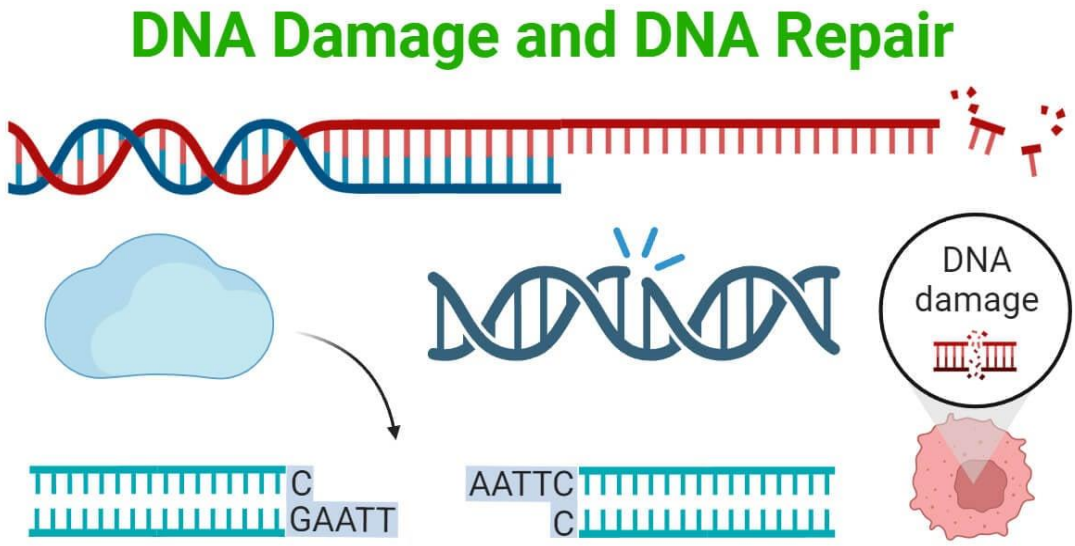
DNA Damage and DNA Repair: Types and Mechanism

DNA is the basic unit of inheritance that maintains the integrity and function of living organisms. However, it is constantly exposed to damaging agents which can cause DNA damage. Additionally, errors can occur during DNA replication and repair processes, leading to harmful mutations.



DNA Damage and DNA Repair

To overcome the harmful effects of DNA damage, cells have various systems such as DNA repair mechanisms, damage tolerance pathways, cell cycle checkpoints, and cell death pathways. These systems work together to repair or tolerate DNA damage, ensuring the overall survival and functionality of cells.

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1. DNA Strand Breaks

DNA strand breaks occur when one or both strands of DNA are interrupted. There are two types: single-strand breaks (SSBs) where one strand is cut, and double-strand breaks (DSBs) where both strands are cut. These breaks can be caused by ionizing radiation like X-rays and gamma rays, as well as certain chemicals.

2. Oxidative Damage

Oxidative damage can occur due to the action of reactive oxygen species (ROS) which leads to the formation of lesions. The highly reactive ROS, such as hydroxyl radicals (•OH), can cause oxidative damage to DNA bases.

3. Alkylation of Bases

Alkylating agents, both endogenous and exogenous, can modify DNA bases by introducing alkyl groups. These modifications can be cytotoxic, mutagenic, or have neutral effects on the cell.

4. Base Loss

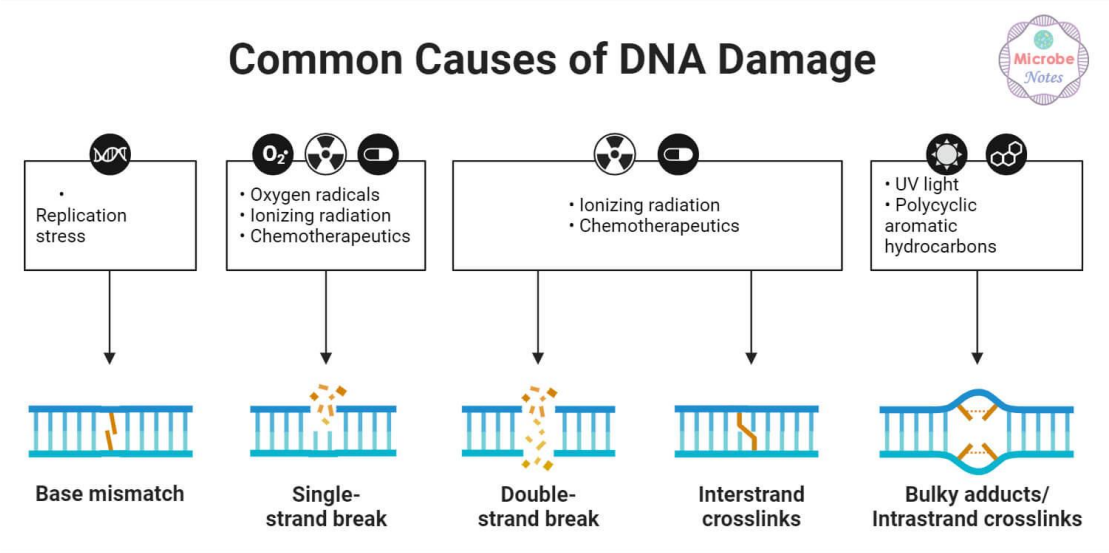
Base loss occurs when the nitrogenous bases in DNA are removed, leaving behind apurinic/apyrimidinic (AP) sites or abasic sites. AP sites are chemically unstable and can lead to DNA strand breaks or mutagenic events if left unrepaired.

5. Bulky Adduct Formation

Bulky adducts are formed when certain chemicals, such as polycyclic aromatic hydrocarbons (PAHs), covalently bind to DNA bases. These adducts create bulky modifications that stick out from the DNA and disrupt its structure. They can interfere with DNA replication, transcription, and repair processes, potentially leading to mutations.

6. DNA Crosslinking

DNA crosslinking occurs when two nucleotides in DNA become covalently linked together. Crosslinks can form within the same DNA strand (intrastrand crosslinks) or between opposite DNA strands (interstrand crosslinks). DNA crosslinks prevent the separation of DNA strands during replication or transcription, leading to the disruption of important cellular processes.



ources/Agents of DNA Damage

DNA damage can also be classified into two types based on its origin or sources: endogenous and exogenous. The major sources of endogenous and exogenous DNA damage are briefly explained below:

1. Endogenous DNA Damage

Endogenous DNA damage originates from internal reactions involving chemically active DNA within cells.

- **Replication errors** are one source of endogenous DNA damage that occurs during DNA replication when incorrect nucleotides are inserted opposite the template bases. During replication, some DNA polymerases with lower fidelity can be involved, leading to potential errors.
- **Topoisomerase enzymes** are another source of endogenous DNA damage. Topoisomerases remove the supercoiling of DNA during replication and transcription. However, misalignment of the DNA ends can stabilize the topoisomerase-DNA cleavage complex and result in the formation of DNA lesions.
- **Reactive oxygen species (ROS)** are produced during cellular processes and can cause oxidative damage to DNA. While ROS plays an important role in normal cellular functions, excessive levels can lead to various DNA lesions and modifications. Excessive ROS has been associated with the development of several human diseases like cancer, Alzheimer's disease, and diabetes.

- **Alkylating agents** are reactive compounds that can add methyl or ethyl groups to DNA bases, leading to chemical modifications. Spontaneous methylation events can generate different methylated bases. Some methylated bases are mutagenic and can lead to specific types of mutations.

2. Exogenous DNA Damage

Exogenous DNA damage is caused by external factors, such as environmental agents, physical forces, or chemicals.

- **Ionizing radiation (IR)** directly damages DNA or indirectly affects it through the generation of highly reactive hydroxyl radicals (•OH) from water molecules. IR can cause different types of damage to the DNA such as base lesions, and single-strand and double-strand breaks.
  - **Ultraviolet (UV) radiation** is another agent of DNA damage. It is the leading cause of skin cancers. UV light can form pyrimidine dimers where two pyrimidines on the same DNA strand are joined together. This alteration in DNA structure can block transcription and replication processes.
  - **Exogenous alkylating agents**, found in sources like tobacco smoke and industrial activities, react with DNA and can cause mutagenic and carcinogenic changes. They primarily target the nitrogenous bases in DNA. Examples of alkylating agents include sulfur and nitrogen mustards.
  - **Aromatic amines**, found in cigarette smoke, fuel, coal, dyes, and pesticides, are also exogenous sources of DNA damage. These agents can create long-lasting lesions in the DNA structure that lead to the substitution of DNA bases and frameshift mutations.
  - **Polycyclic aromatic hydrocarbons (PAHs)** are known carcinogens found in sources like tobacco smoke, automobile exhaust, and other environmental pollutants. PAHs require activation by the liver's P-450 system to produce reactive substances that can potentially damage DNA.