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DNA Repair Mechanisms and Cancer: A Comprehensive Review

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Abstract

DNA repair mechanisms are vital processes that protect the integrity of the genome and ensure that cells function normally over time. Every day, DNA is exposed to damage from normal cellular metabolism, environmental toxins, radiation, and errors that occur during replication. If these damages are not properly repaired, they can lead to permanent mutations, chromosomal instability, and eventually the development of cancer. For this reason, DNA repair is one of the most important safeguards against malignant transformation.

Cells have developed several repair systems to deal with different types of DNA damage. Some pathways correct small, single-base changes, while others repair larger structural damage such as breaks in both strands of DNA. These systems work together in a highly coordinated way to detect damage, signal its presence, remove the affected section, and restore the correct DNA sequence. This coordination is closely linked with cell cycle checkpoints, which help prevent cells from dividing when their DNA is damaged.

When these repair systems are defective, the consequences can be severe. Mutations begin to accumulate at a faster rate, affecting genes that control cell growth, division, and programmed cell death. Over time, this can lead to the transformation of normal cells into cancer cells. Many well-known cancer syndromes are linked to inherited defects in DNA repair genes, and in many sporadic cancers, these pathways are also disrupted. In addition, loss of repair capacity can make tumors more genetically unstable, allowing them to evolve and become more aggressive or resistant to treatment.

Recent research has shown that DNA damage is often closely linked to the process of DNA replication. As cells divide rapidly, especially in cancer, they experience replication stress that can lead to broken or stalled DNA strands. Cancer cells often rely heavily on backup repair pathways to survive this stress. Scientists have also discovered additional mechanisms that help cells tolerate or bypass DNA damage, revealing a more complex network of repair than was previously understood.

These discoveries have important implications for cancer treatment. One of the most promising approaches is to target weaknesses in tumor cells that already have defective repair systems. By blocking alternative repair pathways, it is possible to selectively kill cancer cells while sparing normal cells. Some therapies already in use exploit this idea, and ongoing research is identifying new drug targets that interfere with the DNA damage response.

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1. Introduction

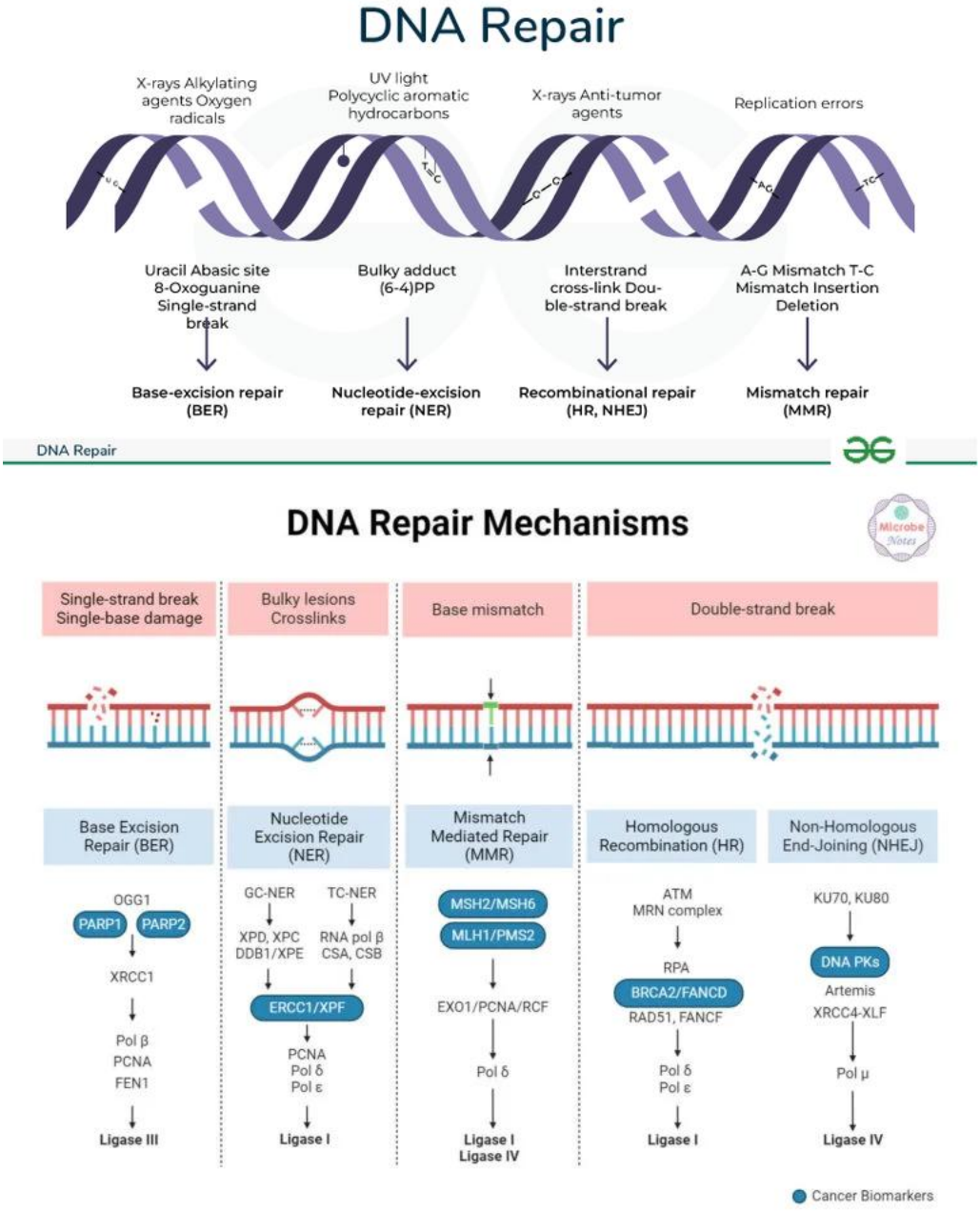
Cells are constantly exposed to DNA damage under normal physiological conditions. It is estimated that each cell can experience **tens of thousands to more than a million DNA lesions per day**, making DNA damage an unavoidable part of cellular life. These lesions arise from both internal and external sources. Endogenously, normal metabolic activity generates **reactive oxygen species (ROS)** that can damage DNA bases, cause strand breaks, and alter nucleotide structure. Spontaneous hydrolytic reactions, replication errors, and byproducts of cellular respiration also contribute significantly to DNA instability. Exogenously, DNA is continuously challenged by environmental agents such as **ultraviolet and ionizing radiation, chemical toxins, pollutants, and certain infectious agents**, all of which can directly or indirectly damage genetic material. Together, these constant insults highlight the necessity of highly efficient and tightly regulated DNA repair systems.

To counteract this continuous damage, cells rely on a complex network of DNA repair pathways that act rapidly and precisely to maintain **genomic integrity**. These systems identify damaged sites, activate signaling cascades, and coordinate repair before the cell proceeds through division. The efficiency of these mechanisms is essential not only for survival but also for preventing the gradual accumulation of mutations over time. When these repair systems function properly, most DNA lesions are corrected without any lasting consequence. However, when DNA repair pathways are impaired or become dysregulated, damage persists and is passed on during cell division, leading to permanent genetic alterations.

The failure of DNA repair is a central factor in the development of cancer. Unrepaired or incorrectly repaired DNA lesions can result in point mutations, deletions, chromosomal rearrangements, and gene amplifications. Over time, these genetic alterations can activate oncogenes or inactivate tumor suppressor genes, initiating the transformation of normal cells into malignant ones. This progressive accumulation of mutations is a key driver of **oncogenesis**, linking defective DNA repair directly to cancer initiation and evolution.

A major concept in cancer biology is **genomic instability**, which refers to an increased tendency of the genome to acquire mutations. This instability is now recognized as one of the defining hallmarks of cancer. It often arises from defects in the **DNA damage response (DDR)** pathways, which normally detect DNA damage, halt the cell cycle, and initiate repair processes. When DDR components are altered, cells lose the ability to properly respond to DNA lesions, allowing damaged DNA to persist and propagate. This creates a permissive environment for genetic diversity within tumors, which in turn accelerates cancer progression.

Importantly, many tumors do not simply result from DDR failure—they actively exploit abnormalities in these pathways to survive. Cancer cells often rely on residual or alternative DNA repair mechanisms to cope with high levels of replication stress caused by their rapid and uncontrolled proliferation. By adapting DDR signaling, tumors can bypass normal growth control checkpoints and continue dividing even in the presence of extensive DNA damage. This dysregulation also contributes to **therapeutic resistance**, as cancer cells may enhance repair capacity or activate compensatory pathways in response to chemotherapy or radiation-induced DNA damage. As a result, targeting DDR pathways has become an important strategy in modern cancer therapy, aiming to exploit the vulnerabilities created by defective DNA repair systems.



2. Major DNA Repair Pathways

2.1 Base Excision Repair (BER)

BER corrects small base lesions and a basic site, maintaining genomic stability by removing damaged bases such as those caused by oxidation or deamination. Enzymes like uracil-DNA glycosylase initiate BER by excising abnormal bases.

2.2 Nucleotide Excision Repair (NER)

NER removes bulky DNA adducts and helix-distorting lesions, such as those caused by UV radiation. Defects in NER contribute to mutagenesis and cancer susceptibility.

2.3 Mismatch Repair (MMR)

MMR corrects replication-associated mismatches. Loss of MMR function leads to microsatellite instability, a feature of several cancers including colorectal and endometrial tumors.

2.4 Double-Strand Break Repair (DSBR)

Double-strand breaks (DSBs) are among the most lethal DNA lesions. Two major pathways repair DSBs:

- **Homologous Recombination (HR):** High-fidelity repair using a sister chromatid template. BRCA1/2 mutations impair HR, increasing cancer risk.
- **Non-Homologous End Joining (NHEJ):** A faster but error-prone process that ligates broken DNA ends.

3. Replication Stress and Fork-Associated Repair in Cancer

Replication forks frequently stall or collapse under stress, producing one-ended DNA breaks that are particularly challenging to repair. Cancer cells experience chronic replication stress and rely on specialized repair mechanisms to survive.

Recent discoveries show that:

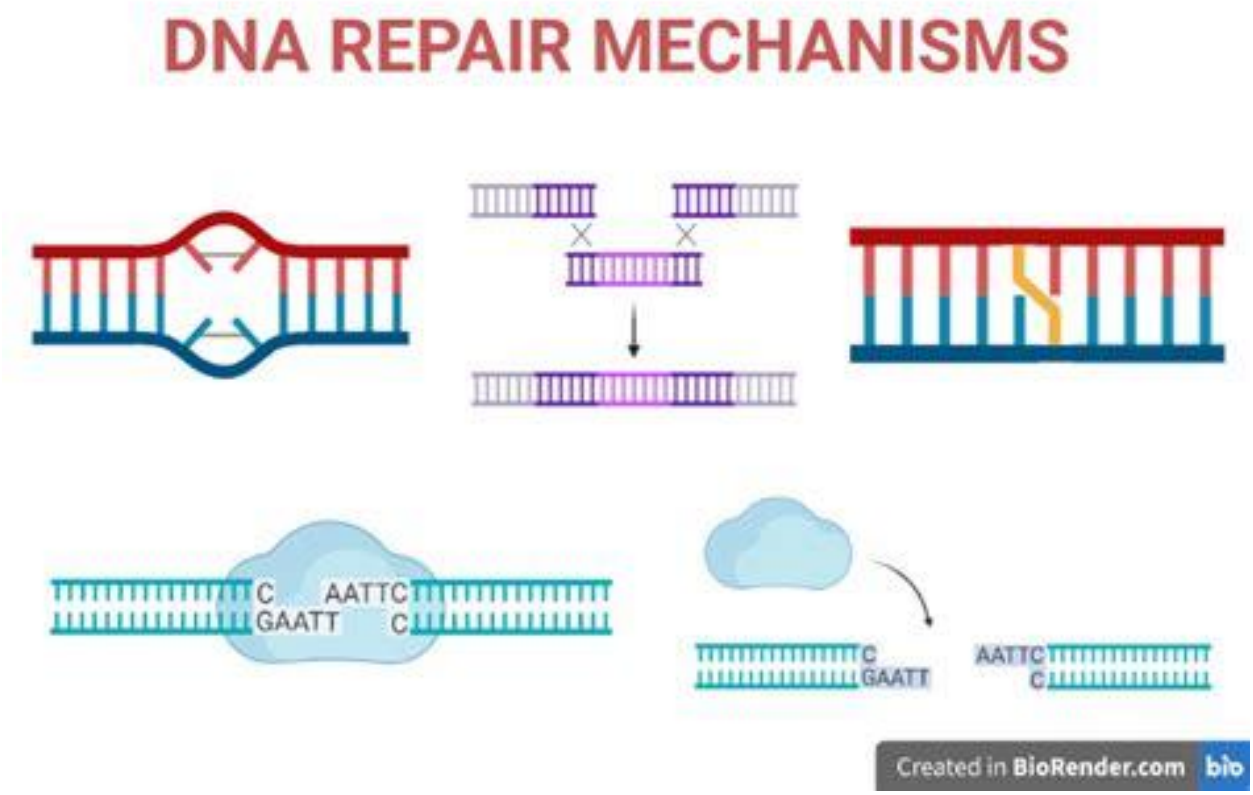
- **Polθ-mediated microhomology-mediated end joining (MMEJ)** operates directly at broken replication forks, contrary to the previous belief that break-induced replication (BIR) was the primary responder.
- MMEJ is faster but more error-prone, contributing to mutagenesis and tumor resilience.
- This mechanism explains why **Polθ inhibitors** are promising therapeutic agents.

4. DNA Repair Defects and Cancer Development

Mutations in key DNA repair genes (e.g., BRCA1/2) induce genomic instability and promote tumorigenesis. Accumulated DNA damage leads to:

- Increased mutation frequency
- Chromosomal rearrangements
- Activation of oncogenes or loss of tumor suppressors
- Enhanced metastatic potential

Cancer cells often retain partial repair capacity, enabling survival while accumulating mutations that drive evolution under therapeutic pressure.



5. Therapeutic Targeting of DNA Repair in Cancer

5.1 Synthetic Lethality Approaches

Tumors with defective HR (e.g., BRCA-mutant cancers) are highly sensitive to PARP inhibitors, which block single-strand break repair and induce lethal DSB accumulation. This strategy exemplifies synthetic lethality—targeting a compensatory pathway essential only in repair-deficient cell

Small-Molecule DDR Inhibitors

Small-molecule inhibitors targeting DDR proteins (e.g., ATR, ATM, DNA-PK, Polθ) are under active clinical investigation. These agents:

- Sensitize tumors to chemotherapy and radiotherapy
- Overcome resistance by disrupting adaptive repair pathways
- Enable rational combination therapies based on biomarker-driven patient selection

Immunotherapy and DNA Repair Defects

- Tumors with faulty DNA repair accumulate mutations that increase neoantigen load, making them more responsive to immunotherapy. Tools such as **PRRDetect** identify tumors with post-replicative repair dysfunction (PRRd), improving patient selection for immunotherapy

Tumor Evolution and Adaptive Resistance

Cancer therapy exerts selective pressure that drives tumor evolution. Adaptive resistance arises from:

- Clonal selection
- Transcriptional reprogramming
- Phenotypic plasticity
- Tumor microenvironment interactions

Understanding these dynamics is essential for designing durable therapeutic strategies.

Conclusion

DNA repair mechanisms play a fundamental and irreplaceable role in cancer biology because they directly determine whether a cell maintains genomic stability or accumulates mutations that lead to malignant transformation. Throughout the process of tumor development, alterations in DNA repair capacity influence every stage from the initial acquisition of genetic mutations to the expansion of abnormal cell populations, and finally to the ability of cancer cells to survive and resist treatment. When DNA repair systems function normally, they act as a strong barrier against cancer by correcting DNA damage and preventing the transmission of errors during cell division. However, when these systems are weakened or disrupted, cells become increasingly vulnerable to genetic instability, which accelerates tumor initiation and supports continuous tumor evolution.

Recent progress in cancer research has significantly deepened our understanding of how DNA repair pathways operate under conditions of stress, particularly during DNA replication. Replication-associated damage has emerged as a key driver of genomic instability, especially in rapidly dividing tumor cells where replication forks frequently stall or collapse. In addition, the discovery of specific weaknesses within the DNA damage response (DDR) has revealed that many tumors depend heavily on alternative or compensatory repair pathways for survival. This dependency creates therapeutic opportunities, as targeting these vulnerabilities can selectively damage cancer cells while sparing normal tissues.

Furthermore, the study of tumor evolution has shown that defects in DNA repair not only initiate cancer but also contribute to its heterogeneity and adaptability. As tumors accumulate genetic

alterations over time, they develop diverse cell populations that respond differently to treatment, leading to drug resistance and disease relapse. Understanding these evolutionary dynamics is therefore essential for improving long-term treatment outcomes.

Overall, ongoing research into DNA repair pathways continues to reshape the field of oncology. By identifying how specific repair mechanisms are altered in different cancer types, scientists are increasingly able to design more precise and effective therapeutic strategies. The growing knowledge of DDR defects, replication stress responses, and synthetic lethal interactions is paving the way for more personalized approaches to cancer treatment. Continued investigation in this area holds strong promise for improving early detection, overcoming treatment resistance, and ultimately achieving better clinical outcomes for patients.

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