Acta Oncologica, 2008; 47: 809–824

informa
healthcare

REVIEW ARTICLE

Genetic variations in DNA repair genes, radiosensitivity to cancer and susceptibility to acute tissue reactions in radiotherapy-treated cancer patients

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Abstract
Ionizing radiation is a well established carcinogen for human cells. At low doses, radiation exposure mainly results in generation of double strand breaks (DSBs). Radiation-related DSBs could be directly linked to the formation of chromosomal rearrangements as has been proven for radiation-induced thyroid tumors. Repair of DSBs presumably involves two main pathways, non-homologous end joining (NHEJ) and homologous recombination (HR). A number of known inherited syndromes, such as ataxia telangiectasia, ataxia-telangiectasia like-disorder, radiosensitive severe combined immunodeficiency, Nijmegen breakage syndrome, and LIG4 deficiency are associated with increased radiosensitivity and/or cancer risk. Many of them are caused by mutations in DNA repair genes. Recent studies also suggest that variations in the DNA repair capacity in the general population may influence cancer susceptibility. In this paper, we summarize the current status of DNA repair proteins as potential targets for radiation-induced cancer risk. We will focus on genetic alterations in genes involved in HR- and NHEJ-mediated repair of DSBs, which could influence predisposition to radiation-related cancer and thereby explain interindividual differences in radiosensitivity or radioresistance in a general population.

Ionizing radiation is a well established carcinogen for human cells although the radiation-related cancer is much less frequent compared to that induced by environmental pollutants, tobacco smoking, viruses and food contaminants. Radiation exposure generates a bulk of DNA injuries including numerous base damages, single and double strand breaks (DSBs) [1].

There are several pathways of cellular DNA repair responsible for correction of specific types of DNA damage generated by radiation. Repair of DSBs presumably involves two main mechanisms, non-homologous end joining (NHEJ) and homologous recombination (HR) (Figure 1) [2]. In yeasts, the HR pathway is predominant in DSBs repair, while in vertebrates the NHEJ pathway is believed to be the major mechanism to repair DNA DSBs [3]. Detailed description of the biochemical pathways of DNA repair is beyond the scope of this article as several reviews on the subject have been recently published [4–8].

In human cells, the radiation-induced carcinogenesis is predominantly associated with chromosomal rearrangements. The association has been proven for radiation-induced thyroid tumors [9]. Chromosomal rearrangements, such as Rearranged in Transformation/Papillary Thyroid Carcinomas (RET/PTC), are frequently detected in patients who developed thyroid cancer after the Chernobyl accident [10,11] or therapeutic irradiation [12].

Radiation-induced DSBs could be directly related to the formation of chromosomal rearrangements [13]. One of the theories explaining the involvement of DNA DSBs into radiation-induced chromosomal rearrangements suggests that the rearrangements are likely to arise from the rejoining of two DSBs located closely in space and time (two-hit mechanism) [14]. According to this theory, a putative mechanism of the rejoining involves the NHEJ pathway of DNA repair. Another theory considers that one radiation-induced DSB is sufficient to initiate an exchange that occurs with an undamaged DNA molecule [15]. In

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(Received 30 October 2007; accepted 31 December 2007)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860801885969

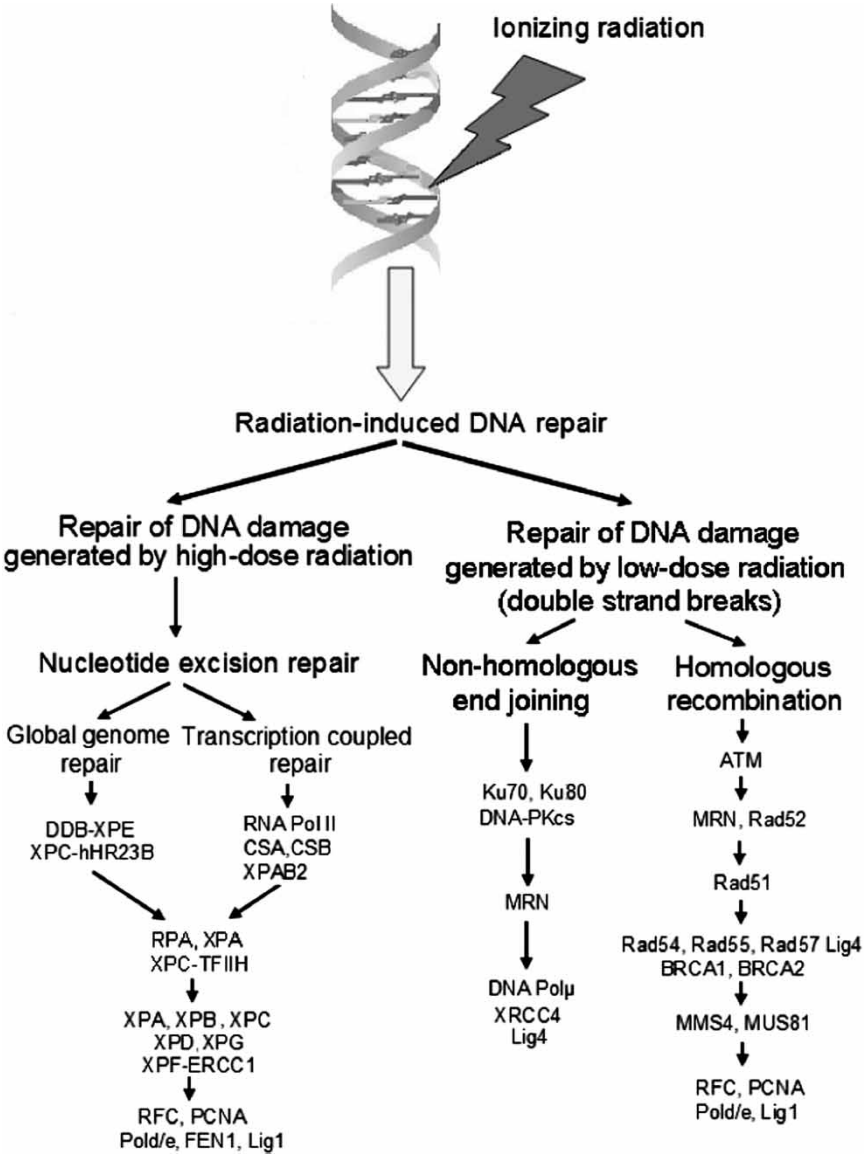

Figure 1. Radiation exposure at low doses mostly results in DNA double strand breaks (DSBs), which are repaired through homologous recombination and non-homologous end joining. The last pathway is the major mechanism of the repair of DNA DSBs in humans and other mammals.

this case, the rearrangement can be generated using HR. However, none of the theories can fully explain all available experimental data on the dose-effect relationship and complexity of radiation-induced aberrations [16].

Analysis of genomic breakpoints in RET/PTC3 rearrangements in post-Chernobyl thyroid tumors showed regions of microhomology composed of 3-5 nucleotides [10,17,18]. The modification of sequences at the breakpoints was minimal, typically involving deletion or duplication of 1-3 nucleotides, characteristic of NHEJ. Breakpoints exhibited no particular nucleotide sequence and no recombination-specific motifs. The features of the junction sequences, particularly the high frequency of small terminal deletions, the apparent splicing of DNA ends at microhomologies, and gap-filling on aligned DSBs, are consistent with the known biochemical properties of the classical NHEJ pathway [19]. This provides strong evidence for a dominant role of NHEJ in repair of DSBs and formation of RET/PTC rearrangements after exposure to radiation.

A number of known inherited syndromes are associated with increased radiosensitivity and cancer risk. Many of them are caused by mutations in DNA repair genes [20]. Recent studies also suggest that variations in the DNA repair capacity in the general population may influence cancer susceptibility [21,22].

In this review, we summarize the current status of DNA repair proteins as potential markers for radiation-induced cancer risk. Since the aberrant repair of

radiation-induced DSBs frequently leads to chromosome rearrangements associated with cancer, we will focus on genetic alterations in genes involved into HR- and NHEJ-mediated repair of DSBs, which could influence predisposition to radiation-related cancer and thereby explain interindividual differences in radiosensitivity or radioresistance in a general population.

Genes involved in the homologous recombination pathway of DNA repair

ATM

The ATM gene encodes an important cell cycle checkpoint kinase, a member of the PI3/PI4-kinase family. This enzyme functions as a regulator of a wide variety of downstream proteins, including tumor suppressors p53 and BRCA1, checkpoint kinase CHK2, checkpoint proteins RAD17 and RAD9, and DNA repair proteins NBS1 and SMC1. DNA damage leads to the activation of ATM. This protein kinase phosphorylates and thereby activates SMC1, which is crucial in controlling DNA replication forks and DNA repair after the damage [23]. NBS1 and BRCA1 are required for the recruitment of activated ATM to the sites of DNA breaks followed by phosphorylation of SMC1 by ATM [24].

The ATM-deficient cells are highly sensitive to DNA damage induced by ionizing radiation [25]. These cells are able then to repair the majority of the radiation-induced DSBs with normal kinetics, but fail to repair a subset of breaks irrespective of the initial number of lesions induced. Furthermore, ATM-deficient cells showed no ability to recover following delayed plating after irradiation compared to NHEJ-defective cells [26]. These observations correlate with an extreme cellular sensitivity of patients with ataxia telangiectasia (AT) to ionizing radiation.

Ataxia telangiectasia is an autosomal recessive disorder associated with mutations in the ATM gene. It is characterized by progressive cerebellar ataxia, ocular apraxia, immunodeficiency, chromosomal instability, radiosensitivity and defective cell cycle checkpoint activation [27]. Ataxia telangiectasia patients have a higher risk to develop cancer [28] and obligate heterozygous carriers of ATM mutations may have an increased risk of cancer, particularly breast cancer [29,30]. Most of population studies failed to show that AT heterozygotes carrying one copy of truncated ATM exhibit significantly increased radiosensitivity [31–36].

Some suggestive evidence was obtained for the association between the ATM codon Asp1853Asn (5557 G>A) single nucleotide polymorphism (SNP) and cancer risk. In France and USA, genetic analysis of breast cancer patients showed strong association between the homozygous carriage of the 5557 G>A variant and high risk of the development of radiotherapy-induced acute skin complications (odds ratio (OR) = 6.76 [37] and 3.1 [38], respectively). This finding was recently confirmed by Andreassen et al. [39] who reported a relationship of the homozygous (AA) and heterozygous (AG) genotypes of the ATM G5557 G>A variant to increased radiosensitivity among Danish breast cancer patients. However, evaluation of the independent cohort of Danish breast cancer patients did not reveal any significant association between this marker and radiosensitivity [40]. For prostate cancer, data on the implication of the ATM codon 1853 polymorphism to radiotherapy-induced complications are controversial. Cesaretti et al. [41] found association between this genetic variant of ATM and the development of radiation-induced proctitis after prostate cancer radiotherapy. However, no relationship was shown between this marker and bladder or rectal toxicity arising from the radiation therapy in Canadian prostate cancer patients [42]. Despite the inconsistence in the association studies, the codon 1853 SNP of ATM seems to play a role in the development of radiotherapy-related complications in breast (and probably prostate) cancer. Additional large-scale population analyses are required for precise confirmation of the involvement of this marker in acute tissue reactions after cancer radiotherapy.

The presence of a large variety of rare missense variants in addition to common polymorphisms in ATM makes it difficult to establish a relationship of this gene to non-radiation and radiation-induced cancer by association studies. However, in those patients who developed cancer after long-term low-dose radiation exposure [36,43,44] the frequency of heterozygous carriers of AT missence mutations has been shown to be significantly increased (up to 10%) compared to the general population where the frequency of AT heterozygotes is estimated to be 0.36–1.0% [45].

It has been suggested that missense mutations but not truncating mutations could underline the relationship between the ATM gene and radiosensitivity [46]. Some experimental data support this hypothesis. Angele et al. [37] found that breast cancer individuals heterozygous for both AT mutations IVS22-77 T>C and IVS48+238 C>G are significantly more sensitive to radiotherapy (OR = 1.75) than patients who are heterozygous only for one of these mutations. In another study, Angele and coauthors [47] showed that after exposure to

ionizing radiation cell cycle progression profile of lymphoblastoid cells carrying both the 3161G and the 2572C (858L) variants of ATM is significantly different from that in cell lines with a wild-type ATM gene. Similarly, cell lines carrying the 2572T > C (F858L) and the 3161C > G (P1054R) ATM variants form more micronuclei than normal cells [48].

The mechanisms by which missense mutations could affect the ATM activity are not fully understood. Of the mutations associated with breast cancer, only two, S2592C and SRI2546del3, produce mutant protein lacking the ATM kinase activity, which also has a dominant negative effect on the wild-type protein. The S2592C substitution could inactivate the kinase function by altering the conformation of ATM or disrupting a potential phosphorylation site in the S*S*QL sequence [49]. Missense mutations situated in regions of the ATM protein, away from the kinase domain, may decrease the ATM kinase function presumably via the protein-protein interaction with intact ATM molecule and further multimerization [49,50]. Thus, even low levels of mutant ATM protein have the potential to interfere with ATM function and might in this way contribute to cancer susceptibility [46]. It is likely that a reduced amount of ATM protein in heterozygotes may be responsible for the intermediate sensitivity to radiation.

MRN complex

Three proteins, MRE11, RAD50 and NBS1, participate in the formation of the so called MRN complex. This complex plays a key role in DNA damage detection and activation of the DNA damage response. The MRN complex serves as a flexible link between the ends of broken DNA, and upon binding to damaged DNA, the MRN complex undergoes a series of conformational changes to activate ATM, increase ATM affinity for its substrates [51], and retain active ATM at sites of DNA damage [52].

Mutations in MRE11 could result in deficiency of the MRE11 protein and lead to ataxia-telangiectasia like-disorder (ATLD) [53]. This autosomal recessive disease is characterized by a higher sensitivity to radiation exposure. Delia et al. [54] reported the impaired response to γ-irradiation of lymphoblastoid cells lines and fibroblasts derived from the ATLD patients and those carrying the ATLD-associated mutations 1422C > A (T481K) and 1714C > T (R571X) in MRE11. However, not all ATLD-linked MRE11 mutations are truncating. Fernet et al. [55] found a missense mutation (630G > C, W210C) in the MRE11 gene from Arabic ATLD patients that is located in the nuclease domain of the Mre11 protein and does not affect its expression. Cells homozygous for the 630G > C mutation express normal levels of MRE11 and RAD50 but a very low level of the NBS1 protein, are unable to form the MRE11 foci and show enhanced radiosensitivity [55]. However, to date, the ATLD patients have not been shown to have an increased risk to develop cancer [53].

The observation why ALTD patients are less vulnerable to cancer than those with AT syndrome might be explained by a much broader function of ATM in the cell compared to that of MRE11. The role of MRE11 is focused on the activation of HR-mediated DNA repair while the ATM protein kinase plays a critical role in maintaining genome integrity by activating a biochemical chain reaction that in turn leads to cell cycle checkpoint activation and repair of DNA damage. ATM targets include well-known tumor suppressor genes such as p53 and BRCA1, both of which play an important role in predisposition to breast cancer [56].

Frameshift mutations of the coding nucleotide $(T)_{11}$ repeat of the RAD50 gene and mutations (484del88) of the microsatellite located in intron 4 of the MRE11 gene leading to the protein truncation have been frequently observed in colorectal and gastrointestinal cancers that developed in patients with deficiency of the DNA mismatch repair (MMR) system [57–59]. MMR-deficient colon cancer cells with mutated RAD50 and MRE11 had impaired expression of both genes, decreased NHEJ repair activity, genome instability and increased sensitivity to γ-irradiation [59]. However, Lefevre et al. [60] found no mutation in the genes constituting the MRN complex in human MMR-stable radiation-induced tumors exhibiting genomic instability.

Mutations in NBS1 are associated with cancer-predisposing Nijmegen breakage syndrome (NBS) that characterized with increased chromosome instability, immunodeficiency and radiosensitivity [61]. Over 90% of patients are homozygous for a founder mutation (657del5): a deletion of five base pairs, which leads to a frameshift and protein truncation. Most of population studies provided evidence for association of this mutation with higher risk of different kinds of cancer, and this risk could be substantial in ethnic groups with high frequency of the founder mutation, for example in Poland and Czech Republic [62–64]. For heterozygous carriers of the 657del5 mutation, the cancer risk tends to increase with age [64].

Several missense mutations such as R215W, S93L, D95N and I171V have been identified in the NBS1 gene in tumor cells of patients with acute lymphoblastic leukaemia [65]. Three of these mutations are located in the FHA or BRCT domains responsible for interaction with ATM and histone H2AX [66].

Inactivating mutations were not found on the second allele in these cells, suggesting that the amino acid substitutions have a dominant negative effect.

In human heterozygotes, the existence of a truncated NBS1 protein produced by alternative translation [67,68] and capable of interaction with MRE11 would be compatible with a dominant negative mechanism. Studies in human populations with high incidence of NBS found increased incidence of cancer in patients heterozygous for NBS-related mutations. The observed frequency of malignances in heterozygous patients significantly exceeded the expected value [63,69]. These results suggest that heterozygous carriers of NBS1 mutations may indeed have an enhanced risk to develop malignant tumors, such as melanoma, breast cancer, and colorectal cancer.

Common polymorphisms in NBS1 were evaluated for possible association with a variety of cancers, but consistent positive results have been obtained only for lung cancer: the C allele of the codon 185 dimorphism (E185Q, G>C) was shown to modulate lung cancer risk in several populations [70–73]. This polymorphic marker has been recently tested for possible relation to enhanced risk of radiotherapy-induced acute complications in breast cancer patients in two large-scale population studies involving more then 2 000 cases and controls [74,75]. Despite that both studies had more than 80% power to detect a 1.9-fold risk in carriers of the NBS1^{185}Q allele no significant association with radiosensitivity was shown. Therefore, it is unlikely that the E185Q SNP of NBS1 could be a major risk factor for clinical radiosensitivity in breast cancer. However, we cannot exclude that this missence mutation could be involved in clinical radiosensitivity as a part of the complex genotype containing susceptibility variants of the major DNA repair genes that have potential to impact increased risk to radiotherapy-induced complications [76].

RAD51 gene family

RAD51 gene family consists of several proteins that show DNA-stimulated ATPase activity and property for preferential binding to single-stranded DNA and forming complexes with each other [77]. RAD51 participates in a common DNA damage response pathway associated with the activation of HR and DSB repair. RAD51 binds to single- and double-stranded DNA and exhibits DNA-dependent ATPase activity. This protein underwinds duplex DNA and forms helical nucleoprotein filaments at the site of DNA break.

Two SNPs, −135 G>C and −172 C>T, have been found in the promoter region of the RAD51 gene [78]. Both are functional and result in increased promoter activity [79]. The +135 G>C has been found to be associated with predisposition to breast cancer, especially at subgroup of patients with mutations in BRCA2 [80,81], to ovarian cancer [82], and acute myeloid leukemia [83]. The +135C allele of RAD51 was reported to be associated with increased risk of radiotherapy-induced acute myeloid leukemia (OR = 2.66) [84]. A synergic interaction between the +135 G>C SNP of RAD51 and the C/T substitution at the 3′ UTR of the HLX1 homeobox gene, which is important for hematopoietic development, was observed. This resulted in a significant 9.5-fold increase in the risk of acute myeloid anemia in carriers of predisposing variants of both genes [84]. However, Damaraju et al. [42] failed to find significant association between the +135 G>C promoter polymorphism and risk of development of radiation-induced complications in patients with prostate cancer treated with radiotherapy.

Because a guanine-to-cytosine substitution at position +135 of the RAD51 is a gain-of-function mutation, it is expected to result in increased activity of RAD51. This effect is opposite to those found for most of the other genetic variations in DNA repair genes, which result in the decrease of function. Interestingly, increased (up to 7-fold) levels of RAD51 have been observed in different tumor cell lines [85]. This finding suggests that up-regulation of RAD51 recombinase may play a role in the increased risk of tumorigenesis [86].

In humans, RAD51 paralogs (RAD51B, RAD51C, RAD51D, XRCC2 and XPCC3) facilitate HR mediated by RAD51 [87]. In chicken DT40 cells, knocking out for any of the RAD51 paralogs results in very similar phenotypes, such as defective HR, chromosome instability, mild sensitivity (only 2-fold higher then that of a wild-type) to γ-irradiation but high sensitivity (8 times higher than in normal cells) to cisplatin, a DNA cross-linking chemotherapeutic agent [88]. Similarity in properties of mutant cells deficient for RAD51 paralogs suggested that these proteins act as a single functional unit during HR.

A polymorphic arginine-to-histidine substitution located at codon 188 (R188H; 31479 G>A) has been found in exon 3 of the XRCC2 gene [89]. XRCC2-deficient DT40 cells transfected with the human XRCC2 R188H variant displayed a more resistant phenotype to cisplatin than wild-type clones due to the restored DNA repair activity of the XRCC2 protein [90]. Genetic studies have shown that the R188H variant of XRCC2 could modulate risk of sporadic breast cancer [89,91,92] and epithelial ovarian cancer [93]. However, this

SNP failed to show significant relation to radiation-induced complications in patients with BC [74,75] as well as to bladder/rectal toxicity in radiotherapy-treated subjects with prostate cancer [42].

Another RAD51 paralog, XRCC3 has been more extensively tested for association with acute side effects of radiotherapy in different types of cancer (Table I). A threonine-to-methionine substitution at codon 241 (T241M, 18067 C>T) of XRCC3 has been frequently evaluated in the case-control studies. However, most of the studies failed to show association of this marker with radiotherapy-induced complications such as meningioma [94] and hypersensitivity to ionizing radiation in breast cancer [74,75,95–97] and gynecologic tumors [98]. Andreassen et al. [99] reported association between the Thr/Thr241 variant of XRCC3 and enhanced risk of radiation-induced subcutaneous fibrosis in 41 Danish breast cancer patients treated with post-mastectomy radiotherapy, but failed to confirm the results in the independent cohort of 120 post-mastectomy subjects [40].The T241M polymorphism of XRCC3 was found to be associated with radiosensitivity in non-cancer subjects (Table I) [100,101]. The XRCC3 M241T was shown to be associated with several types of non-radiation-induced (sporadic) cancer such as melanoma skin cancer [102], basal cell carcinoma [103], differentiated thyroid cancer [104] and bladder cancer [105].

Functional studies showed no significant differences in DNA repair activity between the XRCC3 T241M variant and wild-type protein. Cells having the T241M variant of XRCC3 exhibited the same sensitivity to the interstrand cross-linking agent mytomycin C as those expressing the wild-type protein [106].

These results suggest that the M241T SNP may not be directly associated with radiosensitivity. However, this SNP could be in linkage disequilibrium with another gene (or another genetic variation within XRCC3) responsible for the radiation-induced cancer association. For XRCC3, the association with radiation-induced complications or adverse effects of radiotherapy in cancer was showed for several polymorphic markers including a dinucleotide microsatellite located in intron 3 [107,108] and two SNPs, 5′ UTR 4541A>G and IVS5-14 A>G [42,98]. To date, it is unclear whether these markers are functionally significant and hence should be evaluated.

BRCA1 and BRCA2

BRCA1 participates in early steps of DNA repair, playing a role in regulation and promotion of HR. In response to DSBs, BRCA1 is phosphorylated by kinases including ATM, Rad-3 related, and checkpoint kinase 2, and may act in DNA damage-induced signal transduction [109]. Furthermore, BRCA1 is a component of large multiprotein complexes such as BASC (BRCA1-associated genome-surveillance complex) [110], where it can influence the choice of repair pathway utilized depending upon the type of DNA lesion. A specific role for BRCA1 in these complexes might involve regulation of initial DNA DSB processing by the MRN complex [111], which then allows further progression along the HR pathway. BRCA1 is involved in a wide spectrum of other cellular processes such as cell-cycle regulation, transcriptional regulation and chromatin remodelling.

In contrast to BRCA1, BRCA2 functions are largely limited to DNA repair and recombination. BRCA1 and BRCA2 regulate the core HR machinery via control of the RAD51 recombinase. They bind to RAD51 through eight evolutionary conserved binding domains called the BRC repeats [112]. BRCA1 could also bind to single-stranded DNA via the C-terminal domain, the structure of which is critical to the ability of BRCA2 to promote recombination. Following DNA damage and initial DSB processing, BRCA2 relocalizes to the site of DNA damage [113].

Germ-line mutations in BRCA1 and BRCA2 are associated with breast and ovarian cancer. Women heterozygous for the BRCA1/BRCA2 mutations have an elevated risk of developing breast cancer (up to 85% of multi-case families), ovarian cancer and other cancers [114]. However, most studies failed to find a relationship between heterozygous BRCA1/BRCA2 mutations and increased hypersensitivity to radiation in patients with breast and ovarian cancer [115–123].

Observations on the repair of DSBs induced by ionizing radiation in human carcinoma cells deficient in BRCA1 and BRCA2 revealed normal rejoining of DNA DSBs, therefore suggesting for a lack of the direct role of BRCA1 or BRCA2 in the rejoining of radiation-induced DSBs in the genome of human tumor cells [124]. Loss of BRCA function may therefore not substantially sensitize tumors to ionizing radiation.

Evaluation of common polymorphisms within the BRCA1 and BRCA2 genes did not revealed association with radiotherapy-induced toxicity in cancer patients [41,125]. Although more population studies are required to verify a relationship between the common BRCA1/2 polymorphisms and clinical radiosensitivity in breast and ovarian cancer, the currently available data provide no evidence that genetic alterations in BRCA1/2 play a significant role in predisposition to radiation-induced cancer.

Table I. Summary of case-control and functional studies for association of different variants of the XRCC3 gene with radiosensitivity

Marker	Population	Cancer	Type of radiotherapy (radiation-induced complications)	Cases	Controls	OR	p	Reference
Micro-satellite (AC)n intron 3	U.K. Caucasians	Mostly breast and ovarian	Chest, pelvis	106 radio-sensitive with cancer 137 cancer complicated with radiotherapy-induced acute reactions	215 cancer-free	N/A	0.004 (cancer vs. cancer-free) 0.005 (complicated vs. cancer)	103
T241M	US (North Carolina)	Family history of breast cancer	No	135 cancer-free women including 83 for whom family history of breast cancer was available		N/A	N.S. for prolonged cell cycle G2 delay N.S. for family history of cancer	91
T241M	U.S. (mostly Caucasians; North Carolina)	Breast	Chest	118 cancer females (83% Whites)	224 cancer-free females (83% Whites)	N/A	N.S. for breast cancer risk N.S. for prolonged cell cycle G2 delay	92
T241M	US (Texas)	No cancer	Irradiation of lymphocytes with x-rays	80 smoke-free and cancer-free donors		N/A	< 0.05 (MM+TM vs. TT) for number of radiation-induced chromosome deletions	96
T241M	Denmark	Breast	Chest (radiogenic subcutaneous fibrosis and telangiectasia)	41 females treated with post-mastectomy radiotherapy		Enhance-ment Ratio = 1.17 Enhance-ment Ratio = 1.25	<0.05 (TM vs. TT) for grade 3 subcutaneous fibrosis <0.05 (MM vs. TT) for grade 2-3 telangiectasia	95
T241M	Belgium	No cancer	γ-irradiation during work; γ-irradiation of blood cells taken from cases and controls	32 men (seasonal cleaners of the reactor of the Belgian nuclear power plant)	31 men (office staff of the Belgian nuclear power plant with no radiation exposure)	N/A	<0.012 (MM+MT vs. TT) for frequency of micronuclei in monocytes of exposed workers	97
T241M	Israel	Meningioma	RT against tinea capitis in childhood (radiogenic meningioma)	150 with radiation-induced meningioma 69 with non-radiation-induced meningioma	129 irradiated but did not developed meningioma 92 non-irradiated without meningioma	1.18	N.S. (MM vs. TT) for risk of radiation-induced meningioma	90
T241M	UK	Breast	Chest	26 cancer with changes in breast appearance after radiotherapy	26 cancer with no changes in breast appearance after radiotherapy	N/A	N.S. (cases vs. controls) for risk of altered breast appearance after radiotherapy	93

Table I (*Continued*)

Marker	Population	Cancer	Type of radiotherapy (radiation-induced complications)	Cases	Controls	OR	p	Reference
T241M, 5′ UTR 4541A >G, IVS5-14 A >G	Belgium	Cervical and endometrial	Pelvis (late normal tissue reactions induced by RT)	62 (30 with cervical cancer and 32 with endometrial cancer) including 40 with visible reactions to radiotherapy and 22 with no reaction to raduiotherapy	150 cancer-free women	7.94 2.12 3.71 3.98 10.1	N.S. (for T241M) 5′ UTR 4541A >G: 0.019 for GG (cases vs. controls) 0.024 for GG+AG (cases vs. controls) IVS5-14 A >G: 0.046 for AG (cancer with visible RT reactions vs. cancer with no reactions) 0.025 for AG+GG (cancer with visible RT reactions vs. cancer with no reactions) 0.001 for GG (IVS5-14 A >G)+XRCC1 [194 R/W+399 R/H+692 Q/Q] (cancer with visible RT reactions vs. cancer with no reactions)	94
Micro-satellite (AC)n intron 3	Belgium	Cervical and endometrial	Pelvis	62 (30 with cervical cancer and 32 with endometrial cancer)	118 cancer-free females	2.56	0.055 (homozygotes for allele 16; cases vs. controls)	104
T241M	US (North Carolina): Whites and Blacks	Breast	Chest	1 417 Whites with cancer+ 894 Blacks with cancer (both include 835 treated with radiotherapy to the chest	1 234 cancer-free Whites and 788 cancer-free Blacks	N/A	N.S. (cancer cases vs. controls) N.S. (RT-treated cases vs. non-irradiated cases)	70
5′ UTR 4541A >G, IVS5-14 A >G	Canada (mostly Caucasians)	Prostate	Brachytherapy (RT-induced bladder and rectal toxicity)	124 RT-treated including 83 who developed clinical late toxicity (of these 83, 28 developed grade ≥2 late bladder or rectal toxicity		Hazard Ratio =4.83	5′ UTR 4541A >G: 0.004 for AA (risk of grade ≥2 chronic toxicity)	38
T241M	Germany	Breast	RT after breast conserving surgery (acute skin toxicity: moist desquamation)	446 RT-treated including 77 who exhibited acute skin toxicity		N/A	N.S. (cases with RT-induced skin toxicity vs. cases with no visible RT-related complications)	71
T241M	Denmark	Breast	Chest (radiogenic subcutaneous fibrosis)	120 RT-treated post-mastectomy females		N/A	N.S. (MM vs. TT) for risk of RT-induced subcutaneous fibrosis	37

Abbreviations: N/A, not available; OR, Odds Ratio; RT, radiotherapy; MM, MT, and TT, genotypes of the T241M XRCC3 gene.

Genes involved in the non-homologous end joining pathway of DNA repair

DNA-dependent protein kinase

DNA-dependent protein kinase (DNA-PK) is a multiprotein complex consisting of the regulatory subunit (Ku heterodimer) and catalytic subunit (DNA protein kinase; DNA-PK_{cs}). Ku heterodimer is comprised from Ku70 and Ku80 subunits that bind to free DNA ends at the break site to keep them in proximity. Then DNA-PK_{cs} binds to the Ku heterodimer forming the DNA-PK complex that stimulates DNA-PK_{cs} activity through the autophosphorylation [126]. This interaction also protects free DNA ends at the site of DSB from nuclease digestion prior to ligation.

DNA-PK is a nuclear serine/threonine kinase, a member of the phosphatidylinositol-3-kinase superfamily. Phosphorylated DNK-PK is active and able to phosphorylate a number of other proteins including those that participate in DNA repair such as Ku70, Ku80, Artemis, XRCC4, replication protein A, Werner syndrome protein, H2AX and several others [127].

M059J cells deficient for DNA-PK_{cs} exhibit a radiosensitive phenotype and are defective in the repair of chromosomal DSBs that reflects a crucial role of this enzyme in maintaining chromosome stability [128]. In DNA-PK-proficient M059K cells, irradiation with low doses of x-rays followed by treatment with wortmannin, an inhibitor of DNA-PK and ATM, results in the recruitment of a slow, error-prone repair process that favored the increased formation of chromosome aberrations [129]. The radiosensitivity of M059J can be complemented by fusion with murine SCID cells harboring human chromosome 8 [130], highlighting the dependence on DNA-PK activity for efficient repair of radiation-induced DNA damage. Down-regulation of DNA-PK using an RNA interference approach also results in significantly enhanced sensitivity to ionizing radiation and DNA-damaging agents [131–134].

Studies on BALB/c mice suggest that genetic alterations within the Prkdc, the mouse ortholog of human DNA-PK_{cs}, could be related to increased radiosensitivity and cancer risk. Two BALB/c strain-specific polymorphisms in the coding region of Prkdc, have been identified [135].The unique PrkdcBALB variant gene carrying the M3844V amino acid substitution in the phosphatidylinositol 3-kinase domain and the R2140C SNP downstream of the putative leucine zipper domain is shown to be associated with decreased DNA-PK catalytic subunit activity and increased susceptibility to radiation-induced genomic instability in primary mammary epithelial cells. In addition, these SNP showed association with radiation-induced apoptosis and lymphomagenesis in mice [136]. These data provide evidence for a possible role of DNA-PK in radiation-induced carcinogenesis. However, no data are available so far on whether genetic variations in DNA-PK can influence predisposition to radiation-induced cancer. Polymorphisms in the human Ku70 and Ku80 genes have been only tested for possible relationship to sporadic breast cancer, but no association has been found [87,137,138].

XRCC4/DNA Ligase IV complex

Together with DNA-PK, x-ray repair cross complementing protein 4 (XRCC4) and DNA ligase IV serve as core components of the NHEJ repair complex on DNA ends [139,140]. XRCC4/DNA ligase IV is able to ligate one strand even when the antiparallel strand can not be ligated as long as at least two base pairs (>4 hydrogen bonds) stabilize the two DNA ends at the overhang. Then, the remaining single-stranded break can be repaired as a single-stranded lesion.

Some evidence suggests that genetic alterations in XRCC4 and ligase IV may promote genomic instability and radiosensitivity. Truncated mutations in XRCC4 result in the deficiency of the protein and radiosensitive phenotype of the respective cell lines [141,142]. In XRCC4 mutant cell lines, both efficiency and fidelity in repair of DSBs are significantly reduced [143]. The 180BR cell line derived from a radiosensitive leukemia patient is characterized by the R278H mutation resided in the catalytic center of ligase IV that leads to impaired activity of the mutated enzyme [144]. Mutations in human ligase IV are linked to Ligase IV syndrome, a disorder associated with microcephaly, several immunodeficiency, cell radiosensitivity and chromosome instability [145–147]. The clinical phenotype of this syndrome is similar to that of severe combined immunodeficiency (SCID) observed in mice lacking XRCC4, ligase IV or any other NHEJ factor.

To date, it is unclear whether XRCC4 and LIG4 polymorphisms could confer predisposition to radiation-induced tumors in the general population or be associated with radiosensitivity in cancer patients due to the lack of large population data. There are only few genetic studies that aimed to evaluate a possible relationship between genetic alterations in the XRCC4 and LIG4 genes and radiosensitivity in humans. Wilding et al. [148] failed to find association between the I134T XRCC4 variant and translocation frequencies in peripheral blood lymphocytes from cancer-free former workers of British Nuclear

Fuels facility at Sellafield. In ligase IV, Borgmann et al. [35] reported a 3012delC mutation in lymphoblastoid cell lines from radiosensitive patients who developed severe side effects after radiotherapy of neck and head cancer. However, heterozygotes for this mutation have also been found in cancer-free controls suggesting that this deletion is a relatively common polymorphism in the general population. The deletion did not affect the coding sequence of the ligase IV gene suggesting that this genetic alteration is most likely functionally neutral [35].

Artemis nuclease and DNA polymerase μ

To aid in the successful repair of DSBs, it has been suggested that NHEJ requires the action of a DNA polymerase. DNA polymerases that could participate in NHEJ include enzymes belonging to the X family that comprises, in addition to DNA polymerase β involved in base-excision repair, polymerases γ, λ, σ and μ [149]. DNA polymerase μ (pol μ), a template-dependent polymerase, was shown to participate in radiation-induced DNA repair through the interaction with Ku in a manner dependent on the XRCC4/ligase IV complex [150]. Pol μ also aids the ligation of complementary ends by the XRCC4/ligase IV and Ku complexes. A role of pol λ and pol σ in repair of radiation-induced DSBs is unclear but can not be excluded.

Artemis is a nuclease with 5′–3′ endonuclease activity that removes 5′ overhangs and shortens 3′ overhangs. In vitro phosphorylation of Artemis by DNA-PK activates the hairpin-opening activity of Artemis, which is a prerequisite for V(D)J recombination [151]. This nuclease was found to be a target for ATM-dependent [152] or DNA-PK-mediated [153] phosphorylation after exposure to ionizing radiation.

Irradiated Artemis-deficient human fibroblasts are unable to repair 15–20% of DSBs suggesting that this endonuclease is responsible for processing of a subset of complex DSBs in cells that have no G1 cell cycle checkpoint defects [154]. On the other hand, Artemis cells display at least moderate radiosensitivity [155,156]. Mutations in this nuclease are associated with a variant of human and murine SCID characterized by poorly developed immune system, radiosensitivity and defect in NHEJ [157–160].

No studies on genetic alterations within pol μ, pol λ and Artemis and their possible association with radiation-induced cancer have been reported to date. However, these genes remain to be promising candidates for biomarkers of clinical radiosensitivity in cancer patients.

Conclusion

To date, significant advances have been achieved in evaluating the role of genetic variations within DNA repair genes in clinical radiosensitivity in cancer. Missense mutations in ATM associated with the AT disease phenotype and truncated mutations in NBS1 associated with Nijmegen breakage syndrome are likely to contribute to increased risk of radiation-induced cancer in general population. Several polymorphisms within the RAD51 and XRCC3 have been suggested to be associated with radiosensitivity in cancer.

Most of case-control studies searching for the contribution of genetic alterations within DNA repair genes to susceptibility to radiation-related cancer have been focused on genes involved in HR. However, since NHEJ is likely to be the major mechanism of repair of radiation-induced DSBs in humans, a role of NHEJ-linked genes in predisposition to radiation-induced cancer remains to be explored in greater detail. Additional efforts are needed to find novel genetic variants of DNA repair genes involved in HR that confer susceptibility to radiation-induced cancer as well as to confirm already discovered disease-associated variants.

Recently, several national and international clinical research projects have been initiated to find markers of genetic predisposition to radiation-induced cancer and clinical radiosensitivity in tumor tissues. National projects include Japanese RadGenomics [161], and Assessment of Polymorphisms for Predicting the Effects of Radiotherapy (RAPPER) and Radiation Complications and Epidemiology (RACE) studies, both of which are UK-based [162]. International projects are presented by the European-based Genetic Pathways for the Prediction of the Effects of Irradiation (GENEPI) [163] and Genetic Predictors of Adverse Radiotherapy (Gene-PARE) [164] studies. In contrast to the GENEPI project involved almost only Caucasians, in the Gene-PARE project, approximately 500 African-Americans will be screened for genetic variants associated with clinical radiosensitivity. The projects are expected to include the evaluation of a variety of candidate genes including DNA repair genes.

To date, the small numbers of individuals showing either an early adverse reaction or a late reaction or both that have been included in many association studies exclude the possibility of addressing whether specific SNPs can influence the temporal aspect of this radiosensitivity. Further association studies in well-characterized large cohorts will be necessary to identify genes that influence the temporal aspects of this adverse response to radiotherapy. However, over

the next few years, a considerable molecular characterization of large-scale cohorts of individuals who show therapeutic radiation sensitivity is likely to be achieved. The construction and use of genetic-risk profiles may provide significant improvements in the efficacy of population-based programs of intervention for cancers. This also should help in predicting radiosensitivity that will eventually allow individual tailoring of treatment and reduce the risk of developing acute reactions in anticancer radiotherapy.

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