COMMENTARY

Lung cancer treatment by targeting DNA damage response

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ABSTRACT

The most frequent cancer diagnosis and one of the major causes of mortality worldwide is lung cancer. The reactions from Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC)

Current outcomes for Non-Small Cell Lung Cancer (NSCLC) patients treated with standard chemo- and radiotherapies remain unsatisfactory. New developments in DNA sequencing technology have just begun to take off, offering promising methods for researching various malignancies for methodical mutation detection. There have only been a few DDR inhibition trials for the treatment of SCLC and NSCLC patients to date. However, methods to test various DDR inhibitor combinations or to focus on numerous pathways have not yet been investigated. Future trials should be planned to enable the study of targeted treatments in a biomarker-enriched population, which is justifiable for the improvement of prognosis for SCLC and NSCLC patients, in light of the various biomarkers that have either recently been discovered or are the subject of ongoing investigations.

Key Words: *Lung cancer; DDR; Homologous Recombination (HR)*

INTRODUCTION

Lung cancer is regarded as one of the most prevalent cancers with a high fatality rate. According to statistics from around the world in 2018, over two million new cases of lung cancer were reported. Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) are the two subtypes of lung cancer according on histology The human genome is constantly interacting with internal factors including Reactive Oxygen Species (ROS), methylating substances, hydrolytic deamination, and lipid peroxidation-derived aldehydes as well as exterior factors like Ultraviolet (UV) light, ionising radiation, chemicals, and poisons.

The many processes that could potentially lead to radiotherapeutic resistance have been thoroughly investigated by researchers.However, the precise identification of the mechanisms generating radiotherapeutic resistance was hampered by tumour heterogeneity and other variables.Due to the overall low survival percentage, which is currently reported to be 17%, there is still no effective treatment available despite the discovery of new promising targeted therapies. The most effective treatment currently available is surgery, followed by adjuvant chemotherapy and/or Radiotherapy (RT), but this option is only available to patients who have no metastasis.

Therefore, as the majority of lung cancer patients are metastatic, the first-line therapeutic option may include chemotherapy, Radiofrequency Ablation (RFA), RT, immunotherapy, or a combined treatment depending on the disease's stage and the presence of resistance toward any of the treatment options.

The RTK/RAS/RAF signalling system, the PI3K-mTOR intracellular circuit, the tumour protein *p53*, cell cycle regulators, oxidative stress, mutations in multiple chromatin and RNA splicing components, as well as activation of these pathways, are all frequent abnormalities in lung adenocarcinoma.

DNA repair pathways

Recent studies have looked into potential therapy possibilities to target various DDR pathways in aggressive cancers like SCLC. DSBs can currently be repaired using Homologous Recombination (HR) repair and Nonhomologous End-Joining (NHEJ), SSBs can be repaired using Base Excision Repair (BER), replication errors can be repaired using Mismatch Repair (MMR), and bulky adducts can be repaired using Nucleotide Excision Repair (NER). Many of the DDR pathways can function as compensatory mechanisms when the others are hampered because of their diversity.

One of the most destructive types of DNA damage is a DSB, which can be repaired by the DDR machinery primarily by DNA-PK-mediated NHEJ and ATM-mediated HR repair.

1. Homologous Recombination: The process of homologous recombination guarantees that the DNA is correctly copied and prevents harmful mutation-induced damage.

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According to reports, the HR pathway is a key factor in the emergence of chemotherapeutic resistance in lung cancer. Along with NHEJ, it has also been reported that this route is essential for the DSBs repair.

2. Non-Homologous End Joining: One of the routes utilised in the DNA DSBs-repairing process is NHEJ. All cell cycle phases can effectively be affected by NHEJ, which makes tumour cells resistant to chemotherapeutic agents. It has been shown in numerous studies that blocking the NHEJ pathway significantly lowers the resistance to chemotherapy medicines.
3. Base Excision Repair: A DDR process known as the BER mechanism has also been linked to lung cancer chemotherapeutic treatment resistance. The targeted DNA damage caused by this process includes oxidative damage, depurination, alkylation, and deamination, all of which are required for mammalian cell growth and development Severe diseases including malignancies and neurological problems can develop when the BER pathways stop working Recent research has shown that blocking the BER pathway reduces chemotherapeutic drug resistance in a variety of cancers, including lung cancer.

DDR inhibitors for a targeted lung cancer treatment

Three phosphatidyl inositol 3-kinase-related protein kinases are implicated in genotoxic stress, however, each one is activated by a different kind of injury.

According to reports, ATM reacts to substances that damage DNA, such as IR, which results in DSBs, according to reports, UV radiation causes changes in cell replication that can be detected by ATM and ATR kinase. Another signaling pathway, DNA-PK, has also been demonstrated to be recruited in response to DSBs under specific cellular circumstances, such as environmental carcinogens, IR exposure, and chemotherapeutic agents, as well as in cells with short telomeres. This signaling pathway is similar to the ATM.

1. ATM Inhibitors: ATM inhibitors have the capacity to promote the repair of DNA damage in the H2AX phosphorylation, chromatin is modified, causing foci to develop at the break pages A -H2AX is created when H2AX has been phosphorylated, allowing additional proteins necessary for the mending mechanism's recruitment. And ATM. According to reports, ATR plays a part in controlling the Werner syndrome protein (WRN), which is connected to the replication fork recovery that has stopped, hence restricting the fork collapse.
2. PARP Inhibitors: A class of DDR inhibitors known as PARP inhibitors prevents DNA repair and is thought to have anticancer properties. The interaction between this family of inhibitors and the mutations in BRCA1/BRCA2 that cause synthetic lethality was shown in 2009 by the first human clinical trial using Olaparib as a PARP inhibitor. Due to SCLC's reported sensitivity to this class of inhibitors, recent studies have examined how PARP inhibitors affect it. This has prompted additional research to test PARP inhibitors as potential therapeutics for treating SCLC.

CONCLUSION

Damage to the genetic material (DNA) happens during every cell cycle, and each cell has a repairing system to deal with the damage. Specifically, the DNA of tumor cells.

Chemotherapy and/or radiation treatments cause damage that is significantly larger than the damage experienced by normal cells, and tumor cells typically lack the ability to repair their DNA, in contrast to normal cells. The majority of HRD-NSCLC cases can be found by targeting a target that supports the HR pathway, which may help RT work more effectively. Numerous medications have been created that target the DDR-related proteins ATM and ATR, DNA-PK, and PARP.