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COMPLEXITY OF DNA REPAIR MECHANISMS AND EMERGING TRENDS IN SAFEGUARDING GENETIC INTEGRITY

KHAN M, HAIDER MZ, SAMI A*

Department of Plant Breeding and Genetics, Faculty of Agricultural Sciences, University of the Punjab, Lahore, Pakistan
**Correspondence author email address: adnansami4949@gmail.com*

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Abstract *DNA repair mechanisms are the cellular safeguards that maintain the integrity of our genetic blueprint, ensuring that the information encoded within the DNA molecule remains intact. This review explores the complex DNA repair mechanism, providing insight into the essential mechanisms that rectify different forms of DNA damage. From the nuanced correction of single-base lesions to the intricate coordination of double-strand break repair, the exploration navigates through the varied pathways cells utilize to defend against the continual threats to their genetic material. Major subjects addressed encompass Base Excision Repair (BER), Nucleotide Excision Repair (NER), Homologous Recombination (HR), and Non-Homologous End Joining (NHEJ). We unravel the mechanisms, proteins, and regulatory factors that govern these pathways, each tailored to address specific DNA damage, from chemical modifications to UV-induced thymine dimers and double-strand breaks. In an era of rapidly advancing biotechnology, we highlight emerging trends and future directions in DNA repair research, including using CRISPR-based gene editing techniques and developing small molecules that modulate repair pathways for therapeutic purposes.*

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Introduction

The complex and spiraling double helix structure of deoxyribonucleic acid (DNA) serves as the foundational blueprint of life, encoding the directives for all living organisms' development, growth, and operation. Yet, this essential repository of genetic information is constantly under threat. From the moment of conception to the final breath, DNA is subjected to a barrage of assaults, both internal and external, that can lead to its alteration or fragmentation (Ahmad et al., 2023; Hoeijmakers, 2001). Left unchecked, such DNA damage can result in mutations, genomic instability, and diseases, including cancer. These molecular sentinels stand guard, tirelessly surveying the genome for lesions and aberrations and, when necessary, orchestrating precision repairs (Hao et al., 2023). The intricate dance of DNA repair ensures that the genetic information within each cell remains intact, allowing for faithful replication and transcription. In this comprehensive review, we embark on a journey into the world of DNA repair mechanisms (Kowalczykowski, 2015). We will traverse the intricate pathways and molecular machinery that cells employ to mend a diverse array of DNA damage, ranging from the subtle chemical modifications of individual bases to the devastating double-strand breaks that threaten the structural integrity of the genome. Our exploration will take us through the mechanisms of Base Excision Repair (BER) and Nucleotide Excision Repair (NER), which address the insidious single-base lesions and bulkier DNA distortions (Awwad et al., 2023). We will delve into the elegant choreography of Homologous Recombination (HR) and the rapid but pragmatic Non-Homologous End Joining (NHEJ) mechanisms that come to the rescue when the DNA strands snap (Pollina et al., 2023).

Types of DNA Damage

DNA, the carrier of genetic information in all living organisms, is susceptible to various types of damage, both endogenous (internal) and exogenous (external) (Henpita et al., 2023). DNA damage can result from various factors, including chemical reactions, radiation, metabolic processes, and even errors during DNA replication. Understanding these types of DNA damage is crucial because they can lead to mutations, genetic diseases, and cancer (Almas et al., 2023; Bujarrabal-Dueso et al., 2023). Here are some common types of DNA damage:

Chemical Modifications and Structural Alterations

DNA, the blueprint of life, faces diverse challenges that compromise its integrity through chemical modifications and structural alterations (Irfan et al., 2023). One significant modification is deamination, involving removing amino groups from bases, converting adenine to hypoxanthine or cytosine to uracil. Alkylation, adding alkyl groups to bases, introduces changes in base-pairing properties (Garcia et al., 2023). Oxidation, driven by reactive oxygen species, yields oxidized bases such as 8-oxoguanine. Bulky adducts, formed by binding large chemical groups to DNA bases, distort the DNA structure, interfering with replication and transcription (Haider et al., 2023; Sami et al., 2023). Furthermore, apurinic/apyrimidinic (AP) sites result from the spontaneous or enzymatic removal of bases, leaving abasic sites in the DNA.

Impact on DNA Stability and Functionality

The structural integrity of DNA is crucial for its stability and functionality. During DNA replication or repair, base pair mismatches introduce incorrect pairings and can lead to mutations. Exposure to ultraviolet (UV) radiation induces the formation of pyrimidine dimers, specifically thymine dimers, disrupting the DNA structure. Single-strand breaks (SSBs) manifest as nicks in the sugar-phosphate backbone, while double-strand breaks (DSBs) are induced by ionizing radiation such as X-rays and gamma rays or certain chemical agents (Xu et al., 2023). Cross-links, particularly interstrand cross-links formed by chemicals like cisplatin, hinder the separation of DNA strands during replication and transcription. G-quadruplex structures involving guanine-rich regions contribute to DNA instability. Additionally, DNA strand crossings, manifested as knots and tangles, physically impede replication and transcription processes. These structural disruptions collectively challenge the fidelity and functionality of the genetic code (Concannon et al., 2023).

Base Excision Repair

Base Excision Repair (BER) is a specialized mechanism meticulously crafted to rectify single-base lesions, eliminating damaged or mismatched bases. BER involves a cascade of enzymes, including DNA glycosylases and AP endonucleases that work in concert to excise the damaged base and replace it with the correct nucleotide. This process is crucial for maintaining the integrity of the genome (Weaver et al., 2023).

Nucleotide Excision Repair:

Nucleotide Excision Repair (NER) is a versatile pathway tasked with mending diverse DNA lesions, including bulky adducts and thymine dimers induced by UV radiation. NER relies on a complex of proteins to detect and excise damaged DNA segments, followed by repair synthesis to restore the sequence. Its proficiency in handling various lesions makes NER indispensable for genome maintenance (Bai et al., 2023).

Damage Recognition: The first step involves the recognition of the lesion within the DNA helix. In the global genome NER (GG-NER), a protein complex including XPC and HR23B scans the DNA for abnormalities, while in transcription-coupled NER (TC-NER), damage recognition occurs during active transcription.

DNA Unwinding and Incision: Once the lesion is identified, a set of proteins, including TFIIH, XPB, and XPD, unwind the DNA around the damaged site. This unwinding exposes the lesion, allowing for precise incisions on both sides of the damage by endonucleases XPG and ERCC1-XPF (Frigerio et al., 2023).

Removal of Damaged Segment: After incision, the damaged DNA segment, including the lesion, is excised.

DNA Resynthesis: DNA polymerases and ligases are then recruited to fill in the gap with newly synthesized DNA, using the undamaged strand as a template.

Ligation: The repaired DNA strand is sealed, restoring the integrity of the DNA molecule (Wu et al., 2023).

Homologous Recombination and Non-Homologous End Joining

Homologous recombination (HR) and non-homologous end joining (NHEJ) represent two distinct yet complementary pathways responsible for repairing double-strand breaks (DSBs). HR operates as an error-free mechanism, utilizing a homologous sister chromatid as a template to restore damaged DNA, thereby ensuring genetic fidelity (Guerra et al., 2023). On the other hand, NHEJ is an error-prone process that directly rejoins broken DNA ends, often leading to small insertions or deletions. Both pathways play crucial roles in maintaining genome integrity, with HR predominantly active during the S and G2 phases of the cell cycle, while NHEJ operates throughout the entire cell cycle (Catalano et al., 2023).

HR is a precision repair mechanism:

End Resection: DSB ends are processed to generate 3'-ended single-stranded DNA tails.

Search for Homology: The single-stranded tails invade the intact sister chromatid, searching for regions of homology.

DNA Strand Exchange: Base pairing between the single-stranded tails and the homologous regions of the sister chromatid allows for the formation of a DNA joint molecule called a Holliday junction.

Resolution: The Holliday junction is resolved, leading to the exchange of genetic material and ultimately resulting in the accurate repair of the DSB (Wang and Sheetz, 2023).

Non-Homologous End Joining (NHEJ):

The key steps of NHEJ include:

End Recognition: NHEJ proteins recognize and bind to the broken DNA ends.

End Processing: If the ends are damaged or non-complementary, minimal processing may occur to prepare the ends for ligation.
End Joining: The broken DNA ends are ligated together, often without the need for extensive sequence homology.
Ligase Sealing: A DNA ligase seals the nick, completing the repair (Naz et al., 2023).
Defects in HR and NHEJ can profoundly affect genome stability and human health. Dysregulation of these pathways is associated with various diseases, including cancer, where impaired HR can lead to genetic instability and susceptibility to tumorigenesis. Conversely, defects in NHEJ can result in immunodeficiency disorders, such as severe combined immunodeficiency (SCID), characterized by compromised immune responses due to the failure to generate diverse antigen receptor genes (Ahmed et al., 2023). In conclusion, HR and NHEJ represent two sides of the DNA repair coin, each finely tuned to handle DSBs with unique strengths and weaknesses. Together, they safeguard the integrity of the genome, balancing precision and speed, and ensuring the preservation of genetic information in the face of potentially catastrophic DNA damage. Understanding these mechanisms is pivotal for deciphering fundamental cellular processes and developing targeted therapeutic strategies in the context of various genetic diseases and cancer (Miser-Salihoglu et al., 2023).

Other DNA Repair Pathways

In addition to the major repair pathways mentioned above, cells have developed additional mechanisms to address specific types of DNA damage. Mismatch repair ensures the correction of replication errors, while translesion synthesis allows DNA polymerases to replicate past damaged sites. Interstrand cross-link repair deals with covalent links between DNA strands, ensuring that these links are efficiently resolved (Koeppel et al., 2023).

Regulation of DNA Repair

Recognition of DNA Damage

The regulation of DNA repair begins with the recognition of DNA damage. Specialized proteins, such as XPC in nucleotide excision repair (NER) and MRN complex in homologous recombination (HR), act as sentinels, scanning the genome for aberrant DNA structures or lesions. These recognition factors initiate the repair process by recruiting downstream repair proteins to the damage site (Cinar et al., 2023).

Cell Cycle Checkpoints

The cell cycle is tightly linked to DNA repair, ensuring that repair processes occur correctly. Checkpoints, such as the G1/S and G2/M checkpoints, temporarily halt cell cycle progression to allow DNA repair. Regulatory proteins, like p53, play pivotal roles in coordinating these checkpoints. If DNA damage is too severe to be repaired, cells can be directed toward apoptosis, preventing the propagation of potentially harmful mutations (Cinar et al., 2023).

DNA Damage Signaling Pathways

The regulation of DNA repair encompasses intricate signaling pathways that convey the existence of DNA damage to the cell's nucleus. Notably, the ATM (ataxia-telangiectasia mutated) and ATR (ataxia-telangiectasia and Rad3-related) kinases play pivotal roles in detecting and responding to DNA double-strand breaks (DSBs) and single-stranded DNA (ssDNA), respectively. These kinases set off a cascade of phosphorylation events, activating downstream effectors responsible for DNA repair, cell cycle arrest, and apoptosis (Birkisdóttir et al., 2023).

Balance Between Repair and Apoptosis

One of the most critical decisions in DNA repair regulation is the choice between repair and apoptosis. If the level of DNA damage exceeds the cell's repair capacity or is beyond repair, signaling pathways like the p53 pathway can trigger programmed cell death (apoptosis). Apoptosis prevents the survival and proliferation of cells with potentially harmful genetic alterations (Senkal et al., 2023).

Diseases and Implications

Defects in DNA repair mechanisms can have dire consequences. Inadequate repair can lead to the accumulation of mutations, which is a hallmark of cancer. Mutations in specific DNA repair genes can also result in hereditary disorders characterized by genomic instability, such as Lynch syndrome and xeroderma pigmentosum (Chuang et al., 2023).

Emerging Trends and Future Directions

The field of DNA repair research is continually evolving. Recent advancements include applying CRISPR-based gene editing techniques for precise DNA repair, offering unprecedented opportunities for targeted therapies. Moreover, developing small molecules that modulate DNA repair pathways holds promise for novel cancer treatments and interventions in genetic diseases (Yurchenko et al., 2023).

Conclusion

DNA repair mechanisms are the guardians of the genetic code, tirelessly working to preserve the integrity of our genome. These intricate and interconnected pathways play pivotal roles in protecting us from the consequences of DNA damage, such as mutations and diseases. As our understanding of DNA repair mechanisms deepens and technology advances, we are poised to harness these insights to develop innovative therapeutic strategies and personalized medicine.

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Declarations

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All data generated or analyzed during the study are included in the manuscript.

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Conflict of Interest

Regarding conflicts of interest, the authors state that their research was carried out independently without any affiliations or financial ties that could raise concerns about biases.