Natural Products in the Model Organism *Caenorhabditis elegans*

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Natural products are small molecules naturally produced by multiple sources such as plants, animals, fungi, bacteria and archaea. They exert both beneficial and detrimental effects by modulating biological targets and pathways involved in oxidative stress and antioxidant response. Natural products' oxidative or antioxidative properties are usually investigated in preclinical experimental models, including virtual computing simulations, cell and tissue cultures, rodent and nonhuman primate animal models, and human studies.

natural products | Caenorhabditis elegans | antioxidation | oxidative stress

1. Introduction

1.1. Oxidation and Antioxidation under Physiological and Pathological Conditions

Redox homeostasis is central to life, ranging from bioenergetics to metabolism and biological functions [1]. To defend against oxidative damage, organisms have evolved defenses that primarily rely on antioxidant enzymes, the supply of their substrates and repairing the damage. Antioxidant defenses can be enhanced through physiological signaling, dietary components and potential pharmaceutical interventions, thereby improving the capacity to scavenge oxidants and electrophiles. In 1954, Commoner et al. first described the occurrence of oxidative damage in a biological environment [2]. In 1985, the concept of "oxidative stress" was first applied to the biological logic system, which is defined as any oxidative damage in which excessive production of ROS or inadequate antioxidant defense occurs [3].

An imbalance between the production of oxidants and antioxidant defenses leads to damage to biological systems. This involves the chemistry of reactions of reactive species derived from oxygen, so-called 'oxidative stress.' Oxidative stress has been shown to participate in a variety of diseases, including cardiovascular disease, degenerative disease and cancer, and multiple mechanisms by which oxidants contribute to cellular damage have been revealed [4][5][6]. However, the degree of oxidative stress involved in the pathology of diseases is quite variable. This variability makes it difficult to improve the antioxidant effects of therapy. Most of the antioxidant defense in cells is provided not by either exogenous or endogenous small molecules acting as scavengers but by antioxidant enzymes using their specific substrates to reduce oxidants. The therapeutic use of small molecules has been disappointing, largely due to overoptimism and incorrect assumptions about how antioxidants work [7]. Furthermore, antioxidant enzymes react with oxidants thousands to millions of times faster than small molecules and provide the predominant antioxidant defense [7][8]. Therefore, the major therapeutic opportunities lie in

preventing the production of oxidants that directly damage macromolecules, inhibiting the downstream signaling of oxidants that leads to inflammation or cell death, and increasing both antioxidant enzymes and their substrates. Currently, clinical trials based on this approach are underway [4]. A greater understanding of the mechanisms of action of antioxidants and where and when they are effective may provide a rational approach to addressing oxidative stress.

1.2. Role of Oxidation and Antioxidation Based on the Complex Composition of Natural Products

In the pharmaceutical industry, the approved medicinal products are mostly composed of a single molecule or combinations of single molecules whose pharmacological properties and safety are characterized during the preclinical phase and then validated in human trials [9]. The plants, animals, fungi, bacteria and archaea are a source of drugs of natural origin. Each of them contains hundreds of compounds, which belong to different classifications, such as diterpenoid, flavonoid, coumarin, steroid, hydrocarbon, carboxylic acid, ester, aldehyde, alcohol, ketone, ether, epoxide, phenol and so on [10]. Although many approved drugs isolated from natural sources have been proven to be involved in oxidation or antioxidation in experimental models and human studies [11], their mechanisms of action are usually not yet fully elucidated since it is difficult to identify the effective compounds and dosages. For example, researchers have demonstrated that Glycyrrhizae radix extract is beneficial in preventing oxidative damage in *Caenorhabditis elegans* (*C. elegans*). However, this extract is a mixture of all water-soluble compounds from Glycyrrhizae radix, so it is still unknown which compound plays an antioxidant role in this protective effect [12]. The composition of natural products is complex, thus posing a challenge to clarify their role in the oxidation and antioxidation process clearly. Along with the improved sensitivity of trace detection techniques (e.g., high-resolution mass spectrometry, instrumental neutron activation analysis, atomic absorption spectroscopy, ultra-performance liquid chromatography), an increasing number of newly discovered compounds have been isolated from natural products [13]. By means of plane and spatial structure analysis methods (e.g., nuclear magnetic resonance, atomic spectroscopy, circular dichroism spectrum, single crystal X-ray diffraction), the structures of these novel compounds can be resolved, making it possible to reveal the oxidation and antioxidation effects and mechanisms [14][15].

1.3. Advantages of *C. elegans* as a Model of Oxidation and Antioxidation Assessment

C. elegans was introduced to science as a model organism for development and neurobiology in 1965 [16]. Nematodes share approximately 60–80% of genes and 12 signaling pathways with humans [17][18], and notes on gene function can be obtained from the WormBase online consortium. *C. elegans* shows many advantages, such as self-fertilization, a short life cycle, a small and transparent body, ease of culture, simple operation and low cost, without limitations in ethics, showing great potential as an alternative model for the 3R principle [19][20]. Despite their simple structure, nematodes have complete muscle, subcutaneous tissue, nervous system, gut, gonads, glands and excretory system, and many basic physiological processes and oxidative stress responses of higher organisms are also highly conserved in nematodes [21][22]. Therefore, nematodes have great potential as models

for evaluating the pharmacological and toxicological effects in humans [23], and researchers systematically summarize the advantages and disadvantages of *C. elegans* in the pharmacotoxicology research field and compare this model with other classical models, namely Drosophila, zebrafish, yeast, cell and mammalian in **Table 1**. In recent decades, nematodes have become very popular for high-throughput drug screening. This allows the drug discovery process to be studied throughout the life cycle and the manipulation of individual genes or genomes, such as N-ethyl-N-nitrosourea or ethyl methanesulfonate mutations, RNA interference (RNAi) and CRISPR [24]. Nematodes have been applied to the mechanism of action of addictive drugs [25], the pharmacological effects of neurodegenerative diseases such as Alzheimer's disease (AD) drugs [26], and the neurotoxicity of anticancer drugs [27]. Currently, a large number of mutants have been used to study the molecular mechanism of effective components of natural products. For example, ursolic acid affects the stress response of nematodes by disturbing genes expressions of dopamine receptors [28][29], as also applies in the toxicological mechanism of the extract of Peganum harmala L. seeds [30], and the intestinal toxicity mechanism of Euphorbia factor L1 [31], etc. In addition, there are many reports on the effectiveness of antioxidants in *C. elegans*, as they can be used to establish an antioxidant stress response model for the assessment of antioxidant capacities in vivo [32][33][34][35].

Table 1. Advantages and disadvantages in the pharmacotoxicology of *C. elegans* and other models.

Life Cycle	Metabolism	High-Throughput Screening	Costing	Live Imaging	Ethics and Welfare	3R Phylogenetics	Cognitive Behavior	Homology with Human	Immune System	Genetic Manipulation	
C. elegans	Very short lifespan (approximately 3 weeks), small body (1 mm), short reproductive cycle (3.5d) and large broodsize	As a multicellular organism composed of the brain, pharynx, intestine, gonads,	Available	Easy and low-cost in infrastructure and maintenance	Available	√	√	Different anatomical systems (no brain structure and immune system, etc.)	Extremely simple cognitive behaviors	Approximately 60–80% homologous genes to human; 12 of the 17 signal pathways in humans are conserved in nematodes	No immune system	Highly amenable to genetic manipulations
Drosophila	3 months	The metabolism of the whole body exists, lack of blood circulatory system, and blood–brain barrier, might cause inconsistent and unpredictable results when	Available	Low-cost in infrastructure and maintenance	Unavailable	√	√	Simple and asymmetric brain structure	Relatively simple cognitive behaviors	Approximately 70% of the genes related to disease conditions in mammals are also present in Drosophila	Lack of an adaptive immune system	Highly amenable to genetic manipulations

Life Cycle	Metabolism	High-Throughput Screening	Costing	Live Imaging	Ethics and Welfare	3R Phylogenetics	Cognitive Behavior	Homology with Human	Immune System	Genetic Manipulation	
		applied to humans									
Zebrafish	Fertilizing 200–300 eggs every 5–7 days, an equivalent longevity and generation time to mice (3–5 m)	Some major differences related to anatomy and physiology associated with an aquatic species, but most organs perform the same functions as their human counterparts and exhibit well-conserved physiology	Available	Relatively expensive in infrastructure and maintenance (compared to Drosophila and *C. elegans*)	Unavailable	√	√	A vertebrate animal model,	Limited cognitive behavioral assays	Approximately 70% homologous genes to human; over 80% of known human disease genes have orthologues in zebrafish	Complete immune system	Genetic tools yet to be comprehensive (compared to Drosophila and *C. elegans*)
Yeast	3 days	Unlikely as a suitable model	Available		Available	√	√	A single-celled organism	-	70% homologous genes to human; has no physiologic relevance to humans, but with many mitochondrial proteins that are orthologous to human proteins	-	Powerful genetic [36][37]
Cell	Stable cell lines can be passed on for tens of generations	Cells alone are no longer metabolized in the whole body.	Available		Available	√	√	-	-	Human-derived cells as a research model	-	Amenable to genetic manipulations
Mammalian	Years	The metabolic process of the body is	Large-scale studies	Costly in infrastructure and	Unavailable	×	×	Phylogenetically close to human	Complex cognitive analysis	Almost 100% human homolog	Complete immune system [38]	Costly in genetic manipulations

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2. Establishment of Oxidative Stress Model in *C. elegans*

The lifespan of *C. elegans* is always proportional to its resistance to environmental stress, and stress resistance is dominant in the lifespan of *C. elegans* [39]. Under heat stress, cells show a heat shock response and induce gene expression to prevent cell degeneration and enhance heat resistance. Heat shock experiments usually observe the survival time of nematodes by placing them at a temperature higher than the suitable living environment for some time. This index has been widely used to evaluate the protective effect of substances. For example, Lin et al. exposed nematodes to traditional Chinese herbal tea for 4 days, transferred them to 35 °C and recorded death per hour, indicating this treatment extended the average lifespan of nematodes significantly [40]. The same method was also used to evaluate the antistress effects of Cyclocarya paliurus polysaccharide leaf extract and piceatannol, and the researchers came to similar conclusions [41][42]. There are also some different treatment methods in heat stress experiments; for example, Lu et al. studied the protective effect of calycosin on nematodes under heat stress. On the third day, adult nematodes were cultured at 36 °C for 4 h and then transferred to 20 °C, and their survival was recorded every day [43].

The oxidative stress model of nematodes involves observing the survival of nematodes by exposing them to strong oxidants. Paraquat is a common stimulator of oxidative stress. Nematodes were exposed to NGM plates containing 5–50 mM paraquat, and the survival rate was monitored every 12 h [40][41][42][44]. Alternatively, the paraquat

Life Cycle	Metabolism	High-Throughput Screening	Costing	Live Imaging	Ethics and Welfare	3R Phylogenetics	Cognitive Behavior	Homology with Human	Immune System	Genetic Manipulation
		close to that of human beings.	are limited						genes found in rodents	

[45]

ydrogen peroxide

or 7 h to

des was recorded every 30 min [40][41][46][47]. Oxidative stress can also be tested using juglone, exposing nematodes to lethal juglone at 250 μM for 3 h, 300 μM for 1 h or 150 mM for 24 h, and then the survival rates of nematodes were recorded [28][29][48][49].

The heat shock response in *C. elegans* has revealed three related neuroendocrine signaling pathways: the nuclear hormone receptor pathway, transforming growth factor-β pathway and IGF/insulin-like signaling pathway [50]. Among them, the IIS pathway is the most thoroughly studied and has been demonstrated to play an important role in the signaling regulation of oxidative stress in *C. elegans*. Lin et al. and Shen et al. proved that the improvement of stress resistance mediated by phytomedicine was positively correlated with the activation of IIS pathway [41][42]. To investigate whether forkhead box protein O (DAF-16), a key regulator of antioxidation or heat stress, plays a role in this process, the subcellular distribution of DAF-16 in the TJ356 mutant was observed. The transfer of DAF-16 from the cytoplasm to the nucleus could be inhibited under stress [40]. The mechanism of Cyclocarya paliurus (C. paliurus) polysaccharide enhancing nematode heat tolerance was related to heat shock transcription factor 1 (HSF-1) without affecting the expression of DAF-16 in TJ356 but changed the fluorescence expression of SOD-3::GFP, and altered the expression of heat stress-related genes hsp-16.1 and hsp-16.2, suggesting that the HSF-1 pathway was necessary to improve heat tolerance. The longevity promoter skinhead-1 (SKN-1) regulates oxidative stress resistance. Under H2O2-induced oxidative stress, C. paliurus polysaccharide did not shorten the longevity of SKN-1 mutants, suggesting that the C. paliurus polysaccharide-mediated oxidative stress is dependent on SKN-1 [41].

References

1. Stern, M.; McNew, J.A. A transition to degeneration triggered by oxidative stress in degenerative disorders. Mol. Psychiatr. 2021, 26, 736–746.
2. Commoner, B.; Townsend, J.; Pake, G.E. Free radicals in biological materials. Nature 1954, 174, 689–691.
3. Sies, H.; Cadenas, E. Inorganic and organic radicals: Their biological and clinical relevance-Oxidative stress: Damage to intact cells and organs. Philos. Trans. R Soc. Lond. B Biol. Sci. 1985, 311, 617–631.
4. Peoples, J.N.; Saraf, A.; Ghazal, N.; Pham, T.T.; Kwong, J.Q. Mitochondrial dysfunction and oxidative stress in heart disease. Exp. Mol. Med. 2019, 51, 1–13.
5. Butterfield, D.A.; Halliwell, B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat. Rev. Neurosci. 2019, 20, 148–160.

6. Brahma, M.K.; Gilglioni, E.H.; Zhou, L.; Trepo, E.; Chen, P.; Gurzov, E.N. Oxidative stress in obesity-associated hepatocellular carcinoma: Sources, signaling and therapeutic challenges. Oncogene 2021, 40, 5155–5167.
7. Forman, H.J.; Davies, K.J.; Ursini, F. How do nutritional antioxidants really work: Nucleophilic tone and para-hormesis versus free radical scavenging in vivo. Free Radical Bio. Med. 2014, 66, 24–35.
8. Sies, H. Strategies of antioxidant defense. Eur. J. Biochem. 1993, 215, 213–219.
9. Luethi, D.; Liechti, M.E. Designer drugs: Mechanism of action and adverse effects. Arch. Toxicol. 2020, 94, 1085–1133.
10. An, J.; Hao, D.J.; Zhang, Q.; Chen, B.; Zhang, R.; Wang, Y.; Yang, H. Natural products for treatment of bone erosive diseases: The effects and mechanisms on inhibiting osteoclastogenesis and bone resorption. Int. Immunopharmacol. 2016, 36, 118–131.
11. Pisoschi, A.M.; Pop, A.; Cimpeanu, C.; Predoi, G. Antioxidant capacity determination in plants and plant-derived products: A review. Oxid. Med. Cell. Longev. 2016, 2016, 9130976.
12. Ruan, Q.; Qiao, Y.; Zhao, Y.; Xu, Y.; Wang, M.; Duan, J.; Wang, D. Beneficial effects of Glycyrrhizae radix extract in preventing oxidative damage and extending the lifespan of Caenorhabditis elegans. J. Ethnopharmacol. 2016, 177, 101–110.
13. Huerta, B.; Rodríguez-Mozaz, S.; Barceló, D. Pharmaceuticals in biota in the aquatic environment: Analytical methods and environmental implications. Anal. Bioanal. Chem. 2012, 404, 2611–2624.
14. Harvey, A.L.; Edrada-Ebel, R.; Quinn, R.J. The re-emergence of natural products for drug discovery in the genomics era. Nat. Rev. Drug. Discov. 2015, 14, 111–129.
15. Khalifa, S.A.M.; Elias, N.; Farag, M.A.; Chen, L.; Saeed, A.; Hegazy, M.F.; Moustafa, M.S.; Abd El-Wahed, A.; Al-Mousawi, S.M.; Musharraf, S.G.; et al. Marine natural products: A source of novel anticancer drugs. Mar. Drugs 2019, 17, 491.
16. Brenner, S. The genetics of Caenorhabditis elegans. Genetics 1974, 77, 71–94.
17. Benjamin, L.; Storey, K.B. An overview of stress response and hypometabolic strategies in Caenorhabditis elegans: Conserved and contrasting signals with the mammalian system. Int. J. Biol. Sci. 2010, 6, 9–50.
18. Consortium, C.E.S. Genome sequence of the nematode C. elegans: A platform for investigating biology. The C. elegans sequencing consortium. Science 1998, 282, 2012–2018.
19. Racz, P.I.; Wildwater, M.; Rooseboom, M.; Kerkhof, E.; Pieters, R.; Yebra-Pimentel, E.S.; Dirks, R.P.; Spaink, H.P.; Smulders, C.; Whale, G.F. Application of Caenorhabditis elegans (nematode)

and Danio rerio embryo (zebrafish) as model systems to screen for developmental and reproductive toxicity of Piperazine compounds. Toxicol. Vitr. 2017, 44, 11–16.

20. Ayuda-Durán, B.; González-Manzano, S.; González-Paramás, A.M.; Santos-Buelga, C. Caernohabditis elegans as a model organism to evaluate the antioxidant effects of phytochemicals. Molecules 2020, 25, 3194.
21. Guarente, L.; Kenyon, C. Genetic pathways that regulate ageing in model organisms. Nature 2000, 408, 255–262.
22. Kenyon, C. A conserved regulatory system for aging. Cell 2001, 105, 165–168.
23. Hunt; Piper; Reid The C-elegans model in toxicity testing. J. Appl. Toxicol. 2017, 37, 50–59.
24. Carretero, M.; Solis, G.M.; Petrascheck, M. C. elegans as model for drug discovery. Curr. Top. Med. Chem. 2017, 17, 2067–2076.
25. Engleman, E.A.; Katner, S.N.; Neal-Beliveau, B.S. Caenorhabditis elegans as a model to study the molecular and genetic mechanisms of drug addiction. Prog. Mol. Biol. Transl. 2016, 137, 229–252.
26. Griffin, E.F.; Caldwell, K.A.; Caldwell, G.A. Genetic and pharmacological discovery for Alzheimer's Disease using Caenorhabditis elegans. ACS Chem. Neurosc. 2017, 8, 2596–2606.
27. Wellenberg, A.; Weides, L.; Kurzke, J.; Hennecke, T.; Honnen, S. Use of C. elegans as a 3R-compliant in vivo model for the chemoprevention of cisplatin-induced neurotoxicity. Exp. Neurol. 2021, 341, 113705.
28. Na, J.; Abdelfatah, S.; Efferth, T. The triterpenoid ursolic acid ameliorates stress in Caenorhabditis elegans by affecting the depression-associated genes skn-1 and prdx-2. Phytomedicine 2021, 88, 153598.
29. Na, J.; Efferth, T. Ursolic acid ameliorates stress and reactive oxygen species in C. elegans knockout mutants by the dopamine Dop1 and Dop3 receptors. Phytomedicine 2020, 81, 153439.
30. Miao, X.Z.; Zhang, X.; Yuan, Y.Y.; Zhang, Y.L.; Tan, P. The toxicity assessment of extract of Peganum harmala L. seeds in Caenorhabditis elegans. BMC Complement. Med. 2020, 20, 256.
31. Zhu, A.; Ji, Z.H.; Zhao, J.W.; Zhang, W.J.; Sun, Y.Q.; Zhang, T.; Gao, S.; Li, G.J.; Wang, Q. Effect of Euphorbia factor L1 on intestinal barrier impairment and defecation dysfunction in Caenorhabditis elegans. Phytomedicine 2019, 65, 153102.
32. Büchter, C.; Ackermann, D.; Havermann, S.; Honnen, S.; Chovolou, Y.; Fritz, G.; Kampkötter, A.; Wätjen, W. Myricetin-mediated lifespan extension in Caenorhabditis elegans is modulated by DAF-16. Int. J. Mol. Sci. 2013, 14, 11895–11914.

33. Meng, F.; Li, J.; Wang, W.; Fu, Y. Gengnianchun, a traditional Chinese medicine, enhances oxidative stress resistance and lifespan in Caenorhabditis elegans by modulating daf-16/FOXO. Evid.-Based Compl. Alt. 2017, 2017, 8432306.
34. Chen, P.C.; He, D.; Zhang, Y.; Yang, S.S.; Chen, L.J.; Wang, S.Q.; Zou, H.X.; Liao, Z.Y.; Zhang, X.; Wu, M.J. Sargassum fusiforme polysaccharides activate antioxidant defense by promoting Nrf2-dependent cytoprotection and ameliorate stress insult during aging. Food Funct. 2016, 7, 4576–4588.
35. Lutchman, V.; Dakik, P.; McAuley, M.; Cortes, B.; Ferraye, G.; Gontmacher, L.; Graziano, D.; Moukhariq, F.; Simard, É.; Titorenko, V. Six plant extracts delay yeast chronological aging through different signaling pathways. Oncotarget 2016, 7, 50845–50863.
36. Wang, D.Y. Melacular Toxicity in Caenorhabditis elegans; Springer: Singapore, 2019.
37. Wang, D.Y. Target Organ Toxicology in Caenorhabditis elegans; Springer: Singapore, 2019.
38. Wang, D.Y. Exposure Toxicity in Caenorhabditis elegans; Springer: Singapore, 2020.
39. Link, C.D. C. elegans models of age-associated neurodegenerative diseases: Lessons from transgenic worm models of Alzheimer’s disease. Exp. Gerontol. 2006, 41, 1007–1013.
40. Lin, C.X.; Zhang, X.y.; Zhuang, C.T.; Lin, Y.G.; Cao, Y.; Chen, Y.J. Healthspan improvements in Caenorhabditis elegans with traditional Chinese herbal tea. Oxid. Med. Cell. Longev. 2020, 2020, 4057841.
41. Lin, C.; Su, Z.; Luo, J.; Jiang, L.; Shen, S.; Zheng, W.; Gu, W.; Cao, Y.; Chen, Y. Polysaccharide extracted from the leaves of Cyclocarya paliurus (Batal.) Iljinskaja enhanced stress resistance in Caenorhabditis elegans via skn-1 and hsf-1. Int. J. Biol. Macromol. 2020, 143, 243–254.
42. Shen, P.Y.; Yue, Y.R.; Sun, Q.C.; Kasireddy, N.D.; Kim, K.H.; Park, Y.H. Piceatannol extends the lifespan of Caenorhabditis elegans via DAF-16. BioFactors 2017, 43, 379–387.
43. Lu, L.; Zhao, X.; Zhang, J.; Li, M.; Qi, Y.; Zhou, L. Calycosin promotes lifespan in Caenorhabditis elegans through insulin signaling pathway via daf-16, age-1 and daf-2. J. Biosci. Bioeng. 2017, 124, 1–7.
44. Zhao, S.X.; Cheng, Q.; Peng, Q.; Yu, X.S.; Yin, X.Q.; Liang, M.; Ma, C.W.; Huang, Z.B.; Jia, W.Z. Antioxidant peptides derived from the hydrolyzate of purple sea urchin (Strongylocentrotus nudus) gonad alleviate oxidative stress in Caenorhabditis elegans. J. Funct. Foods 2018, 48, 594–604.
45. Urban, N.; Tsitsipatis, D.; Hausig, F.; Kreuzer, K.; Erler, K.; Stein, V.; Ristow, M.; Steinbrenner, H.; Klotz, L.O. Non-linear impact of glutathione depletion on C. elegans life span and stress resistance. Redox Biol. 2017, 11, 502–515.
46. Saul, N.; Pietsch, K.; Menzel, R.; Steinberg, C.E. Quercetin-mediated longevity in Caenorhabditis elegans: Is DAF-16 involved? Mech. Ageing Dev. 2008, 129, 611–613.

47. Vertino, A.; Ayyadevara, S.; Thaden, J.J.; Shmookler, R.R. A narrow quantitative trait locus in C. elegans coordinately affects longevity, thermotolerance, and resistance to paraquat. Front. Genet. 2011, 2, 63.
48. Shi, Y.C.; Pan, T.M.; Liao, V.H. Monascin from monascus-fermented products reduces oxidative stress and amyloid-β toxicity via DAF-16/FOXO in Caenorhabditis elegans. J. Agr. Food Chem. 2016, 64, 7114–7120.
49. Reigada, I.; Moliner, C.; Valero, M.S.; Weinkove, D.; Langa, E.; Gómez Rincón, C. Antioxidant and antiaging effects of licorice on the Caenorhabditis elegans model. J. Med. Food 2020, 23, 72–78.
50. Prahlad, V.; Cornelius, T.; Morimoto, R.I. Regulation of the cellular heat shock response in Caenorhabditis elegans by thermosensory neurons. Science 2008, 320, 811–814.