ISSN (Print) 1225-9918
ISSN (Online) 2287-3406
Journal of Life Science **2012** Vol. 22. No. 11. 1558~1570 DOI : http://dx.doi.org/10.5352/JLS.2012.22.11.1558

- Review -

Model Systems in Radiation Biology; Implication for Preclinical Study of Radiotherapy

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Received September 19, 2012 / Revised November 14, 2012 / Accepted November 15, 2012

In radiation biology, analysis of various mechanisms in response to radiation has been accomplished with the use of model organisms. These model organisms are powerful tools for providing a biologically intact *in vivo* environment to assess physiological and pathophysiological processes affected by radiation. Accumulated data using these models have been applied to human clinical studies (including the evaluation of radiotherapeutic efficacy) and discovery of radiotherapy reagents. However, there are few studies to provide overall integrated information about these useful model organisms. Thus, this review summarizes the results of radiation biology studies using four well-known model organisms: yeast, *Caenorhabditis elegans*, *Drosophila melanogaster*, and mice.

Key words : Radiation biology, yeast, *C. elegans*, *D. melanogaster*, mouse

Introduction

The molecular, cellular and physiological analyses of various response pathways in humans have been accomplished by using of model organisms including yeast, fruit flies, and mice. These models allow us to understand other molecular mechanisms of cellular system, including cell cycle regulation, apoptosis, and tumorigenesis [73]. In addition, model organisms have been used to examine the pathogenesis of various diseases such as heart disease, neurodegenerative disorders, and cancers as well as discover novel targets for treating these conditions and enhancing the efficiency of targeted therapies [110].

In the same context, several model organisms have been adopted for conducting radiation biology studies [1,7,83]. Data from cell-based assays have helped to identify molecular targets in response to radiation and screen potent drugs. These attempts have resulted in effective outcomes in cellular conditions. Cell-based studies, however, are limited in that they overlook the potential roles of physiological conditions in tissues and organs. Experiments using model organisms could address this limitation because these models provide biologically intact systems available for evaluating the physiological effects of radiation. Moreover, data from studies using yeast, worms, flies, and mice could be applied to human-based medical and medicinal investigations such as evaluating radiotherapeutic efficacy, developing radiotherapeutic adjuvants, and examining the mechanisms of radiation-induced injury in normal tissue.

Each model organism has unique properties, including life cycles, average lifespans, cellular pathways that respond to exogenous signals, and degrees of similarity to human cells in terms of genes and proteins. Based on these properties, each organism has advantages as well as limitations when using these models for different experimental methods. For example, yeast can be a good model for anti-cancer drug screening but it may be difficult to use these cells to directly explain various mechanisms of human diseases such as pulmonary fibrosis [24,110]. It is thus important for investigators to determine which organism is appropriate for their experiments. In this review, we provide an overview of four representative model organisms that have been used for radiation biology investigation: yeast, *Caenorhabditis (C.) elegans*, *Drosophila (D.) melanogaster*, and mice.

Yeast: an amenable and rapid research model eukaryotic organism

Yeasts, including *Saccharomyces (S.) cerevisiae* and *Schizosaccharomyces (S.) pombe*, have been widely employed

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as model systems for eukaryotic cell biology studies including genomics, cancer research, medicinal research, and radiation biology investigations [12,110]. Several reports studying the yeast genome have found that amino acid sequences and the functions of proteins in yeast and mammals, including ubiquitin, cytoskeletal elements, and a number of enzymes, are highly well conserved [12,40,110]. In particular, the analysis of yeast data has provided information about individual gene functions, protein-protein interactions, high-throughput screening, and genome-wide screening which can be applied to other eukaryotic organisms, including humans [11,55,70].

In radiation biology, yeasts have also been frequently used as experimental tools for investigating the DNA damage response following irradiation and mechanisms underlying radiosensitization and radioresistance. A variety of studies using yeasts have been conducted which focused on individual gene functions and protein interactions induced by irradiation [10,27,95]. Other yeast-based studies have demonstrated that an antioxidant defense mechanism is induced in response to ionizing radiation (IR) [69,123]. Several groups have shown that anti-oxidant enzymes, such as superoxide dismutase (SOD) and Yap1, are activated to protect against IR-associated oxidative stress [69,78]. Additionally, many checkpoint and DNA repair genes, including *RAD9, RAD17, RAD24* and *RAD53*, were identified during the response to DNA lesions induced by IR, leading to regulation of radio-sensitivity in *S. cerevisiae* [18,34,64]. These genes may play a role in survival signaling that acts against IR-induced damage. Studies of these genes have provided fundamental information for understanding the mechanisms underlying radioresistant properties of human cancer cells.

In the early 2000s, a genome-wide screening for radiation-affected genes in budding yeast *S. cerevisiae* was conducted. This study revealed that a large number of genes, involved in cell cycle control, nuclear pore formation, DNA damage repair, transcription regulation, Golgi/vacuolar activities, ubiquitin-mediated protein degradation, mitochondrial activities, and cell wall maintenance, were associated with resistance to IR. More than half of these genes shared a similar homology with human genes. Some of these, such as *SAC6* and *DHH1* (putative orthologs of human oncogene *LCP1* and *DDX6*, respectively), are involved in malignancies, indicating that they affect the radioresistant properties during radiotherapy for treating cancer [7]. Another study using the fission yeast *S. pombe* was reported. In this investigation, global gene expression in response to conditions or reagents that induced DNA damage, including oxidative stress, heat shock, osmotic shock, heavy metal stress, DNA-damaging agents, and γ-irradiation was analyzed by DNA microarrays. Comparative analyses have demonstrated that genes involved in the DNA damage response, cell cycle regulators, signal transducers, stress-response genes, and genes involved in the metabolism of carbohydrates, lipids, and proteins are up-regulated by γ-irradiation. Among these, some subsets, such as *rhp51*, *rhp54*, and *dinB* which encode DNA repair proteins, might only respond to γ-irradiation [123].

Altogether, yeast is a simple and efficient model organism for providing fundamental information about IR-induced responses, such as antioxidant defense mechanism and DNA damage response, and investigating functionally related human genes. Such information obtained from yeast has been conveniently applied to the screening of anti-cancer drugs and radiotherapeutic adjuvants [110]. Several radiotherapeutic agents have been examined in yeast-based assay for their protective role against radiation-induced damage [2,3,92]. The data obtained from yeast cell-based studies, however, may have a limited ability to explain IR-induced clinical responses in human tissues or organs. To address this difficulty, data from higher-level eukaryotes, such as fruit flies and mice, are required.

C. elegans: an excellent organism for behavior study

The small nematode *C. elegans* has been an attractive model organism for biological research since it was first used as a model for developmental and behavior studies by Sydney Brenner over 40 years ago [15]. *C. elegans* has several advantages including its small size, rapid life cycle, short lifespan, genetic manipulability, and availability of its complete genome sequence [112,115]. Due to these properties, a number of studies have been performed, which provide the bulk of genotypic and phenotypic data available to researchers. Thus, *C. elegans* has been adopted as a good *in vivo* model organism in the field of radiation biology.

C. elegans was first used to evaluate the response to radiation in 1976 [49]. Subsequent studies have helped identify IR-response genes, including *rad-1* and *rad-2*, the mechanism of radiation-induced DNA damage repair, and radiation quality effect [46,47,84]. After the *C. elegans* genome was fully sequenced, analyses using high-throughput screening

and bioinformatics tools have found that about 53% of the genes are significantly similar to genes of other organisms, including yeasts and humans. Some of these genes are associated with factors that respond to DNA damage induced by oxidative stress, radiation, and chemical mutagens [13,83,114,126].

C. elegans has been used to examine cellular mechanisms involved in the response to radiation, including apoptosis, cell cycle arrest, and DNA damage repair. A variety of investigations have contributed to discovering the mechanism underlying IR-induced apoptosis in germ cells of *C. elegans* [39]. Several components, such as CED-3 (caspase homolog), CED-4 (apoptotic protease-activating factor 1 homolog), CED-9 (Bcl-2 homolog), and CEP-1 (p53 homolog) were playing critical roles in activation of apoptotic pathway after irradiation. [20,33,39,41,61,73,103,104,120,125]. In addition, *C. elegans* has been often used as a model to explain the aging mechanism regulated by oxidative stress which is possibly induced by radiation exposure. Several genetic studies have identified age-related genes, such as *age-1, clk-1, daf-2, daf-16,* and *mev-1* [36,52,59,67,121,127,129]. These genes are responsible for activation of survival signaling pathway such as DNA damage repair and antioxidant defense in response to oxidative stress, resulting in lifespan extension. Another report has presented that IR-induced oxidative damage was alleviated and consequently lifespan of *C. elegans* was extended by treatment of anti-oxidative agent resveratrol, indicating that *C. elegans* could be also an attractive candidate for investigation of pharmacological mechanism, like yeast [128].

C. elegans is also an efficient model for analyzing changes in behavior patterns in response to radiation. This organism has about 300 neurons connected by synapses and gap junctions and is able to display dynamic patterns of behavior, including learning, locomotion, and socialization in response to environmental conditions [23,50,98,102,124]. *C. elegans* shows a decreased locomotory rate in the presence of food; this has been defined as the "basal slowing response" [102]. A previous report showed that IR-induced locomotion of *C. elegans* was reduced in the absence of food, indicating that IR might affect the nervous system and regulate motor-behavior [99,113]. In addition, another study demonstrated that IR-induced responses might act as a modulator that influences food-NaCl associative learning by regulating specific sensory neurons related to GPC-1 (one of the two γ subunits of the heterotrimeric G-protein) in the nervous system, consequently leading to altered learning behavior [100]. Such IR-induced behavior data derived from the *C. elegans* model has helped identify potential risks associated with radiotherapy for treating brain tumors, including decreased learning and memory.

All together, *C. elegans* as an *in vivo* radiation biology model can render significant clues to elucidate the several cellular mechanisms of radiation-induced responses. In addition, *C. elegans* studies can provide fundamental information to describe the aging mechanism and neurological response to IR in different biological systems. These outcomes can help apply for understanding of IR-induced human response, although, like yeast as a model organism, there are significant differences in physiological characteristics between *C. elegans* and mammals [101].

D. melanogaster: a landmark model organism for phenotype analysis

D. melanogaster (fruit fly) has been a preeminent animal model used in modern biological sciences since the heredity study conducted by Morgan in the early 20th century. The concept that chromosomes encode heritable traits was first developed using the fly along with many other outstanding discoveries in the field of genetics and development [96]. In 1927, Muller showed that IR causes chromosomal damage using male fruit fly germ cells. For this finding, Muller received a Nobel Prize in 1946 [82]. *D. melanogaster* has many attractive features that make it a landmark model for studying radiation biology. The fly genome has been completely sequenced and annotated, and contains more than 14,000 genes which have a nearly 75% homology to human genes associated with various diseases including cancer as well as immune and neurodegenerative diseases. Although overall identity between flies and mammals at the nucleotide or protein sequence is approximately 40%, the levels of similarity can be 80 to 90% in conserved functional domains [76,91]. The fly has unique characteristics traditional rodent models lack that makes flies ideal for studying radiation biology. These include as a short lifespan of about 60 days, excellent fertility rates (hundreds of identical offspring can be produced by a single fertile mating pair), and distinct developmental stages.

The fly may be considered as a versatile model organism due to its defined developmental stages: embryo, larva, pupa, and adult. Each stage has its own specific advantages

for investigating the effects of radiation. Embryos are often irradiated in fundamental developmental studies including ones evaluating cell fate determination, gene expression and organogenesis [31,62,106]. Larvae, particularly 3rd instar larvae, are most commonly used for irradiation experiments to study developmental and physiological processes since tissues, known as imaginal discs, grow inside the larva during this developmental stage [5,9,37,58,79,88,107,108,119]. Beginning in the late third instar larval phase and proceeding through the pupal phase, the imaginal disc develops into most structures of the adult body, such as the head, legs, wings, thorax, and genitalia. Exposure to IR during the 3rd larva stage may be used to observe the detrimental effects of radiation on development. Adult flies are suitable for studying radiation resistance owing to the composition of post-mitotic tissues. This makes it possible to determine the effects of radiation without the confounding effects from mitotic tissues [48,89].

Above all, the most invaluable attribute of *D. melanogaster* as an animal model is the establishment of advanced genetic techniques for the production of transgenic flies. Since the initial development of a GAL4/UAS system for specific gene expression in 1993, many modifications and enhancements of this basic system have been created to further refine spatial and temporal expression in the fly body [94]. Moreover, a collection of RNAi (RNA interference) knockdown strains targeting about 90% of the entire fly genome has been constructed and is now available from the Vienna Drosophila RNAi Center (http://www.vdrc.at/) [25]. A great number of genes involved in responses to radiation have been investigated using these transgenic flies, including ones affecting apoptosis, DNA repair, stress responses, cell cycle regulation, and longevity [21,68,80,81,87].

Since the study conducted by Muller mentioned above, many groups have examined the dose-dependent effects of radiation on germ cell damage. Initial experiments involving thousands of *Drosophila* demonstrated that radiation induces mutation rates up to 150 times greater than spontaneous mutation rate [82]. This group hypothesized that radiation can cause severe infertility. These and similar experimental results using mouse sperm indicated that there is no safe threshold dose no matter how low. This serves as the basis for guide-lines to protect human from radiation exposure in the world [118].

Developments in transgenic fly technology have contributed to the characterization of gene functions related to specific conditions such as neurodegenerative diseases, cancer, and diabetes [8,44]. Tumor development is a very complicated process involving various cellular responses including genome integrity, DNA damage response, apoptosis, and cell cycle regulation. These responses are highly conserved among different species, and many genes of these responses identified in *Drosophila* are altered in human cancers [16,19,86,111]. Recently, fruit flies were also used to evaluate the efficacy of cancer therapeutic approaches involving combinations of radiation and chemical reagents [32].

Drosophila have been usually used for studying innate immunity since key elements of the innate immune system are highly conserved between flies and humans [51]. Identification of the Toll and Imd signaling pathways, well-known for mediators of bacterial and fungal infections in the fruit fly, led to the identification of mammalian counterparts of the Toll-like receptor and tumor necrosis factor pathways [72]. Reactive oxygen species (ROS) and IR were also reported to be involved in the *Drosophila* immune response [97,106]. In addition, experiments conducted to study the effect of radiation on innate immunity showed that low dose radiation specifically activates a particular immune pathway in *Drosophila* [105]. Taken together, the findings of these studies illustrate how radiation affects innate immunity at the molecular level.

Considering the results of previous experiments, it is clear that *Drosophila* is a useful animal model in both the discovery for the physiological mechanism of radiation effect and the validation for the efficacy of reagents related to radiation response. Although there are many differences between flies and humans, the degree of biological and physiological conservation enables the use of *D. melanogaster* as an extremely valuable tool for radiation biology studies.

Mus musculus (mouse): a premier mammalian model

Among the higher eukaryotic organisms, mice are one of the most suitable models for investigating IR-mediated human physiological responses, since about 99% of the genes in mice and humans are shared. Additionally, common pathophysiological processes of various diseases, particularly cancer, obesity, diabetes, neurological disorders, and heart disease, are also shared [122]. From the early 1900s to now, many studies, involved in basic biology, ge-

nomics, cancer research, and transplantation biology, have provided much information which has systematically accumulated to form the infrastructure of mouse-based databases and resources (*i.e.*, mouse genome informatics; http://www.informatics.jax.org) [90]. In the same context, a large number of genetically modified mice, including inbred mouse strains, transgenic mice, and knock-out mice, have been established and are commercially available [63]. Mice have a relatively short development period (about 20 days), so researchers can obtain their desired data easily and quickly. For these reasons, the mouse is considered to be a premier model organism for understanding the genetic basis and complicated mechanisms of various human diseases and normal physiological processes such as radioresistance in cancer cells and inflammatory response in the normal tissue during radiotherapy.

Many groups have employed the mouse as an experimental model for protein profiling analysis in the context of the radiation response [4,43,74,93]. One study using C57BL/6 mice found that IR induces differences in protein expression patterns between brain and intestine (organs known to be resistant and sensitive to radiation, respectively) by comparative 2-DE and gel imaging analyses. Based on these results, several proteins, including transaldolase 1 and phosphoglycerate kinase 1, were identified as potential markers of IR responses in brain and intestine, respectively [74]. Other groups demonstrated IR-induced changes of serum protein content in the skin of BABL/c mice and performed IR-induced protein expression profiling in blood-plasma of CBA/CaJ mice primarily using 2-DE proteomic analysis [43,93]. In addition, cardiac mitochondrial proteome and function using C57BL/6N mice was investigated by analyses of several proteomic approaches and interactome network [6]. These data have been used to identify tissue-specific protein biomarkers to help prognose and diagnose the IR-induced response of normal and cancerous tissues.

Mice were also used for investigating IR-induced pathogenesis of various conditions such as thymic lymphomas, hepatic injury, and lung fibrosis [4,38,56,65,66]. One study investigated radiation-induced DNA damage in C57BL/6J mice. This damage might result in the accumulation of mutations in tumor suppressor genes, such as *p53* and *CTIP2*, thus leading to the development of mouse thymic lymphomas [14,65]. In addition to DNA damage, irradiated liver tissues from C3H/HeJ mice were shown to have up-regulated levels of antioxidant enzymes, including glutathione *S*-transferase Pi, peroxiredoxin VI, and cytochrome *c*, which could help protect against radiation injury mediated by IR-generated ROS [1,71]. Another study was performed to investigate different responses to IR in the lungs of C3H/HeJ (a lung fibrosis-resistant strain) and C57BL/6J (a lung fibrosis-sensitive strain) mice. Comparative analysis using a proteomic approach has shown that the expression of several antioxidant proteins, including SOD1, cytochrome *c* oxidase, and glutamate dehydrogenase, were decreased in the irradiated C57BL/6J mice compared to C3H/HeJ mice [4]. This finding suggests that IR leads to the dysregulation of cellular defense systems which protect against oxidative stress and could be responsible for lung toxicity, possibly leading to the development of lung fibrosis. Together, such studies have provided insights into physiological mechanism underlying normal tissue injury and tumorigenesis in humans receiving radiotherapy.

In addition to the use of mouse model for studying normal tissue damage, mice are good model for understanding the enhancement of radiotherapeutic efficiency for treating cancer. When anti-cancer drugs as well as radioprotective agents that prevent normal tissue damage were identified by wide-range screening, they were further assessed by cell-based *in vitro* and *ex vivo* experiments, such as cytotoxicity screens and biochemical assays, to further reveal their functions. Based on data produced by these studies, mice were employed as *in vivo* models to test various chemicals administered in combination with radiotherapy. This was done to confirm for their activities in physiologically relevant environments through the use of tumor xenografts, transplantation techniques and genetically engineered mice [17,60,85].

Tumor xenografts in mice have been used as models for preclinical testing of radiotherapy strategies. An investigation using tumor xenografts in mice to establish an IR-guided drug delivery system for specifically treating lung cancer has been presented. In this study, an anti-cancer drug with specific peptides targeting the radiation-inducible membrane protein, tax-interacting protein-1, was evaluated in a tumor model (lung cancer cells grafted in C57 and athymic nude mice). The results showed that the drug specifically targeted tumor mass, leading to the reduction of tumor volume [45]. In addition to tumor xenograft models, genetically engineered mice, including knockout mice, have been also developed to explore the *in vivo* functions of many

genes in response to IR. Finding from studies involved these animals could support the *in vitro* data, and consequently to render the clues for discovering novel target-specific drugs [22,35,75].

Many groups have adopted and/or (if necessary) modified a specific mouse strain as a disease model based on the characteristics of each strain or using the genetic engineering and tumor xenograft methods. These mouse models have been recently used for obtaining the clinical implication to apply appropriate radiotherapy strategy to many diseases. Several investigations have been conducted to understand radiation-induced lung injury (fibrosis and pneumonitis) using various mouse strains including C3H, CBA, C57BL/6, C57L, BALB/c, C57BR/J, and A/J mice [26,28-30,57,109,117]. Some of these strains have been controversial to be proper models for lung injury model because they have shown the unrelated phenomena to lung fibrosis or pneumonitis in response to radiation. Thus, one study using comparative analysis of several strains have reported that, based on histopathological analyses, CBA, C3H, and, especially, C57L strains are more desirable for investigating radiation-induced lung fibrosis and pneumonitis and developing appropriate radioprotective therapies [56,57]. In addition to lung model, there are more models designed for specific disease. A study using a specifically designed DBA/2J mouse as a glaucoma (a leading cause of visual loss) disease model has reported that the development of glaucoma might be resulted from neuroinflammatory response, which could be prevented effectively by localizing tissue radiation [53,54]. The mouse prostate reconstitution model system have been generated using RM-9 cells (the specific intent to mimic the phenotypic and genetic characteristics of human prostate cancer) to investigate the intratumoral mechanism (regulation of immune and hypoxia response) induced by co-treatment of chemotherapy and radiotherapy [42,77,116]. Many groups have made a great effort to establish the desirable model mice for specific disease although the outcome was still insufficient. These efforts could definitely help to investigate the mechanism of radiation-induced disease development and to enhance the efficacy of radiotherapy with high accuracy in a relatively short time. Moreover, such a disease model may satisfy the preclinical requirements for approval of radiation adjuvants for enhanced radiotherapy or radiation protectors against radiation-induced normal tissue injury for human use.

Altogether, the mice have several important advantages for studying radiation biology compared to other organisms such as yeast, worms, and flies. Unlike lower organisms, the mouse has a highly conserved genome and proteome compared to humans. Genetically engineered mice and disease model mice can directly provide clinical information about the response to radiation. In addition, these mice are also useful for validating the physiological efficacy of candidate radiotherapeutic drugs discovered by cell-based screening.

Conclusions

This review discussed the use of model organisms to conduct the radiation biology investigations. All models can produce valuable information important for understanding the response to radiation (Table 1). This accumulated databases and resources of each organism are generally accessible as well (Table 2). Basic studies in yeast have contributed to elucidating conserved biological responses, promoted the development of genomic methodologies, and provided functional information about IR-responsive eukaryotic proteins through genome-wide high-throughput approaches. Moreover, yeast-based assays may be used for the discovery of radiotherapeutic agents and measuring the enhanced efficacy of radiotherapy for treating cancer. *C. elegans* may be an appropriate model for studying IR-induced basic cellular responses including apoptosis, cell cycle arrest, and DNA damage repair. In addition, *C. elegans* can be used as a basic model to investigate the effect IR on the nervous system. Data from these two organisms, yeast and *C. elegans*, may have a limited ability to apply to directly IR-induced clinical response in human, because they are so simple compared to human physiology. *D. melanogaster* is often used for basic and applied studies of IR-induced responses based on phenotype analysis. Transgenic fly models allowed us to investigate mechanisms of physiological changes induced by IR in humans. However, data from *D. melanogaster* may also be insufficient to explain the IR-mediated physiological response in human owing to different body system between fly and human. Since the mouse is a higher organism, it is the most suitable among the four models for clinical studies to understand human physiological and pathological responses mediated by IR. Mice can be also used to evaluate the effects of drugs administered in combined with radiation. On the other hand, mouse has relatively more expensive and strict care condition and need more time to obtain experimental results than others. Based on these proper-

Table 1. Comparison of four model organisms

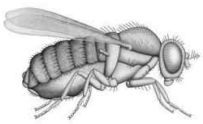
	Yeast	*C. elegans*	*D. melanogaster*	Mouse
Feature				
Advantage of experiments	Simple growth requirements, Rapid cell growth, Ease of genetic manipulation, Genome-wide screening	Short lifespan, Rapid life cycle, Small body size, Transparent body, Ease of genetic manipulation, Knockout mutant libraries, Behavior pattern	Excellent fertility (identical offsprings), Distinct developmental stages, Transgenic flies	Higher functional genetic and proteomic conservation to human homolog, Transplantation, Gene-knockout or -knockin mice, Proteomics (tissue- or organ-based), Construction of disease model
Clinical meanings	Determination of candidate genes and proteins in response to radiation Cell-based drug screening for radiotherapy (basic tool)	Cellular response to radiation, IR-induced aging mechanisms, IR-mediated neuronal pathway	Analysis of IR-induced phenotype changes, IR-affected innate immunity Examination of heritable effects	Disease model in radiation biology, Drug screening for radiotherapy (physiological application), Drug delivery system

Table 2. Websites for database of four model organisms

Yeast	
Saccharomyces Genome Database	http://www.yeastgenome.org/
Mammalian homology to yeast	http://www.yeastgenome.org/mammal/
Yeast homologs of human disease-associated genes	http://mips.gsf.de/proj/yeast/reviews/human_diseases.htm
C. elegans	
WormBase	http://www.wormbase.org/
Caenorhabditis Genetics Center	http://www.cbs.umn.edu/CGC/
D. melanogaster	
Drosophila Genomics Resource Center	https://dgrc.cgb.indiana.edu/
Drosophila functional genomics and proteomics	http://www.gen.cam.ac.uk/~flychip/
Database of human disease gene homologs in *Drosophila*	http://homophila.sdsc.edu/
Vienna *Drosophila* RNAi Center	http://www.vdrc.at/
Mouse	
Mouse Genome Informatics	http://www.informatics.jax.org
International Mouse Strain Resources	http://www.informatics.jax.org/imsr/index.jsp
Mouse Mutant Resource	http://www.jax.org/mmr/index.html

ties, yeast, *C. elegans*, and *D. melanogaster* can be appropriate models for initial step in investigation of radiation biology, such as identifying IR-induced novel biomarker protein, investigating cellular mechanism of the protein, screening novel radiotherapeutic drug, and testing its cytotoxicity. In addition, *D. melanogaster* might be a good model for testing IR-induced simple physiological response and heritable effects as well. Among four organisms, mouse, especially as a disease model, is the best-suited for preclinical study of radiation response, including validation of the physiological efficacy

of novel radiotherapeutic drugs and determination of the appropriate dose for administration.

In radiation biology, model organisms are considered mandatory for confirming *in vitro* data because the responses to radiation might vary in different tissues or cells. The underlying biological mechanisms in humans and these model organisms can be quite different as well. Nevertheless, if investigators comprehend the properties of each model organism and choose the proper one for studying of radiation mechanisms, these models can make valuable contributions to basic radiation biology investigations as well as the development of clinical applications for humans.

Acknowledgement

This work was supported by a 2-Year Research Grant of Pusan National University.

Abbreviations

C. elegans, *Caenorhabditis elegans*; *D. melanogaster*, *Drosophila melanogaster*; IR, ionizing radiation; RNAi, RNA interference; ROS, reactive oxygen species; *S. cerevisiae*, *Saccharomyces cerevisiae*; *S. pombe*, *Schizosaccharomyces pombe*; SOD, superoxide dismutase

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초록 : 방사선 생물학을 위한 모델 시스템; 방사선치료의 전임상 연구

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방사선 생물학에서 방사선에 대한 반응으로 매개되는 다양한 기작에 대한 분석을 위해 여러 종류의 모델 생물체를 사용해 왔다. 모델 생물체는 생물학적으로 온전한 *in vivo* 환경을 제공할 수 있기 때문에 방사선에 의해 발생되는 세포 내 현상은 물론 생리적인 현상이나 병리학적인 현상을 규명하는 데 있어서 모델 생물체를 사용하는 것은 효과적인 방법이 될 수 있다. 지금까지 축적된, 모델 생물체를 이용한 방사선 생물학적 연구결과들은 새로운 방사선치료 보조제의 개발, 방사선치료 효율 증진 등에 적용되어 여러 질병에 대한 임상연구의 기초가 되어왔다. 이렇게 유용하게 사용된 여러 모델 생물체에 있어서, 각각의 모델에 대한 개별적인 정보에 대한 연구는 다양한 방면에서 이루어지고 있지만, 통합적인 비교, 분석 및 정리를 한 경우는 부족한 실정이다. 따라서, 본 논문에서는 방사선 생물학에서 지금까지 많이 사용된 모델 생물체 4종(효모, 예쁜꼬마선충, 초파리, 생쥐)에 대해 각 생물체가 갖는 모델로써의 특징과 장단점 그리고 방사선 생물학 연구에 이용된 사례 등을 서술하고자 한다.