DNA Damage Signaling and Cellular Repair Mechanisms

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Introduction

DNA is chemically stable enough to preserve genetic information, yet every cell experiences continual damage from ultraviolet radiation, reactive oxygen species, replication errors, ionizing radiation, environmental chemicals, and normal metabolism. The DNA damage response is therefore not a single repair reaction but a coordinated network that recognizes abnormal DNA, signals the problem, slows cell-cycle progression, repairs lesions, and determines whether a cell should recover, become senescent, or die. Different lesions require different pathways. Small base modifications may be handled by base excision repair, replication mismatches by mismatch repair, double-strand breaks by homologous recombination or end joining, and bulky helix-distorting lesions by nucleotide excision repair. Two related kinases, ATM and ATR, organize much of the signaling response but do not directly remove damaged nucleotides. Understanding how these pathways interact is essential because inadequate repair promotes mutation and cancer, while excessive or persistent signaling can destroy functional tissue. The balance between genome preservation and continued transcription, replication, and survival is therefore a central problem in cell biology.

ATM, ATR, and the Cellular Damage Signal

ATM and ATR respond to different forms of genomic stress while sharing some downstream targets. ATM is strongly activated by DNA double-strand breaks, often through the MRN complex, and phosphorylates proteins involved in checkpoint control, chromatin organization, repair, and apoptosis. ATR is activated principally by stretches of single-stranded DNA coated with replication protein A, a structure common at stalled replication forks and during processing of several lesions. ATR works with ATRIP and checkpoint kinase 1 to stabilize replication and delay cell-cycle progression until the problem is resolved. These signaling systems create time for repair and reduce the chance that damaged DNA will be replicated or segregated into daughter cells. The tumor suppressor p53 can be stabilized during prolonged stress and may induce p21-mediated arrest, senescence, or apoptosis. The response must remain proportional. Weak signaling can permit chromosome instability, whereas prolonged checkpoint activation can impair tissue renewal. ATM and ATR therefore function as coordinators that translate physical DNA abnormalities into broader decisions about replication, transcription, cell-cycle timing, and cell fate.

Nucleotide Excision Repair Has Two Recognition Routes

Nucleotide excision repair removes bulky lesions such as ultraviolet-induced photoproducts by excising a short damaged DNA segment and rebuilding the missing strand from the intact template. Global-genome NER and transcription-coupled NER share the same core excision machinery but detect damage differently. Global-genome NER surveys transcribed and nontranscribed regions for distortions, using the XPC complex and, for some ultraviolet lesions, UV-DDB to recognize abnormal DNA structure. Transcription-coupled NER begins when elongating RNA polymerase II stalls at a lesion on the transcribed strand of an active gene. The stalled polymerase is not simply an obstacle; it becomes a signal that the cell must prioritize removal of a transcription-blocking lesion. Current reviews emphasize that RNA polymerase II, CSB, CSA, and UVSSA form an organized early response before the pathway converges with general NER factors. This division of labor allows the cell to protect the entire genome while also giving rapid attention to lesions that interrupt essential gene expression. (Marteijn et al., 2014; Tufegdzic Vidakovic et al., 2023)

From a Stalled Polymerase to Excision and Restart

Transcription-coupled repair is initiated when lesion-arrested RNA polymerase II recruits Cockayne syndrome protein B, an ATP-dependent remodeling factor encoded by *ERCC6*. CSB helps organize the damaged transcription complex and supports recruitment of CSA, UVSSA, USP7, and additional proteins. UVSSA is especially important for stabilizing the repair assembly and coordinating recruitment of the general NER machinery. TFIIH then opens the DNA around the lesion through activities associated with XPB and XPD, while XPA and replication protein A help verify the damaged structure and organize the repair bubble. XPF–ERCC1 and XPG make incisions on opposite sides of the lesion, releasing a short oligonucleotide containing the damage. DNA polymerases fill the resulting gap, and ligase restores continuity. Successful repair also requires disassembly of repair proteins, restoration of chromatin, and recovery of RNA synthesis. A chemically repaired DNA strand is not sufficient if transcription remains suppressed. The entire process therefore links lesion recognition, protein remodeling, nuclease activity, DNA synthesis, and controlled restart of gene expression.

Repair Failure Reveals the Biological Stakes

Inherited repair disorders demonstrate that mutation prevention and transcription recovery are related but distinct biological goals. Xeroderma pigmentosum can result from defects in several NER genes and is characterized by extreme ultraviolet sensitivity and a greatly increased risk of skin and eye cancers because damaged bases persist and can become mutations during replication. Cockayne syndrome, commonly associated with pathogenic variants in *ERCC6* or *ERCC8*, produces growth failure, neurological degeneration, developmental problems, and photosensitivity but does not create

the same dramatic skin-cancer predisposition. UV-sensitive syndrome, which may involve UVSSA, impairs recovery of transcription after ultraviolet damage while generally lacking the severe neurodevelopmental features of Cockayne syndrome. These differences reveal that repair proteins often perform functions beyond a single excision step. DNA-repair capacity also affects cancer therapy because platinum compounds and other treatments create lesions that interfere with replication or transcription. Tumors with strong repair activity may resist some drugs, while systemic inhibition of repair can damage healthy tissues. Repair pathways are therefore both guardians of normal cells and potential therapeutic vulnerabilities.

Conclusion

The DNA damage response preserves genome stability by coordinating lesion detection, checkpoint signaling, transcription control, repair chemistry, and cell fate. ATM and ATR organize major responses to double-strand breaks, stalled replication, and related stress, while nucleotide excision repair removes bulky helix-distorting lesions through two recognition branches. Global-genome NER surveys DNA broadly, whereas transcription-coupled NER is triggered when RNA polymerase II stalls on the transcribed strand. CSB, CSA, UVSSA, USP7, TFIIH, XPA, XPF–ERCC1, XPG, polymerases, and ligases act in a controlled sequence that opens the damaged region, removes the lesion-containing fragment, restores DNA, and permits transcription to resume. The clinical consequences of pathway failure show why this coordination matters: xeroderma pigmentosum is dominated by mutagenesis and cancer risk, whereas Cockayne syndrome and UV-sensitive syndrome demonstrate the importance of transcriptional recovery and broader cellular maintenance. DNA repair is therefore not merely molecular housekeeping. It is a continuous decision system that determines whether cells preserve information, tolerate stress, stop dividing, or sacrifice themselves to protect the organism.

References

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