RAMA UNIVERSITY

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FACULTY OF ENGINEERING &TECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY

Effect of mutation

Sickle cell anemia

❖A variant of adult hemoglobin, known as hemoglobin S can occur due to a missense mutation, which causes the amino acid valine to take the place of glutamic acid.

❖If one inherits the aberrant gene from both parents, it leads to a condition known as sickle cell disease.

❖The disease gets its name from the fact that red blood cells, which are usually disc-shaped, contract and resemble a sickle.

❖Those with the condition suffer from anemia, regular infections and pain. Estimates suggest that the condition occurs in 1 in 500 African Americans and about 1 in 1,000 to 1,400 Hispanic Americans.

Xeroderma pigmentosum

Xeroderma pigmentosum (XP) is a genetic disorder in which there is a decreased ability to repair DNA damage such as that caused by ultraviolet (UV) light. Symptoms may include a severe sunburn after only a few minutes in the sun, freckling in sun exposed areas, dry skin and changes in skin pigmentation.

Factors causing mutation

❖There are various factors responsible for causing mutations.
❖These factors are called as mutagen.
❖Mutagen increases the frequency of mutations above the natural background level.
There are basically three types of mutagen:

❖Physical mutagen

❖Chemical mutagen

❖Biological mutagen

Physical mutagen

Physical mutagen is a mutation agent which is in the form of physical substances, such as short wave (ultraviolet and radiation ray such as alpha, beta, and gamma).

Some physical mutagens can cause ionization while some others cannot.

X-rays, gamma rays, cosmic rays are ionizing radiation which ionizes water of the cell to release hydroxyl free radical (OH).

The hydroxyl radical is a powerful oxidizing agent. Hydroxyl radical oxidises the phosphodiester bond of DNA.

Higher dose of X-rays can even causes death of an organism.

Ionizing radiation, by definition, "ionizes," that is, it pushes an electron out of its orbit around an atomic nucleus, causing the formation of electrical charges on atoms or molecules.

If this electron comes from the DNA itself or from a neighboring molecule and directly strikes and disrupts the DNA molecule, the effect is called *direct action*.

Direct action occurs when alpha particles, beta particles or x-rays create ions which physically break one or both of the sugar phosphate backbones or break the base pairs of the DNA.

This initial ionization takes place very quickly, in about 0.000000000000001 of a second. However, today it is estimated that about two-thirds of the damage caused by x rays is due to *indirect action*.

This occurs when the liberated electron does not directly strike the DNA, but instead strikes an ordinary water molecule.

This ionizes the water molecule, eventually producing what is known as a *free radical*. A free radical reacts very strongly with other molecules as it seeks to restore a stable configuration of electrons.

A free radical may drift about up to 10,000,000,000 times longer than the time needed for the initial ionization (this is still a very short time, about 0.00001 of a second), increasing the chance of it disrupting the crucial DNA molecule.

This also increases the possibility that other substances could be introduced that would neutralize free radicals before they do damage.

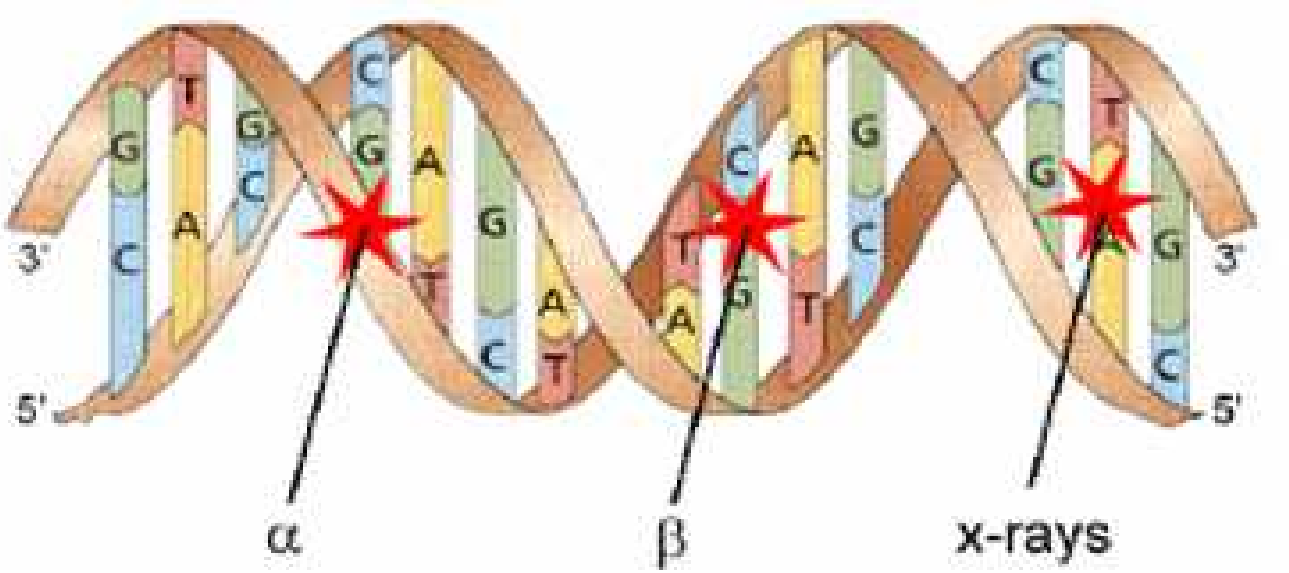

Figure: Direct action of ionizing radiation on DNA

❖UV light is a non-ionizing radiation.

❖ It causes the formation of thymine dimer (Pyrimedine dimer).

❖ If two thymine occur together in one strand of DNA, UV light causes fusion to form thymine dimer.

❖Nitrogenous bases absorbs UV lights and the absorption is maximum at 260 nm. At the site of thymine dimer confirmation of DNA is changed, so rate of error during DNA replication is high.

UV damage occurs via two distinct types of mutations:

➢Dimerizing mutations

➢Oxidative mutations

Dimerizing Mutations

The most common photochemical product in DNA is a cyclobutane pyrimidine dimer. This type of mutation occurs when DNA directly absorbs the incident UV rays. The product forms when two adjacent pyrimidines (thymines, TT, or cytosines, CC) become linked covalently by their C=C double bonds. These four carbons form a cyclic ring (cyclobutane) that links the two pyrimidines, thus creating a chemical intermediate that is not normally found in DNA. This photochemical product causes a structural kink in the DNA that prevents the pyrimidines from base pairing, and prevents 'DNA replication. These dimerizing reactions are typified by a high level of CC----TT and C----T transversion mutation.

Oxidative Mutations

UV exposure doesn't always lead directly to mutations in the DNA. In fact, UV-radiation commonly causes the creation of a free radical that then interacts with and oxidizes DNA bases. These oxidized bases don't pair correctly during replication, causing mutations.

One example of this is a G to T transversion mediated by reactive oxygen species. The oxidation of guanine into 8-oxoguanine prevents the hydrogen bonding required to base pair with cytosine. Instead, during replication, 8-oxoguanine can base pair with adenine via two hydrogen bonds. When the second strand is synthesized, the base position originally occupied by a guanine is then replaced with a thymine, leading to a G to T transversion.