CYSL-1 Interacts with the O_2-Sensing Hydroxylase EGL-9 to Promote H_2S-Modulated Hypoxia-Induced Behavioral Plasticity in *C. elegans*

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The *C. elegans* HIF-1 proline hydroxylase EGL-9 functions as an O_2 sensor in an evolutionarily conserved pathway for adaptation to hypoxia. H_2S accumulates during hypoxia and promotes HIF-1 activity, but how H_2S signals are perceived and transmitted to modulate HIF-1 and animal behavior is unknown. We report that the experience of hypoxia modifies a *C. elegans* locomotive behavioral response to O_2 through the EGL-9 pathway. From genetic screens to identify novel regulators of EGL-9-mediated behavioral plasticity, we isolated mutations of the gene *cysl-1*, which encodes a *C. elegans* homolog of sulfhydrylases/cysteine synthases. Hypoxia-dependent behavioral modulation and H_2S-induced HIF-1 activation require the direct physical interaction of CYSL-1 with the EGL-9 C-terminus. Sequestration of EGL-9 by CYSL-1 and inhibition of EGL-9-mediated hydroxylation by hypoxia together promote neuronal HIF-1 activation to modulate behavior. These findings demonstrate that CYSL-1 acts to transduce signals from H_2S to EGL-9 to regulate O_2-dependent behavioral plasticity in *C. elegans*.

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