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Original Article

V_A and PUFA protection against 60Co γ-ray-induced abnormal expression of DNA damage-related genes in *C. elegans*

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Abstract: Radiotherapy is one of the most important methods in cancer treatment. However, radiation therapy can cause damage to normal tissues and even death. Vitamin A (V_A) and polyunsaturated fatty acid (PUFA) can enhance the sensitivity of radiotherapy and protect normal cells, but the mechanisms are unclear. *Caenorhabditis elegans* (*C. elegans*) are used as a model organism, as the spectrum of DNA damage response is in accord with humans. To confirm the roles of Vitamin A and PUFA in preventing radiation DNA damage and to explore the mechanisms at the molecular level, wild-type *C. elegans* supplemented with V_A or PUFA were irradiated with 200 Gy or 400 Gy of 60Co γ-ray. Expression of 6 potential DNA damage related genes was quantified by qRT-PCR. Results showed that 60Co caused abnormal expression of multiple DNA damage-related genes. Treating C. elegans with V_A or PUFA and irradiating C. elegans with 60Co, results indicated that V_A and PUFA function to protect nematodes with lower DNA damage. Expression of multiple DNA damage-related genes has shown some improvement, especially *cep-1* and *rad-51*. Results indicate that V_A and PUFA could protect against 60Co γ-ray by regulating expression of DNA damage-related genes in *C. elegans*.

Keywords: *C. elegans*, 60Co γ-ray, gene expression, V_A, PUFA

Introduction

Ionization radiation (IR) has been applied to cancer treatment with remarkable achievements. During radiotherapy, radiation can damage normal cells at the same time. It is critical to increase the sensitivity of tumor cells to radiation, improving the efficiency of killing tumor cells while reducing damage to healthy cells [1, 2].

Many types of radiation protection agents have been used to reduce the adverse effects of radiotherapy. V_A, known as retinol, is an alicyclic unsaturated alcohol that includes V_A1 and V_A2 subtypes. It has been confirmed that supplemental V_A can mitigate the side effects of acute radiation in rats, such as thymic involution, adrenal enlargement, leukopenia, thrombocytopenia, gastrointestinal ulceration, and impaired wound healing [3]. Retinoids act as a scavenger of such radiation products, thereby providing protection against 60Co-induced chromatid damage in human peripheral blood lymphocytes [4]. PUFA contains two or more than two double bonds and a carbon chain length of 18~22 straight carbon atom chain fatty acid. It is an important cell membrane component and a key element in the relative liquidity of cell membranes to ensure normal physiological functioning of cells. Growing evidence has suggested that ω3 PUFAs play a role as adjuvant agents, together with chemo/radiotherapy, exhibiting antineoplastic activity against colorectal cancer [5]. n-3 PUFA has the potential to increase cancer sensitivity to conventional therapies. This could allow the use of lower doses of radiation, bringing about a reduction in detrimental health effects [6].

DNA is the principle target of ionizing radiation because the nucleus is the largest organelle in

the cell. Ionizing radiation is an effective DNA-damaging agent, leading to a chain of events culminating in cell biological damage [7, 8]. Many radiation related genes and pathways in cancer and their response towards radiation can influence the effects of radiotherapy [9].

C. elegans is a free-living soil nematode. The adult is approximately 1 mm in length [10]. It has been estimated that about 42% of human disease genes have a *C. elegans* counterpart. Furthermore, a number of human genes and pathways involved in cancer are highly conserved in *C. elegans* [11-13]. *C. elegans* has been widely used as a model organism in solving the cancer problem [14]. An increasing number of studies have demonstrated that many genes are altered in their expression to react to the environment, protecting *C. elegans* from harsh environmental stress, such as heat, IR, and oxidative-damaging agents.

The present study aimed to explore the roles of V_A and PUFA in radiation protection, along with molecular mechanisms associated with DNA damage-related genes. The model organism of *C. elegans*, which can enrich V_A and PUFA, was used for these experiments. A total of 6 DNA damage-related genes in *C. elegans* (*cep-1, rad-51, lem-3, brd-1, baf-1, and atl-1*) were selected as potential genes.

C. elegans cep-1, the single ortholog of the mammalian p53 tumor suppressor protein, is essential for promoting DNA damage-induced apoptosis in the *C. elegans* germline [15, 16]. Transcriptional profiling in *C. elegans* indicated that the apoptotic response to DNA damage is regulated through *cep-1* mediated transcriptional induction of *egl-1* and *ced-13* [17]. Moreover, *rad-51* plays key roles in the faithful repair of DNA breaks [18]. The protein encoded by *rad-51* accumulates in spots in the nuclei following DNA double-strand break (DSB) in *C. elegans* [19]. Furthermore, *baf-1* interacts with LEM domain proteins *lem-3*, together playing an important role in DNA damage response in *C. elegans,* with the potential of promoting the reorganization of damaged chromatin [20]. Interaction between *brd-1* and *atl-1, cep-1, and rad-51* connections is involved in DNA repair in *C. elegans*.

To identify the roles of V_A and PUFA in radiation protection, as well as the regulatory effects on DNA damage-related genes, changes of expression of 10 genes were quantified after treatment with 60Co γ-ray. The 6 of them which expressed significant differences were selected to be quantified in supplemented V_A and PUFA groups. Present observations suggest that V_A and PUFA act as radiation protection agents which regulate multiple DNA damage-related genes, such as *cep-1 and rad-51*, providing protection against 60Co γ-ray in *C. elegans*.

Materials and methods

C. elegans strains and growth conditions

Liquid NGM was autoclaved and cooled to 50-60°C. The NGM culture medium was agitated to ensure complete dissolution of the compounds, then the medium was dispensed into petri dishes. *C. elegans* strains used in this study were the wild-type Bristol strain N2 and were grown at 20°C on NGM agar plates seeded with *E. coli* strain OP50.

Ionizing radiation experiments

A total of 5,000 C. elegans cultured on NGM were cultured for 48 hours, then exposed to 0 Gy (without radiation), 200 Gy, and 400 Gy of 60Co γ-irradiation using a GMII 60Co radiation machine (Beijing gamma high and New Technology Co., Ltd.) for 0 minutes, 66 minutes, and 133 minutes, respectively. The number of living worms was counted after radiation. Next, 5,000 worms treated with 0 Gy, 200 Gy, and 400 Gy were transferred to a fresh NGM medium. The number of living worms was counted 48 hours later, evaluating the effects of radiation on C. elegans fecundity.

V_A and PUFA treatment and toxicity experiments

V_A (C20H30O, MW: 286.456, Shanghai Yuanye Bio-Technology Co., Ltd) and PUFA (Sigma) were dissolved in 95% ethanol, respectively. They were then added into the NGM culture medium for five generations to ensure that the drug was absorbed by C. elegans. C. elegans absorbing V_A or PUFA were named the V_A + group and PUFA + group. The control group refers to C. elegans cultured without V_A and PUFA.

To confirm whether V_A and PUFA affect C. elegans growth, especially in death, V_A and PUFA

Table 1. Primer sequences of housekeeping genes and genes of interest for qRT-PCR

Genes	Primer F (5' to 3')	Primer R (5' to 3')
cdc-42	TGTTTGCTTCTCCGTGGTTGCT	CGTTGACACTGGTTTCTGCTTG
atl-1	GATGTGTGCCTTTGAGGATGA	TTTCTCTCGGGTCTTGTTTCG
baf-1	CATCGTGAGTTCGTCGGAGAG	TCAGAAGGAGATACTGTCCGAAC
brd-1	CGAGATGGGACAACTTGGTGA	TCTTTGCTGTAGTCGTGGAATA
cep-1	CGACGCAAGTAGTCTCCCATA	ACAACACTGAATCGTGCCCTG
lem-3	ATGAGTGCTGACAAACTGGGTAG	TCCGAGACGCTGCCTGTTACT
rad-51	CCCATTGGAGGTCACATCATC	AGTAGGTCGCTTCGGCTTCTG

toxicity experiments were performed. Different concentrations of V_A and PUFA were added into the NGM culture medium for five generations to ensure that the drug was absorbed by C. elegans. A subsample of approximately 5,000 nematodes was withdrawn to the new medium and cultured for another 2 or 3 days. *C. elegans* survival was detected to ensure the effects of V_A and PUFA on nematode mortality. For *C. elegans* counting, worms were washed down with M9 and diluted 50 times, then left at 62°C for 1 minute. Next, 1 mL nematode suspension was added to the 35 mm culture dish. The subpopulation of *C. elegans* was then counted under a stereoscope.

To test the effects of V_A and PUFA on radiation resistance, V_A and PUFA were supplemented into the NGM culture medium to make the final concentration of 0.25 μg/mL V_A and 1 μg/mL PUFA, respectively, for 2 days of culturing. A subsample of approximately 5,000 nematodes was the withdrawn to the new medium, which added 5 μg/mL V_A and 10 μg/mL PUFA, respectively. Culturing then continued for 3 days. The V_A + group, PUFA + group, and control group were each irradiated by 60Co with 0 Gy, 200 Gy and 400 Gy doses.

Quantitative real-time reverse transcription-PCR

Total RNA was isolated from adult wild-type worms treated with or without 60Co using RNAiso Plus reagent (Takara, Dalian, China). Qualified total RNAs were reversely transcribed into first-strand cDNAs using the RT reagent Kit (Takara, Dalian, China). Real-time qPCR was performed in an ABI 7500 real-time PCR amplifier (ABI, USA) using SYBR® PCR kit (TaKaRa, Dalian, China). The *cdc-42*, a type of housekeeping gene, was used as internal control. Genes and primers used for PCR in this study are shown in **Table 1**. The $2^{-\Delta\Delta CT}$ value was calculated to reflect relative expression of genes affected by the 60Co treatment. Each PCR reaction was repeated in triplicate for stable results.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 statistical software package (SPSS Inc, Chicago, IL, USA). One-way analysis of variance (ANOVA) and two-tailed Student's t test were used to evaluate the significance of differences between multiple groups and two groups, respectively. Data representations include mean ± SD and $P<0.05$ indicates statistical significance.

Results

V_A and PUFA showed no effects on C. elegans mortality

A total of 5 μg/mL V_A and 10 μg/mL PUFA were supplemented into the medium, respectively, for 2 days of culturing. A subsample of approximately 5,000 nematodes was then withdrawn to the new medium, which added 5,000 μg/mL V_A and 8,000 μg/mL PUFA, respectively. Culturing continued for 3 days. There were no significant differences in survival both in the V_A + group and PUFA + group, compared with the control group, even in different concentrations of V_A or PUFA groups (**Figure 1**). Results indicate that V_A and PUFA showed no effects on C. elegans mortality, thus the addition of agents would not impact subsequent experiments.

60Co γ-ray affects expression of multiple C. elegans genes

To determine whether 60Co γ-ray affects *C. elegans* DNA damage-related genes expression, this study treated adult wild-type worms with 200 Gy or 400 Gy of 60Co γ-ray, examining expression of 6 selected genes (cep-1, rad-51, lem-3, brd-1, baf-1, and atl-1).

Results showed that 60Co increased expression of 5 genes (*cep-1, rad-51, brd-1, baf-1, and atl-1*), while decreasing expression of 1 gene (*lem-3*) to various degrees. Results of multiple comparisons indicated that 2 genes (*rad-51* and *atl-1*) expressed significantly higher in 400

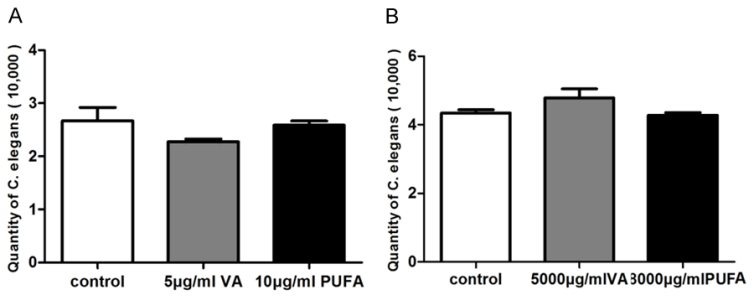

Figure 1. V_A and PUFA toxicity experiments. The quantity of C. elegans supplemented V_A or PUFA cultured for 2 days (A) Another 3 days (B), Error bars indicate SD.

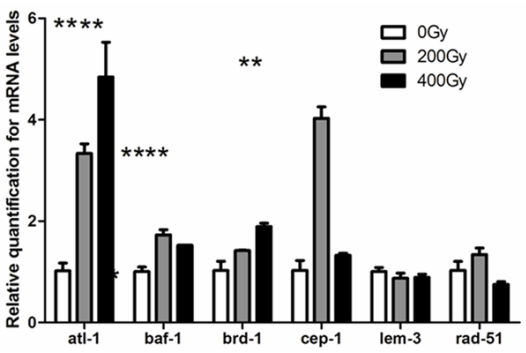

Figure 2. Effects of 60Co γ-ray on expression of genes in wild type C. elegans N2. Expression levels, relative to cdc-42, were determined by quantitative real time RT-PCR. Error bars indicate SD, *P<0.05 and **P<0.01 compared to 0 Gy controls.

Gy groups than 200 Gy groups. Another 2 genes (*baf-1* and *rad-51*) expressed higher in 200 Gy groups than 0 Gy and 400 Gy groups. Expression of *lem-3* decreased after irradiation, but no differences between 200 Gy and 400 Gy were seen (**Figure 2**).

Protective effects of V_A and PUFA

V_A and PUFA were supplemented into the NGM culture me-dium to make the final con-centrations of 0.25 μg/mL V_A and 1 μg/mL PUFA. C. elegans of absorbing V_A or PUFA were irradiated with 200 Gy and 400 Gy 60Co, respectively, subsequently detecting the gene expression.

The $2^{-\Delta\Delta CT}$ value in the control group, without agent and radiation, was arbitrarily set to 1. Thus, the $2^{-\Delta\Delta CT}$ value in V_A + group and PUFA + groups was closer to 1, compared with control group. Results indicated that protection of the drug effects were significant. Results of gene expression showed that all genes had significant differences. Expression of *brd-1* and *atl-1* had significant differences, while the data of two genes were changed regularly. These were ideal experimental results. There were no significant differences in the three groups of 0 Gy, 200 Gy + V_A, and 400 Gy + V_A in *brd-1*. The two groups showed PUFA lower than 0 Gy. The effects of PUFA are possibly better. Drug compensation of *atl-1* was significantly lower than groups of radiation. Three genes (*cep-1, rad-51, lem-3*) focused on 200 Gy and 0 Gy, compared with 200 radiation and drug compensation. Coincidence expected experimental results. Statistical results of *baf-1* were different. For three samples of 400 Gy, expression of many genes had significant differences, but there was no rule change (**Figure 3**).

Discussion

IR is currently regarded as an essential element of an effective care program for most types of cancer. IR is a factor that promotes and induces tumor cell damage. This effect applies to normal cells as well. Minimizing the side effects from radiation is a thorny problem for high-efficiency radiotherapy [21, 22].

Many studies have demonstrated that IR can cause DNA damage. In germ cells, IR can either stimulate cell cycle arrest and DNA repair or induce apoptosis [23]. The severity of DNA damage and DNA repair-related gene expression is involved in radiation doses. Multiple studies have clarified some genes closely related to DNA repair or DNA damage-induced apoptosis. Moreover, *rad-51*, DNA filament assembly, and strand exchange are key steps of homologous recombination (HR) repairs DNA DSB [24, 25]. In the present study, *rad-51* was induced by IR and its expression was increased significantly. Results were consistent with a previous study. After IR treatment, *C. elegans* repaired DNA DSB by improving expression of *rad-51* and related genes.

Furthermore, *ced-9* could be inactivated by *egl-1*, consequently antagonizing the ability of *ced-4* activating *ced-3*. In addition, *cep-1* could activate the transcription of *egl-1* and *ced-13*

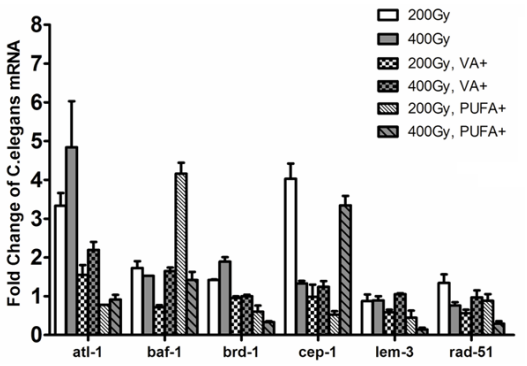

Figure 3. Protective effects of V_A and PUFA on 60Co γ-ray-induced abnormal expression. The $2^{-\Delta\Delta CT}$ value was calculated compared with control group which without agent and radiation. Error bars indicate SD, *P<0.05 and **P<0.01 compared to no agent controls.

[17]. Thus, *cep-1, egl-1, ced-3, ced-4,* and *ced-9* form a core apoptotic pathway to modulate programmed cell death and DNA-damage-induced germline cell death in *C. elegans* [26, 27]. *cep-1* is one of the most important genes in the development of insect larvae. It encodes a homologue of human tumor suppressor gene p53 and promotes apoptosis induced by DNA damage. It is required for normal meiotic division of germ cells [15, 28]. Present results showed that expression of *cep-1* was increased after radiation, especially in 200 Gy. It can be assumed that apoptotic pathways were activated by *cep-1* excessive expression. Mechanisms of these related genes, however, require further study. In the protection plus V_A and PUFA, 200 Gy after irradiation of mRNA expression tended to be normal. This indicates that PUFA and V_A can protect against γ-ray-induced *cep-1* abnormal expression.

Research has shown that *rad-51* is related with chromosome morphology and formation of diakinesis univalent, playing an important role in meiosis [19]. Some apoptosis was dependent on *sir-2 and cep-1*, accompanied by an increase in *rad-51* foci [29]. It could be hypothesized that *cep-1* and *rad-51* work together. After irradiation, expression of *rad-51* increased, compared with CK. In 200 Gy plus drug compensation, expression of mRNA was decreased, even lower than the 0 Gy group. It is interesting that with an irradiation dose of 200 Gy, the change trend of the mRNA expression of two genes, *cep-1* and *rad-51*, was the same.

Lem-3 has the activity of DNA, *in vitro*, and the mutant of *lem-3* is very sensitive to DNA damage [30]. In mitosis, the effects of *lem-3* and *baf-1* mutants may be the same. They are very sensitive to DNA damage. It has been shown that *baf-1* and LEM domain proteins play a very important role in promoting chromatin reorganization after DNA damage. At the same time, the nonspecific binding of *baf-1* and DNA double strand is the correct chromosome segregation. Do *baf-1* and *lem-3* work together? According to the data of *baf-1* in this study, referring to data in 0 Gy, 200 Gy and 400 Gy groups, this can be seen from the effects of radiation on baf-1 genes. Of course, expression of *baf-1* increased after irradiation. However, expression of *lem-3* was not decreased significantly after radiotherapy. Interestingly, expression of *lem-3* was decreased after the addition of 200 Gy, which is worthy of further study.

Brd-1 may be a gene for DNA damage repair. Susceptibility to breast cancer has shown *brd-1* with *atl-1, cep-1, and rad-51* connections [31, 32]. *Brd-1* and *cep-1* may also play a role in cell apoptosis. *Brd-1* and *rad-51* participate in the DNA repair process. In the process, there is a gene *brc-1* with it. Translation proteins play an important role in transcriptional regulation, cell cycle, and meiosis. The present study demonstrates that E3 ubiquitin ligase activity plays a role in the regulation of cellular responses in DNA, *brd-1* and *brc-1* forming two heterologous dimers, and E3 ubiquitin ligase [33].

Moreover, *atl-1* is required for early embryonic development and normal chromosome segregation and expression in cell mitosis and meiosis. The trend of *brd-1* and *atl-1* genes is the same. The mRNA expression of three radiation doses, 0 Gy, 200 Gy and 400 Gy, increased gradually. There was a negative correlation between the radiation dose. After 200 Gy plus drug exposure, expression of *brd-1* was decreased, as well as 400 Gy, compared with the control group. The change trend of *brd-1* was the same as that of *atl-1*. Interestingly, this study found a phenomenon in the two genes on the body, under the same irradiation dose. The effects of PUFA were better than V_A. In 200 Gy and 400 Gy plus PUFA and V_A, expression changes of *brd-1* were obvious and the trend of drug compensation was also clear. Similarly, the same phenomenon was found in *atl-1*. Thus, it was speculated that PUFA may work

more effectively than V_A. Of course, further research is necessary.

Present results showed fewer surviving nematodes and a higher expression of apoptotic genes previously characterized after treatment with 60Co. Compared to other studies on genetic effects of *C. elegans* apoptosis, present results implied that radiation-induced cell death in *C. elegans* was closely related to genes, especially *cep-1* and *rad-51*. Expressions level of these genes were greatly increased with the increase of radiation doses, suggesting that *cep-1* and *rad-51* were sensitive to radiation and may be core genes of radiation-induced apoptosis.

IR induces sequential steps of cellular, tissue, organ, and total body injuries by inducing complex biological responses that interfere with gene and protein expression [34, 35]. *C. elegans* is an ideal *in vivo* model system in the field of radiation biology. The present study used *C. elegans* aiming to explore the association with gene expression changes after radiation. This study presents a genetic characterization of these radiation-related genes in *C. elegans*, aiming to develop a primary genetic study in *C. elegans,* examining the mechanisms of radiotherapy. Furthermore, it is noteworthy that genes *cep-1* and *rad-51* were discovered to be obviously sensitive to radiation. Thus, they may be potential targets for radiotherapy.

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Disclosure of conflict of interest

None.

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References

[1] Jaffray DA and Gospodarowicz MK. Radiation therapy for cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: Disease Control Priorities. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development/The World Bank (c) 2015 International Bank for Reconstruction and Development/The World Bank; 2015.

[2] Kumar S, Singh RK and Meena R. Emerging targets for radioprotection and radiosensitization in radiotherapy. Tumour Biol 2016; 37: 11589-11609.

[3] Levenson SM, Gruber CA, Rettura G, Gruber DK, Demetriou AA and Seifter E. Supplemental vitamin A prevents the acute radiation-induced defect in wound healing. Ann Surg 1984; 200: 494-512.

[4] Sanford KK, Parshad R, Price FM, Tarone RE and Kraemer KH. Retinoid protection against x-ray-induced chromatid damage in human peripheral blood lymphocytes. J Clin Invest 1992; 90: 2069-2074.

[5] Miccadei S, Masella R, Mileo AM and Gessani S. Omega3 polyunsaturated fatty acids as immunomodulators in colorectal cancer: new potential role in adjuvant therapies. Front Immunol 2016; 7: 486.

[6] Serini S, Ottes Vasconcelos R, Fasano E and Calviello G. How plausible is the use of dietary n-3 PUFA in the adjuvant therapy of cancer? Nutr Res Rev 2016; 29: 102-125.

[7] Kam WW and Banati RB. Effects of ionizing radiation on mitochondria. Free Radic Biol Med 2013; 65: 607-619.

[8] Prise KM, Schettino G, Folkard M and Held KD. New insights on cell death from radiation exposure. Lancet Oncol 2005; 6: 520-528.

[9] Rey S, Schito L, Koritzinsky M and Wouters BG. Molecular targeting of hypoxia in radiotherapy. Adv Drug Deliv Rev 2017; 109: 45-62.

[10] Brenner S. The genetics of caenorhabditis elegans. Genetics 1974; 77: 71-94.

[11] Harris TW, Chen N, Cunningham F, Tello-Ruiz M, Antoshechkin I, Bastiani C, Bieri T, Blasiar D, Bradnam K, Chan J, Chen CK, Chen WJ, Davis P, Kenny E, Kishore R, Lawson D, Lee R, Muller HM, Nakamura C, Ozersky P, Petcherski A, Rogers A, Sabo A, Schwarz EM, Van Auken K, Wang Q, Durbin R, Spieth J, Sternberg PW and Stein LD. WormBase: a multi-species resource for nematode biology and genomics. Nucleic Acids Res 2004; 32: D411-417.

[12] Kenyon C. The plasticity of aging: insights from long-lived mutants. Cell 2005; 120: 449-460.

[13] Baumeister R and Ge L. The worm in us - csaenorhabditis elegans as a model of human disease. Trends Biotechnol 2002; 20: 147-148.
[14] Kirienko NV, Mani K and Fay DS. Cancer models in C. elegans. Dev Dyn 2010; 239: 1413-1448.
[15] Derry WB, Putzke AP and Rothman JH. Caenorhabditis elegans p53: role in apoptosis, meiosis, and stress resistance. Science 2001; 294: 591-595.
[16] Schumacher B, Hofmann K, Boulton S and Gartner A. The C. elegans homolog of the p53 tumor suppressor is required for DNA damage-induced apoptosis. Curr Biol 2001; 11: 1722-1727.
[17] Greiss S, Schumacher B, Grandien K, Rothblatt J and Gartner A. Transcriptional profiling in C. elegans suggests DNA damage dependent apoptosis as an ancient function of the p53 family. BMC Genomics 2008; 9: 334.
[18] Masson JY and West SC. The Rad51 and Dmc1 recombinases: a non-identical twin relationship. Trends Biochem Sci 2001; 26: 131-136.
[19] Alpi A, Pasierbek P, Gartner A and Loidl J. Genetic and cytological characterization of the recombination protein RAD-51 in caenorhabditis elegans. Chromosoma 2003; 112: 6-16.
[20] Dittrich CM, Kratz K, Sendoel A, Gruenbaum Y, Jiricny J, Hengartner MO. LEM-3-A LEM domain containing nuclease involved in the DNA damage response in C. elegans. PLoS One 2012; 7: e24555.
[21] Hall S, Rudrawar S, Zunk M, Bernaitis N, Arora D, McDermott CM and Anoopkumar-Dukie S. Protection against radiotherapy-induced toxicity. Antioxidants (Basel) 2016; 5: 22.
[22] Berkey FJ. Managing the adverse effects of radiation therapy. Am Fam Physician 2010; 82: 381-388, 394.
[23] Sakashita T, Takanami T, Yanase S, Hamada N, Suzuki M, Kimura T, Kobayashi Y, Ishii N and Higashitani A. Radiation biology of caenorhabditis elegans: germ cell response, aging and behavior. J Radiat Res 2010; 51: 107-121.
[24] McClendon TB, Sullivan MR, Bernstein KA and Yanowitz JL. Promotion of homologous recombination by SWS-1 in complex with RAD-51 paralogs in caenorhabditis elegans. Genetics 2016; 203: 133-145.
[25] Ward JD, Muzzini DM, Petalcorin MI, Martinez-Perez E, Martin JS, Plevani P, Cassata G, Marini F and Boulton SJ. Overlapping mechanisms promote postsynaptic RAD-51 filament disassembly during meiotic double-strand break repair. Mol Cell 2010; 37: 259-272.
[26] Fairlie WD, Perugini MA, Kvansakul M, Chen L, Huang DC and Colman PM. CED-4 forms a 2: 2 heterotetrameric complex with CED-9 until specifically displaced by EGL-1 or CED-13. Cell Death Differ 2006; 13: 426-434.
[27] Del PL, Gonzalez VM, Inohara N, Ellis RE and Nunez G. Disruption of the CED-9.CED-4 complex by EGL-1 is a critical step for programmed cell death in caenorhabditis elegans. J Biol Chem 2000; 275: 27205-27211.
[28] Schumacher B, Hofmann K, Boulton S, Gartner A. The C. elegans homolog of the p53 tumor suppressor is required for DNA damage-induced apoptosis. Curr Biol 2001; 11: 1722-1727.
[29] Adamo A, Woglar A, Silva N, Penkner A, Jantsch V and La Volpe A. Transgene-mediated cosuppression and RNA interference enhance germline apoptosis in Caenorhabditis elegans. Proc Natl Acad Sci U S A 2012; 109: 3440-3445.
[30] Dittrich CM, Kratz K, Sendoel A, Gruenbaum Y, Jiricny J and Hengartner MO. LEM-3 - A LEM domain containing nuclease involved in the DNA damage response in C. elegans. PLoS One 2012; 7: e24555.
[31] Boulton SJ, Martin JS, Polanowska J, Hill DE, Gartner A and Vidal M. BRCA1/BARD1 orthologs required for DNA repair in Caenorhabditis elegans. Curr Biol 2004; 14: 33-39.
[32] Aoki H, Sato S, Takanami T, Ishihara T, Katsura I, Takahashi H and Higashitani A. Characterization of Ce-atl-1, an ATM-like gene from Caenorhabditis elegans. Mol Gen Genet 2000; 264: 119-126.
[33] Polanowska J, Martin JS, Garcia-Muse T, Petalcorin MI and Boulton SJ. A conserved pathway to activate BRCA1-dependent ubiquitylation at DNA damage sites. EMBO J 2006; 25: 2178-2188.
[34] Greenberger J, Kagan V, Bayir H, Wipf P and Epperly M. Antioxidant approaches to management of ionizing irradiation injury. Antioxidants (Basel) 2015; 4: 82-101.
[35] Menon SS, Uppal M, Randhawa S, Cheema MS, Aghdam N, Usala RL, Ghosh SP, Cheema AK and Dritschilo A. Radiation metabolomics: current status and future directions. Front Oncol 2016; 6: 20.