

THE ROLE OF DNA REPAIR MECHANISMS IN CANCER DEVELOPMENT

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Annotation: The stability of the human genome depends on the efficiency of DNA repair systems that safeguard cells against mutagenic damage. DNA molecules are continuously exposed to harmful agents such as ultraviolet radiation, ionizing radiation, reactive oxygen species, and chemical mutagens. To maintain genetic integrity, cells have developed precise repair mechanisms that detect and correct DNA lesions. Failure in these processes leads to mutation accumulation, chromosomal instability, and, ultimately, cancer. The principal DNA repair pathways include base excision repair, nucleotide excision repair, mismatch repair, and double-strand break repair. Each system operates through specific enzymes and signaling cascades to maintain genomic fidelity. Mutations in repair genes such as BRCA1, BRCA2, MLH1, and TP53 are strongly linked to hereditary and sporadic cancers. This article discusses the biological principles of DNA repair, the consequences of their dysfunction, and the therapeutic implications for oncology.

Key words: DNA repair, cancer, genomic instability, mutations, base excision repair, homologous recombination, mismatch repair, BRCA genes.

Main Part

DNA damage is an inevitable event in every living cell. Both endogenous metabolic by-products and environmental agents attack DNA, causing thousands of lesions daily. To ensure survival and proper replication, cells activate a sophisticated system known as the DNA damage response, which involves sensing, signaling, and repair. When these mechanisms fail, mutations accumulate in critical regulatory genes, leading to oncogenic transformation.

Types of DNA Damage

DNA lesions include single- and double-strand breaks, base oxidation, alkylation, and crosslinking. Ultraviolet light induces pyrimidine dimers, while reactive oxygen species cause base modifications such as 8-oxoguanine. Ionizing radiation generates double-strand breaks, the most lethal form of DNA damage. Chemical carcinogens, such as polycyclic aromatic hydrocarbons, create bulky adducts that distort the DNA helix.

Base Excision Repair (BER)

BER corrects small, non-helix-distorting lesions that arise from oxidation, deamination, or alkylation. Specialized DNA glycosylases recognize and remove damaged bases, leaving abasic sites that are processed by AP endonucleases. DNA polymerase β fills the gap, and DNA ligase seals the nick. Defects in BER enzymes increase oxidative stress sensitivity and contribute to colon and gastric cancers.

Nucleotide Excision Repair (NER)



NER removes bulky lesions that interfere with transcription and replication. The process involves lesion recognition, dual incision of the damaged strand, removal of a short oligonucleotide, and gap filling by DNA polymerase δ or ϵ . Mutations in NER genes cause xeroderma pigmentosum, a condition associated with extreme UV sensitivity and high risk of skin cancer.

Mismatch Repair (MMR)

MMR corrects replication errors such as base mispairing and small insertion-deletion loops. The system relies on the MutS and MutL homologs (MSH2, MSH6, MLH1, PMS2) to recognize mismatches and initiate excision of the error-containing strand. Inactivation of these genes results in microsatellite instability, a hallmark of Lynch syndrome and many colorectal and endometrial cancers.

Double-Strand Break Repair (DSBR)

Double-strand breaks are repaired by two principal pathways: homologous recombination (HR) and non-homologous end joining (NHEJ). HR uses the sister chromatid as a template for accurate repair, while NHEJ directly ligates broken ends but often introduces small insertions or deletions. Mutations in HR genes such as BRCA1, BRCA2, and RAD51 cause chromosomal instability and predispose to breast, ovarian, and prostate cancers.

DNA Repair Failure and Tumorigenesis

Defective DNA repair leads to persistent genetic instability, the driving force of cancer evolution. Mutations in tumor suppressor genes like TP53 disable cell cycle checkpoints, allowing damaged cells to proliferate. The accumulation of oncogenic mutations creates clones with selective growth advantages. Cancers such as melanoma, glioblastoma, and leukemia often exhibit signatures of impaired repair, evidenced by specific mutation patterns and chromosomal abnormalities.

Therapeutic Implications

Targeting DNA repair deficiencies has become a promising strategy in modern oncology. Tumors with defective homologous recombination are particularly sensitive to PARP inhibitors such as olaparib, which prevent single-strand break repair and induce synthetic lethality. Other inhibitors targeting ATR, Chk1, and DNA-PK enhance the sensitivity of tumor cells to radiation and chemotherapy. Understanding a tumor's repair profile allows clinicians to design individualized treatments that exploit its molecular weaknesses.

Conclusion

DNA repair mechanisms represent one of the most vital protective systems in human biology, preserving genomic stability and preventing malignant transformation. Their precision and complexity ensure that cells can survive in an environment full of DNA-damaging agents. When these systems fail, mutations accumulate in oncogenes and tumor suppressor genes, driving cancer initiation and progression. Each repair pathway—base excision, nucleotide excision,



mismatch, and double-strand break repair—contributes to the overall defense against genomic instability.

The loss of repair fidelity not only promotes tumorigenesis but also determines how cancer cells respond to therapy. Advances in molecular biology have transformed the understanding of these mechanisms from basic cellular processes to actionable clinical targets. Therapies that exploit DNA repair deficiencies, such as PARP inhibition in BRCA-mutated tumors, represent a shift toward precision medicine.

In a broader context, DNA repair studies illuminate the delicate balance between mutation and stability that governs both evolution and disease. The continued exploration of these mechanisms will improve early cancer detection, refine prognostic evaluation, and enable the development of highly specific, less toxic therapeutic strategies. Protecting and manipulating the DNA repair machinery stands at the frontier of future cancer prevention and treatment.

Each DNA repair pathway contributes uniquely to the preservation of genetic information. The base excision repair (BER) system removes small base modifications that occur daily as a result of oxidative stress and alkylation, preventing point mutations in critical genes. The nucleotide excision repair (**NER**) pathway eliminates bulky DNA adducts and thymine dimers caused by ultraviolet radiation and chemical exposure, preserving the transcriptional and replicative integrity of the genome. The mismatch repair (MMR) system ensures replication fidelity by correcting errors that escape the proofreading function of DNA polymerase, while the double-strand break repair (DSBR) pathways—non-homologous end joining (NHEJ) and homologous recombination repair (HRR)—restore the most lethal DNA lesions that threaten chromosomal stability.

Disruption of any of these mechanisms leads to specific molecular signatures of cancer. For instance, mutations in MLH1 or MSH2 cause microsatellite instability typical of colorectal and endometrial cancers, while defects in BRCA1 or BRCA2 impair homologous recombination, predisposing individuals to breast, ovarian, and prostate cancers. The loss of p53 function, a central regulator of the DNA damage response, further exacerbates genomic instability by allowing damaged cells to escape apoptosis and continue proliferating. Collectively, these defects transform normal cellular processes into oncogenic pathways that drive tumorigenesis.

From a clinical standpoint, understanding DNA repair failures has revolutionized cancer diagnostics and therapy. The discovery of synthetic lethality, where simultaneous defects in two repair pathways result in cell death, has enabled the development of targeted therapies. The most prominent example is the use of PARP inhibitors in BRCA-mutated cancers. By blocking single-strand break repair, PARP inhibitors force tumor cells to rely on defective homologous recombination, ultimately leading to their demise. Such targeted approaches exemplify how molecular understanding of DNA repair can be translated into precise and effective cancer treatments.

Moreover, the expression profiles of DNA repair proteins now serve as valuable biomarkers for predicting therapy response and disease prognosis. Tumors with high repair capacity often resist radiation and chemotherapeutic agents that act by inducing DNA damage, while repair-deficient tumors exhibit increased sensitivity. Therefore, evaluating the repair competency of individual



tumors allows clinicians to design personalized treatment plans, reducing toxicity to normal tissues and improving overall outcomes.

Beyond therapy, the study of DNA repair has profound implications for cancer prevention and early detection. Environmental carcinogens that cause DNA lesions, such as tobacco smoke, ultraviolet radiation, and dietary mutagens, can be identified and mitigated through molecular epidemiology studies based on repair gene polymorphisms. Individuals carrying germline mutations in repair genes can undergo genetic screening and preventive interventions to reduce cancer risk.

On a broader scale, DNA repair research has illuminated the delicate equilibrium between genomic stability and adaptability. While the repair machinery maintains fidelity, a limited degree of mutagenesis is essential for evolution and immune diversity. However, when this balance is lost, cancer emerges as a pathological byproduct of evolutionary mechanisms gone awry. This duality underscores the intricate relationship between repair efficiency, mutation tolerance, and the survival of both cells and species.

In conclusion, DNA repair mechanisms are not only molecular repair tools but also dynamic regulatory systems that determine cellular fate under stress. Their impairment initiates a cascade of events leading from mutation to malignancy, influencing every stage of cancer development—from initiation and progression to metastasis and therapy resistance. As scientific understanding deepens, targeting DNA repair defects continues to transform oncology from a one-size-fits-all approach to precision medicine. The integration of molecular diagnostics, targeted therapeutics, and genomic profiling ensures that DNA repair biology will remain at the forefront of cancer research, offering new hope for prevention, treatment, and ultimately, cure.

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