

Dayong Wang

Target Organ
Toxicology in
*Caenorhabditis
elegans*

 Springer

Target Organ Toxicology
in *Caenorhabditis elegans*

Dayong Wang

Target Organ Toxicology
in *Caenorhabditis elegans*

 Springer

Dayong Wang
School of Medicine
Southeast University
Nanjing, China

ISBN 978-981-13-6009-1 ISBN 978-981-13-6010-7 (eBook)
<https://doi.org/10.1007/978-981-13-6010-7>

Library of Congress Control Number: 2018967724

© Springer Nature Singapore Pte Ltd. 2019

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Nematode *Caenorhabditis elegans* is a classic model animal widely used in the study of life sciences. Meanwhile, it has been further frequently used for toxicity assessment and toxicological study of various environmental toxicants or stresses. One of the important reasons is the sensitivity of nematodes to various environmental exposures. The second reason is the conserved property for most of the molecular events and the signaling pathways between nematodes and mammals or human beings. The third reason is from the classic model animal properties of *C. elegans* with well-described genetic and developmental backgrounds and rich and available genetic and molecular resources. In nematodes, once exposed to environmental toxicants, the toxicants can enter the primary targeted organs (such as intestinal cells) and even be translocated into secondary targeted organs (such as reproductive organs and neurons).

Structurally, *C. elegans* do not have some important organs (such as the heart, liver, lung, and kidney) due to the lack of the mesoderm during the development. Nevertheless, the *C. elegans* has epidermal system, nervous system, excretory system, muscle system, coelomocyte system, alimentary system, and reproductive system. Especially, the development and the corresponding molecular control of these systems in *C. elegans* can reflect the processes in mammals to a great degree. These backgrounds provide important developmental basis for the study of target organ toxicology in nematodes.

In this book, we have raised these four important concerns:

1. What are the protective responses of different organs and the neuronal and molecular basis of avoidance behavior of nematodes to environmental toxicants or stresses?
2. What's the molecular basis of primary biological barriers for nematodes against the toxicity of environmental toxicants or stresses?
3. What are the toxic effects of environmental toxicants or stresses on different organs in nematodes?
4. How the molecular signaling pathways in different organs of nematodes regulate the toxicity of environmental toxicants or stresses?

Based on these concerns, in Chaps. 1 and 2, we first introduced the protective responses of different organs and avoidance behavior of nematodes to environmental toxicants or stresses. In Chaps. 3 and 4, we introduced the molecular basis of intestinal and epidermal barriers for nematodes against the toxicity of environmental toxicants or stresses. In Chaps. 5, 6 and 7, we introduced the toxicity induction in the intestine, epidermis, neurons, muscle, and reproductive organs in nematodes exposed to environmental toxicants or stresses. Finally, in Chaps. 8, 9, 10 and 11, we introduced the intestinal, epidermal, neuronal, and germline signaling pathways required for the regulation of toxicity of environmental toxicants or stresses.

Nanjing, China

Dayong Wang

Contents

1	Protective Responses of Different Organs to Environmental Toxicants or Stresses	1
1.1	Introduction	1
1.2	Protective Responses to Environmental Toxicants or Stresses in the Intestine	1
1.2.1	Superoxide Dismutase (SOD) Proteins	2
1.2.2	MTL-1 and MTL-2	3
1.2.3	Heat Shock Proteins (HSPs)	3
1.2.4	PMK-1, SKN-1/Nrf, and GST-4	5
1.2.5	Transcriptional Factor DAF-16	7
1.2.6	Antimicrobial Proteins	8
1.2.7	Mitochondrial Unfolded Protein Response (UPR)	11
1.2.8	Endoplasmic Reticulum (ER) UPR	11
1.2.9	Autophagy	11
1.3	Protective Responses to Environmental Toxicants or Stresses in Epidermis	14
1.3.1	Antimicrobial Proteins	15
1.3.2	Autophagy	17
1.4	Protective Responses to Environmental Toxicants or Stresses in Neurons	17
1.4.1	SKN-1/Nrf	17
1.4.2	JNK Signaling	17
1.4.3	ERK Signaling	19
1.4.4	Antimicrobial Proteins	20
1.4.5	Autophagy	21
1.5	Protective Responses to Environmental Toxicants or Stresses in Muscle	21
1.6	Perspectives	22
	References	23

2	Avoidance Behavior of Nematodes to Environmental Toxicants or Stresses	27
2.1	Introduction	27
2.2	Neurons Involved in the Regulation of Avoidance Behavior to Environmental Toxicants or Stress	30
2.2.1	ASH Sensory Neurons	30
2.2.2	ADL Sensory Neurons	34
2.2.3	ASK Sensory Neurons	38
2.2.4	ASJ Sensory Neurons	39
2.2.5	ADF Sensory Neurons	42
2.2.6	ASI Sensory Neurons	43
2.2.7	AWB Sensory Neurons	45
2.2.8	AWC Sensory Neurons	46
2.2.9	BAG Sensory Neurons	46
2.2.10	OLL Sensory Neurons	48
2.2.11	Interneurons	48
2.3	Neuronal Circuit for the Avoidance Behavior to Environmental Toxicants or Stresses and the Underlying Molecular Basis	52
2.3.1	ASI-ADF-ASH and ASH-RIC-ASI Neuronal Circuits	52
2.3.2	ADL-AIB Neuronal Circuit	55
2.3.3	ASJ-RIM/RIC Neuronal Circuit	59
2.3.4	AWB-AIZ/RMG Neuronal Circuit	60
2.3.5	OLL-RMG Neuronal Circuit	61
2.4	Intestinal Function in Regulating the Avoidance Behavior to Environmental Toxicants or Stresses	63
2.5	Perspectives	65
	References	66
3	Intestinal Barrier for Nematodes Against Toxicity of Environmental Toxicants or Stresses	71
3.1	Introduction	71
3.2	Crucial Role of Intestinal Barrier Against the Toxicity of Environmental Toxicants or Stresses	72
3.3	Molecular Basis for Intestinal Barrier Against the Toxicity of Environmental Toxicants or Stresses	76
3.3.1	Identification of Genes Required for the Function of Intestinal Barrier Against the Toxicity of Environmental Toxicants or Stresses	76
3.3.2	PKC-3-SEC-8-WTS-1 Signaling Cascade	78
3.3.3	ACT-5-PKC-3 Signaling Cascade	83
3.3.4	Fatty Acid Transport Protein ACS-22	84

3.4	Modulation of Intestinal Integrity During the Aging	86
3.5	Intestinal Barrier and Stress-Related Signaling Pathways	89
3.6	Perspectives	89
	References	92
4	Epidermal Barrier for Nematodes Against Toxicity of Environmental Toxicants or Stresses	97
4.1	Introduction	97
4.2	Molecular Basis for the Function of Epidermal Barrier Against the Toxicity of Environmental Toxicants or Stresses	98
4.2.1	ACS-20	98
4.2.2	MLT-7-Mediated Signaling Cascades	102
4.2.3	BLI-1-Mediated Signaling Cascade	108
4.2.4	UNC-52-Mediated Signaling Cascade	111
4.2.5	TSP-15	113
4.2.6	DAPK-1	116
4.3	Epidermal Barrier and Activation of Innate Immune Response	116
4.4	Perspectives	120
	References	121
5	Toxicity Induction in the Intestine and Epidermis in Nematodes Exposed to Environmental Toxicants or Stresses	123
5.1	Introduction	123
5.2	Toxicity Induction in Intestine in Nematodes Exposed to Environmental Toxicants or Stresses	124
5.2.1	Activation of Oxidative Stress in the Intestine	124
5.2.2	Enhancement in Intestinal Permeability	126
5.2.3	Damage on Intestinal Development	128
5.2.4	Suppression of Innate Immune Response	131
5.2.5	Prolonged Defecation Behavior	136
5.2.6	Increase in Fat Storage	136
5.3	Toxicity Induction in Epidermis in Nematodes Exposed to Environmental Toxicants or Stresses	140
5.3.1	Maintenance of Normal Function of Epidermal Barrier in Wild-Type Nematodes	140
5.3.2	Toxicity Induction in Epidermis in Nematodes Exposed to Environmental Toxicants or Stresses Under the Certain Conditions	141
5.4	Perspectives	143
	References	144

6	Toxicity Induction in Neurons and Muscle in Nematodes Exposed to Environmental Toxicants or Stresses	147
6.1	Introduction	147
6.2	Toxicity on Development and Functions of Neurons in Nematodes Exposed to Environmental Toxicants or Stresses.	148
6.2.1	Development and Function of GABAergic Neurons	148
6.2.2	Development of Dopaminergic Neurons	155
6.2.3	Development and Function of Sensory Neurons	164
6.2.4	Interneurons	176
6.2.5	Complex Behaviors	179
6.2.6	Neurotransmission	184
6.3	Toxicity on Development and Functions of Muscle in Nematodes Exposed to Environmental Toxicants or Stresses.	187
6.3.1	Development of Muscle	187
6.3.2	Functions of Muscle.	190
6.4	Perspectives	192
	References	192
7	Reproductive Toxicity Induction in Nematodes Exposed to Environmental Toxicants or Stresses	197
7.1	Introduction	197
7.2	Reproductive Toxicity on Brood Size	198
7.3	Reproductive Toxicity on Generation Time.	199
7.4	Reproductive Toxicity on Egg-Laying Behavior	199
7.4.1	Reproductive Toxicity on Egg-Laying	200
7.4.2	Reproductive Toxicity on Vulva Development.	201
7.4.3	Contribution of Neurotransmission to Reproductive Toxicity on Egg-Laying	201
7.5	Reproductive Toxicity on Gonad Development	203
7.5.1	Reproductive Toxicity on Gonad Morphology.	203
7.5.2	Reproductive Toxicity in Inducing Germline Apoptosis	203
7.5.3	Reproductive Toxicity in Inducing Germline DNA Damage.	210
7.6	Reproductive Toxicity on Gametogenesis	212
7.6.1	Damage on Sperms	212
7.6.2	Damage on Oocytes	215
7.7	Reproductive Toxicity on Male Nematodes.	216
7.7.1	Reproductive Toxicity in Increasing the Rate of Male Formation	216
7.7.2	Reproductive Toxicity on Male Structures.	216

7.7.3	Sex-Specific Response to Environmental Toxicants or Stresses.	217
7.7.4	Effects from the Mating	218
7.8	Perspectives	219
	References	220
8	Intestinal Signaling Pathways Required for the Regulation of Toxicity of Environmental Toxicants or Stresses	223
8.1	Introduction	223
8.2	p38 MAPK Signaling Pathway	224
8.2.1	Intestinal Signaling Cascade of p38 MAPK Signaling Pathway Regulates the Toxicity of Environmental Toxicants or Stresses	224
8.2.2	Downstream Targets for Intestinal PMK-1 in Regulating the Toxicity of Environmental Toxicants or Stresses	225
8.2.3	Upstream Regulators for Intestinal PMK-1 in Regulating the Toxicity of Environmental Toxicants or Stresses	229
8.3	Insulin Signaling Pathway	229
8.3.1	Intestinal Signaling Cascade of Insulin Signaling Pathway Regulates the Toxicity of Environmental Toxicants or Stresses	229
8.3.2	Targets of DAF-16 in Regulating the Toxicity of Environmental Toxicants or Stresses	230
8.3.3	Upregulators of Insulin Signaling Pathway in Regulating the Toxicity of Environmental Toxicants or Stresses	237
8.3.4	Genetic Interaction Between SKN-1 and DAF-16 or DAF-2 in Regulating the Toxicity of Environmental Toxicants or Stresses	239
8.4	Development-Related Signaling Pathways	239
8.4.1	TGF- β Signaling Pathway	239
8.4.2	<i>let-7</i> and Its Targets	241
8.5	Metabolism-Related Signaling Pathways.	245
8.5.1	SBP-1	245
8.5.2	MDT-15	247
8.5.3	FAT-3	247
8.6	G-Protein-Coupled Receptors (GPCRs) and G Proteins	247
8.6.1	GPCRs	247
8.6.2	G Proteins.	249
8.7	Cytoplasmic Signals.	252
8.7.1	Protein Kinase D (PKD).	252
8.7.2	Mitochondrial UPR	254
8.7.3	Endoplasmic Reticulum (ER) UPR	254

8.7.4	Autophagy	256
8.7.5	Transcriptional Factors	257
8.8	Epigenetic Signals	262
8.8.1	microRNAs (miRNAs)	262
8.8.2	Long Noncoding RNAs (lncRNAs)	267
8.9	Intestinal Signals Are Neuroprotective	268
8.10	Perspectives	271
	References	273
9	Epidermal Signaling Pathways Required for the Regulation of Toxicity of Environmental Toxicants or Stresses	277
9.1	Introduction	277
9.2	Insulin Signaling Pathway	278
9.3	Peroxidase SKPO-1	279
9.4	Collagens	279
9.5	SNF-12 and STA-2	281
9.6	G-Protein-Coupled Receptors (GPCRs) and G Proteins	282
9.6.1	Epidermal GPCR DCAR-1	282
9.6.2	Gaq Signaling	286
9.7	Effect of Epidermal Signals on Neurons	287
9.8	Effect of Epidermal Signals on the Intestine	287
9.9	Perspectives	289
	References	290
10	Neuronal Signaling Pathways Required for the Regulation of Toxicity of Environmental Toxicants or Stresses	293
10.1	Introduction	293
10.2	JNK and ERK MAPK Signaling Pathways	294
10.2.1	JNK Signaling Pathway	294
10.2.2	ERK Signaling Pathway	294
10.3	TGF- β Signaling Pathway	298
10.3.1	DAF-7-Mediated TGF- β Signaling Pathway	298
10.3.2	DBL-1-Mediated TGF- β Signaling Pathway	299
10.4	Neuronal G-Protein-Coupled Receptors (GPCRs) and G Proteins	301
10.4.1	Neuronal GPCRs	301
10.4.2	Go α Signaling	308
10.4.3	ARR-1/Arrestin	309
10.5	Neuropeptide Proteins	309
10.6	Effects of Neuronal Signals on Functions of Molecular Signals in Intestine	313
10.6.1	INS-7	313
10.6.2	Dopaminergic Signaling	315
10.6.3	XBP-1	317
10.6.4	Serotonin and Wnt Signaling	317
10.7	Perspectives	320
	References	321

- 11 Germline Signaling Pathways Required for the Regulation of Toxicity of Environmental Toxicants or Stresses 325**
- 11.1 Introduction 325
- 11.2 Crucial Role of Germline for the Toxicity Induction of Environmental Toxicants or Stresses 326
 - 11.2.1 Role of GLP-1 in Regulating the Toxicity of Environmental Toxicants or Stresses 326
 - 11.2.2 Genetic Interaction Between GLP-1 and Insulin Signal in the Regulation of Toxicity of Environmental Toxicants or Stresses 328
- 11.3 ERK Signaling Pathway 330
- 11.4 Insulin Signaling Pathway 333
- 11.5 Perspectives 335
- References 337

Chapter 1

Protective Responses of Different Organs to Environmental Toxicants or Stresses



Abstract Environmental toxicants or stresses at low doses or for short-term duration will induce various protective responses in organisms. We here introduced and discussed the different protective responses activated in different organs (intestine, epidermis, neurons, and muscle) in nematodes exposed to environmental toxicants or stresses. The protective responses activated in different organs will provide the first defense line for nematodes against the environmental toxicants or stresses.

Keywords Protective response · Intestine · Epidermis · Neurons · Muscle · Environmental exposure · *Caenorhabditis elegans*

1.1 Introduction

In nematode *Caenorhabditis elegans*, exposure to various environmental toxicants or stresses can cause the toxicity at multiple aspects on animals [1–6]. Meanwhile, it is found that environmental toxicants or stresses at low doses or for short-term duration can induce different forms of protective response. These responses provide important mechanisms for nematodes against the adverse effects from environmental toxicants or stresses. In nematodes, different protective responses may be activated in different organs after exposure to environmental toxicants or stresses. In this chapter, we introduced the protective responses of nematodes to environmental toxicants or stresses in intestine, in epidermis, in neurons, and in muscle.

1.2 Protective Responses to Environmental Toxicants or Stresses in the Intestine

Intestine barrier is one of the primary biological barriers for nematodes against the toxicity of environmental toxicants or stresses [1, 2].

1.2.1 Superoxide Dismutase (SOD) Proteins

SODs are well-known proteins with the function in defending against the oxidative stress in organisms. In nematodes, there are five SODs, SOD-1, SOD-2, SOD-3, SOD-4, and SOD-5. SOD-3, a mitochondrial iron/manganese SOD, is expressed constitutively in intestinal cells [7]. Engineered nanomaterials (ENMs), such as titanium oxide nanoparticles (TiO₂-NPs) and nanopolystyrene particles, could induce the toxicity on the function of both primary targeted organs (such as intestine) and secondary targeted organs (such as reproductive organs) in nematodes [8–14]. We here selected SOD-3::GFP as an example to explain the SOD-mediated intestinal protective response of nematodes to environmental toxicants. In nematodes, it was observed that prolonged exposure to TiO₂-NPs (1 µg/L) could significantly increase the expressions of *sod-2* and *sod-3* and the expression of SOD-3::GFP (Fig. 1.1)

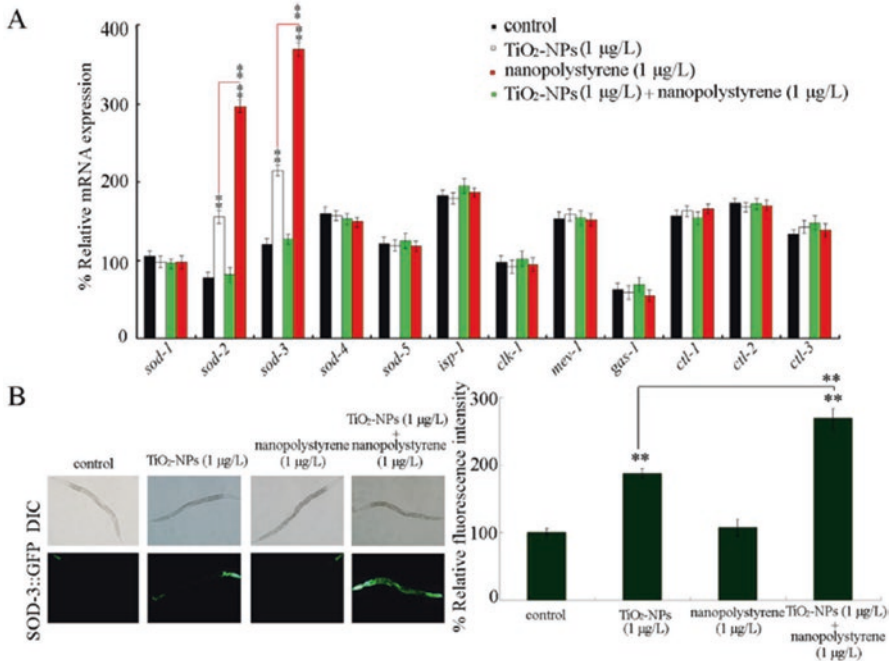


Fig. 1.1 Combinational exposure to TiO₂-NPs and nanopolystyrene particles altered the molecular basis for oxidative stress in wild-type nematodes [15]. **(a)** Combinational exposure to TiO₂-NPs and nanopolystyrene particles altered transcriptional expressions of genes required for the control of oxidative stress. **(b)** Combinational exposure to TiO₂-NPs and nanopolystyrene particles affected the expression of SOD-3::GFP. **(c)** Combinational exposure to TiO₂-NPs and nanopolystyrene particles affected the expression of SKN-1::GFP. Arrowheads indicate the signal of SKN-1::GFP in the nucleus. Prolonged exposure was performed from L1-larvae to adult day 1. Control, without TiO₂-NPs and nanopolystyrene particles exposure. Bars represent means ± SD. ***P* < 0.01 vs. control (if not specially indicated)