

Environmental Hypoxia is a Driver of Sonic Hedgehog-dependent Troglomorphic Evolution in *Astyanax* Cavefish

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Abstract

Astyanax mexicanus cavefish (CF) have evolved numerous troglomorphic traits since their divergence from surface fish (SF) ancestors about 20,000 years ago. A large number of these traits are under the control of Sonic Hedgehog (Shh), a signaling morphogen that is overexpressed along the midline in CF relative to SF embryos. The Shh-dependent traits include eye degeneration and increases in the olfactory lobes, hypothalamus, jaws, and oral taste buds. Eye degeneration and tastebud enhancement are antagonistic tradeoffs governed by the pleiotropic *shh* gene. CF have also evolved multiple changes in circulatory system development, highlighted by larger hematopoietic domains, more erythrocytes, and reversals in normal heart asymmetry, which are also controlled by Shh signaling. Although Shh signaling is an important factor in CF troglomorphism, the *shh* gene is not associated with any of the many QTL identified by genetic analysis, suggesting that upstream processes, rather than mutation of the *shh* locus itself, may be important in Shh regulation. Due to the absence of primary productivity, cave pools harboring *Astyanax* CF are deficient in dissolved oxygen. Accordingly, the Hypoxia Inducing Factor (HIF) transcription factors and their downstream targets are constitutively active during CF development. To determine if oxygen deficiency is an upstream regulator of Shh signaling, we subjected early SF embryos to 8 or 16 hours of hypoxia in the laboratory and assayed the effects on *shh* expression, erythrocyte formation, heart asymmetry, and eye development. The results indicated that hypoxia can cause *shh* overexpression, increase erythropoiesis, reverse heart asymmetry, and induce eye degeneration in SF embryos. We conclude that environmental hypoxia may be responsible for the evolution of troglomorphic traits in *Astyanax* CF through hyperactivation of the Shh signaling pathway.

Keywords

Astyanax mexicanus, cavefish, Sonic Hedgehog, Troglomorphy, environmental hypoxia

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Conflicts of interest