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Journal of Veterinary Medicine and Research

Editorial

DNA Double-Strand Break Repair and Anti-Cancer Therapy

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Submitted: 02 April 2014

Accepted: 03 June 2014

Published: 07 June 2014

EDITORIAL

DNA double-strand breaks (DSBs) are deleterious because they frequently lead togenomic instability, cell death or cancer [1]. However, the formation of DSBs is also a key molecular event underlying the therapeutic effects of many anti-cancer agents. Cells have evolved complex network of DSB sensing and repair systems, collectively referred to as the DNA damage response and repair (DDR) pathway [2]. Manipulation of the DDR pathway has recently emerged as an alternative strategy in cancer therapy [3]. The two major DSB repair mechanisms are the error-prone non-homologous end-joining (NHEJ) and error-free homologous recombination (HR). NHEJ repairs DSBs by direct ligation of the DSB ends that are either processed or unprocessed [4]. The classical NHEJ pathway requires the actions of several independent protein complexes—the Ku70/Ku80 heterodimer, the DNA-PKcs-Artemis nuclease and the XLF-XRCC4-LIG IV ligase—together with the polymerases λ and μ. NHEJ operates throughout the cell cycle whereas HR is mainly active in the S/G2 phases since it requires a donor template [5]. Besides cell cycle dependent selection, the pathway choice of NHEJ and HR is additionally controlled by the competition between the loading of 53BP1 and BRCA1 onto DSB-containing chromatin [6-9]. Proper DSB repair also requires the activities of DNA damage responsive protein kinases, which facilitate the activation of checkpoints to ensure cell cycle delay during DSB repair. The two key kinases are ATM and ATR. ATM, activated by DSBs, phosphorylates CHK2 and transduces the signal to p53 for G1/S checkpoint arrest whereas the ATR kinase is activated by single-strand DNA and phosphorylates CHK1 for G2/M arrest [10,11].

One of the pertinent effects of many anti-cancer treatments is induction of DSBs in the genome. For instance, ionizing radiation (IR) leads to unbiased introduction of DSBs, which, if unrepaired, can trigger mitotic catastrophe and cell death [3,12]. Radiomimetic drugs (e.g. bleomycin) have similar effects as radiotherapy. DSBs can be also created amid repair and the processing of other types of DNA lesions. For example,Topo I inhibitors, such as irinotecan, create single-strand breaks (SSBs) that can subsequently be converted to DSBs during DNA replication. Topo II inhibitors, such as etoposide and doxorubicin, generate DSBs throughout the cell cycle. Replication inhibitors can cause replication fork collapse and the formation of one-ended DSBs, whereas DNA interstrand crosslinks created by cisplatin and mitomycin C can be processed into DSBs during repair. Since most cancer cells undergo unrestricted cellular proliferation, DNA replication is a clear target for chemotherapeutic intervention. In fact, combinational anti-cancer treatment strategies are often used to maximize the therapeutic efficacy and minimize the development of anti-cancer drug resistance. Because most of the DSBs induced by IR and Topo II inhibitors can be repaired by NHEJ, inhibition of NHEJ is expected to block a significant fraction of DSB repair in IR-treated tumor cells. Indeed, the DNA-PKcs inhibitor NU7026 has been shown to enhance sensitivity to IR and etoposide in patient-derived B-CLL cells [13], and a dual DNA-PK and mTOR inhibitor CC-115 is currently in Phase I clinical trial.Formation of secondary DSBs likewise occurs in cells treated with Topo I poisons, replication inhibitors or crosslinking agents. And since this class of DSBs is largely dependent on HR for repair, strategies for HR blocking are presently also being explored [3]. Another strategy to silence DDR is to target the ATM-CHK2 and/or the ATR-CHK1 pathways. The ATM inhibitor KU55933 has been used in combination with IR and Topo II inhibitors [12], and the ATR inhibitor VE-821 has been shown to effectively sensitize cells to cisplatin [14]. Specific CHK1 and CHK2 or dual inhibitors showed sensitization in combination with gemcitabine and irinotecan have also entered Phase I trials [15].

Recent advances in the understanding of the intertwinement of DDR and DSB repair pathways have led to yet another promising approach in cancer therapy utilizing synthetic lethality. The best example is the use of poly(ADP-ribose) polymerase (PARP) inhibitors to treat BRCA1/2-deficient tumors [16]. PARP inhibitors block the repair of SSBs and therefore promote their conversion to DSBs that increase the demand for HR. Since BRCA1/2-deficient cells are HR-impaired, they are particularly sensitive to the toxic effects of accumulated DSBs. PARP inhibitors can also be used to treat ATM- or MRE11-deficient tumors [17]. Currently Phase I and II studies that involve the PARP inhibitor olaparib have shown promising effects on treating BRCA-deficient breast, ovarian and prostate cancers [18]. Given the fact that development of anti-cancer drug resistance is the most common cause of treatment failure, further exploration of synthetic lethal relationships seems a promising avenue for devising potential "resistance-proof" strategies in our continuing effort to conquer cancer. However, highly individualized synthetic lethal approaches that are tailored to fit the molecular phenotypes of the tumor are clearly needed in the future. In the case of treating BRCA-defi-

cient tumors with PARP inhibitors, resistance can also arise from secondary mutations in the BRCA genes or from down-regulation of the NHEJ pathway [12,19]. Thus, establishment of biomarkers that allow quicker evaluation of DDR and DSB repair activities in cancer cells is definitely among the first steps in the process of developing strategies to better manage cancer in patients.

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Cite this article

Xu Y, Her C (2014) DNA Double-Strand Break Repair and Anti-Cancer Therapy. J Vet Med Res 1(1): 1001.