

RADIATION BIOLOGY

Brahme A.

Karolinska Institute and Stockholm University, Sweden

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Contents

1. Introduction
 2. Cell Cycle Growth Control and Damage Repair
 3. Molecular Biology of Radiation Sensitivity in Tumors and Normal Tissue
 4. From Cell Survival Curves to Dose Response Relations for Organized Tissue
 - 4.1. The Cell Survival Curve
 - 4.2. The Dose Response Relation
 - 4.3. The Responsiveness of Tumors and Normal Tissue to Radiation
 5. Radiation Quality and Radiation Effects
 - 5.1. Physical and Chemical Effects of Radiation Quality
 - 5.2. Radiobiological Effects of Radiation Quality
- Acknowledgments
Glossary
Bibliography
Biographical Sketch

Summary

The rapidly increasing body of genetic information that is now becoming available, not least through projects like the Human Genome Project (HUGO), will rapidly increase our knowledge about genes and improve understanding of their radiation sensitivity. Different organs of the human body have greatly differing responses to partial or heterogeneous irradiation, depending on the functional organization of the different tissues and the part of the genome that is actively transcribing. In addition, different radiation types have widely varying biological effects depending on their ionization density. Therefore high LET beams irradiating mainly serial tissues, such as spinal cord, constitute the greatest threat in terms of acute and rapid radiation response. At the other extreme, low LET exposure of a tissue with mainly parallel response may be well tolerated, since the organ can compensate for the loss of function and most of the damage is repairable. This is the reason why low LET radiation beams can be used effectively to cure many tumors. The recent discovery of low-dose radiation sensitivity is a further illustration of the complexity of the interaction between radiation damage and advanced cellular surveillance systems. Knowledge about these processes is fundamental both for estimating radiation-induced morbidity in radiation protection contexts and for assessing the response of different organs during radiation therapy.

The field of radiation biology is now in a state of rapid development, largely because of the increasing body of knowledge in the area of molecular and cellular biology and radiation science. The aim of this article is to describe some of the main phenomena of

human radiation biology, and to indicate where information gained in future years may be most influential.

1. Introduction

The field of radiation biology is necessarily an interdisciplinary one, covering a very broad range of sciences: from the interaction of different radiation modalities with matter, via the molecular biology of radiation damage, to the study of different types of subcellular structure. Radiation biology also covers cellular radiation responses, and the effects of radiation on functional subunits of different organs and organ systems and the whole organism. In principle, radiation biology also covers radiation effects on different essential enzymes and other molecules, and the influence of nutrients and protective and sensitizing agents that are important to the life of all organisms in our surrounding environment. By necessity, however, the present brief overview must be limited to some of the most important effects of radiation on humans at the cellular and organ level. The article is largely focused on subjects of importance to the understanding of radiation therapy and, to some degree, radiation protection. Since all higher organisms on earth are built of cells we will start by analyzing the effect of radiation at the most basic cellular and subcellular levels, and continue with the responses of partially or wholly irradiated organs. Finally, the varying effects of different radiation modalities, depending on their microscopic energy deposition, will also be covered.

2. Cell Cycle Growth Control and Damage Repair

Under normal conditions, almost all cells in an organism are influenced by various kinds of growth factor that make cells divide at more or less regular intervals, in order to replace dying cells and renew and develop tissues and organs. This process is characterized by the *cell cycle*: a cell moves from the S-phase, where a new set of the genomic material with all the molecules important to heredity is synthesized, so that in the later mitotic M-phase there are two copies of the genome. One copy is needed by each daughter cell that leaves the divided cell in the M-phase of the cell cycle. The two principal cell phases, S and M, are separated by two cell cycle gaps, G1 and G2, during which the cell prepares for synthesis and cell division, respectively, as illustrated in the lower part of Figure 1. In addition to gaps G1 and G2 there is a third, G0, where cells may be resting if they are not immediately needed for some particular function in the organ or tissue where they were born.

Different tissues have different proportions of their cells actively circulating through the cell cycle. The epithelial cells in the intestines, for example, have a fairly rapid turnover, whereas brain cells normally divide at a very low rate. The speed of normal cell division has important consequences for the radiation sensitivity of the cells (Figure 1). Cells that proliferate rapidly through the cell cycle are driven by various growth factors via the RAS gene (left-hand side of Figure 1). However, if the cell is now exposed to some external damaging agent, such as a chemical, physical, or radiation effect, the integrity of the heredity material, primarily in the form of double-stranded DNA (deoxyribonucleic acid, the spiral-like molecule condensed to chromosomes in the cell

nucleus), may become severely affected. At this point it is no longer advisable for the cell either to start the S-phase to generate a new genome or to split the already-doubled genome in the M-phase. This is because severe molecular changes produced by (for example) radiation damage will not ensure accurate repair, replication, or division of the nuclear material.

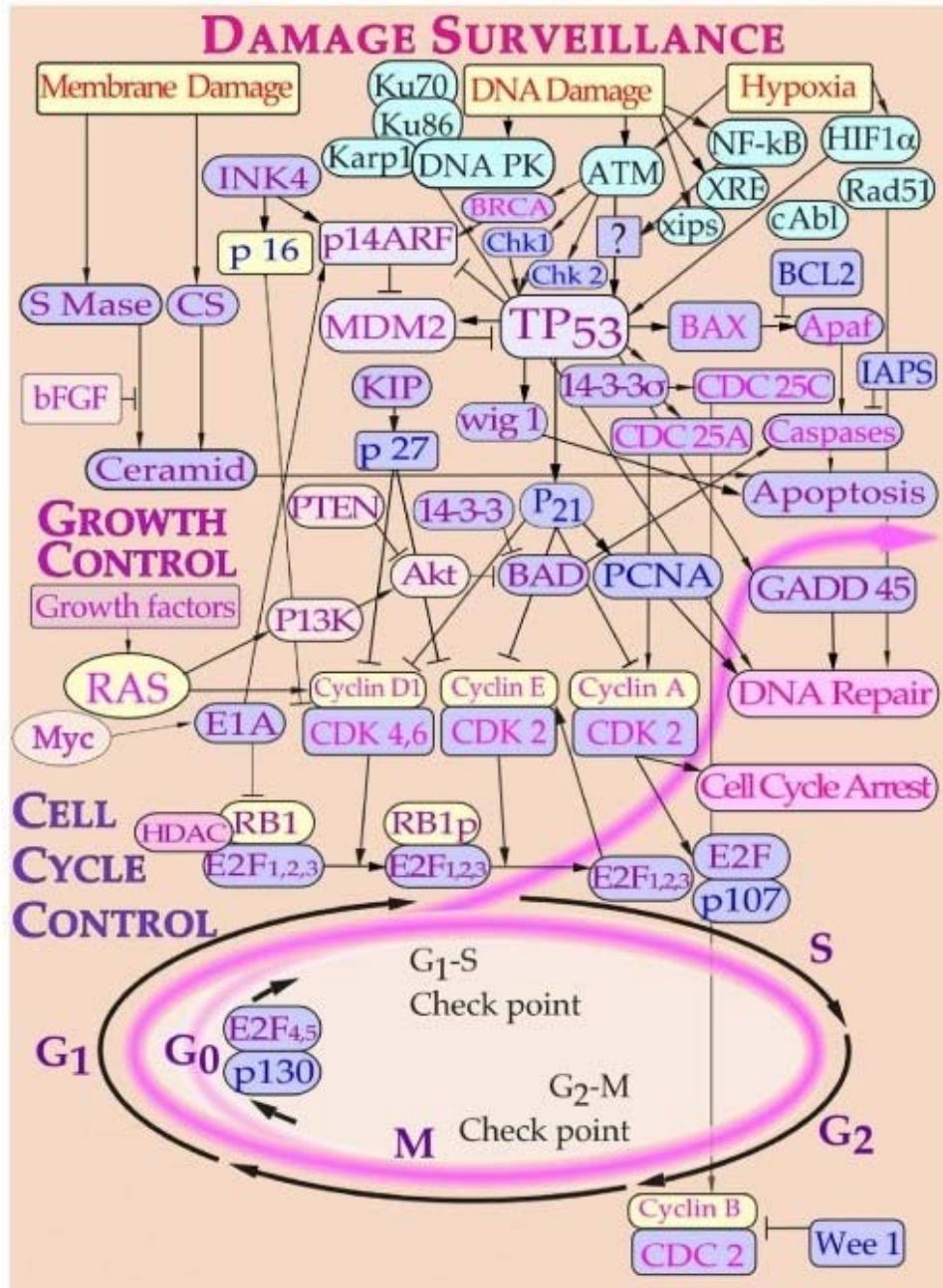


Figure 1. Schematic representation of a damage and cell cycle controls.

A complex surveillance system addressing this process exists in the cell (Figure 1). Some of the main actors are the TP53 and RB1 gene products that, together with different cyclins (A–G), control the progress of the cell cycle. Under normal circumstances different growth factors like RAS stimulate the phosphorylation of the

RB1 protein in the RB1-E2F-HDAC complex, so that the histone deacetylase (HDAC) is lost. After further phosphorylation, now by the cyclin-E -cyclin dependent kinase 2 (CDK2) complex, the E2F-transcription factor is released to activate genes required to start the S-phase. When stimulated by radiation damage to DNA, the TP53 protein activates one of its downstream genes—the CDK inhibitor P21—which in turn inhibits the cyclin-CDK complexes and thereby blocks further phosphorylation of RB1. In this way cells are blocked at the G1-S and G2-M checkpoints of the cell cycle to allow repair of induced DNA damage, for example through the GADD-45 pathway.

If the degree of damage is more severe, so the cellular surveillance system adjudges that it can not repair all the damage inflicted, TP53 may activate its *apoptotic* pathway through which the whole cell is eliminated using built-in “suicide machinery” (upper right corner of Figure 1). This more drastic response is sometimes needed to prevent cells replicating or dividing their DNA before it is fully repaired, in order to minimize the risk of conserving damaged DNA. Obviously, to avoid total destruction of a tissue it is not desirable that all cells follow the apoptotic pathway. An anti-apoptotic control is therefore also present in the cell: for example, through the BCL-2 survival gene. Clearly, this results in cell survival, but involves the risk that some DNA damage is not repaired. Only a small fraction of cells, in organs or grown in culture, will have access to the apoptotic pathway.

In all of the above mechanisms, it is quite understandable that cells in organs that depend on actively cycling and cell division may be relatively responsive to irradiation, since they have both a strong active drive through the cell cycle and less time to repair inflicted damage. This correlates with what is seen in radiation accidents and in the clinical use of radiation. In the case of accidents the reactions of the intestines and blood-forming organs are often the most severe, while organs like the lungs and the kidneys are very sensitive during radiation therapy.

3. Molecular Biology of Radiation Sensitivity in Tumors and Normal Tissue

Besides the cell cycle control, many other genetic factors can influence the radiation sensitivity of tumors and normal tissues. Obviously, in the case of a tumor the state of proto-oncogenes is most important, since these materials generally encode the proteins responsible for the signal transduction cascade of growth factors that normally stimulates cell division or differentiation. When such genes are mutated or erroneously expressed they can promote tumor development, and are therefore called *oncogenes*. Functionally, there are four main groups of proto-oncogenes, depending on how they influence normal cell processes:

1. autocrine growth factors (hst, int, sis)
2. growth factor receptors (erb, fms, sea)
3. signal transduction factors (ras, mos, src)
4. nuclear transcription factors (myc, fos, jun).

(Some examples of oncogenes belonging to each group are given in parentheses.) Several mechanisms—structural alterations (mutations, deletions), amplification, or loss of control mechanism due to insertional mutagenesis, transduction, or translocation—

can lead the genome to activate oncogenes. Most of these are triggered by external factors such as chemical agents or radiation; others are activated by viruses (viral oncogenes) that can act by inserting or transforming genes.

Most of the *c.* 100 proto-oncogenes known today have a positive stimulant effect on cell proliferation, and therefore have a dominant influence relative to the other, possibly normal, alleles. There is also a second important group of so-called *tumor suppressor genes* that, by contrast, are recessive in relation to a normal allele since they promote neoplasia by loss of function. The classic example of such a gene is the retinoblastoma (RB) gene, which is responsible for both the hereditary and non-hereditary sporadic form of the associated eye disease. In the hereditary form one mutation is somatic, and the other is transmitted germinally from an affected parent. In the sporadic form, however, both mutations are somatic. This explains the linear development of the hereditary form over time, whereas the sporadic form has a much slower parabolic onset. More recently the RB gene has been shown to be affected in breast and lung carcinoma and in osteosarcoma, and it has a very important function in the regulation of cell cycle progression as discussed above (Figure 1).

One of the most commonly mutated or lost genes in human cancers, TP53, also belongs to the tumor suppressor group, as do many recently discovered tumor-specific genes including BRCA 1, 2, and 3 (breast cancer susceptibility genes), DCC and MCC (deleted or mutated in colon carcinoma respectively), APC (adenomatous polyposis coli), and WT (Wilm's tumor).

The very interesting gene product TP53 is a DNA binding transcription factor that can induce apoptosis or cell cycle arrest in the G1 phase of the cell cycle, as discussed above. It therefore seems to influence a cell's decision as to whether to rest and repair induced DNA damage, or to eliminate itself by apoptosis due to the severity of damage. Because of its central role in handling DNA damage, the TP53 gene is found mutated in many types of cancer, including glioblastoma, astrocytoma, colorectal, breast, brain, and lung carcinoma.

It is interesting to note that if the tumor suppressor gene TP53 is mutated in a cell, the risk that this cell line may develop neoplasia is immediately increased, since such a cell will find it more difficult to handle DNA damage to its genome. Fortunately, for the same reason radiation therapy may be the ideal way of treating a tumor arising from this process, since generally the tumor cells will still be associated with poor ability to handle the DNA damage inflicted in a controlled way by the therapeutic beams. This mechanism may explain why radiation therapy has recently been shown to be very effective for node-negative breast cancer patients who have certain mutations in their TP53 gene. The situation is not always as simple as this, however, because TP53 mutations may also decrease the cells' ability to induce apoptosis. This may show up in an increased survival of the cells after irradiation, even though they are damaged and have not been repaired with a high degree of fidelity.

Besides the oncogenes and tumor suppressor genes that are largely responsible for tumor induction, a large number of other genes may also be affected to influence tumor

development and alter the radiation sensitivity of the patient. At least four gene families can be identified:

1. cell cycle control genes (RB1, TP53, cyclin A-G, cdc-2, cdk 2-7, E2F 1-5, GADD-45: *cf.* Figure 1);
2. DNA repair or “mutator” genes (XPA-G, ERCC 1-5, XRCC 1-7, ATM, DNA-PK, Ku 70, 86, RAD 1–57, MSH 2, 3, 6, PMS 1, 2, MLH 1, 3, Mut, Hex, RecA, LexA, UvrA);
3. DNA processing and topology genes (Topo I, II α , II β); and
4. detoxification and stress-response genes (GS, MRP, HSP).

It is clear that the processing of both normal and damaged DNA may be affected if some of these genes have an impaired function. This may, in turn, promote tumor development and alter the radiation sensitivity of the cells.

As discussed above, the cell cycle control is fundamental to the ability of the cells to halt DNA syntheses and to handle inflicted DNA damage before they continue cycling. For this purpose, the cyclins must function together with RB1, TP53, and the DNA dependent protein kinase (DNA-PK) and ATM gene products to handle damaged DNA. The large group of DNA repair genes then has to take on the process of trying to eliminate strand breaks and repair damage sites. Base and nucleotide damage is handled by the excision repair gene products (XP A-G and ERCC), whereas more complex radiation damage is handled by the numerous Rad and XRCC gene products. For mismatch repair, sets of Mut and Hex genes are employed by the cell. During the repair process several DNA-processing genes are active: these include the topoisomerases, which are active in unwinding the DNA from the nucleosomes and in separating the strands in order to transcribe DNA or give the enzymes of the repair system access to compacted areas of the DNA. Other genes that can influence radiation sensitivity are the detoxification and stress-response genes that may increase glutathione levels to improve radical scavenging or the level of heat-shock proteins. It is likely that the status of many of the above genes with regard to polymorphism, amplification, and transcription factors and mutations may be combined as useful genetic predictors of radiation sensitivity, both for tumors and (probably even more importantly) for normal tissues.

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Biographical Sketch

Anders Brahme is Professor of Medical Radiation Physics at the Department of Oncology-Pathology, Karolinska Institutet and Department of Medical Radiation Physics, Stockholm University, and Manager of the Research Center for Radiation Therapy, Karolinska Institutet. He got his Master of Science degree in electrical engineering at the Royal Institute of Technology in 1969 and his Ph.D. thesis on the application of the Microtron accelerator for radiation therapy was presented 1975 at Stockholm University. Since then he has been active in the development of radiation dosimetry, quality assurance and radiation therapy equipment and techniques for most types of radiation from electrons and photons to neutrons, protons and heavy ions. He initiated the development of inverse radiation therapy planning and intensity modulated radiotherapy using scanning beams and dynamic multileaf collimator systems. During the last two decades he has been mainly active in the field of radiotherapy optimization using accurate radiobiological models describing the response of tumors and normal tissues. By such techniques he has been able to maximize the expectation value of the complication free tumor cure under consideration of intensity modulation, dose fractionation, radiation modality, the number of beam portals and their angles of incidence as well as uncertainties in geometrical and biological parameters.