Mutation and Mutagen:

Mutations are an important player in many issues in biology. They work for populations by increasing genetic diversity and increasing species odds for survival in varying environments. They also work against us in bacterial resistance to antibiotics , sickle cell anemia, and cancer.

Genetic mutations occur when bases of a DNA or RNA sequence are changed. This often occurs during DNA replication in preparation for cell division or when mistakes are made during transcription and translation in protein synthesis. Point mutations occur when changes in DNA bases do not affect the triplet reading frame of tRNA. Substitution or inversions are point mutations. Though they may change one or two amino acids, the majority of the DNA sequence is unaltered. Silent mutations are point mutations that do not alter the amino acid outcome. Often, more than one codon will code for a certain amino acid, so silent mutations are harmless. Frameshift mutations like deletions and insertions change the entire codon reading frame by shifting each base over one position. Frameshift mutations can be disastrous.

In genetics, a **mutagen** is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level. As many mutations can cause cancer, mutagens are therefore also likely to be carcinogens. Not all mutations are caused by mutagens: so-called "spontaneous mutations" occur due to spontaneous hydrolysis, errors in DNA replication, repair and recombination

Effects of mutagens

Mutagens cause changes to the DNA that can affect the transcription and replication of the DNA, which in severe cases can lead to cell death. The mutagen produces mutations in the DNA, and deleterious mutation can result in aberrant, impaired or loss of function for a particular gene, and accumulation of mutations may lead to cancer.

Different mutagens act on the DNA differently. Powerful mutagens may result in chromosomal instability, causing chromosomal breakages and rearrangement of the chromosomes such as translocation, deletion, and inversion. Such mutagens are called clastogens.

Mutagens may also modify the DNA sequence; the changes in nucleic acid sequences by mutations include substitution of nucleotide base-pairs and insertions and deletions of one or more nucleotides in DNA sequences. Although some of these mutations are lethal or cause serious disease, many have minor effects as they do not result in residue changes that have significant effect on the structure and function of the proteins. Many mutations are silent mutations, causing no visible effects at all, either because they occur in non-coding or non-functional sequences, or they do not change the amino-acid sequence due to the redundancy of codons.

Types of mutagens

Mutagens may be of physical, chemical or biological origin. They may act directly on the DNA, causing direct damage to the DNA, and most often result in replication error. Some however may act on the replication mechanism and chromosomal partition. Many mutagens are not mutagenic by themselves, but can form mutagenic metabolites through cellular processes, for example through the activity of the

cytochrome P450 system and other oxygenases such as cyclooxygenase. Such mutagens are called promutagens (example: aflatoxin B1)

Physical mutagens:

- Ionizing radiations such as X-rays, gamma rays and alpha particles may cause DNA breakage and other damages. The most common sources include cobalt-60 and cesium-137.
- Ultraviolet radiations with wavelength above 260 nm are absorbed strongly by bases, producing pyrimidine dimers, which can cause error in replication if left uncorrected.
- Radioactive decay, such as ^{14}C in DNA which decays into nitrogen.

Chemical mutagens:

A large number of chemicals may interact directly with DNA. However, many such as Polycyclic aromatic hydrocarbons (PAHs), aromatic amines, benzene are not necessarily mutagenic by themselves, but through metabolic processes in cells they produce mutagenic compounds.

- Reactive oxygen species (ROS) – These may be superoxide, hydroxyl radicals and hydrogen peroxide, and large number of these highly reactive species are generated by normal cellular processes, for example as a by-products of mitochondrial electron transport, or lipid peroxidation. A number of mutagens may also generate these ROS. These Reactive oxygen species ROS may result in the production of many base adducts, as well as DNA strand breaks and crosslinks.
- Reactive oxygen species (ROS) are **potent oxidants that attack chromosomal DNA and free nucleotides, leading to oxidative DNA damage that causes genetic alterations**.

- Deaminating agents, for example nitrous acid which can cause transition mutations by converting cytosine to uracil.
- Polycyclic aromatic hydrocarbon (PAH), when activated to diol-epoxides can bind to DNA and form adducts.
- Alkylating agents such as ethylnitrosourea. The compounds transfer methyl or ethyl group to bases or the backbone phosphate groups. Guanine when alkylated may be mispaired with thymine. Some may cause DNA crosslinking and breakages. Nitrosamines are an important group of mutagens found in tobacco, and may also be formed in smoked meats and fish via the interaction of amines in food with nitrites added as preservatives. Other alkylating agents include mustard gas and vinyl chloride.
- Aromatic amines and amides have been associated with carcinogenesis since 1895 when German physician Ludwig Rehn observed high incidence of bladder cancer among workers in German synthetic aromatic amine dye industry. 2-Acetylaminofluorene, originally used as a pesticide but may also be found in cooked meat, may cause cancer of the bladder, liver, ear, intestine, thyroid and breast.
- Alkaloid from plants, such as those from Vinca species[], may be converted by metabolic processes into the active mutagen or carcinogen.
- Bromine and some compounds that contain bromine in their chemical structure.
- Sodium azide, an azide salt that is a common reagent in organic synthesis and a component in many car airbag systems
- Psoralen combined with ultraviolet radiation causes DNA cross-linking and hence chromosome breakage.
- Benzene, an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes.

Base analogs

- Base analog, which can substitute for DNA bases during replication and cause transition mutations.

Intercalating agents

- Intercalating agents, such as ethidium bromide and proflavine, are molecules that may insert between bases in DNA, causing frameshift mutation during replication. Some such as daunorubicin may block transcription and replication, making them highly toxic to proliferating cells.

Metals

Many metals, such as arsenic, cadmium, chromium, nickel and their compounds may be mutagenic, but they may act, however, via a number of different mechanisms. Arsenic, chromium, iron, and nickel may be associated with the production of ROS, and some of these may also alter the fidelity of DNA replication. Nickel may also be linked to DNA hypermethylation and histone deacetylation, while some metals such as cobalt, arsenic, nickel and cadmium may also affect DNA repair processes such as DNA mismatch repair, and base and nucleotide excision repair.

Biological agents

- Transposon, a section of DNA that undergoes autonomous fragment relocation/multiplication. Its insertion into chromosomal DNA disrupt functional elements of the genes.
- Virus – Virus DNA may be inserted into the genome and disrupts genetic function. Infectious agents have been suggested to cause cancer as early as

1908 by Vilhelm Ellermann and Oluf Bang, and 1911 by Peyton Rous who discovered the Rous sarcoma virus.

- Bacteria – some bacteria such as *Helicobacter pylori* cause inflammation during which oxidative species are produced, causing DNA damage and reducing efficiency of DNA repair systems, thereby increasing mutation.

Protection against mutagens

Fruits and vegetables are rich in antioxidants.

Antioxidants are an important group of anticarcinogenic compounds that may help remove ROS or potentially harmful chemicals. These may be found naturally in fruits and vegetables. Examples of antioxidants are vitamin A and its carotenoid precursors, vitamin C, vitamin E, polyphenols, and various other compounds. β-Carotene is the red-orange colored compounds found in vegetables like carrots and tomatoes. Vitamin C may prevent some cancers by inhibiting the formation of mutagenic N-nitroso compounds (nitrosamine). Flavonoids, such as **epigallocatechin-3-gallate** EGCG in green tea, have also been shown to be effective antioxidants and may have anti-cancer properties. Epidemiological studies indicate that a diet rich in fruits and vegetables is associated with lower incidence of some cancers and longer life expectancy, however, the effectiveness of antioxidant supplements in cancer prevention in general is still the subject of some debate