

Regulation of the Egg-Laying Behavioral Response to Hypoxia

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Response to changes in levels of oxygen is a fundamental process in human physiology and plays a major role in pathologies as diverse as cardiovascular disease, stroke and cancer. More generally, the capacity to respond to fluctuations in O₂ is an important adaptation for many organisms, including *C. elegans*. Diminished access to O₂ can elicit metabolic, developmental and behavioral responses.

Much remains unknown about the molecular and neural mechanisms underlying behavioral modifications triggered by chronic exposure to low O₂. We are using egg-laying behavior of *C. elegans* as a model for studying behavioral responses to decreased O₂ concentrations. Upon exposure to hypoxic conditions (0.5% O₂), worms decrease their egg-laying rate (Miller and Roth, *Current Biology* **19**, 1233, 2009).

The conserved prolyl hydroxylase EGL-9 is a key component of the response to hypoxia. *egl-9* was originally identified in a *C. elegans* screen for mutants defective in egg laying. EGL-9 defines an evolutionarily conserved family of enzymes that hydroxylate the transcription factor hypoxia-inducible factor (HIF-1) using available O₂, thus targeting HIF-1 for degradation. Increase in HIF-1 activity as a result of reduced inhibition by EGL-9 under hypoxic conditions is the basis for many adaptations to hypoxia, including metabolic and behavioral changes, by *C. elegans*. Additionally, *hif-1* loss-of-function (*lf*) mutations suppress the egg-laying defect of *egl-9(lf)* mutants, indicating that *egl-9* function requires *hif-1* activity. Thus, it is likely that the inhibition of egg laying under hypoxia is controlled by the *egl-9/hif-1* pathway. Previous work has demonstrated that the sites of action of EGL-9 for controlling egg laying are in the nervous system and the uv1 cells of the somatic gonad (Chang and Bargmann, *PNAS* **105**, 7321, 2008).

To find downstream effectors of HIF-1 or parallel pathways that control egg laying in response to hypoxia, we are conducting screens using an *egl-9(lf)* background to identify second-site mutations that suppress the egg-laying defect of *egl-9* mutants. As *hif-1(lf)* suppresses the egg-laying defect of the *egl-9(lf)* mutant, we expect downstream effectors of *hif-1* in the control of egg laying to similarly suppress this defect. So far, we have identified 17 suppressors of the *egl-9* egg-laying defect, at least 13 of which are not alleles of *hif-1*. These suppressors might represent mutations in new genes required for behavioral adaptation to hypoxia.

Poster

Session topic: Neurobiology: Behavior

No. characters (counting spaces): 2489