Regulation of egg-laying behavior by the conserved EGL-9/HIF-1 hypoxia-response pathway

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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 O_2 provides an important adaptation for many organisms, including *C. elegans*. Diminished access to O_2 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 O_2. We are using the egg-laying behavior of *C. elegans* as a model for studying behavioral responses to decreased O_2 concentration. Upon exposure to hypoxic conditions (0.5% O_2), 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 O_2, 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 *C. elegans* adaptations to hypoxia, including metabolic and behavioral changes. Additionally, *hif-1* loss-of-function *(lf)* mutations suppress the egg-laying defect of *egl-9(lf)* mutants. 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), but the molecular players controlling egg laying downstream of HIF-1 remain unknown.

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 mutations of downstream effectors of *hif-1* in the control of egg laying to similarly suppress this defect. From a screen of 100,000 haploid genomes, 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. We are mapping and characterizing these mutants and will continue screening for more suppressors.

Poster
Worm neuro topic meeting; circuits and behavior
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