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Review on the Role and Function of Proteins, Enzymes in the Mechanisms and Pathways of DNA Repair

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Abstract: DNA is integrated, stable and highly reactive but endogenous and exogenous origin agents impact the integrity since which damage the structure in the nucleotide sequence. The stability of DNA is by DNA repair mechanisms. For this there are several DNA-repair pathways that recognize lesions in DNA and remove them through a number of diverse reaction sequences. Defects in DNA-repair proteins are associated with several hereditary syndromes, which show a marked predisposition to cancer. Although DNA repair is essential for a healthy cell, DNA-repair enzymes counteract the efficiency of a number of important antitumor agents that exert their cytotoxic effects by damaging DNA. DNA-repair processes differ greatly in their nature and complexity. Whereas some pathways only require a single enzyme to restore the original DNA sequence, others operate through the coordinated action of 30 or more proteins.
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1. Introduction

Maintenance of genomic integrity is of crucial importance for all organisms. Damage to the DNA that makes up gene is constantly inflicted by a large number of endogenous and exogenous agents and can have severe effects if it persists (Rydberg *et al.,* 1982). Modifications of DNA can lead to mutations, which alter the coding sequence of DNA and can lead to cancer in mammals. Other DNA lesions interfere with normal cellular transactions, such as DNA replication or transcription, and are deleterious to the cell. Cells have evolved several ways to counteract these adverse effects of damaged DNA. There are various DNA repair pathways that can remove lesions from DNA. The importance of DNA repair is underscored by several syndromes that are caused by defects in DNA-repair genes. A hallmark feature of these diseases is a dramatically increased predisposition to cancer. Damage to DNA leads to a number of responses in the cell, which are tightly coordinated with DNA repair. The cell cycle is arrested in response to DNA damage to allow time for repair before replication and cell division (Kuraoka *et al*., 1996). If the damage load is too large for a cell to be repaired, the cell may undergo apoptosis to avoid the propagation of highly defective cells. Furthermore, some specialized DNA polymerases tolerate damage during replication and bypass lesion in a process that either gives an accurate replication product or a mutation (Elledge *et al.,* 2003).

2. DNA Damage and Responses

DNA is not indefinitely stable in aqueous solution & numerous sources of damaging agents of endogenous & exogenous origins additionally contribute to the decay and instability of DNA. Crude estimates of the number of DNA-damage events in a single human cell range from 104–106 per day, requiring therefore in an adult human (1012 cells) about 1016–1018 repair events per day. Since alterations in only a small number of base pairs in the genome are in principle sufficient for induction of cancer, it is clear that DNA-repair systems effectively counteract this threat **(Kuraoka *et al*., 1996).**

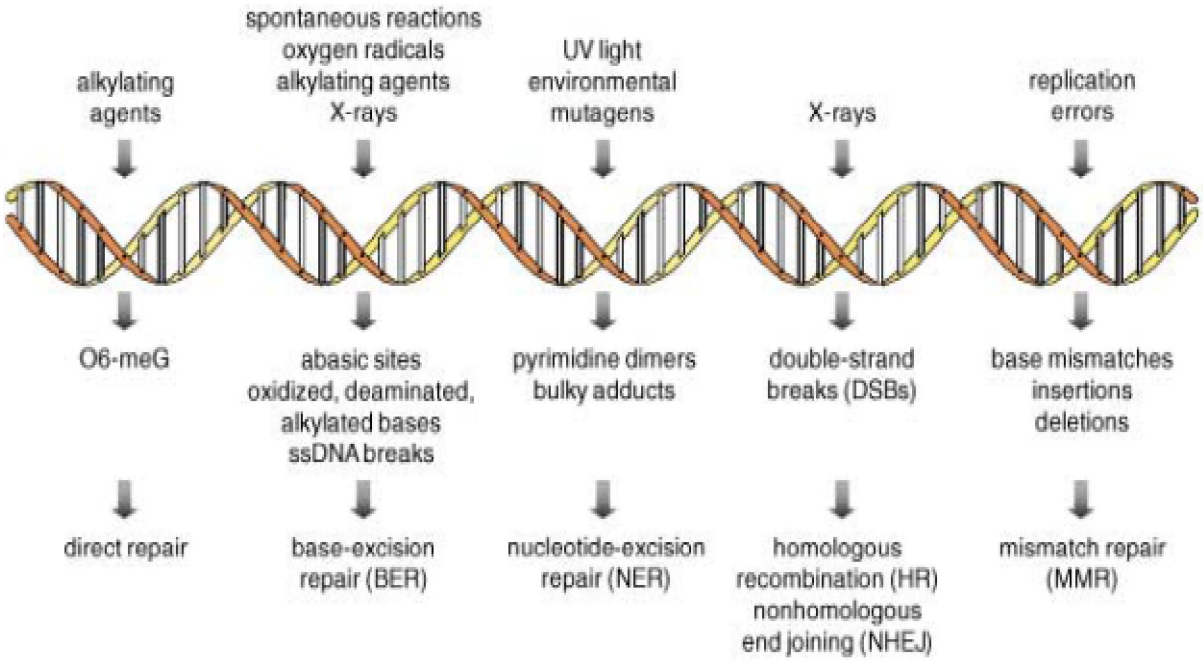

Figure. Most common DNA-damaging agents, lesions, and repair pathways (Kuraoka *et al.,* 1996).

Damage to the Nucleobases of DNA

The simplest reaction that is potentially harmful to DNA is hydrolysis. The glycosidic bond of purine nucleotides is rather prone to acid-catalyzed hydrolysis (Jasin and Haberb, 2016). Abasic sites, which are the products of depurination, have lost the genetic coding information and can thus lead to mutations during replication. Recent studies, in which a highly sensitive probe for the aldehyde group of a basic sites was used, led to an estimate of the spontaneous generation of almost 10000 abasic sites per human cell per day. Abasic sites are very base-labile and can also spontaneously further fragment to form cytotoxic single-strand beaks. A second hydrolytic reaction can occur at the exocyclic amine groups of C, 5-MeC, A, and G, leading to the bases uracil, thymine, hypoxanthine, xanthine, respectively.[10] These deaminationscan lead to alterations in the coding sequence. The formation of uracil from cytidine is the most important of these lesions and has been estimated to occur 100–500 times per day in a human cell (Rydberg *et al.,* 1982,). In addition to water, many reactive species that can modify DNA are generated as a consequence of normal cellular metabolism. Reactive oxygen species (ROS) such as superoxide radical anions, hydrogen peroxide, or hydroxyl radicals are formed as by-products of oxygen metabolism and can react with DNA to give rise to one of over 100 oxidative modifications in DNA found to date(Jasin and Haberb, 2016). The most prominent oxidative base adducts include 8-oxoguanine, which is mutagenic and can block transcription, and thymine glycol, which is only mildly mutagenic but blocks DNA replication and transcription. Modification of DNA bases by ROS can also occur in an indirect fashion. Polyunsaturated fatty acids, for example, are readily oxidized to form bifunctional electrophiles such as malondialdehyde (Kuraoka *et al*., 1996).

3. Dna Repair Mechanism

The efficiency of repair of a given lesion can vary over several orders of magnitude and there appears to be a general correlation between the efficiency with which a given lesion is repaired and the amount of helical distortion it causes (Kuraoka *et al*., 1996).

3.1. Repair by Direct Reversal

UV-induced pyrimidine dimers and O_6-alkylguanine adducts can be repaired by direct reversal of damage by photolyases and alkylguanine transferases, respectively, in bacteria and lower eukaryotes. In mammals, only O_6- alkylguanine adducts are repaired in this way. O_6-alkylguanine transferase (AGT) activity is found in most living organisms and counteracts the mutagenic effects of

O_6- ethyl guanine (Kuraoka *et al*., 1996). AGT reverses O_6-alkylguanine to guanine by transferring the alkyl group from DNA to a reactive cysteine group of the protein in an irreversible reaction. This covalent attachment of the alkyl group to the cysteine residue inactivates the enzyme. AGT is thus a suicide enzyme that is targeted for proteolytic degradation after a single turnover. Structure studies revealed that the active site of AGT is located it the interior of the protein, some distance away from the DNA-binding surface. The protein is thought to employ a nucleotide-flipping mechanism to bring the substrate base and AGT active-site nucleophile into close proximity (Elledge *et al.,* 2003). The importance of AGT in protecting mammals from toxic and mutagenic effects of alkylating agents has been demonstrated in mice. Transgenic mice that over express AGT develop significantly fewer tumors in response to the methylating agent N-methyl-N-nitrosourea, whereas mice that are deficient in AGT are much more susceptible to the tumor-inducing and toxic effects of this agent than wild-type mice. AGT is an important enzyme in antitumor therapy since it counteracts the cytotoxic effects of antitumor agents of the chloroethyl nitroso urea (CENU) class, for example, BCNU (N,N-bis (2-chloroethyl) N-nitroso urea) or temozolomide (Volker et al., 200). The levels of AGT present in tumors have been shown to be a major determinant for the success of antitumor therapy with CENUs. CENUs initially react with the O6 carbonyl group of guanine to form adduct 22, which is subsequently converted into the 1,O6-ethanoguanine adduct 23. The adduct 23 rearranges over several hours to the physiologically active ICL 24. AGT counteracts the formation of 24 by reacting with 22 or 23 to restore the guanine base or to form the protein–DNA adduct 26. Evidence for the formation of adduct 26 has been obtained, but it has only been isolated in quantities too small to allow its detailed characterization. Noll & Clarke addressed this problem with a chemical biological approach and introduced 1, O6-ethanoxanthine 27, a stable analogue of 23, into DNA (Schrer, 2003). Ethanoxanthine 27 reacts with AGT to form the stable protein–DNA adduct 28. This approach should allow the generation of the covalent AGT–DNA adduct 28 in large amounts, which may be used to solve the first structure of AGT bound to DNA (Volker *et al*., 200).

3.2. Base-Excision Repair

Damage to DNA bases resulting from deamination, oxidation, and alkylation is mainly repaired by base-excision repair (Jasin and Haberb, 2016). BER is initiated by DNA glycosylases, which recognize damaged bases and excise them from DNA by hydrolyzing the N-glycosidic bond between the base and the sugar phosphate backbone of DNA to generate an abasic site. Three glycosylases additionally have APlyase activity, which enables them to cleave the bond between the sugar and the phosphate 3’ to the damaged site. AP endonuclease APE1 (also called HAP-1 or Ref-1) is the second enzyme in the pathway and hydrolyzes the phosphodiester bond 5’ to the abasic site to generate a nick. In the main BER pathway, that is, the short patch repair polymerase b (Polb) incorporates a single nucleotide and removes the abasic site by virtue of its AP lyase activity (Sancar and Sancar, 1988).

3.3. Nucleotide-Excision Repair

Nucleotide-excision repair is the pathway that removes bulky base adducts (such as those formed by UV light, various environmental mutagens, and certain chemotherapeutic agents) from DNA. Although its main biological role is likely to deal with UV damage to DNA, NER is remarkable in its broad substrate specificity (Kuraoka *et al*., 1996). NER might therefore allow an organism to deal with unexpected environmental DNA damaging agents. Simple mismatches or bubbles are, however, not substrates for NER, which indicates that distortion of the DNA backbone alone is not sufficient to qualify as an NER substrate. A bipartite model for recognition has been proposed that involves recognition of a helical distortion followed by localization and verification of the chemically modified base (Missura *et al.,* 2001). This two-step process results in the excision of the damaged oligonucleotide. The core NER reaction has been reconstituted with purified proteins, which has lead to considerable progress in our understanding of the biochemical basis of the pathway (Singleton & Sainsbur, 2006). The steps involved in NER are the recognition of damaged residues and bubble formation, dual incision of the damaged DNA strand 5’ and 3’ to the lesion, release of an oligonucleotide 24–32 nucleotides in length containing the damage, and repair synthesis and ligation of the resulting gap. About 30 proteins contribute to NER: XPC-hHR23B, the nine subunits of TFIIH, XPA, the trimeric ssDNA-binding protein RPA, and XPG are involved in damage recognition and bubble formation, the two endonucleases XPG and ERCC1-XPF make the incision 3’ and 5’ to the damage, and the polymerases Pold and Pole, the sliding clamp PCNA, the pentameric clamp loader RFC, and DNAligase I are involved in the repair synthesis and ligation steps. Additional factors have been shown to contribute to NER, but are not required for the core reaction in vitro. The pathway described in the previous

paragraph applies to repair of nontranscribed DNA, which makes up the bulk of genomic DNA. This is also DNA lesion that causes helical distortion is initially recognized by XPC/ hHR23B. b) XPC/hHR23B recruits TFIIH to the lesion and the two helicase subunits of TFIIH, XPB, and XPD cause partial opening of the DNA around the lesion. c) TFIIH attracts XPG and XPA/RPA to the lesion, further DNA opening takes places, and a bubble of about 25 base pairs is formed recognition has been proposed that involves recognition of a helical distortion followed by localization and verification of the chemically modified base (Missura *et al.,* 2001). This two-step process results in the excision of the damaged oligonucleotide. The core NER reaction has been reconstituted with purified proteins, which has lead to considerable progress in our understanding of the biochemical basis of the pathway (Singleton & Sainsbur, 2006). The steps involved in NER are the recognition of damaged residues and bubble formation, dual incision of the damaged DNA strand 5' and 3' to the lesion, release of an oligonucleotide 24–32 nucleotides in length containing the damage, and repair synthesis and ligation of the resulting gap. About 30 proteins contribute to NER: XPC-hHR23B, the nine subunits of TFIIH, XPA, the trimeric ssDNA-binding protein RPA, and XPG are involved in damage recognition and bubble formation, the two endonucleases XPG and ERCC1-XPF make the incision 3' and 5' to the damage, and the polymerases Pold and Pole, the sliding clamp PCNA, the pentameric clamp loader RFC, and DNAligase I are involved in the repair synthesis and ligation steps. Additional factors have been shown to contribute to NER, but are not required for the core reaction in vitro (Araujo *et al*., 2001).

3.4. Mismatch Repair

DNA replication is a highly complex and accurate process with an overall error rate of only 1 in 1010. Replication polymerases introduce about one erroneous nucleotide per 105 nucleotide, and the 3'-5'-proofreading activity associated with polymerases contributes another factor of 100 to the replication fidelity by excising mispaired nucleotides before they are further extended by the polymerase. The remaining factor of 103 is contributed by the mismatch repair (MMR) system, which eliminates base–base mismatches as well as nucleotide deletions and insertions introduced by polymerases (Carell *et al*., 200). MMR is in essence conserved from bacteria to humans, although there are important differences among various organisms. MMR is unique among the DNA repair pathways in that MMR enzymes face the task of identifying one of two chemically unaltered bases in a mispair or loop as aberrant. The manner in which this strand discrimination takes place is one of the most important differences in the MMR systems of prokaryotes and eukaryotes. In E. coli, this discrimination is made possible by methylation of specific sequences of the genomic DNA (Laat *et al.,* 1998). Immediately following replication, only the parental strands, not the daughter strands, are methylated and MMR occurs before methylation of the daughter strand by methyltransferase enzymes. The MMR machinery uses the partially methylated status of the DNA to discriminate between the original template strand and the newly synthesized one. In this situation, the nonmethylated strand is, by definition, the strand carrying the erroneous information and excision always occurs on this strand. Eukaryotes do not have such a straightforward mechanism to discriminate between new and old strands after replication, and the basis for strand discrimination in MMR in eukaryotes is presently unknown. Current models suggest that the MMR machinery is tightly coupled to the replication apparatus and that this connection serves to identify the newly synthesized strand through a replication memory (Henricksen *et al.,* 1995). Much of what we know about MMR was originally discovered in bacteria, and similarities and differences in higher systems were subsequently discovered (Yokoi *et al.,* 2000). The basic features of MMR have been reconstituted in vitro with purified proteins from E. coli. The initiator of MMR is the MutS homodimer, which binds to mismatches and insertion/deletion loops. The affinity of MutS for a given mismatch or loop is to a first approximation proportional to the overall repair rate (Yokoi *et al.,* 2000). After binding to the mismatch, MutS triggers ATP-dependent assembly of the repair some, during which MutS moves away from the mismatch and the MutL homodimer is recruited. MutL is thought to serve as a bridging factor between MutL and MutH, which upon encountering a partially methylated GATC site nicks the newly synthesized strand 5' of the nonmethylated GATC sequence (Sancar and Sancar, 1988). This nick serves as an entry point for helicase I (UvrD) and one of several endonucleases (Exo VII, RecJ, or ExoI), which degrade the nicked strand past the mismatch. The ssDNA thus generated is protected by the single-strand binding protein (SSB), and the gap is filled by DNA polymerase III, while DNA ligase repairs the nick. Consistent with the differing mechanism of strand discrimination, no MutH homologues have been found in eukaryotes. In contrast, three homologues each of MutS (MSH2, MSH3, and MSH6) and MutL (MLH1, MLH3, and PMS2) are involved in MMR in eukaryotes. (PMS2 = post meiotic segregation, named after the phenotype of an MMR-deficient yeast strain.) The homodimeric

MutS initiates bacterial MMR, whereas one of two heterodimers, hMutSa (consisting of MSH2 and MSH6) or MutSb (consisting of MSH3 and MSH6), initiates MMR in eukaryote. MutSa binds to single mismatches and to small insertion/ deletion loops, where as MutSb only binds to insertion/deletion loops of various sizes (Kuraoka *et al.,* 1996).

3.5. **Repair of Double-Strand Breaks**

DSBs can be induced by a number of endogenous and exogenous sources and are necessary or accidental intermediates in a number of cellular transactions. Although DSBs are formed much less frequently than other forms of endogenous damage, the consequences of DSBs can be very severe (Kuraoka *et al.,* 1996). In line with the severity of this form of damage, two independent pathways for the repair of DSBs have evolved. One of these, homologous recombination (HR), is an intrinsically accurate repair pathway that uses extensive regions of DNA homology as coding information. The homologous DNA is usually the sister chromatid and may also be the homologous chromosome. Nonhomologous end joining on the other hand involves the relatively simple coordinated rejoining of the broken DNA ends and uses no or extremely limited regions of homology as a template for repair (Sancar, 1994). This process is not necessarily accurate and deletions of a few nucleotides are often introduced at the site of the DSB. Based on the availability of radiation sensitive mutants in higher and lower eukaryotes, it was initially thought that NHEJ is the predominant or perhaps exclusive pathway for repair of DSBs in higher eukaryotes, including humans, and that HR was predominant in lower eukaryotes, such as the yeast. In general, HR is important for rapidly dividing cells and is particularly important in the S and G2 phases of the cell cycle, during which a sister chromatid is available as a template for HR. NHEJ appears to be more important in quiescent or terminally differentiated cells and in the stages of the cell cycle such as G1 during which a sister chromatid is not available (Elledge *et al.,* 2003). The two pathway fulfill specialized roles in the repair of DSBs. HR is important for meiosis or the repair of DNA interstrand crosslinks, whereas NHEJ is required for the joining of DNA fragments in the generation of diversity in the immune system in V(D)J recombination and telomere maintenance (Missura *et al*., 2001).

3.5.1 Repair by Homologous Recombination

HR is a highly complex pathway that uses an intact homologous DNA molecule as a template to repair a DSB accurately (Kuraoka *et al.,* 1996). The first step in DSB repair by HR is the processing of the ends of the break to generate 3' single stranded tails. These single-stranded tails are then used in the search for a homologous template and in the formation of joint molecules, the central recognition steps in HR. The joint molecules provide a template for repair synthesis. Sealing of the nick following successful synthesis leads to the formation of branched DNA structures called Holliday junctions, in which the two parent DNA duplexes are linked together. The Holliday junctions can migrate along the joined DNA (a process called branch migration) and finally undergo resolution at an appropriate location in the DNA to regenerate two intact copies of duplex DNA. The biochemistry of HR has been studied in some detail in bacteria (Iyer *et al.*, 1996). Most of what we know about HR in eukaryotes originated from the identification of genes involved in the process using yeast genetics. These studies revealed the existence of the RAD52 group of genes that play a central role in HR. Of these, RAD50, MRE11, and XRS2 were shown to be involved in the initial processing of DSBs to form 3' single-stranded ends, whereas RAD51, RAD52, RAD54, RAD55, RAD57, and RAD59 were shown to play a role in the homologous pairing and the strand invasion step (Marnett 2000). HR in higher eukaryotes is mediated by homologues of the yeast RAD52 group of genes, although some additional genes are present. Reconstitution of homologous recombination in eukaryotes has not yet been achieved, but the biochemical roles of some of the proteins involved are emerging and will be discussed here in the order of the steps involved (Nocentini *et al.,* 1997). a) Initial recognition of a DSB may involve binding of the Rad52 protein. Nucleolytic processing of the DNA ends to form 3'- ssDNA overhangs involves the Rad50/Mre11/Nbs1 complex, probably in conjunction with another nuclease. b) The ssDNA ends are bound by the ssDNA-binding protein RPA and with the help of Rad52 and the Rad51 paralogs (Rad51B, C, D and XRCC2, 3), Rad51 is loaded onto the ssDNA to form a nucleoprotein filament. The BRCA2 protein has a role in regulating Rad51 activity and may directly stimulate the formation of the nucleoprotein filament (Sijbers *et al*., 1996).This nucleoprotein filament searches for homologous duplex DNA, and a strand-exchange reaction generates a joint molecule between the damaged and undamaged DNA, a step stimulated by Rad54. c) In a process that is not wellunderstood, DNA polymerases and their associated factors carry out repair synthesis and Holliday junctions are formed. d) Holliday junctions are resolved by endonucleolytic cleavage and rejoining in a reaction that may involve the Mus81 protein and in which two intact DNA molecules are formed (Proc, 1994).

3.5.2. End Binding and Processing

Biochemical and electron-microscopy studies have shown that Rad52 preferentially binds to the ends of DSBs, especially to ends with ssDNA overhangs (Jelinic *et al*., 2017). Although genetic evidence for this role of RAD52 has not yet been obtained, these results suggest that Rad52 may serve as an initial DSB-binding factor and as such may play a role in channeling breaks into the HR rather than the NHEJ pathways. DSBs are subsequently processed by a 5'-3' exonuclease to generate 3' ssDNA overhangs (Elledge *et al.,* 2003).

4. Hereditary Human DNA-Repair-Deficient Disorders

Table 1 Hereditary human DNA-repair-deficient disorders *(*(Nocentini *et al.,* 1997)

S.No	Disease	DNA-repair Affected	Cancer Susceptibility	Symptoms
1	Hereditary breast cancer	RDSB by homologus recombination	Breast, ovarian cancer	Breast, ovarian cancer
2	Xeroderma pigmentosum variant	Nucleotide Excision Repair	Skin carcinoma and Melanoma	Skin & eye photosensitivity
3	Hereditary nonpolyposis colorertal cancer	DNA Mismatch Repair	Colon, Ovary & Endometrium	Early development of tumor

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