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Molecular Mechanisms of DNA Damage Response and Repair

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Introduction

The stability of the genome is fundamental to the survival of all living organisms, as it ensures the faithful transmission of genetic information across generations and the proper functioning of cellular processes. However, DNA is continuously challenged by both endogenous and exogenous factors that can damage its structure. Reactive oxygen species, replication errors, chemical mutagens and ultraviolet or ionizing radiation all contribute to DNA lesions. If left unrepaired, such damage can lead to mutations, chromosomal instability and ultimately diseases such as cancer, neurodegeneration and immunodeficiency. To counter these threats, cells have evolved intricate mechanisms collectively referred to as the DNA Damage Response (DDR). This system integrates signaling pathways that detect DNA lesions, halt cell cycle progression and coordinate repair through specialized pathways tailored to the type of damage encountered. Understanding the molecular mechanisms of DDR and repair is central to modern biology and medicine, as it not only reveals how cells maintain genomic integrity but also guides therapeutic strategies in oncology and beyond [1].

Description

The DNA damage response is a highly orchestrated process that begins with the detection of DNA lesions. DNA damage sensors, such as the MRN complex (Mre11-Rad50-Nbs1), recognize Double-Strand Breaks (DSBs), while proteins such as RPA (replication protein A) bind to Single-Stranded DNA (ssDNA) exposed during replication stress or repair intermediates. Upon detection, these sensors recruit and activate transducer kinases, primarily ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related), which then phosphorylate downstream effectors such as CHK1, CHK2 and p53. This signaling cascade coordinates cell cycle checkpoints, halting progression at G1/S, intra-S, or G2/M phases to provide time for repair or to initiate apoptosis if the damage is irreparable [2]. The type of DNA lesion dictates which repair pathway is employed. Base damage, resulting from oxidation, alkylation, or deamination, is primarily corrected by base excision repair (BER). In this pathway, DNA glycosylases recognize and remove damaged bases, creating an abasic site. Endonucleases then cleave the DNA backbone, allowing DNA polymerases to insert the correct nucleotide, followed by ligation to restore integrity. For bulky lesions such as thymine dimers caused by UV light, Nucleotide Excision Repair (NER) is utilized. NER involves the recognition of DNA helix distortions, excision of a short single-stranded DNA segment containing the lesion and subsequent resynthesis using the undamaged strand as a template.

MisMatch Repair (MMR) is another critical pathway, ensuring the fidelity of DNA replication by correcting misincorporated bases and small insertion–deletion loops. The MutSα and MutLα complexes recognize mismatches, recruit endonucleases and coordinate excision and resynthesis of the erroneous DNA. Defects in MMR lead to microsatellite instability, a hallmark of Lynch syndrome and certain sporadic cancers, underscoring the importance of this pathway in preventing mutagenesis. Double-strand breaks represent the most lethal form of DNA damage, as they sever the continuity of the genome. Cells employ two major pathways to repair DSBs: Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ).

HR is an error-free mechanism that uses the sister chromatid as a template, making it active primarily in S and G2 phases of the cell cycle. The process begins with end resection mediated by nucleases such as CtIP and the MRN complex, generating single-stranded DNA that is coated by RPA. BRCA1, BRCA2 and RAD51 then facilitate strand invasion into the homologous template, enabling accurate repair. In contrast, NHEJ directly ligates broken DNA ends without the need for homology, making it faster but more error-prone. Proteins such as Ku70/80, DNA-PKcs and XRCC4-Ligase IV orchestrate this process, which operates throughout the cell cycle but predominates in G1.

In addition to these canonical pathways, specialized mechanisms address unique forms of damage. TransLesion Synthesis (TLS) allows replication to bypass lesions using specialized low-fidelity polymerases, preventing replication fork collapse but at the cost of increased mutagenesis.

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Fanconi Anemia (FA) pathway proteins coordinate the repair of interstrand crosslinks, complex lesions that block replication and transcription. The FA core complex monoubiquitinates FANCD2 and FANCI, which recruit nucleases, helicases and HR proteins to resolve the crosslink. The DDR not only governs repair but also interfaces with other cellular processes, particularly chromatin remodeling. DNA is packaged into chromatin and access to damaged sites requires structural alterations mediated by ATP-dependent remodelers and histone modifications. Phosphorylation of histone H2AX to form γ-H2AX is a key early event in DSB signaling, recruiting mediator proteins such as MDC1 and 53BP1 to amplify the DDR. Ubiquitination, acetylation and methylation of histones further regulate the assembly and disassembly of repair complexes. Thus, chromatin dynamics are integral to the efficiency and specificity of DNA repair.

Conclusion

The molecular mechanisms of DNA damage response and repair are central to maintaining genomic stability and safeguarding human health. Through a complex interplay of detection, signaling and repair pathways, cells are able to confront a wide spectrum of DNA lesions and prevent the accumulation of mutations. Failures in these mechanisms contribute to a range of diseases, most notably cancer, but also rare inherited syndromes that underscore the critical role of DDR in physiology. By elucidating the structural and biochemical details of repair pathways, scientists have identified vulnerabilities in tumor cells that can be therapeutically exploited, ushering in a new era of targeted treatments. As research progresses, integrating molecular insights with clinical applications promises not only to improve cancer therapy but also to shed light on the fundamental principles of genome maintenance. The DNA damage response thus stands as both a guardian of life and a key to advancing biomedical innovation.

Acknowledgement

None.

Conflict of Interest

None.

Reference

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