C. elegans behavior and an immune response to pathogens are regulated by the conserved EGL-9/HIF-1 hypoxia-response pathway by controlling the activity of a cytochrome P450

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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 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, implying that it might be a transcriptional target of HIF-1 (Shen et al. 2005). We found that cyp-36A1 is required for transcription of many EGL-9-regulated genes. We postulate that CYP-36A1 generates a hormone that regulates transcription through activation of a nuclear hormone receptor. Interestingly, the set of CYP-36A1-regulated genes is enriched for immune response genes, and cyp-36A1(lf) partially suppresses the resistance of egl-9(lf) to the pathogen Pseudomonas aeruginosa, suggesting that CYP-36A1 promotes the transcriptional response to pathogen exposure. Pseudomonas exposure can activate HIF-1 (Kirienko et al. 2013), providing an explanation for co-option of this hypoxia response pathway for pathogen response. 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 behavior and pathogen response.

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