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A cytochrome P450 and nuclear hormone receptor control hypoxia-regulated behaviors and stress responses

Low oxygen levels can elicit metabolic, developmental and behavioral responses in many organisms, including *C. elegans*. Much remains unknown about the molecular and neural mechanisms underlying behavioral modifications triggered by hypoxia.

The conserved transcription factor HIF-1 is a key mediator of the response to chronic hypoxia. HIF-1's activity is regulated by EGL-9, which promotes degradation of HIF-1 in the presence of oxygen but not in hypoxia. *egl-9* mutation mimics chronic hypoxia exposure, as both result in increased HIF-1 activity. Both hypoxia-exposed worms (Miller and Roth, *Current Biology* 2009) and *egl-9* mutants lay eggs at a slower rate than the wild type; the egg-laying defect of *egl-9(lf)* is suppressed by *hif-1(lf)*, indicating that HIF-1 mediates this modulation of egg laying.

We screened for suppressors of the *egl-9* egg-laying defect to identify HIF-1's downstream effectors required for this hypoxia-regulated behavior. From this screen, we identified a loss-of-function allele of the cytochrome P450 gene *cyp-36A1*. *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 it might be a transcriptional target of HIF-1 (Shen…Powell-Coffman, *J. Biol. Chem.* 2005). In addition to regulating egg-laying behavior downstream of *egl-9*, *cyp-36A1* controls two other *egl-9*-modulated behaviors, locomotion and defecation. We also found that *cyp-36A1* is required for the transcription of many EGL-9-regulated genes. Further screens identified the nuclear hormone receptor *nhr-46* as acting downstream of *cyp-36A1*. We postulate that CYP-36A1 generates a hormone that regulates transcription through activation of this receptor. Interestingly, the set of CYP-36A1-regulated genes is enriched for stress response genes, and *cyp-36A1(lf)* suppresses the resistance of *egl-9(lf)* to oxidative stress, ER stress, and infection by pathogenic bacteria, suggesting that CYP-36A1 promotes a transcriptional response that provides protection against various stressors. We propose that CYP-36A1 mediates a broad transcriptional response downstream of EGL-9/HIF-1, suggesting a novel indirect mechanism by which HIF-1 regulates transcription and influences multiple processes including several behaviors and stress responses.

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