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Review Article

Influence of *XRCC1* Genetic Polymorphisms on Ionizing Radiation-Induced DNA Damage and Repair

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It is well known that ionizing radiation (IR) can damage DNA through a direct action, producing single- and double-strand breaks on DNA double helix, as well as an indirect effect by generating oxygen reactive species in the cells. Mammals have evolved several and distinct DNA repair pathways in order to maintain genomic stability and avoid tumour cell transformation. This review reports important data showing a huge interindividual variability on sensitivity to IR and in susceptibility to developing cancer; this variability is principally represented by genetic polymorphisms, that is, DNA repair gene polymorphisms. In particular we have focussed on single nucleotide polymorphisms (SNPs) of *XRCC1*, a gene that encodes for a scaffold protein involved basically in Base Excision Repair (BER). In this paper we have reported and presented recent studies that show an influence of *XRCC1* variants on DNA repair capacity and susceptibility to breast cancer.

1. Introduction

During evolution, mammalian cells have optimised distinct pathways to repair DNA preserving genome integrity and avoiding fixing of harmful mutations. DNA lesions could be caused by external insults as well as by exposure to mutagenic substances. They could also be produced endogenously, for example, by reactive oxygen species generated during physiological processes.

Five main different repair mechanisms have been described in humans: MMR (Mismatch Repair), BER (Base Excision Repair), NER (Nucleotide Excision Repair), HRR (Homologous Recombination Repair), and NHEJ (Nonhomologous End Joining).

MMR is a postreplicative mechanism that ensures the application of the Watson-Crick base pairing principle on DNA double helix, discriminating mismatches resulting from DNA polymerase errors, and rectifying them to avoid mutation [1].

Generally, BER corrects DNA base lesions due to oxidative, alkylation, deamination damages via two general pathways: short patch and long patch [2]; NER is a more versatile pathway that senses the distortion caused by a base damaged by chemical (i.e., cross-linking agents) or physical (i.e., UV) agents and excises a tract of few nucleotides around the lesion [3].

In BER and NER mechanisms, single-strand breaks (SSBs) are an enzymatic consequence of the repair of damaged DNA but they could represent a serious risk for cells if they are not filled by a polymerase and rejoined by DNA ligase. In fact during DNA replication SSBs could be converted to more lethal DNA double-strand breaks (DBSs). DSBs could generate deletions, chromosome translocations, hence genomic instability [4, 5] and in some circumstances induce cell cycle arrest and apoptosis [6, 7].

Homologous Recombination Repair (HRR) and Nonhomologous DNA-End Joining (NHEJ) are the two major pathways of DSBs repair. A third system, single-strand annealing (SSA), shares HRR and NHEJ components. The fundamental difference between HRR and NHEJ is the dependence on DNA homology template [8].

All DNA repair pathways are finely regulated and many of the genes involved in these mechanisms are highly conserved from bacteria to humans. This high conservation degree indicates the importance of repair pathways in living organisms.

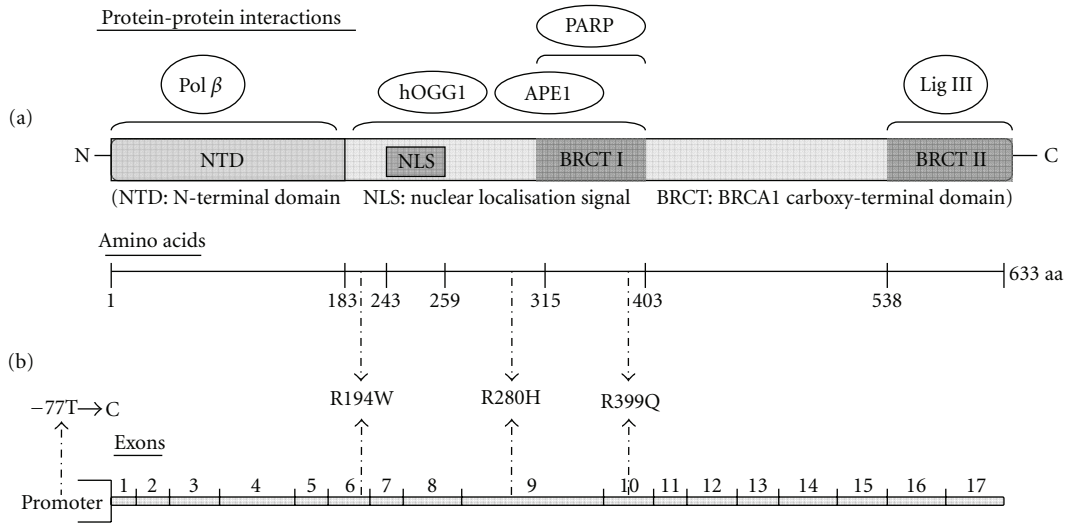

Figure 1: Human XRCC1 protein and gene structure. (a) The diagram shows XRCC1 domains and the regions of interaction with other components of BER. (b) The diagram shows the structure of the gene with the most common and studied single nucleotide polymorphisms (SNPs): −77 T → C, R194W, R280H and R399Q. Each of them is detailed in the text.

In literature it has been well documented that defects in DNA repair are associated with human disorders. Several genetic diseases are linked to mutations in genes involved in DNA repair, that is, XP Xeroderma Pigmentosum, CS Cockayne Syndrome, FA Fanconi Anemia, and NBS Nijmegen Breakage Syndrome. Furthermore, studies conducted on knockout and mutant animal models have suggested the key function of specific components of DNA repair machineries.

Despite the lack of a pathological phenotype, humans bearing variant alleles of DNA repair genes could show a different individual response to DNA damage.

The principal source of interindividual variability is represented by genetic polymorphisms. The presence of polymorphic alleles in DNA repair genes may alter the repair capacity modifying the biological responses to exogenous and endogenous DNA insults, both at cellular and tissue level, and the individual susceptibility in developing different kind of disease, such as cancer.

In this review we focussed on the influence of DNA repair polymorphisms on human individual sensitivity to Ionising Radiation (IR) treatment and susceptibility to cancer; in particular we are interested in better understanding whether SNPs in *XRCC1* gene, encoding, for a scaffold protein involved basically in BER pathway, could impair DNA repair efficiency so increasing the risk to develop tumour, such as sporadic breast cancer.

2. *XRCC1* Polymorphisms and IR Exposure

XRCC genes, abbreviation of X-ray cross complementing, are components of several different damage recovery pathways, and XRCC proteins do not show similarity in biochemical functions.

The human *XRCC1* (X-ray repair cross-complementing group 1) gene, located on chromosome 19q13.2, encodes for a 633aa protein (Figure 1) that plays an important role in BER and single-strand breaks repair (SSBR), following exposure to endogenous reactive oxygen species, IR or alkylating agents [9, 10]. Additionally, XRCC1 seems to take part also in DSBs repair [11, 12]. Lévy et al. [11] demonstrated that the DNA-dependent protein kinase (DNA-PK), a key factor in NHEJ, is able to phosphorylate XRCC1 (Ser 371) after ionizing radiation that causes XRCC1 dimer dissociation. This posttranslation modification seems to be important for rejoining DSBs in response to DNA damage caused by IR, as also showed by the failure of S371L mutant XRCC1 to rescue DSBs repair defect in deficient EM9 cells.

In 2004 Audebert et al. showed an involvement of the XRCC1/Lig III complex in DSBs rejoining. The complex, otherwise involved in BER, could act in an alternative end-joining mechanism that complements DNA-PK/XRCC4/Lig IV dependent NHEJ [12].

A lot of information about XRCC1 function has been derived from mutant mammalian cell lines; *XRCC1* mutants were initially identified in the AA8 strain of Chinese hamster ovary (CHO) cells, and four of these, denoted EM7, EM9, EM-C11 and EM-C12, represent a model to study the consequence of the lack or a reduced level of this protein [13].

The XRCC1 is a scaffold protein that interacts with other many components of BER as DNA polymerase β, APE1, hOGG1, poly-(ADP-ribose) polymerase and DNA ligase III in the NH2-terminal, central, and COOH-terminal regions, respectively, as resumed in Figure 1 [14–16].

In 1998 Shen et al. [17] described three polymorphisms of *XRCC1* gene, which resulted in non-conservative amino-acid changes at evolutionary conserved regions: C → T substitution in codon 194 of exon 6 (Arg to Trp); G → A substitution in codon 280 of exon 9 (Arg to His) and G → A substitution in codon 399 of exon 10 (Arg to Gln). (Figure 1)

Recently, Hao et al. [18] identified, in Chinese population, another variant in the *XRCC1* gene located in the

5′UTR (5′-untraslated region), −77 T → C. (Figure 1). Afterwards this polymorphism was also confirmed to be present, with a higher frequency, in Caucasian population [19, 20].

All these single nucleotide polymorphisms (SNPs) could alter the XRCC1 function and impair DNA repair efficiency or accuracy. In 1983, Setlow [21] claimed that healthy subjects differ in their intrinsic capacity in repairing DNA damage and this variation could be a result of variants in DNA repair genes that consequently can modify the individual susceptibility to radiation exposure.

A report by Lunn et al. [22] suggested that *XRCC1* codon 399 polymorphism located within the BRCT domain [23] which interacts with PARP, may result in deficient DNA repair. More recently, Taylor et al. (2002) showed that although BRCT1 domain is critical for efficient single-strand break repair and cell survival, 399 polymorphism located within this domain did not appear to significantly affect XRCC1 function. On the contrary, by using molecular dynamics techniques Monaco et al. (2007) predicted the structure of wild-type and polymorphic form of BRCT1 domain of XRCC1 demonstrating that the polymorphism in exon 10 changed the XRCC1's secondary structure. These contrasting results call for further investigations to clarify whether the Arg → Gln substitution in codon 399 could affect DNA repair capability [24, 25].

Hu and co-workers (2001) evaluated whether amino acid substitution variants of DNA repair genes, that is, *XRCC1-399*, contribute to ionizing radiation (IR) susceptibility as measured by prolonged cell cycle G_2 delay. In γ-irradiated lymphocytes from disease-free controls, they found a higher mitotic delay in subjects with Arg/Gln and Gln/Gln genotypes than homozygous wild-type ones. The difference, however, was not statistically significant. In conclusion, they indicated that the *XRCC1* Arg/Gln genotype may influence cellular response to IR, particularly in women with positive family history (FH) of breast cancer [26].

In order to elucidate the influence of the most common SNP of *XRCC1* (Arg399Gln) on the individual DNA repair capacity, Cornetta et al. [27] assessed the repair capacity through alkaline Comet assay in human peripheral blood cells of healthy subjects treated *in vitro* with X rays. They observed that subjects with *XRCC1* variant Gln/Gln genotype exhibited lower values of DNA damage than those with homozygous wild-type (Arg/Arg) and heterozygous (Arg/Gln) genotypes, both at basal level and after treatment. On the contrary, the baseline DNA damage, measured as Tail Moment, was found to be increased in healthy individuals bearing the *XRCC1* 399Gln variant allele in Weng and colleagues' work [28].

Hence, Cornetta et al. [27] concluded that individuals bearing Gln/Gln genotype had fewer DNA breaks and resolved open breaks faster than homozygote wt and heterozygote subjects. Anyway, as they noticed, the Comet assay does not provide information about the fidelity of DNA repair and misrepaired lesions could lead to chromosomal-type damage. Angelini et al. [29] demonstrated that subject exposed to IR (both X- and γ-rays) with *XRCC1* variant genotypes had a higher frequency of micronuclei (MN) with respect to wild type ones. Furthermore, a high chromosomal damage could trigger off apoptosis in cells with 399 polymorphic genotypes consequently resulting protective through the elimination of potentially transformed cells. This hypothesis is supported by Seedhouse et al. [30] who showed a protective effect of *XRCC1*-399 variant allele against the development of therapy-related acute myeloblastic leukemia (t-AML).

On the contrary, Aka et al., [31] showed that *XRCC1-399* polymorphism resulted in higher residual DNA values, measured by Comet assay, after γ-ray treatment and Godderis et al., [32] in collusion with Rzeszowska-Wolny et al. [33], performing Comet assay and MN analysis, concluded that *XRCC1*-399 did not seem to influence DNA damage repair after γ-rays exposure.

The individual susceptibility to IR can also differ in subjects affected by cancer, as interindividual variation in therapeutic exposure to ionising radiation response revealed. Moreover, cancer patients seem to be more radiosensitive than healthy persons: Scott et al. [34] found that about 40% of breast cancer (BC) patients are radiosensitive in comparison to about 9% of healthy controls.

Recently, our group analysed the response to IR exposure in sporadic BC patients and healthy controls by measuring DNA damage through alkaline Comet assay [35]. We did not observe a great interindividual variation in either group but we found that BC patients were more radiosensitive and exhibited a significantly higher mean of basal and IR-induced DNA damage when compared to healthy controls. Anyhow, in this study the impairment of BC repair capacity did not result to be associated with *XRCC1*-399 polymorphism. But, interestingly the reduced repair ability in BC patients was related to high degrees of tissue side effects.

This is in agreement with results reported by Alapetite and colleagues who observed that BC patients with most severe complications showed impaired rejoining as analysed through alkaline Comet assay [36].

3. *XRCC1* Polymorphisms and Risk of Developing Cancer

Related to an impaired DNA repair capacity and an increased mutagenesis, polymorphisms in DNA repair genes could also modify the risk of developing cancer. Epidemiological studies were focussed on assessing a possible link between genetic factors, in particular low penetrance genes as well as SNPs, and increased/decreased risk of tumour. Along this line Breast Cancer (BC) is a very interesting field of research.

It is the most common cause of cancer death in women worldwide. Most etiologic factors are established [37–39], but concerning the association between DNA repair SNPs and the sporadic form of this tumour, literature data are often contradictory.

Recently, in 2009, Huang et al. [40] performed a meta-analysis that collected data about the association between breast cancer and the *XRCC1* polymorphisms Arg194Trp (9411cases and 9783 controls), Arg399Gln (22 481 cases and 23 905 controls) and Arg280His (6062 cases and 5864 controls) in different inheritance models [dominant model:

Table 1: Reported studies about the association of *XRCC1-399* polymorphism and DNA repair capacity.

XRCC1-399 GENOTYPE	IR EXPOSURE	EFFECTS ON DNA REPAIR CAPACITY	REFERENCES
Variant	γ-rays	Higher mitotic delay index	Hu et al., 2001 [26]
Variant	X-and γ-rays	Higher MN frequency	Angelini et al., 2005 [29]
Variant	γ-rays	No-one on DNA damage values (Comet) Higher background frequency of MN	Rzeszowska et al., 2005 [33]
Variant	γ-rays	Higher residual damage (Comet)	Aka et al., 2006 [31]
Gln399Gln	X-rays	Lower DNA damage (Comet)	Cornetta et al., 2006 [27]
Variant	γ-rays	No-one on DNA damage values (Comet) and MNCB	Godderis et al., 2006 [32]
Variant	No	Higher basal DNA damage (Comet)	Weng et al., 2009 [28]

Variant= Arg399Gln + Gln399Gln.

Table 2: Reported studies about the association of *XRCC1-399* and BC risk.

Protective effect	Breast Cancer Association Consortium, 2006 [41]
	Saadat et al., 2008 [42]
Risk factor	Duel et al., 2001 [43]
	Moullan et al., 2003 [44]
	Smith et al., 2003 [39]
	Zhang et al., 2006 [45]
	Huang et al., 2009 [40]
	Sterpone et al., 2010 [20]

homozygous wild-type versus (homozygous mutant+heterozygous) and recessive model: (homozygous wild-type+heterozygous) versus homozygous mutant).

Reference to SNPs in codon 194 and 280, they did not appear to be risk factors for breast cancer but case-control studies on Arg399Gln have provided conflicting results.

About *XRCC1* Arg399Gln polymorphism, in 2006, Breast Cancer Association Consortium [41] reported that there was no evidence of an association of BC with this SNP and with a large meta-analysis Saadat et al. [42] concluded that this polymorphism was associated with BC risk in studies from Asian countries but not from Western countries, when using a recessive model. On the other hand, Huang [40] suggested that both under recessive and dominant models, the Arg399Gln was associated with a trend of increased breast cancer risk, regardless of ethnic subgroups division. In agreement with this conclusion and several other studies [39, 43–45], our group showed a slightly increase of BC risk in Caucasians using dominant model: women bearing at least one *XRCC1-399* variant allele seem to be at higher risk of developing this tumour [20].

Additionally, we found that the presence of variant allele at codon 399 combined with the variant allele in the promoter, −77 C which alone was not associated with BC, determined a significantly higher risk of developing this cancer: this combination could affect strand breaks repair as a consequence of the reduced availability of XRCC1 transcript, even in the variant form.

To date, only one other study reported the analysis of haplotypes considering the promoter SNP together with 194, 280 and 399 polymorphisms in BC patients and healthy controls. In collusion with our analysis [20], Brem et al. did not find any association between BC and promoter polymorphism; BC risk was positively associated with −77, 194, and 399 wild-type alleles and 280 variant allele haplotype, even if the *P* value was not significant [19].

The haplotype risk association could be an interesting and more complete approach than association studies in which only individual *XRCC1* SNPs are considered, thus leading to errors in risk estimation.

4. Conclusions

In this review we have focussed on the effect of genetic basis on interindividual differences in response to DNA damaging agents. In particular we have considered DNA damage caused by ionizing radiation, commonly used in the care of tumour.

The consequences of IR exposure could be very serious and radiation injury may develop months to years later after treatment with numerous and individual manifestations. Hence, radiation-induced DNA damage and its repair play a critical role for the susceptibility of patients affected by cancer to side effects after radiotherapy.

In conclusion, as the reported studies want to support (see Table 1 and Table 2), it is an important goal of biological

and clinical research to detect genetic components like DNA repair gene polymorphisms as possible indicators of radiosensitivity in order to adjust radiotherapy protocols for both sensitive and resistant patients.

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