

A Comprehensive Understanding of Dietary Effects on *C. elegans* Physiology

Jie-jun ZHOU, Lei CHUN[#], Jian-feng LIU[#]

Collaborative Innovation Center for Brain Science, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China

© Huazhong University of Science and Technology 2019

Summary: Diet has been shown to play an important role in human physiology. It is a predominant exogenous factor regulating the composition of gut microbiota, and dietary intervention holds promise for treatment of diseases such as obesity, type 2 diabetes, and malnutrition. Furthermore, it was reported that diet has significant effects on physiological processes of *C. elegans*, including reproduction, fat storage, and aging. To reveal novel signaling pathways responsive to different diets, *C. elegans* and its bacterial diet were used as an interspecies model system to mimic the interaction between host and gut microbiota. Most signaling pathways identified in *C. elegans* are highly conserved across different species, including humans. A better understanding of these pathways can, therefore, help to develop interventions for human diseases. In this article, we summarize recent achievements on molecular mechanisms underlying the response of *C. elegans* to different diets and discuss their relevance to human health.

Key words: diet; gut microbiota; metabolites; *C. elegans*

Diet plays a vital role in the maintenance of metabolic balance, immune homeostasis, and longevity. With the improvement in living conditions and an increasingly rapid pace of life, traditional diets comprising coarse grain have been replaced by diets rich in sugars, fats, and meat. These dietary shifts are correlated with a dramatic rise in the occurrence of cancer, obesity, type 2 diabetes, and cardiovascular diseases^[1, 2]. Interestingly, long-term diet interventions, particularly with protein and animal fat supplements, result in dramatic changes to the dynamics of gut microbiota^[3, 4]. Gut microbiota plays a pivotal role in the regulation of many physiological processes as documented in some species of organisms. Recolonization of bacteria from young donors into the gut of middle-aged short-lived African turquoise killifish was found to increase the lifespan and delay behavioral decline^[5]; the mouse gut microbiota can alleviate inflammatory arthritis^[6], Parkinson's disease^[7], and protect against allergic inflammation in the lungs through increasing circulating levels of short-chain fatty acids (SCFA)^[8]. Dysbiosis of human gut microbiota is likely to be associated with diseases

like Henoch-Schönlein purpura in children^[9], type 2 diabetes^[10, 11], and cancer^[12, 13]. Diet affects public health mainly through the provision of different nutrients and modulation of gut microbial diversity; however, the detailed mechanisms underlying dietary regulation of health still remain poorly understood.

Given the complexity of dietary effects on humans and the vulnerability of gut microbiota to external factors such as antibiotics^[14], it is far from easy to gain a systemic understanding of dietary effects on human health. *C. elegans* and its bacterial diets serve as a powerful, efficient interspecies model system that mimics host-microbiota mutualism; this system has been used successfully for the identification of metabolic factors and signaling pathways that regulate gene expression and overall physiological processes^[15, 16]. And these worms have been shown to display distinct phenotypes on different diets, such as development rate, brood size, locomotion, fat storage and lifespan^[17–19]. Another big advantage of this system is that both *C. elegans* and its bacterial diets are amenable to large-scale, high-throughput genetic screening^[20, 21]. Importantly, more than 40 percent of *C. elegans* genes are highly conserved with those of humans; findings from this interspecies model could, therefore, provide clues for our understanding of how diet affects human health.

Jie-jun ZHOU, E-mail: jiejunzhou0828@163.com

[#]Corresponding authors, Lei CHUN, E-mail: lichun@hust.edu.cn; Jian-feng LIU, E-mail: jfliu@mail.hust.edu.cn

1 Both HT115 and OP50 Bacterial Diets Are Used for RNA Interference in *C. elegans*

C. elegans is short-lived, easy and cost-efficient to culture, and can be maintained at a range of temperatures between 15°C to 25°C. In the laboratory, OP50 and HT115 strains of *E. coli* are widely used to feed *C. elegans*, but only HT115 can be used for RNA interference (RNAi). Recently an RNAi-compatible *E. coli* OP50 xu363 strain has been generated, making it possible to study the dietary effects of OP50 on host phenotype by RNAi^[21]. Almost all nutrients required for *C. elegans* development and survival are provided by its bacterial diet. Hence, single gene RNAi on two different strains provides an ideal system for the study of the mechanism underlying responses of *C. elegans* to different metabolites such as vitamins, nitric oxide, and fatty acids^[18, 22].

2 Bacterial Diet Functions as Gut Microbiota

C. elegans is normally cultured on a single bacterial strain, and these bacterial cells colonize the intestinal lumen, forming the gut microbiota^[23]. The gut microbiota can aid in conversion of nutrients into molecules that have greater health benefits or are better absorbed^[10, 24]. They also release some functional small molecules that contribute to overall health. For example, several kinds of bacteria that are promoted by dietary fiber have been shown to synthesize butyric acid and propanoic acid in mice^[10]. Similar mechanisms have been demonstrated in *C. elegans*; when fed with bacteria secreting more colanic acid polysaccharide, these worms display a longer lifespan by the activation of ATFS-1, a mitochondrial unfolded protein response (UPR^{mt}) transcription factor, that regulates mitochondrial dynamics^[20].

Bacterial diets could also modulate the potency of medications^[25, 26]. The efficacy of drugs is highly variable among patients^[27], in which the gut microbiota

is likely to play a critical role. Recently, Scott *et al* unveiled the complexity underlying host-microbe-drug interactions. Their studies revealed that fluoropyrimidine, a compound used for the treatment of colorectal cancer, has distinct efficacies in *C. elegans* fed on different bacterial diets^[25]. Further research attributed this effect to metabolic drug interconversion regulated by bacterial vitamins B6 and B9 and ribonucleotide metabolism. These findings highlight the potential therapeutic power of intestinal microbiota and its manipulation to ensure host metabolic health and to devise better cure for diseases^[28].

3 Neurons Sense the Differences in Bacterial Diets

The ability of worms to sense the signal molecules released by bacterial diets is indispensable for survival under natural conditions. Many neurons and receptors have already been reported to be involved in these diet sensation pathways (fig. 1A). ODR-3, a Gα-protein expressed in AWC neurons, is required for the recognition of food odors and the food-invoked signal is transmitted through glutamate release^[29]. NLP-18, a neuropeptide receptor expressed in AWB neurons, is required for generating preference for different food odors^[29]. ADF neurons have been shown to recognize familiar food via an increase in the release of serotonin, which in turn increases the pharyngeal pumping rate^[30]. ASI neurons can suppress reversal and omega turns when food is depleted, which stimulates worms to search a much wider area for food^[31]. Clearly, food sensation by AWC, AWB, ADF, and ASI neurons is important for *C. elegans* survival in response to changing environments.

Do these food-sensation pathways also play a role in response to different diets? A common feature among these neurons is the presence of a long cilium, which can almost contact the outside environment directly. Previous studies have already revealed extended lifespan in gene mutants including *daf-19*,

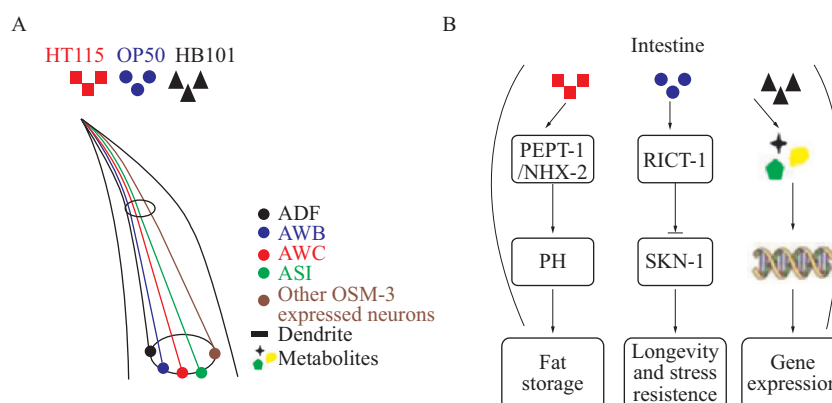


Fig. 1 A: Many neurons and receptors are involved in the diet sensation pathways. B: The intestine responds to diet as a sensor of internal energy status

che-2, *che-13*, *osm-1*, and *osm-6*, in which the function of the sensory cilium is impaired^[32]. Additional studies have indicated that *osm-3* mutants on a HT115 or OP50 diet display different rates of aging; mutant worms were found to live longer on OP50 diet, but not on HT115 diet, than wild type worms. Differences in lipopolysaccharide (LPS) structure on the bacteria cell wall were detected and this was mediated by NMUR-1, a homolog of mammalian neuromedin U receptors^[33]. Interesting questions such as the identity of the specific neuron that recognizes diverse structures of LPS and the potential role of the intestine in the diet-mediated signal transduction remain unanswered.

4 The Intestine Responds to Diet via Selective Uptake of Nutrients

The intestine is the main organ that directly contacts different diets and is responsible for the uptake of nutrients; therefore, it should be the terminal executor that determines how many and what kinds of nutrients should be ingested (fig. 1B). For example, the fat storage in worms is significantly affected by their bacterial diet. More triacylglycerol (TAG) is stored in the intestines of worms fed on OP50 than that in worms fed on HT115; this has been shown to be dependent on the intestinal peptide transporter, PEPT-1^[34]. Further studies have elucidated that PEPT-1 affects fatty acid absorption by interacting with a sodium-proton exchanger NHX-2 to sustain the intracellular pH of intestinal epithelial cells^[34, 35]. It is likely that PEPT-1 functions spontaneously and is not directly associated with diet sensation. Overall, these studies provide evidence that diet cues could modify the intracellular microenvironment to modulate the efficiency of selective absorption of certain nutrients.

The intestine also functions as a sensor of internal energy status. In rats, the rapamycin complex was shown to repress insulin/PI3K/AKT signaling^[36–38] while integrating signals from nutrients and energy status^[39, 40]. A homolog of Rictor/TORC2 in *C. elegans*, RICT-1, functions as a nutrient sensor that regulates fat metabolism, growth, and aging^[17, 41]. *rict-1* mutant worms store much more fat and have shorter lifespans when fed on OP50, a condition that can be rescued by the expression of wild type RICT-1 in the intestine. In contrast, *rict-1* mutant worms show no phenotype when fed on HB101 or HT115, compared with wild type, suggesting a role for RICT-1 as an intestinal hub that integrates nutrient or energy status of the bacterial diet and the cytoplasm of intestinal cell. This observation that cells can modulate fat storage in a deliberate fashion to prevent energy wastage or excessive synthesis is exciting. However, it is still unclear whether RICT-1 is sufficient to mediate the sensory process or if other factors are also involved.

5 Metabolites from Different Diets Regulate Physiological Processes of *C. elegans*

How do dietary metabolites absorbed by the intestine regulate physiological processes? Metabolomic research has uncovered that worms fed on different bacterial diets show significant differences in metabolic profiles as well as in levels of amino acids, fatty acids, lactate, o-phosphocholine, etc^[42–44]. These differences strongly affect worm health. ALH-6, a 1-pyrroline-5-carboxylate dehydrogenase, which converts proline to glutamate, has been shown to cause toxicity on OP50 when its function is disrupted^[45]. Further research has indicated that OP50 provides more proline, leading to increased accumulation of PC5, a metabolic intermediate that is toxic and accelerates aging.

In contrast, the high level of certain metabolites can be beneficial for nematode survival. For instance, worms in which *nhr-114*, a nuclear hormone receptor, is mutated, are sterile when fed on OP50, but this phenotype was not observed when fed on HT115. This difference is mainly because of greater levels of tryptophan in HT115, which mediates a somatic detoxifying signaling pathway that protects germline stem cells (GSCs) from harmful metabolites^[18]. Other metabolites such as vitamins^[46], short chain fat acids (SCFA)^[11, 47], and unsaturated fatty acids like docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), arachidonic acid (AA), and oleic acid (OA)^[48–50] have also been proven to be beneficial for the worms. Specifically, DHA has been shown to promote lipid peroxidation, which contributes to longevity^[51]; AA, a ω -6 polyunsaturated fatty acid, extends lifespan by activating autophagy signaling^[52]; ω -3 and ω -6 polyunsaturated fatty acids have been shown to allocate somatic and germline lipids to ensure the offspring survival under nutrient or oxidative stress^[53]; and short chain fatty acids (C10, C11, C12) can up-regulate the expression of the fatty acid mono-desaturase gene *fat-7* through *nhr-49* to improve low-temperature adaptation in worms^[54].

Unsaturated fatty acids like DHA, EPA, and AA are currently in the market as popular health products. They are believed to promote lipid metabolism to prevent high blood pressure or hyperlipemia. They are also thought to improve intelligence, with benefits especially in children. In summary, these metabolites are of great value to human health, and a better understanding of how they work will be beneficial.

6 Crosstalk between Neurons and the Intestine in Response to Different Diets

A diet typically comprises a mixture of different signal molecules. These can activate neurons and at

the same time modulate intestinal cell function. So, do signals from sensory neurons crosstalk with signals from the intestine? It has been shown that exogenous supply of polyunsaturated fatty acids (PUFAs) such as AA or EPA facilitate AWA neuron function, whereas dihomo-gamma-linolenic acid (DGLA) is thought to have a deleterious effect on AWA neuron function. PUFAs may act directly on TRPV channels to activate ASH neurons^[55]. Interestingly, when the levels of AA or DGLA are above a certain threshold in the intestine, they are sufficient to activate autophagy and extend lifespan in *ad libitum*-fed *C. elegans*^[52]. These observations imply that neurons and the intestine can respond to the same molecule, and their responses may not always be positively correlated.

Another study has confirmed that the crosstalk between neurons and the intestine exists. ALH-6 regulates mitochondrial homeostasis and longevity in a diet-dependent manner. Adult *alh-6* mutant worms show fragmented mitochondrial morphology and shortened lifespan when fed on OP50, but not on HT115. Mutated *nmur-1* was found to reverse the mitochondrial morphology and longevity change caused by the *alh-6* mutation^[45]. This is indicative that the diet-dependent phenotype of *alh-6* mutant manifests only when intestinal cells absorb enough proline and neurons function normally to initiate the mitochondrial response in the intestine. Therefore, the intestine may function as a hub to integrate signals sensed by neurons and other tissues in response to different diets, and this crosstalk is likely to be important for *C. elegans* responding to diet signals more potently and profitably.

7 Systemic Influence of Diet on Gene Expression of Host

Diet is important for many physiological processes, but the detailed underlying mechanisms remain obscure. It has been well documented that in different organisms, dramatic changes in the levels of gene expression result in following dietary shift^[56, 57]. As different bacteria provide nutrients in different proportions and affect different physiological processes in distinct ways, genes expression levels are regulated to offset the possible adverse effects of diet. Worms that were fed on DA1877 bacteria isolated from the natural environment were found to display altered development rate, brood size, and lifespan compared to worms fed on OP50 or HT115. Concomitantly, the expression levels of 389 genes—including those involved in fatty acid metabolism, pathogen-response, and molting—were significantly altered^[58–60]. The change in gene expression levels in response to DA1877 was found to be independent of amphid sensory neurons^[60]. Overall, these observations imply that the levels of metabolites ingested by worms are the key factor regulating gene

expression (fig. 1B).

8 Conclusions and Future Perspectives

The impact of diet on the physiology of *C. elegans* is profoundly complicated. Diet may function as gut microbiota, nutrients, or pathogenic bacteria simultaneously. The interspecies model comprising *C. elegans* and its bacterial diet is amenable to large-scale, high-throughput genetic screening, making it an invaluable resource for our understanding of underlying interactions and the mechanisms involved. To maintain homeostasis, worms must be able to sense food source and abundance in a sensitive manner and then assess food quality and their own energy state; finally, they must integrate signals and exploit endocrine and transcriptional mechanisms to systemically promote or inhibit related pathways to counter environmental change. The human gut microbiota are much more complex and they are influenced by host body condition, environment, and daily diet; therefore, the mechanisms underlying dietary effects cannot be translated directly from studies performed with *C. elegans* under relatively stable conditions. These studies do, however, provide valuable clues for the mechanisms by which the host responds to distinct diets.

Conflict of Interest Statement

The authors declare that there is no conflict of interest relevant to this article.

Acknowledgments

We thank Bi ZHANG, Guang LI, Xu LIU, and other members of Professor Liu's laboratory for their assistance in this manuscript.

REFERENCES

- 1 Tilman D, Clark M. Global diets link environmental sustainability and human health. *Nature*, 2014,515 (7528):518-522
- 2 Mcevoy CT, Temple N, Woodside JV. Vegetarian diets, low-meat diets and health: a review. *Public Health Nutr*, 2012,15(12):2287-2294
- 3 Bushman FD, Lewis JD, Wu GD. Diet, gut enterotypes and health: is there a link? *Nestle Nutr Inst Workshop Ser*, 2013,77:65-73
- 4 Xu Z, Knight R. Dietary effects on human gut microbiome diversity. *Br J Nutr*, 2015,113(Suppl):S1-S5
- 5 Smith P, Willemsen D, Popkes M, et al. Regulation of life span by the gut microbiota in the short-lived African turquoise killifish. *Elife*, 2017,6:e27014
- 6 Jubair WK, Hendrickson JD, Severs EL, et al. Modulation of inflammatory arthritis by gut microbiota through mucosal inflammation and autoantibody generation. *Arthritis Rheumatol*, 2018,70(8):1220-1233
- 7 Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. *World J Gastroenterol*, 2015,21(37):10609-10620
- 8 Trompette A, Gollwitzer E S, Yadava K, et al. Gut

- microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med*, 2014,20(2):159-166
- 9 Wang X, Zhang L, Wang Y, *et al.* Gut microbiota dysbiosis is associated with Henoch-Schonlein Purpura in children. *Int Immunopharmacol*, 2018,58:1-8
 - 10 Zhao L, Zhang F, Ding X, *et al.* Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science*, 2018,359(6380):1151-1156
 - 11 Koh A, De Vadder F, Kovatcheva-Datchary P, *et al.* From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell*, 2016,165(6):1332-1345
 - 12 Gopalakrishnan V, Spencer CN, Nezi L, *et al.* Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*, 2018,359(6371):97-103
 - 13 Matson V, Fessler J, Bao R, *et al.* The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*, 2018,359(6371):104-108
 - 14 Gibson MK, Crofts TS, Dantas G. Antibiotics and the developing infant gut microbiota and resistome. *Curr Opin Microbiol*, 2015,27:51-56
 - 15 Watson E, Macneil LT, Ritter AD, *et al.* Interspecies Systems Biology Uncovers Metabolites Affecting *C. elegans* Gene Expression and Life History Traits. *Cell*, 2014,156(6):1336-1337
 - 16 Zhang J, Holdorf AD, Walhout AJ. *C. elegans* and its bacterial diet as a model for systems-level understanding of host-microbiota interactions. *Curr Opin Biotechnol*, 2017,46:74-80
 - 17 Soukas AA, Kane EA, Carr CE, *et al.* Rictor/TORC2 regulates fat metabolism, feeding, growth, and life span in *Caenorhabditis elegans*. *Genes Dev*, 2009,23(4):496-511
 - 18 Gracida X, Eckmann C R. Fertility and germline stem cell maintenance under different diets requires *nhr-114/HNF4* in *C. elegans*. *Curr Biol*, 2013,23(7):607-613
 - 19 Brooks KK, Liang B, Watts JL. The influence of bacterial diet on fat storage in *C. elegans*. *PLoS One*, 2009,4(10):e7545
 - 20 Han B, Sivaramakrishnan P, Lin CJ, *et al.* Microbial Genetic Composition Tunes Host Longevity. *Cell*, 2017,169(7):1249-1262
 - 21 Xiao R, Chun L, Ronan EA, *et al.* RNAi Interrogation of Dietary Modulation of Development, Metabolism, Behavior, and Aging in *C. elegans*. *Cell Rep*, 2015,11(7):1123-1133
 - 22 Gusarov I, Gautier L, Smolentseva O, *et al.* Bacterial nitric oxide extends the lifespan of *C. elegans*. *Cell*, 2013,152(4):818-830
 - 23 Clark L C, Hodgkin J. Commensals, probiotics and pathogens in the *Caenorhabditis elegans* model. *Cell Microbiol*, 2014,16(1):27-38
 - 24 Hoyles L, Jimenez-Pranteda ML, Chilloux J, *et al.* Metabolic retroconversion of trimethylamine N-oxide and the gut microbiota. *Microbiome*, 2018,6(1):73
 - 25 Scott TA, Quintaneiro LM, Norvaisas P, *et al.* Host-Microbe Co-metabolism Dictates Cancer Drug Efficacy in *C. elegans*. *Cell*, 2017,169(3):442-456
 - 26 García-González AP, Ritter AD, Shrestha S. Bacterial Metabolism Affects the *C. elegans* Response to Cancer Chemotherapeutics. *Cell*, 2017,169(3):431-441
 - 27 Offer SM, Diasio RB. Is It Finally Time for a Personalized Medicine Approach for Fluorouracil-Based Therapies? *J Clin Oncol*, 2016,34(3):205-207
 - 28 Iida N, Dzutsev A, Stewart CA, *et al.* Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science*, 2013,342(6161):967-970
 - 29 Harris G, Shen Y, Ha H, *et al.* Dissecting the signaling mechanisms underlying recognition and preference of food odors. *J Neurosci*, 2014,34(28):9389-9403
 - 30 Song BM, Faumont S, Lockery S, *et al.* Recognition of familiar food activates feeding via an endocrine serotonin signal in *Caenorhabditis elegans*. *Elife*, 2013,2:e329
 - 31 Gray JM, Hill JJ, Bargmann CI. A circuit for navigation in *Caenorhabditis elegans*. *Proc Natl Acad Sci USA*, 2005,102(9):3184-3191
 - 32 Apfeld J, Kenyon C. Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. *Nature*, 1999,402(6763):804-809
 - 33 Maier W, Adilov B, Regenass M, *et al.* A neuromedin U receptor acts with the sensory system to modulate food type-dependent effects on *C. elegans* lifespan. *PLoS Biol*, 2010,8(5):e1000376
 - 34 Spanier B, Lasch K, Marsch S, *et al.* How the intestinal peptide transporter PEPT-1 contributes to an obesity phenotype in *Caenorhabditis elegans*. *PLoS One*, 2009,4(7):e6279
 - 35 Nehrke K. A reduction in intestinal cell pH_i due to loss of the *Caenorhabditis elegans* Na⁺/H⁺ exchanger NHX-2 increases life span. *J Biol Chem*, 2003,278(45):44657-44666
 - 36 Takano A, Usui I, Haruta T, *et al.* Mammalian target of rapamycin pathway regulates insulin signaling via subcellular redistribution of insulin receptor substrate 1 and integrates nutritional signals and metabolic signals of insulin. *Mol Cell Biol*, 2001,21(15):5050-5062
 - 37 Tremblay F, Marette A. Amino acid and insulin signaling via the mTOR/p70 S6 kinase pathway. A negative feedback mechanism leading to insulin resistance in skeletal muscle cells. *J Biol Chem*, 2001,276(41):38052-38060
 - 38 Haruta T, Uno T, Kawahara J, *et al.* A rapamycin-sensitive pathway down-regulates insulin signaling via phosphorylation and proteasomal degradation of insulin receptor substrate-1. *Mol Endocrinol*, 2000,14(6):783-794
 - 39 Edinger AL, Thompson CB. Akt maintains cell size and survival by increasing mTOR-dependent nutrient uptake. *Mol Biol Cell*, 2002,13(7):2276-2288
 - 40 Long X, Ortiz-Vega S, Lin Y, *et al.* Rheb binding to mammalian target of rapamycin (mTOR) is regulated by amino acid sufficiency. *J Biol Chem*, 2005,280(25):23433-23436
 - 41 Mizunuma M, Neumann-Haefelin E, Moroz N, *et al.* mTORC2-SGK-1 acts in two environmentally responsive pathways with opposing effects on longevity. *Aging Cell*, 2014,13(5):869-878
 - 42 Gao AW, Chatzispayrou IA, Kamble R, *et al.* A sensitive mass spectrometry platform identifies metabolic

- changes of life history traits in *C. elegans*. *Sci Rep*, 2017,7(1):2408
- 43 Reinke SN, Hu X, Sykes BD, *et al.* *Caenorhabditis elegans* diet significantly affects metabolic profile, mitochondrial DNA levels, lifespan and brood size. *Mol Genet Metab*, 2010,100(3):274-282
 - 44 Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*, 2016,16(6):341-352
 - 45 Pang S, Curran SP. Adaptive capacity to bacterial diet modulates aging in *C. elegans*. *Cell Metab*, 2014,19(2):221-231
 - 46 Banerjee R, Ragsdale S W. The many faces of vitamin B12: catalysis by cobalamin-dependent enzymes. *Annu Rev Biochem*, 2003,72:209-247
 - 47 Amanda Jacobson LLMR. A Gut Commensal-Produced Metabolite Mediates Colonization Resistance to Salmonella Infection. *Cell Host Microbe*, 2018,24(2):296-307
 - 48 Wei CC, Yen PL, Chang ST, *et al.* Antioxidative Activities of Both Oleic Acid and Camellia tenuifolia Seed Oil Are Regulated by the transcription Factor DAF-16/FOXO in *Caenorhabditis elegans*. *PLoS One*, 2016,11(6):e157195
 - 49 Wu K, Gao X, Shi B, *et al.* Enriched endogenous n-3 polyunsaturated fatty acids alleviate cognitive and behavioral deficits in a mice model of Alzheimer's disease. *Neuroscience*, 2016,333:345-355
 - 50 Han S, Schroeder EA, Silva-Garcia CG, *et al.* Mono-unsaturated fatty acids link H3K4me3 modifiers to *C. elegans* lifespan. *Nature*, 2017,544(7649):185-190
 - 51 Sugawara S, Honma T, Ito J, *et al.* Fish oil changes the lifespan of *Caenorhabditis elegans* via lipid peroxidation. *J Clin Biochem Nutr*, 2013,52(2):139-145
 - 52 O'Rourke EJ, Kuballa P, Xavier R, *et al.* omega-6 Polyunsaturated fatty acids extend life span through the activation of autophagy. *Genes Dev*, 2013,27(4):429-440
 - 53 Lynn DA, Dalton HM, Sowa JN, *et al.* Omega-3 and -6 fatty acids allocate somatic and germline lipids to ensure fitness during nutrient and oxidative stress in *Caenorhabditis elegans*. *Proc Natl Acad Sci USA*, 2015,112(50):15378-15383
 - 54 Ma DK, Li Z, Lu AY, *et al.* Acyl-CoA Dehydrogenase Drives Heat Adaptation by Sequestering Fatty Acids. *Cell*, 2015,161(5):1152-1163
 - 55 Kahn-Kirby AH, Dantzer JL, Apicella AJ, *et al.* Specific polyunsaturated fatty acids drive TRPV-dependent sensory signaling in vivo. *Cell*, 2004,119(6):889-900
 - 56 Du D, Shi YH, Le GW. Microarray analysis of high-glucose diet-induced changes in mRNA expression in jejunums of C57BL/6J mice reveals impairment in digestion, absorption. *Mol Biol Rep*, 2010,37(4):1867-1874
 - 57 Carsten LD, Watts T, Markow TA. Gene expression patterns accompanying a dietary shift in *Drosophila melanogaster*. *Mol Ecol*, 2005,14(10):3203-3208
 - 58 Murfin KE, Whooley AC, Klassen JL, *et al.* Comparison of *Xenorhabdus bovienii* bacterial strain genomes reveals diversity in symbiotic functions. *BMC Genomics*, 2015,16:889
 - 59 Dunbar TL, Yan Z, Balla KM, *et al.* *C. elegans* detects pathogen-induced translational inhibition to activate immune signaling. *Cell Host Microbe*, 2012,11(4):375-386
 - 60 Macneil LT, Watson E, Arda HE, *et al.* Diet-induced developmental acceleration independent of TOR and insulin in *C. elegans*. *Cell*, 2013,153(1):240-252

(Received Dec.12, 2018; revised Mar. 14, 2019)