On the Evolution of Eyes: Would You Like It Simple or Compound?

Charles S. Zuker

In his book *On the Origin of Species*, Darwin devoted a section to "difficulties on the theory." One such difficulty dealt with the evolution of organs of extreme perfection and complication and focused on the eye. On page 785 of this issue (*1*), Quiring and co-workers report the isolation of the *Drosophila* homolog of the vertebrate *Pax-6* gene; this fly homolog is encoded by the *eyeless* gene, a locus required for the development of the fly eye. What is remarkable about this result is that *Pax-6* has also been implicated as a key regulator of eye development in vertebrates (see below). But the eyes of flies and humans are thought to have evolved completely independently of each other. As Salvini-Plawen and Mayr wrote in their 1970 study on the evolution of eyes (*2*), "It requires little persuasion to become convinced that the lens eye of a vertebrate and the compound eye of an insect are independent evolutionary developments."

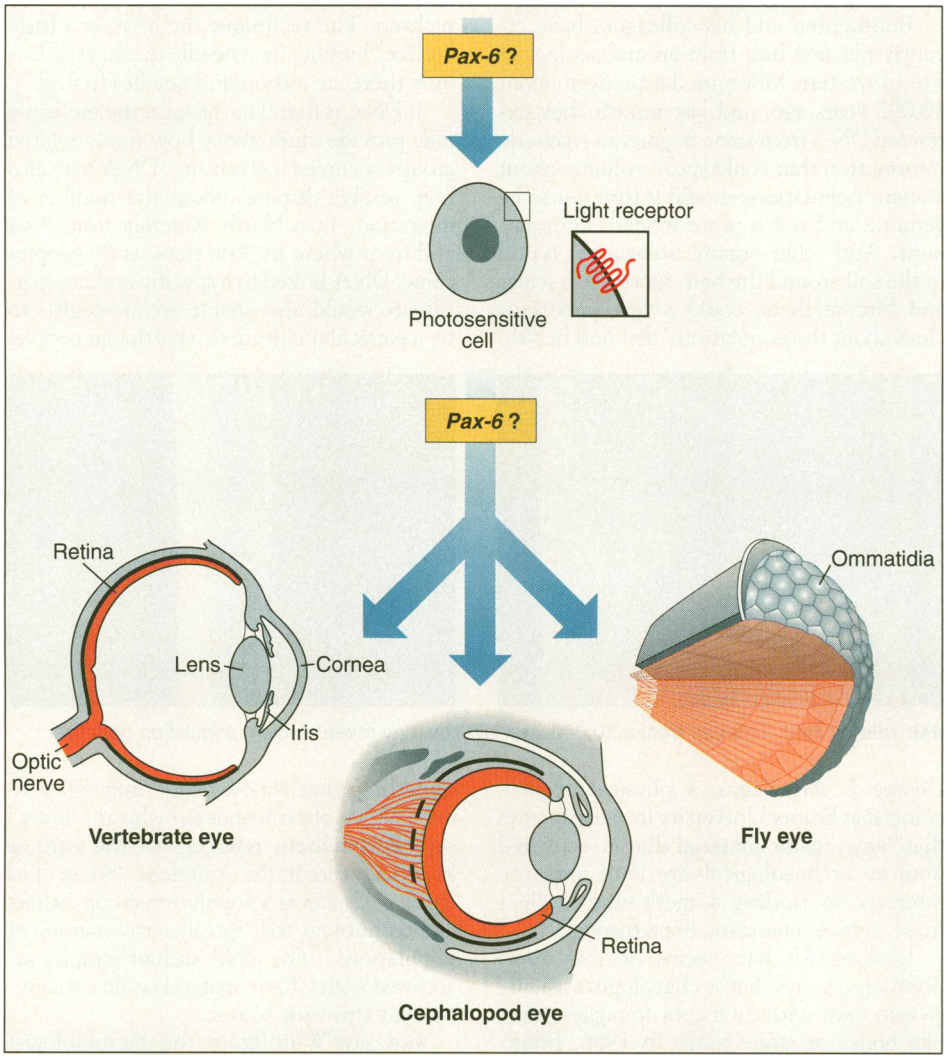

ILLUSTRATION: K. SUTLIFF

Fig. 1. Controller of all eyes? Possible sites of action of *Pax-6* in the development of three very different types of eyes—human (vertebrate), octopus (cephalopod), and the compound eye of *Drosophila*.

The finding that homologous genes may control similar developmental pathways in *Drosophila* and in vertebrates is neither surprising nor unexpected. Since the discovery of the homeobox nearly a decade ago, we have learned that flies and humans share many molecular strategies in their developmental programs (*3*). For instance, elegant experiments by McGinnis and collaborators demonstrated that *Hox4B*, the human homolog of the *Drosophila Deformed* gene (*Dfd*) could mimic the function of a *Dfd* autoregulatory circuit when introduced into *Drosophila* embryos (*4*). This conservation has also been demonstrated in exquisite detail for tyrosine kinase receptor signaling pathways, in which an entire signaling cascade has been conserved between flies and humans (*5*).

What is unexpected about this finding is that differentiation of organs as different as the eye of flies and humans may be under the control of a homologous gene cascade. Phylogenetic studies on the structure and development of eyes led to the proposal that eyes have evolved independently many times (perhaps as many as three or four dozen) (*2*). The finding of a highly homologous molecule functioning as a key regulator of eye morphogenesis in flies and vertebrates strongly argues for a common developmental origin.

An examination of external sensory receptors throughout evolution reveals that most metazoan phyla are characterized by the presence of specialized light-sensing organs. Although only 6 of the more than 30 metazoan phyla have optical systems capable of producing images (Cnidaria, Mollusca, Annelida, Onychorphora, Arthropoda, and Chordata) (*6*), these 6 phyla contain over 95% of all species, possibly because of the tremendous evolutionary advantage of a well-developed visual system.

All visual systems share a structurally similar light receptor molecule (*7*), suggesting that the choice of a 7-transmembrane receptor coupled to a vitamin A–derived chromophore preceded the evolution of the different types of eyes. Thus, the ancestral photosensitive cell likely contained a rhodopsin-like molecule and a simple G protein–coupled signaling cascade. These simple photosensitive cells may have evolved into organized eye spots, which then evolved into image-forming eyes (Fig. 1). *Pax-6* may participate in the specification of the phylogenetically ancestral photosensitive cell, in setting up an eye field, or in eye organogenesis. In this regard, it would be very interesting to determine where and when *Pax-6* is expressed in flatworms, an organism with primitive eye spots consisting only of photosensitive cells. Also, the eyes of cephalopods (such as octopus and squid) are remarkably similar to those of vertebrates but, because of their

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different developmental origin, have been cited as an extreme example of convergent evolution. The finding of a *Pax*-6 homolog in the squid *Loligo vulgaris* by Gehring and co-workers provides a great opportunity to study the expression (and hopefully function) of *Pax*-6 in two structurally similar, yet ontogenically distinct, visual systems.

The *Pax* gene represents a family of paired box-containing genes originally identified in *Drosophila* and subsequently found in vertebrate species, including turtles, zebrafish, frogs, quail, mouse, rats, and humans (8). The *Pax* genes are transcription factors that have been implicated in the control of vertebrate embryonic development, much like paired-box genes are involved in the development of the *Drosophila* embryo (3). In mouse, mutations have been identified in the *Pax-1*, *Pax-3*, *Pax*-6, and *Pax*-8 genes. Expectedly, each causes defects in organogenesis that reflect the sites of expression of the Pax gene in question (8, 9). The *Pax*-6 gene is expressed in the neural tube primordium and in the developing brain and developing eye. In the eye, *Pax*-6 transcripts are found in the eye primordia and later in the developing lens, retina, and corneal tissue. This expression pattern is conserved in all vertebrate species examined to date. Figure 2 shows an in situ hybridization of *Pax*-6 in a developing *Xenopus* embryo, demonstrating expression in the eye primordia.

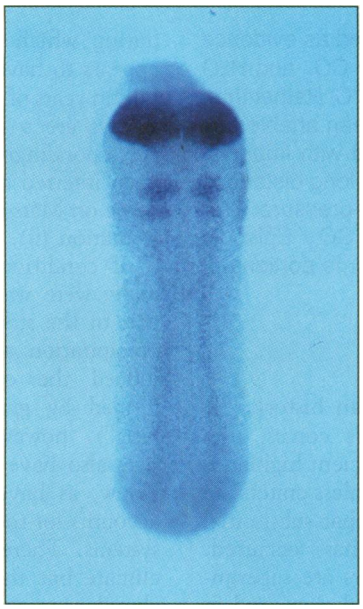

Fig. 2. *Pax-6* in frog eyes. Whole-mount in situ hybridization of *Pax-6* in a stage-23 *Xenopus* embryo (courtesy of N. Hirsch and W. Harris).

A strong indication of the fundamental role of *Pax*-6 in eye development came from the study of *Pax*-6 mutations in mice and humans (9). Mice homozygous for a mutant *Pax*-6 allele fail to develop eyes, and heterozygous animals have small eyes (thus the mutant name *small eye* or *Sey*). In humans, mutations or deletions of the *Pax*-6 gene are responsible for hereditary aniridia, a malformation of the eye characterized by a severe hypoplasia of the iris. Together, these findings have led to a model in which *Pax*-6 functions as a transcription factor responsible for setting up a hierarchical cascade of gene control leading to the development of the eye and visual system. Elucidating the precise role of *Pax*-6 in the determination of the eye primordia and the acquisition of specific cell identities will require an in-depth analysis of eye morphogenesis (and *Pax*-6 expression) in *Pax*-6 null mutants and in animals carrying various *Pax*-6 alleles (hypomorphs). The recent advent of selective gene inactivation or activation combined with knockout technology (*10*) provides a very powerful approach to define spatially and temporally the role of *Pax*-6 in eye development.

The *Drosophila* compound eye is composed of 800 facets or ommatidia, each containing photoreceptor neurons, accessory cells, and a lens. The fly eye develops from an initially undifferentiated monolayer of cells in the eye imaginal disk. During morphogenesis, cells are recruited into specific cell fates by an inductive cascade of determinative events mediated by cell-cell contacts and local signals. Pattern formation and differentiation in the eye disk is marked by a morphogenetic furrow that proceeds in a posterior to anterior direction. Ahead of the morphogenetic furrow, cells are undifferentiated; immediately behind the furrow, cells form differentiating clusters, and more posteriorly these clusters acquire their final differentiated state [for a review see (*11*)].

The *eyeless* mutants are characterized by a mild to severe reduction in the size of the eye, which depends on the severity and penetrance of the allele in question (there are some 20 *eyeless* alleles, most of them spontaneously arising—likely resulting from insertion of transposable elements). Quiring and co-workers indicated that *eyeless* is transiently expressed at the earliest stages of eye disk development, suggesting a role in the earliest determinative events. On the basis of these results, Gehring and co-workers proposed that *eyeless* is a master control gene in the eye morphogenetic pathway.

Although these authors have not yet carried out double-labeling experiments with *eyeless* and genes known to be required early in eye disk development, this model should be readily testable by assessing the requirement for *eyeless* in the expression and function of genes known to be involved in specific aspects of compound eye development. We may then have a crisper and clearer view of how *eyeless* contributes to the development of the visual system. It will also be important to determine whether *Pax*-6 rescues (either partially or fully) the phenotype of *eyeless Drosophila* mutants. It is worth noting that Zipursky and co-workers recently isolated a homeodomain-containing *Drosophila* gene, *sine oculis*, that is essential for the initial events of pattern formation in the development of the compound eye (*12*). Remarkably, Oliver, Maihlos, and Gruss (*13*) have now isolated a vertebrate homolog of *sine oculis* which, lo and behold, is also expressed in the developing mouse eye.

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