Pharmacological Modulation of DNA Damage Response Pathways in Cancer Therapy

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Abstract:

When DNA is damaged, cells activate the DNA Damage Response (DDR), a protective mechanism that prevents harmful mutations and chromosomal changes that can lead to cancer. DDR coordinates DNA repair with cell cycle control, ensuring that cells do not divide with damaged genetic material [1]. It evolved to protect organisms from both internal and external DNA-damaging agents. Interestingly, many cancer therapies such as radiation and chemotherapy work by damaging DNA, making DDR a key factor in treatment resistance[2] Radiotherapy, used in about 50% of cancer cases, relies on causing DNA damage to kill tumor cells. A specific type of injury caused by radiation is complex DNA damage (CDD), where multiple lesions occur close together on the DNA helix. CDD is particularly toxic because it is difficult for the cell to repair. The severity of CDD increases with higher linear energy transfer (LET), meaning that high-LET radiation (like carbon ions) causes more damage than low-LET radiation (like X-rays) [3]. However, this can also increase the risk of harming healthy tissue. Recent research focuses on developing DDR inhibitors that block repair in cancer cells, making them more sensitive to treatment. Several of these drugs are in preclinical and clinical testing, both alone and in combination with other therapies[4].

Keywords: DNA damage response (DDR), DNA, cancer, Radiotherapy.

Introduction:

Genetic alterations that result in unchecked cell proliferation are the cause of human cancer. Errors in DNA replication or improperly repaired DNA damage can result in mutations. A tiny percentage of somatic mutations might provide the cell a selection advantage that could help it to grow or live preferentially, but most continuously acquired mutations are harmless due to a variety of cell-intrinsic processes that reduce DNA alterations[5]. Although the rates of mutational processes vary greatly, the majority of human malignancies have hundreds of insertions, deletions, and rearrangements in addition to 1000–20,000 point mutations[6]. Malignant cell transformation can be brought on by the accumulation of abnormal somatic mutations. Human cells have therefore developed many levels of repair systems to guard against these mistakes.DNA damage response (DDR) mechanisms carefully repair broken sequences or trigger senescence or death in permanently damaged cells[7]. Defects in the DDR process may encourage the proliferation of cancer cells by causing de novo driver mutations, producing tumor heterogeneity, and avoiding apoptosis. Genomic instability is a significant characteristic of cancer[8].

Mechanism of DNA Damage Response

Base modification, intrastrand crosslinks, interstrand crosslinks (ICL), DNA–protein crosslinks, single-strand breaks (SSBs), and DSBs are among the several forms of DNA damage caused by DNA-damaging agents. Proteins involved in the DNA damage response recognize and handle each form of DNA damage. A biological process called the DNA Damage Response (DDR) recognizes and reacts to DNA damage in order to maintain the integrity of the genome[9]. It includes several processes, such as apoptosis, cell cycle checkpoints, and DNA repair. Sensor proteins (like the MRN complex) that identify damage, transducer proteins (like ATM and ATR) that transmit the signal, and effector proteins that start cell death or repair are important participants in DDR[10].

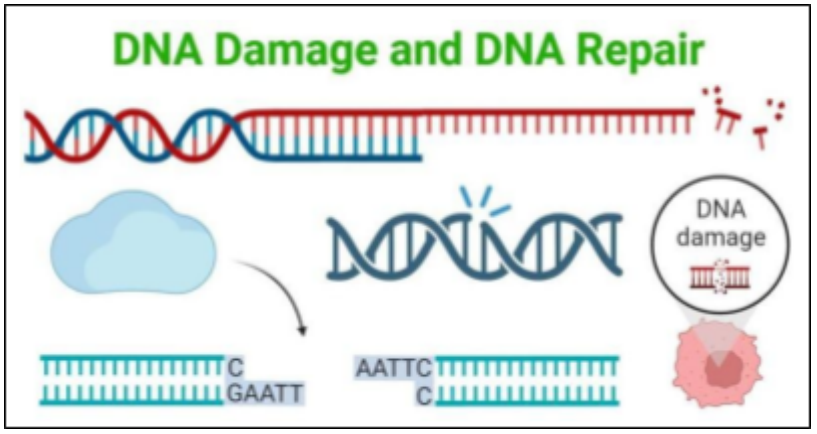

Fig.1 DNA Damage and DNA Repair[10]

The development of several genetic abnormalities over many years is necessary for the complicated illness known as cancer. Both within and across cancer types, these mutations differ[11]. The DNA of cancer cells is damaged by current therapies such as radiation, alkylating chemicals, and platinum compounds, but they also cause serious side effects by harming healthy cells that develop quickly. Additionally, some cancer cells become resistant to these medications. The development of tailored medicines that can selectively target cancer cells has recently benefited from a better understanding of the DNA damage response (DDR) [12]. Compared to conventional therapy, these DDR-based therapeutics could be less harmful and more successful.

DNA damage response alerts the immune system

The DNA Damage Response (DDR) is triggered when cells sustain DNA damage. Its functions include alerting the immune system and repairing the damage or halting cell division. Danger signals such as cytokines and chemokines (like interferons) are released by damaged cells [13]. Damaged DNA fragments that enter the cytoplasm and trigger cGAS-STING and other pathways.The expression of ligands for immune cell receptors, such as natural killer cells, has increased[14][15].

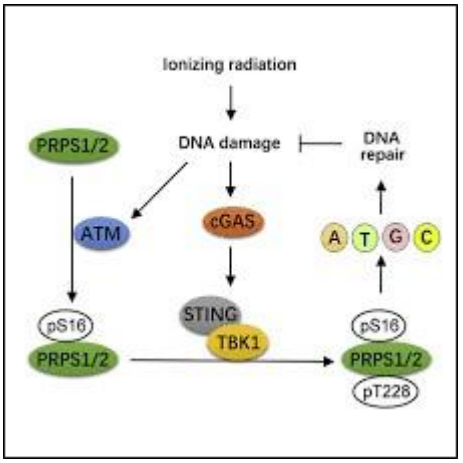

Fig.2 DNA damage response alerts the immune system[30]

DNA damage response and targeted drug development

New targets for cancer therapy have been identified by recent molecular discoveries of DNA damage response mechanisms. By preventing the repair of double-strand breaks, ATM kinase inhibitors like KU55933 make tumor cells more sensitive to substances that damage DNA. In a similar vein, DNA-PKcs inhibitors improve the efficiency of chemotherapy and radiation[16][29]. The most promising of them are Chk1 inhibitors, which are clinically developed and selectively sensitize p53-deficient tumor cells to DNA damage while being less harmful to healthy cells. On the other hand, Chk2 inhibition may extend the therapeutic window by shielding healthy tissues from harm brought on by cancer treatments, even while it does not improve tumor sensitivity. Furthermore, apoptosis can be induced in tumors with functioning p53 by medications like nutlin-3 that activate p53 by interfering with its interaction with MDM2[18] [28].

To guarantee safety, more study is required since worries about potential harmful effects on healthy cells persist. All things considered, by enhancing tumor sensitivity and decreasing adverse effects, targeting DNA damage response components presents encouraging opportunities to enhance cancer treatments[19] [20] [21].

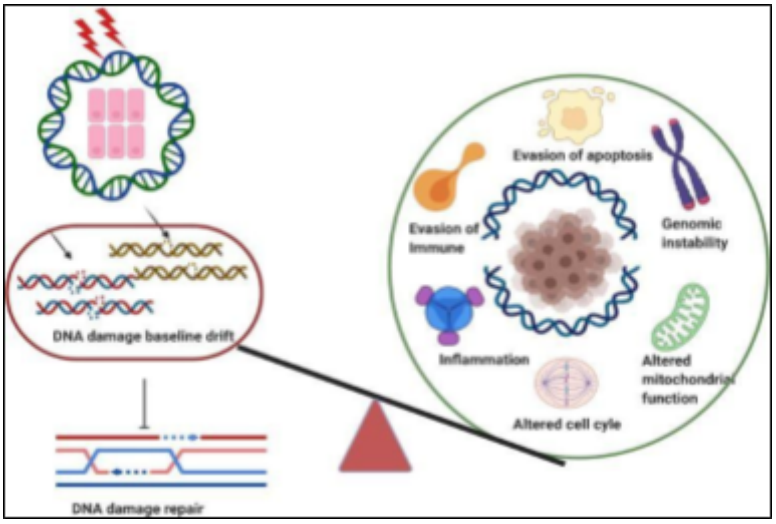

Fig.3 DNA damage repair[22]

Conclusion:

A crucial cellular defense mechanism, the DNA Damage Response (DDR) finds and fixes DNA lesions to preserve genomic integrity. Given that genomic instability is a defining feature of cancer, its function is particularly important. New approaches to cancer treatment have been made possible by our growing understanding of DDR pathways, especially by taking advantage of flaws in the processes by which tumor cells repair themselves[23]. By using certain inhibitors to target important components like ATM, ATR, DNA-PKcs, and Chk1, cancer cells can become more sensitive to traditional therapies like chemotherapy and radiation therapy while causing the least amount of damage to healthy tissues[24]. Furthermore, the DDR's capacity to regulate immunological responses increases its potential for therapeutic use.Even with encouraging advancements, a thorough assessment of toxicity and resistance pathways is necessary to optimize the therapeutic advantages of DDR-targeted treatments. In order to turn these discoveries into safer, more effective, and more selective cancer therapies, additional investigation and clinical testing will be essential[25] [26] [27].

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