Chapter 3

Dietary Modification of Mouse Response to Total-Body-Irradiation

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Additional information is available at the end of the chapter

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Abstract

Exposure to ionizing radiation (IR) could induce deleterious effects including cancer. Diet, as one of the major factors to influence susceptibility to many diseases, plays a critical role in maintaining human heath. It is known that unbalanced diet could result in health consequences, for example, high-calorie diet could lead to obesity, which could increase the risk of diabetes, heart disease, fatty liver, and some forms of cancer. Although the impact of diet on susceptibility to IR is thought to be big, the evidence is not clear due to lack of study. In this work, effects from dietary fat on modulation of mouse responses to total-body-irradiation (TBI) were studied. The mice were fed after weaning at postnatal age of 4 weeks with a standard diet (MB-1), a very high-fat diet (HFD32), and a very low-fat diet (CE-2 Low Fat), containing of 4.4%, 32.0%, and 0.4% of crude fat, respectively. A mouse model for radiation-induced adaptive response (AR) was applied to this work. The priming low-dose TBI at a dose of 0.5 Gy from X-rays was given at postnatal age of 6 weeks, and the challenge high dose of TBI was given at postnatal age of 8 weeks. The mouse response to low dose of TBI was evaluated by the efficacy of the priming low dose to rescue the animals from bone marrow death induced by the challenge high dose in the 30-day survival test. The mouse response to high dose of TBI was evaluated by comparing the LD50 in the 30-day survival test. In addition, dietary modulation of the residual (late) genotoxic effect from TBI was also evaluated by comparing the incidence of micronucleated erythrocytes in bone marrow using micronucleus test. Results showed that for the mice fed with the MB-1, a successful AR was demonstrated. While for the mice fed with either HFD32 or CE-2 Low Fat, no AR was observed, and all the animals died within 15 days after TBI with the challenge high dose at 7.5 Gy regardless the priming low dose at

0.5 Gy. When comparing the LD50 in the 30-day survival test, the LD50 values for the animals fed with the MB-1, HFD32 diet, and CE-2 Low Fat were 7.1 Gy, 6.0 Gy, and 6.2 Gy, respectively. As to the micronucleus test, for the mice fed with MB-1, the priming low dose at 0.5 Gy could significantly reduce the incidence of micronucleated erythrocytes in bone marrow that were caused by a challenge high dose at 4.0 Gy, while for the mice fed with either HFD32 or CE-2 Low Fat no such effect was observed. These findings indicated that under an unbalanced diet, namely, either of very high fat or of very low fat, alterations in mouse responses to TBI were induced. These findings confirmed that diet played a pivotal role in the response of the animals to radiation exposure, and suggested the possibility to modulate radiosensitivity through diet intervention in humans.

Keywords: Total body irradiation, diet, adaptive response, bone marrow death, micronucleated erythrocytes, mice

1. Introduction

Studies on radiation risk have been increasingly highlighted for special attention from both the academic and the public. Ionizing radiation (IR) could induce both genetic changes and epigenetic alterations. IR-induced genomic instability is a well-documented phenomenon, which can be observed even in the progeny of irradiated animals, suggesting the involvement of epigenetic mechanisms, such as the modulation of genome methylation or the regulation of micro-RNA expression [1]. Recent data suggest that exposures to IR even at low dose could also result in epigenetic modifications [2]. On the other hand, though being still small in the advances in understanding, to more it would have been known that responses to IR are epigenetically regulated. Epigenetic mechanisms may play a key role in the response of our body to IR. For examples, in the experimental animal models, diet-induced obesity modulated epigenetic responses (DNA methylation and microRNA regulation) to IR in mice [3]; antioxidant diets containing blueberry or strawberry extract were capable of mitigating the effects from exposure to heavy particles on behavioral alterations in rats [4, 5]. Multiple dietary, lifestyle and environmental factors, in addition to genetic factors, have a big impact on the health of our body [6]. Nutrients come from the diet, which include carbohydrates, fats, dietary fiber, minerals, proteins, vitamins, and water. Dietary factors have a profound effect on many aspects of health including aging and do so, at least partly, through interactions with the genome, which result in altered gene expression with consequences for cell function and health throughout the life course. In fact, dietary factors were associated with varied diseases and disease risk factors. Studies show that nutrition has a strong impact upon epigenetic processes, nutritional epigenetics emerges as a novel mechanism underlying gene-diet interactions, holding promise in having important roles in regulating health state, including age-related disease development, aging and longevity [7, 8].

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Dietary, lifestyle and the environmental factors are critical to the state of health. Epigenetic mechanisms play an important role in shaping our phenotype via mediating between the nutrient inputs and the ensuing phenotypic changes throughout our entire life. Some epigenetic alterations may lead to accumulation of gene expression dysregulation and thus they are important in age-related diseases. In fact, interaction between nutrients and genes is responsible for regulating metabolic processes; and dietary and other environmental factors induce epigenetic alterations that may have important consequences for the initiation and development of pathological conditions such as obesity, metabolic syndrome, cancer, and alterations of the biological responses [6–8]. A recent study on twins even shows that our environment, more than our heredity, plays the starring role, especially as we age, in determining the state of our immune system which is the primary defense of the body against disease [9]. The pioneering work by Doll and Peto provided strong evidence that dietary factors may be as important as smoking behavior in explaining variation in cancer risk [10]. A healthy well-balanced diet contributes to a good quality of life, including both the health inside the body (i.e., the body growth, mental development, prevention of many diseases and infections, maintenance of the health state, longevity, etc.) and the way we look externally. For examples, individuals consuming a diet containing high amount of fruits and vegetables exhibit fewer age-related diseases: a greater intake of high-antioxidant foods such as berries may increase health span and enhance cognitive and motor function in aging [11], and the Mediterranean diet, which is rich in fruits, vegetables, nuts, legumes, unrefined grains, olive oil, and fish, with a moderate amount of alcohol intake and low intake of dairy products, meat, and poultry, could benefit health, namely, reduction of overall mortality, increased longevity and reduced incidence of chronic diseases [12]; diets containing a high proportion of plant foods are associated with lower risk of several common cancers [6]. A poor unbalanced diet could cause malnutrition, a condition due to eating a diet in which nutrients are not enough (i.e., starvation and a deficiency of one or more particular nutrients) or too much (i.e., intake of too many calories) for proper function of the cells, leading to health problems ranging from mild to severe and life-threatening. For example, a diet containing high amount of fat, resulting in overweight and obesity, leading consequently to high risks especially for cardiovascular disease, cancer, diabetes, osteoarthritis, and chronic kidney disease (13–16); higher intakes of red processed meats appear to be causal for colorectal cancer in contrast to an inverse correlation between higher intakes of fish and colorectal cancer risk [17]; high consumption of instant noodles is associated with a higher prevalence of metabolic syndrome in women [18]; and even regular consumption of sugar-sweetened sodas might influence metabolic disease development through accelerated cell aging [19].

Malnutrition includes both undernutrition and overnutrition. According to the International Federation of the Red Cross, in 2011, there were 1.5 billion people who suffered obesity worldwide while 925 million were undernourished [20]. Because of the established health risks and substantial increases in prevalence (increased risk of diabetes, heart disease, fatty liver, and some forms of cancer), obesity is now a global major health problem in developed countries and a growing one in the developing world [21]. In the United States, around half of the population are overweight, and one-third are obese. Epidemiological studies also show that the poor unbalanced diet is a major contributor to the leading causes of chronic disease and

death [22]. The aggregate economic cost of obesity in this one country is estimated to be in excess of US$ 60 billion per year [21]. Worldwide, in 2010, overweight and obesity were estimated to cause 3.4 million deaths [23]. Metabolic disorders are among the fastest growing health problems worldwide, with a tendency for manifestation at earlier ages in recent years and with a higher rate in women than men [24]. The proportion of overweight adults (including obese) worldwide increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women. In 2013, the prevalence of overweight and obesity increased in children and adolescents: in developed countries, 23.8% in boys and 22.6% in girls; in developing countries, 12.9% in boys and 13.4% in girls [23]. In the meantime, undernourishment (undernutrition) remains an important concern in the developing countries. Because severe acute undernutrition is associated with loss of a person's body fat and wasting of their skeletal muscle, causing many of those affected susceptible to disease, the infants and young children are the most vulnerable as they require extra nutrition for growth and development but have comparatively limited energy reserves. Studies present overwhelming evidence that early childhood nutritional status affects both the short- and long-term health status and development [25]. In children, undernutrition could have drastic and wide-ranging health consequences, such as increased gastrointestinal and respiratory infections and mortality risk; undernutrition is also closely associated with immunological alterations, development of noncommunicable diseases in adulthood, and cognitive and behavioral impairment in childhood and adolescence [26–29]. Epidemiological studies suggest that excessive adiposity, decreased physical activity, and unhealthy poor diets are key players in the pathogenesis and prognosis of many common cancers. As a fact, poor diet (including its resultant obesity and protein-energy malnutrition) is also a major risk factor for premature death, anemia, cardiovascular diseases, cancers, respiratory diseases, and injuries that are the most prominent causes of mortality [30, 31].

The potential role of epigenetic elements in the regulation of radiation effects deserves to be further investigated as such studies would give new insights into the mechanistic study on radiation effects and its risk [32]. Although the impact of diet on susceptibility to IR is thought to be big, the evidence is not clear due to lack of study. Elucidating the diet-related epigenetic mechanisms would facilitate a better understanding of radiation risk and prompt the development of more efficient strategies against radiation. There is a crucial need in better understanding the interactions between IR effects and dietary factors. Fat is one of the three main macronutrients in addition to carbohydrate and protein. It is an important foodstuff for many forms of life and serves both structural and metabolic functions: insulating body organs against shock; providing sources of essential fatty acids; providing energy sources and stores; being essential for digestion, absorption, and transportation of fat-soluble vitamins; playing a critical role in maintaining body temperature, healthy skin and hair [33–36]. Fat also serves as a useful buffer toward a host of diseases, and visceral fat is a significant producer of several hormones involved in inflammatory tissue responses and obesity, insulin resistance, and diabetes [37]. It is known that high-fat diet is responsible for most of the obese cardiovascular diseases, and cancer [38], and on the other hand, low-fat diet also shows potential health risk [34, 39, 40]. In this study, to understand the mechanisms that link nutritional factors to alterations in responses to IR, as the first approach, effects from dietary fat on possible alteration in response

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to total-body-irradiation (TBI) were comparatively studied in young female mice fed with a standard diet, a very high-fat diet, and a very low-fat diet.

2. Materials and methods

2.1. Animals and diets

Three-weeks-old C57BL/6J Jms strain female mice, wean just from breastfeeding, were purchased from SLC, Inc. (Hamamatsu, Japan). To avoid possible effects from the developmental condition of the animals, any mouse with a significantly different body weight (more or less than the mean ± 2 SD) upon arrival was omitted from this study. The selected mice were maintained in a conventional animal facility under a 12-h light/12-h dark photoperiod (lights on from 7:00 a.m. to 7:00 p.m.). Animals housed in autoclaved cages (1 mouse per cage) with sterilized wood chips were randomly assigned to three experimental groups and allowed free access to acidified water (pH = 3.0 ± 0.2) and a standard laboratory chow MB-1 (Funabashi Farm Co., Funabashi, Japan), a high-fat diet HFD32 (CLEA Japan, Inc. Tokyo, Japan), or a low-fat diet CE-2 Low Fat (CLEA Japan, Inc. Tokyo, Japan), respectively. The percentages of crude fat in the ingredient of MB-1, HFD32, and CE-2 Low Fat were 4.4%, 32.0%, and 0.4%, respectively. The metabolizable energy in kcal/100g for MB-1, HFD32, and CE-2 Low Fat was 354.0, 507.6, and 309.2, respectively. Animals were acclimatized to the laboratory conditions for 3 weeks before use. Based on our previous studies and preliminary trials, in the present study at least 20 mice were used in each experimental group and the experiment was repeated at least once. All experimental protocols involving mice were reviewed and approved by The Institutional Animal Care and Use Committee of the National Institute of Radiological Sciences (NIRS). The experiments were performed in strict accordance with the NIRS *Guidelines for the Care and Use of Laboratory Animals*.

2.2. Irradiation

X-rays were generated with an X-ray machine (Pantak-320S, Shimadzu, Japan) operated at 200 kVp and 20 mA, using a 0.50 mm Al + 0.50 mm Cu filter. An exposure rate meter (AE-1321M, Applied Engineering Inc, Japan) was used for the dosimetry. The dose rate for delivering irradiations at a low dose at 0.50 Gy and high doses ranging from 5.0 Gy to 8.0 Gy was at about 0.30 and 0.85 Gy/min, respectively. The mice held in acryl containers without anesthesia were exposed to TBI at room temperature.

2.3. Biological endpoints

Diet intake, body weight gain, organ weight, and intra-abdominal fat weight: The diet intake and body weight gain of the animals in each experiment group were recorded daily. The animals at age of postnatal 13 weeks were anesthetized by inhalation of gaseous isoflurane (2-chloro-2-(difluoromethoxy)-1, 1, 1-trifluoro-ethane) (CDS019936, Sigma-Aldrich, Japan) and then euthanized by cervical dislocation. Weight of some main organs and intra-abdominal fat

(IA fat) was weighed. These parameters obtained from mice fed with different diets were comparatively studied.

Bone marrow nucleated cells, the peripheral blood hemogram, and serum biochemical examination: The mice at postnatal age of 6 weeks and/or 8 weeks, or 13 weeks were anesthetized for collection of peripheral blood from the right femoral artery under anesthesia and then killed by cervical dislocation. Bone marrow cells were collected from both humeri and femora and the bone marrow nucleated cells were counted. As peripheral blood is the only tissue routinely available from human subjects, the peripheral blood hemogram and serum biochemical parameters were assessed in the present work to provide information for possible comparative clinical study in the future. Values of blood hemogram and blood biochemistry were comparatively studied in mice fed with different diets. The blood collected with a heparinized syringe in vacutainer blood collection tubes containing EDTA (Venoject II, Terumo Co., Japan) were immediately subjected to differential blood cell count (erythrocytes, leucocytes, and thrombocytes) and measurement of blood hemoglobin concentration using a blood cell differential automatic analyzer (SYSMEX K-4500, Sysmex Corporation, Japan). For biochemical examination, the serum of the blood collected without anticoagulant treatment was assessed using a biochemical automatic analyzer (DRI-CHEM 7000V, Fujifilm Corporation, Japan). The data for each experimental group were from at least five mice.

The 30-day survival test: The number of deaths that occurred within the 30-day period after TBI at high doses (from 5.0 Gy to 8.0 Gy) was recorded. The median lethal dose (lethal dose 50%, LD50) was used to comparatively study the radiosensitivity in mice fed with different diets. As a good in vivo model to study the response of mice to low-dose-induced adaptive response (AR), the mouse AR model for rescue of IR-induced bone marrow death [41] was adopted, verified, and confirmed under the experimental conditions in our research facilities, and finally applied to this study. In brief, the efficient priming dose of X-rays was 0.50 Gy. The timing for delivery of the priming dose and challenge dose was on postnatal ages of 6 and 8 weeks of the mice, respectively. When the priming dose induced a significant suppression of the mortality caused by the challenge dose, AR was considered as being successfully induced. Different challenge doses were chosen depended on the endpoint. A challenge dose at 7.50 Gy was used for verification and confirmation of the experimental conditions ensuring the successful induction of AR in mice fed with the standard diet MB-1. This dose was also tested as the challenge dose in mice fed with the high-fat diet HFD32 and low-fat diet CE-2 Low Fat. A challenge dose at 4.0 Gy was used to obtain more survivors in the 30-day survival test for investigations on the residual damage in the hematopoietic system.

Micronucleus test: The bone marrow micronucleus test was carried out accordingly [42] with minor modifications [43, 44]. Mice were sacrificed the following day after the 30-day survival test. Bone marrow smears prepared from both femora were processed for the enumeration of micronucleated polychromatic erythrocytes (MNPCEs) and micronucleated normochromatic erythrocytes (MNNCEs). The slides were coded to avoid any observer bias. The micronuclei were scored using a light microscope at a magnification of 1000×. At least 5000 cells per mouse were counted and the data for each experimental point were from at least 5 mice.

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2.4. Statistical analysis

For LD50 determination, curvilinear regression of second degree was applied to the survival data using the programs embedded in KaleidaGraph Software (Version 4.1.2, Synergy Software, Hulinks Inc., Tokyo, Japan). Statistical evaluation of all the data was done using Student's *t*-test except for the micronucleus data where the χ^2 test was performed. Statistical significance was assigned to $P < 0.05$.

3. Results

3.1. Intake of diet and metabolizable energy

The amount (weight in gram, g) of diet consumption by each mouse was recorded daily, based on which the mean values of both diet intake (Figure 1A) and metabolizable energy intake (Figure 1B) daily per mouse in each experimental group was calculated. When compared to the weight of the diet intake by the control animals fed with the standard diet MB-1, the weight of the diet intake by the mice fed with the low-fat diet CE-2 Low Fat in the first 2 weeks was significantly lower while it was markedly increased in the last week in the period of the experiment. On the other hand, mice fed with the high-fat diet HFD32 consumed significantly less amount of diet from the second week to the tenth week after diet onset (Figure 1A). As for the amount of metabolizable energy daily intake, it was significantly bigger in the mice fed with the high-fat diet throughout the experimental period while it was markedly smaller in the mice fed with the low-fat diet for most of the time in the period of the experiment (Figure 1B). Generally, there was a statistically significant difference on the mean metabolizable energy daily intake between the control group fed with MB-1 diet and that fed with an unbalanced diet (either HFD32 or CE-2 Low Fat). The animals fed with HFD32 diet took a significantly bigger amount of energy while the animals fed with the CE-2 Low Fat diet took a markedly smaller amount of energy.

3.2. Body weight gain, main organ weight, and IA fat weight

Body weight gain, main organ weight, and IA fat weight of the mice were studied to evaluate the effects from eating a diet containing different amount of dietary fat on physiological development. Body weight of each mouse was recorded daily until the end of the study at postnatal age 13 weeks (10 weeks after the diet onset). The mean body weight of mice in each experimental group continuously increased throughout the experiment (Figure 1C). When compared to the mice fed with the standard diet MB-1, significantly higher body weight was observed from 1.5 weeks after onset of the high-fat diet HFD32 to the end of the study while markedly lower body weight was recorded from as early as half week after onset of the low-fat diet CE-2 Low Fat to the end of the study. Ten weeks after the animals fed with different diets, the weight of some main organs and the IA fat were measured. As shown in Figure 1D, the weight of brain, liver, and kidney of the animals fed with the high-fat diet HFD32 were significantly higher compared to that of the animals fed with the standard diet MB-1. Notably,

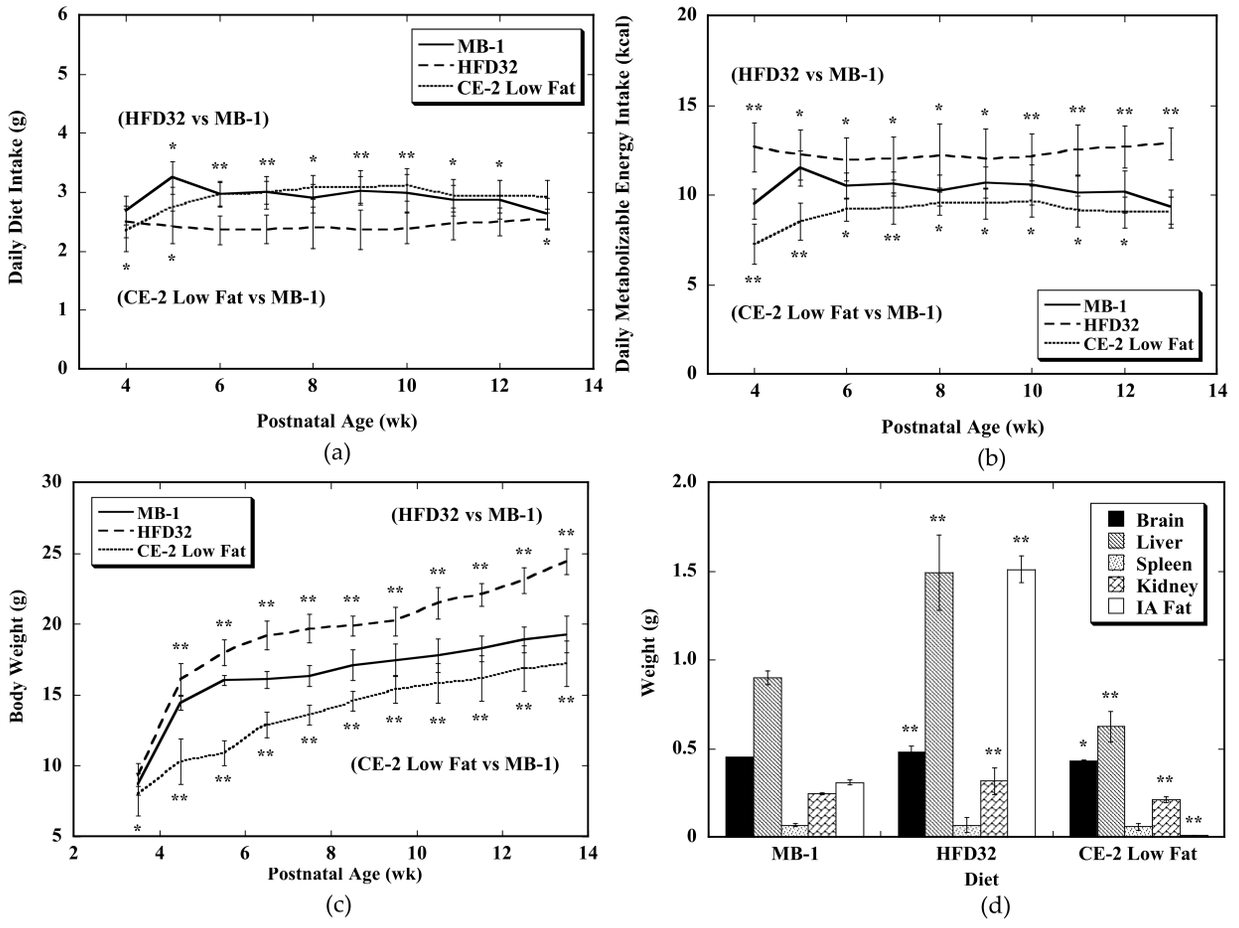

Figure 1. (a) Daily Intake of Different Types of Diets *ad libitum* after Weaning in Mice (b). Daily Metabolizable Energy Intake from Different Types of Diets ad libitum after Weaning in Mice (c). Effect from Consuming Different Types of Diets on Body Weight Gain of Mice (d). Effect from Consuming Different Types of Diets on Organ Weight and Intra-abdominal Fat Weight of Mice at Postnatal Age 13 Weeks

the weight of IA fat from the mice fed with HFD32 and from mice fed with CE-2 Low Fat were dramatically higher and lower than from the mice fed with MB-1. In addition, pathological study on liver showed characteristics of fatty liver and fatty tissue was noticeable in these organs. On the contrary, the weight of these organs and the IA fat were markedly lower in the animals fed with the low-fat diet CE-2 Low Fat.

3.3. Bone marrow nucleated cell count, peripheral blood hemogram, and biochemical examination

The peripheral blood was collected from animals in each experimental group at age of postnatal 13 weeks (10 weeks after onset of different diets). The hemogram was measured and biochemical examination of the serum was performed. For peripheral blood hemogram (Figure 2), mice subjected to the high-fat diet HFD32 displayed a significant decrease in both red blood cell count (RBC) and white blood cell count (WBC) when compared to the control that fed with the standard diet MB-1. Mice fed with the low-fat diet CE-2 Low Fat showed a significant

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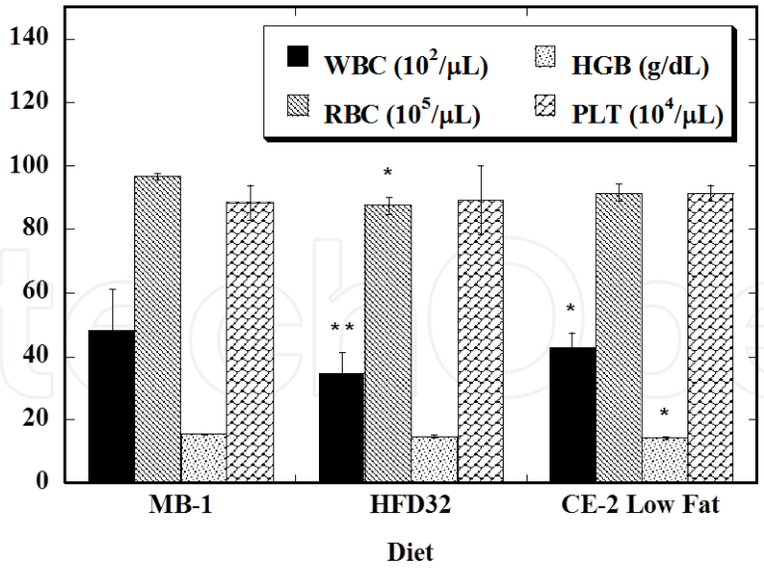

Figure 2. Effect from Consuming Different Types of Diets on Peripheral Blood Hemogram of Mice at Postnatal Age 13 Weeks.

reduction of both WBC count and hemoglobin concentration (HGB). No difference on blood platelet count (PLT) among the experimental groups was observed. For the bone marrow nucleated cells in both humeri and femora, the number ($\times 10^7$) per mouse was 5.1 ± 0.8, 4.4 ± 0.5, 4.8 ± 1.0 in MB-1, HFD32, and CE-2 Low Fat group, respectively. The decrease in the number of bone marrow nucleated cells from the animals of HFD32 and CE-2 Low Fat groups was not of statistic significance when compared to that from MB-1 group. For biochemical examination of the serum collected from mice at postnatal age of 6 weeks (Table 1A) and postnatal age of 8 weeks (Table 1B), animals subjected to the unbalanced diet of either the high-fat diet HFD32 or the low-fat diet CE-2 Low Fat showed a significant alteration in may parameters. For example, at postnatal age of 6 weeks (3 weeks after diet onset), increase in glucose concentration (GLU-PIII) and total cholesterol concentration (TCHO-PIII) and decrease in the creatinine concentration (CRE-PIII) and alkaline phosphatase activity (ALP-PIII) were observed in mice fed with HFD32, while increase in CRE-PIII, uric acid concentration (UA-PIII), TCHO-PIII, ammonia concentration (NH_3), glutamic oxaloacetic transaminase (aspartate aminotransferase) activity (GOT/AST), glutamic pyruvic transaminase (alanine aminotransferase) activity (GPT/ALT-PIII), and K^+ concentration and decrease in GLU-PIII, triglyceride concentration (TG-PIII), total bilirubin concentration (TBIL-PIII), total protein concentration (TP-PIII), albumin concentration (ALB-P), gamma-glutamyl transferase activity (GGTP), and leucine aminopeptidase activity (LAP-P) were detected in mice fed with CE-2 Low Fat. At postnatal age of 8 weeks (5 weeks after diet onset), significant alteration in concentration of most parameters in general chemistry test in mice fed with either HFD32 or CE-2 Low Fat was detected when compared to that in the mice consuming the standard diet MB-1. For example, markedly increased GLU-PIII was observed in the animals fed with either of the unbalanced diet HFD32 or CE-2 Low Fat; increased TCHO-PIII, TG-PIII, TBIL-PIII, and TP-PII were detected in the mice fed with high-fat diet HFD32; and decreased TG-PIII, TBIL-PIII, inorganic phosphorus concentration (IP-P), TP-PIII, ALB-P, magnesium concentration (Mg), and NH_3 were observed in mice fed with low-fat diet CE-2 Low Fat. Marked alteration

in enzyme activity was also detected in most of the parameters, such as GGTP, GOT/AST, GTP/ALT-PIII, etc., in enzymology test in the mice fed with the unbalanced diet HFD32 and/or CE-2 Low Fat.

Biochemical examination	Experimental group		
	MB-1	HFD32	CE-2 Low Fat
General chemistry			
Glucose concentration (GLU-PIII, mg/dL)	143.0 ± 12.7	176.7 ± 5.8*	54.7 ± 5.8**
Urea nitrogen concentration (BUN-PIII, mg/dL)	31.6 ± 3.8	26.6 ± 0.8	27.2 ± 3.9
Creatinine concentration (CRE-PIII, mg/dL)	0.2 ± 0.0	0.1 ± 0.0**	0.4 ± 0.1**
Uric acid concentration (UA-PIII, mg/dL)	5.4 ± 1.9	4.6 ± 1.0	8.4 ± 2.1*
Total cholesterol concentration (TCHO-PIII, mg/dL)	67.5 ± 0.7	103.0 ± 9.7*	10.2 ± 1.1**
Triglyceride concentration (TG-PIII, mg/dL)	272.0 ± 51.3	309.3 ± 43.5	112.0 ± 18.1**
Total bilirubin concentration (TBIL-PIII, mg/dL)	5.9 ± 0.7	5.1 ± 2.4	1.9 ± 0.6**
Calcium concentration (Ca-PIII, mmol/L)	9.0 ± 1.0	5.1 ± 2.4	7.7 ± 0.1
Inorganic phosphorus concentration (IP-P, mg/dL)	23.1 ± 2.9	21.3 ± 1.8	18.0 ± 1.3
Total protein concentration (TP-PIII, g/dL)	7.7 ± 0.7	7.2 ± 0.7	6.1 ± 0.3**
Albumin concentration (ALB-P, g/L)	4.2 ± 0.5	4.5 ± 1.2	3.0 ± 0.2**
Magnesium concentration (Mg, mg/dL)	3.2 ± 0.2	2.7 ± 0.2	3.3 ± 0.2
Ammonia concentration (NH_3, μg/dL)	737.0 ± 98.1	781.0 ± 71.6	1434.0 ± 42.3**
Enzymology			
Gamma-glutamyl transferase activity (GGTP, U/L)	169.5 ± 58.5	128.0 ± 54.8	21.4 ± 15.0**
Glutamic oxalacetic transaminase (aspartate aminotransferase) activity (GOT/AST, U/L)	66.3 ± 16.3	54.3 ± 14.0	185.0 ± 26.9**
Glutamic pyruvic transaminase(alanine aminotransferase) activity (GPT/ALT-PIII, U/L)	33.3 ± 6.5	27.0 ± 4.4	28.7 ± 4.7
Creatine phosphokinase activity (CPK-PIII, U/L)	6183.3 ± 2664.4	6122.7 ± 3660.2	10263.8 ± 3750.2*
Lactate dehydrogenase activity (LDH-PIII, U/L)	4048.0 ± 544.9	4011.7 ± 401.9	3763.7 ± 420.4
Alkaline phosphatase activity (ALP-PIII, U/L)	868.0 ± 32.5	778.7 ± 27.0*	801.7 ± 38.4
Leucine aminopeptidase activity (LAP-P, U/L)	277.0 ± 12.7	216.3 ± 67.0	108.8 ± 32.3**
Creatine phosphokinase isozyme MB activity (CKMB-P, U/L)	242.5 ± 81.3	181.3 ± 86.8	423.8 ± 85.7
Electrolyte			
Na^+ (mEq/L)	148.0 ± 2.8	142.7 ± 6.7	142.3 ± 8.4
K^+ (mEq/L)	11.2 ± 1.1	9.2 ± 0.3	22.9 ± 0.9**
Cl^- (mEq/L)	126.0 ± 8.5	118.3 ± 2.1	115.7 ± 1.5

*: $P < 0.05$, **: $P < 0.01$

(a)

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Biochemical examination	Experimental group		
	MB-1	HFD32	CE-2 Low Fat
General chemistry			
Glucose concentration (GLU-PIII, mg/dL)	169.7 ± 11.1	295.7 ± 45.6*	225.0 ± 14.7**
Urea nitrogen concentration (BUN-PIII, mg/dL)	32.8 ± 2.5	23.7 ± 3.3*	31.2 ± 3.0
Creatinine concentration (CRE-PIII, mg/dL)	0.2 ± 0.0	0.1 ± 0.0**	0.3 ± 0.1*
Uric acid concentration (UA-PIII, mg/dL)	8.4 ± 0.7	7.3 ± 1.2	3.8 ± 0.2
Total cholesterol concentration (TCHO-PIII, mg/dL)	64.0 ± 3.0	104.3 ± 11.2**	61.3 ± 2.5
Triglyceride concentration (TG-PIII, mg/dL)	256.3 ± 12.2	299.7 ± 17.9*	66.0 ± 20.1**
Total bilirubin concentration (TBIL-PIII, mg/dL)	6.7 ± 1.2	15.3 ± 4.4*	1.8 ± 0.1**
Calcium concentration (Ca-PIII, mmol/L)	8.0 ± 0.3	6.4 ± 0.4**	8.7 ± 0.4**
Inorganic phosphorus concentration (IP-P, mg/dL)	15.7 ± 2.5	22.5 ± 5.2	10.8 ± 0.6**
Total protein concentration (TP-PIII, g/dL)	6.8 ± 1.0	10.9 ± 2.1*	5.8 ± 0.3*
Albumin concentration (ALB-P, g/L)	4.0 ± 0.7	6.9 ± 2.3	2.6 ± 0.2**
Magnesium concentration (Mg, mg/dL)	2.9 ± 0.1	2.5 ± 0.1**	2.5 ± 0.1**
Ammonia concentration (NH_3, μg/dL)	796.3 ± 145.5	877.3 ± 115.2	464.0 ± 89.1**
Enzymology			
Gamma-glutamyl transferase activity (GGTP, U/L)	139.0 ± 80.0	409.7 ± 102.4	5.3 ± 4.5**
Glutamic oxalacetic transaminase (aspartate aminotransferase) activity (GOT/AST, U/L)	42.3 ± 12.9	84.3 ± 27.9*	161.5 ± 60.1**
Glutamic pyruvic transaminase(alanine aminotransferase) activity (GPT/ALT-PIII, U/L)	25.3 ± 7.8	84.3 ± 27.9**	29.3 ± 17.9
Creatine phosphokinase activity (CPK-PIII, U/L)	7722.8 ± 3123.5	12597.3 ± 7131.1	6554.0 ± 3169.2*
Lactate dehydrogenase activity (LDH-PIII, U/L)	3476.0 ± 500.4	7082.5 ± 2107.8*	1380.8 ± 122.2**
Alkaline phosphatase activity (ALP-PIII, U/L)	637.7 ± 41.5	15837.3 ± 3645.5**	763.5 ± 31.5**
Leucine aminopeptidase activity (LAP-P, U/L)	200.8 ± 58.1	417.3 ± 178.1*	78.5 ± 7.9**
Creatine phosphokinase isozyme MB activity (CKMB-P, U/L)	226.3 ± 107.0	326.7 ± 67.5	222.6 ± 64.0
Electrolyte			
Na^+ (mEq/L)	146.0 ± 1.4	140.0 ± 2.8	148.3 ± 1.2
K^+ (mEq/L)	8.9 ± 0.2	9.1 ± 1.5	5.6 ± 0.3**
Cl^- (mEq/L)	116.5 ± 0.7	113.0 ± 1.4	116.3 ± 2.3

*: P < 0.05, **: P < 0.01

(b)

Table 1. A. Biochemical Examination on the Serum of Mice at Postnatal Age of 6 Weeks Table 1B. Biochemical Examination on the Serum of Mice at Postnatal Age of 8 Weeks

These results showed that dietary fat had a big impact on the development of mice. These results indicated that consuming an unbalanced diet containing different amount of dietary fat could cause a series of detrimental health consequence, manifesting as alterations in body weight, organ weight, IA fat weight, peripheral blood hemogram, and serum biochemistry.

3.4. LD50 in the 30-day survival test

Alteration in sensitivity to TBI-induced bone marrow death due to mice consuming different diets was comparatively studied using LD50 in the 30-day survival tests. The curvilinear regression of second degree was applied to the data analysis; survival curve for each group fitted well a quadratic polynomial expression (Figure 3). The regression analysis yielded LD50 as 7.1 Gy, 6.0 Gy, and 6.2 Gy, respectively, for the animals fed with the standard diet MB-1, the high-fat diet HFD32 and the low-fat diet CE-2 Low Fat. These results indicated that mice fed with an unbalanced diet containing different amount of dietary fat became highly sensitive to the killing effect from TBI at high doses.

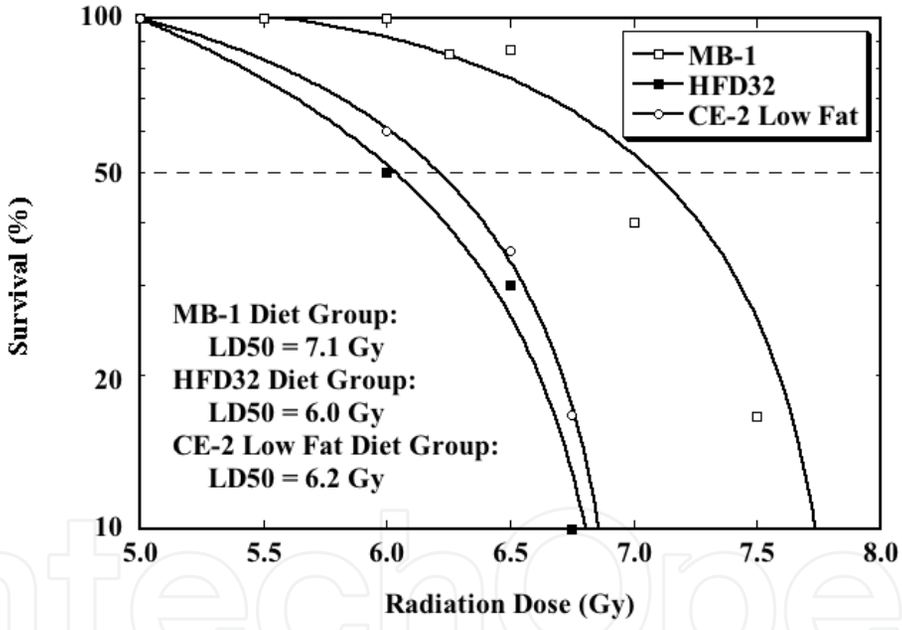

Figure 3. 30-Day Survival after Total Body Irradiation of Mice Fed with Different Kinds of Diets at Postnatal Age 8 Weeks

3.5. Induction of AR

Reproducibility of the mouse model for AR induction was verified and confirmed by delivery of the priming low dose at 0.5 Gy and challenge high dose at 7.50 Gy using mice fed with the standard diet MB-1. The priming dose markedly increased the survival rate from 16.7% to 80.0% in the 30-day survival test (Figure 4A). These results clearly indicated that AR was successfully induced with efficient reliability and reproducibility in our experimental setup.

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Serving as the positive control, the effect from consuming an unbalanced diet containing different amount of dietary fat on AR induction was comparatively studied. As for the mice fed with the high-fat diet HFD32, all animals died within 15 days after the challenge dose, regardless of receiving the priming dose (Figure 4B). As for the mice fed with the low-fat diet CE-2 Low Fat, all animals died within 13 days after the challenge dose, regardless of receiving the priming dose (Figure 4C). Considering the sensitivity to TBI-induced bone marrow death was higher in mice fed with an unbalanced diet and 7.5 Gy would be too high to be used as the challenge dose in the AR induction study; a dose at 6.5 Gy which resulted in a survival rate at 30.0% and 35.0%, respectively, in mice fed with the high-fat diet HFD32 and low-fat diet CE-2 Low Fat in the 30-day survival test (Figure 3) was also tested as a challenge dose. The survival rate was respectively 29.4% and 33.3% for these mice, showing that no AR was induced in the mice fed with an unbalanced diet containing different amount of dietary fat. These results indicated that the response to low dose of TBI altered in mice fed with either a high-fat diet or a low-fat diet when compared to that fed with the standard diet.

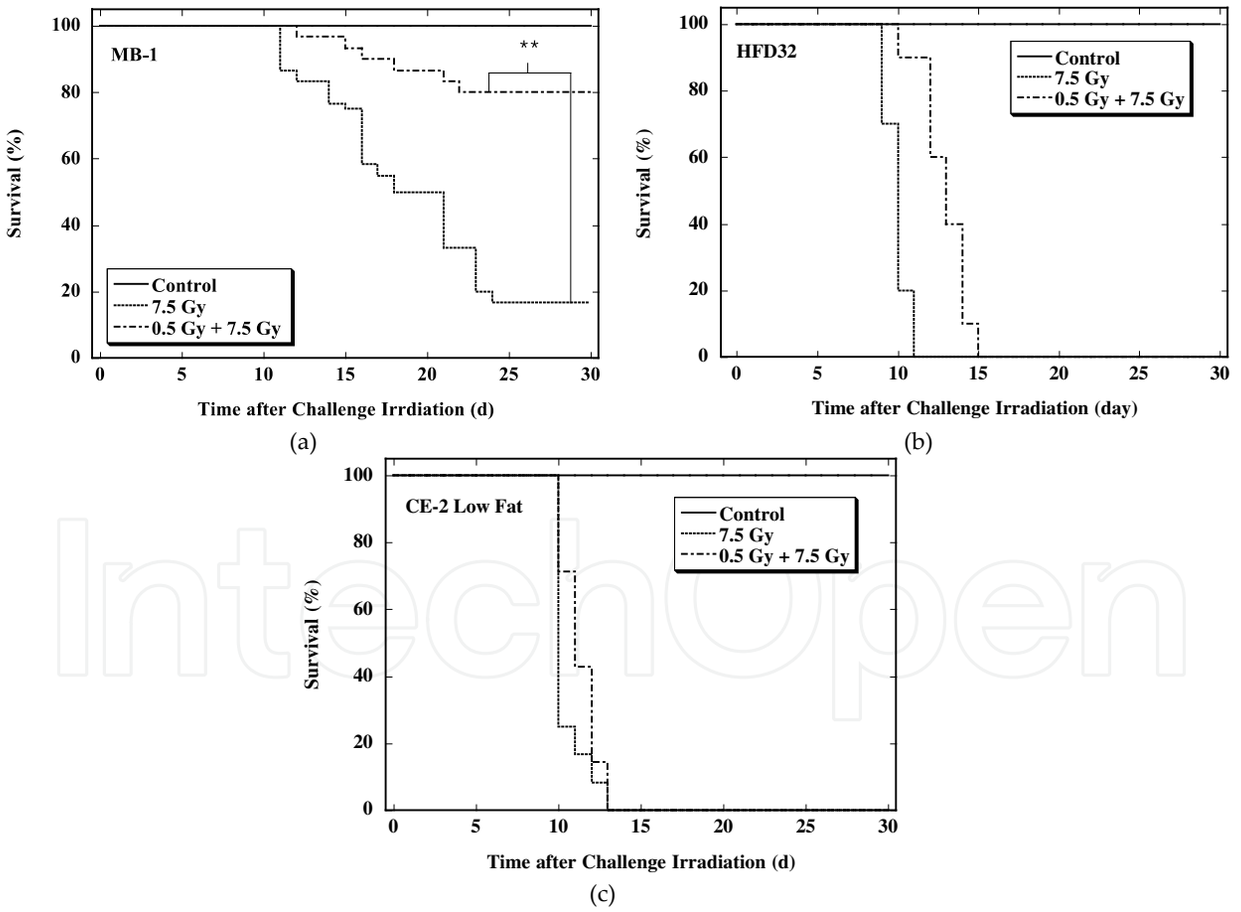

Figure 4. (a). Induction of Adaptive Response in Mice Fed with the Standard Diet MB-1. (b).Induction of Adaptive Response in Mice Fed with the High-Fat Diet HFD32. (c). Induction of Adaptive Response in Mice Fed with the Low-Fat Diet CE-2 Low Fat.

3.6. Residual damage in bone marrow erythrocytes

As bone marrow failure was the main cause for the animal death in the AR mouse model, to evaluate alterations in TBI-induced cytotoxicity and genotoxicity due to consuming a diet containing different amount of dietary fat, the residual damage in the bone marrow cells of the animals was measured 1 day after the 30-day survival test. The percentage of polychromatic erythrocytes (PCEs) to the sum of PCEs and normochromatic erythrocytes (NCEs) is an indicator for mutagen-induced cytotoxicity to bone marrow proliferation in the erythroid lineage [45], and micronucleus test is a tool for genotoxic assessment. Though the percentage of PCEs to the sum of PCEs and NCEs was lower for mice fed with the low-fat diet CE-2 Low Fat, it was not of statistical difference when compared to that for the mice fed with the standard diet MB-1 (data not shown). Results obtained in mice fed with the MB-1 diet (the positive control group for AR induction) showed that the priming low dose at 0.5 Gy significantly reduced the occurrences of both MNPCEs in PCEs (Figure 5A) and MNNCEs in NCEs (Figure 5B) in the femur bone marrow when respectively compared to that receiving the challenge dose alone. On the other hand, in the animals fed with either a high-fat diet or a low-fat diet, the priming dose failed to induce a marked reduction of the occurrences of MNPCEs and MNNCEs (Figure 5C, 5D, 5E, and 5F) when respectively compared to that receiving the challenge dose alone. These results were consistent with the results obtained on AR induction in the 30-day survival test. In addition, though the increase was not of a statistical significance, when compared to the incidences of MNPCEs and MNNCEs induced by the challenge dose alone in the animals fed with the standard diet MB-1, increased incidences was always recorded in mice fed with an unbalanced diet containing different amount of dietary fat. These results indicated that consuming a diet containing different amount of dietary fat had a significant impact on the cytotoxic and genotoxic effect on the bone marrow erythrocytes.

4. Discussion

The mouse model for IR-induced AR was applied to present work and alterations in response of mice to TBI were investigated under diets containing different amount of dietary fat. The mouse response to low dose of TBI was evaluated by the efficacy of the priming low dose to rescue the animals from bone marrow death induced by the challenge IR at higher doses in the 30-day survival test. The mouse response to high doses of TBI was studied by comparing the LD50 values in the 30-day survival test. In addition, dietary modulation of the residual (late) genotoxic effect from TBI was also evaluated by comparing the incidence of micronucleated erythrocytes in bone marrow using micronucleus test. Results demonstrated that under an unbalanced diet, namely, either of very high fat or of very low fat, alterations in the response of mice to TBI were induced at both low dose and high doses: abolishment of AR induction by the low dose which was efficient in mice fed by the standard diet, increase in the radiosensitivity to bone marrow failure induced by high doses, and increase in genomic instability after high dose. These findings confirm that dietary fat plays a pivotal role in the response of the animals to IR exposure and provide new insight into the study on the epigenetic

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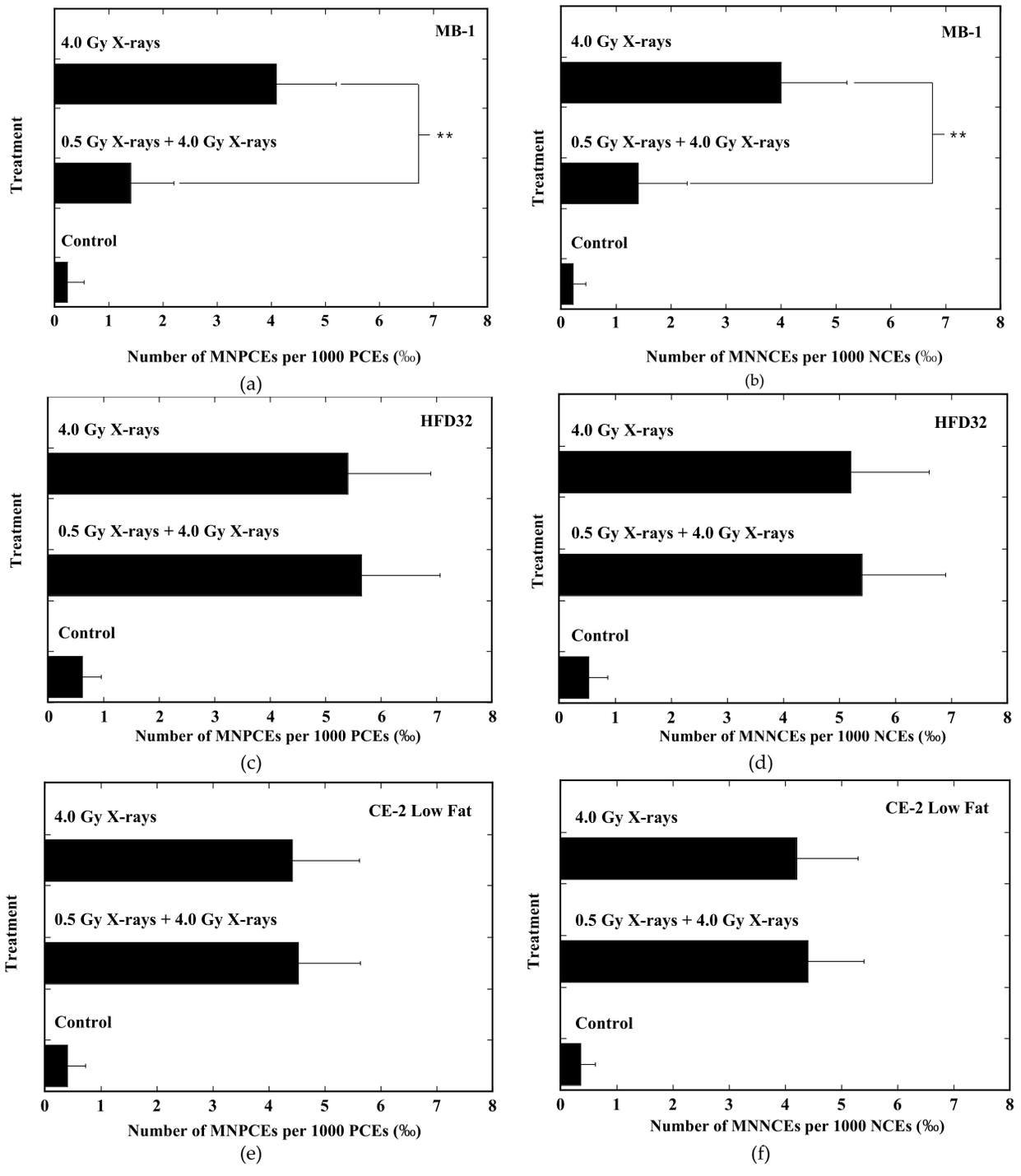

Figure 5. (a) Incidence of MNPCEs induced by TBI in Femur Bone Marrow Erythrocytes of Mice Fed with the Standard Diet MB-1. (b). Incidence of MNNCEs induced by TBI in Femur Bone Marrow Erythrocytes of Mice Fed with the Standard Diet MB-1. (c). Incidence of MNPCEs induced by TBI in Femur Bone Marrow Erythrocytes of Mice Fed with the High-Fat Diet HFD32. (d). Incidence of MNNCEs induced by TBI in Femur Bone Marrow Erythrocytes of Mice Fed with the High-Fat Diet HFD32. (e). Incidence of MNPCEs induced by TBI in Femur Bone Marrow Erythrocytes of Mice Fed with the Low-Fat Diet CE-2 Low Fat. (f).Incidence of MNNCEs induced by TBI in Femur Bone Marrow Erythrocytes of Mice Fed with the Low-Fat Diet CE-2 Low Fat.

contribution to radiation risk. These findings aid knowledge for radiation risk reduction and suggest the possibility to modulate radiosensitivity through diet intervention in humans.

Although the results obtained in this phenomenal study clearly show that dietary fat has a big impact on mouse response to TIB, the underlying mechanisms remain unclear. It is well known that disturbance of hormonal balance, production and secretion of cytokines and growth factors could result in alterations in radiation susceptibility as these intercellular and intracellular messengers play important roles in preserving and restoring functions of tissues compromised by IR [44–48]. As dietary fat plays a critical role in such as physiological development and maintaining metabolic and immune function of the body [33–37], disturbed hormonal level, metabolic environment, and immune functions due to eating an unbalanced diet containing either very high fat or very low fat would be responsible for the altered response of the mice to TBI. In fact, results obtained in this study on biochemical examination of serum showed clearly that an unbalanced diet could result in alterations in many parameters and these findings could suggest the resultant disturbed metabolism and physiological development of the animals. It is known that consumption of a high-fat diet correlates with increased oxidative stress and chronic inflammation in many organs [49, 50]. Oxidative stress could result in increased sensitivity to IR [51–54]. Cumulative evidences also show that high-fat diet causes disturbance of nutrient balance, leading to dysregulation of the adipoinsular axis, a dual hormonal feedback loop involving insulin and leptin, and alterations in hormone production and secretion, i.e., increased insulin and decreased leptin [55]. On the other hand, as dietary fat clearly serves a number of essential functions, diet with adequate energy from fat is needed to promote normal growth and normal sexual maturation; maternal energy deficiency due to very low-fat intakes is one key determinant in the etiology of low birth weight [34]. C57BL/6J strain mice fed with a very high-fat diet provide a good experimental model of diet-induced obese in a way closely matching the development of human metabolic syndrome, and a good experimental model for studying the molecular mechanisms as well [56]. The present work indicates that C57BL/6J strain mice could be also used as a good model to study the effect from an unbalanced diet containing very low fat. There is growing evidence showing that diet can strongly influence epigenetic processes [57]. Given the importance of dietary fat on the alterations in responses to IR at whole body level, in the future, in particular for this reason, a significant amount of interest should be given to the molecular analysis of mechanisms involving epigenetic regulation such as metabolic and immune disruptions under conditions with very high-fat diet and very low-fat diet.

The present study reinforces the importance of understanding the dietary factors for that there is a striking modification effect on the response to IR. Developing active prevention strategies would be a practical approach to meeting the critical need to reduce the radiation risk, in addition to the improvement of overall health and the quality of life. In fact, understanding of the ability and mechanisms of dietary modification will fuel the development of effective countermeasures to reduce radiation risk. Further work is required to understand the mechanisms through which specific dietary factors produce epigenetic

changes and to identify those changes that are likely to be causal in the alterations in response to radiation. As to the diet fat, it is known that a healthy low-fat diet is not a diet containing fat approximately down to zero. More attention needs to be devoted to the effect of dietary fat reduction on the nutrient density, especially for children [34]. Notably, recent study shows that it is more than just the amount of fat, the types of fat really matter. Bad fats may increase the risk of certain diseases, while good fats support overall health. Future study may focus on the types of fat in the diet and their possible modification effect on response to IR. In addition, there are many factors that impact eating behaviors in humans, i.e., the profile of food choice depends on the gender and age. Studies described remarkable differences between genders in food choice: women had higher intakes of fruit and vegetables, higher intakes of dietary fiber and lower intakes of fat. The motivation of weight control was more prominent in women who were more likely to diet or restrain their eating behavior. Age-related changes in the chemosensory perceptual systems motivated the choice of other foods, and therefore a varied diet [58]. Eating takes place in a context of environmental stimuli known as ambience, which has influence on nutritional health. Various external moderators such as social and physical surroundings and internal factors such as food variables also affect food intake and food choice [59, 60]. In humans, as the relationship among stress, dietary restraint, and food preference is complicated, for an example, it was reported that high-stressed women preferred sweet, high-fat food more than did low-stressed women, whereas low-stressed women ate more low-fat than high-fat food [61, 62]. As many factors that impact the eating behaviors, given the complexity of the epigenetic machinery, it is also important to unravel the differential role of the various epigenetic participants in a given physiopathological condition [24]. In further study, it is important to further decipher for various nutritional factors the role and the mechanisms involved in driving epigenetic-related alterations in responses to radiation, as well as to assess the role of the presence of other factors at different ages and in both sexes.

Dietary, lifestyle, and environmental factors could affect many biological and pathological processes. It is known that making positive diet and lifestyle changes, namely, eating a healthy diet, getting enough exercise, and refraining from tobacco and excessive alcohol use, could confer numerous health benefits including possibly preventing the onset of chronic diseases. This suggests that these processes are interventable through dietary intervention. In fact, there is a move to improve nutritional status in malnourished patients through the use of multimodal interventions including nutritional supplements in the prevention and management of disease-related malnutrition [63]. It is shown that dietary intervention by distribution of nutritious supplementary foods to young children in conjunction with household support is an appropriate strategy for the prevention of moderate acute malnutrition and severe acute malnutrition in young children [64], and adequate treatment by dietary intervention is important for reversing these effects [65]. Nutrition intervention (nutritional counseling and oral nutritional supplements) is also used to prevent therapy-associated weight loss and interruption of chemotherapy and/or radiotherapy in cancer patients [66, 67]. Adequate nutrition during cancer plays a deci-

sive role in treatment response and quality of life in humans [68]. On the other hand, calorie restriction (CR) has been shown to be effective as one of the dietary interventions. Although it still requires intense efforts for the interventions to unravel the complexity of the epigenetic, genetic, and environment interactions and to evaluate their potential reversibility with minimal side effects, encouraging trials suggest the prevention and therapy of age- and lifestyle-related diseases such as by individualized tailoring to optimal epigenetic diets [24]. In addition to the extension of the maximal lifespan of a diverse group of species, CR without malnutrition was demonstrated to reduce the morbidity of a host of diseases including broadly effective in cancer prevention in laboratory rodents [69, 70]. In animals, in addition to cardiovascular-specific effects, CR caused a variety of improvements related to overall health; in humans, studies noted favorable changes in multifarious biomarkers, particularly those related to cardiovascular and glucoregulatory function [71]. CR could decelerate the rate of aging and inhibit tumor formation in mammals [72–74]. It could also decrease the tumors that were induced by chemicals and IR in rodents and nonhuman primates [70, 75–83]. Even after exposure to IR, CR could still be effective for reducing cancer incidence in mice [82, 83]. These studies showed that dietary intervention could alter the phenotype and epigenotype in animal models [84], and demonstrated the feasibility of an active means to prevent or reverse the adverse effects from unbalanced diet or malnutrition. All these experimental and clinical works indicate that dietary intervention would hold special potential to treat certain diseases as both useful support to conventional therapy and countermeasure as well against IR-induced detrimental effects. Notably, dietary intervention is not limited to administration of nutritious supplementary foods only, some biologically active chemicals, such as calorie restriction mimetics, should be taken into account based on the mechanism studies [85]. For an example, extensive studies indicated that resveratrol, a natural biologically active polyphenol present in different plant species, has anti-diabetic action in animal models and in diabetic humans [49, 50, 86, 87]. A healthy diet is the key to maintaining well-being and preventing health problems. Health consequences due to poor unbalanced diet-induced malnutrition are getting worse, as an example for obesity, not only is it increasing but no national prevention success has made so far [23]. Making healthy food choices is more important than ever. A global action with simple and effective countermeasures against poor unbalanced diet-induced health consequences is urgently needed. This is of great significance and importance for prevention of diet-related health problems and reversibility of the altered biological responses including responses to IR.

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