Radi-N2 & You

Radiation Effects on Cells and DNA

Ionizing radiation is all around us, and it has been this way since the creation of the Earth. As such, life on Earth has evolved in an environment exposed to ionizing radiation, and has adapted to be able to thrive in its presence. It comes from space (cosmic radiation), the ground (terrestrial radiation), from air, water, and even food. We are also exposed to human-made sources of ionizing radiation such as medical x-rays and CT (computed tomography) scans.

When ionizing radiation interacts with cells, several outcomes are possible:

1. It may pass directly through the cell without causing any damage;
2. It may damage the cell, but the cell will repair itself;
3. It may affect the cell's ability to reproduce correctly; or
4. It may kill the cell (**apoptosis**). The death of one cell is not a serious problem – millions of cells die every day - but if too many cells in one organ such as the liver die at once, the organism will die.

As DNA is a critical molecule for living things, it is constantly being repaired through a number of different mechanisms. While most DNA damage can undergo DNA repair, the repair is not 100% efficient. When normal repair processes fail, and when cellular apoptosis does not occur, the DNA may be irreparably damaged. Cells with damaged DNA that survive and reproduce can lead to cancer, and failure to correct damage in cells that form **gametes** (reproductive cells) can result in mutations being passed on to offspring. Fortunately, the repair process in human cells is very efficient at keeping up with the rate of DNA damage caused by radiation around us. When cells are exposed to ionizing radiation, damage can occur either by **direct action** or **indirect action**.

Direct Action

Direct action of radiation involves radiation interacting with the atoms in DNA molecules or other cellular structures critical to the survival of cells. This interaction may result in the cells failing to reproduce or cause 'direct' interference with a critical cellular system. In the case of DNA, direct action occurs when alpha particles, beta particles or x-rays create ions that can:

a) Chemically alter bases;
b) Break sugar phosphate backbones; or
c) Break the hydrogen bonding connecting base pairs; (see Figure 1).

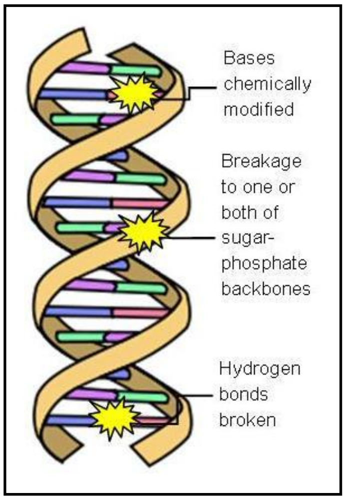

Figure 1: Potential direct effects of ionizing radiation on DNA molecules.

DNA damage (also called **DNA lesions**) is different from DNA **mutation**, although both are types of errors in DNA. DNA damage results in changes to the chemical structure of DNA whereas mutations are changes to the sequence of nucleotide base pairs. However, a failure to repair DNA damage can result in mutations. Mutations can prevent genes from making correct proteins, which can be very harmful for an organism. Not all cells are equally sensitive to radiation. Cells that divide frequently are much more sensitive than cells that divide rarely. Blood cells tend to be the most sensitive to radiation and muscle and nerve cells are the least sensitive. The fast-growing cells of a tumour are very sensitive to radiation, which is why radiation is used in to kill cancer cells in cancer therapy. Developing embryos, which also contain rapidly dividing cells, are also very sensitive to radiation and extra care is taken to minimize the radiation exposure of pregnant women.

Indirect Action

In addition to interacting directly with DNA, when a cell is exposed to ionizing radiation, the radiation can interact with the water in a cell. When the radiation interacts with water molecules, it can break the bonds holding the molecule together resulting in hydrogen (H^+) and hydroxyls (OH^-) ions. These ions can then combine with other ions to form substances such as hydrogen peroxide (H_2O_2) which can lead to the destruction of a cell. The OH^- ions can also attack DNA.

Types of DNA Damage and Repair

A. Damage to Bases

The vast majority of DNA damage from radiation involves chemical modification of the bases themselves. These modifications affect DNA's structure by introducing improper chemical bonds that warp its shape. Damage to bases on a single strand can be fairly easily repaired as long as an undamaged sequence on the complementary DNA strand is available to use as a template. There are a number of different base repair mechanisms depending on the amount of damage.

Sometimes a single base on one of the strands is chemically altered, such as through oxidation. In this case, a cell will typically cut out and replace the base through a process called **Base Excision Repair (BER)**. The damaged base (think of it like a diseased tooth) is removed by the enzyme **DNA glycosylase**, similar to the way a dentist pulls out a tooth. An enzyme called **AP endonuclease** recognizes the site of the missing 'tooth,' and nicks the sugar phosphate DNA backbone to allow a **DNA polymerase** to synthesize the required missing base. Finally, **DNA ligase** rejoins the nick in the DNA backbone. Sometimes a cluster of bases is damaged by high energy radiation. In this case, the group of damaged bases is cut out and replaced with DNA as directed by the undamaged template strand. This process, called **Nucleotide Excision Repair**, involves endonucleases cutting out the damaged segment of DNA, DNA polymerases replicating the original DNA segment, and DNA ligase rejoining the sugar phosphate backbone.

B. Breaks to the Sugar Phosphate Backbone

High energy ionizing radiation can blast through the sugar phosphate backbone causing either **single strand breaks (SSB)** or **double strand breaks (DSB)**. For single strand breaks, the first step is detection of the break by **poly (ADP-ribose) polymerase** (PARP). The job of this enzyme is to signal other repair proteins to come to the break. Polynucleotide kinase (PNK) then cleans up the broken ends of the backbone molecules DNA polymerase fills the gap until only a tiny nick remains. The nick is joined together using DNA ligase. This process is called **Single Strand Break Repair**. Unlike single strand breaks, double strand breaks can be extremely harmful to cells as they can interfere with replication and protein synthesis. They can also lead to chromosomal rearrangements, in which pieces of one chromosome become attached to another chromosome. A number of cancers are associated with such rearrangements. Double-strand breaks are repaired through one of two mechanisms: **non-homologous end-joining** (NHEJ) and **homologous recombination** (HR). In NHEJ, an enzyme called DNA ligase IV uses pieces of DNA adjacent to the break to join and fill in the ends. In contrast, during HR, the homologous (sister) chromosome is used as a template for repair. NHEJ is the main way of repairing breaks due to ionizing radiation.

C. Breaking of Hydrogen Bonds

Sometimes ionizing radiation can break the hydrogen bonding connecting base pairs. Since the hydrogen bonds are not **covalent** (electrons are not shared by the atoms), they can be broken and rejoined relatively easily.