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Biochemical aspects of radiation biology

U. Hagen

Institut für Strahlenbiologie, Gesellschaft für Strahlen- und Umweltforschung, D-8042 Neuherberg (Federal Republic of Germany)

Summary. In order to analyze the mechanisms of biological radiation effects, the events after radiation energy absorption in irradiated organisms have to be studied by physico-chemical and biochemical methods. The radiation effects in vitro on biomolecules, especially DNA, are described, as well as their alterations in irradiated cells. Whereas in vitro, in aqueous solution, predominantly OH radicals are effective and lead to damage in single moieties of the DNA, in vivo the direct absorption of radiation energy leads to 'locally multiply-damaged sites', which produce DNA double-strand breaks and locally denatured regions.

DNA damage will be repaired in irradiated cells. Error free repair leads to the original nucleotide sequence in the genome by excision or by recombination. "Error prone repair" (mutagenic repair), leads to mutation. However, the biochemistry of these processes, regulated by a number of genes, is poorly understood. In addition, more complex reactions, such as gene amplification and transposition of mobile gene elements, are responsible for mutation or malignant transformation.

Key words. Radiation effects; radiolysis; radicals; DNA damage; DNA strand breaks; nucleoprotein; base damage; DNA synthesis; DNA repair; mutagenic repair; error prone repair; gene amplification; transposition; endonuclease.

Introduction

To understand the mechanisms involved in the biological effects of ionizing radiation, the individual steps that take place after the absorption of radiation energy in living organisms have to be analyzed by biochemical methods. Such steps are the primary physico-chemical events affecting biomolecules, leading to molecular structural alterations, especially in the desoxyribonucleic acid (DNA). The study of radiolytic reactions in irradiated aqueous solutions of biomolecules results in a basic understanding of the events affecting these molecules in vivo, i.e. in irradiated organisms. One major difference between in vitro and in vivo observations is that in vivo, in addition to the action of radicals formed in water, the direct absorption of radiation energy is responsible for alterations of biomolecules leading to the biological radiation effect.

DNA damage will be reduced in irradiated organisms by subsequent repair reactions. Most of the repair reactions lead to full recovery of the cell, i.e. they are error free. Other repair reactions lead to an altered nucleotide sequence in the DNA, i.e. under certain circumstances to a mutation. Such reactions are described hereafter as error prone or mutagenic repair. At present the enzymatic processes involved in these DNA repair reactions are the main topic of biochemical studies in radiation biology. They may contribute to the mechanisms of the cellular and genetic endpoints of radiation effects as cell death, chromosome aberrations, mutations and carcinogenic transformation to a tumor cell.

The main emphasis of this article will not be on a detailed description of the literature. Rather, a more personal view will be offered on important results, on the current aspects of research and on open questions. There are also a number of books and review articles relevant to the subject; these will be mentioned later in this review.
Several important questions will not be dealt with in this chapter, as for example the mechanisms of cell death in relation to DNA double strand breaks and chromosome aberrations. This topic will be addressed in the subsequent paper by Alper and Cramp[1]. Topics concerning the modification of radiation effects by the oxygen concentration or by use of densely ionizing radiation sources as neutrons or heavy particles will be marginally considered. Moreover, the genetic control of DNA repair cannot be discussed here in detail.

Radiation chemistry of biomolecules in vitro

Much of the knowledge of primary radiation events acting on biomolecules was gained from studies of its radiolysis in vitro, either in dry state or in aqueous solutions. In the dry state the configuration of primary radicals can be studied mostly by electron-spin-resonance spectroscopy (ESR). In dry proteins, radicals first located on carbon are transferred to disulfide bonds, leading to the highly reactive reducing disulfide radical anion ($RSS^{\cdot -}R$) or to the oxidizing thiyl radical $R/S^{\cdot}$[50]. Further subsequent reactions in the protein lead to alteration of the macromolecular structure and loss of enzymatic functions[9].
The radiolysis of DNA can be studied on its single moieties, as on bases, nucleosides, nucleotides, synthetic polynucleotides or on double stranded DNA. Studies on single crystals as well as on oriented dry DNA showed the prevalence of the primary formation of the thymine anion radical ($T^{\cdot -}$) and the guanine cation radical ($G^{\cdot +}$)[28,62], leading by subsequent reactions to numerous types of damage in the various DNA moieties, to breaks of the sugar-phosphate backbone of DNA and to intra- and intermolecular crosslinks[28].
More detailed studies were made on the radiolysis of DNA and its constituents in aqueous solution. In water, the radicals $H^{\cdot}$, $OH^{\cdot}$ and solvated electrons (e^-_{aq}) are formed, attacking biomolecules by

H-abstraction: $RH + OH^{\cdot} \rightarrow R^{\cdot} + HOH$
or by
OH-addition: $R' + OH^{\cdot} \rightarrow R'OH^{\cdot}$.

In the presence of oxygen, these radicals can be transformed into peroxiradicals:

$$R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$$

This reaction prevents recombination to the original biomolecule:

$$R^{\cdot} + H^{\cdot} \rightarrow RH$$

and therefore increases the radical yield in the medium in the presence of oxygen. In addition, O_2 reacts very fast with the solvated electron; thus recombinations of the biomolecules with the electron:

$$RH^{\cdot} + e^-_{aq} \rightarrow RH$$

is prevented[26,61]. These reactions are the chemical basis of the phenomenon that the biological radiation effect is enhanced in the presence of oxygen ('oxygen effect', 'Oxygen Enhancement Ratio' = OER).
Studies on the radiolysis of DNA and its moieties in water have been summarized in books[28,61] or in review articles[5,23,29,59,60,63,67]. Comparing the radiosensitivity of bases in irradiated DNA shows that there is a clear prevalence of thymine (T) destruction over cytosine (C) over adenine (A) and guanine (G), which is in agreement with studies on free bases, nucleosides or nucleotides[23,28]. In irradiated DNA the oxidation products of thymine (thymine glycol and thymine hydroxyhydroperoxide) on the C5-C6-double bond are the best known radiation products. In purines, an opening of the imidazol ring leads to formamidopyrimidine derivatives. In addition, intramolecular purine C(5')-C(8) cyclization occurs and in DNA a respective intermolecular crosslink is observed[15].
Most of these studies were made after high radiation doses, where the DNA is heavily degraded and the orginal double stranded structure is lost. Therefore it is necessary to detect already a few base lesions in DNA after low doses with sensitive methods, in order to evaluate its biological significance. Instead of chemical methods, enzymatic or immunological methods have to be used. By using specific endonucleases, such as the so-called 'gamma endonuclease' which splits the nucleotide strand on the position of base damage[23] or the DNA glycosylase[4], thymine damage will be detected. Another method calls for the use of specific antibodies, which were developed for some types of base damage as for thymine glycol[51,70] or against 8.5' cycloadenosine[15,16,71].
The mechanisms of DNA strand break formation was studied by chemical product analysis of sugar components on model compounds and oligonucleotides as well as by enzymatic endgroup analysis on DNA[22,59,61]. Oxidation of the sugar as well as a loss of a whole nucleotide are the predominant reactions, leading to single strand breaks (SSB) in a single DNA strand of the double helix. Other types of damage, as loss of base, lead to alkalilabile lesions (ALL) in the nucleotide strand. This damage to DNA on bases and sugars rises linearly with dose. Breaks of both strands in DNA (double-strand breaks, DSB) occur in vitro only by coincidence of two opposite SSB and thus rise quadratically with dose[12,19].
Radiation-induced damage in DNA will also lead to loss of functions as studied by the transformation activity of bacteriophage DNA[28] or by the transcription in vitro[20,21]. It could be shown, that transcription stops at the

site of SSB, whereas it proceeds over damaged bases possibly inserting a wrong ribonucleotide at this position. In order to understand DNA damage in irradiated organisms, it is also necessary to study in vitro DNA-protein interactions [54, 55] as well as the biochemistry of irradiated membranes [73].

DNA damage in irradiated cells

Given the present knowledge about the radiolysis of DNA in solutions, one can ask whether the DNA in irradiated cell will be damaged by the same mechanisms. Here, in addition to the attack of water radicals, a direct absorption of radiation energy in DNA takes place. This energy deposition leads also to a more extended type of damage to DNA, designated as 'bulky lesions' or 'locally multiply-damaged sites' [66, 68]. Evidence for this is seen in the linear shape of the dose effect curve for DSB in vivo, indicating nucleotide damage on both strands by one single event [33].

There exists also a multiple lesion on the bases without a strand break, which can be described as locally denatured region, possibly containing a cluster of base damage [17, 30, 39]. On these sites, the DNA will be split by the S1-nuclease to a DSB, designated therefore as S1-nuclease sensitive sites (S1-sites). S1-sites are only formed by the direct radiation effect, i.e. in irradiated phage particles or in irradiated cells, but not in DNA irradiated in aqueous solutions. S1-sites rise as do DSB: linearly with dose. Their frequency is about equal to that of DSB.

In mammalian cells the DNA is protected from diffusible water radicals by surrounding proteins. This can be demonstrated by comparing the DNA lesions in mature condensed chromatin with those in the nascent active one and with free DNA. The relation of radiosensitivity of thymine damage in DNA for these conditions is 1:2:6 [69].

The close association of DNA and proteins in chromatin leads also to DNA-protein crosslinks, which are preferentially induced under hypoxic conditions and may contribute to cell lethality [42].

Whereas no information is available about the effects of DNA damage in cells on transcription, extensive studies were made on the radiation-induced inhibition of DNA replication. As summarized by Painter [47], the characteristic two-component dose effect curve is due to a sensitive part in the low dose range up to 5 Gy which reflects inhibition of initiation of DNA synthesis, probably by SSB in the replicons, whereas the second component is due to inhibition of chain elongation. A new approach to studying DNA functions in vivo is the analysis of gene expression of irradiated plasmids after transfection into unirradiated mammalian cells [49].

Error free repair of radiation-induced DNA damage

As DNA is subject in living cells to damage by numerous agents, cells have to repair the damage to survive. DNA repair must be regarded, in addition to replication and recombination, as an essential feature of the genetic material in all life forms. DNA repair can restore the original DNA structure by reversal or removal of the primary damage. Such repair can be designated also as 'error free repair', in contrast to the 'mutagenic error prone repair' (see below). In case of damage in one DNA strand, for example, an SSB or single base damage, the respective repair reactions after ionizing irradiation resemble those after UV-irradiation which are described as 'excision repair'. Briefly, the damaged part of DNA is excised, the gap is filled by a polymerase and the nick in the DNA strand is closed by ligase [13]. However, in contrast to the UV-induced repair, nothing is known about the genes involved in repair of SSB or base damage induced by ionizing radiation, although respective enzymes for repair have been isolated (see below). In case of multiple lesions, DSB and S1-sites, their repair may be controlled by recombination processes.

In this paper, the kinetics of removal of DNA damage induced by ionizing radiation will be described as well as the underlying enzymatic reactions. For strand breaks, several components of repair kinetics were reported with half times of 2, 15 and 160 min, indicating that different mechanisms are involved [10]. It is assumed that the slow component reflects the repair of DSB by recombination events. The presence of two components of early repair for strand breaks mentioned may be due to different types of endgroups at the DNA breaks. Indeed it was shown in thymocytes, that strand breaks with intact 5'phosphate endgroups are more rapidly repaired than those with damaged end groups which possibly need additional exonuclease activity [34]. Repair of strand breaks, followed by conventional methods of macromolecular weight analysis, however, does not mean full restoration of the genomic integrity. In non-dividing retina cells in rabbits, for example, the repair of the broken DNA to the original size of chromosomal units takes about one month [35].

In the repair of SSB, three enzymatic steps are involved: excision of the broken ends by an exonuclease; filling the gap in the single strand by a DNA polymerase; and ligase activity to close the nick. In vitro, only exonuclease III was effective in removing the damaged 3' end of a SSB. In this way, the subsequent steps of repair by polymerase and ligase can be performed in vitro [44]. Indirect indications for such an exonuclease step on the 3'end in irradiated cells were obtained testing the radiation-induced strand-breaks for their ability to serve as a template for DNA polymerase [40].

The action of the DNA polymerase during repair can be measured by nucleotide incorporation apart from the semiconservative DNA synthesis, designated as 'repair synthesis' or 'unscheduled DNA synthesis'. Although it occurs predominantly after UV-irradiation [13], it can be detected also after X-irradiation [46].

The repair kinetics of base damage may be at the same rate as that for strand breaks. It can be followed either by

specific endonucleases or antibodies[23, 63]. Where both methods are available, as is the case for thymine dimers, each indicates about the same number of damaged bases, but the repair detected by antibody sites is much faster than by the endonuclease sensitive sites[43]. Thus information is still lacking about the kinetics of base repair in irradiated mammalian cells. In one study, the repair of S1-sites was followed in yeast cells[17]. Its kinetics corresponds to the kinetics of DSB and is controlled also by recombination processes.

For the first step of repair of single base damage a number of enzymes are described, which split the nucleotide strand at the 3'site of the damaged base, to enable an excision in the 5'direction concomitant with a polymerase action. These endonucleases are isolated from *E. coli* and from *M. luteus*, specific for oxidative damage on pyrimidine, and are known as gamma-endonuclease or X-ray endonuclease or endonuclease III[7, 23, 63]. In addition, DNA glycosylase activities are known to remove oxidized thymine, resulting apyrimidinic sites which are split by a apurinic-apyrimidinic (AP) endonuclease, common to all living cells.

Sometimes, these three enzymatic activities are combined in one protein. The enzyme in *M. luteus* has an endonuclease activity for thymine glycol as well as an AP-activity, and in *E. coli* endonuclease III has both glycosylase and endonuclease activity. There is evidence that the radiation-induced opening of the imidazol ring of purines is repaired by a specific cyclase activity[6]. Also, exonuclease III with its AP endonuclease activity is involved in repair of H_2O_2-induced DNA damage[8].

Furthermore the surrounding environment of damaged DNA determines the kinetics of repair. The repair of transcriptionally active chromatin is about 3 times faster than in unfolded regions[48]. The same phenomenon was observed while measuring repair kinetics in specific active and inactive genes[2, 25, 41], showing a preferential, more rapid repair of thymine damage on active genes.

Much more is known about the enzymatic reactions and genes of UV-induced DNA damage in bacteria and in yeast. Extensive summaries of data on genes and enzymes involved in UV-repair are given by Friedberg[13, 14] and increasing evidence is being obtained, to suggest that in mammalian cells corresponding repair genes are active[13].

Mutagenic error prone repair

Radiation-induced DNA damage may lead to a variety of repair reactions, which alter the nucleotide sequence in the genome and change the expression of genes. Such phenomena are due to point mutations (for instance, transversion, transition, base pair insertion, base pair deletion) or are caused by more complex reactions such as gene amplification or transposition of mobile gene elements. The transformation of a mammalian cell as the first step of carcinogenesis may be due to point mutations, transposition or gene amplification as well as to large deletions and chromosomal aberrations.

Little is known about the biochemistry of the underlying mechanisms of transposition or gene amplification. It has been demonstrated that the transposition of mobile Ty-elements in yeast is enhanced by gamma-irradiation, UV-light or alkylating agents[45]. It is not known, however, which enzymatic processes are involved in the transposition: a real transfer of the gene element or a transcriptional process.

Ionizing radiation induces the amplification of certain genes about 10–30 times. For the SV40 gene sequences[37, 38] it was shown that the sites of DNA damage by X-irradiation are not the same as the sites of gene amplification. Furthermore, the induction of gene amplification is mediated by a diffusible factor generated by the irradiation.

There is also evidence for a possible involvement of endogenous retroviruses in radiation-induced carcinogenesis by transposition or gene amplification[11]. Studies on radiation-induced cell transformation in culture show that this process is enhanced and controlled by tumor-promoting factors (TPA)[24].

More biochemical information is available regarding the process of 'mutagenic' misrepair (error prone repair) on the site of DNA damage, leading to a change of the nucleotide sequence and under certain circumstances to a change of gene expression, which could be a mutant. However, we can detect only mutants that are able to form a clone.

The essential point in the mechanism of mutation induction is that, as far as we know for *E. coli* and for yeast, error prone repair is inducible. Models for the underlying mechanism have been developed mostly for UV-light-induced mutagenesis; in addition much more is known about the genetic control of mutagenesis than about the action of enzymes involved in the misrepair of DNA damage.

There is a well studied model for *E. coli*, the SOS repair, showing that damage to DNA will lead via various steps to expression of genes which are normally repressed[27, 64, 65, 72]. Among these genes are those which lead to enzymatic functions catalyzing repair steps which are error prone and result in insertion of a wrong base. Apparently, DNA damage induces this gene expression, but the corresponding enzymes are not known. It has been shown that also in other bacteria similar SOS-mechanisms may be operating for UV-induced mutagenesis[35, 36].

The mechanisms of mutagenesis in eukaryotes may be quite different. For yeast, a model of inducible mutagenic repair was developed which is based on a mismatch repair controlled by the REV2 gene after UV-irradiation[57, 58]. In this model, local mismatched regions due to damaged bases are recognized by the REV2 gene product, and repaired, but misrepair leads to an altered nucleotide sequence. Also the repair of S1-sites in yeast may be

controlled by mutagenic repair in addition to recombination repair [17].

An essential point regarding the mechanisms of mutagenesis is the question whether the site of point mutations is identical with the position of induced DNA damage, which is called 'targeted mutagenesis'. In contrast, error prone repair processes may result in mutations at sites other than position of the site of induced DNA damage (untargeted mutagenesis) [29, 31, 32]. There are at present arguments for and against such an untargeted mutagenesis.

There are also studies concerning the mechanisms of radiation-induced mutagenesis in mammalian cells, and there is a broad spectrum of effects on the nucleotide sequence for mutations after gamma irradiation [18]. However, the enzymatic mechanisms in the inducibility of mutation in mammalian cells is a topic of a controversial discussion [27, 52, 53]. We only know that there is an inducible repair in mammalian cells, but there is no evidence that this repair is also mutagenic.

It should be considered that repair of DNA damage may not yield a full recovery of all cell functions. This topic of repair and recovery will be discussed by Alper and Cramp in this review [1].

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