LETTER TO THE EDITOR

Pleiotropy and eye degeneration in cavefish

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In an article recently published in *Heredity*, Wilkens (2010) reviews the mechanisms of regressive evolution in the cavefish, *Astyanax mexicanus*. *A. mexicanus* consists of a surface-dwelling morph with eyes and pigmentation, and many cave-dwelling morphs that have lost or have a reduced form of both traits. The two morphs are capable of interbreeding, allowing the mechanisms of regressive evolution to be probed by genetic analysis. In the past, three theories have been proposed to explain the loss of eyes in cave organisms: (1) neutral mutation and genetic drift, (2) positive selection against eyes due to energy conservation or their possible liability and (3) indirect selection against eyes based on increase in beneficial traits that are negatively linked to optic development by pleiotropy. The first idea was favored until about the turn of this century (Culver and Wilkens, 2000), but since then new genetic and developmental evidence has tipped the scale toward the third idea—pleiotropy (Jeffery, 2005; Protas *et al.*, 2008). In this review, Wilkens (2010) re-evaluates the genetic and developmental data and concludes that there is no validity for the second or third (selectionist) theories, reverting to neutral mutation as the most plausible explanation for eye degeneration. Here, I contest some of the facts and interpretations presented in the Wilkens (2010) review and call attention to published developmental data implicating pleiotropy in *A. mexicanus* eye regression (Yamamoto *et al.*, 2009) that were apparently not considered in drawing its conclusions.

The pleiotropic *sonic hedgehog* (*shh*) genes show expanded expression along the cavefish embryonic midline and have inhibitory effects on development of the lens and optic cup (Yamamoto *et al.*, 2004). A major finding of the Yamamoto *et al.* (2009) study was that *A. mexicanus* surface fish overexpressing a *shh* transgene showed coupled eye degeneration and enhancement of oral and taste bud development, revealing a developmental trade-off between these regressive and constructive traits mediated by pleiotropy. Quantitative trait loci mapping results suggest that neither of the two *A. mexicanus shh* genes are mutated in cavefish (Protas *et al.*, 2007), prompting Wilkens (2010) to propose that eye regression is possibly mediated by disruptive mutations in modifier genes (called ‘eye genes’) acting upstream of *shh*. If this proposal is correct, the ‘eye genes’ would regulate the pleiotropic *shh* system described above and therefore would not be effectively neutral. It remains to be seen whether increased oral and gustatory traits improve fitness in cavefish, but if so this would establish a pathway from genes to phenotypes in which eye regression is caused at least in part by indirect selection and antagonistic pleiotropy.

On the basis of segregation of the lens and optic cup (retina and pigment epithelium) size in cavefish × surface fish crosses, Wilkens (2010) also proposes that regressive processes proceed independently in the two major parts of the degenerating cavefish eye. This is held in contrast to the

alternative viewpoint that the lens alone controls optic degeneration events, which was allegedly concluded from partial recovery of eye development after a normal surface fish lens was transplanted into a cavefish optic cup during embryogenesis (Yamamoto and Jeffery, 2000). However, no such claim is made in this or subsequent lens transplantation studies, which instead conclude that at least two processes govern eye regression, one centered in the lens and another in the optic cup (possibly the pigment epithelium; Strickler *et al.*, 2007). The lens transplantation studies demonstrate that retinal development is not completely independent of the lens, as contended by Wilkens (2010). As shown by Strickler *et al.* (2007), the lens is necessary to prevent cell death in the retina, including its photoreceptor cells, which gradually turn over and are replaced in the normal and degenerating retina. The recovery of photoreceptor cells in cavefish hosts containing a transplanted surface fish lens, observed by Yamamoto and Jeffery (2000) and Strickler *et al.* (2007), cannot be explained by variability in eye phenotypes within the cavefish population, as also claimed by Wilkens (2010), because replaced photoreceptor cells are not seen in the opposite (degenerating) eye of the same host, which did not receive a lens transplant. In summary, the genetic and developmental data are not conflicting on this point. Lens growth and its capacity to influence the optic cup also must segregate independently in the genetic crosses described by Wilkens (2010), explaining why their relative size is not a reliable indicator of their developmental interaction.

It is critical to understand the different mechanisms involved in cavefish eye degeneration because this information can provide clues about the evolutionary forces driving the regressive process. In this regard, multiple causes of eye degeneration are consistent with the recent discovery of as many as 12 quantitative trait loci, and thus genes, governing eye loss in cavefish (Protas *et al.*, 2008). This opens the possibility that several different evolutionary forces could synergistically drive eye regression. If this is the case, more than one of the three theories described above may be correct. The solution of this problem will require identification of ‘eye genes’ and the mutations responsible for eye regression. This goal is not beyond our means.

Conflict of interest

The author declares no conflict of interest.

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