DNA Damage Signaling and Cellular Repair Mechanisms

Posted on October 2, 2018

Introduction

Every human cell experiences DNA damage from ultraviolet radiation, reactive oxygen species, replication errors, chemicals, radiation, and normal metabolism. The DNA damage response is the network that detects these lesions, signals their presence, pauses cell-cycle progression where necessary, repairs the damage, and determines whether a cell should recover, become senescent, or undergo programmed death. The original essay correctly identifies ATM and ATR kinases, RNA polymerase II stalling, nucleotide excision repair, Cockayne syndrome proteins, UVSSA, and apoptosis as central concepts. Its terminology is frequently garbled, and it treats several pathways as though they were interchangeable. Nucleotide excision repair removes bulky, helix-distorting lesions through two recognition branches: global-genome NER, which surveys the genome, and transcription-coupled NER, which responds when elongating RNA polymerase II stalls on the transcribed strand. Understanding how transcription, signaling, and repair are coordinated explains inherited photosensitivity disorders, cancer susceptibility, and cellular responses to chemotherapy.

Sources and Types of DNA Damage

DNA lesions differ in chemical structure and biological consequence. Ultraviolet light produces cyclobutane pyrimidine dimers and 6–4 photoproducts that distort the double helix. Reactive oxygen species can modify bases, create single-strand breaks, and damage the sugar-phosphate backbone. Ionizing radiation can generate double-strand breaks and clustered damage. Alkylating agents and some chemotherapy drugs create adducts or crosslinks. Replication can introduce mismatches or encounter damaged templates. No single repair system handles all of these lesions. Base excision repair acts mainly on small base modifications, mismatch repair corrects replication errors, homologous recombination and end joining repair double-strand breaks, and nucleotide excision repair removes a wide range of bulky lesions.

The DNA Damage Response as a Decision Network

The DNA damage response is more than repair chemistry. Sensor proteins recognize abnormal DNA or stalled molecular machines, mediator proteins organize signaling platforms, transducer kinases phosphorylate targets, and effector pathways alter replication, transcription, cell-cycle progression, metabolism, and survival. This organization allows a small lesion to produce a coordinated cellular

response. The response must be proportional. Insufficient signaling permits mutation and chromosome instability, while excessive or prolonged signaling can kill functional cells or promote tissue degeneration. Cells continually balance genome preservation with the need to maintain transcription and division.

ATM and ATR Signaling

ATM and ATR are related protein kinases that coordinate different but overlapping damage responses. ATM is strongly activated by DNA double-strand breaks, often through the MRN complex. It phosphorylates proteins involved in checkpoint control, repair, chromatin organization, and apoptosis. ATR responds principally to stretches of single-stranded DNA coated by replication protein A, which appear at stalled replication forks and during processing of several lesions. ATR works with ATRIP and checkpoint kinase 1 to stabilize forks and delay cell-cycle progression. Ultraviolet damage can activate ATR indirectly when replication or repair exposes single-stranded DNA. These kinases do not repair lesions themselves; they create time and conditions in which appropriate repair can occur.

Cell-Cycle Checkpoints

Damage signaling can slow entry into DNA synthesis, delay progression within S phase, or prevent mitosis. The tumor suppressor p53 is stabilized after several forms of stress and can induce the cyclin-dependent kinase inhibitor p21, promoting arrest. Checkpoints reduce the chance that damaged DNA will be replicated or segregated into daughter cells. Arrest is not always permanent. Once repair succeeds, signaling is reduced and the cell may resume division. When damage is extensive or persistent, p53 and other pathways can promote senescence or apoptosis. Checkpoint failure contributes to cancer by allowing cells to proliferate with mutations and chromosome abnormalities.

How DNA Damage Blocks Transcription

RNA polymerase II moves along the template strand to synthesize messenger RNA. Bulky lesions can obstruct the polymerase because damaged bases cannot be read or accommodated normally. Stalling interrupts expression of the affected gene and creates a potentially dangerous protein–DNA complex. Long and actively transcribed genes are especially vulnerable because they present a large target. The biological consequence depends on lesion position, gene function, cell type, and duration. A short interruption may be repaired without lasting effect, while persistent transcription arrest can trigger stress signaling and cell death. Transcription inhibition is therefore both a direct functional consequence of damage and a signal that recruits specialized repair.

Global-Genome Nucleotide Excision Repair

Global-genome NER surveys both transcribed and nontranscribed DNA for helix distortion. The XPC complex is a major damage sensor, while the UV-DDB complex helps recognize certain ultraviolet photoproducts in chromatin. Recognition is based less on one chemical group than on abnormal DNA structure and base pairing. Chromatin remodeling and ubiquitin signaling improve access. Once a lesion is recognized, the pathway recruits the general NER machinery. GG-NER protects the whole genome, including inactive genes and noncoding regions. Defects can greatly increase mutation burden because lesions remain available to block replication or be bypassed inaccurately. (Marteijn et al., 2014; Schärer, 2013)

Transcription-Coupled Nucleotide Excision Repair

Transcription-coupled NER begins when RNA polymerase II stalls at a lesion on the transcribed strand of an active gene. The polymerase is not a conventional damage sensor, but its arrest reveals that a template cannot be read. TC-NER rapidly prioritizes removal of the obstruction so transcription can resume. This branch uses CSA, CSB, UVSSA, USP7, and additional factors before converging with the core NER machinery. It does not repair every oxidative lesion merely because transcription is affected; different pathways can cooperate depending on lesion chemistry. The defining feature is preferential repair linked to stalled transcription. (Lans et al., 2019; van der Weegen et al., 2020)

CSB: Remodeling the Stalled Complex

CSB, encoded by *ERCC6*, is an ATP-dependent chromatin-remodeling protein that associates with stalled RNA polymerase II. It helps organize the early TC-NER complex, alters local chromatin, and supports recruitment of downstream factors. CSB is not simply a protein that removes the polymerase. It coordinates recognition of productive stalling and creates access for repair. Mutations can cause Cockayne syndrome or related phenotypes. Because CSB also participates in transcription regulation and responses to oxidative stress, disease effects are broader than loss of ultraviolet lesion repair alone.

CSA and Ubiquitin Regulation

CSA, encoded by *ERCC8*, functions in a ubiquitin-ligase complex containing CUL4A, DDB1, and RBX1. It is recruited to the stalled transcription complex through interactions involving CSB and helps regulate protein stability and assembly. Ubiquitination in TC-NER is not simply a signal for destruction; it can control recruitment, remodeling, and timely removal of factors. After repair, the complex must be disassembled so transcription can restart. Mutations in CSA can cause Cockayne syndrome, demonstrating that precise regulation of repair proteins is essential for development and nervous-

system maintenance.

UVSSA and USP7

UVSSA was identified through studies of UV-sensitive syndrome, a disorder characterized by ultraviolet sensitivity without the severe developmental and neurological features typical of Cockayne syndrome. UVSSA associates with stalled RNA polymerase II complexes and recruits the deubiquitinating enzyme USP7. This interaction helps stabilize CSB and coordinate early TC-NER. The discovery clarified why cells with UV-sensitive syndrome fail to restore transcription efficiently after ultraviolet exposure even though global-genome NER remains functional. It also demonstrated that similar cellular repair defects can produce different clinical phenotypes depending on which proteins and additional functions are affected.

Recruitment of TFIIH

After lesion recognition by either GG-NER or TC-NER, the pathways recruit TFIIH, a multi-subunit complex also required for transcription initiation. Its XPB and XPD helicase-related activities open the DNA around the lesion and verify that a genuine damaged structure is present. XPA and replication protein A help organize the repair bubble and ensure correct strand positioning. The use of a general transcription factor in repair illustrates the close relationship between transcription and genome maintenance. Mutations in TFIIH components can produce xeroderma pigmentosum, trichothiodystrophy, combined syndromes, or other phenotypes because both repair and transcription functions may be affected.

Dual Incision and Removal

Nucleotide excision repair removes a short oligonucleotide containing the lesion rather than reversing one damaged base directly. The XPF–ERCC1 nuclease cuts on the 5′ side, while XPG cuts on the 3′ side. These coordinated incisions release a fragment of roughly two to three dozen nucleotides in human cells. The undamaged complementary strand remains as a template. Precise assembly is essential because uncontrolled nuclease activity would convert a bulky lesion into a more dangerous break. Defects in XPF, ERCC1, or XPG can create severe repair syndromes and sensitivity to ultraviolet light or crosslinking agents.

Repair Synthesis and Ligation

After excision, DNA polymerases fill the gap using the intact strand. Proliferating cell nuclear antigen and replication factor C support synthesis, while DNA ligase seals the remaining nick. Chromatin must then be restored, and repair proteins must leave the site. Completion is not defined only by replacing

nucleotides. The cell must also recover transcription, normalize signaling, and reestablish nucleosome organization. Failure at a late step can leave a structurally repaired region that still does not function normally. Researchers therefore measure both unscheduled DNA synthesis and recovery of RNA synthesis when evaluating NER.

The Fate of Stalled RNA Polymerase II

A stalled polymerase can be remodeled, moved backward, restarted after repair, or targeted for ubiquitination and degradation when obstruction cannot be resolved. The outcome depends on lesion type, duration, transcription complex, and cellular state. Removing RNA polymerase II may allow access but sacrifices the incomplete transcript and requires reinitiation. Persistent stalling activates stress pathways, including p53 stabilization and apoptosis. The original essay suggests that absence of Cockayne proteins directly causes one fixed outcome. In reality, cells use several overlapping strategies, and research continues to define how polymerase fate is selected.

Transcription Restart

Successful TC-NER must restore RNA synthesis. Repair factors leave, chromatin is reorganized, and transcription machinery resumes at or near the interrupted gene. Restart is actively regulated rather than an automatic consequence of lesion removal. Cells may suppress new transcription initiation during acute damage to avoid further collisions and then gradually restore expression. Defects in recovery can be harmful even when some repair occurs because essential long genes remain silent. Neurons, which are long-lived and depend on sustained transcription, may be particularly sensitive to these failures.

Xeroderma Pigmentosum

Xeroderma pigmentosum is caused by inherited defects in several NER genes or, in the variant form, translesion DNA synthesis. Affected people can have extreme ultraviolet sensitivity and a dramatically increased risk of skin and eye cancers because photoproducts persist and become mutations during replication. Some complementation groups include neurological disease. Protection from ultraviolet exposure, surveillance, early treatment of lesions, and specialized care are essential. XP demonstrates the tumor-prevention role of genome-wide lesion repair. It should not be confused with Cockayne syndrome, where cancer risk is not increased to the same extent despite severe photosensitivity in many patients. (GeneReviews, 2022)

Cockayne Syndrome

Cockayne syndrome commonly results from pathogenic variants in *ERCC6* or *ERCC8*. Features can include growth failure, progressive neurological dysfunction, developmental impairment, retinal or hearing problems, and photosensitivity. The disease is associated with defective recovery of transcription after damage and broader abnormalities in transcription and mitochondrial or oxidative-stress responses. Patients do not typically show the enormous skin-cancer predisposition characteristic of XP. This difference suggests that developmental degeneration and cancer risk reflect distinct consequences of repair failure, cell death, mutation, and tissue renewal.

UV-Sensitive Syndrome

UV-sensitive syndrome can result from variants involving UVSSA or, in some cases, proteins also linked to Cockayne syndrome. Patients generally show photosensitivity and abnormal cellular recovery of transcription but lack severe neurodevelopmental degeneration. The milder phenotype helped researchers discover that CSA and CSB perform additional cellular functions beyond the core lesion-removal reaction. Comparing related disorders is therefore a powerful method for identifying which molecular activities are necessary for cancer prevention, development, and long-term tissue maintenance.

DNA Repair and Cancer Therapy

Several anticancer drugs work partly by producing lesions that block replication or transcription. Platinum compounds create bulky adducts and crosslinks, while other therapies generate breaks or oxidative damage. Tumor repair capacity can influence sensitivity and resistance. High NER activity may remove some drug-induced lesions, reducing treatment effect; low repair can increase sensitivity but also cause toxicity in normal tissue. Repair proteins are therefore potential biomarkers and therapeutic targets. Inhibition must be selective because systemic suppression of genome maintenance can increase mutation, tissue injury, or secondary cancer.

Research Methods

Scientists study these pathways through ultraviolet irradiation, lesion-specific antibodies, recovery-of-RNA-synthesis assays, unscheduled DNA synthesis, live-cell imaging, proteomics, gene knockout, patient cells, structural biology, and sequencing. Measuring only cell survival can obscure the exact defect. A cell may survive despite slow repair, or die through excessive signaling even after some lesions are removed. Modern approaches map repair across the genome and show that chromatin, transcription level, sequence, and nuclear organization influence repair speed. The pathway is therefore more dynamic than a simple linear diagram suggests.

Conclusion

The DNA damage response protects genomic stability by linking lesion detection, kinase signaling, checkpoints, repair, transcription control, and cell fate. ATM and ATR coordinate major signaling responses, while nucleotide excision repair removes bulky helix-distorting lesions. Global-genome NER surveys the genome through factors including XPC and UV-DDB. Transcription-coupled NER begins when RNA polymerase II stalls and recruits CSB, CSA, UVSSA, USP7, and the core NER machinery. TFIIH opens the DNA, XPF–ERCC1 and XPG excise the damaged fragment, polymerases fill the gap, and ligase restores continuity. When repair fails, persistent transcription stress can activate p53, senescence, or apoptosis. The clinical consequences—xeroderma pigmentosum, Cockayne syndrome, and UV-sensitive syndrome—show that preventing mutation and maintaining transcription are related but distinct biological goals.

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