DNA REPAIR MECHANISMS

Dr Moni Kumari

PG Botany Department

GAYA COLLEGE, GAYA

M.Sc semester II and B.Sc part 2nd

Date : 10 July 2020

PART 1

Living organisms have the crucial task to preserve their genome and faithfully transmit it across generations. Transmission of genetic information is constantly in a selective balance between the maintenance of genetic stability versus elimination of mutational change and loss of evolutionary potential. To maintain the integrity of cell DNA repair system plays an important role.

DNA lesions can alter the primary structure of the double helix thereby affecting transcription and replication. Erroneous repair of lesions can lead to mutations in the genome that can be inherited to daughter cells with deleterious consequences for individual's health. As a consequence, eukaryotic cells have evolved a complex signaling network of repair processes known as the DNA damage response (DDR).

Major DNA damage causes due to the various reasons

- Endogenous damage can result from DNA base lesions like hydrolysis (deamination, depurination, and depyrimidination) and alkylation (6-*O*-Methylguanine) or oxidation (8-oxoG) by intracellular free radical oxygen species (ROS) that can occur as by-products of mitochondrial respiration
- Mutations can also arise during normal cellular metabolism for instance by erroneous incorporation of deoxyribonucleotides (dNTPs) during replication.
- Environmental sources of damage can be physical [e.g., ultraviolet (UV) light, ionizing radiations (IRs), and thermal disruption] or chemical (e.g., chemotherapeutic drugs, industrial chemicals, and cigarette smoke) and their effects varies from the formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine 6-4 pyrimidone photoproducts (6-4PPs) following UV exposure, to the introduction of single and double DNA strand breaks upon IR treatment, or to inter- and intrastrand DNA crosslinks, which result from various chemotherapeutic drugs

It has been proposed that DNA damage from endogenous sources gives rise to 20 000 lesions per mammalian cell per day

DNA repair is a collection of processes by which a cell identifies and corrects **damage** to the **DNA** molecules that encode its genome.

DNA repair ensures the survival of a species by enabling parental **DNA** to be inherited as faithfully as possible by offspring. It also preserves the health of an individual.

DNA repair is a very complicated process, involving many factors. For instance to date, 168 genes that encode proteins involved in DNA repair have been identified in the human genome. They are involved in diverse processes, starting from detection of a damage site in the DNA, through several steps of enzymatic transformation of the damaged DNA, to recombination and signaling to stop the cell cycle or initiate apoptosis.

Five major DNA repair pathways

(1) Base excision **repair** (BER)
(2) Nucleotide excision **repair** (NER)
(3) Mismatch **repair** (MMR)
(4) Homologous recombination (HR)
(5) Non-homologous end joining (NHEJ)

These DNA repair pathways are active throughout different stages of the cell cycle, allowing the cells to **repair** the **DNA damage**.

Double-strand break **repair** (including homologous recombination and nonhomologous end joining), and crosslink **repair** (Sancar et al., 2004).

These pathways each require a number of proteins. By contrast, O-alkylated bases, such as O^6-methylguanine can be repaired by the action of a single protein, O^6-methylguanine-DNA methyltransferase (MGMT). MGMT removes the alkyl group in a suicide reaction by transfer to one of its cysteine residues.

Photolyases are able to split covalent bonds of pyrimidine dimers produced by UV radiation.

DNA damage and mutation have different biological consequences. While most **DNA** damages can undergo **DNA repair**, such **repair** is not 100% efficient. Un-repaired **DNA** damages accumulate in non-replicating cells, such as cells in the brains or muscles of adult mammals, and can cause aging.

If not repaired, such damage can result in mutations, diseases and cell death

There are various forms of DNA damage, such as base modifications, strand breaks, crosslinks and mismatches.

Healthy diet with fruits and vegetables can decrease **DNA** oxidization and inflammation in the body, especially carotenoids and vitamin C intake.

During DNA synthesis, most DNA polymerases "check their work," fixing the majority of mispaired bases in a process called **proofreading**.

Immediately after DNA synthesis, any remaining mispaired bases can be detected and replaced in a process called **mismatch repair**.

Repair mechanism	Lesion feature	Genotoxic source (examples)
Base excision repair (BER)	Oxidative lesions	Reactive oxygen species (ROS)
Nucleotide excision repair (NER)	Helix-distorting lesions	UV radiation
Translesion synthesis	Various lesions	Various sources
Mismatch repair (MMR)	Replication errors	Replication
Single stand break repair (SSBR)	Single strand breaks	Ionizing radiation, ROS
Homologous recombination (HR)	Double-strand breaks	Ionizing radiation, ROS
Non-homologous end joining (NHEJ)	Double-strand breaks	Ionizing radiation, ROS
DNA interstrand crosslink repair pathway	Interstrand crosslinks	Chemotherapy

Figure: Distinct DNA repair systems are specialized to repair the various types of DNA lesions.

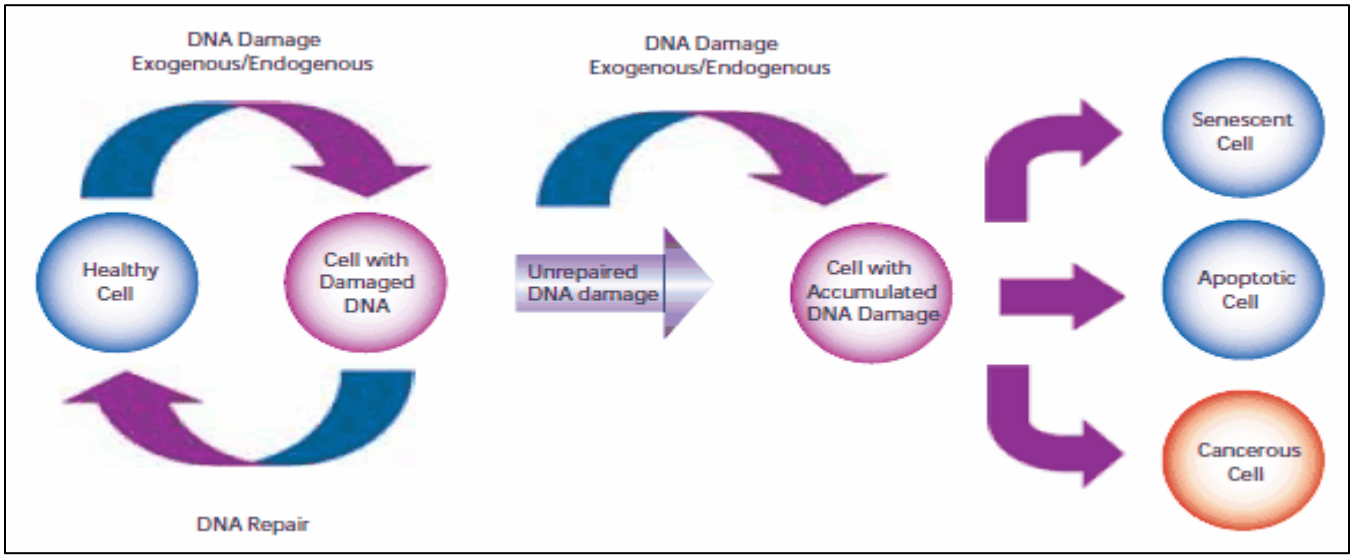


Figure: Fate of cell containing DNA damage

DIRECT REPAIR

Direct reversal of DNA damage is a mechanism of repair that does not require a template and is applied to two main types of damage.

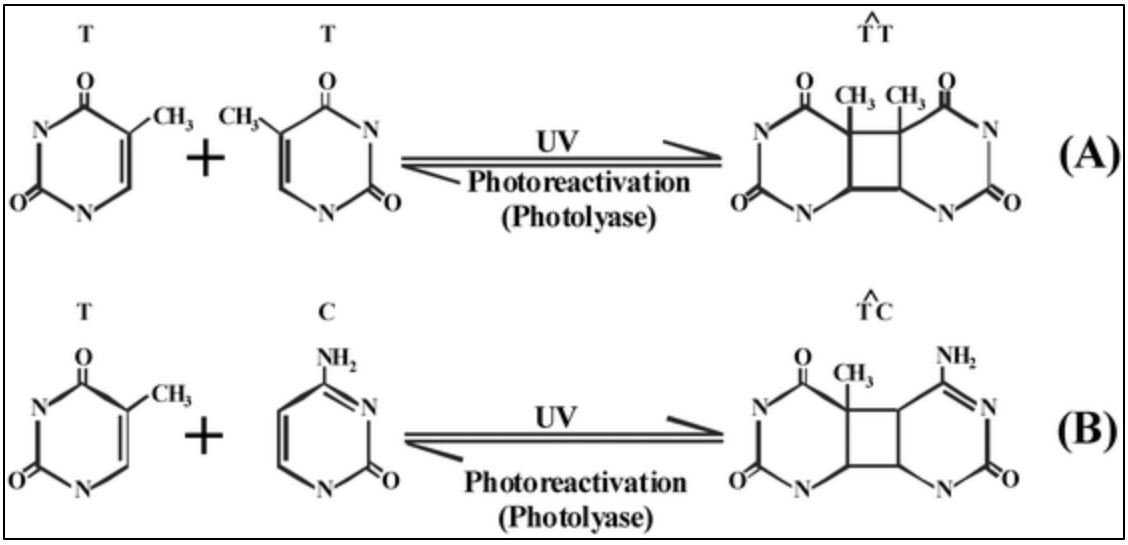
Direct reversal repair (DDR): directly restores the native nucleotide residue by removing the non-native chemical modification

Since the types of damage they counteract can occur in only one of the four bases. Such direct reversal mechanisms are specific to the type of damage incurred and do not involve breakage of the phosphodiester backbone.

(1) UV light induces the formation of pyrimidine dimers which can distort the DNA chain structure, blocking transcription beyond the area of damage.

Direct reversal through photoreactivation can inverse this dimerization reaction by utilizing light energy for the destruction of the abnormal covalent bond between adjacent pyrimidine bases. This type of photoreactivation does not occur in humans.

Photolyases are able to split covalent bonds of pyrimidine dimers produced by UV radiation. They bind to a UV lesion in a light-independent process, but require light (350-450 nm) as an energy source for repair.



(2) The damage caused by alkylating agents reacting with DNA can also be repaired through direct reversal. Methylation of guanine bases produces a change in the structure of DNA by forming a product that is complimentary to thymine rather than cytosine. The protein methyl guanine methyl transferase (MGMT) can restore the original guanine by transferring the methylation product to its active site.

Humans and many other organisms have an enzyme that can remove the methyl group, reversing the reaction and returning the base to normal