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New Perspectives on Eye Development and the Evolution of Eyes and Photoreceptors

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Walter Gehring has been involved in studies of Drosophila genetics and development, particularly in the analysis of cell determination in the embryo and transdetermination of imaginal discs. He has made significant contributions to the study of the heat shock genes, various transposons and the homeotic genes which are involved in the genetic control of development. He and his group have discovered the homeobox, a DNA segment characteristic for homeotic genes which is not only present in arthropods and their ancestors, but also in vertebrates up to man. He has been involved in the development and application of enhancer trapping methods. He and his collaborators have identified Pax 6 as a master control gene for eye development, which led to a new theory about the monophyletic origin of the eyes in evolution.

Abstract

Recent experiments on the genetic control of eye development have opened up a completely new perspective on eye evolution. The demonstration that targeted expression of one and the same master control gene, that is, Pax6 can induce the formation of ectopic eyes in both insects and vertebrates, necessitates a reconsideration of the dogma of a polyphyletic origin of the various eye types in all the animal phyla. The involvement of Pax6 and six1 and six3 genes, which encode highly conserved transcription factors, in the genetic control of eye development in organisms ranging from planarians to humans argues strongly for a monophyletic origin of the eye. Because transcription factors can control the expression of any target gene provided it contains the appropriate gene regulatory elements, the conservation of the genetic control of eye development by Pax6 among all bilaterian animals is not due to functional constraints but a consequence of its evolutionary history. The prototypic eyes postulated by Darwin to consist of two cells only, a photoreceptor and a pigment cell, were
Introduction

In the course of evolution several basically different eye types have been generated, like the camera-type eye, the compound eye, and the mirror eye (Figure 1). These eye types are different not only with respect to their morphology and physiology but also with respect to their mode of development. This has led to the dogma that eyes have evolved in all animal phyla 40 to 60 times independently (Salvini-Plawen and Mayr 1961). However, recent genetic experiments cast serious doubts on this notion and argue strongly in favor of a monophyletic origin of the various eye types followed by divergent, parallel, and convergent evolution. In his latest book, Ernst Mayr (2001) admits that his earlier notion may no longer be correct. In the following article I discuss the evidence arguing for a monophyletic origin of the eyes, and I shall follow the eye back to its origins from single-celled photoreceptors.

The Genetic Control of Eye Development

Mutations affecting eye development are easily detectable and the eyeless (ey) mutation in Drosophila was discovered as early as 1915 by Hoge. A similar mutation was found in mice and designated as Small eye because the heterozygous animals have reduced eyes, whereas the homozygous fetuses that die in utero lack not only the eyes but also the nose and a large part of the forebrain, including the pineal organ (Hill et al. 1991). A hereditary syndrome called aniridia causes a very similar phenotype in humans; reduced iris in heterozygous individuals, and two homozygous mutant aborted fetuses have been described that lacked eyes and nose completely and suffered brain damage. The Small eye and Aniridia genes were cloned by Walther and Gruss (1991) and Ton et al. (1991), respectively, and correspond to the highly conserved Pax6 gene. The Pax6 homolog of Drosophila was cloned by Quiring et al. (1994) and surprisingly turned out to correspond to the eyless (ey) gene of Hoge. The fact that small eye, aniridia, and eyeless are mutations in homologous genes suggested to me that Pax6 might be a master control gene specifying eye development in both vertebrates and insects.

To test this hypothesis I decided to construct a Pax6 gain-of-function mutation to express Pax6 ectopically in an attempt to induce ectopic eye structures. It is relatively easy to abolish eye formation but more difficult to induce an eye ectopically. Two of my collaborators, Georg Halder and Patrick Callaerts, used the yeast transcription factor gal4 to drive eyeless cDNA into imaginal discs other than the eye disc (Figure 2). After several months of failure, they succeeded in inducing ectopic eye structures on the antennae, legs, and wings, which made the front page of the New York Times with an article titled “Scientists Out Do Hollywood.” Callaerts later showed by recording electroretinograms that some of the ectopic eyes on the antennae are fully functional.

Subsequently, we also tested the mouse Pax6 gene in Drosophila and showed that it is capable of inducing ectopic eyes in Drosophila (Figure 3). These eyes are, of course, Drosophila eyes and not mouse eyes, because we have only exchanged the main switch to trigger eye development and all of the other genes required for forming an eye (which we estimate to be ~2,000) are provided by the Drosophila host.

These experiments lead to the conclusion that Pax6 is a master control gene on the top of the genetic cascade leading to eye morphogenesis and that this master switch can initiate eye development both in insects and mammals. Pax6 encodes a gene regulatory protein with two DNA binding domains—a paired domain as well as a homeodomain. The various Pax genes found in mice and flies clearly illustrate the principle of evolutionary tinkering (Jacob 1977).
The nine members of the gene family did not arise independently de novo but rather by recombination of bits and pieces of preexisting genes like paired domains, octapeptides, homeodomains, and parts thereof. Pax6 has a paired domain and a homeodomain but lacks the octapeptide motif. Its nearest relatives are Pax2, 5, and 8, which have a paired domain plus an octapeptide, but only a partial homeodomain consisting of the N-terminal arm and the first α-helix. It will be interesting to identify their last common precursor, which may still exist in some cnidarians (see later discussion).

**Deciphering the Eye Genetic Program**

Because the first spontaneous ey mutants, ey² and ey⁰, are caused by transposon insertions (Quiring et al. 1994) they are not null mutations. They still produce a normal transcript in parts of the nervous system, but they fail to be expressed in the eye disc because of the fact that the two transposons in ey² and ey⁰ have inserted into an eye-specific enhancer located in the first intron of the gene (Hauck et al. 1999). Therefore, we induced a true null mutation in ey by mutagenesis with ethylmethanesulfonate (Flister et al. unpublished data; Punzo et al. 2004). However, this null mutation only removed the compound eyes in most flies and not the ocelli, suggesting the presence of a second gene with partially redundant function. Indeed, in collaboration with M. Busslinger we discovered a second Pax6 homolog in *Drosophila* (Czerny et al. 1999) which we designated *twin of eyeless* (*toy*). This second gene is only found in holometabolous insects, *Drosophila*, and silkworms but not in the more primitive hemimetabolous insects, like grasshoppers or springtails. Null mutations in toy have a much more severe phenotype (Flister et al. unpublished data; Kronhamn et al. 2002), they are essentially headless, forming only the proboscis and the thorax but no antennae and head structures, except two spheres of eye facets found back in the thorax, which presumably reflect the residual activity of the ey⁺ gene, which is still present in these flies (Punzo et al. 2004). Ectopic expression of toy is also capable of inducing ectopic eyes (Figure 2B). My analysis indicates that ey and toy arose from a duplication and diverged in function, so that toy acts upstream of ey and activates it in normal development leading to the intercalation of an additional gene into the eye morphogenetic pathway (see later discussion).

We also identified direct target genes of ey in particular *sine oculis* (so), a homeobox gene that is also conserved in both vertebrates and invertebrates (Niimi et al. 1999). The so enhancer contains five binding sites for toy and ey (Punzo et al. 2002) all of which are recognized by TOY protein, whereas EY binds only to two of them. All five binding sites have to be mutated to abolish enhancer activity completely. So protein forms a heterodimer with *eyes absent* (eya) a protein phosphatase. The so gene alone, when ectopically expressed, does not induce ectopic eyes; however, in combination with eya eye structures are induced, but less efficiently than by ey, and there is a positive feedback loop from so/eya to ey (Figure 4).

**Figure 1.** Different eye types. (A) Camera-type eye of an owl. (B) Compound eye of a horsefly. (C) Mirror-type eye of a scallop. (D) Prototypic eyes consisting of a single photoreceptor cell and pigment cell in the planarian *Polycelis auricularia*. 
Following these studies on single genes, I undertook a more global approach to decipher the entire eye morphogenetic pathway of *Drosophila* and eventually compare it to that of the mouse. My colleagues and I have begun to use DNA microarrays to determine the patterns of gene expression at consecutive stages of eye development. By comparing the genes expressed in a leg disc in which an eye field has been induced with those in a normal leg disc, we have determined the earliest genes expressed on the top of the genetic hierarchy. The large fraction of these early genes are transcription factors (Figure 5), whereas very few of the structural genes are expressed at this early stage (Michaut et al. 2003).

Darwin and the Problem of Eye Evolution

Charles Darwin in *The Origin of Species* (1882) had great difficulties with eye evolution and devoted an entire chapter to it, “Difficulties of the Theory,” in which he discusses “organs of extreme perfection and complication:

To suppose that the eye with all its inimitable contrivances for adjusting the focus to different distances, for admitting different amounts of light and for the correction of spherical and chromatic aberration, could have been formed by natural selection, seems, I freely confess, absurd in the highest degree.

But then he continues:

Reason tells me, that if numerous gradations from a simple and imperfect eye to one complex and perfect can be shown to exist, each grade being useful to its possessor, as is certainly the case; if further, the eye ever varies and the variations be inherited, as is likewise certainly the case; and if such variations should be useful to any animal under changing conditions of life, then the difficulty of believing that a perfect and complex eye could be formed by natural selection, though insuperable by our imagination, should not be considered as subversive of the theory.
This pushes the question of eye evolution back to the problem of how the first primitive eye, the prototype, evolved. The evolution of an eye prototype would seem to be a highly improbable stochastic event, because selection can only work after the various components are assembled into a prototype that is at least partially functional as a photoreceptor organ. “The simplest organ which can be called an eye consists of an optic nerve, surrounded by pigment-cells and covered by translucent skin, but without any lens or other refractive body.”

Such primitive eyes are found, for example, in certain flatworms. Hesse (1897) described the eyes of *Planaria torva*, which consists of three photoreceptor cells and a single pigment cell only. There is a planarian species *Polyedris auricularia*, which has multiple eyes with one photoreceptor cell and one pigment cell only, which corresponds exactly to the Darwinian prototype (Figure 1D).

For the present discussion we adopt Darwin’s definition of an eye as an organ consisting of at least two different cell types, photoreceptor cells and pigment cells. The “eyes” of protists are organelles (not organs) formed within a single cell and arise by the assembly of molecules within a cell rather than by the assembly of different cells, which is a fundamental difference with respect to the genetic control of morphogenesis.

Because the evolution of a prototypic eye is a highly improbable stochastic event that is not driven by selection, the hypothesis of a polyphyletic origin of the eyes, arising 40 to 65 times independently, is extremely unlikely and incompatible with Darwin’s ideas. Furthermore, all three major eye types (the camera-type, the compound eye, and the mirror eye) are found within the same class of molluscs, in the bivalvia, making an independent evolutionary origin even more unlikely.

Our finding of the same master control gene for eye development in mammals and insects suggested that Pax6 might be the universal master control gene in both vertebrates and invertebrates. To test this hypothesis we tested the mouse *Pax6* gene in *Drosophila* and reciprocally the *Drosophila ey* and *toy* genes in *Xenopus* (Onuma et al. 2002). As shown in Figures 3 and 6 in both cases ectopic eye structures can be induced, suggesting that the genetic cascade leading to eye formation is similar in vertebrates and invertebrates. Furthermore, not only *Pax6* is highly conserved in eye development, but also so, the direct target gene of *Pax6* is involved in morphogenesis of the vertebrate and invertebrate eyes, suggesting that the camera-type eye and the compound eye share similar eye morphogenetic programs. However, we have also found clear differences, for example, the *Retina*
homeobox gene (Rx) (Mathers et al. 1997) is expressed in the retina of the mouse, but not in Drosophila, where it is expressed in the brain only (Eggert et al. 1998). Nevertheless, the eye morphogenetic programs of mice and flies are so similar that they suggest a common evolutionary ancestry.

**Monophyletic Origin of the Different Eye Types in Bilateria**

True Pax6 homologs (orthologs) have been found in all bilateria analyzed so far, ranging from planarians to humans,
including C. elegans. This nematode has lost its eyes because it lives underground, but it has retained its Pax6 gene. The reason for retaining the Pax6 gene lies in the pleiotropic function of Pax6, which specifies not only the eye but also the nose and parts of the brain. Therefore, there is selective pressure to maintain Pax6 despite of the reduction of the eyes. This interpretation is supported by the fact that C. elegans has lost its rhodopsin gene(s); because the only function of rhodopsin is light reception, there is no selective pressure to maintain the rhodopsin gene. For C. elegans, the squid (Loligo), the seasquirt (Phallusia), and the lancelet (Amphioxus) we have shown that their Pax6 genes are capable of inducing ectopic eyes in Drosophila. The only exception to this rule are the two Pax6 genes of the planarian (Dugesia tigrinina), which apparently have diverged too much. However, we also have obtained functional genetic evidence that Pax6 and six (so) genes are also involved in eye morphogenesis in Dugesia.

By injection of double-stranded RNA (RNA interference) against sine oculis we have been able to prevent eye regeneration in Dugesia (Pineda et al. 2000). We have also developed methods for electroporation of planarians in toto that allowed us to apply a different strategy for testing the genetic control of eye development by Pax6. If Pax6 is highly conserved, it is to be expected that its target sites are also conserved to specify the same genetic circuitry. Therefore, we analyzed the Pax6-responsive P3-enhancer, which is found in front of the rhodopsin genes ranging from fruitflies to humans (Berghammer et al. 1999). By fusing three copies of P3 to a minimal promoter driving green fluorescent protein (GFP) Horn and Wimmer (2000) have constructed transposon-derived vectors that function in a wide variety of organisms. Transgenic animals generally express the P3-GFP construct in their eyes (Figure 7A).

By electroporation we transformed the totipotent neoblasts with the P3-GFP construct. These stem cells are capable of replacing somatic cells as well as germ cells, which are turning over. When the transformed neoblasts enter the eye region, they begin to express the GFP marker and gradually become photoreceptor cells until the eyes of the host are green fluorescent (Figure 7C and D). Neoblasts can also colonize the gonad and become germ cells, which allowed us to obtain F1 progeny with completely green eyes (Figure 7B) and to establish stable transgenic lines from them. These results indicate that not only Pax6 is conserved but also its target sites and the genetic circuits leading to eye morphogenesis.

The functional conservation of Pax6 and so from planarians to humans strongly suggests a monophyletic origin of the bilaterian eye. Because transcription factors can control the expression of any target gene (provided it contains the appropriate gene regulatory elements), there are no functional constraints linking Pax6 to eye development. Therefore, the link between Pax6 and so to eye development...
must simply be a consequence of a common evolutionary
history. Therefore, I have proposed that all bilaterian eye
types go back to a single root, a Darwinian prototype as,
for example, found in planarians (Figure 1; Hesse 1897).

Starting from this prototype, selection has generated in-
creasingly more performant eyes and that the various eye
types arose by divergent, parallel, and convergent evolution
(Figure 8).

**Figure 8.** Hypothetical evolution of photosensitive cells containing rhodopsin as a light receptor and monophyletic
evolution of the various eye types. The eye prototype consisting of a photoreceptor cell and a pigment cell is assembled under
the control of *Pax6* (after Gehring and Ikeo 1999).
In cnidarians eyes are found only sporadically in some Hydrozoans, like *Cladonema* (Figure 9) and in box-jellyfish (cubozoans) like *Tripedalia*, and we do not know whether other jellyfish have lost their eyes in the course of evolution or whether they never acquired them. Neither in corals (Miller et al. 2000; Plaza et al. 2003) nor jellyfish (Gröger et al. 2000; Kozmik et al. 2003; Sun et al. 1997, 2001) a bonafide *Pax6* gene has yet been found, but in *Tripedalia* Kozmik et al. (2003) have described a *PaxB* gene that might be an ancestral gene of *Pax6*. The paired domain of *PaxB* of *Tripedalia* shows 82% sequence identity to mammalian *Pax2* and 75% to *Pax6*, and it also contains an octapeptide like *Pax2*, but it has a complete homeobox like *Pax6*, whereas *Pax2* retains only the N-terminal part of the homeobox. This indicates that *PaxB* is structurally a mosaic between *Pax2* and *Pax6*, which is also supported by functional studies. In *Drosophila* *PaxB* can partially complement *Pax2* mutants (*sparkling*) and also induce ectopic eyes like *Pax6* (Kozmik et al. 2003). Therefore, we consider *PaxB* to be a candidate ancestral gene of both *Pax6* and *Pax2*. In the hydrozoan *Cladonema*, Stierwald et al. (2004) have obtained evidence that the *six 1* and *six 3* homologs are both involved in eye regeneration (Figure 9), the same genes that are also controlling eye development in vertebrates, which lends strong support for the hypothesis of a monophyletic origin of the eye.

In *Tripedalia* the transition from unicellular eye organelles to multicellular eye organs can be observed. The planula larva of *Tripedalia* forms unicellular photoreceptors scattered over the epidermis (Figure 10), whereas the adult jellyfish forms elaborate multicellular eyes (Nordström et al. 2003). These unicellular photoreceptors contain both the putative photosensory microvilli and the shielding pigment granules within the same cell, which also carries a motor cilium that enables the larva to show phototactic behavior. These unicellular photoreceptors closely resemble some unicellular photosensitive protists. We propose that in the course of evolution these unicellular photoreceptors has duplicated and differentiated into at least two different cell types, photoreceptor cells and pigment cells, as they are found in adult *Tripedalia* jellyfish and in the Darwinian prototype eyes of planarians (*Polyedris auricularia*).

The Evolution of Eyes and Brain

Because the eye in vertebrates develops as an evagination of the brain and is part of the brain it has generally been assumed that brain evolved before the eye. Furthermore, the
detailed visual processing occurs in the brain rather than in
the eye, that is, we actually see with the brain. Nevertheless,
we have proposed that the eye came first in evolution
(Gehring and Ikeo 1999). The sensory organs are gathering
information, whereas the brain is an information-processing
organ, similar to a computer. If no information is acquired,
there is no need for an elaborate information-processing
organ. As more information is acquired by the eyes and other
sensory organs, the brain evolves in parallel to process this
information and transmit it to the effector organs, like the
muscles. This is supported by the fact that both the eyes (and
nose) and parts of the brain are specified by Pax6. Evidence
for the idea that the eyes evolved first, comes from the study
of jellyfish like Cladonema, which have elaborate eyes but no
brain. The eyes are located at the base of the tentacles (Figure
9) and transmit their response directly to the muscles without
processing by the brain. Of course, we cannot rule out the
possibility that Cladonema has lost its brain, but it seems
unlikely for a free-living pelagic animal to lose its brain in the
course of evolution. Therefore, I consider it likely that the
eyes evolved first, before the brain. This point of view
is supported by the observation that the unicellular photoreceptor
organelles in Tripedalia larvae have evolved in the
apparent absence of an elaborate nervous system
(Nordström et al. 2003).

**Retrograde and Intercalary Evolution**

Horowitz (1945) considered the evolution of biosynthetic
pathways, which are in general linear, leading from the
original substrate(s) over many successive enzymatic steps to
the final biosynthetic product. A rather simple Darwinian
solution to the problem of linearity was found by Horowitz
by assuming a retrograde mode of evolution (Figure 11A).
Originally the respective organism could not synthesize the
respective product and had to take it up from the
environment. When the supply in the environment was
exhausted, those organisms whose had the last enzyme in the
pathway could make use of the immediate precursor and
convert it to the final product, until the supply of the
immediate precursor was also exhausted. Then only those
organisms could survive that possessed the second last
enzyme and so on until the biosynthetic pathway was
completely established.

For the evolution of morphogenetic pathways, like eye
morphogenesis, I propose a mechanism of intercalary
evolution (Figure 11B). The eye prototype, which is due to
a purely stochastic event that assembles a photoreceptor and
a pigment cell into a visual organ, requires the function of at
least two classes of genes, a master control gene, Pax6, and
the structural genes encoding rhodopsin, for instance, the
top and the bottom of the genetic cascade. Starting from
such a prototype increasingly more sophisticated eye types
arose by recruiting additional genes into the morphogenetic
pathway. At least two mechanisms of recruitment are known
that lead to the intercalation of additional genes into the
genetic cascade. These mechanisms are gene duplication and
enhancer fusion. A case of gene duplication can be illustrated
with ey and toy. More primitive insects as spring tails and
grasshoppers possess a single Pax6 gene, whereas Drosophila
ey and toy genes have functionally diverged in evolution, and
the positive autocatalytic feedback loop found in Pax6 has
evolved into a heterocatalytic loop by which toy activates ey,
leading to the intercalation to ey underneath toy into the
morphogenetic pathway. The second mechanism, enhancer
fusion, has been described in lens proteins mainly by
Piatigorsky and Wistow (1989) and can also by illustrated by the
Drosophila lens protein drosocrystallin (Janssens and
Gehring 1999). This protein is not conserved in evolution and
found only in insects but not in vertebrates. The analysis
of the amino acid sequence of the drosocrystallin protein
clearly indicates that it belongs to the family of cuticle
proteins. By fusing it to a lens-specific enhancer, the
Drosocrystallin gene has been recruited into the eye
developmental pathway. In some cases the recruitment need
not be associated with gene duplication, if the gene can still
fulfill its original function; in other cases the recruitment may
be accompanied by a gene duplication leaving an active gene
copy behind to ensure the original function of the gene.

**The Origin of Photoreceptor Cells in Metazoa**

For the origin of metazoan photoreceptor cells I have put
forward two hypotheses: one based on cell differentiation
and a more speculative model based on symbiosis.

The more conventional idea is to assume that metazoa
arose from a colony of flagellate-like cells like Volvox and
Eudorina (Figure 12) in which all of the cells originally
possessed a photoreceptor organelle, an “eyespot” that
transmits its signals to the flagella and allows for phototactic
behavior. Subsequent cellular differentiation would lead to
an arrangement as found in the Tripedalia larva (Figure 10),
which possesses unicellular photoreceptors scattered among
the other ciliated cells in the ectoderm of the larva. The
photoreceptor cells not only possess microvilli, presumably
containing the visual pigment, but also melanin pigment
granules shielding the basal side of the cell, as well as a cilium,
which is thought to be used for steering of the larva toward
or away from the light source. The next step would involve
the differentiation of the unicellular photoreceptors into two
cell types, a photoreceptor cell and a pigment cell and their
assembly into a prototypic eye.

The alternative symbiotic hypothesis is based on the
observation that the eye organelle in flagellates like Volvox or
Chlamydomonas is located in the chloroplast, suggesting that
light perception goes all the way back to cyanobacteria that
became integrated into eukaryotic cells as chloroplasts.
Indeed, the sequencing of the complete genome of the
cyanobacterium Nostoc has revealed the presence of a proteorhodopsin gene (Kaneko et al. 2001). A proteorhodopsin
gene has also been found in the dinoflagellate Pyrocystis
and shown to be controlled by the internal clock (Okamoto
and Hastings 2003). Another observation supporting the
symbiont hypothesis comes mainly from the work of Greuet (1965, 1969), who described the photoreceptor organelles of some dinoflagellates like *Erythropsis* and *Warnovia*, which are as elaborate as the human eye but assembled in a single cell (Figure 13). They consist of a cornea-like surface layer, a lens-like structure, a retina-like structure with stacked membranes (or microvilli), and a pigment cup, all in a single cell. Because dinoflagellates are common symbionts in corals, sea anemones, and other cnidarians, dinoflagellates might have transferred the genes required for photoreception to the...
cnidarians, which would also explain their sporadic occurrence in different groups of cnidarians.

This symbiont hypothesis, which I call the Russian doll model, assumes that light sensitivity first arose in cyanobacteria, the earliest known fossils on Earth. These cyanobacteria were subsequently taken up by eukaryotic red algae as primary chloroplasts surrounded by an outer and inner bacterial membrane separated by a proteoglycan layer. Subsequently, the red algae were taken up by dinoflagellates as secondary chloroplasts surrounded by an additional third membrane coming from the primary red algal host. In some species of dinoflagellates like *Erythropsis* and *Warnowia*, which do not have any chloroplasts, these secondary chloroplasts may have been transformed into elaborate photoreceptor

Figure 13. Eye organelle of the unicellular dinoflagellates *Erythropsis* and *Warnowia*. (A) *Erythropsis*. (B) Eye organelle of *Erythropsis*. (C) *Warnowia*. (D) Eye organelle of *Warnowia*. (E) Nucleus and eye organelle of *Warnowia*. (F) Birefringence, the retina-like structure detected in polarized light in *Warnowia*. (G) Ultrastructure of the eye organelle of *Warnowia*. (H) Ultrastructure of the retina-like structure with stacked membranes and large pigment granules. A–F courtesy of Makiko Seimiya and Jean and Colette Febvre; G–H from Greuet 1969.
organelles as suggested by Greuet. Because dinoflagellates (also called zooxanthellae) are commonly found as symbionts in cnidarians, dinoflagellates may have transferred their photoreceptor genes to cnidarians. This is the most speculative step in the Russian doll model, but it can be tested by looking for dinoflagellate genes in the cnidian genomes. These two hypotheses, the cellular differentiation and the Russian doll model, are not mutually exclusive and are subject to further investigations.

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References


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