Increased longevity in an extreme environment is orchestrated by hif-1 and skn-1

December 12, 2011

Image courtesy of Dana Miller

Nematode worms, which thrive in 50 ppm hydrogen sulfide, a concentration roughly 100 times higher than the limit at which humans can detect this toxic (and noxious) early Earth gas.

Mice exposed to hydrogen sulfide exhibit lower metabolic rates and core body temperatures reminiscent of hibernation. Similarly, rats demonstrate increased survival following severe hemorrhage if they are first administered this same toxic compound at sub-lethal doses, inducing a state of suspended animation. The tantalizing possibility of placing humans into a similar state of sulfide-induced hibernation could have far-reaching future applications, including: slowing down a trauma patient's metabolic clock as she or he is transported to intensive care; prolonging the health of donated organs prior to transplantation; and better protecting a cancer patient from the ill effects of radiation or chemotherapy targeted at a malignant tumor. In their earlier work on animal responses to hydrogen sulfide, Fred Hutchinson Cancer Research Center investigators Dr. Dana Miller and Dr. Mark Roth (Basic Sciences Division) first demonstrated life-prolonging effects in the simpler and genetically more tractable organism, *Caenorhabditis elegans*, shown in the accompanying photomicrograph. Akin to mammalian hibernation responses that delay death under severe environmental conditions, responses of this nematode worm to 50 parts per million hydrogen sulfide include increased heat tolerance and lifespan. The focus of these investigators on *C. elegans* is an attempt to better elucidate general molecular mechanisms underlying responses to sulfide, which remain obscure in more complicated mammalian models. Hutchinson Center researcher Mark Budde and principal investigator Roth also previously demonstrated that the transcription factor referred to as hypotoxia-inducible factor 1 (*hif-1*) is required for a nematode's survival following exposure to hydrogen sulfide. *Hif-1* is the nematode homologue of a conserved transcription factor known for its role in orchestrating mammalian responses to low oxygen concentrations.

A new paper first-author by Miller, who recently started her own lab group in the Biochemistry Department at the University of Washington, was aimed at broadly understanding the transcriptional responses of *C. elegans* to hydrogen sulfide using a DNA expression array and real-time quantitative PCR. Dr. Jeff Delrow (FHCRC DNA Array Facility) and Dr. Jerry Davison (FHCRC Computational Biology) contributed their expertise to the team's microarray analyses. With the microarray dataset in hand, Miller *et al.* found that hydrogen sulfide induced rapid transcriptional changes to numerous genes. These responses appeared as early as 1 hour after initial exposure, and they increased further by 48 hours, the time required for *C. elegans* to develop into first-day adults and exhibit both increased lifespan and thermotolerance. Functional annotation of genes up-regulated during the response suggested that many of them are associated with protein homeostasis, including transcripts related to aging and stress resistance as well as those involved in protein turnover via the ubiquitin proteosome system. Comparing hydrogen sulfide exposure of *hif-1* loss-of-function mutants to control animals, Miller and collaborators went on to show that *hif-1* is essential for these transcriptional responses. Interestingly, there proved to be little overlap between transcriptional targets of *hif-1* in environments high in hydrogen sulfide *versus* low in oxygen. The authors also observed that many up-regulated genes

were Sdz genes (so named for their *skn-1* dependent zygotic expression), suggesting that sulfide-induced transcriptional changes are *skn-1* dependent. By feeding their nematodes bacteria containing either a vector for small interfering RNA directed against *skn-1* or an empty vector as a control, the investigators confirmed their hunch: *skn-1* acts to both up- and down-regulate genes in response to hydrogen sulfide. As a final test of *skn-1* function, the authors verified that *skn-1* homozygous mutants failed to survive in a hydrogen sulfide environment in which hetrozygotes and wild type animals thrive. Protein homeostasis plays an increasingly appreciated role in aging, senescence and neurodegenerative disorders such as Alzheimer's disease. The findings of Miller *et al*. suggest that, during adaptation to hydrogen sulfide in nematodes, *skn-1* and *hif-1* seem to work together to remodel the protein turnover machinery, which increases lifespan and thermotolerance of these worms via effects on protein homeostasis.

Miller DL, Budde MW, Roth MB. 2011. HIF-1 and SKN-1 coordinate the transcriptional response to hydrogen sulfide in *Caenorhabditis elegans*. *PLoS ONE* 6:e25476.

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