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.

International Worm Meeting (Physiology: Aging and Stress)
Talk
Character count: 2920 (max 3000)