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Targeting DNA repair mechanisms: A frontier in molecular oncology research.

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Introduction

Cancer is fundamentally a disease of the genome, characterized by the accumulation of genetic mutations that drive uncontrolled cell growth and resistance to therapy. One of the most critical processes that maintain genomic stability is the cell's ability to repair DNA damage. When DNA repair mechanisms fail or are dysregulated, it leads to mutagenesis and oncogenesis. Recent advances in molecular oncology research have focused on exploiting these defective repair pathways as a therapeutic strategy, offering new hope for precision oncology. Understanding the complex landscape of DNA repair has led to the identification of novel biomarkers, drug targets, and treatment approaches that specifically exploit cancer cell vulnerabilities. In particular, targeting defective repair pathways such as homologous recombination deficiency (HRD) or mismatch repair (MMR) has emerged as a promising strategy to improve cancer treatment outcomes [1, 2].

Under normal conditions, cells are equipped with a network of repair mechanisms to correct DNA damage caused by environmental factors, replication errors, or cellular metabolism. These include base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and homologous recombination repair (HRR). When these pathways are disrupted, damaged DNA accumulates, triggering mutations in oncogenes and tumor suppressor genes. In many cancers, mutations in BRCA1, BRCA2, or MLH1 compromise DNA repair capacity, leading to genomic instability—a hallmark of cancer. These deficiencies not only contribute to tumor progression but also create therapeutic windows that can be exploited using targeted agents [3, 4].

As therapies based on DNA repair mechanisms gain traction, ethical considerations surrounding genetic testing, patient consent, and data sharing must be addressed. Germline mutations in repair genes often have implications beyond cancer, affecting family members and necessitating genetic counseling. Looking forward, the integration of AI-based prediction models, multi-omics approaches, and real-world evidence will be crucial in refining DNA repair-targeted strategies. The most well-known application of targeting DNA repair mechanisms is the use of PARP inhibitors (PARPi) in cancers with BRCA mutations. PARP enzymes are involved in single-strand break repair; inhibiting them leads to accumulation of DNA damage and eventual cell death, particularly in cells already deficient in homologous recombination. This concept of synthetic lethality—where two non-lethal mutations result in cell death when combined—has transformed the treatment landscape of breast, ovarian, pancreatic, and prostate cancers harboring BRCA mutations. Drugs like olaparib, rucaparib, and niraparib have received regulatory approval and are being explored in new combinations and indications [5, 6].

Personalized medicine in oncology is entering an era where DNA repair profiling could become as routine as histological grading, significantly changing the therapeutic paradigm. Additionally, tumors with mismatch repair deficiency (dMMR) exhibit high

microsatellite instability (MSI), making them responsive to immune checkpoint inhibitors. The FDA has approved pembrolizumab for the treatment of MSI-high or dMMR cancers regardless of tissue origin—an unprecedented tissue-agnostic approval based on molecular features rather than tumor location. Beyond PARP inhibitors, researchers are now exploring novel strategies to target other repair pathways, such as ATR, CHK1, and DNA-PK inhibitors, often in combination with chemotherapy, radiotherapy, or immunotherapy. These combinations are aimed at amplifying DNA damage while blocking the cell's capacity to repair, tipping the balance toward apoptosis [7, 8].

The use of CRISPR-based gene editing has also accelerated the discovery of genes involved in DNA repair and their role in drug sensitivity. Furthermore, high-throughput sequencing and NGS-based assays are allowing for real-time monitoring of DNA repair deficiencies, facilitating patient stratification and personalized treatment planning. Despite significant progress, several challenges remain in translating DNA repair targeting strategies into routine clinical practice. Resistance to PARP inhibitors, often through restoration of homologous recombination, poses a major obstacle. Additionally, identifying reliable biomarkers to predict treatment response and resistance mechanisms is an area of active research. Tumor heterogeneity and clonal evolution also complicate treatment outcomes. Therefore, longitudinal genomic profiling and adaptive therapy strategies are required to stay ahead of tumor resistance mechanisms [9, 10].

Conclusion

The exploitation of DNA repair mechanisms in molecular oncology research represents a promising and evolving frontier in cancer therapeutics. From the advent of PARP inhibitors to emerging checkpoint inhibitors and synthetic lethality-based strategies, this field offers innovative ways to outmaneuver cancer at its genomic core. Continued research, ethical oversight, and technological advancements will be essential in harnessing the full potential of DNA repair-targeted treatments and ultimately improving outcomes for cancer patients worldwide.

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