Nonsense-mediated decay facilitates the hypoxia response

Hypoxia (low O\textsubscript{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\textsubscript{2}-dependent prolyl-hydroxylase EGL-9 and the transcription factor HIF-1 (EGLN/PHD and HIF-1\textsubscript{α} 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 \textit{egl-9}(\textit{lf}) mutation, causes adult \textit{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 \textit{egl-9} Egl phenotype we isolated an OCHRE nonsense mutation in the gene \textit{smg-1}. \textit{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 \textit{smg-1} mutation is likely a null allele, indicating that wild-type \textit{smg-1} directly or indirectly facilitates the hypoxia-induced inhibition of egg laying. Our \textit{smg-1} mutation suppresses multiple \textit{egl-9} alleles, including an almost complete deletion allele, indicating that this is not simply informational suppression of \textit{egl-9}. Mutations in the genes \textit{smg-2, -3, -4} and -5, all of which are necessary for NMD, also each suppress \textit{egl-9}, indicating that \textit{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 \textit{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.