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Review

Application of Lymphocyte Chromosome Aberrations for Biodosimetry of Low-Dose-Rate Chronic Irradiation

Kimio Tanaka[1, 2]*, Kenichi Satoh[2] and Atushi Kohda[1]

[1]*Institute for Environmental Sciences, 2-121 Hachazawa, Takahoko, Rokkasho, Kamikita, Aomori 039-3213, Japan.*
[2]*Research Institute for Radiation Biology and Medicine, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan.*

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Dose response and dose-rate effects in the low-dose-rate (LDR) range have not been evaluated with respect to chromosome aberrations. The incidences of chromosome aberrations were analyzed in splenic lymphocytes from mice that were continuously exposed to γ-ray at the LDR for evaluation of the dose response and dose-rate effects. The frequency of dicentric chromosomes and translocations detected by fluorescence *in situ* hybridization (FISH) increased almost linearly up to 8,000 mGy at 0.91 mGy/h and to 700 mGy at 0.045 mGy/h. In no-exposed mice, translocations increased in a linear quadratic manner with age. After adjustment for age, value of linear coefficient of the dose-response relationship for the frequency of translocations at each dose rate decreased as the dose rate was reduced, suggesting a dose-rate effects in the LDR range. These results will be useful for establishment of a biodosimetry method for individuals who are occupationally or accidentally exposed to chronic LDR radiation. On the basis on the present findings, retrospective dosimetry was performed for two populations of subjects who had been exposed to radioactive fallout from nuclear explosion tests. The merit and drawbacks of using dicentric chromosomes or translocations as indices in chronic exposure at the LDR are discussed.

Key words: biodosimetry, chromosome aberrations, low-dose-rate, nuclear explosion test, ageing

1. Introduction

For individuals who are exposed accidentally to ionizing radiation, it is essential to estimate the dose that has been received. To complement physical dosimetry, methods for determining the biological dose of radiation are necessary for more accurate evaluation of biological effects in any given individual. Chromosome aberrations in lymphocytes can be a sensitive and convenient indicator of the biological dosimetry. Two major classes of chromosome aberrations are induced by ionizing radiation in cells at the G_0 and G_1 stage phases: i) unstable-type chromosome aberrations, which include dicentric chromosomes, centric ring chromosomes and acentric fragments, and ii) stable-type chromosome aberrations such as translocations and inversions (Fig. 1). Exchanged–type chromosome aberrations such as dicentric chromosome or translocation require DNA double strand breaks in two un-replicated chromosomes and mis-repaire of the DNA breaks. Dicentric chromosomes in lymphocytes are commonly used to estimate an individual's exposure dose after a radiation accident. The current approach to biological dosimetry assumes that exposure to irradiation is homogeneous and that irradiated lymphocytes are distributed uniformly throughout the body. The dose-

*Kimio Tanaka: Institute for Environmental Sciences, 2-121 Hachazawa, Takahoko, Rokkasho, Kamikita, Aomori 039-3213, Japan
E-mail: ksk275-tanaka@amy.hi-ho.ne.jp

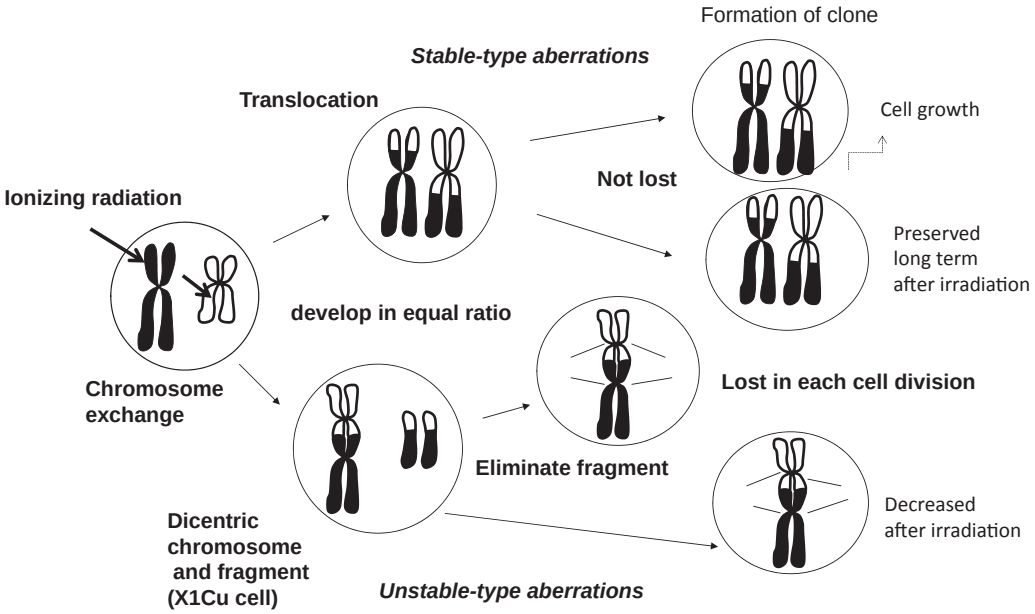

Fig. 1. Scheme of ionizing radiation-induced chromosome aberrations in cells. Two types of chromosome aberrations (unstable-type aberrations such as dicentric chromosome and stable-type aberrations such as translocation) are induced.

response curve for low-LET (linear energy transfer) γ- or X-radiation resulting from acute, high-dose-rate (HDR) exposure is expressed in $Y = c + \alpha D + \beta D^2$, where Y is the yield of dicentric chromosomes, D is the dose, c is the background value of dicentric chromosome aberrations, α is the linear coefficient and β is the dose-squared coefficient. For chronic exposure to low-LET radiation in the medium–dose-rate (MDR) or LDR range, the yield of dicentric chromosomes is decreased, and can be expressed by the simple equation: $Y = c + \alpha D$.

In the field of human health, there is increasing concern about the biological effects of exposure to low-dose LDR radiation. Chronically exposed individuals such as workers at nuclear facilities, medical radiologists, and residents in regions with high nuclear contamination are shown to have a slightly higher frequency of dicentric chromosomes or translocations[1-4], but individual biodosimetry has not been performed. There is a lack of information on biodosimetry for chronic exposure, such as the chronological effects of dose response and dose-rate on the frequency of translocations and dicentric chromosomes, in individuals who are continuously exposed to LDR radiation. Accordingly, the aim of the present study was to evaluate the suitability of the chromosome method for monitoring of chronic exposure to ionizing radiation in the LDR range while adjusting the yield of chromosome aberrations with reference to age. No previous reports have addressed dose-rate effects within the LDR range, using the approach employed in the present study.

2. New information on dose and dose rate dependency in chronic exposure and age adjustment

In the context of chronic exposure, dose and dose-rate responses have not been well investigated in terms of chromosome aberrations because data from human population are confounded such as smoking. For this reason, animal studies have been used to investigate this issue. To assess chronic LDR radiation exposure, we evaluated the frequencies of dicentric chromosomes and translocations in splenic lymphocytes from mice under experimentally regulated conditions. The Institute for Environmental Sciences has been investigating the biological effects of LDR-γ-irradiation using unique irradiation facilities, which make it possible to continuously irradiate mice at 20 times different 3LDR levels [20 mGy/22h/day (0.91 mGy/h; abbreviated as 20 mGy/day), 1 mGy/22h/day (0.045 mGy/h; abbreviated as 1 mGy/day) and 0.05 mGy/22h/day (2.25×10^{-3} mGy/h; abbreviated as 0.05 mGy/day), which are approximately 8,000, 400 and 20 times higher than background external γ-radiation, respectively] of ^{137}Cs-γ-radiation under specific pathogen-free conditions while the mice are being reared. Mice were chronically irradiated with LDR γ-rays from the age of 8 weeks (56 days after birth) for up to 400, 700 and 700 days, respectively. Mice were exposed for 22h each day. The dose-rate of 0.05 mGy/day corresponds to that of the annual mean limiting dose for radiation facility workers and also the mean daily air dose measured in the government-designated evacuation zone in Fukushima Prefecture that was set up after the Fukushima Dai-ichi

Table 1a. Estimated correlation coefficients in weighted multiple regression analysis for dicentric chromosomes

Irradiated groups	Regression coefficient	Estimated	S.E.	p-value
Control	θ_{01}	0.152	0.0228	*0.000
	θ_{02}	0.132	8.0×10^{-3}	0.103
1 mGy/day	θ_1	2.76×10^{-4}	1.07×10^{-4}	*0.011
20 mGy/day	θ_2	6.15×10^{-4}	5.07×10^{-5}	*0.000

*significant These two correlation coefficient values (θ_1 and θ_2) were significant at 0- 8,000 mGy dose range.

Table 1b. Estimated correlation coefficients in weighted multiple regression analysis for translocations

Irradiated groups	Regression coefficient	Estimated	S.E.	p-value
Control	θ_{01}	0.3165	0.0898	*0.000
	θ_{02}	2×10^{-6}	4×10^{-7}	*0.000
0.05 mGy/day	θ_1	-0.0055	0.0062	0.378
1 mGy/day	θ_2	0.0007	0.0003	*0.011
20 mGy/day	θ_3	0.0019	0.00004	*0.000

*significant These two correlation coefficient values (θ_2 and θ_3) were significant at 0- 8,000 mGy dose range.

nuclear power plant accident. Non-irradiated control mice were kept for the same period as the irradiated mice. In accordance with the 2010 UNSCEAR report[5], LDR and MDR are defined as 0.1 mGy/min (132 mGy/22h/day) or less and 0.1 to 99 mGy/min, respectively.

For observations of dicentric chromosomes, 3 to 11 mice were grouped for irradiation at each total dose of 20 mGy/day and 1 mGy/day and also for non-exposure at the same age (controls). For observations of translocations, 3 to 5 mice were grouped for irradiation at each total dose of 20 mGy/day, 1 mGy/day and 0.05 mGy/day, and also for non-exposure at the same age (controls). The mice were sacrificed, and their spleens were removed under sterile conditions. For chromosome analysis, spleen cells were isolated and cultured. Metaphases for dicentric chromosomes and translocations were analyzed by centromere FISH and multicolor-FISH (M-FISH), respectively. Each clonal metaphase showing translocation (Fig.1) was scored as one cell in the present biodosimetry analysis to obtain the dose and dose-rate response in terms of chromosome aberration yield.

On the whole, it is well known that the frequency of translocations in healthy individuals increases highly significantly in a curvilinear manner with age[6-8]. Most of these age-related translocations occur upon chronic exposure in the LDR range. For this reason there is inherent difficulty in performing chromosome studies on individuals who have been accidental or occupationally exposed to low-dose or LDR radiation at levels of as low as the natural background. Therefore, it is extremely important to clarify how age-related translocation should be adjusting for when measuring the total dose during chronic exposure to LDR ionizing radiation.

The dose-response relationships for the frequencies of dicentric chromosomes and translocations were obtained for each of the dose rates using age-adjusted multiple linear regression analysis on the assumption that the relationship between age and these chromosome aberration frequencies could be represented by a linear model or a quadratic model.

Therefore, for dicentric chromosomes, the time trend curves of each of the groups can be expressed as βj, j= 0, 1 and 2, as follows: control group : $\beta 0(t) = \theta_{01} + \theta_{02} t$

1 mGy/day group: $\beta 1(t) = \beta 0(t) + \theta_1 D1(t)$

20 mGy/day group: $\beta 2(t) = \beta 0(t) + \theta_2 D2(t)$

For translocations, the time trend curves for each of the groups can be expressed as βj, j= 0, 1, 2 and 3, as follows: control group : $\beta 0(t) = \theta_{01} + \theta_{02} t^2$

0.05 mGy/day group: $\beta 1(t) = \beta 0(t) + \theta_1 D1(t)$

1 mGy/day group: $\beta 2(t) = \beta 0(t) + \theta_2 D2(t)$

20 mGy/day group: $\beta 3(t) = \beta 0(t) + \theta_3 D3(t)$

The equations obtained and the parameters for the regression fits were obtained by multiple regression analysis. We estimated the unknown correlation coefficient values (θ_{01} and θ_{02} ; θ_1 and θ_2 for dicentric chromosomes; θ_1, θ_2 and θ_3 for translocations) using the weighted least squares estimator with respect to the number of observed cells using SPSS software.

2.1. Age-response relationships of dicentric chromosome and translocation frequencies

In the non-irradiated group, translocation frequencies increased with age in a linear quadratic manner, as expressed by $Y = 0.317 + 2 \times 10^{-6} t^2$, where Y is the number of translocations per 100 cells and t is age -56. Correlation coefficient value of θ_{02} in the non-irradiated group were shown to be statistically significant (significant θ_{02} in Table 1b). In contrast, the frequencies of dicentric

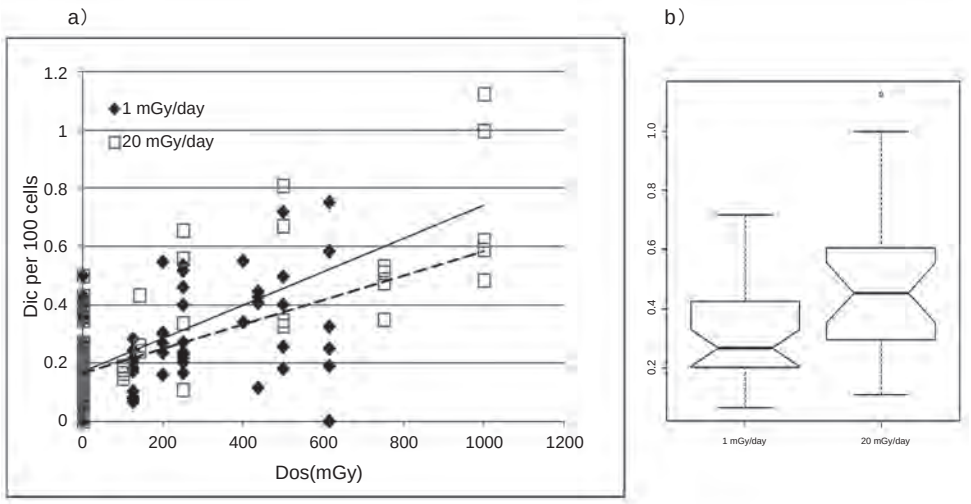

Fig. 2. a) Frequencies of dicentric chromosomes per 100 lymphocytes from mice in the LDR groups (20 mGy/day: □ , solid line; lmGy/day: ◇ , broken line) exposed to radiation. Dose responses within the 0- 1,000 mGy region are shown. Each symbol indicates the value for an individual mouse. The X axis represents the total dose (mGy) and the Y axis the Dic rate (number of Dic per 100 metaphases). Dic: dicentric chromosome.
b) Box plot shows a significant difference in the frequency of dicentric chromosome (Dic) between the two groups exposed to LDR of 20 mGy/day and 1 mGy/day within the 0-1,000 mGy region.

chromosomes in non-exposed age-matched mice showed no correlation with increasing age[9] (not significant θ_{02} in Table 1a).

2.2. Dose-response relationships of dicentric chromosome and translocation frequencies

Our mouse study using age adjustment revealed that dicentric chromosomes detected by the centromere FISH method increased almost linearly as the total accumulated doses increased up to 8,000 mGy at a LDR of 20 mGy/day[9, 10] (singnificant θ_1 and θ_2 in Table 1a, Fig. 2a). The results for 1 mGy/day also fitted the linear regression model (Fig. 2a), indicating that the frequency of dicentric chromosomes increased with dose. Similarly, the frequency of translocations increased almost linearly up to 8,000 mGy at 20 mGy/day and 700 mGy at 1 mGy/day (significant θ_3 and θ_2 in Table 1b, Fig. 3)[11]. On the other hand, the correlation coefficient value (θ_1) for LDR irradiation at 0.05 mGy/day was not statistically significant (p value as the linear portion of the slop θ_1 in Table 1b) because of wide variability in the values, indicating that translocations observed during exposure to a dose rate of 0.05 mGy/day did not increase linearly with dose.

2.3. Dose-rate effects on frequencies of dicentric chromosome and translocation

The values of the correlation coefficient in the equations for dicentric chromosomes at 20 mGy/day and 1 mGy/day at doses of less than 8,000 mGy (θ_1 and θ_2 in Table 1a) were significant. We also tested for differences between the 20 mGy/day and 1 mGy/day groups, and between the 1 mGy/day and non-irradiated groups (see box plots in Fig. 2b), and these revealed significant inter-group differences, respectively. This indicated a reduced frequency of dicentric chromosomes in this dose-rate region from 20 mGy/day (0.91 mGy/h) to 1 mGy/day (0.045 mGy/h), and 1 mGy/day to the background level[12].

For translocations, the values of correlation coefficient for the linear portion of the slope (θ_2 and θ_3 in Table 1b) decreased significantly with reduction of the dose rate from 20 mGy/day to 1 mGy/day (Fig. 3). To clarify whether the dose-response relationship for translocations differed significantly between the LDRs of 20 mGy/day and 1 mGy/day, or whether the linear dose-response relationship at 1 mGy/day differed significantly from the spontaneous background level, the equations and parameters for the multiple linear regression fits were obtained[11]. The two correlation coefficients (θ_2 and θ_3 in Table 1b) were statistically significant (Fig. 3). On the other hand, the value of correlation coefficient value (θ_1) for LDR irradiation at 0.05 m Gy/day was not statistically significant (p value as a linear coefficient θ_1 in Table 1b), because the results for 0.05 mGy/day did not fit either the linear regression or the linear quadratic regression model. These results indicated that there were dose-rate effects on the frequencies of dicentric chromosomes and translocations within the dose rate range from less than 20 mGy/day to the background level, although there is uncertainty about the yield of chromosome aberrations in the lowest dose rate (0.05 mGy/day).

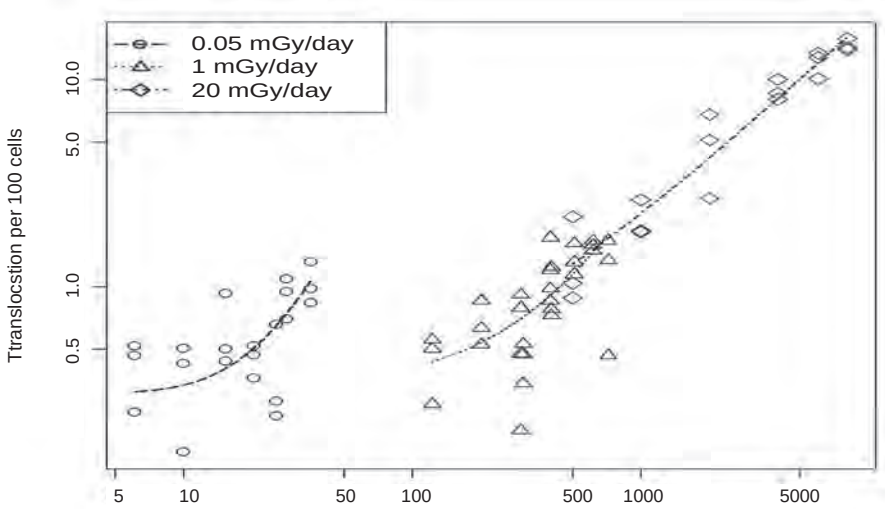

Fig. 3. Number of translocations per 100 lymphocytes from mice in the 20 mGy/day (◇, broken line), 1 mGy/day (△, dotted line) and 0.05 mGy/day (○, dashed line) groups exposed to radiation within the dose range of 8,000 mGy are shown on both logarithmic scale. Each symbol indicates the value for an individual mouse. The X axis represents the total dose (mGy) and the Y axis the translocation rate (number of translocations per 100 cells).

3. Practical difficulties with actual application

These results for age-, dose- and dose rate-dependent increases in chromosome aberrations will be of importance for establishing a suitable biodosimetry method using the frequency of dicentric chromosomes or translocations as an indicator of occupational or accidental exposure to chronic LDR radiation. We therefore performed tentative retrospective dosimetry of subjects in two populations that have been exposed to fallout from a nuclear explosion test.

3.1. Residents in radio-contaminated villages near the Semipalatinsk nuclear explosion test sites (SNETS)

In order to assess the biological effects, frequencies of chromosome aberrations in peripheral blood lymphocytes were determined by conventional Giemsa staining method in 116 residents (age ranges 45 to 73 years) living in 3 villages (such as Dolon) and 46 residents in a non-contaminated village[13-15]. Samples of 10 or 20 ml whole blood drawn from these subjects were transferred to Japan under cool storage. The blood transportation method has been modified to make it more suitable for chromosome analysis[16]. Metaphases with multiple complex chromosome aberrations were excluded from the scores for dicentric and ring chromosomes, because these are considered not to be radiation-induced[17]. The frequencies of chromosome aberrations detected in residents of Dolon (2.55×10^{-3} for dicentric and ring chromosomes; 1.74×10^{-3} for dicentric chromosomes) in the present study were used for calculation of external dose using chromosome aberration rate and dose response curves for *in vitro* chronic ^{137}Cs γ- ray irradiation with lymphocytes at a MDR of 0.2 mGy/min[18], where 8.5×10^{-4} was used as the constant (*c*) background value[19]. We estimated external doses in a residents of Dolon as 37.4 and 33.8 mGy of γ-ray equivalent, which were less than those estimated previously (around 140-440 mGy) using physical methods such as luminescence dosimetry of old bricks, measurement of soil contamination and electron spin resonance (ESR) [20, 21].

3.2. Fishermen exposed to fallout radiation from the Bikini nuclear explosion experiment

Other than the crew of the *5th Fukuryu-maru*[22, 23], no reports have documented any health examination data or details of the estimated doses to which the various crews were exposed.

We investigated both stable- and unstable-type chromosome aberrations in 19 crew members of fishing boats and a cargo ship (age ranges 76 to 90 years) and compared them with those of 9 age-matched controls. G-banding analysis was considered to be the most suitable method for the present study, as the subjects had been exposed to low-dose radiation 60 years previously, and therefore many metaphases had to be evaluated for biological effects. Both stable- and unstable-type aberrations were examined for estimation of the exposure dose. The G-banding method, rather than the FISH method, were used for scoring both types of abnormalities of dicentrric chromosomes and translocations to observe as high a number of metaphases as possible. The frequencies in nine seamen showing a significantly higher percentage of stable-type aberrations than the normal range were used to evaluate each individual's exposure dose (equivalent dose of atomic

Table 2. Merits and demerits in usage of dicentric chromosomes and translocations as an index of chronic exposure at LDR in humans.

	Dicentric chromosomes (by Giemsa staining, Centromere FISH, Qdr method)	Translocations (by G-banding, subset FISH[a], M-FISH)
Analyzed cells	· Many metaphases required · Easy scoring · Automatic scanning required	· No need for many metaphases · Time-consuming analysis · High cost · Automated karyotype analysis needed
Detection limit dose	Slightly or moderately sensitive Around 100 mGy or less	· Medium, although 4-fold higher incidence than dicentrics · Around 100 - 500 mGy
Age effects	· No increase	· Strong curvilinear aging effects · Age adjustment needed
Applicable for LDR range[b] (20 -1 mGy/day = 0.045 mGy/h)	· Possibly applicable for LDR up to 1 mGy/day (difficult at LDR of 0.05 mGy/day) · Need to adjust reduction rate after exposure in future · Qdr method is applicable · No suitable calculation curve at LDR	· Applicable up to LDR of 1 mGy/day (difficult at a LDR of 0.05 mGy/day) · No suitable calculation curve at LDR

[a] Subset FISH : FISH method using two or more whole-chromosome probes with single or dual colors[43]. [b] A reference show limit dose rate (0.44 - 0.84 mGy/day)[41].

bomb radiation) using a standard calibration curve, which we had obtained for healthy Hiroshima atomic bomb survivors using the G-banding method[24]. Most stable-type chromosome aberrations in the 80-90-year age range are considered to be aging-related, because stable-type chromosome aberrations such as translocations increase rapidly with age, specifically from 50 to 80-year[6-8]. Then, the frequency of aging-related chromosome aberration (1.67%) was subtracted from the percentage of stable-type chromosome aberrations in exposed individuals. Thus, the three highest exposure doses (equivalent to atomic bomb radiation) were estimated to be 298 mSv, 179 mSv and 165 mSv, respectively[25].

For dicnetric chromosomes, the Qdr method[26-28] was applied. Similarly, the mean exposure dose obtained by the Qdr method was about 81 mGy (95% confidence interval; 24 mGy - 431 mGy) using X1Cu cells[29] (Fig.1) harboring dicentric or ring chromosomes with fragments, and acentric rings from the data pooled from the all 19 exposed individuals, because of the small number of X1Cu cells. Previously, the exposure doses received by the crews of the *5th Fukuryu-maru* had been estimated to be 1.7-6.6 Gy using the Qdr method 15 and 20 years after exposure[23], indicating that the mean exposure dose of the 19 seamen in the present study was about 20 -80 times lower than that[25]. Three of the 19 subjects were also analyzed preliminary by ESR, whose estimated exposure doses were found to be higher, at around 170-300 mGy than those determined by chromosome analysis (personal communication with Dr. S. Toyoda). Tooth dose estimated by the ESR in atomic bomb survivors was higher than the dose measured using translocations in the lower dose range[30].

4. Current status and future perspectives

Both dicentrics and translocations in peripheral blood lymphocytes can apply for biodosimetry of chronic exposure in the LDR range. The merit and demerit using dicentric chromosomes or translocations as an index of the chronic exposure at LDR are summarized in Table 2. A standard calibration curve for obtaining dose (equivalent dose of acute exposure) has been commonly used using *in vitro* HDR γ-ray irradiation of peripheral blood obtained from healthy adults. However, the estimated exposure dose obtained is lower than expected. This is because no suitable standard dose-response calibration curve in the LDR range is currently available. In the future, a standard calibration curve for biodosimetry of chronic exposure at each dose rate in the LDR range will be necessary. Continuous long-term exposure and fractionated exposure at LDR may yield different frequency of chromosome aberrations. Also, the validity of using dicentric chromosomes or translocations for evaluation of the biological dose resulting from chronic low-dose internal exposure needs to be confirmed.

Scoring of translocations using the FISH technique with chromosome-painting probes will be applicable for measurement of doses resulting from chronic radiation exposure because, for LDR exposure, the translocation yield remains relatively constant with time, unlike the situation for dicentric chromosomes, whose occurrence gradually decreases (Fig.1). The suitability of translocation revealed by the FISH method for biodosimetry of low-dose or LDR radiation has been discussed extensively[31, 32]. Translocations appear in a ratio almost equal to that of dicentric chromosomes soon after irradiation[33] (Fig.1), and the present study suggested a

possibility that translocations increase along with the total accumulated dose of LDR irradiation. Then, the incidence of translocations is approximately 4 times higher than that of dicentric chromosomes in the chronic irradiation[11]. Accordingly, translocations would provide a more suitable index, especially for younger individuals, than dicentric chromosomes for biodosimetry of chronic exposure at LDR. However, age adjustment is necessary when using translocations for biodosimetry of aged individuals, as the presence of high frequencies of age-dependent translocation will always be problematic[6-8]. Translocation frequencies in healthy Japanese are required for estimation of exposure dose with age adjustment.

On the other hand, because dicentric chromosomes are eliminated at each cell division after irradiation due to their unique morphology of two centromeres on one chromosome (Fig.1), dicentric chromosomes would appear to have less biological significance than translocations. However, the frequency of dicentric chromosomes showed a linear increase along with dose in mice subjected to long-term LDR irradiations [20 mGy/day (0.91 mGy/h) and 1 mGy/day (0.045 mGy/h)] [9, 10, 12]. Chromosome analysis of residents in an area of high background radiation in China yielded a similar result[34]. In our separate experiment, chronological decreases in the frequencies of translocations and dicentric chromosomes were examined further in mice kept for 300 days after completion of chronic LDR (20 mGy/day) irradiation at 4,000 mGy, and it was found that the frequencies of dicentric chromosomes decreased slowly for up to 300 days after irradiation. The rate of decrease in the frequency of dicentric chromosomes in mice exposed to radiation at this dose rate was much slower than that observed in mice exposed to an acute high dose[35] (unpublished result). This may be attributable to the life span of lymphocytes as well as the number of immature lymphocytes recruited from the bone marrow or thymus to the spleen. This also suggests that it might be possible to estimate the total cumulated dose in accidentally or occupationally exposed individuals by determining the rate of decrease in the frequency of dicentric chromosomes after exposure, although adjustment of the reduction rate after completion of irradiation would be necessary. This might also explain why individuals chronically exposed to LDR radiation, such as nuclear facility workers, radio-medical technologists and residents at SNETS have higher incidences of dicentric chromosome than non-exposed individuals[1-3, 13, 34]. Under chronic irradiation, the incidence of dicentric chromosomes was lower than that of translocations[11]. It has also been reported that X1Cu cells[29], which have dicentric or centric ring chromosomes along with fragments in the same metaphase (Fig.1), represent cells that have not undergone division following radiation exposure and have retained these chromosome anomalies over a long period[26, 27, 29]. Thus, the Qdr method[27, 28] is more applicable to chronic exposure at LDR, although X1Cu metaphases with dicentric or ring chromosome plus fragments must be obtained in quite low incidence and it is uncertain whether the incidence of acentric ring chromosomes would show a Poisson distribution[27].

For accurate biodosimetry of chronic exposure at LDR, it will be necessary to estimate the lowest dose and dose-rate limit detectable by different methods using lymphocyte chromosomes. Sensitivity in the low-dose range varies among the methods of chromosome analysis, dose rates employed and age of examined individuals. The G-banding method is 1.2 times more sensitive for detection of translocations than FISH using two pairs of painted chromosomes[36, 37], although cytogeneticists require a high level of quality for detection of chromosome aberrations. The dose response for 30 mGy of estimated in terms of dicentric chromosomes of HDR-irradiated lymphocytes *in vitro* was a significantly higher and above that for the back ground[38]. Confounding factors such as smoking, exposure to medical procedures, alcohol intake and life style would influenced the frequencies of chromosome aberrations when evaluate the health effects of low-dose or LDR radiation. A higher minimum dose was observed under *in vivo* condition. There was a significant tendency for the incidence of dicentric chromosome to be higher among individuals with occupational exposure to radiation with an estimated individual whole-body dose of less than 100 mGy or around 100 mGy[39]. On the other hand, the low-dose limits determined using translocations were within the range 107-384 mSv assuming that all translocations had been induced by background radiation[40]. The minimum dose and dose rate detectable by FISH for chronic exposure increases linearly with age, being 160-305 mGy per year (0.44-0.84 mGy/day) [41]. Retrospective dosimetry using translocations in 10 subjects 10 years after exposure in Goiânia accident, indicated that this method is feasible for low level below 500 mGy[42]. Although there is some uncertainty about the accuracy of the estimated dose in the chronic exposure of low dose range of less than 100 mGy, exposure doses equivalent to acute radiation in each individual can be estimated at 100 mGy or more using the frequencies of translocations, dicentric chromosomes and X1Cu cells. M-FISH, which uses painted whole chromosomes, will be a more powerful tool for detection of lower doses than the currently used subset FISH method[43] using only two or three painted chromosome probes. So far, the application of these biodosimetry methods to chronic LDR exposure has much difficulty, too. There are still several technical limitations to rapid and accurate estimation of chronic exposure at LDR, and the various methods of dosimetry are constantly being

debated[27]. Thus, there is a need to employ biological dosimetry combination with physical dosimetry.

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Conflict of interest disclosure

The authors have no conflicts of interest directly relevant to the content of this study.

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