CSIR NET Life Science Unit 3

DNA Repair

DNA

DNA stands for deoxyribonucleic acid which is the hereditary material present in almost all organisms including humans. Generally, all the cells in a human body have the same DNA. Most of the DNAs are present in the cell nucleus (referred to as nuclear DNA). There are also some DNAs that are present in the mitochondria (a structure within our cells that is responsible for converting food into energy that can be used by our bodies) which are called mitochondrial DNA (or mtDNA).

DNA damage can happen in human cells due to several reasons and it can be as frequent as 10,000 times per living cell. These DNA lesions can occur because of exposure to different kinds of radiation and result in either a single strand or double-strand breakage. The other consequences of DNA damage include base loss, pyrimidine dimer, or cross-linkage. DNA damage and repair happen in most cells on their own as the cells have their own repair systems which can enforce genome stability and in some higher eukaryotes, it can even prevent cancer. DNA damage is mended through various DNA repair pathways which prevents apoptosis (cell death).

On this page, we will learn about what is DNA repair, types of DNA damage, types of DNA repair, and other facts surrounding it.

Sources of DNA Damage

DNAs are constantly being attacked by genotoxic agents which can cause different types of DNA damage. DNA lesions have the capacity to block genomic replication and transcription which can cause mutations and double-strand breaks (DSBs). Sources of DNA damage is broadly classified into the below two categories:

- **Endogenous Sources of DNA Damage** - Mutations acquired over a certain time span can cause genomic instability and endogenous sources contribute a lot to these mutations. Endogenous sources of DNA damage are some agents or reactive oxygen species which are produced by the usual metabolic activities. The two most common sources are DNA replication errors and intracellular oxidative stress.
- **Exogenous Sources of DNA Damage** - One can find exogenous sources of DNA damage all around us. The UV (ultraviolet) radiations from the sun, ionizing radiation from space, radioisotopes on earth which occur

naturally, certain industrial chemicals like hydrogen peroxide and vinyl chloride, are all exogenous sources of DNA damage.

Types of DNA Damage

Based on the source of DNA damage, there are many different types of DNA damages that can occur.

Damages Due to Endogenous Sources

There are mainly five types of DNA damage that are caused by endogenous sources:

- Base oxidation (for instance 8-oxo-7 or 8-dihydroguanine, 8-oxo-7), as well as, there could be DNA strand interruptions caused by reactive oxygen species.
- Alkylation of bases can happen (mostly methylation) for example formation of 1-methyladenine, 7-methylguanine, 6-O-Methylguanine, etc.
- Bulky adduct formation - This occurs due to the covalent bonding of large-sized chemical carcinogens and its main source is heavy cigarette smoking. Few examples of this type are aristolactam I-dA adduct, benzoapyrene diol epoxide-dG adduct, etc.
- Hydrolysis of bases - Examples of this are depyrimidination, deamination, and depurination.
- Mismatch of bases - This happens because of DNA replication errors where a wrong DNA base gets stitched into a place in a newly forming DNA strand. It could also occur when a DNA base is either skipped or inserted by mistake.

Damages Due to Exogenous Sources

Some examples of DNA damages due to exogenous sources are:

- Crosslinking of adjacent thymine and cytokines bases due to UV-B light rays. This results in pyrimidine dimers and is called direct DNA damage.
- Free radicals get created by UV-A light. This type of damage is called indirect DNA damage.
- Cosmic rays or radioactive decay can cause ionization radiation which can break DNA strands.

- An increase in the rate of depurination (this is loss of purine bases from the backbone of DNA) can occur due to thermal disruption at high temperatures. It also causes single-strand breaks.

What is DNA Repair and its Significance?

The cells within an organism need to have the ability to maintain and conserve their DNA sequence for the survival of the cell and the normal functioning of the organism. DNA repair is how a cell gives a corrective response to DNA damage and alternations. Organisms depend on the genetic information in DNA to survive and reproduce which makes it crucial to maintain the integrity of DNA molecules. In the event that DNA damage cannot be repaired, the following major issues might happen:

- It affects the function and survival of somatic cells.
- Fertility in reproductive cells can get adversely affected.
- Can cause gene mutation which could later develop into tumour cells.

DNA damage repair in most cases can restore the structure of DNA but at times it might not be able to eliminate the DNA damage yet allowing the cells to tolerate the damage and survive. The only biological macromolecule that can be repaired in the cell is DNA. Through DNA repair, the genetic stability of species is guaranteed which is very crucial for reducing incidents of defect repair.

Types of DNA Repair

The DNA repair process is pretty complicated with many steps involved in it which have different lengths and time scales. The MRN complex is the first repair protein that arrives at the DNA nick. MRN is made up of 3 different proteins: RAD50, MRE11, and NBS11. These proteins initiate the process of non-homologous double-strand break repair.

Types of DNA repair pathway is classified into the following types:

Photoreactivation

Another term for this is direct repair and it only repairs the pyrimidine dimers which are present on the DNA's double helix structure. These are caused by UV radiation.

MMR

The DNA mismatch repair involves repairing to correct the mismatch in DNA molecules due to insertions and deletions during the replication process.

Excision Repair

This is present in all types of biological cells and the primary DNA repair mechanism in human cells. The main targets of excision repair are nucleotides and bases.

- BER or base excision repair refers to the removal of damaged bases. This repair is done by glycosylase by hydrolysing the glycosidic bonds.
- NER or nucleotide excision repair targets the distortions in the DNA double helix (such as thymine dimer) or the distortions that happen due to the addition of large chemicals to the bases.

Homologous Recombination Repair

This is also termed as DSBs or double-strand breakage repair. Here the template of an undamaged DNA single strand is used to finish the resynthesis of damaged DNA.

SOS Repair

This DNA repair occurs when the cells are in a critical state due to severe DNA damage. This type of repair can only improve the survival rate of cells and maintain the gene's integrity. This DNA repair is also called error-prone repair since many mistakes are still left after SOS repair. It is easier for the cells to mutate after an SOS repair.