# Devices of several kinds Repair and damage to DNA

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*Abstract-* **This review article describes the basic types of DNA damage caused by exogenous and endogenous factors, analyzes the potential consequences of each type of damage, and discusses the need for different types of DNA repair. The mechanisms by which minor damage to DNA can eventually lead to the introduction of heritable mutations are examined. The main features of the role of DNA damage in aging and carcinogenesis are outlined, and the role of iatrogenic DNA damage in human health and disease (with curative intent and as a long-term side effect of genotoxic therapies) is explained. Cells are constantly exposed to DNA damage resulting from replication or transcription, cellular metabolic activities leading to the production of DNA-damaging agents such as UV light.**

***Key words*- DNA damage, DNA repair,**

**INTRODUCTION:**

The journey of DNA repair system discovery in recent years,

The availability of high-quality DNA data from in vivo and in vitro research reported in the literature, international conferences, funding, and collaborations among scientific communities have increased. In addition, new technologies related to translational research, targets for clinical therapy, and expertise among scientists have been rapidly developed, suggesting that after a century of steady progress, DNA damage repair and the study of genomic stability have entered a new era. This field continues to offer unprecedented opportunities to explore the mystery of structural integrity and functional harmonization of our genomic DNA, while advancing clinical disease prevention and therapeutic options, particularly precision cancer therapy.

Because of their sessile nature, plants must be constantly exposed to environmental stressors, including UVB, ozone, desiccation, rehydration, salinity, low and high temperatures, and air and soil pollutants, including metals and semimetals. Several chemical mutagens and cross-linking agents (e.g., mitomycin C, cisplatin), alkylating agents, aromatic compounds, ionizing radiation, and fungal and bacterial toxins are other important environmental DNA-damaging agents [1]. Apart from the severe effects on structural, enzymatic and non-enzymatic components of the plant, the above stressors can also negatively affect the plant genome.

Most macromolecules in the cell are simply degraded and replaced when damaged. In contrast, the nuclear genome, which is the blueprint for all cellular functions, has specialized and energetically costly repair mechanisms to rapidly repair DNA damage. This suggests that DNA damage is a particularly dangerous type of macromolecular damage and is therefore likely to adversely affect cellular homeostasis.

Maintenance of genome stability is an ongoing process. Deoxyribonucleic acids are chemically unstable under physiological conditions (aqueous, oxygenated, and pH 7.4) (Lindahl, 1993). DNA is also susceptible to chemical attack by electrophiles and free radicals. While exogenous sources of genotoxic stress can be severe, endogenous threats are constant and relentless.

The most common DNA damage is hydrolytic cleavage of the glycosidic bond between the DNA base and the sugar phosphate group, resulting in abasic sites. Hydrolytic deamination of DNA bases is also common. Products of normal cellular metabolism can cause oxidation, nitrosylation, and alkylation of DNA bases (De Bont and van Larebeke, 2004). Breaks in the phosphate-deoxyribose backbone occur as a result of high-energy radiation or during DNA metabolism (replication, decatenation). Spontaneous DNA damage occurs at a rate of 10 4105 events per cell per day (Lindahl, 1993; De Bont and van Larebeke, 2004).

Damage to DNA consists of any change that introduces a deviaon from the usual doublehelical structure" [1]. One of the most commonly used and, in the authors' opinion, the most comprehensive, is of DNA damage given by the US Naonal Library of Medicine, [United Medica l Language system (UMLS)]:

"Drug- or radiaon-induced injuries in DNA that introduce deviaons from its normal double-helical conformaon. These changes include structural distortions which interfere with replication and transcription, as well as point mutations which disrupt base pairs and exert damaging effects on future generations through changes in DNA sequence". The later definition, however, implies that DNA damage is always a product of some external influence, that is, it is not produced by physiological means. This is not true, however, as the most part of DNA damage occurs as a result of normal cellular metabolism.

**Classification of factors causing DNA damage**

Factors of exogenous and endogenous origin

DNA damage can occur under the influence of factors external to the cell (factors of exogenous origin, e.g. environmental factors) or potentially aggressive agents produced by normal cellular metabolism (factors of endogenous origin). The consequences for cellular DNA damage caused by endogenous factors can be more severe and/or more extensive than the effects of most exogenous

DNA-damaging factors. DNA-damaging events caused by endogenous factors generally occur much more frequently than damage caused by exogenous factors.
For example, several thousand nitrogenous bases are lost daily from DNA in eukaryotic cells alone as a result of spontaneous base hydrolysis.

**Types of DNA damage**
**Damage of endogenous origin**
**Conversion of one base to another, producing a mismatch**
The four nitrogenous bases in DNA can be converted directly into each other or into rare bases that are mateable with bases other than the original mating partner (non-canonical mating). Base conversion often occurs through the hydrolysis of nitrogenous bases in DNA. Deamination of nitrogenous bases is a very common form of hydrolytic damage to DNA. For example, deamination of cytosine produces uracil (Fig. 1).

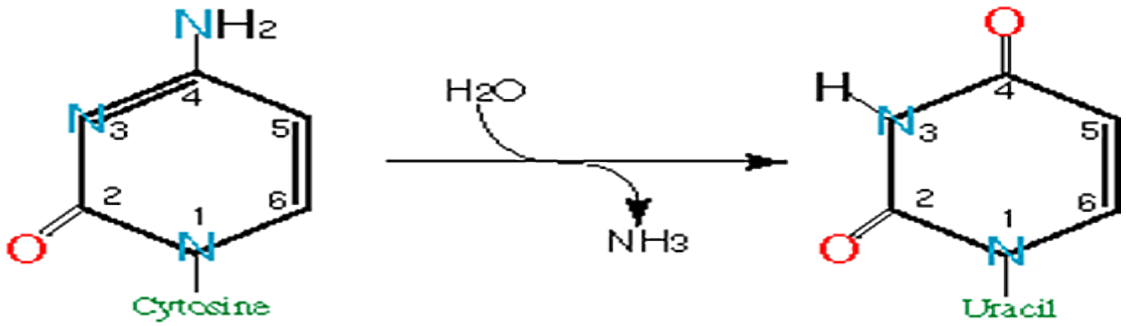


**Figure 1.** Deamination of cytosine to uracil.

Uracil pairs more efficiently with A than with G, resulting in a mismatch. In the next round of DNA replication, this results in a C:G pair being replaced by an A:T pair. Adenine can be spontaneously deaminated to hypoxanthine (Fig. 2), with the latter pair pairing more readily with C than with T.


**Figure 2.** Deamination of adenine to hypoxanthine.

**Damage of Exogenous Origin**
**Loss of nitrogen bases by hydrolysis**
A typical example of hydrolytic loss of nitrogenous bases is DNA depurination, a very common type of DNA damage that occurs spontaneously 5 x 10 - 1 x 10 times per genome per day in human cells [4]. In vitro experiments show that DNA depurination occurs much faster than depyrimidination. At neutral pH and a temperature of 37 °C, the rate of loss of pyrimidine bases from DNA is about 5% of the rate of loss of purine bases [5-6]
Exogenous drugs can cause many different types of DNA damage, depending on the type of drug and the substrate on which it acts. Some of this damage is only specific to exogenous drugs (e.g. dimerization), while others can also be caused by endogenous factors (e.g. base alkylation, strand breaks, etc.).

**Dimerization**
Dimers of any kind are not normally found in DNA. Virtually all types of electromagnetic radiation (EMR) can cause dimerization between bases in DNA, although dimer formation is usually caused by UV electromagnetic radiation. EMR with higher energy than UV, such as ionizing radiation (IR), preferentially causes DNA breaks (both direct and indirect), while EMR with lower energy ( IR ) usually exerts its genotoxic effects on DNA by increasing the amount of free radicals in the cell (oxidative damage).
UV sources have a higher percentage of radiation, which is between UV-B and UV-A. Such solar UV radiation should produce a higher fraction of dewar isomers. Since photoisomerization is most efficient at about 320 nm, which corresponds to the UV absorption maximum of 4-4 PPs. Consequently, it was assumed that all 6-4 PPs should be converted to dewar isomers when exposed to sunlight. The ability of UV radiation to damage a particular base is determined by the flexibility of DNA. The nature of the bases plays a major role, as the distribution of the dimeric photoproduct is highly dependent on the pyrimidine bases involved. Sequences that facilitate binding and unwinding are favorable sites for damage formation [7,8].

**DNA Repair Mechanisms** DNA repair can occur by one of two basic mechanisms involving either reversal of DNA damage or removal of damaged elements [9]. To use a simplified analogy, suppose that damage is represented by a knot (damage reversal), while in other cases it is necessary to cut out a piece of string with knots (damage excision) and replace it with a new segment of yarn [10-11] (Table 1).

**Table 1:** DNA Repair Mechanisms

| S.No. | Damage | Damaging Agent | Example | Repair |
|---|---|---|---|---|
| **1** | BER | Reactive oxygen species, X-Rays, alkylating agents, Spontaneous reactions | Oxidation (8OxoG) Uracil, Single strand Break | Removal of base by N-glycosylase abasic sugar removal, replacement |
| **2** | MMR | Replication error | A-G mismatch, T-C mismatch, Insertion, Deletion | Removal of strand by exonuclease, digestion and replacement |
| **3** | NER | UV lights and polycyclic aromatic hydrocarbons | Bulky adducts, intrastrand cross link | Removal of DNA fragment and replacemen |
| **4** | DSBR | X-Rays, Ionozing radiation antitumor agent | Double strand break, Interstrand crosslink | Unwinding, alignment, ligation |

**Common Pathway of DNA repair mechanisms**

**a.** Detection of lesions: Proteins are bound to the DNA lesion
**b.** Removal of damaged DNA: nucleases, glycosylases, etc. remove the damaged portion
**c.** Repair/resynthesis: DNA ligase, DNA polymerase
**d.** Effects on other cellular processes: Replication and/or cell division to allow more time for repair
**e.** Consequence: accurate repair - survival, inability to repair - cell death, misrepair - genome instability.

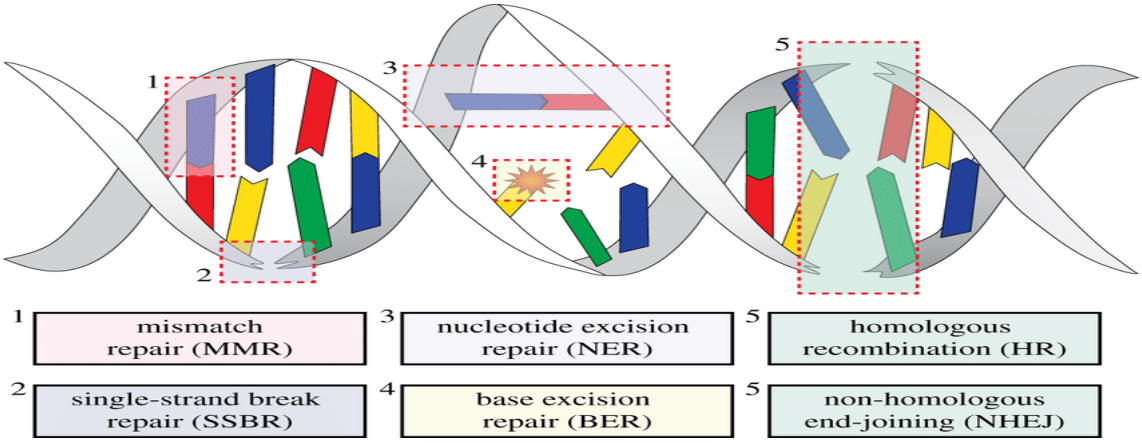


**Figure 3.** Different types of DNA lesions and corresponding DNA repair systems. Distinct DNA lesions have distinct consequences for a cell.

**Base excision repair:** As the name implies, this is the main mechanism responsible for repairing damaged DNA bases. In this repair mechanism, the DNA helix or backbone is not cut out, but only the bases at the target site are removed. Only the damaged bases are removed by cleaving the N-glycoside bond. There are five main enzymes involved in the BER pathway. These are N-glycosylases, AP endonuclease, Flap endonuclease, DNA polymerase and ligase. At least twelve glycosylases have been identified. They act on the respective fundamentally damaged area.

A DNA strand break must have a hydroxyl at its 3' end and a phosphate at its 5' end for ligation to occur. PNKP (polynucleotide kinase phosphate) is responsible for these ends at BER. The protein has a kinase domain that phosphorylates the 5' ends and a phosphate domain that removes the phosphate from the 3' end. Many enzymes that repair the single strand breaks are: Tyrosyl DNA phosphodiesterase (TdP-1) repairs multiple 3-blocking ends, apartaxin (APTX), an end-processing enzyme that specifically repairs the 5-adenylate intermediate DNA ligase activity after this strand break repaired by DNA synthesis and ligation. (Figure 4).

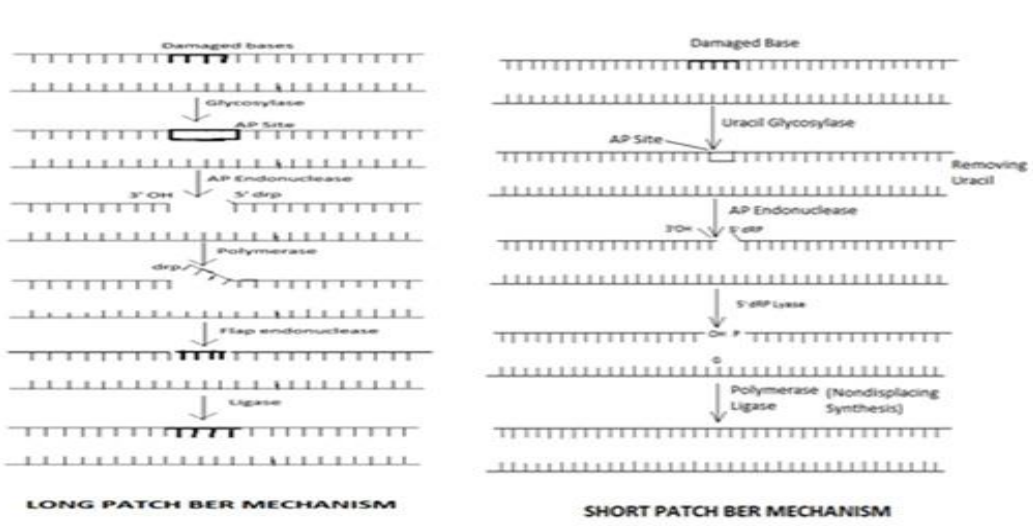


**Figure 4:** Base Excision Repair mechanism pathways.

**Mismatch repair:** Mismatches are the incorrect base pairings that occurred during replication. They play an important role in the repair of incorrectly inserted bases that escaped the replication polymerase during the post-replication proofreading activity. The mechanism is triggered by either insertion or deletion of misinserted bases using MMR proteins. The mechanism proceeds stepwise and involves three main steps: the first is recognition, the second is excision, d L and Mut H are involved in carrying out the three steps. The parental DNA contains the palindromic sequence GATC. Adenine is methylated by the enzyme deoxyadenine methylase (DAM). Thus, the parental strand is methylated. During replication, two new strands are formed[12-16] (Figure 5).

**Double-strand break repair:** The most dangerous type of DNA damage is double-strand breaks (DSBs). For example, a single DSB can lead to cell death. Inaccurate repair can lead to deletions or chromosomal aberrations, which in turn cause cancer and other genetic instability syndromes. Therefore, DSB repair is critical for cell survival and maintenance of genome integrity. DSB repair occurs through two main mechanisms: NHEJ and HR. These two mechanisms differ in that they require a homologous DNA template and the reliability of DNA repair. HR is error-free because it uses information from undamaged sister chromatids as a template. NHEJ is error-prone and eliminates DSBs by direct ligation and broken ends on contrasting HR. HR is restricted to late S and G2 phases, whereas NHEJ works in all phases and cell cycles of mammalian cells.

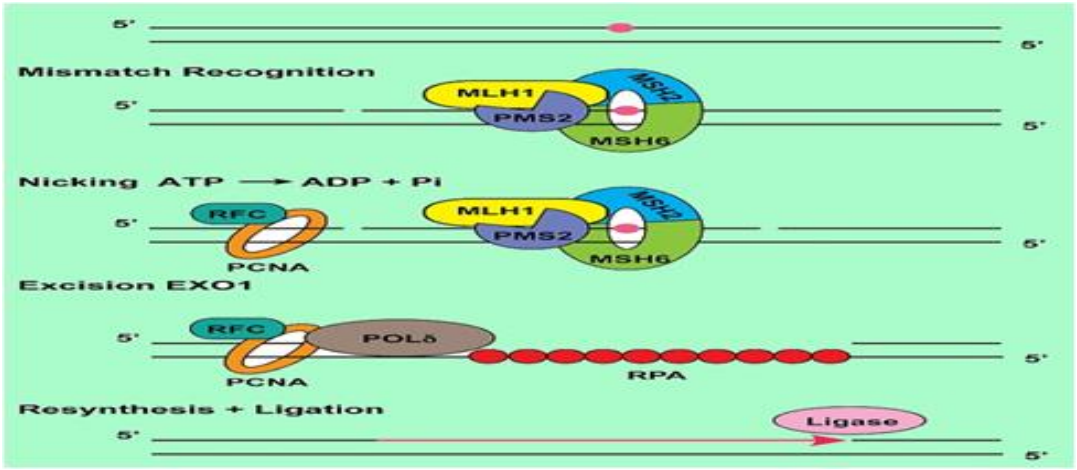


**Figure 5:** Mismatch Repair mechanism of DNA repair.

## CONCLUSION

To date, numerous research papers and reviews have been published on DNA damage and repair mechanisms. DNA damage, reaction, and repair have attracted the attention of researchers, while intensive research has led to new fundamental insights into the mechanisms of deformation evolution. In conclusion, we believe that extensive research into the basic biology of DNA damage, reaction, and repair, combined with the rapid development of new technologies and further advances in targeted cells, will lead to significant advances in the near future. Hopefully, more robust figurative study results will also be obtained.

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