Unconventional functions of HIF-1 and the prolyl-hydroxylase EGL-9 in a heat stress response

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An evolutionarily conserved prolyl-hydroxylase EGL-9 and its substrate hypoxia-inducible factor (HIF), a transcription factor, regulate cellular and systemic responses to low O_2 (hypoxia) and drive critical changes in gene expression that enable animals to adapt to hypoxic stress. HIF-1 is also necessary for surviving in heat stress (Treinin *et al*., Physiol Genomics 14: 17-24, 2003), but the pathways by which HIF-1 regulates responses to heat stress are unclear. I observed that there are no obvious differences in developmental rates between *hif-1(lf)* mutants and wild-type animals at 15, 20 or 25°C. However, *hif-1(lf)* mutants grown at 27°C (mild heat stress) are developmentally delayed compared to wild-type animals. To determine whether the heat-induced developmental-delay phenotype of *hif-1(lf)* mutants involves the canonical EGL-9/HIF-1 pathway, I tested *egl-9(lf)* and *egl-9(lf) hif-1(lf)* double mutants at 27°C (The *egl-9(lf)* allele is null and the *hif-1(lf)* is a presumptive null). Surprisingly, both *egl-9(lf)* mutants and *egl-9(lf) hif-1(lf)* double mutants grow like wild-type animals at 27°C. These data indicate that *egl-9* functions downstream of or in parallel to *hif-1*, unlike its standard function upstream of *hif-1*. These data indicate that HIF-1 and EGL-9 regulate heat stress responses during development at 27°C and suggest an unconventional HIF-1/EGL-9 pathway.

To identify factors that potentially act in a HIF-1 and/or EGL-9 pathway that regulate the heat stress response, I performed a genetic screen for mutants that suppress the heat-induced developmental-delay defect of *hif-1(lf)* animals. From a screen of 12,800 mutagenized haploid genomes, I isolated 8 suppressors, which I am now characterizing. The mammalian EGL-9 counterpart, EGLN1, has a critical role in normal development and physiology and has attracted attention as a potential therapeutic target for a wide range of diseases. However, targeting EGLN1 can cause unexpected detrimental side effects that remain poorly understood. Thus, it is critical to understand how EGLN1 regulates signaling pathways beyond its canonical roles. Analysis of the suppressors I have isolated might reveal a novel signaling pathway by which HIF-1 and EGL-9 regulate stress responses and possibly provide insight into new potential therapeutic targets.

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