

For reprint orders, please contact: reprints@futuremedicine.com

DNA repair in lung cancer: potential not yet reached



“DNA repair is critical in maintaining genomic integrity and survival of all cells, and is especially important in the lungs.”

Hirva Mamdani^{1,2} & Shadia I Jalal^{*,1,2}

First draft submitted: 3 March 2016; Accepted for publication: 4 March 2016; Published online: 6 April 2016

DNA repair is critical in maintaining genomic integrity and survival of all cells, and is especially important in the lungs. Lung tissue is exposed to a wide array of exogenous chemicals and insults on a constant basis. Many of these agents are capable of inducing DNA damage and repairing this damage is critical to maintain proper lung function. DNA damage resulting from these agents ranges from double strand breaks, single strand breaks, base damages, bulky adducts, intra- and inter-strand cross links as well as breakdown of replication fork lesions. Upon recognizing DNA damage, cells initiate a myriad of signaling pathways collectively referred to as DNA damage response (DDR). The activation of DDR leads to DNA repair, suppression of global translation, cell cycle arrest and ultimately, either cell survival or cell death [1]. Major DNA repair pathways include homologous recombination (HR), nonhomologous end joining (NHEJ), base excision repair (BER), nucleotide excision repair (NER), direct enzymatic repair (DR) and mismatch repair (MMR), with

certain pathways more active than others in various types of DNA damage. Mutations in DNA repair genes contribute to cancer development but can be exploited in favor of cancer therapy.

Exposure to tobacco smoke, containing an average of 10^{10} particles/ml and over 60 carcinogens, is a major risk factor for both NSCLC and small-cell lung cancer (SCLC). These carcinogens lead to formation of DNA adducts. In the presence of effective DNA repair processes, these adducts are rapidly eliminated by NER and BER pathways. If unrepaired damage is still present during DNA replication, usually the replication is arrested, eventually resulting in cell death. Alternatively, the DNA adducts are bypassed incorrectly resulting in genetic mutations in oncogenes or tumor suppressor genes leading to development of malignant clone. Since smokers are constantly exposed to carcinogens, their susceptibility to development of these mutations increases, culminating into development of cancer. Although, approximately 80–90% of lung cancer patients are

KEYWORDS

- BRCA • DNA damage response
- DNA repair genes • ERCC1 • HR
- lung cancer • NER • PARP inhibitors
- platinum resistance

“Mutations in DNA repair genes contribute to cancer development but can be exploited in favor of cancer therapy.”

¹Division of Hematology/Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

²Indiana University Melvin & Bren Simon Cancer Center, 980 W Walnut Street, Indianapolis, IN 46202, IN, USA

*Author for correspondence: Tel: +1 317 274 3658; Fax: +1 317 274 0396; sjalal@iupui.edu

smokers, only 10% of the heavy smokers actually develop lung cancer, indicating a potential for genetic predisposition to this disease, including defects in DNA repair mechanisms. For example, a molecular epidemiologic case control study investigating the association between development of lung cancer and the activity of DNA repair enzyme OGG, which repairs the oxidative DNA lesion induced by smoking, found that individuals in the lowest tertile of OGG activity had an increased risk of NSCLC compared with individuals in the highest tertile (odds ratio [OR]: 4.8; 95% CI: 1.5–15.9) [2]. Another association study with 1655 single nucleotide polymorphisms (SNPs) in 211 DNA repair genes evaluating 6911 individuals pooled from four genome-wide case–control studies in the International Lung Cancer Consortium identified three DNA repair genes associated with lung cancer (*UBE2N*, structural maintenance of chromosomes *IL2* and *POLB*). Two additional genes (*RAD52* and *POLN*) were borderline significant [3]. In addition, suboptimal DNA repair capacity (DRC) as measured by the host cell reactivation assay was found to be associated with a higher risk of lung cancer in never smokers as well (OR: 1.92; 95% CI: 1.3–2.9). There was a 3.38-fold higher risk for individuals with DRC below the first quartile compared with individuals with DRC above the third quartile [4]. Interestingly, it has also been found that patients with multiple primary NSCLC tumors have higher burden of DNA damage compared with patients with single primary tumor after controlling for age, sex, smoking history and treatment [5]. Collectively these data suggest that defective DNA repair might be associated with increased risk of lung cancer.

“...defective DNA repair might be associated with increased risk of lung cancer.”

DNA repair plays a major role in sensitivity of lung cancer to platinum therapy. Platinum-based chemotherapy agents, including cisplatin and carboplatin, represent the backbone for chemotherapy in lung cancer. Platinum exerts its antineoplastic effect by inducing formation of DNA lesions (intrastrand crosslinks, inter-strand crosslinks and DNA–protein crosslinks). This DNA damage results in inhibition of DNA replication and activation of apoptotic pathways ultimately leading to cell death [6]. The bulky DNA adducts formed by cisplatin are predominantly repaired by NER pathway using either global genomic NER (GG-NER) or transcription coupled NER (TC-NER), and to a lesser extent by HR pathway [7]. The main limitation

for clinical efficacy of platinum agents is development of intrinsic or acquired resistance to these therapies. Multiple mechanisms have been implicated including decreased accumulation of cisplatin into the cells and increased metabolism, but enhanced repair of platinum-induced DNA damage appears to be the most important mechanism conferring platinum resistance. The search for a DNA repair biomarker for predicting sensitivity to platinum has been ongoing. XPA and ERCC1 play a pivotal role in NER pathway. Several studies have shown correlation of overexpression of ERCC1 or XPA proteins with cisplatin resistance [8,9]. ERCC1 expression is perhaps the most extensively analyzed in clinical trials and was evaluated as a biomarker for overall survival following cisplatin-based adjuvant chemotherapy in patients with resected lung cancer. The initial study demonstrated that only patients with ERCC1-negative tumors benefited from adjuvant cisplatin-based therapy compared with ERCC1-positive tumors. ERCC1 expression was evaluated by immunohistochemistry using the 8F1 antibody [10]. Unfortunately, repeat evaluation using the same antibody failed to confirm these results [11]. The rationale for ERCC1 as a possible predictive biomarker for cisplatin response remains scientifically sound as ERCC1 forms a heterodimer with XPF and together they perform a critical incision step in NER response to platinum. ERCC1–XPF complex is also involved in HR and ICL repair [12]. In addition, low ERCC1 expression has been connected to testicular cancer sensitivity to platinum as well. However, ERCC1 as a predictive biomarker has failed in the clinical setting likely due to technical limitations as it does not seem that the antibodies used for immunohistochemistry are appropriate since none of the available antibodies accurately differentiate the functional ERCC1 isoform [13]. Other possible biomarkers for platinum response include a number of NER or HR genes including *BRCA1*, *XPA*, *RAD51* and *EME1* [14,15]. It is likely that a single protein will not be predictive as repair of platinum-induced damage is orchestrated by multiple DNA repair components. The function of these components is not uniformly reflected via gene expression and both the DNA repair protein as well as the assay used to measure its function is critical.

The same defective DNA repair pathways that contribute to carcinogenesis and confer sensitivity or resistance to chemotherapeutic agents

can be exploited as potential therapeutic targets. Although germline mutations in *BRCA* gene are uncommon in NSCLC, BRCAness defined as somatic molecular defects in the cellular DNA repair machinery, resulting in a phenotype similar to that caused by *BRCA* germline mutations is commonly observed in NSCLC. A recent study evaluating data from The Cancer Genome Atlas (TCGA) revealed that 53% of lung adenocarcinoma (LUAD) and 51% of squamous cell lung cancer (SQCC) had somatic alterations in at least one HR or *FA* (Fanconi Anemia) gene. The most common homozygous deletions noted were in *RAD51* (3%) in LUAD and *XRCC1* (1%) in SQCC. LUAD had frequent somatic gene mutations in *BRCA2* (5%), *BRCA1* (3%), *RAD54B* (3%) and *BRIP1* (3%), while SQCC had somatic mutations in *BRCA1* (6%), *BRCA2* (6%), *FANCA* (3%) and *PALB2* (3%) [16]. The tumor suppressor proteins BRCA1 and BRCA2 regulate the initial steps of HR by orchestrating the assembly of the DNA recombinase-RAD51 onto broken DNA ends at the site of double strand breaks (DSBs) and stalled replication forks. Defects in *BRCA1* or *BRCA2* cause a profound defect in HR that predicts sensitivity to PARP inhibition through synthetic lethality [17]. A Phase III ECLIPSE study (NCT01082549) evaluating the combination of a weak PARP1 inhibitor with gemcitabine–carboplatin as first-line treatment in metastatic NSCLC has been recently completed. A similar Phase III trial was negative in triple-negative breast cancer [18]. As PARP is not involved in the repair of platinum-induced DNA damage, it is unlikely the combination will be more synergistic. Nevertheless, PARP inhibitors can potentially have a role in the treatment of a subset of NSCLC tumors, possibly the BRCA-like ones.

DNA repair pathways are being explored as potential therapeutic targets in SCLC as well. Being an extremely chemosensitive tumor,

platinum-based chemotherapy remains the backbone of the treatment in both limited- and extensive-stage SCLC. However, a subset of tumors demonstrates inherent or acquired resistance to platinum. Therefore, it is of paramount importance to explore the ways of circumventing this resistance. Proteomic analysis of SCLC cell lines has identified overexpression of several DNA repair proteins, especially PARP1 [19]. In a Phase I study of BMN 673 that included 23 previously treated SCLC patients, two patients had a partial response, while three had prolonged stable disease suggesting single-agent activity in some patients with SCLC [20]. However, the true clinical significance of PARP inhibition remains to be proven with larger clinical trials.

In summary, DNA repair might be involved in an individual's susceptibility to lung cancer. Lung cancer including small cell, squamous cell and adenocarcinomas are characterized by their high mutational burden resulting from decades of smoking-induced DNA damage. DNA repair plays an important role in determining platinum response in lung cancer. In addition, DNA repair defects have been recently described in lung cancer tumor samples suggesting discovery of new agents that exploit these defects should be pursued. Currently, there are no reliable biomarkers available to predict sensitivity to platinum agents but DNA repair pathways continue to represent the most likely players in platinum resistance.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Woods D, Turchi JJ. Chemotherapy induced DNA damage response: convergence of drugs and pathways. *Cancer Biol. Ther.* 14(5), 379–389 (2013).
- 2 Paz-Elizur T, Sevilya Z, Leitner-Dagan Y, Elinger D, Roisman LC, Livneh Z. DNA repair of oxidative DNA damage in human carcinogenesis: potential application for cancer risk assessment and prevention. *Cancer Lett.* 266(1), 60–72 (2008).
- 3 Kazma R, Babron MC, Gaborieau V *et al.* Lung cancer and DNA repair genes: multilevel association analysis from the International Lung Cancer Consortium. *Carcinogenesis* 33(5), 1059–1064 (2012).
- 4 Gorlova OY, Weng SF, Zhang Y, Amos CI, Spitz MR, Wei Q. DNA repair capacity and lung cancer risk in never smokers. *Cancer Epidemiol. Biomarkers Prev.* 17(6), 1322–1328 (2008).
- 5 Orlov I, Park BJ, Mujumdar U *et al.* DNA damage and repair capacity in patients with lung cancer: prediction of multiple primary tumors. *J. Clin. Oncol.* 26(21), 3560–3566 (2008).
- 6 Rabik CA, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat. Rev.* 33(1), 9–23 (2007).
- 7 Furuta T, Ueda T, Aune G, Sarasin A, Kraemer KH, Pommier Y. Transcription-coupled nucleotide excision repair as a determinant of cisplatin sensitivity of human cells. *Cancer Res.* 62(17), 4899–4902 (2002).

- 8 Wu X, Fan W, Xu S, Zhou Y. Sensitization to the cytotoxicity of cisplatin by transfection with nucleotide excision repair gene xeroderma pigmentosum group A antisense RNA in human lung adenocarcinoma cells. *Clin. Cancer Res.* 9(16 Pt 1), 5874–5879 (2003).
- 9 Takenaka T, Yoshino I, Kouso H *et al.* Combined evaluation of Rad51 and ERCC1 expressions for sensitivity to platinum agents in non-small cell lung cancer. *Int. J. Cancer* 121(4), 895–900 (2007).
- 10 Olaussen KA, Dunant A, Fourret P *et al.* DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N. Engl. J. Med.* 355(10), 983–991 (2006).
- 11 Friboulet L, Olaussen KA, Pignon JP *et al.* ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. *N. Engl. J. Med.* 368(12), 1101–1110 (2013).
- 12 Arora S, Kothandapani A, Tillison K, Kalman-Maltese V, Patrick SM. Downregulation of *XPF-ERCC1* enhances cisplatin efficacy in cancer cells. *DNA Repair (Amst.)* 9(7), 745–753 (2010).
- 13 Cobo M, Isla D, Massuti B *et al.* Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a Phase III trial in non-small-cell lung cancer. *J. Clin. Oncol.* 25(19), 2747–2754 (2007).
- 14 Welsh C, Day R, McGurk C, Masters JR, Wood RD, Koberle B. Reduced levels of XPA, ERCC1 and XPF DNA repair proteins in testis tumor cell lines. *Int. J. Cancer* 110(3), 352–361 (2004).
- 15 Tomoda Y, Katsura M, Okajima M, Hosoya N, Kohno N, Miyagawa K. Functional evidence for Emel as a marker of cisplatin resistance. *Int. J. Cancer* 124(12), 2997–3001 (2009).
- 16 Waqar SN, Devarakonda SHK, Michel LS *et al.* BRCAness in non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 32(15 Suppl.), Abstract 11033 (2014).
- 17 Farmer H, McCabe N, Lord CJ *et al.* Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature* 434(7035), 917–921 (2005).
- 18 O’Shaughnessy J, Schwartzberg L, Danso MA *et al.* Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J. Clin. Oncol.* 32(34), 3840–3847 (2014).
- 19 Byers LA, Wang J, Nilsson MB *et al.* Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. *Cancer Discov.* 2(9), 798–811 (2012).
- 20 Wainberg ZA, Rafii S, Ramanathan RK *et al.* Safety and antitumor activity of the PARP inhibitor BMN673 in a Phase I trial recruiting metastatic small-cell lung cancer (SCLC) and germline *BRCA*-mutation carrier cancer patients. *J. Clin. Oncol.* 32(15 Suppl.), Abstract 7522 (2014).