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Book Chapter

Role of DNA Repair in Genome Stability, Tumor Prevention, and Main Complications in Case of Repair Failure

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DNA Repair Systems

A preserved genome is essential for the preservation and continuation of life. DNA, however, is known to be an intrinsically reactive molecule and is highly susceptible to chemical modifications from endogenous or exogenous agents; exogenous factors include environmental hazards such as toxic heavy metals and radiation, whereas endogenous factors comprise molecules or reactive species released by cellular metabolism inside the body or after cell damage and the loss of cell membrane integrity [1]. For example, naturally occurring

reactive oxygen species (ROS) inside cells can thus lead to various types of endogenously caused-DNA damage, which can be in the form of deamination, methylation, or oxidation of bases, but also as single- or double-strand breaks. Similarly, exposure to exogenous agents such as ultraviolet (UV) light, ionizing radiation, benzopyrene, or alkylating agents can also lead to the accumulation of various types of lethal DNA lesions [2].

DNA damage caused by either endogenous or exogenous sources can ultimately lead to DNA mutations. Mutations refer to changes in the DNA sequence, which can occur due to either exposure to DNA damaging agents (in this case mutagens) or to errors during DNA replication. Some mutations are beneficial and in fact play an important role in evolution and development of life, while others are associated with diseases, tumorigenesis, and aging. Because the accumulation of mutations can be unfavorable and lead to drastic carcinogenic consequences, cells have evolved complex DNA repair, damage tolerance, cell cycle checkpoints, and cell death pathways to maintain the integrity of the genome [2].

There are several types of mutations, ranging from single base-pair alterations to multi base-pair deletions, insertions, duplications, and inversions [3]. Depending on the type and location of the mutation, the effect can be classified as beneficial, neutral, detrimental, or lethal. However, recent research has shown that several other factors might play a role in determining the effect of a certain mutation, as in the case of “Epistasis” where the effect of a gene mutation is dependent on the presence or absence of other mutations in a manner that the environmental genetic background of such a particular DNA mutation might play a role in changing its effect [4]. Mutations that cause death or reduced life expectancy of individuals are referred to as lethal mutations, as in the case of Tay Sachs disease, where life expectancy is around 4-5 years of age [5].

Preserving one’s genome after such genomic attacks and mutations is thus vital for an organism. For this purpose, the DNA repair machinery efficiently localizes and eliminates DNA

lesions to maintain genomic integrity and stability, and minimize the formation of mutations. The cell cycle includes four different stages and three checkpoints; upon detection of DNA damage, the cell cycle halts, and the DNA damage response (DDR) is activated; depending on the type of lesion, different DNA repair pathways can be initiated. There are at least six major DNA repair pathways, including direct reversal/repair (DR), base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) repair pathways [2,4] (Figure 1). Normally, if the damage is unrepairable, the cell undergoes apoptosis or necrosis [6].

Certain DNA lesions can be directly repaired. The O6-alkylguanine (O6-AG)-DNA methyltransferase (*MGMT*) also known as O6-alkylguanine-DNA alkyltransferase (AGT) can indeed repair DNA damage by removing alkyl groups from thymine or guanine bases without removing the base itself [7]. Other DNA repair pathways include multi-enzyme complexes that work together or sequentially to remove specific types of damaged bases. For example, the BER pathway involves numerous proteins that aid in maintaining genome integrity by repairing small single base DNA lesions caused by DNA alkylation or oxidation [8] including 8oxoGuanine (8oxoG), the most abundant BER substrate, which results from the oxidation of guanine, and if left unrepaired can lead to transversion mutations [9]. The NER pathway plays an important role in repairing UV-induced photoproducts, bulkier DNA lesions such as base adducts created by genotoxic agents like cisplatin, and DNA crosslinks [10]. In these two excision repair pathways, the damaged nucleotide and in some cases the neighboring DNA is excised and replaced with newly synthesized DNA using the normal DNA replication machinery. The MMR pathway plays a role in correcting single base-pair mismatches and misaligned short nucleotide repeats introduced accidentally by the DNA polymerase during DNA replication; if left unrepaired they can lead to point or frameshift mutations [11]. MLH-1, MSH-2, MSH-6, and PMS-2 are the most clinically relevant MMR proteins, which participate in the repair of such errors by excising the DNA harboring the mismatch site and re-

synthesizing the correct DNA. Both HR and NHEJ are DNA repair pathways involved in repairing double-strand breaks (DSB). Proteins encoded by BRCA1, BRCA2, RAD51, and PALB2 genes mediate HR, which functions by resecting part of the DNA sequence around the DSB, after which the homologous sister chromatid is used as a template for the synthesis of the new non-damaged DNA. HR can thus only operate during the S and G2 phases of the cell cycle during which the sister chromatids are present. NHEJ, in contrast, repairs DSBs by directly ligating the loose ends of the DSBs and can therefore function throughout the cell cycle, but is more error-prone [12].

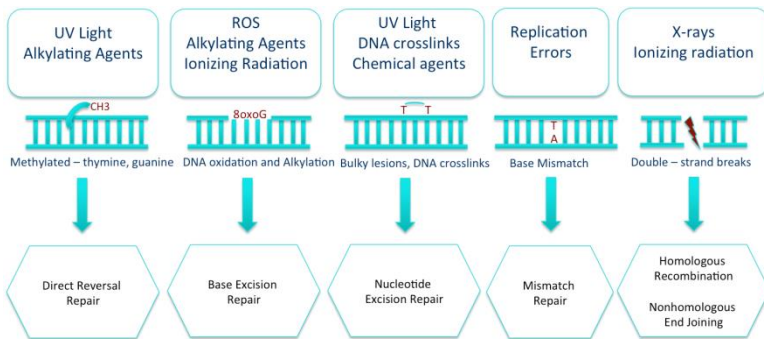


Figure 1: DNA damage and the associated DNA repair pathways.

Defects in DDR Genes and Cancer

Cancer is a disease that develops gradually. According to the mutator phenotype hypothesis, the ability of cancer cells to divide, invade, and metastasize is due to mutations in driver genes that regulate DNA repair and genetic stability. Such mutations result in deficiencies in DNA repair pathways leading to an increased mutation rate; those mutations can take place in other DNA repair genes thereby initiating a cascade of mutations in the genes that maintain genomic stability [13-15]. Eventually, this leads to genomic instability which is believed to be the main cause of tumorigenesis [16-18]. Thus, such deficiencies in DNA repair genes are the hallmark behind genomic and epi-genomic instability in case of cancer development [14].

The cancer cell genome has been shown to include several mutation classes such as substitutions, insertions, or deletions of small or large DNA segments, rearrangements, gene amplifications, copy number reduction, etc [19-22]. Several epigenetic changes that alter both chromatin structure and gene expression have also been identified in cancer cells [23,24]. Furthermore, some cancer cells have acquired exogenous DNA sequences from tumorigenic viruses such as Epstein Barr virus, hepatitis B virus, human T lymphotropic virus-1, and human herpes virus-8 [25].

DNA damage and mutations play an important role in cancer development; this is particularly obvious in case of genetic defects in the DNA repair machinery [26]. For instance, individuals with somatic or inherited germline mutations affecting DNA repair genes typically exhibit an increased risk of developing cancer. In what follows, is a list of the most commonly occurring cancer-related DNA repair defects.

Cancer-Related Defects in HR Genes: BRCA1 and 2 are tumor suppressor genes that control cell growth and differentiation. Besides their role in the regulation of gene expression, they are also known to take part in the repair of DSBs in the HR pathway. Upon HR activation, DSBs are resected into a 3'-single-stranded DNA (ssDNA) overhang, which is directly coated with the high affinity ssDNA-binding protein, RPA. After that, BRCA1, BRCA2, and PALB2 form a crucial network of proteins to mediate the replacement of RPA by RAD51, which is the main effector protein in the subsequent steps of the HR pathway [27,28]. Lung, ovarian, breast, pancreatic, and prostate carcinoma are now known to be associated with mutations in HR genes, particularly BRCA1 and BRCA2 [29-32]. A recent analysis estimated the lifetime risk of developing prostate cancer by age 85 to be 29% and 60% for BRCA1 and BRCA2 carriers, respectively, and that the risk of developing male breast cancer is 18- and 80-fold higher in BRCA1 and BRCA2 carriers, respectively [31,32]. Besides that, it was estimated that breast cancer families with BRCA2 mutations have a 10-fold higher risk of developing pancreatic cancer than families without such mutation [29,34].

Cancer-Related Defects in BER Genes: MUTYH gene encodes for the MYH DNA glycosylase enzyme, a BER protein that functions in repairing oxidative DNA damage resulting from exposure to various carcinogens. In particular, MYH is known to bind the mismatched 8oxoG:A base-pair resulting from misincorporation of adenine opposite 8oxoG during replication of 8oxoG-containing DNA, after which it excises the mismatched adenine, thereby preventing T:A transversion mutations in the following rounds of DNA replication [35]. Somatic and germline MUTYH gene mutations are known to be associated with a high risk of developing polyposis and colorectal cancer [36]. Furthermore, recent studies to understand the role of the mutated MUTYH gene in the development of extracolonic cancer estimated that biallelic MUTYH carriers have a 19- and 17-fold increased risk of developing urinary bladder and ovarian cancer, respectively, compared with the general population, and that monoallelic MUTYH carriers are at increased risk of developing gastric, liver, breast, and endometrial cancer [37]. Another study suggests that monoallelic MUTYH carriers may progress to ovarian cancer if somatic MUTYH mutations co-occur, leading to a homozygous somatic state [38]. Both mutated MUTYH related-cancer types can occur due to the failure of MUTYH driven-BER mechanism in MUTYH-mutated individuals [38].

Cancer-Related Defects in NER Genes: ERCC1 is a multifunctional protein that plays an essential role in the NER pathway. Together with XPF, it forms the structure-specific endonuclease XPF/ERCC1 complex which is known to be essential for repairing various bulky DNA lesions, pyrimidine dimers, DNA crosslinks, and DSBs. ERCC1 has been identified as the most frequently deficient DNA repair protein in non-small-cell lung cancer (NSCLC). Besides that, mammalian cells with mutated ERCC1 and XPF genes develop various genetic disorders, which result from deficient NER pathway, including Xeroderma pigmentosum (XP), trichothiodystrophy (TTD), and Cockayne syndrome (CS) [39-42]. In the same context, studies published by the Cancer Genome Atlas (TCGA) and others, demonstrate that somatic mutations in ERCC2, a DNA helicase

that also plays an important role in NER, were identified in approximately 12% of bladder cancer [43-46].

Cancer-Related Defects in MMR genes: MSH2, MSH6, MLH1, and PMS2 play an essential role in mediating the MMR pathway, which aids in repairing base-base mismatches, insertions, and deletions generated during DNA replication and recombination. Several types of cancer are associated with a deficient MMR pathway, including colorectal, endometrial, gastrointestinal, and ovarian cancers. A deficient MMR pathway is known to occur in 15-20% of colon and 10% of rectal cancers [47-50]. For instance, mutations in MLH1, MSH2, and MSH6 are the cause behind the occurrence of hereditary nonpolyposis colorectal cancer (HNPCC), the latter being characterized by colorectal, endometrial, and other cancer clusters [51,52]. Several studies have also demonstrated the existence of MMR mutations in ovarian cancer, one of which noted that the incidence of germline MMR mutations in ovarian cancer is 2%, while other inactivated gene forms occur in up to 29% of the cases [53-55].

Cancer-Related Defects in DR Genes: As previously mentioned, MGMT functions as an alkyl-acceptor that irreversibly transfers the methyl group from the O⁶-methylguanine and O⁴-methylthymine into its internal acceptor site (the sulfur atom of its active site cysteine), thereby repairing such alkylated adducts. Loss of MGMT function, mainly due to hyper-methylation-mediated silencing of its promoter, or mutation, has been associated with various tumor types, including glioma, gastrointestinal, esophageal, breast, and prostate cancer [56-58]. A recent analysis demonstrated the loss of MGMT protein expression in 44.5% (65/137) of gastrointestinal stromal tumors, with 10.9% (15/137) exhibiting MGMT promoter methylation [57]. Besides that, loss of MGMT protein occurs frequently in esophageal cancer patients from north India, where the absence of such protein is associated with 65% of the cases (52/80), together with a significant hyper-methylation of the MGMT promoter region [58].

Cancer-Related Defects in the tp53 Gene: tp53 is a tumor suppressor gene that encodes for the p53 protein, which in turn plays an important role in protecting the cell from DNA damage. It is a transcription factor that facilitates the DDR by halting the cell cycle to allow for the repair machinery to restore genome stability. It controls genes involved in the regulation of the cell cycle and/or apoptosis [59]. Under normal conditions, it is expressed at low levels; upon detecting DNA lesions, a series of post-translational modifications including phosphorylation and acetylation take place leading to the accumulation and activation of p53. As a transcriptional activator, p53 regulates and activates several genes involved in various DNA repair pathways (NER, BER, MMR, NHEJ, and HR) and induces either cell cycle arrest or apoptosis depending on the extent of DNA damage [59,60]. As such, p53 plays a central role in maintaining genomic integrity. It is thus no surprise that over 50% of human cancers are indeed associated with loss of function p53 mutations [61,62]. Some cancers with p53 mutations are in addition chemo-resistant, which reinforces the critical role of p53 in cancer progression [59].

Cancer-Related Defects in the PTEN Gene: PTEN is also a tumor suppressor gene that encodes for the PTEN (phosphatase and tensin homolog) protein, a lipid phosphatase that plays a major role in the regulation of the phosphatidylinositol 3 kinase (PI3K)/AKT cascade, one of the most important signaling pathways activated in response to DNA damage. PI3K/AKT regulates cell cycle progression, induction of cell death, transcription, translation, stimulation of angiogenesis, and stem cell self-renewal [63-65]. By dephosphorylating phosphoinositide signaling molecules like PIP3, PTEN can inhibit signal transduction [66] and thereby block cell migration and cell-cycle arrest [67,68]. New evidence also suggests that PTEN can regulate DDR factors such as Chk1 and p53, therefore playing an indirect role in maintaining genomic integrity [69]. PTEN loss of function mutations are associated with genetic mutations, epigenetic mutations, and gene silencing mechanisms; this loss of function is present in several cancers such as gastric cancer [70] and breast cancer [71]; loss of PTEN causes the increase in PIP3 levels and the persistent activation of PI3K

effectors which causes uncontrolled cell proliferation, apoptosis resistance, angiogenesis, genomic instability, stem cell self-renewal, cellular senescence, and cell migration [72].

When loss of function in direct or indirect DNA repair proteins occurs, more genomic alterations ranging from point mutations to chromosomal alterations are bound to occur. This is referred to as “genomic instability” [73] and is proving to be one of the major hallmarks of cancer, since it also affects other hallmarks such as oxidative stress, proteotoxic stress, metabolic stress, DNA damage and DNA replication, and mitotic stress [74].

DNA Repair Deficiency Disorders and Increased Risks of Cancer

DNA repair deficiency disorders are caused by germline mutations in DNA repair genes. Several hereditary diseases characterized by genetic defects in DNA repair mechanisms are known to be associated with increased risk of cancer [75]. This is the case of Bloom’s Syndrome, Xeroderma Pigmentosum, Lynch Syndrome, Ataxia telangiectasia, and several other disorders described in this section.

Bloom’s Syndrome (HR-deficient)

Bloom’s syndrome is an autosomal recessive disease that occurs due to a loss of function mutation in BLM [76]. BLM encodes for the RecQ helicase, a DNA helicase that functions in HR repair of DSBs. BLM has also been shown to have a function in the early sensing of DNA damage, where it assembles with p53 and hRAD1 at sites of stalled replication and DSBs. It interacts with several other proteins to promote survival in response to DNA damage, DNA blockage, chromatin remodeling, etc. Thus, BLM has a significant role in maintaining genomic integrity and stability [76,77].

Previous *in vivo* studies have shown that the loss of function of BLM plays a significant role in enhancing the tumorigenesis of both basal cell carcinoma (BCC) (a type of skin cancer) and rhabdomyosarcomas (RMS) [78]. Not only that, but it has also

been demonstrated that any deficiency in the levels of BLM induces hyper-recombination in epithelial cells [79] and promotes tumorigenesis [80]. This evidence further proves that BLM is necessary for maintaining genomic stability.

Xeroderma Pigmentosum (NER-deficient)

Xeroderma pigmentosum (XP) is an autosomal recessive disorder that is characterized by increased sensitivity to sunlight. Individuals with XP present freckle-like pigmentation and lesions in the areas where the skin was exposed to the sunlight. XP patients are at high risk of developing skin cancer, both non-melanoma and melanoma, before the age of 10. XP patients are 10,000 times more likely to develop non-melanoma skin tumors and 2,000 times more likely to have melanoma before the age of 20 as compared to healthy people [81].

The disorder is the consequence of genetic defects in XP repair proteins, the latter being involved in mediating various steps in the NER pathway, thereby leading to a defective NER system. For instance, XP cells are unable to perform unscheduled DNA synthesis (UDS) after UV irradiation. UDS is a part of the NER pathway; it refers to the DNA synthesis that occurs after the removal of the DNA damage during the repair process. There are different classifications of XP; Classical XP (XP-A to XP-G) which is characterized by a deficiency in the removal of DNA damage through NER, and XP-V cells which are characterized by the ability to tolerate DNA lesions by replicating damaged templates through TLS. Due to their inability to remove mutations effectively and their ability to tolerate lesions, XP cells have an increased level of mutagenesis [81,82]. In addition to that, mutagenesis in XP can also be increased due to UV-induced signature mutations in tumor suppressor genes such as p53 [81,83].

Lynch Syndrome (MMR-deficient)

This disease is the most frequent - autosomal dominant - cause of hereditary colorectal cancer. It is caused by a germline mutation in one of the MMR genes (MLH1, MSH2, MSH6, PMS2, and EPCAM), which leads to the loss of function of its protein and thus a defective MMR pathway [49,84]. Lynch

syndrome is known to be associated with a high lifetime risk of developing several types of tumors, including colorectal (20-70%), endometrial (15-70%), gastric (6-13%), and ovarian (4-12%) cancer [49]. Furthermore, its association with increased risk of urothelial carcinoma has been noted as well [85]. A deficient MMR pathway leads to a high mutational incidence in the repetitive DNA sequences, leading to microsatellite instability. It is important to note that 95% of Lynch syndrome-associated cancer present microsatellite instability [85,86].

Ataxia Telangiectasia (NHEJ, HR- deficient)

Ataxia telangiectasia is a single gene autosomal recessive disorder that is characterized by mutations of both alleles of the ATM (ataxia-telangiectasia mutated) gene. The ATM gene codes for the ATM serine/threonine kinase responsible for initiating cell cycle arrest and DNA repair in response to DSBs. ATM is considered to be the main regulator of the DDR as it is responsible for activating several downstream effectors through phosphorylation; those proteins include BRCA1, SMC1, Ch2, etc. ATM is also responsible for the phosphorylation of p53. As such, ATM function is associated with genome integrity [87,88]. Mutations in the ATM gene thus inevitably affect the DNA repair capacity of cells. In fact, individuals with Ataxia telangiectasia have a 50 to 150-fold increased risk of developing cancer [89].

Other Disorders: Two human syndromes are associated with mutations in genes encoding DNA helicases that play important roles in HR, NHEJ, or excision repair pathways. When mutated, these genes lead to a defective repair mechanism [90-95]. Werner Syndrome is an autosomal recessive disorder resulting from an inherited mutation in the WRN gene, which encodes for the WRN ATP-dependent helicase, a member of the RecQ helicase family, while Rothmund Thomson syndrome results from a germline mutation in the RECQL4 gene. Fanconi anemia is another autosomal recessive disorder resulting from a mutation in FA genes, the latter being involved in the HR pathway [96]. These three syndromes with different deficiencies in DNA repair pathways are also associated with increased risks of developing cancer [97-101].

DNA Repair and Cancer: The Link

Perhaps the best way to study the role of DNA repair pathways in tumorigenesis is to investigate the molecular bases of inherited genetic disorders associated with defects in genes encoding DNA repair factors. Many of these defects have indeed been shown to favor cancer development. In recent years, this relationship between DNA repair and cancer has gained a lot of attention, notably with the finding that defects in the MMR are the cause of hereditary non-polyposis colorectal cancer (HNPCC) and enhance cancer development [102]. However, recent studies have also revealed the complexity of this relationship. Depending on the disease stage and the DNA repair pathway, defects in DNA repair factors may either increase or decrease the rate of survival. Mutations in DNA repair genes can thus be considered as double-edged swords in the context of radio- and chemotherapy [103]. In the future, a better understanding of the molecular mechanisms underlying the functions of the DNA repair machinery will certainly facilitate the development of more targeted and personalized anti-cancer treatments to overcome these difficulties.

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