The hypoxia-inducible factor HIF and its negative regulator EGL-9 (mammalian ELGN) are the central mediators of the metazoan response to chronic hypoxia and in humans play major roles in pathologies as diverse as cardiovascular disease, stroke, and cancer. EGL-9 is a prolyl hydroxylase that promotes degradation of the HIF transcription factor α-subunit (HIFα) in the presence of oxygen but not in hypoxia; stabilized HIFα, acting with its constitutively active partner HIFβ, drives adaptations to hypoxia by upregulating expression of its transcriptional targets. In addition to promoting the classical hypoxia response, HIF drives cytoprotective mechanisms in response to stresses, including infection, proteotoxicity, and oxidative stress, and modulates neural circuit function to regulate behavior. The mechanisms by which HIF mediates these non-canonical functions remain poorly defined.

To identify novel functionally important HIF effectors that regulate physiology and behavior, we analyzed the modulation of *C. elegans* egg laying, the behavior that led our laboratory to discover *egl-9* and the first known functional role for any member of the EGL-9/HIF pathway. Animals mutant for *egl-9*, in which HIF-1 is constitutively active, are defective in egg laying and become bloated with eggs as adults. We performed a screen for suppressors of the egg-laying defect of *egl-9(lf)* animals. From this screen, we identified *cyp-36A1*, which encodes a cytochrome P450 enzyme. *cyp-36A1* is upregulated in hypoxia in a *hif-1*-dependent manner and contains HIF-1 binding sites in its promoter, suggesting that *cyp-36A1* is a transcriptional target of HIF-1. *cyp-36A1* is required for numerous HIF-dependent processes, including modulation of gene expression, stress resistance, and behavior. CYP-36A1 acts cell non-autonomously by regulating the activity of the nuclear hormone receptor NHR-46, suggesting that CYP-36A1 functions as a biosynthetic enzyme for a hormone ligand of this receptor. ChIP-seq studies of human cells have identified several cytochrome P450 genes as putative HIF targets. We suggest that cell non-autonomous regulation of HIF effectors through upregulation of one or more CYP enzymes and subsequent activation of nuclear hormone receptor(s) is evolutionarily conserved and similarly occurs in other organisms, including humans.