

Review Article

Formation and Regulation of Adaptive Response in Nematode *Caenorhabditis elegans*

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All organisms respond to environmental stresses (e.g., heavy metal, heat, UV irradiation, hyperoxia, food limitation, etc.) with coordinated adjustments in order to deal with the consequences and/or injuries caused by the severe stress. The nematode *Caenorhabditis elegans* often exerts adaptive responses if preconditioned with low concentrations of agents or stressor. In *C. elegans*, three types of adaptive responses can be formed: hormesis, cross-adaptation, and dietary restriction. Several factors influence the formation of adaptive responses in nematodes, and some mechanisms can explain their response formation. In particular, antioxidation system, heat-shock proteins, metallothioneins, glutathione, signaling transduction, and metabolic signals may play important roles in regulating the formation of adaptive responses. In this paper, we summarize the published evidence demonstrating that several types of adaptive responses have converged in *C. elegans* and discussed some possible alternative theories explaining the adaptive response control.

1. Introduction

In many organisms, a mild (usually sublethal and/or non-lethal) exposure to a stressor increases resistance to subsequently higher doses of the same or different stressors. This adaptive response phenomenon was put forward in the 1970s–80s [1] and has been well characterized in manifold combinations of stress and model organisms [2–4]. Such adaptive responses can be broadly categorized as hormesis, cross-adaptation, and special adaptive responses. In addition to hormesis, which renders protection against higher doses or concentrations of the same substance, cross-adaptation, which is defined as the capacity of cells or organisms to become resistant to a different lethal agent, usually occurs as well [5, 6]. Dose-response relationship research has been based on the low dose-expose adaptive response leading to adjustments of the series of management or regulations related to environment and poisons, and this research has garnered increasing attention from toxicologists. Presently, it is postulated that oxidative stress is at least the conserved

mechanism of adaptive response because of the reactive oxygen species (ROS) pretreatment or mild oxidative stress could increase resistance when organisms are challenged with higher doses or concentrations of that particular agent or stressor [6, 7].

The nematode *Caenorhabditis elegans* has emerged as an important model animal and has been widely used in environmental stress or toxicity assessments because of the features of easy maintenance, short lifespan, and small body size, and the fact that results of trials on *C. elegans* can be predictive of outcomes in higher organisms [8, 9]. In 1995, the adaptive response phenomenon to oxidative stress was discovered in nematode [10]. Since then, three types of adaptation to the response have been found, and related research on its mechanism of formation has been conducted [1, 11, 12].

We describe some of the researches that have been conducted in the areas of adaptive response in *C. elegans*, including the types, formation, mechanisms, and influencing factors responsible for the effects of the phenomenon. We

also suggest further research into *C. elegans* that will complement studies on adaptive response that are being conducted on other model systems.

2. Three Types of Adaptive Response in *C. elegans*

2.1. Hormesis Effect in *C. elegans*. *C. elegans* presents a clear adaptive response following exposure to a stressor. Hormesis occurs when a low-level stress elicits adaptive beneficial responses that protect against subsequent severe exposure to the same stress. In 2002, Cypser and Johnson found that pretreatment with heat as well as hyperoxia or juglone (a chemical that generates ROS) pretreatment could significantly increase subsequent resistance to the same challenge [13]. *C. elegans* preexposed to 2.5 μM of metals (Pb, Hg, Cu, and Cr) showed a moderate but significant reduction in the locomotive behavioral (assessed by endpoints of head thrash and body bend) defects that were induced by subsequent exposure to 50 and 100 μM of the same metals [11]. *C. elegans* treated under control conditions (0 mM MeHg) were significantly ($P < 0.05$) more sensitive to subsequent exposure to MeHg than those pretreated with 0.3 or 0.6 mM MeHg [14]. Prolonged exposure to low doses of alcohol induced a multifaceted “withdrawal syndrome,” and the observed decreased reversal frequency was most likely result from an adaptation to alcohol caused by inhibition of feeding and a food-deprived behavioral state in *C. elegans* [15]. Short-term exposure to antipsychotic drugs altered the frequency of turns/reversals off food, whereas drug withdrawal after 24 hr treatment was accompanied by a rebound in the number of turns/reversals in *C. elegans* [16]. Exposure of adult *C. elegans* to hypersmotic conditions protected their offspring from the same, which may be correlated with the changes in the sugar content of adults and embryos [17]. More interestingly, it was reported that nematodes can even adapt to high salt swell and then return to their initial body volume when exposed to low-salt agar [18].

2.2. Cross-Adaptation in *C. elegans*. Cross adaptation was first observed in *C. elegans* during preexposure of *C. elegans* to oxygen which conferred a protective effect against the lethality imposed by subsequent X-irradiation [1]. Cross-tolerance between juglone and oxygen was further observed by Cypser and Johnson in *C. elegans* [13]. Pretreatment with mild UV irradiation prevented the formation of locomotive behavioral defects and activated a remarkable reduction of the stress response and oxidative damage in 50 and 100 μM metal (Hg, Pb, and Cr) exposed nematodes [5]. Similarly, pre-treatment with UV irradiation suppressed the reproductive toxicity, as assessed by endpoints of blood size and generation time, that is normally induced by the subsequent cadmium exposure in nematodes [4]. Nonlethal stress such as mild heat shock had the beneficial effects on stress resistance and prevented the formation of the neurobehavioral defects and the activation of severe stress responses in lead and mercury exposed nematodes at concentrations of 50 and 100 μM [12].

2.3. Special Adaptive Response in *C. elegans*. It is proposed that lifespan extension by dietary restriction is an example of hormesis. Animals restricted to a balanced diet, containing as little as 60% of the calories they would consume *ad libitum*, have life expectancies up to 50% greater than controls [19]. Complete caloric deprivation—that is, starvation—can also mimic a hormetic treatment to increase lifespan, and young adult worms deprived of all food for 1–3 days display an extension in mean lifespan of 30–40% [20]. Similarly, glucose restriction extended lifespan by inducing mitochondrial respiration and increasing oxidative stress [21]. Moreover, it was observed that pre-exposure to low doses of plumbagin with toxicity to *C. elegans* by generating free radicals extended the lifespan of animals [22]. Pretreatment with low concentrations of the polyphenol tannic acid (TA) also induced a potent life-prolonging phenotype in *C. elegans* [23]. More interestingly, it was reported that the intermittent fasting (IF), another form of dietary restriction, also effectively extended the lifespan of *C. elegans*, and RHEB-1 regulated the IF in part by the insulin signaling effector DAF-16 [24].

3. Factors Influencing the Response Formation

3.1. Developmental Stage of Nematodes. Adaptation to stress has been observed in young *C. elegans* but not in mature or old individuals [10]. Young nematodes survived by increasing their content of superoxide dismutase (SOD); however, older nematodes did not and hence suffered loss of viability when treated with the quinone plumbagin or with hyperoxia, both of which are expected to increase production of ROS [10]. When exposed to a low concentration of the xenobiotic juglone, young nematodes mounted a robust hormetic stress response and survived a subsequent exposure to a higher concentration of juglone that is normally lethal to naïve animals [25]. Old nematodes, in contrast, were unable to mount this adaptive response [22].

3.2. Length of Pretreatment Duration. Lengths of time of pretreatment have important influences on adaptive response. Oxidative stress pre-treatment conferred a protective effect against the subsequent severe X-irradiation [1]. While the major protection effect was seen at 1 hr, the survival rate behind X-ray irradiation with pre-exposure to 90% of oxygen for 3 hr after oxygen pre-exposure was significantly lower than 2 hr [1]. There were significant decreases in head thrashes and body bend in heat-shock pre-treated nematodes for 1.5 and 2 hr compared to controls, but no changes were formed in 0.5 hr heat-shock pre-treated nematodes [12].

3.3. Pretreated Doses of the Agents. Pre-treatment with UV irradiation prevented the formation of locomotive behavioral defects (assessed by endpoints of head thrash and body bend) in 50 and 100 μM metal (Hg, Pb, and Cr) exposed nematodes [5]. The significant decrease in head thrashes and body bends could be observed in UV irradiated nematodes at 15, 20, and 30 $\text{J}/\text{m}^2/\text{min}$ compared to controls, but no noticeable changes were recorded when pretreated with UV less than 5 $\text{J}/\text{m}^2/\text{min}$ [5]. Similarly, the suppression

of reproductive toxicity could be observed in UV-irradiated nematodes at 15, 20, and 30 J/m²/min compared to controls, but no obvious alterations were recorded in nematodes treated with UV irradiation less than 5 J/m²/min [4]. Mild metal (Pb, Hg, Cu, Cr) exposure conferred an increased resistance when nematodes were challenged with higher concentrations of the same metal, but pre-treatment with several metals enhanced the stress response induced by subsequent metal exposure in *C. elegans* [11]. Pre-exposure to 2.5 μM of metals caused a reduction of locomotive behavioral defects and an increase of *hsp-16.2::gfp* expression that was induced by the subsequent 50 and 100 μM of metal exposure; in contrast, the hormesis was further decreased in nematodes that were examined following 50 μM metal pre-treatment [11].

3.4. Length of the Subsequent Treatment Duration. Sensitivities of nematodes to 400 Gy of X-rays at intervals between 0 and 5 hr after pre-exposure to 90% of oxygen for 1 hr were statistically significant [1]. The major beneficial effect was seen at intervals of 1 hr, although a residual protective effect was still apparent even 3 hr after oxygen pre-exposure [1]. The survival rate of nematodes incubated with oxygen pre-exposure for 5 hr before irradiation was even lower than control [1].

3.5. Dose of the Subsequent Treated Agents. Pre-treatment with mild heat shock effectively prevented the formation of the neurobehavioral defects and the activation of severe stress response in metal exposed nematodes at concentrations of 50 and 100 μM, but the heat pre-treatment could not prevent the formation of neurobehavioral defects in 200 μM of metal exposed nematodes [12]. Pre-treatment with UV irradiation prevented the reproductive toxicity (assessed by endpoints of blood size and generation time) caused by Cd in concentration of 50 and 100 μM compared to controls, but no obvious alterations were recorded in the concentration of 150 μM [4]. Similarly, the locomotive behavioral defects induced by 50 and 100 μM of metal (Hg, Pb and Cr) in UV preirradiated nematodes could be suppressed, but no obvious alterations were recorded in nematodes treated with 200 μM of metal [5]. Combined, this information suggests that the adaptive response in *C. elegans* can only be imposed within a certain range of stress or toxicant and is ineffectual when the extent of the challenge is too great.

4. Regulation Mechanisms of Adaptive Response

Hormesis is the induction of beneficial effects by exposure to low doses of harmful chemical or physical agents. We indicate here that the nematode, *C. elegans*, displays broad adaptive response abilities, but the biological mechanisms underlying these abilities have not yet been fully elucidated. Nevertheless, the studies conducted so far show that they may at least involve antioxidant defense system enhancement, stress protein (hsps) induction, signaling pathways modulation, and metabolic regulation.

4.1. Oxidative Stress and Antioxidant Defense System. The resistance to high amounts of ROS is explained by the prominent adaptive responses of the antioxidant defense system, which is of vital importance in the protection against oxidative stress. These effects may be due to increased formation of ROS within the mitochondria, causing an adaptive response that culminates in the subsequently increased stress resistance, which is assumed to ultimately cause a long-term reduction of oxidative stress.

Naphthalene quinone or high oxygen treatment can induce nematodes to produce ROS, and these ROS may cause the activity of peroxidase to increase, thus conferring resistance to nematodes facing subsequent stress treatments [10]. It was further observed that there was a noticeable elevation of SOD and CAT activities and an obvious decrease of oxidative damage in metal-exposed nematodes at high concentrations after mild UV or metal pre-treatment [5, 12]. At the molecular level, the adaptive response was thought to be mediated by the induction of a constellation of genes whose products confer resistance to the damaging agent. *age-1* mutant was characterized by resistance to paraquat, heat and oxygen resistance for superoxide dismutase genes (*sod-1* through *4*), and catalase genes (*clt-1* and *clt-2*), known to encode antioxidant enzymes, and expression levels of these genes were elevated in *age-1* young adults during the lifespan [26]. In *C. elegans*, SKN-1 mediates protective responses to oxidative stress, and genetic analysis indicated that *skn-1* activity was required for lifespan extension by low-dose plumbagin [22]. So far, it is believed that the adaptive response is mediated by events that suppress the mitochondrial O₂^{•-} production, and the oxidative stress-inducible hormesis is associated with a reduction of the mitochondrial O₂^{•-} production by activation of the antioxidant system in *C. elegans* [27].

However, some researchers argue the opposite. Yanase et al. observed that the expression of two superoxide dismutase genes—*sod-1* and *sod-3*—was relatively unaffected in hyperoxia pre-exposed *C. elegans*, which suggests that the SOD activity may not play a role in the adaptive response against a specific oxidative stress [1].

4.2. Heat-Shock Proteins (HSPs). Small heat-shock proteins (HSPs) appear of general importance for adaptations because their expression correlates well with the presence of various stressors. Pre-exposure of *C. elegans* to oxygen conferred a protective effect against the lethally imposed X-radiation, probably due to dramatically increased expression of the heat shock protein genes, *hsp-16.1* and *hsp-16.48* [1]. Previous studies in *C. elegans* have demonstrated that HSPs, of the HSP70 family, could be upregulated following exposure to heavy metals [11, 14]. After exposure to 2.5 μM of metals, the induction of *hsp-16.2::gfp* expression, caused by the subsequent 50 and 100 μM of metal exposure, was significantly suppressed [11]. A sublethal exposure to MeHg rendered *C. elegans* resistant to the subsequent exposure to the organometal, showing a potential role of HSP-4 in MeHg-induced hormesis [14]. In *C. elegans*, HSP-16.2 expression was identified as a valuable predictor of the ability to withstand a lethal thermal stress, and its levels correlate well with

the hormetic effects in response to heat treatment [28]. HSP-16 could affect lifespan by reducing oxidative stress through raising the pool of reduced glutathione (GSH) in nematodes [29]. Lifespan extension under moderate oxidative stress was also associated with the increased expression of HSP-16.2 [30, 31].

4.3. Metallothioneins. Metallothioneins (MTs) are small, cysteine-rich metal-binding proteins involved in metal detoxification, homeostasis, and protection from oxidative stress. In *C. elegans*, *mtl* knockout animals displayed increased sensitivity to MeHg exposure; a slight decrease in baseline activity of *mtl-1* and *mtl-2* was observed when nematodes were further exposed to MeHg [14]. The normal formation of cross-adaptation responses to metal toxicity may need sufficient MTs protein to be available in tissues of nematodes. During the formation of cross-adaptation responses, the induction of *mtl-1* and *mtl-2* promoter activity was sharply increased in 50 or 100 mM of metal exposed nematodes after mild heat-shock treatment compared with those treated with mild heat-shock or metal exposure alone [12]. Moreover, after pre-treatment with mild heat shock, no noticeable increase of locomotive behaviors could be noted in metal (Pb, Hg) exposed *mtl-1* or *mtl-2* mutant strains, and overexpression of MTL-1 and MTL-2 at the L2-larval stage could significantly suppress the adverse effects on locomotive behaviors following metal exposure [12].

4.4. Glutathione (GSH). Sublethal exposure to MeHg rendered *C. elegans* resistant to subsequent exposure to the organometal, and an increase in expression of *gst-4* gene indicated that *gst-4* gene may be involved in this response: the increase in *gst-4* catalyzes the conjugation of MeHg to GSH, causing GSH and total glutathione levels to decrease [14]. MeHg exposure induced significant decreases in GSH, GSH/GSSG ratio, and total glutathione levels which suggests an increased conjugation of GSH to MeHg, facilitating its elimination from the system [14].

4.5. Signaling Pathways. In *C. elegans*, the insulin/insulin-like growth factor-like signaling (ILS) pathway mediates both intrinsic stress resistance and lifespan [13]. Lifespan extension from stress hormesis by thermal stress and juglone-induced oxidative stress require *daf-16*, a downstream target of the insulin/IGF-1 receptor [22, 30]. Both DAF-16 and SKN-1 signals were required for the adaptation to low concentrations of juglone and plumbagin [22, 25]. Mean lifespan extension by plumbagin was dependent on the activated expression of a *skn-1* target, a transcription factor that promotes antioxidant gene expression in response to oxidative stress [22]. Reduced insulin/IGF-1-like signaling from the DAF-2/ILS receptor increased the nuclear accumulation of SKN-1 and activated a subset of *skn-1* dependent genes (including *gst-4*) independently of DAF-16 [22]. When exposed to a low concentration of the xenobiotic juglone, young nematodes mounted a robust hormetic stress response; however, old nematodes were unable to mount this adaptive response because DAF-16 and SKN-1 were reduced

[25]. Extreme hypertonic stress response was also linked to the transcriptional targets of DAF-16-mediated insulin signaling pathway [32]. Moreover, Kim et al. found DAF-16 nuclear accumulation in cells throughout the body and accumulated excess fat after exposure to hypergravity for 3 hr [33].

The protection in oxidative stress resistance appears to be accomplished by small HSPs through a glucose-6-phosphate dehydrogenase-dependent increase in NADPH generation needed to maintain GSH in its reduced form via the GSSG-reductase and by using this redox modulator as an essential cofactor of their in vivo chaperone activity against oxidized proteins [28]. This function in stress resistance and longevity is further embedded into the insulin/IGF-1 signaling pathway that has been shown in several studies to be a central determinant of lifespan in *C. elegans* [28].

In low concentration of polyphenol tannic acid (TA) exposed *C. elegans*, accompanied with the potent life-prolonging properties, enhanced thermal stress resistance, reduced growth, and slightly increased oxidative stress resistance, the mitogen-activated protein kinase kinase SEK-1 (SAPK/ERK kinase) played a key role in the formation of hormesis effect [23]. *hif-1* gene encoding a bHLH-PAS protein was required for adaptation to hypoxia because the majority of *hif-1*-defective nematodes died in the condition of 1% oxygen although the wild-type nematodes can survive and reproduce in these conditions [34]. *egl-3* gene encoding a neuropeptide was required for adaptive response to alcohol exposure because a mutation deficient in *egl-3* was resistant to the withdrawal behavior caused by alcohol exposure [15]. MDT-15 integrated several transcriptional regulatory pathways to monitor both the availability and quality of ingested materials and abrogates induction of specific detoxification genes in response to certain xenobiotics or heavy metals, thus rendering nematodes hypersensitive to toxin exposure [35].

For the adaptive response under the hyperosmotic environments, Solomon et al. suggest that OSR-1 plays a central role in integrating stress detection and adaptation responses by invoking multiple signaling pathways to promote survival under hyperosmotic environments [36]. Genetic epistasis analysis indicated that OSR-1 regulated survival under osmotic stress via a conserved p38 MAP kinase signaling cascade and regulates osmotic avoidance and resistance to acute dehydration likely by distinct mechanisms [36].

4.6. Metabolic Signals. Minois has proposed an alternative description wherein hormesis is seen as a consequence of metabolic regulation coupled to the expression of stress response proteins [37]. Nematodes are able to survive well on agar containing up to 500 mM NaCl after being grown on 200 mM NaCl for 2 weeks. The analysis demonstrated that expression levels of glycerol 3-phosphate dehydrogenase, an enzyme that is rate limiting for hypertonicity-induced glycerol synthesis, increased 15- to 20-fold when grown on 200 mM NaCl agar [18]. Schulz et al. found that the impaired glucose metabolism (glucose restriction) extended life expectancy by promoting mitochondrial metabolism, causing increased ROS formation [21]. The adaptation to hyperosmotic conditions was correlated to changes in the

sugar content of adults and embryo, and mutations in genes products which alter sugar homeostasis altered the ability of embryos to survive in hyperosmotic conditions in the adaptive parental effect [17].

4.7. RNA Interference. The recent research further indicated that elimination of RNA interference by silencing key enzymes in microRNA biogenesis, *dcr-1* or *pash-1*, restored the diminished intrinsic thermotolerance of aged and H₂O₂-elimination compromised (catalase-2 and peroxiredoxin-2 deficient) nematodes, which uncovers a novel posttranscriptional element in the regulation of heat stress adaptation under oxidative conditions [38].

5. Conclusions

From studies to date, three forms of adaptive response have been found in *C. elegans*: two basic forms response (hormesis and cross adaptation) and one special adaptive response. Compared with research on hormesis, only limited studies relating to cross-adaptation in nematodes have been conducted. Consequently, in-depth investigations are needed to decipher the widespread adaptive response to the same challenge, which will be an important prerequisite for cautious regulation mechanisms of corresponding research. For cross adaptation, it is recommended that joint exposure to the toxin be combined in order to fully analyze the system of possible interactions between coercion or toxins and stress or poison. And it is still controversial whether dietary restriction is an example of an adaptive response. Nevertheless, dietary restriction, or starvation, and aging factors have a central role in reducing the phenomenon of adaptive response, and lifespan extension does exist when exerted in *C. elegans* chronologically.

Factors influencing the formation of adaptive responses are focused on three aspects: the time lengths and doses of pre-exposure agents or stress; the time lengths and doses of subsequent challenges; the sensitivity of *C. elegans* to the challenge. All these data reveal that degree is the crucial impact factor, regardless of previous or subsequent coercion or poison exposure, as well as the sensitivity to the challenge.

Adaptive response formation could be suppressed because time of pre-exposure is too long, doses too high, or sensitivity to agents is too great. Conversely, stress or poison processing cannot produce toxic or animals for the corresponding stress or poison processing is not sensitive (such as mature adult larvae relative to stress or poison to deal with not sensitive) also difficult to form the response. Similarly, if the length of pre-exposure time is too long, doses too high or sensitivity to the subsequent exposure agents too great, the formation of adaptive response could be suppressed. In contrast to pre-treatment, more robust responses tend to be mounted if animals have corresponding moderate resistance to the subsequent stress agents. With continued research, more factors related to pre- or subsequent stress, poison processing, and animal sensitivity will be discovered. Additionally, the pre- and subsequent is just a relative processing, not on the strict development of larva or adult

age, and the period of choice between laboratories is not consistent.

As for the illustration of the intricacies of regulatory mechanisms of environmental stresses, antioxidant stress systems, heat shock proteins, metallothionein and nucleoside of GSH, signaling pathways, and metabolic regulation have been shown to be involved in response formation, but in-depth investigations are needed to decipher the underlying mechanisms. In view of antioxidant stress systems, heat shock proteins, metallothionein and nucleoside of GSH corresponding to the self-protection system, a very important question arises: what function do the other genes serve in response formation? That is, in addition to the animal's self-protection system, are there other molecules or genetic mechanisms used to regulate the formation of adaptive responses? Characterized by a rich background of research in genetics and developmental biology, the *C. elegans* model provides the most detailed and comprehensive information about the biochemistry and molecular biology involved in adaptive response. The nematode model also allows for suggestions of additional mechanisms that could be fundamental principles of adaptive response and gives us many new roads of exploration to determine the common and disparate mechanisms that underlie the many forms of adaptive response.

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