Chapter 1

Introduction and Overview

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Abstract The adverse effect of radiation on human health, especially cancer induction, is a major concern, especially after the Fukushima Daiichi Nuclear Power Plant (FNPP) accident. We have learned the consequences of radiation for human health through radiological tragedies and nuclear disasters. Archival materials on Thorotrast patients have enabled us to perform molecular pathological analysis, in order to elucidate the carcinogenic mechanism of internal radiation exposure. Radiation-induced cancer is not merely attributed to resulting genetic mutations, but is in fact a complex consequence of the biological response to radiation and ingested radionuclides. Therefore, the FNPP accident prompted us to launch “A comprehensive dose evaluation project on animals affected by the FNPP accident” to establish an archive system composed of samples and data from animals around FNPP. Using those archived samples, we have been able to report some achieved results. The final goal of this archive system is to enable research that will contribute to the common understanding of the radioprotection of the ecosystem as well as humans.

In reality, however, it is becoming difficult to continue this project, due to reduced research spending at academic institutions and the weathering memory for the accident of people.

Keywords Thorotrast · Radiation exposure · Fukushima Daiichi Nuclear Power Plant accident · Evacuation zone · Livestock · Japanese macaque

1.1 Introduction

Exposure to radiation above a certain level obviously has adverse effects on human health. Radiation is not detectable by our five senses, and half of people exposed to 4 Gy of photons would die within 60 days if the whole body were exposed, which

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M. Fukumoto (ed.), *Low-Dose Radiation Effects on Animals and Ecosystems*,
https://doi.org/10.1007/978-981-13-8218-5_1

Questions frequently asked

- “No immediate effects” ; Does it mean secure?
How about the risk of cancer? No impact on offspring?
- Are low levels of radiation good for health?
- Is artificial radiation bad, but Radon hot spring good for health?
- Is internal exposure more dangerous than external one?

Facts with certainty

- Total body exposure to 4 Gy: LD50/60 (half die within 60 days by the small energy equivalent to increasing 0.001°C of body temperature)
Cancer risk increases if survived acute exposure
- Cancer risk is higher if exposed earlier.
- Human effects of exposure to < 0.1Gy are unknown.
- Radiation specific pathological changes are unknown.

Fig. 1.1 Radiation effects on humans; what people want to know is hard to know and what we know is limited

is only enough energy to raise the body temperature by 0.001 °C [1]. There is, therefore, a general belief that ionizing radiation is dangerous at any dose. The world's most reliable data about the effect of radiation on human health is the epidemiological survey on atomic-bomb survivors of Hiroshima and Nagasaki (Hibakusha) [2]. After radiation exposure, symptoms occurring within months are called acute (or early) effects, and those that develop after years to decades of a symptomless incubation period are called late (or delayed) effects. A life span study of Hibakusha (LSS) revealed that the incidence of cancer (relative cancer risk), which is a late effect, was proportional to dose. The Fukushima Daiichi Nuclear Power Plant (FNPP) accident has not caused acute effects on people in general; however, it is difficult to predict whether late effects will appear in the future. The most concerning of these late effects is cancer (Fig. 1.1).

1.2 External and Internal Radiation

The data from Hibakusha relate to an instantaneous external exposure to high-dose-rate radiation, but cannot speak to long-term internal exposure at low-dose-rate (LDR). Thorotrast is an angiographic contrast medium composed of a colloidal solution of thorium dioxide, which is a natural α -particle emitter. It was administered to wounded soldiers during World War II, and more than half of Thorotrast accumulated in the liver. Liver cancers have been evoked by this internal exposure decades after the administration. Thorotrast-induced liver cancers include intrahepatic cholangiocellular carcinoma (arising from epithelial cells of the bile duct), angiosarcoma (from vascular endothelial cells), and hepatocellular carcinoma (from liver parenchymal cells) and occur at a frequency of about 3:2:1, respectively. More than 80% of non-Thorotrast liver cancer is hepatocellular carcinoma, while the rate

of angiosarcoma is negligible. These differences show how Thorotrast-induced liver cancer is crucial to understand the oncogenic mechanisms of persistent LDR internal radiation in humans [3]. Supported by the War Victims' Relief Bureau, former Ministry of Health and Welfare of Japan, approximately 400 Thorotrast patients underwent the postmortem pathological examination. Paraffin-embedded blocks, clinical course, thorium concentration and other information were comprehensively gathered. This systematic archive is valuable for elucidating the molecular mechanisms of human cancers induced by internal radiation exposure, particularly as it is composed of the world's largest number of related cases with the highest quality of radiological and pathological information [4]. The profile of cancer induction is quite different between Hibakusha and Thorotrast patients, indicating that the mechanisms underlying the carcinogenic effect of radiation vary between external and internal exposure and, therefore, have to be analyzed differently [3]. LSS revealed that the likelihood of cancer is different depending on the originating organ [5]. However, pathological characteristics specific to radiation carcinogenesis have not been found. In disasters, such as the aftermath of nuclear weapons and nuclear power plant accidents, released radioactive materials cause both external and internal radiation exposure. Once radioactive materials are ingested, they are not evenly distributed throughout the body, but become enriched in specific organs dependent on their chemical and physical properties, and the target organs are heavily exposed. Even in an organ, the distribution of radionuclides and irradiation at the microscopic level is not homogeneous [6]. In addition, deposited radionuclides form a much more complicated exposure profile than in external exposure, due to physical radioactive decay, biological excretion of radioactive materials [7], and dynamic remodeling of the organ [8].

1.3 The Biological Effect of Radiation

From the classical radiobiological standpoint, it is necessary to clarify the existence of a dose-effect relationship, in order to prove that a certain biological phenomenon (effect) is attributed to radiation. Radiation exerts no effect unless its energy is absorbed in the cell. Therefore, it is impossible to discuss the biological effect of radiation unless specifying both the quality and dose of radiation. A variety of biological effects of radiation are principally explained as being caused by a particular series of events. A cell is injured directly by radiation or indirectly by reactive oxygen species produced by radiation. Among the injured cellular components, DNA double-strand breaks (DSBs) are considered to have the most serious effect on the cell. DSBs undergo the repair process and can be divided into the following three patterns: (1) cell death due to irreparable breaks induced by high intensity/dose radiation, (2) genetic alterations due to incomplete repair, or (3) recovery to a normal cell with intact, unmutated DNA (Fig. 1.2). Cell death results in deterministic acute effects, while genetic alterations result in stochastic effects such as cancer induction and transgenerational (or hereditary) effects. Among stochastic effects,

Fig. 1.2 Traditional but too much simple thinking of cellular effects of radiation

cancer induction is people's major concern and is thought to be a consequence of accumulated genetic mutations and the clonal expansion of a cell toward a cancerous state. Cancer development takes a long period of time and is therefore a late effect of radiation. Here arises a big question: what conditions does radiation work toward either the direction of cell death or cell immortality (carcinogenesis), two extreme events?

There is still much that is unknown about the effects of radiation. Radiation damage to DNA is relatively well studied, but damage to other cell components and epigenetic changes also need to be better understood [9]. Since cells have coping and restoration mechanisms, it is understandable that long-term exposure to LDR radiation is less harmful than acute exposure to high-dose-rate radiation when exposed to the same cumulative dose. However, this may not be true to all situations [10]. The effect of radiation is the result of complex biological reactions including the non-targeting effect [11] and all effects, from cellular changes beginning at exposure to overt changes, must be considered. These concepts indicate that the abovementioned three-way model (Fig. 1.2) is too simple to explain the multifaceted nature of radiation damage. Several problems are to be considered when cancer biology is analyzed (Figs. 1.3 and 1.4).

Both irradiated and bystander cells can be the cell of origin for radiation-induced cancer. There is no clear consensus as to whether internal and external exposures exert the same biological effect if the dose is equal. Even the organ dose of plutonium after the nuclear bombing of Nagasaki Hibakusha was evaluated to be far lower than external exposure; however, the impact to the individual cell nucleus by a single α -particle is not negligible [12]. We should, therefore, remember that there is great uncertainty in dose evaluation itself, especially in internal dose assessment.

- 1. Internal exposure & External exposure
(different dose distribution)
- 2. Leukemia & Solid cancers
(molecular mechanisms of carcinogenesis)
- 3. Cell death & Cancer formation
(Cell immortalization)
(Acute effects & Late effects)
- 4. Cells irradiated & Cell of origin for cancer
(tissue stem cells, bystander effect, adaptive response)
- 5. Dose/dose-rate needed for cancer induction
(dose accumulation / dose evaluation)

Common
Long incubation period

Fig. 1.3 In order to elucidate the mechanisms of radiation carcinogenesis, various conditions should be considered. However, it is common that radiation carcinogenesis takes a long time, no matter what kind of exposure

- 1. Cancer stem cells
- 2. Non-targeted effects (bystander effects, adaptive responses)
- 3. Epigenetic changes (methylation, acetylation, RNA interferences)

Fig. 1.4 Carcinogenic pathway. Molecular changes in radiation carcinogenesis are common among different carcinogens. Molecular changes proved in thorotrast-induced liver tumors are written in red ink. The paradigm shift in radiation biology and cancer biology shows the possibility that a cell not directly irradiated can be a cell of origin of cancer

In addition, we experience problems with the units related to radiation. Radioactivity is measured by how many radioactive decays occur per second, for which the Becquerel (Bq) unit is used. The unit of absorbed dose is gray (Gy, J/kg). Mass communications generally use sievert (Sv) instead of Gy to express radiation dose. Sv takes all the conditions into consideration for evaluating the effect on the human body, including modifiers such as radiation quality, exposure period, the differences between exposed organs, and internal/external exposure. Using conversion factors, physically measured Bq is converted to the biological unit Sv. The totally different concepts of equivalent dose, effective dose, and committed dose for a person's lifetime are also expressed by the same unit, Sv [13]. However, it is ambiguous whether the conversion factors from other units to Sv have the appropriate numerical value. Sv was originally elaborated as a measure of the health effect of low levels of ionizing radiation on the human body but is used for the even deterministic effect which is a discontinuous event from the stochastic effect. Many people, including researchers, misunderstand that Sv exists as a physical unit for measuring absorbed dose since the unit was proposed. Equivalent dose expressed by Sv may be measurable by a monitor but is modified to account for the effectiveness of the type of radiation based on the absorbed dose. It is emphasized again that the final aim of Sv is not for general dose estimation, but for the protection of human health.

1.4 The FNPP Accident and Our Project

Following the Great East Japan Earthquake on March 11, 2011, the FNPP accident released a large amount of radioactive materials into the environment. When farmers within a 20-km radius from FNPP were ordered to evacuate shortly after the beginning of the disaster, livestock were released due to unprecedented confusion and compassion for the animals. After the area was defined as the evacuation zone on April 22, 2011, livestock formed herds and roamed empty streets (Fig. 1.5). There was concern that contaminated meat would come on the market. Therefore, on May 12, 2011, the prime minister ordered Fukushima Prefecture to euthanize livestock within the evacuation zone. I came to the idea that the livestock intended for death should, instead, be used to study radiation protection for humans. Since experiments of this type are impossible, effects of radiation exposure on humans and the ecosystem can be learned only through radiation and nuclear disasters. It is undeniable that studies of radiation biology and protection have progressed by the accumulation of data from major disasters, such as Hibakusha and the Chernobyl NPP (CNPP) accident. We should not, of course, cause nuclear accidents, but we need to learn as much as possible from the FNPP accident. In other words, in the face of the unprecedented pollution over such a wide area, investigating the various impacts of the FNPP accident and conveying these analytical and strategic findings to posterity is a responsibility that has been imposed on the scientific community in Japan. Therefore, we launched “A com-

Fig. 1.5 The ex-evacuation zone set on April 22, 2011. (a) Gate set at Kawauchi Village (September 28, 2011); livestock formed herds and roamed empty streets. (b) Cattle became wild in front of a house damaged by the tsunami (Tomioka Town January 25, 2012), (c) wild boars (Tomioka Town, February 28, 2012), (d) unleashed pigs (Tomioka Town, January 25, 2012). (The photos are provided by courtesy of Prof. H. Yamashiro)

prehensive dose evaluation project concerning animals affected by the Fukushima Daiichi Nuclear Power Plant accident” [14]. Following tough negotiations with administrative agencies, nearly half a year after the accident, we were finally allowed to enter the evacuation zone and perform sampling on August 29, 2011. The sampling of livestock continued until the end of March 2013, at which time all the livestock in the zone were euthanized. After that, we have concentrated on research using archives and have shifted to the sampling of wild Japanese macaques [15].

1.5 Results of the Project to Date

Several achievements from the project have already been published and are briefly described below.

1. In all of the organs of any of affected animals, the deposition of radioactive cesium (Cs) was observed and was found to be the highest in skeletal muscle. A

linear correlation between the radioactive Cs concentration in the peripheral blood and in each organ was also determined. The levels of radioactive Cs in the organs of fetuses and infants were higher than in the corresponding maternal organs. The organ-specific deposition of radionuclides with relatively short half-lives was detected, including silver-110 m (half-life: 249.8 days) in the liver and tellurium-129 m (33.6 days) in the kidneys [16].

2. Plasma levels of malondialdehyde and superoxide dismutase activity in affected cattle were positively correlated, and glutathione peroxidase activity was inversely correlated with the internal dose rate of radioactive Cs, suggesting that chronic exposure to LDR radiation induces mild oxidative stress in the affected cattle [17].
3. DNA double-strand breaks in peripheral blood lymphocytes of affected cattle were determined by immunocytochemical staining for γ -H2AX. While the extent of DNA damage appeared to be independent of the distance from FNPP and the estimated radiation dose from radioactive Cs, we observed age-dependent accumulation of DNA damage. The levels of DNA damage decreased slightly over the 472-day sample collection period. When analyzing long-term exposure effects of LDR radiation, it is necessary to consider the effect of adaptive response and aging of individuals [18].
4. Testis and bone marrow are highly radiosensitive. However, no morphological changes were detected in the testis of cattle, boar, or inobuta (wild boar and domestic pig hybrid) stayed in the ex-evacuation zone for about 1 year after the accident [19, 20]. Spermatogenesis in large Japanese field mice was found to be enhanced [21], and internal dose-rate-dependent myelosuppression was present in the bone marrow of adult wild macaques without obvious health effects [15]. It remains to be elucidated whether these phenomena, attributed to chronic exposure to LDR radiation, will benefit or adversely affect animals.
5. The expression of genes related to immunity was altered in the small intestine of affected swine and inobuta. Chronic LDR radiation may evoke a persistent slight inflammatory status [22].
6. Strontium-90 (^{90}Sr) was detected in the teeth and bones of affected cattle and could provide useful information about internal exposure. The fluctuation in the teeth is suggested to reflect the contamination levels of environmental ^{90}Sr [23].
7. Using 2-D differential gel electrophoresis and time-of-flight (TOF) mass spectrometry, a proteome analysis of rice leaves revealed that the majority of the differentially expressed proteins after low-level gamma radiation were within the general (non-energy) metabolism and stress response categories [24].

As a result of this project, the biological impact of the FNPP accident on animals has been shown to be subtle; the change was most strongly correlated with internal dose-rate among the four combinations of indicators, external/internal and dose/dose-rate. Overall, obvious adverse effects have, so far, been undetectable, which is thought to be due to the adaptability of animals. However, it remains to be elucidated whether long-term exposure to LDR radiation will impair the

ability of animals to compensate in the future. Every summer since 2013, we have held a meeting, gathering researchers from all over Japan to seriously study problems in relation to the FNPP accident. The meeting is open to the public, as well, and we present up-to-date results, host frank scientific discussion about the problem, and share information [25].

1.6 Current Issues and Future Prospects

Radiation causes a significant increase in the incidence of thyroid cancer [26]. Increased incidence of thyroid carcinoma due to iodine-131 (^{131}I , half-life: 8.02 days) from the CNPP accident, which scattered about ten times as much radioactive materials as the FNPP accident, was not noticed until about 5 years after the accident [27]. If the occurrence frequency of the radiation effect is dependent on the total dose, even 50-year follow-up observation is necessary for the FNPP accident. From our dose evaluation, the initial exposure by short half-life radionuclides such as ^{131}I was not negligible (data not shown). The ratio of ^{131}I concentration to ^{129}I (half-life: 1.57×10^7 years) concentration released by the FNPP accident is known. Using accelerator mass spectrometry, ^{129}I is measurable, and a retrospective reconstruction of ^{131}I levels from the levels of accident-derived ^{129}I was successful [28]. We also believe that the dose attributed to ^{131}I can be evaluated from ^{129}I concentration in the thyroid gland. The lens is relatively radio-sensitive, and radiogenic cataracts have been documented as a major ocular complication, one of the deterministic but late effects. Their threshold dose and the incubation period are now of major concern in relation to the radiation effect [29]. Careful observation must be maintained, in order not to overlook even small changes in animals. If any ecological change is found, it will be a warning to consider the potential impact on humans. Various changes in the ecosystem after the FNPP accident have been reported. However, it is often unknown whether they are really due to radiation, since these changes have not necessarily been reported in association with dose or dose rate. As mentioned elsewhere, efforts are needed to create links between laboratory-controlled experiments and in situ field analysis in cooperation with radiation biologists and ecologists for the establishment of trusted radioecology data [30].

Currently, we are focusing on sampling materials from wild Japanese macaques as the main subject of our analysis. As seen in macaques inhabiting the area affected by the FNPP accident, wildlife contamination by radioactive Cs is continuing even now, 8 years after the accident (Fig. 1.6), which demonstrates that animals are still subject to the so-called high-dose-rate environment. To understand the human response to long-term exposure to very LDR radiation, Japanese macaques are the most suitable wild animal, since they do not recognize or fear radiation and do not

Fig. 1.6 Wild Japanese macaques (monkeys) are the most suitable to know radiation effects on humans. **(a)** Cumulative numbers of animals sampled in this project (as of October 25, 2018). **(b)** Wildlife contamination by radioactive cesium is continuing even now without signs of falling down in the affected area

smoke or drink, which is the most confounding factor in analyzing the effects of low-dose (LD) radiation on humans. The life span of Japanese macaques is approximately 20 years, and many individuals born after the FNPP accident have been observed. Therefore, they provide extremely crucial data for understanding the effect of chronic, very LDR radiation on humans including transgenerational effects and should be vigilantly monitored over time. We started evaluating the cumulative dose of individual macaques by electron spin resonance (ESR) analysis of their teeth. Despite the fact that macaques are the closest species to humans, they are not among the reference animals chosen by ICRP [31], because the areas where nuclear disasters have occurred in the past have not been inhabited by macaques. Therefore, the administrative agencies of Japan judge that the results obtained in wild Japanese macaques cannot be compared with other related study results, which disappointingly means that they officially hold no significance as the subject of comparative analysis.

At the time they were taken, it was unknown whether the archived pathological specimens of Thorotrast patients would be useful for the future. However, great strides in technology have allowed us to perform genetic analysis using old paraffin-embedded blocks. With PCR, we performed genetic analysis on the archived paraffin blocks of Thorotrast-induced liver tumors decades after autopsy. We showed that gene mutations are not caused by the direct action of radiation, but as a result of the biological reaction to radiation [3]. As mentioned above, we are currently achieving successful results with the archived samples of affected animals. Maintaining the archive in a form that any researcher can use makes it pos-

sible to detect small effects attributed to long-term exposure to LDR radiation that are not currently known. For example, results acquired by comprehensive gene analysis using next-generation DNA sequencing or epigenetic analysis will extend the knowledge of how radiation influences human health and is scientifically necessary for further radioprotection efforts. The biological impact of radiation is influenced by various factors such as dose, dose-rate, and quality of radiation and species, age and gender (if any), and so on of organisms. Therefore it is difficult to scientifically describe the influence of LD/LDR radiation. In the future, new knowledge will be enhanced by analyzing research data accumulated with deep learning of artificial intelligence. For those purposes, accumulation of detailed data as accurate as possible is desired.

Our project after the FNPP accident has two key trajectories concerning the effect of LDR radiation. One is the fear of what will ultimately happen to the natural environment due to the FNPP accident. The other is the need for field studies to clarify the influence of long-term LDR radiation on the natural environment, which is now in progress. Regardless of which goal we adopt, it is clear that we need to think about the protection of the environment and humans after radiological accidents [32].

Acknowledgments I sincerely appreciate all the people and researchers who have been involved in the project. This project became executable with the support of the Emergency Budget for the Reconstruction of Northeastern Japan, MEXT, Japan, Grants-in-Aids for scientific research from JSPS (Kakenhi 26253022, 15H01850) Discretionary Expense of the President of Tohoku University, and the Program for the Promotion of Basic and Applied Research for Innovations in Bio-oriented Industry.

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