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Review

Stressed worms: Responding to the post-genomics era

Tali Z. Gal [a], Itamar Glazer [b], Hinanit Koltai [a,*]

[a] *Department of Genomics, ARO, The Volcani Center, Bet Dagan 50250, Israel*
[b] *Department of Nematology, ARO, The Volcani Center, Bet Dagan 50250, Israel*

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Abstract

Nematodes are among the most successful organisms in withstanding stress conditions associated with water loss, and viable individuals have been recovered from dry desert soils. Little is known about the biochemical and molecular events underpinning nematodes' physiological responses to dehydration. Post-genomics research in *Caenorhabditis elegans* may offer an opportunity to understand the stress response better. This review focuses on recent progress in understanding the molecular mechanisms of water-loss associated stress response in the model nematode *C. elegans* and in parasitic nematodes and discusses the scope for applying the knowledge and tools derived from a model organism for the study of wild, environmentally-adapted, parasitic nematodes, in the light of the emergence of genomics research of non-model organisms.

Keywords: Parasitic nematodes; Water stress; Genomics; *Caenorhabditis elegans*

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1. Introduction

Nematodes are aquatic organisms; their movement requires a layer of water surrounding their bodies. Changes in the environment may impose temporary lack of water, leading to dehydration that adversely affects the nematodes' motility and survival [1]. Viable specimens of nematodes have been recovered from dry desert soil, an indication that nematodes are among the most successful organisms in withstanding desiccation [2]. Nematodes' adaptations to extreme environmental conditions considerably prolong their life span and enable them to withstand harsh regimes [3]. More specifically, a unique juvenile stage, the 'dauer larvae' (DL), has evolved in several nematode families, including the free-living nematode *Caenorhabditis elegans* [4]. Dauer larvae can survive exposure to water deficit for long periods [4–6].

Abbreviations: DL, dauer larvae; IJ, infective juvenile; LEA, late embryogenesis abundant; RNAi, RNA interference

* Corresponding author. Tel.: +972 3 9683039; fax: +972 3 9669583.
E-mail address: hkoltai@volcani.agri.gov.il (H. Koltai).

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Drought, extreme temperatures and osmotic stress were found to induce similar cellular damage, such as disruption of homeostasis and ion distribution in the cells or denaturation of functional and structural proteins [7–9]. The molecular mechanisms that lead to the physiological responses to water-deficit associated damage have been investigated in various organisms during the last few years. Nevertheless, it is increasingly evident that the fragmented data and, at best, the linear pathways that are known, form only parts of a complex genetic network. In order to gain a broad picture of the genetic pathways associated with stress conditions, genomics studies could enable all or most of the genes within an organism, and their interactions during stress induction, to be studied simultaneously, instead of a single gene or pathway at a time.

Here, we discuss recent progress in studying the molecular mechanisms of the water-deficiency associated stress response in *C. elegans* and in other free-living and parasitic nematodes. We also discuss the importance, pitfalls and future prospects of utilizing genomics tools and the knowledge of *C. elegans*, to generate information about the functions of the networks of genes that are involved in stress tolerance.

2. *C. elegans* as a model for water-deficit stress studies

Several studies have established roles for individual genes and signaling pathways in the *C. elegans* stress response. The existence of a significant role for heat shock factor (HSF) in the thermosensitivity of *C. elegans* was demonstrated by silencing HSF using specific RNAi. Interestingly, nematodes with RNAi-silenced HSF also displayed a reduced life span, which indicates that, in the absence of stress, HSF is required for normal growth and development in *C. elegans*. It was suggested that HSF provides a link between two pathways – the developmental process and the ability to resist stress – and in so doing integrates the two, perhaps as an essential feature of the *C. elegans* life history in its natural habitat [10].

We have recently demonstrated a functional role for late embryogenesis abundant (LEA) protein (Ce-LEA-1) in the response to stress conditions in *C. elegans* [11]. Group 3 LEA proteins, which are prominent components of the stress response in various organisms [12] are thought to be mainly involved in counteracting the irreversible damaging effects of the increased ionic strength that develops in the cytosol during desiccation, perhaps through the binding of both anions and cations to the helical region of the protein [13]. The steady-state level of *Ce-lea-1* mRNA increased upon dehydration of *C. elegans* DL, and the partial reduction in its steady-state level of mRNA reduced DL survival under desiccation, osmotic and heat stress conditions. Therefore, it was suggested that Ce-LEA-1 is a critical component of the nematodes' strategy for tolerating the water-losses associated with dehydration, osmotic and heat stresses [11]. The common need for Ce-LEA-1 for survival during the stresses examined, might support the concept of a molecular mechanism in nematodes that is common to several stress responses (see below; [11]).

Solomon et al. [14] isolated several osmotic shock resistant (*osr*) mutants that can withstand high osmolarity. *osr-1* gene encodes a predicted protein that lacks any domains that would suggest a specific molecular function. *osr-1*(*rm1*) mutants accumulated high levels of glycerol. Ablation of the expression of three genes of the *pmk-1*/p38 conserved pathway reduced *osr-1*(*rm1*) mutant survival. Similarly, expression of UNC43/CaMKII was required for the viability of *osr-1*(*rm1*) nematodes under chronic osmotic stress [14]. Thus, it was suggested that under normal conditions, OSR-1 has an inhibitory role: by inhibition of signal transduction pathways, including CaMKII and a conserved p38 MAPK pathway, it enables the nematodes to avoid a hyperosmotic environment. When hyperosmotic conditions actually prevail, OSR-1 functions are inhibited and this, in turn, activates the specific signaling pathways to promote adaptation and survival [14]. Unlike HSF [10], *osr-1*(*rm1*) did not exhibit other phenotypes that are usually associated with general stress resistance (e.g., extended life span), indicating that OSR-1 regulates osmotic stress response specifically. Further studies of OSR-1 may facilitate the understanding of metazoans integration of multiple responses and their survival in hyperosmotic environments [14].

3. Molecular studies of water stress in non-model nematodes

Studies on the water-deficiency associated stress response have also been performed on several non-model nematodes. The nematodes studied included insect–parasitic nematodes that were isolated from soils worldwide, in ecosystems that include arid climates [15] and the free-living mycophagous nematode *Aphelenchus avenae* [16]. These nematodes can survive in semiarid conditions by entering anhydrobiosis [15,16], which is a reversible physiologically state of dormacy, that results from the absence of water up to and beyond the point at which metabolism is arrested [17].

The physiological changes elicited by desiccation in the DL stage, which is also the infective juvenile (IJ) stage, of the insect–parasitic nematode *Steinernema feltiae* included decreased levels of glycogen [18] and increased levels of trehalose [19]. Trehalose is considered one of the most prominent water protectants. It is a soluble, non-reducing disaccharide of glucose and it appears to contribute to the maintenance of the integrity of cellular structures during environmental stresses [20]; it was demonstrated in vitro to stabilize proteins and other biological structures against stress damage [21]. Trehalose is associated with biological membranes through hydrogen bonds, and thus, effectively protects the membranes during desiccation by maintaining their fluidity [22].

In addition to the two-fold increase in trehalose content that was measured upon dehydration of the *S. feltiae* IS-6