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Review

Homologous recombination and prostate cancer: A model for novel DNA repair targets and therapies

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Abstract

Using elegant targeting techniques such as IMRT, radiation oncology has improved the therapeutic ratio of prostate cancer radiotherapy through increased physical precision (e.g. increased local control through dose-escalation without increased normal tissue toxicity). The therapeutic ratio might be further improved by the addition of ''biologic precision and escalation'' pertaining to the use of molecular inhibitors of DNA damage sensing and repair. Indeed, proteins involved in the ATM-p53 damage signaling axis and the homologous (HR) and non-homologous end-joining (NHEJ) pathways of DNA double-strand break (DNA-dsb) rejoining pathways may be attractive candidates to elucidate cancer risk, prognosis, prediction of response and to develop sensitizers towards oxic and hypoxic prostate tumor cells. This review highlights DNA-dsb in prostate cancer research in terms of novel molecular inhibitors, the role of the microenvironment in DNA-dsb repair and potential DNA-dsb biomarkers for clinical trials.

Keywords: Hypoxia; Prostate cancer; DNA repair; DNA double-strand breaks; End-joining; Homologous recombination; Cell cycle; Biomarkers; RAD51; ATM; ATR; Carcinogenesis; Chemotherapy; Radiotherapy; Androgen deprivation

Prostate cancer radiotherapy and the therapeutic ratio

This past year in Canada more than 20,000 patients were diagnosed with prostate cancer and 2000 men will die of their disease. These numbers are approximately 10-fold higher in the United States. Similar data exist for most Western countries.

Radiotherapy is an important curative treatment option in prostate cancer as a single modality or combined with hormonal treatment. Each daily treatment during a fractionated prostate radiotherapy protocol leads to a number of DNA lesions clustered with the chromatin. Ionizing radiation (IR) induces DNA single- or double-strand breaks (DNA-ssb or DNA-dsbs), altered or lost DNA bases and DNA-DNA or DNA-protein cross-links. The DNA-dsb is initially recognized by the TRF2 and MRE11-RAD50-NBS1 (MRN) complexes (reviewed in Choudhury et al. [26]) and thereafter activates the ATM-CHK2-p53 and ATR-CHK1 sensing and transduction kinase pathways to enact G1, S and G2 cell cycle checkpoints. These checkpoints run parallel to the recruitment of DNA-dsb repair proteins within the homologous (HR) and non-homologous (NHEJ) pathways of repair [26] (See Fig. 1a).

In modern radiotherapy, biological targeting using novel inhibitors requires an understanding of tissue responses pertaining to relative cell proliferation, DNA repair and cell death (e.g. apoptosis, mitotic catastrophe and/or tumor cell senescence) [41] (Fig. 1a). In addition, prostate cancer patients exhibit large patient-to-patient variability in normal tissue reactions after radiotherapy that may relate to individual genetic profiles. For example, dose-escalated pelvic and prostate radiotherapy is associated with toxicity to the bladder and rectum; this can be objectively scored by clinicians or patients based on validated questionnaires and scales (e.g. RTOG, LENT-SOMA scoring scales). To date, little is known about the genetic variation underlying such recorded inter-individual differences in normal tissue reactions following prostate radiotherapy.

Similarly, prediction of response is also required for the radiocurability of tumors. In intermediate-risk prostate cancer (i.e. Stage T1/T2 localized to the prostate; Gleason score (GS) <8 and prostate-specific antigen (PSA) <20 ng/ml), increasing rates of local control of the order of 55—80% have been achieved using dose-escalated IMRT/conformal treatment. Yet, this risk group is clinically heterogeneous whereby both prognosis and clinical radio-response are highly variable. Currently, prediction of radiocurability (reflected by a prolonged PSA nadir) is predicated upon the use of the pre-treatment PSA, pathologic Gleason score, the number of diagnostic positive biopsies, PSA doubling time and T-stage [59]. Despite the use of these traditional factors, the biochemical failure following radiotherapy (i.e. increasing PSA after an initial nadir) can range from

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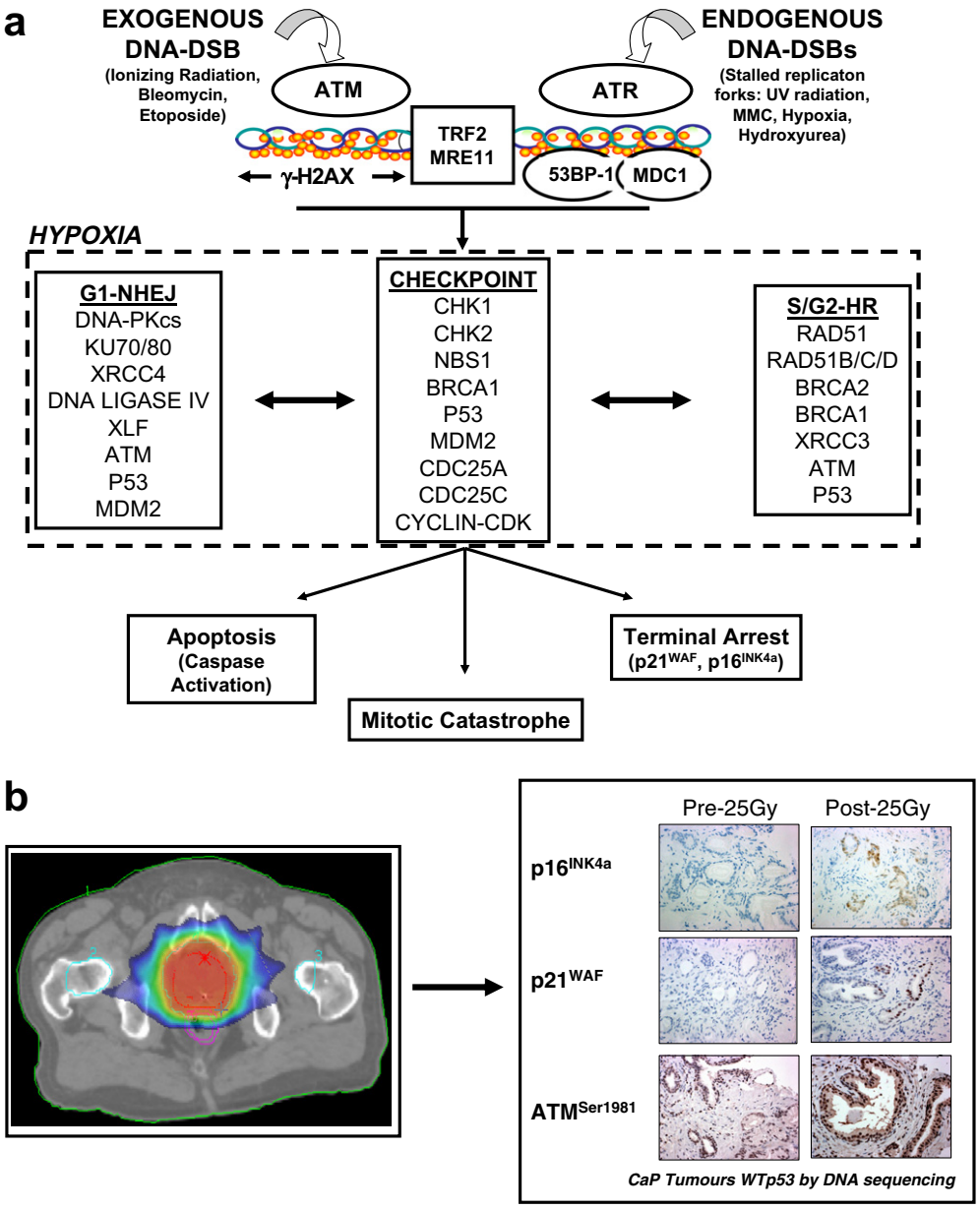

Fig. 1. (a) Cells have a series of ATM- and ATR-dependent pathways to deal with exogenous (chemotherapy and radiotherapy) and endogenous (DNA-recombination associated) DNA double strand breaks (DNA-dsbs). Appropriate checkpoint control and DNA repair determines cell survival or cell death. Depending on the tissue type, cell death will occur through activation of apoptosis, mitotic catastrophe or terminal growth arrest. Initially DNA break sensing by TRF2-MRN leads to the recruitment of 53BP-1, MDC1, BRCA1 and specific DNA-dsb repair proteins within γ-H2AX-positive irradiated chromatin. Both ATM and DNA-PKcs redundantly phosphorylate H2AX around the sites of DNA damage. This activates a number of proteins as cell cycle checkpoint controls to drive the G1, S and G2/M arrests following DNA damage. NHEJ repair involves the DNA-PK, XRCC4/DNA-Ligase IV and ATM–Artemis complexes. This pathway is preferential to the G1 phase of the cell cycle and is error-prone. The HR pathway is preferential to the S and G2 phases of the cell cycle when a sister chromosome or chromatid is available for direct base-pairing to effect error-free repair of a DNA-dsb. In addition to DNA-dsb induction, cellular anoxia/hypoxia can alter the response to DNA breaks through activation of ATM/ATR pathways in the absence of exogenous breaks and also by repressing HR repair [26,54]. (b) Unpublished data from the author's translational oncology program showing evidence of up-regulation of $p16^{INK4a}$, $p21^{WAF}$ and auto-phosphorylation of the ATM protein ($ATM^{Ser1981}$) in WTp53-expressing prostate tissues (e.g. compare staining pre- and post-25Gy). Tissues were derived from high-risk prostate cancer patients treated in a novel Phase I study giving 25 Gy in five fractions of IMRT pre-operative radiotherapy prior to radical prostatectomy.

20% to 45% in this group and it would be helpful to have novel genetic and microenvironmental (e.g. hypoxia) biomarkers to aid in predicting clinical response [59]. These would include biomarkers of DNA damage signaling and repair.

Novel biomarkers could also help in the current controversy regarding the cellular repair within prostate cancers *in vivo* during clinical treatment. Selected clinical data support prostate cancer having an intrinsic low α/β ratio (e.g. a