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REVIEW

Strong association between cancer and genomic instability

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Abstract After a first wave of radiation-induced chromosomal aberrations, a second wave appears 20–30 cell generations after radiation exposure and persists thereafter. This late effect is usually termed "genomic instability". A better term is "increased genomic instability". This effect has been observed in many cell systems in vitro and in vivo for quite a number of biological endpoints. The radiation-induced increase in genomic instability is apparently a general phenomenon. In the development of cancer, several mutations are involved. With increasing genomic instability, the probability for further mutations is enhanced. Several studies show that genomic instability is increased not only in the cancer cells but also in "normal" cells of cancer patients e.g. peripheral lymphocytes. This has for example been shown in uranium miners with bronchial carcinomas, but also in untreated head and neck cancer patients. The association between cancer and genomic instability is also found in individuals with a genetic predisposition for increased radiosensitivity. Several such syndromes have been found. In all cases, an increased genomic instability, cancer proneness and increased radiosensitivity coincide. In these syndromes, deficiencies in certain DNA-repair pathways occur as well as deregulations of the cell cycle. Especially, mutations are seen in genes encoding proteins, which are involved in the G_1/S-phase checkpoint. Genomic instability apparently promotes cancer development. In this context, it is interesting that hypoxia, increased genomic instability and cancer are also associated. All these processes are energy dependent. Some strong evidence exists that the structure and length of telomeres is connected to the development of genomic instability.

Introduction

For the evaluation of radiological risks in the low dose region (<100 mSv), cancer is the most important health effect. Many studies have shown a statistically significant increase in radiation-induced cancer in medium and high dose ranges. However, in general, a significant effect could not be observed in the low dose region. Therefore, the risk in the low dose region is determined by extrapolation. The epidemiological data and also a number of experimental data can be described by a linear dose response without a threshold (LNT) (UNSCEAR 2006; ICRP 2007). However, this dose response has not been proven and is often disputed. Frequently, it has been postulated that a better knowledge of the mechanisms how radiation-induced cancers develop may help to obtain a better understanding of the dose response in the low dose range (UNSCEAR 2000; Streffer et al. 2004). During recent years, so-called non-targeted effects and their interplay with respect to the development of late health effects after radiation exposures have been studied (UNSCEAR 2006). One of these effects is the increase in genomic instability by ionizing radiation. Certain aspects of this phenomenon will be reviewed in the following, and the association between genomic instability and the development of cancer will be discussed.

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Increase in genomic instability after radiation exposure

Until about 20 years ago, it was generally accepted that increases in the frequency of chromosomal aberrations are expressed directly after an exposure to ionizing radiation that is during the first mitotic cell divisions with the main effect at the first post-radiation mitosis. In the surviving cells, the rate of chromosomal aberrations would then return to normal values. However, around 1990, it was found that a second, new wave of chromosomal aberrations occurs about 20–30 cell generations after the exposure. This phenomenon was called "instability of the genome" (Pampfer and Streffer 1989) or "genomic instability" (Kadhim et al. 1992). The first observations and interpretations of this phenomenon were obtained after radiation exposure to pre-implantation mouse embryos. With this biological system, it was easily and directly possible to follow the number of cell divisions after the first three to four cell cycles. Thus, the chromosomal aberrations could be measured at the first (1-cell- to 2-cell-embryo), second (2-cell- to 4-cell-embryo) and third mitotic division (4-cell- to 8-cell-embryo), without or after X-ray exposure, which took place 1–3 h post-conception (p.c.) in the 1-cell stage (zygote). It was found that the number of chromosomal aberrations increased in this system already without radiation exposure (an expression of a certain genomic instability present in general without exogenous stress), and it was further increased at all developmental stages after the radiation exposure (Table 1; Weissenborn and Streffer 1988).

In further experiments, the zygote (1-cell) stage was irradiated as described previously, and the embryonic/foetal development was allowed in utero. After 19 days p.c., the mouse has almost completely developed, and the foetuses were taken out from the mother just before birth. Skin fibroblasts were cultured from these foetuses, and then the chromosomal aberrations were measured in the skin fibroblasts. Again, the number of aberrations was enhanced in the fibroblasts from those foetuses, which had been irradiated in the zygote stage, around 30 cell generations earlier (Table 2; Pampfer and Streffer 1989). Some of these foetuses developed a malformation in a mouse strain with a definite genetic predisposition for this malformation (gastroschisis). In these foetuses, the increase in genomic instability was even higher than in others, which appeared quite normal and showed a smaller but still significantly increased genomic instability (Pampfer and Streffer 1989; Streffer 2004).

A similar radiation-induced increase in genomic instability was observed during the following years with many different cell systems in vitro and in vivo (UNSCEAR 2006). It can be concluded that the increase in genomic instability developing after exposure to ionizing radiation and expressed 20–30 cell generation later is a general phenomenon. This effect can be considered in some way as a "late effect", and it apparently contributes to the development of late health effects of ionizing radiation. Apparently, the increased instability is not limited to a specific part of the genome (e.g. one chromosome) but the whole genome (all chromosomes) is affected. The increased genomic instability after radiation exposure has been observed not only on the level of chromosomes, but also on the level of genes, microsatellites, etc. This late radiation effect "increased genomic instability" is frequently just called "genomic instability". However, the better term is "increased genomic instability", as a certain genomic instability does exist in all living cells and organisms per se, and this phenomenon is increased after radiation exposure.

The cells that express the increased genomic instability have not themselves been exposed to ionizing radiation, but their ancestors had. Therefore, one speaks of a so-called epigenetic or non-targeted effect. The genomic instability can be transmitted not only to the next cell generation, but also to the next animal generation (UNSCEAR 2006; Dubrova 2003; Nomura 2000; Pils et al. 1999). It persists over many cell generations and also over generations of the mammalian organism (Streffer 2004). The pattern of chromosomal aberrations in the cells with increased genomic instability is the same as with "spontaneous" chromosome aberrations. There is no specific signature, whereas the pattern is different from those chromosomal

Table 1 Chromosomal aberrations in pre-implantation mouse embryos without and with exposure to X-ray (1 Gy) 1 h post-conception (p.c.) (Weissenborn and Streffer 1988)

Developmental stage (Division of blastomeres)	Chromosomal aberrations per 100 metaphases	
	Without X-rays	With X-rays
1-cell–2-cell-embryo	2.3	20.1
2-cell–4-cell-embryo	4.2	16.3
4-cell–8-cell-embryo	7.7	18.6

Table 2 Chromosomal aberrations in fibroblasts of fetuses (19 days post-conception, p.c.) of C 57 Bl and HLG mice irradiated as zygotes 1 h p.c. (Pampfer and Streffer 1989)

Mouse strain	Dose of X-rays (Gy)			
	Control 0	0.5	1.0	2.0
Metaphases with chromosomal aberrations (%)				
C 57 Bl	2.8	12.5	21.7	27.5
HLG	7.3	9.8	12.0	17.4

aberrations, which are observed during the first mitotic cell division directly after radiation exposure (Streffer 2004).

Genomic instability and cancer

For many years, it has been well known that genomic instability occurs in cancer cells where it leads to aneuploidy and frequent chromosome breaks (Kufe et al. 2003; Walther et al. 2009). The following questions are important for the development of cancer in general and especially after exposure to ionizing radiation:

- To what degree does genomic instability promote the development of cancer?
- What is the dose dependence for the development of genomic instability?
- Is there an association between cancer prone individuals and genomic instability?
- Does the genomic instability occur not only in the cancer cells but also in other cells of the cancer patients?
- Can genomic instability be used as a predictor for cancer?

Dose response for the induction of genomic instability

Genomic instability increases in cells in vitro and in vivo and also in tissues in vivo after exposures to high as well as low LET radiation. The effect has been observed after exposures to radiation doses in the range of 100 mGy to several Gy (UNSCEAR 2006). In the dose range of several 100 mGy to 1 Gy, a linear dose response has been observed in several cases (UNSCEAR 2006; Table 2). However, in some cases, it has also been reported that no dose response is evident, similar to what has been observed for other "non-targeted effects" like the bystander effects. Kadhim et al. (1992) studied genomic instability in murine haemopoietic stem cells after exposure with α-particles. As many as about 40–60% of the stem cells developed genomic instability after an exposure leading to one hit per cell on average. Such an exposure would result in an average dose of 300–400 mGy to the cells.

With an elaborate experimental design, it could be shown that genomic instability also developed in cells, which had not been hit (UNSCEAR 2006). Okada et al. (2007) irradiated human lung fibroblasts with carbon ions or γ-rays (^{137}Cs) with an averaged low dose of 1 mGy at low dose rate (1 mGy per 6 h). A significant increase in early senescence (decrease in cell growth) and immunofluorescent foci associated to DNA double-strand breaks was observed 25–30 cell generations after the radiation exposure with carbon ions. A slight decrease in cell growth also occurred after γ-radiation, but this effect was not statistically significant. With the carbon ions, the dose distribution was very heterogeneous since only 1 in 18 cells was hit under the conditions used. These data show that apparently small doses can cause an increase in genomic instability at least with high LET radiation, and it appears that a direct hit of the cell nucleus is not necessary.

Genomic instability and syndromes with increased radiosensitivity

For quite a number of well-described genetic syndromes, it has been found that the affected individuals develop an increased rate of malignancies and that they show an increased radiosensitivity as well as an increased genomic instability (Table 3). The increased radiosensitivity was often observed only after treatments with ionizing radiation for cancer therapy. Then, cells of these patients were studied in vitro with respect to cell killing, chromosomal damage, DNA repair and other biological endpoints (ICRP 1998), and the corresponding molecular genetic analysis was performed. In a number of cases, it was possible to localize the gene responsible for the genetic predisposition to increased radiosensitivity.

Besides the data obtained from humans, a number of experimental data concerning such genetic predispositions have been published for mice. Thus, similar to the situation

Table 3 Human syndromes with genetic predisposition for increased radiosensitivity, cancer proneness and genomic instability

Syndrome	Cancer proneness	Genomic instability
Ataxia telangiectesia	Increased (UNSCEAR 2006) Pollard and Gatti (2009)	Increased (UNSCEAR 2006)
Bloom's syndrome	Increased (UNSCEAR 2006)	Increased (UNSCEAR 2006)
Fanconi's anaemia	Increased (UNSCEAR 2006; Takata et al. 2009)	Increased (UNSCEAR 2006; Takata et al. 2009)
Li Fraumeni	Increased (Tabori et al. 2007)	Increased (Tabori et al. 2007)
Neurofibromatosis	Increased (Kobayashi et al. 2006)	Increased (Kobayashi et al. 2006)
Nijmegen breakage syndrome	Increased (Pollard and Gatti 2009)	Increased (Pollard and Gatti 2009)
Retinoblastoma	Increased (Dimaras et al. 2008)	Increased (Dimaras et al. 2008)

in humans, analogous associations between these phenomena have been shown with SCID-mice (severe combined immune-deficient-mouse), which show increased radiosensitivity, enhanced cancer rates and increased genomic instability (UNSCEAR 2000, 2006). Wang et al. (2008) studied the influence of the protein SIRT 1 (from the sirtuin family) on genomic instability, DNA damage response and carcinogenesis. In embryonic mouse fibroblasts with a mutation in SIRT 1, it was observed that genomic instability increased, DNA repair measured by the comet assay after γ-irradiation was diminished, and cell cycle abnormalities occurred at the G_1/S-phase check point. The authors also constructed genetically modified mice, which were heterozygous for SIRT 1 (SIRT $1^{+/-}$) and/or for p53 ($p53^{+/-}$). In the case of SIRT $1^{+/-}$ $p53^{+/-}$-mice, about 76% of the mice developed a cancer until the age of 20 months, whereas with SIRT $1^{+/-}$ $p53^{+/+}$-mice and with $p53^{+/-}$ SIRT $1^{+/+}$-mice these numbers were around 10 and 14%, respectively. SIRT 1 apparently acts in coordination with p53 as a tumour suppressor. These data with humans and with mice clearly show:

- The association between genomic instability and cancer induction is apparent.
- In the syndromes with high radiosensitivity, a deficiency of DNA repair occurs in one or several pathways and/or disturbances in the regulation of the cell cycle are found (ICRP 1998; UNSCEAR 2006; Streffer et al. 2004). A number of patients with some of these syndromes have mutations in the ATM-gene, the p53-gene and/or the Rb-gene. All these genes or their proteins, respectively, are involved in the G_1/S-phase checkpoint of the cell cycle.

From the clinical experience in cancer therapy with ionizing radiation, it can be concluded that there exist additional individuals with genetic predispositions to high radiosensitivity for whom the genetic pathways and possible mutations have not yet been evaluated (UNSCEAR 2000; Streffer et al. 2004). Thus, it can be expected that a number of individuals with further syndromes who look normal but suffer from radiosensitive syndromes with such genetic predispositions will be observed in the future (Streffer et al. 2004).

Increased genomic instability in cancer patients

It is quite interesting that in those individuals with a genetic predisposition towards a high radiosensitivity and cancer proneness the genomic instability has been observed not only in the cancer cells but also in "normal" cells e.g. in lymphocytes or fibroblasts of these individuals. Furthermore, it has been observed that even in cancer patients without a corresponding genetic disposition an increased genomic instability is observed, for example also in lymphocytes. Thus, the number of chromosomal aberrations was found to be significantly increased in lymphocytes of uranium miners who had developed a bronchial carcinoma, which apparently was caused by the high exposures to radon and its radioactive daughters at their working places in the mines, several decades earlier (Kryscio et al. 2001). In further experiments, micronuclei were determined using a methodology based on binucleated cells (incubation with cytochalasin B) in lymphocytes of unexposed healthy persons (HP), of uranium miners without a bronchial carcinoma (UM) and of uranium miners with a bronchial carcinoma (UMC). The number of micronuclei increased in the order HP < UM < UMC; these increases were, however, statistically not significant (Table 4; Streffer et al. 2002).

Micronuclei can originate from whole chromosomes or acentric fragments resulting from chromosomal breaks caused e.g. by ionizing radiation. If a micronucleus originates from acentric fragments only, it will contain no centromere (MnC−), while a centromere is present in the micronucleus (MnC+), if a whole chromosome has contributed to its formation. These different types of micronuclei can be distinguished by a specific "fluorescence in situ hybridization (FISH)" with human DNA probes for centromeres and the subsequent analysis by fluorescence microscopy (Kryscio et al. 2001). The analysis of these two types of micronuclei (MnC+ and MnC−) showed that in unexposed human lymphocytes around 80% of the

Table 4 Numbers of micronuclei (Mn) per 1,000 binucleated cell (BNC) and Mn with centromeres (MnC+) in percent (%) in lymphocytes of 14 healthy persons (HP), of 14 healthy uranium miners (UM) and of 14 uranium miners with bronchial cancers (UMC) (Streffer et al. 2002)

		HP (14)	UM (14)	UMC (14)
Mn/1,000 BNC	Average value	18.8	21.4	42.4
	SD	3.9	10.2	39.3
	P-value (*t*-test)	–	ns	ns
Mn with centromeres (MnC+) (%)	Average value	76.4	62.1	54.9
	SD	3.1	3.5	3.1
	P-value (*t*-test)		<0.0001	≤0.0001

Table 5 Numbers of micronuclei (Mn) per 1,000 binucleated cells (BNC) and Mn with centromeres (MnC+) in percent (%) in lymphocytes of 14 healthy persons and of 41 patients with head and neck cancer

		Healthy persons (14)	Patients with head and neck cancer (41)
Mn/1,000 BNC	Average	23 (12–49)	35 (20–64)
	Mean	21	32
Mn with centromeres (MnC+) (%)	Average	82 (70–87)	65 (56–77)*
	Mean	83	65*

* $P < 0.01$

micronuclei carry a centromere (MnC+) (Tables 4 and 5). On the other hand, radiation-induced micronuclei originate in most cases from acentric fragments and appear without centromeres (MnC−). Directly after an X-ray dose of 1.0 Gy a strong increase in the total number of micronuclei is observed, but the relative proportion of MnC+ decreases to about 35% and after 2.5 Gy to about 10% (Kryscio et al. 2001). After the radiation exposure, the number of micronuclei decreased rapidly within some months to normal values (Mueller et al. 2004). However, several decades after the radiation exposure of the miners, their lymphocytes again showed an increase in micronuclei albeit not statistically significant. In these micronuclei, the relative proportion of MnC+ was found significantly decreased in the lymphocytes of UM and even more in the lymphocytes of UMC compared to unexposed healthy persons (Table 4; Streffer et al. 2002). This increased number of chromosomal aberrations and correspondingly of acentric fragments, which causes the decrease in the relative proportions of MnC+ decades after the exposure to ionizing radiation from radon and its radioactive daughters should be interpreted as an increase in genomic instability (Kryscio et al. 2001; Streffer et al. 2002).

In a very analogous way, it was found by our group that patients with head and neck cancers exhibit an increased number of micronuclei in their lymphocytes in comparison with healthy persons (Table 5). However, again this increase in the total number of micronuclei (Mn) is not statistically significant. On the other hand, the relative proportion of MnC+ was again lower in the patients with head and neck cancer than in healthy persons, and this decrease was highly significant (Table 5). The individual variation of the absolute numbers of micronuclei in the lymphocytes of the patients with cancer is much higher than the individual variability of the relative numbers of MnC+. These differences of individual variability (total number of Mn versus relative number of MnC+) are certainly one important reason that the measurements of the total micronuclei resulted in no significant effect but the determinations of MnC+ did. It is therefore recommended to analyse not only the total number of Mn, but to also use the FISH-methodology with centromere DNA probes in order to determine MnC+ and MnC−. By this methodology, it is possible to obtain a measure for genomic instability. The data on the uranium miners and on the patients with head and neck cancer show that cancer patients have apparently a generally increased genomic instability, which manifests not only in the cancer cells but also in the non-cancer cells like lymphocytes. The disease of a cancer is apparently expressed not only locally but also in cells and tissues outside the cancer.

Increased genomic instability plays apparently an important role for cancer development and other late effects after radiation exposure (Streffer 2004). The increase in genomic instability is caused by ionizing radiation in a very general manner around 20–30 cell generations after exposure. During cancer development, several mutations are involved and are necessary. An increased genomic instability increases the probability for the next mutation and facilitates cancer development through this process (Little 2006). But also conflicting data have been reported. Thus, no significantly increased genomic instability was observed in lymphocytes of atomic bomb survivors in Japan (Hamasaki et al. 2009), while increased genomic instability was observed in the normal epidermis of atomic bomb survivors who suffered from a basal cell carcinoma (Naruke et al. 2009).

Mechanistic aspects for the induction of genomic instability

The mechanism of the development of genomic instability is not clear until now. A number of possible mechanisms have been discussed (UNSCEAR 2006). However, quite a number of recent scientific data favour and support the idea and consideration that the structures of the chromosome-stabilizing telomeres are most important in this regard (Mullenders et al. 2009; Streffer 2009). The increase in chromosomal instability may be linked to telomere shortening and changes in their structure, which may be promoted by deregulatory processes in the cell cycle and cell proliferation. Studies in patients with the malignant disease

Table 6 Length of telomeres (kb) and chromosomal aberrations per cell in lymphocytes of healthy persons and of patients with M. Hodgkin (M.H.)

Population	Number of patients	Length of telomeres (kb)	Chromosomal aberr. per cell
Healthy persons	30	11.7	0.003
Prospect. patients with M. Hodgkin	73	8.3*, [a]	0.026**
M.H. pat. with second. cancers after treatment	28	6.6**	0.164**

The group of patients was divided in two groups. One group of treated patients without secondary cancers who were observed prospectively for the development of secondary cancers and a second group of treated patients who had developed a secondary cancer after treatment. The telomere length and the chromosomal aberrations were measured in the peripheral lymphocytes before any treatment by ionizing radiation (M′kacher et al. 2007)

* $P < 0.001$, ** $P < 0.0001$

[a] 2 Patients with secondary cancer with telomere length 6 and 7.5 kb, respectively

M. Hodgkin, who were treated with ionizing radiation, showed already before treatment a reduction in the length of the telomeres in peripheral lymphocytes, when compared to unirradiated control persons. The reduction in telomeres was most significant in those patients who had developed a secondary cancer after treatment and in these patients a remarkable increase in chromosomal instability also occurred (Table 6). In another group of M. Hodgkin patients who were followed prospectively after radiotherapy, 2 patients developed a secondary cancer during the study and again the telomeres were shorter in these patients. This result was obtained again before treatment for the secondary cancer (Table 6). In these patients, chromosome aberrations were also measured in the lymphocytes, and the number of chromosomal aberrations was significantly higher in those patients whose cells showed reduced telomere lengths. A good association between the increase in genomic instability and reduction in the telomeres was seen (Table 6) (M′kacher et al. 2007). Thus, the length of telomeres and genomic instability may serve as predictors for a developing cancer.

In the context of the association between genomic instability and cancer development, Huang et al. (2007) have assumed that hypoxia also plays an important role in the development of both processes. The hypoxia-inducible factor, HIF-α, can be phosphorylated and binds to the hypoxia-responsive element (HRE), which leads via a VEGF stimulation to angiogenesis. On the other hand, non-phosphorylated HIF-1α "competes with Myc for Sp1 binding in the non-HRE promoter" (Huang et al. 2007). This binding results in a down-regulation of the DNA-repair genes NBS1 and MSH2 and as a consequence an increase in genomic instability occurs.

Summary and conclusions

DNA structure is not stable in itself. It is kept stable throughout life by DNA-repair processes. These processes

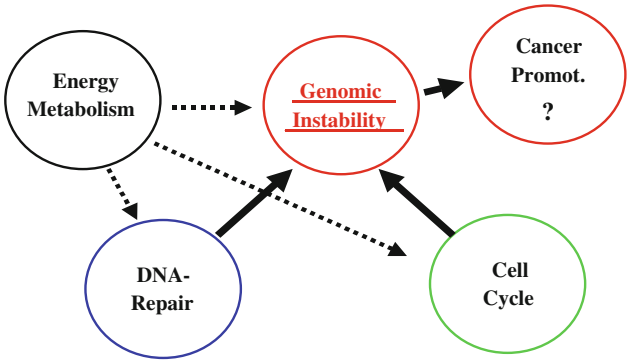

Fig. 1 Interaction of several processes that lead to the increase in genomic instability by deficiency of DNA repair and disturbances in the regulation of the cell cycle. Genomic instability is a promoting process for cancer development. All processes are dependent on energy. Defects in energy metabolism, e.g. by hypoxia, increase genomic instability

are very dependent on the individual genetic disposition. The increase in genomic instability after exposure to ionizing radiation is apparently a general phenomenon. It occurs 20–30 cell generations after high as well as low LET radiation exposures and has been observed with many biological endpoints in cellular systems in vitro as well as in cells and tissues in vivo. Genomic instability persists for many further cell generations, and it can be transmitted from one generation to the next generation in mammals. No specific signature has been found for radiation-induced genomic instability. In the low dose region (<100 mGy), the effect is superimposed by the "spontaneous" noise therefore.

A strong association between cancer and genomic instability exists in syndromes with a genetic predisposition for increased radiosensitivity. Individuals with these syndromes show a deficiency in DNA repair and/or a deregulation of cell proliferation usually in the G_1/S-phase check point. The increased genomic instability not only is seen in cancer cells but also appears in "normal" cells, e.g. lymphocytes of cancer patients. Thus, cancer is apparently

a disease that is more general and not localized to the local primary cancer and its metastases. Increased genomic instability may be an indicator for cancer and may promote cancer development. Other stressors like hypoxia which also promote cancer are also associated with genomic instability. The mechanism of induction of genomic instability is apparently connected to the structure and lengths of telomeres. For all these processes (DNA repair, cell proliferation, etc.), energy metabolism plays a key role. Therefore, an interaction of these processes with various pathways of intermediate energy metabolism as shown in Fig. 1 may be important.

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