DNA damage by ionizing radiation (and other sources):

Ionizing radiation (IR) consisting of electromagnetic radiation, or photons, is the type of radiation most commonly used for the treatment of patients with radiotherapy. Typical energies of the photons produced by 4–25 MV linear accelerators found in radiotherapy departments range from less than 100 keV to several MeV (the maximum energy of the machine being used). From its name, the principal damaging effects of this type of radiation arise from its ability to ionize or eject electrons, from molecules within cells.

The pattern and density of ionizations and their relationship with the size of the DNA double helix are shown in Fig.1. The clusters are such that many ionizations can occur within a few base pairs of the DNA. These clusters are a unique characteristic of IR, in contrast to other forms of radiation such as UV or DNA-damaging drugs such as topoisomerase inhibitors. Only a few percent of the damage is clustered, but when these clusters occur in DNA, the cell has particular difficulty coping with the damage.

Ionized molecules are highly reactive and undergo a rapid cascade of chemical changes, which can lead to the breaking of chemical bonds. This can disrupt the structure of macromolecules such as DNA, leading to severe consequences if not repaired adequately or in time. Ionizing radiation deposits its energy randomly, thus causing damage to all molecules in the cell. However, there are multiple copies of most molecules (e.g. water, mRNA, proteins, and others) and most undergo a continuous rapid turnover, limiting the consequences of damaging just a few molecules of one type. In contrast, DNA is present in only two copies, has very limited turnover, is the largest molecule thus providing the biggest target, and is central to all cellular functions.

The consequence of permanent damage to DNA can therefore be serious and often lethal for the cell.

Because of the importance of DNA, cells and organisms have developed a complex series of processes and pathways for ensuring that the DNA remains intact and unaltered in the face of continuous attack from within (e.g. oxidation and alkylation owing to metabolism) and from the outside (e.g. ingested chemicals, UV and ionizing radiation). These include different forms of DNA repair to cope with the different forms of DNA damage induced by different agents. Specialized repair systems have therefore evolved for detecting and repairing damage to bases [base excision repair (BER)], single-strand breaks [single strand break repair (SSBR), closely related to BER], and double-strand breaks [homologous recombination (HR) and non-homologous end-joining (NHEJ)]. All these lesions are produced by ionizing radiation.

To give an idea of the scale of damage, 1Gy of irradiation will cause in each cell approximately 105 ionizations, _ 1000 damages to DNA bases, around 1000 single-strand DNA breaks (SSBs) and around 20–40 double-strand DNA breaks (DSBs). To put this into further perspective, 1Gy will kill only about 30 per cent of cells for a typical mammalian cell line, including human. This relatively limited cytotoxicity, despite large numbers of induced lesions per cell, is the consequence of efficient DNA repair.

Cellular DNA comprises two opposing strands linked by hydrogen bonds and forming a double helical structure. Each strand is a linear chain of the four bases – adenine (A), cytosine (C), guanine (G) and thymine (T) – connected by sugar molecules and a phosphate group, the so-called sugar–phosphate backbone. The order of the bases is the code determining not only which protein is made but whether a gene is active (transcribed) or not. In turn, this double helix is wound at regular intervals around a complex of a specific class of proteins (histones), forming nucleosomes, resembling beads on a string. Many other proteins are also associated with the DNA; these control DNA metabolism, including transcription, replication and repair. The DNA plus its associated proteins is called chromatin. There are further levels of folding and looping, finally making up the compact structure of the chromosomes.

This structure poses various challenges to the cell for repairing DNA damage.

1. Specialized proteins have to be sufficiently abundant and mobile to detect damage within seconds or minutes of it occurring.
2. The chromatin usually needs to be remodelled (e.g. the structure opened up) to allow access of repair proteins .

The DNA damage response:

The DNA damage response (DDR) is a highly complex and coordinated system that determines the cellular outcome of DNA damage caused by radiation. The DDR is not a single pathway, but rather a group of highly interrelated signalling pathways, each of which controls different effects on the cell.

This system can be divided into two parts:

1. The sensors of DNA damage .
2. The effectors of damage response .

The sensors consist of a group of proteins that actively survey the genome for the presence of damage. These proteins then signal this damage to three main effector pathways that together determine the outcome for the cell.

These effector pathways include :

1. programmed cell death pathways that kill damaged cells.
2. DNA repair pathways that physically repair DNA breaks .

3. pathways that cause temporary (or permanent) blocks in the progress of cells through the cell cycle – the damage checkpoints.