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Nonsense-mediated decay facilitates the hypoxia response

Hypoxia (low O_2) results in physiological changes at the cellular, tissue and organismal levels. The major hypoxia response pathway is conserved from worms to mammals and is controlled by the O_2-dependent prolyl-hydroxylase EGL-9 and the transcription factor HIF-1 (EGLN/PHD and HIF-1α in mammals, respectively). This conserved pathway has been implicated in normal development as well as in various human disorders, including heart disease and tumor progression. Increased activity of HIF-1, produced by either hypoxia or an *egl-9(lf)* mutation, causes adult *C. elegans* hermaphrodites to retain eggs inside the uterus, resulting in an Egl phenotype and indicating that the hypoxia response inhibits egg laying. After screening for suppressors of the *egl-9* Egl phenotype we isolated an OCHRE nonsense mutation in the gene *smg-1*. *smg-1* encodes a conserved kinase key in the pathway for nonsense-mediated decay (NMD), an RNA surveillance mechanism that degrades aberrant mRNA transcripts with premature termination codons and maintains cellular homeostasis in response to transcript errors. Our *smg-1* mutation is likely a null allele, indicating that wild-type *smg-1* directly or indirectly facilitates the hypoxia-induced inhibition of egg laying. Our *smg-1* mutation suppresses multiple *egl-9* alleles, including an almost complete deletion allele, indicating that this is not simply informational suppression of *egl-9.* Mutations in the genes *smg-2,-3,-4* and *-5,* all of which are necessary for NMD, also each suppress *egl-9*, indicating that *smg-1* suppression results from a loss of function of the NMD machinery and establishing a role for the NMD process in potentiating the hypoxic response. Some but not all of the other *hif-1*-dependent behavioral responses -- inhibition of defecation and locomotion rates – are affected by NMD-pathway mutations, indicating that NMD is needed to express only some HIF-1-dependent hypoxia responses and that the interaction between the hypoxia response and NMD extends beyond egg laying and likely reflects a major integration of these two important and evolutionarily conserved stress-response pathways.