**CYP-36A1 Acts Downstream of the Conserved EGL-9/HIF-1 Hypoxia-response Pathway to Regulate *C. elegans* Egg-Laying Behavior**

**Cory Pender** and Bob Horvitz
HHMI, Dept. Biology, MIT, Cambridge, MA 02139

Response to changes in levels of $O_2$ 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 physiological adaptation for many organisms, including *C. elegans*. Diminished access to $O_2$ can elicit metabolic, developmental and behavioral responses. Upon exposure to hypoxic conditions (0.5% $O_2$), worms decrease their egg-laying rate (Miller and Roth 2009). We are using the egg-laying behavior of *C. elegans* as a model for studying behavioral responses to decreased $O_2$ concentrations and for revealing novel aspects of the molecular genetic pathway that functions in response to hypoxia.

The prolyl hydroxylase EGL-9 is a key component of the evolutionarily conserved molecular pathway that responds to hypoxia. Our laboratory discovered *egl-9* many years ago in a *C. elegans* screen for mutants defective in egg laying. EGL-9 defines a 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. *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.

To find downstream effectors of HIF-1 or pathways that regulate egg laying in parallel to HIF-1, we are screening for mutations that suppress the egg-laying defect of *egl-9* mutants. We identified an allele of the cytochrome P450 gene *cyp-36A1* as a recessive suppressor of the *egl-9* egg-laying defect. Previous work has shown that *cyp-36A1* is upregulated in hypoxia in a *hif-1*-dependent manner and contains the putative HIF-1 binding motif in its promoter, suggesting that *cyp-36A1* might be a direct transcriptional target of HIF-1 (Shen *et al.* 2005). Interestingly, another cytochrome P450 gene, *cyp-13A12*, was identified in our laboratory as acting downstream of *egl-9* in the O2-ON locomotory response to changing oxygen levels. CYP-13A12 functions in the generation of an eicosanoid and is downregulated upon hypoxia exposure or in *egl-9* mutants (Ma *et al.* 2013). By contrast, our data indicate that CYP-36A1 generates a hormone that activates a nuclear receptor, and that this pathway is upregulated in *egl-9* mutants. We suggest that different cytochrome P450 enzymes act broadly, through multiple mechanisms, downstream of the EGL-9 and HIF-1 in response to alterations in $O_2$ concentrations.

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