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The impact of pharmacogenetics on radiation therapy outcome in cancer patients. A focus on DNA damage response genes

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ABSTRACT

More than half of cancer patients are treated by radiation therapy, with a wide inter-patient variability in tumour response. Recent advances have been made in understanding molecular mechanisms that govern the behaviour of tumour cells and tissues exposed to ionizing radiation. Accumulating data suggest an important role of DNA damage response genes, including DNA repair (especially double-strand breaks), apoptosis and cell-cycle control genes. It has been hypothesized that frequent germinal polymorphisms, most often single-nucleotide polymorphisms, in DNA damage response genes may impact tumour response and clinical outcome for patients receiving a radiotherapy-based treatment. We reviewed literature covering the relationships between candidate gene polymorphisms in DNA damage response and the efficacy of a radiation-based treatment. Although several methodological limitations may preclude a definitive conclusion, single nucleotide polymorphisms of several candidate genes such as ERCC- or XRCC-family genes seem to be potential predictive biomarkers of radiotherapy efficacy, even though not strictly involved in radiotherapy-induced double-strand breaks repair. In order to improve the relevance of clinical results, and our interpretation of them, we draw a parallel between clinical findings and available preclinical data on polymorphism functionality. Clinical findings require validation in larger replication studies and open the prospect of future clinical trials.

Introduction

The treatment of cancer is most often based on a multimodality strategy, commonly involving surgery, chemotherapy (CT) and radiotherapy (RT). The latter plays a key role as more than half of the patients presenting with a cancer will undergo RT,[1] with variable efficacy. For about two decades, great efforts in clinical research have been made in clinical research to optimize RT modalities (intensity-modulation, stereotaxy, altered fractionation), allowing dose escalation in the targeted tumour while limiting damage to surrounding normal tissues. On the other hand, recent progress in our understanding of the biological basis of cells and tissue response to ionizing radiation has highlighted some key molecular markers which could predict the efficacy or toxicity of RT. Numerous genes are involved in these molecular processes such as DNA repair, apoptosis, cell-cycle control, signal transduction pathway and tumour microenvironment modulation.[2]

Apart from some rare but often deleterious genetic mutations, the normal human genome presents numerous germinal variations in DNA sequence called polymorphisms. These variations can be short tandem repeats, copy number variations of a gene or, in more than 90% of cases, single-nucleotide polymorphisms (SNPs). Unlike genetic mutations, SNPs occur very frequently (10 million common SNPs with a minor-allele frequency exceeding 5%)[3] and do not carry major deleterious clinical consequences, whatever the nature of the SNP, i.e. synonymous (silent) SNPs or non-synonymous SNPs (amino acid substitution).[4,5] However, such genetic variations can alter gene expression or protein function, predisposing subjects to disease or influencing their response to a given treatment. Of note, silent SNPs may also modify gene expression, even if the underlying mechanisms remain unclear.[6] Several SNPs have already been linked to susceptibility to cancer.[7] More recently, converging data have suggested that genetic variants could also contribute to inter-patient variability in radioresponse and cancer treatment outcome.[8,9]

Ionizing radiation alters DNA structure, producing specific lesions such as base impairment, single-strand breaks (SSB) and double-strand breaks (DSB), that can lead to cell-cycle arrest

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and apoptosis.[10] A 1 Gy dose can produce more than 2000 base damage, 1000 SSB, 40 DSB and 30 DNA cross-links.[11] To note, DSB are the most lethal DNA damage induced by RT. Each type of DNA alteration can be recognized and removed by specific DNA repair mechanisms[12] (Fig. 1).

Cell-cycle checkpoints are another major component of the DNA damage response,[2] even though some limitations of radiation-induced cell cycle checkpoints have been suggested.[20] Checkpoints are surveillance mechanisms acting between cell cycle phase transitions (G1/S and G2/M) that prevent DNA damage accumulation and genomic instability[21] (Fig. 2).

One of the main cell death mechanisms in response to irradiation is apoptosis, even though pro-apoptotic mechanisms are lost or impaired during progression in most solid tumours.[24] P53 plays a pivotal role in both radiation-induced intrinsic and extrinsic apoptosis pathways, as its activation can lead damaged cells to engage in rapid interphase apoptosis (Fig. 3). Alternative cell death modalities related to ionizing radiation have been described, such as autophagy, mitotic cell death and senescence. The latter, mainly involving p21, is currently raising growing interest.[23,24]

DNA repair, cell-cycle checkpoints and apoptosis process have been described as constituting part of a signalling network referred to as DNA damage response (DDR), with continuing interactions and cross-talk, which can drive phase-specific repair mechanisms when DNA is damaged.[22] DDR defects are implicated in tumorigenesis, but can also modulate sensitivity to DNA-damaging agents in tumour cells. This can require the development and use of combined treatment modalities for DNA damage,[25] in which ionizing radiation plays a central role.

In this radiobiological context, we chose to focus this review on gene polymorphisms in DNA repair, apoptosis and cell-cycle control pathways, which may play a role in RT response. We thus reviewed available literature data dealing with relationships between SNPs in candidate genes and clinical efficacy for cancer patients receiving a radiotherapy-based treatment, whatever the type of tumour.

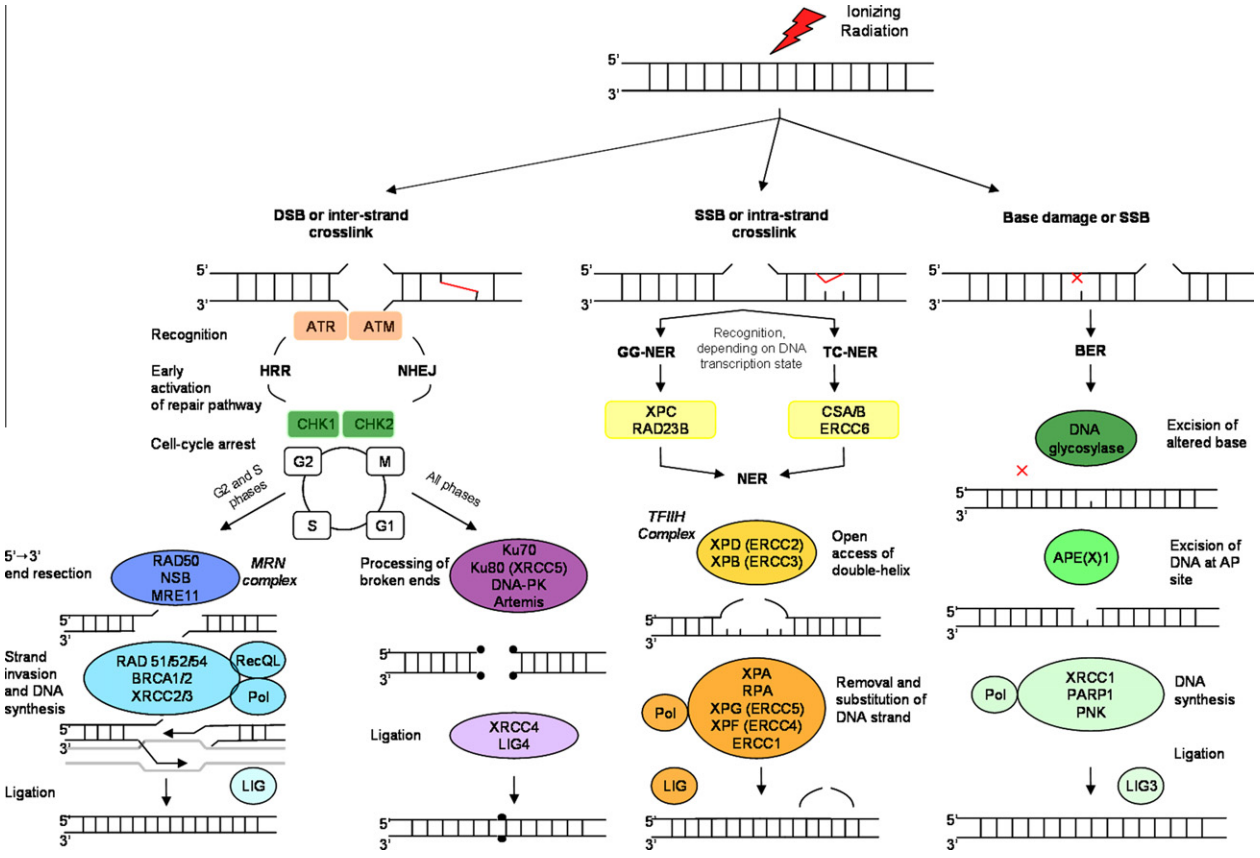

Fig. 1. DNA repair mechanisms. Double-strand breaks (DSB) are the most lethal DNA damages induced by radiotherapy. DSB repair mechanisms include both homologous and non-homologous recombination pathways.[13] There is first a recognition of impaired DNA (ATM, ATR), followed by a cell-cycle arrest (CHK1, CHK2). Homologous recombination repair (HRR) pathway restores damaged DNA using the homologous chromosome as a template during S and G2 phases of the cell-cycle. Multiple proteins are involved in DNA synthesis (RAD family, NSB, MRE11, XRCC2, XRCC3, RecQL, BRCA1, BRCA2 and others).[14] Non-homologous end joining (NHEJ), the main DSB repair mechanism in humans, is able to link the extremities of the broken DNA, without resynthesis of lost DNA. For NHEJ, several proteins are concerned, such as Ku70, Ku80 (XRCC5), DNA-PK, XRCC4 and LIG4.[13] Response to DSB thus involves complex signal-transduction, cell-cycle-checkpoint and repair pathways.[15] SSB also require a specific repair process, involving the nucleotide excision repair (NER) complex. NER is divided into two sub-pathways: the global genome NER (GG-NER) and the transcription-coupled NER (TC-NER), depending on the transcription state of DNA. These two sub-pathways only differ in damaged DNA recognition: XPC-RAD23B complex in GG-NER, or CSA and CSB/ERCC6 in TC-NER. XP-genes family encode for most proteins involved in the successive phases of DNA repair, allowing open access to the double-helix (XPD/ERCC2, XPB/ERCC3) and the removal and substitution of the DNA strand (XPA, RPA, XPG/ERCC5, XPF/ERCC4 and ERCC1).[16] NER also plays a key role in repairing a variety of distorting lesions, notably platinum-induced DNA adducts[17] and intrastrand cross-links.[18] Base excision repair (BER) pathway allows accurate removal of damaged bases as well as correction of SSB. Firstly, a specific DNA glycosylase and the endonuclease APE1 excise the altered base or strand, and then XRCC1, PARP1, PNK and LIG3 contribute to synthesis and stabilisation of DNA.[19] Abbreviations: ATR: Ataxia-telangectasia and Rad-3 related; ATM: Ataxia-telangectasia mutated; CHK: Checkpoint; RAD: Radiation response yeast homolog; NSB1: Nijmegen breakage syndrome 1; MRE11: Meiotic recombination homolog 11; BRCA: Breast cancer protein; XRCC: X-ray repair cross-complementing group; Pol: DNA polymerase; LIG: Ligase; DNA-PK: DNA related protein kinase; CSA/B: Cockrane syndrome A/B; XP : Xeroderma pigmentosum complementing group; ERCC : Excision repair cross-complementing group; APE1: Apurinic-apyriminidic endonuclease 1; PARP1: PolyADP ribose polymerase 1; PNK: Polynucleotide kinase.