DNA damage and repair

Part 1

Introduction

DNA is the repository of genetic information in each living cell, its integrity and stability are essential to life. DNA, however, is not inert; rather, it is a chemical entity subject to assault from the environment, and any resulting damage, if not repaired, will lead to mutation and possibly disease.

DNA damage exists in all cellular organisms . While DNA damage is distinguished from mutation, mutation can result from unrepaired DNA. While most DNA damage can be repaired, such repair systems are not 100% efficient. Un-repaired DNA damage accumulates in non-replicating cells, such as neurons or myocytes of adult mammals, and can cause aging. DNA damage can be subdivided into two types:

1) endogenous damage caused by reactive oxygen species (ROS) that are derived from metabolic by product. Also includes replication error.

2) exogenous damage caused by radiation (UV, X-ray, gamma), hydrolysis, plant toxins, and viruses.

Agents that Damage DNA

1- **Highly reactive oxygen radicals produced** during normal cellular respiration as well as by other biochemical pathways

2- **Ionizing radiation** such as gamma rays and x-rays

3-**Ultraviolet rays**, especially the UV-C rays (~260 nm) that are absorbed strongly by DNA but also the longer-wavelength UV-B that penetrates the ozone shield.

4- **Aromatic hydrocarbons**, including some found in cigarette smoke

5-**Plant and microbial products**, e.g. the Aflatoxin

6- **Chemicals used in chemotherapy**, especially chemotherapy of cancers.

Types of DNA damage

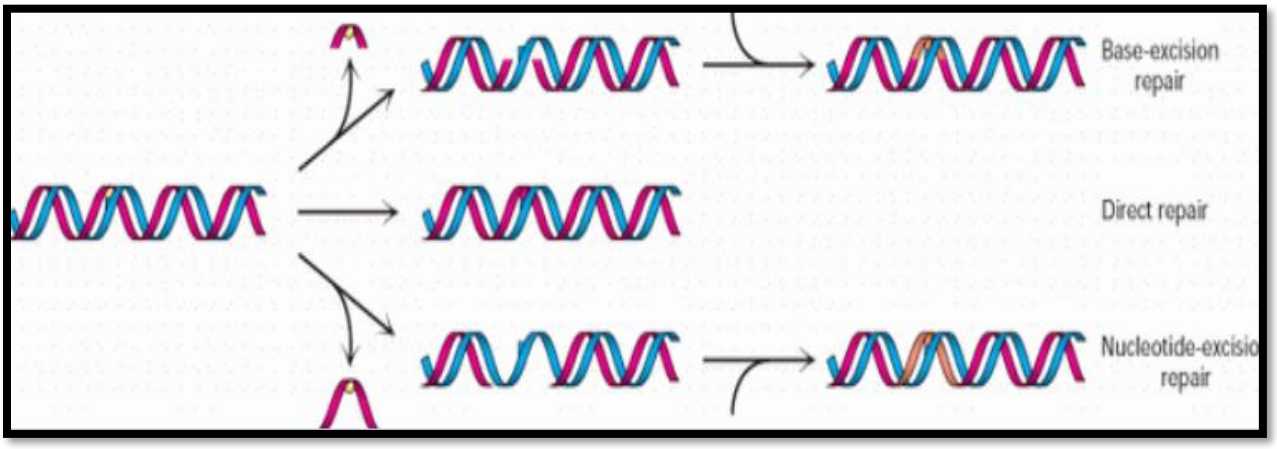
Type of Damage	Examples
Single-base alteration	Depurination
	Insertion or deletion of nucleotide
	Alkylation of base
Two-base alterations	UV light–induced thymine-thymine (pyrimidine) dimer
Chain breaks	Ionizing radiation
	Oxidative free radical formation
Cross-linkage	Between bases in same or opposite strands
	Between DNA and protein molecules (eg, histones)

DNA Repair

DNA repair can be grouped into two major functional categories:

A) Direct Damage reversal

B) Excision of DNA damage



A) Direct Damage Reversal

Most cases of DNA damage are not reversible. For cases that are reversible, our body uses direct reversal repair mechanism to correct the damaged base.

Direct reversal repair is a mechanism of repair where the damaged area or lesion is repaired directly by specialised proteins in our body. It is the simplest form of DNA repair and also, the most energy efficient method. It does not require a reference template unlike the other single-strand repair mechanism. Moreover, it does not involve the process of breaking the phosphodiester backbone of the DNA.

The direct reversal of the damage, which may be a more efficient way of dealing with specific types of DNA damage that occur frequently. Only a few types of DNA damage are repaired in this way, particularly pyrimidine dimers resulting from exposure to ultraviolet (UV) light and alkylated guanine residues that have been modified by the addition of methyl or ethyl groups at the O6 position of the purine ring.

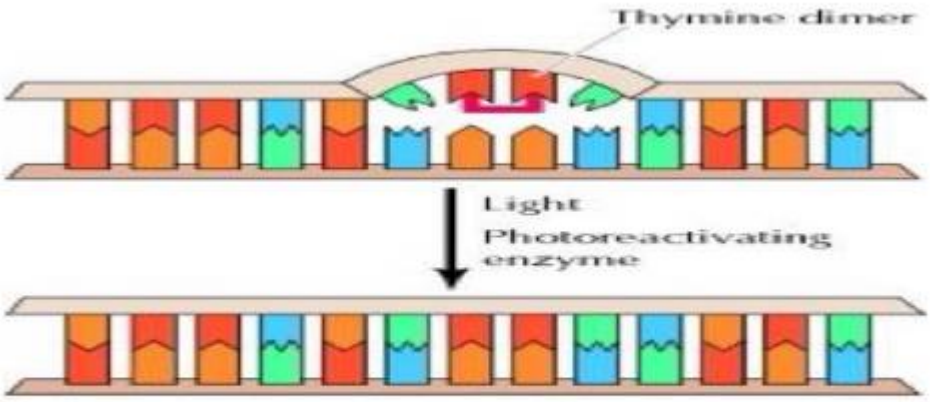


Figure 1: Direct repair of thymine dimers

An example of reversible DNA damage repairable via Direct Repair is Alkylation which can be repaired via direct removal of the Alkyl groups. Alkylating agents are carcinogens that is capable of alkylating DNA in our body. It is widely used to create medicines (e.g., treatment of leukaemia, tumors) and industrial chemicals. Alkylated DNA bases resulted in improper base pairing and ultimately, lead to cell death.

An example of Alkylation is Methylation which is the addition of a methyl group (CH3) to a guanine (G) nucleotide. This resulted in a complementary pairing to thymine (T) instead of cytosine (C).

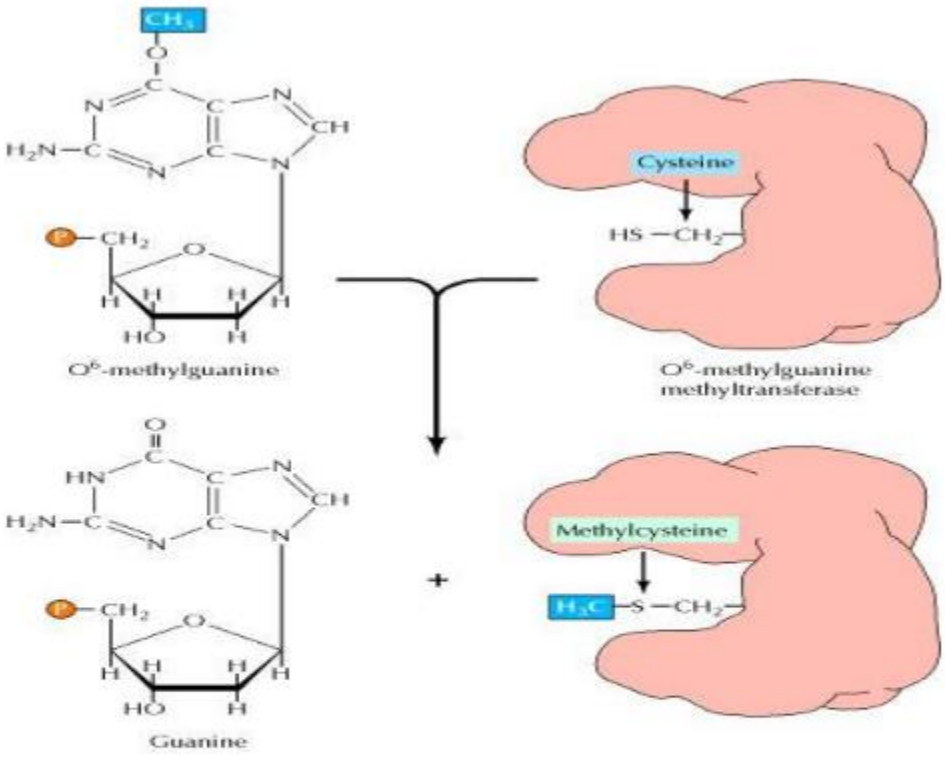


Figure 2: Repair of O6-methylguanine

O6-methylguanine methyltransferase transfers the methyl group from O6-methylguanine to a cysteine residue in the enzyme's active site