EGL-9/HIF-1-mediated regulation of egg laying in response to hypoxic stress

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Hypoxia (low O_2) results in physiological changes at the cellular, tissue and organismal levels. The major hypoxia response pathway is conserved from worms to mammals and is controlled by the O_2-dependent prolyl-hydroxylase EGL-9 and the transcription factor HIF-1 (EGLN and HIF-1α in mammals, respectively). In normoxic conditions, EGL-9 uses ambient O_2 to hydroxylate HIF-1; hydroxylated HIF-1 is then poly-ubiquitinated and undergoes proteasomal degradation. In hypoxic conditions, O_2 is limited and EGL-9 is unable to hydroxylate HIF-1, leading to HIF-1 stabilization. Stable HIF-1 then translocates to the nucleus and transcribes target genes, thus initiating the hypoxia response. This conserved pathway in mammals has been implicated in normal development as well as in heart disease and tumor progression.

Increased activity of HIF-1, produced by either hypoxia or an *egl-9(lf)* mutation, causes adult *C. elegans* hermaphrodites to retain eggs inside the uterus, resulting in an Egl phenotype. Previously, we showed that the egg-laying defects of *egl-9(lf)* mutants are controlled downstream of HIF-1 through the cytochrome P450 enzyme CYP-36A1 and the nuclear hormone receptor NHR-46. Interestingly, our genetic studies indicate that a parallel pathway functions downstream of EGL-9 to control egg laying independently of the CYP-36A1/NHR-46 pathway. Identification of this parallel pathway would better define the effects of hypoxia on egg laying.

From a genetic screen, we isolated 7 independent mutations that suppress the *egl-9(lf)* egg-laying defect, but do not affect transcription of a reporter for the CYP-36A1/NHR-46 pathway. From a second screen, we isolated an additional 11 independent mutations that enhance the ability of *cyp-36A1(lf)* to suppress the egg-laying defect of *egl-9(lf)* mutants. Genes represented by these 18 mutants are candidates for acting in parallel to CYP-36A1 to control *egl-9(lf)* egg-laying. Through further genetic analysis, we hope to identify novel effectors of the EGL-9/HIF-1-mediated hypoxia stress response. Given the conserved nature of this pathway these efforts might help us better understand general downstream effectors of the hypoxia response, a critical pathway in animal biology and human disease.