous cell types and sister cell types through eye development. Indeed, to be homologous, cell types should be the product of the same lineage of cell divisions through ontogenesis, and the ontogenetic path must have originated in a common ancestor. The way Arendt [64••] identifies homologous cell-types is based on the expression of developmental genes and also on the effector genes responsible for the cell's function. This is an interesting and potentially powerful approach, although it probably will not be the definitive answer to all questions about eye evolution. The main danger is that an original cell type can be disguised by co-option of entire regulatory circuits. The many experiments conducted that involve ectopic expression of eyes illustrate how easy it is to override the specification of cell identity, especially in closely related cell types. Based on similar arguments, Oakley [65•] has pointed to the possibility that new eyes might arise from naturally occurring ectopic expression of conserved regulatory modules. Recruitment of regulatory circuits across cell types could be a common evolutionary mechanism for acquiring new functions [66–68]. The problem in identifying homologies from patterns of gene expression is then obvious because developmental genes can be expected to have conserved links to effector genes, and functional convergences or parallelism would thus result in extensive expression of homologous developmental genes in non-homologous cell-types. Certainly, a high degree of genetic promiscuity among cell-types would promote the ability to evolve.

The combinatorial code of gene expression is thus likely to deceptively indicate homology in cases where certain physiological functions have been transferred from one cell type to another by co-option of genetic regulatory circuits. Promiscuous use of the genome can possibly be revealed if the cell pedigree is traced back through the ontogenetic process, but comparisons between distantly related animal groups with highly diverged ontogenies will be difficult at best.

For understanding eye evolution we are left with a number of cues from morphology and ontogenetic paths, from developmental genes and their interactions, and from physiology and effector genes. All of these cues can be deceptive, and none is principally more important than any other. Hypotheses on eye evolution will also have to agree with phylogenetic trees, datings of molecular divergence, and the fossil record. The best we can do is to aim for a synthesis, and it is reassuring that rigorous attempts in this direction are beginning to appear [14,64••].

Conclusions

Within this short review it has not been possible to discuss the situation in each phylum. The eyes in vertebrates, cephalopods, clams, insects, flatworms, and jellyfish have served as examples (Figure 3), but there are many more interesting and intriguing cases that deserve attention. The best studied groups, vertebrates and arthropods, are known to have a handful of coexisting photoreceptive systems responsible for different tasks. Some of these systems are based on non-neural photoreception, with cryptochromes or opsins, others are morphologically distinct photoreceptors with axons, but without accessory cells, and yet others are eyes of varying degrees of sophistication. It is not unlikely that the early metazoans already had several simple photosensory systems, which reflect the basic classes of flavoproteins and opsins known today. It is also possible that early (deep Precambrian) phylogenetic divisions, and subsequent parallel evolution (late Precambrian/early Cambrian) have repeatedly led to the development of eyes originating from some of the photosensory systems but only rarely or never originating from others.

Developmental genes and their regulatory circuits are known to be very conservative, probably because of a limited number of genes, mechanistic constraints in gene interactions and multiple roles of individual genes [69,70]. Parallel eye evolution from homologous photosensory systems would thus be expected to maintain close similarities in developmental genetics. If *Pax* genes had an ancient role in regulating opsin transcription before the first eyes evolved, then the present similarities in regulatory networks might be the result of constraints in gene regulation mechanisms. On top of these 'straight lines' of evolution there might be numerous cases of co-option of regulatory circuits, replacements or losses of genes in regulatory circuits, ectopic replication of entire eyes, and new cases of induction added to make more sophisticated eyes. The anticipated result of such events would display fragments of reliable cues mixed in with many contradictory traits, not unlike the situation described in this review.

Eye evolution has left traces in the biochemistry of the transduction cascade, and in the sequences of effector proteins and their genes. Other traces are found in the ontogenetic process, the lineage of all contributing cell types, and in the developmental regulatory genes. In addition, fossils have left traces, much like blurry snapshots of the past. Unfortunately, there is no single approach that will give us a definitive answer on how eyes have evolved. We simply need to know more about all of the above, and we need to get a much better coverage of the phylogenetic tree. There is little chance that any single discovery will allow us to claim that eye evolution is now understood, but we can expect a steady trickle of information from different disciplines, which

will gradually make the picture clearer and more detailed.

Update

Since the submission of this review two studies with potential importance for eye evolution have been published. The first of these studies [71] reports that *Hox* genes set up bilateral symmetry in a sea anemone, similar to the action of *Hox* genes in Bilateria. On the one hand, if this is a consequence of bilateral symmetry dating back to a common ancestor of both Cnidaria and Bilateria, the two groups can be expected to share more of the early phases of eye evolution. On the other hand, it remains possible that an original, and yet unknown, role of *Hox* genes naturally lends itself to setting up bilateral symmetry, and that this has happened independently in Bilateria and some Cnidaria. The finding nevertheless stresses the urgency of further investigating the transduction machinery and typical eye developmental genes in cnidarians. The second study [72•] presents fossil evidence of the existence of a bilaterian animal some 50 Ma prior to the Cambrian explosion. The seemingly well-preserved animals are small (less than 0.2 mm) and the morphology strongly suggests they were slow moving. Interestingly, these early bilaterians appear to have had several bilateral pairs of shallow epithelial pits, which could have been photoreceptive. The finding is in perfect agreement with the eye evolution scenario proposed here and in earlier works [10,11]. But it is perhaps wise to await the response from other palaeontologists before too many conclusions are drawn from these fossils.

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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. Budd GE: **The Cambrian fossil record and the origin of phyla**.
•• *Integr Comp Biol* 2003, **43**:157-165.
This analysis of the fossil evidence from the important periods before and during the Cambrian explosion provides an unbiased and critical interpretation of available data. It makes clear distinctions between well and poorly supported interpretations, in a way that is unusual in the palaeontological literature. This study serves as the most modern palaeontological reference for comparison with recent findings in molecular biology and developmental genetics.

2. Chen J-Y, Oliveri P, Gao F, Dornbos SQ, Li C-W, Bottjer DJ, Davidson EH: **Precambrian animal life: probable developmental and adult cnidarian forms from southwest China**. *Dev Biol* 2002, **248**:182-196.

3. Dzik J: **Anatomical information content in the Ediacaran fossils and their possible Zoological affinities**. *Integr Comp Biol* 2003, **43**:114-126.

4. Clapham ME, Narbonne GM, Gehling JG: **Paleoecology of the oldest known animal communities: Ediacaran assemblages at Mistaken Point, Newfoundland**. *Paleobiology* 2003, **29**:527-544.

5. Waggoner B, Collins AG: **Reduction ad absurdum: testing the evolutionary relationships of Ediacaran and paleozoic problematic fossils using molecular divergence dates**. *J Paleontol* 2004, **78**:51-61.

6. Adoutte A, Balavoine G, Lartillot N, Lespinet O, Prud'homme B, de Rosa R: **The new animal phylogeny: reliability and implications**. *Proc Natl Acad Sci USA* 2000, **97**:4453-4456.

7. Miyata T, Suga H: **Divergence pattern of animal gene families and relationship with the Cambrian explosion**. *Bioessays* 2001, **23**:1018-1027.

8. Bromham L: **What can DNA tell us about the Cambrian explosion?** *Integr Comp Biol* 2003, **43**:148-156.

9. Levinton J, Dubb L, Wray GA: **Simulations of evolutionary radiations and their application to understanding the probability of a Cambrian explosion**. *J Paleontol* 2004, **78**:31-38.

10. Nilsson D-E: **Eye ancestry: old genes for new eyes**. *Curr Biol* 1996, **6**:39-42.

11. Land MF, Nilsson D-E: *Animal eyes*. New York: Oxford University Press; 2002.

12. Fortey R: **The Cambrian explosion exploded?** *Science* 2001, **293**:438-439.

13. Horspool W, Song P-S: *Handbook of organic photochemistry and photobiology*. Boca Raton: CRC Press; 1995.

14. Arendt D, Wittbrodt J: **Reconstructing the eyes of Urbilateria**. *Philos Trans R Soc Lond B Biol Sci* 2001, **356**:1545-1563.

15. Iseki M, Matsunaga S, Murakami A, Ohno K, Shiga K, Yoshida K, Sugai M, Takahashi T, Hori T, Watanabe M: **A blue-light-activated adanylyl cyclase mediates photoavoidance in *Euglena gracilis***. *Nature* 2002, **415**:1047-1051.

16. Ceriani MF, Darlington TK, Staknis D, Mas P, Petti AA, Weitz CJ, Kay SA: **Light-dependent sequestration of Timeless by cryptochrome**. *Science* 1999, **285**:553-556.

17. van der Horst GTJ, Muijtjens M, Kobayashi K, Takano R, Kanno S, Takao M, de Wit J, Verkerk A, Eker APM, van Leenen: *et al.*: **Mammalian Cry1 and Cry2 are essential for maintenance of circadian rhythms**. *Nature* 1999, **398**:627-630.

18. Whitmore D, Sassone-Corsi P: **Cryptic clues to clock function**. *Nature* 1999, **398**:557-558.

19. Krishnan B, Levine JD, Lynch MK, Dowse HB, Funes P, Hall JC, Hardin PE, Dryer SE: **A new role fore cryptochrome in a *Drosophila* circadian oscillator**. *Nature* 2001, **411**:313-317.

20. Roenneberg T, Merrow M: **Light reception: discovering the clock-eye in mammals**. *Curr Biol* 2002, **12**:R163-R165.

21. Deininger W, Fuhrmann M, Hegemann P: **Opsin evolution: out of the wild green yonder?** *Trends Genet* 2000, **16**:158-159.

22. Ridge KD: **Algal rhodopsins: phototaxis receptors found at last**. *Curr Biol* 2002, **12**:R588-R590.

23. Arnheiter H: **Eyes viewed from the skin**. *Nature* 1998, **391**:632-633.

24. Moutsaki P, Bellingham J, Soni BG, David-Gray ZK, Foster RG: **Sequence, genomic structure and tissue expression of carp (*Cyprinus carpio* L.) vertebrate ancient (VA) opsin**. *FEBS Lett* 2000, **473**:316-322.

25. Berson DM, Dunn FA, Takao M: **Phototransduction by retinal ganglion cells that set the circadian clock**. *Science* 2002, **295**:1070-1073.

26. Jenkins A, Munoz M, Tarttelin EE, Bellingham J, Foster RG, Hankins MW: **VA opsin, melanopsin, and an inherent light response within retinal interneurons**. *Curr Biol* 2003, **13**:1269-1278.

27. Menaker M: **Circadian photoreception**. *Science* 2003, **299**:213-214.

28. Salvivi-Plawen LV, Mayr E: **On the evolution of photoreceptors and eyes**. *Evol Biol* 1977, **10**:207-263.

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

30. Fernald RD: **Evolution of eyes**. *Curr Opin Neurobiol* 2000, **10**:444-450.

31. Nilsson D-E: **Eyes as optical alarm systems in fan worms and ark clams**. *Philos Trans R Soc Lond B Biol Sci* 1994, **346**:195-212.

32. Piatigorsky J: **Gene sharing in lens and cornea: facts and implications**. *Prog Retin Eye Res* 1998, **17**:145-174.

33. Piatigorsky J, Kozmik Z, Horwitz J, Ding L, Carosa E, Robison WG Jr, Steinbach PJ, Tamm ER: **α-crystalline of the scallop lens. A dimeric aldehyde dehydrogenase class 1/2 enzyme-crystalline**. *J Biol Chem* 2000, **275**:41064-41073.

34. Gehring WJ: **The master control gene for morphogenesis and evolution of the eye**. *Genes Cells* 1996, **1**:11-15.

35. Gehring WJ, Ikeo K: ***Pax6* mastering eye morphogenesis and eye evolution**. *Trends Genet* 1999, **15**:371-377.

36. Gehring WJ: **The genetic control of eye development and its implications for the evolution of the various eye types**. *Int J Dev Biol* 2002, **46**:65-73.

37. Wawersik S, Maas RL: **Vertebrate eye development as modeled in *Drosophila***. *Hum Mol Genet* 2000, **9**:917-925.

38. Baker NE: **Master regulatory genes; telling them what to do**. *Bioessays* 2001, **23**:763-766.

39. Kumar JP, Moses K: **Eye specification in *Drosophila*: perspectives and implications**. *Semin Cell Dev Biol* 2001, **12**:469-474.

40. Ashery-Padan R, Gruss P: **Pax6 lights-up the way for eye development**. *Curr Opin Cell Biol* 2001, **13**:706-714.

41. • Zuber ME, Gestri G, Viczian AS, Barsacchi G, Harris WA: **Specification of the vertebrate eye by a network of eye field transcription factors**. *Development* 2003, **130**:5155-5167.

This study gives a very thorough description of the extent and timing of expression of the various control genes in Xenopus eye development. The discussion also contains a thoughtful comparison with the conditions in Drosophila.

42. Jang C-C, Chao J-L, Jones N, Yao L-C, Bessarab DA, Kuo YM, Jun S, Desplan C, Beckendorf SK, Sun YH: **Two Pax genes, eye gone and eyeless, act cooperatively in promoting *Drosophila* eye development**. *Development* 2003, **130**:2939-2951.

43. Jarman AP: **Developmental genetics: vertebrates and insects see eye to eye**. *Curr Biol* 2000, **10**:R857-R859.

44. Neumann CJ, Nusslein-Volhard C: **Patterning of the zebrafish retina by a wave of Sonic hedgehog activity**. *Science* 2000, **289**:2137-2139.

45. Pichaud F, Treisman J, Desplan C: **Reinventing a common strategy for patterning the eye**. *Cell* 2001, **105**:9-12.

46. Malicki J: **Cell fate decisions and patterning in the vertebrate retina: the importance of timing, asymmetry, polarity and waves**. *Curr Opin Neurobiol* 2004, **14**:15-21.

47. Glardon S, Holland LZ, Gehring WJ, Holland ND: **Isolation and developmental expression of the amphioxus *Pax-6* gene (*Amphipax-6*): insights into eye and photoreceptor evolution**. *Development* 1998, **125**:2701-2710.

48. Pichaud F, Desplan C: **Pax genes and eye organogenesis**. *Curr Opin Genet Dev* 2002, **12**:430-434.

49. Pineda D, Rossi L, Batistoni R, Salvetti A, Marsal M, Gremigni V, Falleni A, Gonzalez-Linares J, Deri P, Salo E: **The genetic network of prototypic planarian eye regeneration is Pax6 independent**. *Development* 2002, **129**:1423-1434.

50. Saló E, Pineda D, Marsal M, Gonzalez J, Gremigni V, Batistoni R: **Genetic network of the eye in Platyhelminthes: expression and functional analysis of some players during planarian regeneration**. *Gene* 2002, **287**:67-74.

51. Callaerts P, Muñoz-Marmol AM, Glardon S, Castillo E, Sun H, Li WH, Gehring WJ, Saló E: **Isolation and expression of a Pax-6 gene in the regenerating and intact Planarian Dugesia(G)tigrina**. *Proc Natl Acad Sci USA* 1999, **96**:558-563.

52. Simpson TI, Price DJ: **Pax6; a pleiotropic player in development**. *Bioessays* 2002, **24**:1041-1051.

53. Li X, Oghi A, Zhang J, Krones A, Bush KT, Glass CK, Nigam SK, Aggarwal AK, Maas R, Rose DW, Rosenfeld MG: **Eye protein phosphatase activity regulates Six1-Dach-Eye transcriptional effects in mammalian organogenesis**. *Nature* 2003, **426**:247-254.

54. Lacalli T: **Body plans and simple brains**. *Nature* 2003, **424**:263-264.

55. Lee PN, Callerts P, de Couet HG, Martindale MQ: **Cephalopod Hox genes and the origin of morphological novelties**. *Nature* 2003, **424**:1061-1065.

56. • Lowe CJ, Wu M, Salic A, Evans L, Lander E, Stange-Thomann N, Gruber CE, Gerhart J, Kirschner M: **Anteroposterior patterning in hemichordates and the origins of the chordate nervous system**. *Cell* 2003, **113**:853-865.

Although not directly focused on eye evolution, this study gives a good insight into the possibly very simple organization of ancestral chordates. Hemichordates have a diffuse nervous system, here proposed to be ancestral in chordates, and patterning of the nervous system in Hemichordates is here shown to be very similar to that of chordates. Potentially, this means that early chordates might have had to invent or reinvent eyes independently from other bilaterian phyla.

57. Sun H, Dickinson DP, Costello J, Li W-H: **Isolation of *Cladonema Pax-B* genes and studies of the DNA-binding properties of cnidarian Pax paired domains**. *Mol Biol Evol* 2001, **18**:1905-1918.

58. •• Kozmik Z, Daube M, Frei E, Norman B, Kos L, Dishaw LJ, Noll M, Piatigosky J: **Role of Pax genes in eye evolution: a cnidarian *PaxB* gene uniting Pax2 and Pax6 functions**. *Dev Cell* 2003, **5**:773-785.

The *PaxB* gene of the jellyfish *Tripedalia* is here shown to display an ancestral structure and function resembling both *Pax2* and *Pax6* in Bilateria. The finding suggests that a cnidarian type *PaxB* gene was duplicated in early Bilateria to produce *Pax2* and *Pax6*. *PaxB* is expressed in the jellyfish eye and is also able to induce ectopic eyes in *Drosophila*.

59. • Nordström K, Wallén R, Seymour J, Nilsson D: **A simple visual system without neurons in jellyfish larvae**. *Proc R Soc Lond B Biol Sci* 2003, **270**:2349-2354.

This study reports the discovery of the simplest visual system known. Planula larvae of the jellyfish *Tripedalia* are shown to have photoreceptor cells containing a pigment cup within the cell in addition to a motile cilium. The larvae have no nervous system, and there is thus no means for the photoreceptor cells to control anything but their own cilium. The finding calls for investigations of opsins and transduction proteins in these unusual photoreceptors.

60. Collins AG: **Phylogeny of medusozoa and the evolution of cnidarian life cycles**. *J Evol Biol* 2002, **15**:418-432.

61. Galliot B, Schmid V: **Cnidarians as a model system for understanding evolution of regeneration**. *Int J Dev Biol* 2002, **46**:39-48.

62. Miller DJ, Hayward DC, Reece-Hoyes JS, Scholten I, Catmull J, Gehring WJ, Callerts P, Larsen JE, Ball EE: ***Pax* gene diversity in the basal cnidarian *Acropora millepora* (Cnidaria, Anthozoa): implications for the evolution of the Pax gene family**. *Proc Natl Acad Sci USA* 2000, **97**:4475-4480.

63. Hoshiyama D, Suga H, Iwabe N, Koyanagi M, Nikoh N, Kuma K, Matsuda F, Honjo T, Miyata T: **Sponge *Pax* cDNA related to *Pax-2/5/8* and ancient gene duplication in the *Pax* family**. *J Mol Evol* 1998, **47**:640-648.

64. •• Arendt D: **Evolution of eyes and photoreceptor cell types**. *Int J Dev Biol* 2003, **47**:563-571.

The author develops the concept of homologous and sister cell types in eye evolution. It can be seen as a continuation and elaboration of an earlier study by Arendt and Wittbrodt [14], and taken together the two studies represent the most modern detailed synthesis of available data on eye evolution in animals.

65. • Oakley TH: **The eye as a replicating and diverging, modular developmental unit**. *Trends Ecol Evol* 2003, **18**:623-627.

As a contribution to the ongoing debate on eye evolution this study emphasizes the role of naturally occurring 'ectopic expression' of eye

developmental genes. The author argues that new photosensory systems or eyes might have originated this way, which will make it hard to discriminate between ancestral and replicated eyes in animals.

66. Wray GA: **Do convergent developmental mechanisms underlie convergent phenotypes?** *Brain Behav Evol* 2002, **59**:327-336.

67. Rudel D, Sommer RJ: **The evolution of developmental mechanisms**. *Dev Biol* 2003, **264**:15-37.

68. Sander K, Schmidt-Ott U: **Evo-devo aspects of classical and molecular data in a historical perspective**. *J Exp Zool* 2004, **302**:69-91.

69. Hodin J: **Plasticity and constraints in development and evolution**. *J Exp Zool* 2000, **288**:1-20.

70. Richardson MK, Brakefield PM: **Hotspots of evolution**. *Nature* 2003, **424**:894-895.

71. Finnerty JR, Pang K, Burton P, Paulson D, Martindale MQ: **Origins of bilaterian symmetry: Hox and Dpp expression in a sea anemone**. *Science* 2004, **304**:1335-1337.

72. • Chen J-Y, Bottjer DJ, Oliveri P, Dornbos SQ, Gao F, Ruffins S, Chi H, Li C-W, Davidson EH: **Small bilaterian fossils from 40 to 55 million years before the Cambrian**. *Science* 2004; Online ahead of print.

The authors describe the oldest known fossil animal with eyes. The fossils date back to about 590 Ma ago and thus predate other fossilised eyes by more than 60 Ma. The structures interpreted as eyes are three pairs of shallow epithelial pits located in the front half of the animal.