Review Article

Clinical translation for targeting DNA damage repair in non-small cell lung cancer: a review

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Contributions: (I) Conception and design: X Mao, IL Fong, NK Lee; (II) Administrative support: IL Fong, NK Lee; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Despite significant advancements in screening, diagnosis, and treatment of non-small cell lung cancer (NSCLC), it remains the primary cause of cancer-related deaths globally. DNA damage is caused by the exposure to exogenous and endogenous factors and the correct functioning of DNA damage repair (DDR) is essential to maintain of normal cell circulation. The presence of genomic instability, which results from defective DDR, is a critical characteristic of cancer. The changes promote the accumulation of mutations, which are implicated in cancer cells, but these may be exploited for anti-cancer therapies. NSCLC has a distinct genomic profile compared to other tumors, making precision medicine essential for targeting actionable gene mutations. Although various treatment options for NSCLC exist including chemotherapy, targeted therapy, and immunotherapy, drug resistance inevitably arises. The identification of deleterious DDR mutations in 49.6% of NSCLC patients has led to the development of novel target therapies that have the potential to improve patient outcomes. Synthetic lethal treatment using poly (ADP-ribose) polymerase (PARP) inhibitors is a breakthrough in biomarker-driven therapy. Additionally, promising new compounds targeting DDR, such as ATR, CHK1, CHK2, DNA-PK, and WEE1, had demonstrated great potential for tumor selectivity. In this review, we provide an overview of DDR pathways and discuss the clinical translation of DDR inhibitors in NSCLC, including their application as single agents or in combination with chemotherapy, radiotherapy, and immunotherapy.

Keywords: DNA damage repair (DDR); non-small cell lung cancer (NSCLC); DNA damage repair inhibitor (DDR inhibitor)

Submitted Nov 14, 2023. Accepted for publication Jan 31, 2024. Published online Feb 28, 2024.
doi: 10.21037/tlcr-23-742
View this article at: https://dx.doi.org/10.21037/tlcr-23-742

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Introduction

DNA damage and genomic instability in non-small cell lung cancer (NSCLC)

In recent decades, lung cancer (LC) research has shown significant advancements in screening, diagnosis, and treatment, thanks to the rapid development of technologies such as low-dose computed tomography (LDCT) scan, minimal invasive techniques (1), stereotactic ablative radiotherapy (SABR), new targeted therapy, and new immunotherapy. These advancements have improved the survival rate of LC patients by 56% in men and 32% in women (2). Despite this progress, LC remains the leading cause of cancer death, with an estimated 2.2 million new cases and 1.8 million deaths recorded in 2020 (3).

LC has two major pathological subtypes: the predominant NSCLC (85%) and small cell lung cancer (SCLC; 15%). NSCLC can be further divided into lung adenocarcinoma (LUAD; 50%), squamous cell carcinoma (LUSC; 40–30%), and large cell carcinoma (LCC; 20–10%) respectively.

The stability of the genome is paramount to the survival and reproduction of all cells. Friedberg *et al.* reported that human body is subjected to between 10,000 and 1,000,000 instances of DNA damage per day (4). DNA damage caused by endogenous (for example free radicals) (5,6) or exogenous (for example ionizing radiation) factors (7-9) can lead to genome instability and diseases such as cancer. DNA double strand breaks (DSBs) are the most severe type of damage, as accumulation of incorrectly repaired or unrepaired DSBs can cause mutation, genomic instability, or induce cell death (10).

LC generally exhibits a distinct genomic profile compared with other tumors, with high somatic mutational burden (11). Smoking is the main cause of LC, accounting for 90% of cases, however, approximately 20% of newly-diagnosed LUAD cases are attributed to non- or light-smokers in developed countries now. Smokers have higher somatic mutational burden than non-smokers (12) and smokers carry additional genomic instability processes that are likely to contribute to tumor progression (13). NSCLC primary tumors exhibit high genomic diversity with heterogenous tumor driver mutations present that clones may not all carry the same mutation making it very difficult for the patient to benefit from targeted therapies.

DNA damage is repaired by specific cellular pathways during normal cell cycle. When DNA damage fails to be repaired or excised, the mutations will eventually trigger carcinogenesis. For instance, epidermal growth factor receptor (EGFR) exon 19 deletion corrected with decreased expression of ERCC1 impacts ERCC1 foci formation in response to DNA cross-link damage, contributing to DNA damage repair (DDR) deficiency (14). Germline variants of ataxia-telangiectasia mutated (ATM), tumor suppressor 53 protein (TP53), breast cancer 2 (BRCA2), EGFR, and Parkinson's Disease-Associated protein 2 (PARK2) had been linked to cancer risk in Mendelian disorders (15). Chromosomal instability may cause tumor heterogeneity and drug resistance, and epigenetic silencing of DNA repair genes may promote tumorigenesis. For instance, over 60% NSCLC cases present aneuploidy. Chromosomal instability elevates in the NSCLC patients with ROS1 fusion treated with crizotinib (16). In addition to mutations, epigenetic silencing of DNA repair genes may promote tumorigenesis. The Aurora kinase (AURK) family is involved in mitosis and chromosomal segregation. Abnormalities in AURK proteins can be associated with genomic instability. Overexpression of AURKA (17-22) or AURKB (23-25) was corrected with poor prognosis of overall survival (OS) in NSCLC. Some researches revealed that AURKA and AURAB was associated with resistance of EGFR-TKI (26-28), chemotherapy (29-31) and/or radiotherapy (17,32,33) in LC in pre-clinical models.

Target therapy and immune checkpoint inhibitors (ICIs)-based treatment with/without chemotherapy have been widely used in NSCLC. Despite a number of inhibitors had been developed for targeting EGFR, ALK, ROS1, KRAS, MET, NTRK, HER2 and RET, LUSC and LCC rarely present mutations in tyrosine kinase receptors compared with LUAD.

DNA repair in NSCLC

Various DNA repair pathways, including direct reversal repair (DRR), base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ), homologous recombination (HR), and interchain crosslinking repair, can circumvent DNA damage.

DNA damage caused by various agents such as alkylation, oxidation, ultra-violet (UV) radiation, and cross-linking requires different repair mechanisms. The mechanism of DRR is involved in reversing the *O*-alkylated DNA damage caused by methylguanine methyl transferase (MGMT) (34). DRR also removes photolesions caused by UV radiation with DNA-photolyase (35,36). The activity of the DNA repair enzyme 8-oxoguanine DNA N-glycosylase (OGG), is associated with LC (37). BER can repair small base