Hypoxia increases the frequency of worms entering dauer in DAF-7/TGF-β-defective animals

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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(lf)* 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(lf)* mutation suppresses the *daf-7(lf)* 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(lf)* mutants and increased in *daf-7(lf)* 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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