Cells, tissues or entire organisms can physiologically respond to low oxygen conditions (hypoxia) during normal development or in pathological states. Hypoxia-inducible factor (HIF), a transcription factor, regulates cellular and systemic responses to low oxygen levels and drives critical changes in gene expression that enable animals to adapt to hypoxic stress. HIF-1-deficient mice are embryonic lethal, but C. elegans hif-1(If) mutants exhibit no obvious developmental defects under standard laboratory conditions, allowing investigation of HIF-1 function in C. elegans development. C. elegans enters dauer developmental arrest in response to starvation, high pheromones, and/or high temperature and dauer formation is regulated by highly conserved TGF-β signaling pathways. Whether hypoxia modulates dauer formation is unknown.

We have observed that hypoxia does not induce dauer formation in wild-type animals, but it increases the frequency of worms entering dauer developmental arrest in DAF-7/TGF-β-defective animals, indicating that there might be crosstalk between HIF-1 and TGF-β signaling in C. elegans. A hif-1(If) mutation suppresses the daf-7(If) dauer-constitutive phenotype, indicating that hif-1 is epistatic to daf-7 and that hif-1 acts downstream of or parallel to daf-7. HIF-1-dependent cysl-2 expression is decreased in hif-1(If) mutants and increased in daf-7(If) mutants compared to wild-type animals. daf-7; hif-1 double mutants decrease the expression of cysl-2 compared to wild-type animals. Together, our studies indicate that daf-7 might negatively regulate the HIF pathway. We are examining how HIF-1 interacts with downstream components of TGF-β signaling pathways that also regulate dauer formation. HIF-1 and TGF-β are highly expressed in numerous types of tumors, but little is known about how HIF-1 and TGF-β pathways interact in development and disease. Further analysis of the interaction between hif-1 and daf-7 might reveal regulatory mechanisms of hypoxia signaling and interaction between the HIF-1 and TGF-β pathways that are evolutionary conserved.

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