Hot worms can handle heavy metal.
Focus on "HIF-1 is required for heat acclimation in the nematode Caenorhabditis elegans"

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LIFE DEVELOPED in a stressful environment. Stressors at the cellular level include heat, hypoxia, oxidative or reductive substances, mechanical or osmotic pressure, and toxic compounds like heavy metals. Various molecular pathways, more or less specific for the different stressors, developed during evolution to combat the molecular consequences of cell stress. Thermal stress induces the induction of a highly conserved protein family, the heat shock proteins (HSP) (2). Experiments with several species have shown that increased levels of these proteins can protect the organism against stress-induced damage. Moreover, cells given a nonlethal HSP-inducing preshock subsequently survive an otherwise lethal exposure to elevated temperatures, a phenomenon called heat acclimation (7). Heat acclimation is most effective when animals are exposed to temperatures at the upper limits of their comfort zone. This process is marked by changes in gene expression and posttranslational modifications of proteins as well.

Thermal acclimation, however, not only confers resistance against heat stress but also against other stress forms like hypoxia or heavy metals. For example, heat-treated mouse embryos were found to be increasingly resistant to the teratogenic metal cadmium as well as to damage resulting from subsequent thermal challenge (5). As in the heat shock response, HSP is expressed in response to exposure to stressors such as oxidizing conditions and toxic compounds. Such cross-tolerance suggests a common evolutionary origin for a variety of general stress protective pathways, enabling an organism to combat the onslaught of stressors, developed during evolution to combat the molecular consequences of cell stress. Thermal stress induces the induction of a highly conserved protein family, the heat shock proteins (HSP) (2). Experiments with several species have shown that increased levels of these proteins can protect the organism against stress-induced damage. Moreover, cells given a nonlethal HSP-inducing preshock subsequently survive an otherwise lethal exposure to elevated temperatures, a phenomenon called heat acclimation (7). Heat acclimation is most effective when animals are exposed to temperatures at the upper limits of their comfort zone. This process is marked by changes in gene expression and posttranslational modifications of proteins as well.

The cellular response to hypoxia represents a more specific stress response mechanism than the general-purpose HSP pathway. The hypoxic response is mediated by the hypoxia-inducible factor-1 (HIF-1), comprising two constitutively expressed subunits, α and β. Protein stability of the α-subunit, but not the β-subunit, is dependent upon oxygen (9). Hypoxia results in stabilization of HIF-1α via inhibition of oxygen-dependent prolyl-hydroxylation. Consequently, the enhanced expression of HIF-1 target genes mediates oxygen transport, the supply of oxygen via angiogenesis, and metabolic adaptation via increased glucose uptake and increased expression of glycolytic enzymes.

In this release of Physiological Genomics, Treinin et al. (Ref. 8; see page 17 in this release) test the hypothesis that heat acclimation in the model organism Caenorhabditis elegans is mediated by hif-1, the ortholog of mammalian HIF-1α. They applied a heat acclimation protocol to wild-type worms as well as to animals with partial or complete loss-of-function mutations affecting either HIF-1α expression or the expression of genes in the insulin receptor pathway (e.g., daf-2). Control worms were raised at 20°C, while experimental animals were heat acclimated by 18 h of conditioning at 25°C, a temperature reflecting the upper range of their normal level of heat tolerance. Both control and experimental worms were then subjected to environmental stresses including heat (35°C or 37°C), heavy metal exposure (cadmium chloride, in four increasing concentrations), and chemical hypoxia (sodium azide). Environmental tolerance was assessed as percent survival.

The researchers found that in roundworms the product of the hif-1 gene plays a crucial role in heat adaptation. Wild-type heat acclimated worms had higher levels of HIF-1α protein, and animals with the egl-9 and vhl-1 mutations, causing overexpression of HIF-1α, had greatly enhanced heat survival. The role of hif-1 was confirmed by the inability of HIF-1α loss-of-function mutants to acclimate to heat, as reflected by their extremely poor percent survival at higher temperatures. Since mutations in the daf-2 gene, which mediates the C. elegans insulin receptor pathway, are known to lead to increased thermostolerance as well as tolerance to hypoxia, Treinin et al. (8) also tested the response of mutants in the insulin receptor pathway to heat. They found that mortality was not increased in daf-2(e1370) mutants at 35°C, but was considerably higher at 37°C, unless animals were previously heat acclimated. This suggested that the insulin receptor pathway was not responsible for heat adaptation, since heat acclimation was still possible despite mutations in this pathway.

The hif-1 gene was also implicated in cross-tolerance against cadmium chloride and sodium azide treatment, suggesting a common mechanism. Heat-acclimated
wild-type animals were able to survive increasing levels of insult from both of these stressors, whereas HIF-1α loss-of-function mutants could not. Treinin et al. hypothesized that HIF-1α is important in short-term heat acclimation, but not necessarily in long-term acclimation, due to the fact that two mutants that overexpress HIF-1 have an attenuated response to heat stress. Non-acclimated egl-9( n571) and vhl-1(ok161) animals, subjected to heat stress without acclimation, briefly survive at higher levels than wild-type animals, but then their survival curve falls off sharply.

Although it is possible that HIF-1 target genes like the glucose transporter-1 or the glycolytic enzymes are useful in metabolic adaptation toward heat, the molecular consequences of decreased heat adaptation in the hiP-1 loss-of-function strain have yet to be identified. These experiments would help to identify the common molecular denominator that mediates both hypoxia and heat acclimation. Although heat induction of HIF-1α has been described before in mammals (6), it is interesting that the functional role of HIF-1α for heat acclimation has been identified in C. elegans.

HIF-1α knockout mice are not viable. The animals die around embryonic day E9.5 suffering from multiple organ deformations as a consequence of a lack of adaptation toward the hypoxic environment (3). With increasing body size, diffusion of oxygen is limited and the formation of blood vessels is a necessity. Therefore, the small organism C. elegans is an exception, allowing the investigation of HIF-1α in adult animals. In mammals, knowledge about the effects of misexpression of HIF-1α in adults stems mostly from the study of pathophysiological conditions such as ischemic or malignant diseases. Lately, conditional knockout mice were developed (1) to better understand the physiological functions of HIF-1α in adults. It will be interesting to explore whether HIF-1α has a similar function for adaptation toward heat or other stressors in mammals. Heat as well as hypoxia are used to induce tolerance for subsequent injuries. For example, hypoxic preconditioning induces tolerance to hypoxic-ischemic injury in neonatal rat brain and is associated with changes in gene expression (4). This effect seems to be mediated, at least in part, by HIF-1α. Therefore, understanding the physiological role of HIF-1α in stress conditions will also help to develop clinical strategies using these functions in pathophysiological conditions.

REFERENCES