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Review Article
Role of DNA Repair Deficiency in Cancer Development

Alaa Saud Alhegaili

Department of Medical Laboratory Sciences, Prince Sattam bin Abdulaziz University, P.O. Box 422, Al-Kharj 11942, Kingdom of Saudi Arabia

Abstract

The DNA is constantly under attack from endogenous and exogenous damaging agents. The damaged DNA must be repaired quickly to avoid genomic instability and to prevent the occurrence of a malignant transformation. Once a lesion is detected, the DNA repair mechanism initiates and replaces the structurally altered base or any other abnormality. The cell repair mechanisms include direct reversal, excision repair (base excision repair [BER] and nucleotide excision repair [NER]), mismatch repair (MMR), homologous recombination repair (HR) and non-homologous end joining (NHEJ). Unrepaired DNA could lead to mutation, cell death or cancer. This review will discuss how the defects in DNA repair play a vital role in cancer initiation, development and progression.

Key words: DNA repair, DNA damage, cancer, genetic testing, treatment

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Corresponding Author: Alaa Saud Alhegaili, Department of Medical Laboratory Sciences, Prince Sattam bin Abdulaziz University, P.O. Box 422, Al-Kharj 11942, Kingdom of Saudi Arabia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Multiple external and internal genotoxicants constantly introduce genomic and mitochondrial DNA compounds to their potentially harmful effects. The DNA damage is caused by many endogenous sources, such as reactive oxygen species (ROS). Endogenous DNA damage occurs because of normal cellular metabolism, leading to DNA base modifications, such as oxidation and alkylation or sites of base losses. In addition, there are numerous exogenous factors, such as exposure to chemicals or UV light and ionizing radiation. All these damaging agents introduce modifications to the DNA, which may subsequently lead to mutation, cell death or cancer[1,2]. As a result, creatures developed a protective mechanism called the DNA repair pathway. Whenever the DNA repair system is ineffective, DNA defects and abnormalities are produced, which turn into carcinogens. Furthermore, a tendency to metastasis was thought to be associated with high DNA repair genetic alterations. The likelihood of DNA repair must be considered when using chemotherapy and radiation therapy[3]. The DNA lesions that result in an abnormal base or nucleotide section can cause either one or both DNA strand segments to break. Mutations are more likely to occur when DNA is damaged. Genetic susceptibility is one of the most important factors influencing the spread of cancer. The DNA repair processes protect genomic integrity, which is crucial in mending DNA lesions caused by carcinogens or substances that damage DNA. Ineffective DNA repair plays a key role in cancer initiation, growth and transformation. Improved treatment intervention will be possible if DNA repair processes in the tumor are thoroughly understood. The connection involving DNA repair processes and cancer will be covered in this paper.

Xeroderma pigmentosum (XP): Skin cancer risk and dermatological, ophthalmic and neurological symptoms are all features of the autosomal recessive syndrome known as XP. Patients typically have an excessive amount of lentigines (freckle-like coloring) in sun-exposed regions by age two, a skin feature diagnostic of XP[4]. In 50% of cases, patients present with significant sun allergy that results in intense sun exposure[5-7]. Atrophic skin, colored seborrheic warty lesions and telangiectasias are all associated with higher sunlight exposure and the absence of sun protection. The PDF and XPG mutant patients exhibit extreme light absorption in younger years[8]. Ocular defects restricted to Ultraviolet light regions, such as the eyelids, retina and cornea, are relatively common with photophobia. Patients having XPC are particularly vulnerable to eye injury, including acute keratitis, opacification and vasculature. Progressive neuronal death affects about one-third of individuals, having the XPA groups thought to be the most seriously impacted[5].

Clinical manifestations can range from cognitive incapacity, motor deficits and blatant quadriparesis to as modest as the absence of superficial muscle responses and increased-frequency sensorineural deafness[9]. Basal cell and aggressive squamous-cell carcinomas are anticipated to be 10,000 times more common in patients with XP than in the general population, with a median start age of 10 years[10-12]. A 2,000-fold increase in the likelihood of carcinoma has been predicted with a 20 years average starting duration. Surprisingly, the moderate XP collective variants known as XPC, XPE and XPV that only cause minimal light absorption and no neurological problems exhibit the greatest penetrance for malignancies[13]. This is believed to be the outcome of accelerated UV harm buildup without sun exposure in this clinical setting, which delayed treatment because they lacked explicit skin abnormalities. Different types of cancers, such as myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and brain and spinal cord tumors, have been reported in XP patients[14-16]. Interestingly, XP-related skin cancers and MDS/AML have a higher incidence of del5q and del7q karyotype changes, which are connected ith TP53 somatic mutations[14,17]. The wide range of phenotypes observed in XP indicates structural NER deficiencies. The NER mechanism, controlled by 30 enzymes, recognizes and eliminates ultraviolet-induced cyclobutene pyrimidine dimers (CPD) and 6-4 pyrimidine-primidone through two sub-branches called universal genetic restoration and transcription-integrated repair[18,19]. Whereas transcription-coupled repair detects degradation on the produced strand utilizing NER enzymes: Cockayne syndrome A and B, universal genome repair depends on XPC and XPE to detect DNA breaks. The XPD and XPB helicase-consisting transcribed the convergence of both sub-pathways bringing in complexes to unfold injured DNA. This enables XPA to stabilize single-strand DNA before endonucleases XPF/ERCC1, XPG cut away the damaged DNA section and reproduction polymerases replace it. The TXPV/POLH reproduces previously damaged Ultraviolent-induced thymine adducts or AP spots throughout the translesion formation[20].

Ataxia-telangiectasia (AT): Ataxia secondary to neurological deterioration, telangiectasias, immunodeficiency with recurring respiratory diseases, early ageing, ultraviolet exposure sensitivity and a heightened chance of getting malignancies of the lymphoid source are all features of AT, a multi-systemic illness[21,22]. Between the ages of 1 and 4 is when

AT typically first manifests, with instability showing up as an aberrant walking pattern in a youngster who had experienced healthy growth. In addition to extrapyramidal signs, common neurological clinical manifestations comprise dysarthria, decreased motor function synchronization, impairment of fine motor abilities, development of sensorimotor deficits and dysarthria. By their second decade of life, the majority of patients use wheelchairs. Telangiectasias are the second most prevalent trait, with a mean beginning between the ages of 5-8[23]. They typically affect the bulbar cornea but can also affect the forehead and ears, which are subjected to sunlight. Ocular telangiectasias ought to be distinguished from physiologic ocular vasculature since they are permanent and do not change with the seasons or the passage of time. Another noticeable characteristic of two-third of AT patients is immunodeficiency, which is shown by a failure of immunological response to vaccinations, reduced populations of B and T cells and diminished synthesis of at least one immunoglobulin subtype. It should be noted that a small percentage of AT patients have increased IgM contemporaneous with IgA or IgG deficit, hence, caution should be exercised to avoid misdiagnosing these patients as having hyper-IgM disease[24].

The primary reasons for sinopulmonary diseases and a higher propensity of autoimmune or inflammatory disorders, including ITP, cutaneous granulomatous syndrome and vitiligo, include immunodeficiency and immunological imbalance. Diabetes with insulin resistance, poor growth, gonadal loss and early pubertal development are other prevalent endocrine conditions[25]. In 25% of AT patients, cancer and respiratory failure is the leading cause of mortality in the second or third decade of life. Most of these cancers are lymphoid-related and AT patients younger than 20 have an increased risk of developing B-cell NHL, Hodgkin lymphoma (HL) and other cancers[26]. Surprisingly, EBV disease was discovered to be connected to every occurrence of HL and 50% of instances of NHL. There have been reports of other carcinomas involving liver, stomach and brain tumors[26]. Despite the earlier controversy, breast cancer has become recognized as a type of tumor, with AT patients having a 30-fold higher likelihood of developing it. According to a theory that links genetic dosage to cancer development, people who have typical AT and are deficient in ATM kinase functioning have a greater chance of developing lymphoid malignancies than people who still have considerable AT tasks[27].

Bloom syndrome (BS): Some clinical signs of BS are development loss, a sun-sensitive skin rash, hormonal issues and immunosuppression. The BS newborns have a normal look but are undersized for their gestational age and some have eating problems that prevent them from thriving[28]. Ultraviolet light cutaneous rashes, including hypopigmented macules, telangiectasia erythema of the forearms and butterfly rash on the forehead, are among the most common symptoms in infants and young infants children[29]. Immune deficiency manifests itself clinically as recurring respiratory tracts and gastrointestinal diseases resulting from dysregulated T cells and hypogammaglobulinemia[30]. Acute, long-term lung illness is a frequent BS consequence that is thought to be related to recurring respiratory conditions brought on by immunosuppression. Identified endocrine sequelae that age- relatedly emerge in BS patients include insulin sensitivity, type 2 diabetes, dyslipidemia, hypothyroidism, decreased fertility and low social standing[31]. Neurologically, most BS patients possess average IQ and relatively limited instances of moderate cognitive impairment have been described. At least a third of BS patients will develop a carcinoma by age 25 and 80% will be diagnosed by age 40, which is equivalent to the pattern of malignancies in the general population, but at onset in adolescence. Among the 144 BS patients, 223 malignancies were documented. The most frequent hematological malignancies were AML, which typically occurs at an average age of eighteen years and malignancies, which usually occur at an average age of twenty years[32,33].

Base excision repair (BER): Base excision repair, a critical DNA repair mechanism, is utilized to repair DNA damage brought on by oxidative, alkylating and deamination processes. The two most often employed techniques by which BER initiates DNA damage repair are short patches (repair tract of a particular gene) and extended patches[34]. While long patch BER fixes sections with two or more nucleotides, short patch BER fixes regions with a single nucleotide. Without the four components of DNA glycosylase, AP endonuclease, DNA polymerase and DNA ligase, the BER process cannot function (Fig. 1). The BER removes uracil generated by cytosine demethylation from the DNA, which is its primary physiological activity.

Additionally, the uracil N-glycosylase (UNG) enzyme is the crucial DNA repair enzyme, which catalyzes the hydrolysis of the N-glycosylic bond to remove the uracil (U) from DNA and initiates the BER pathway[35]. The BER predominantly purges minor, non-helix-distorting nucleotide errors from the chromosome. The DNA repair enzymes that are mono-functional glycosylases, such as uracil-DNA glycosylases (UDGs) and activate the BER mechanism[36].

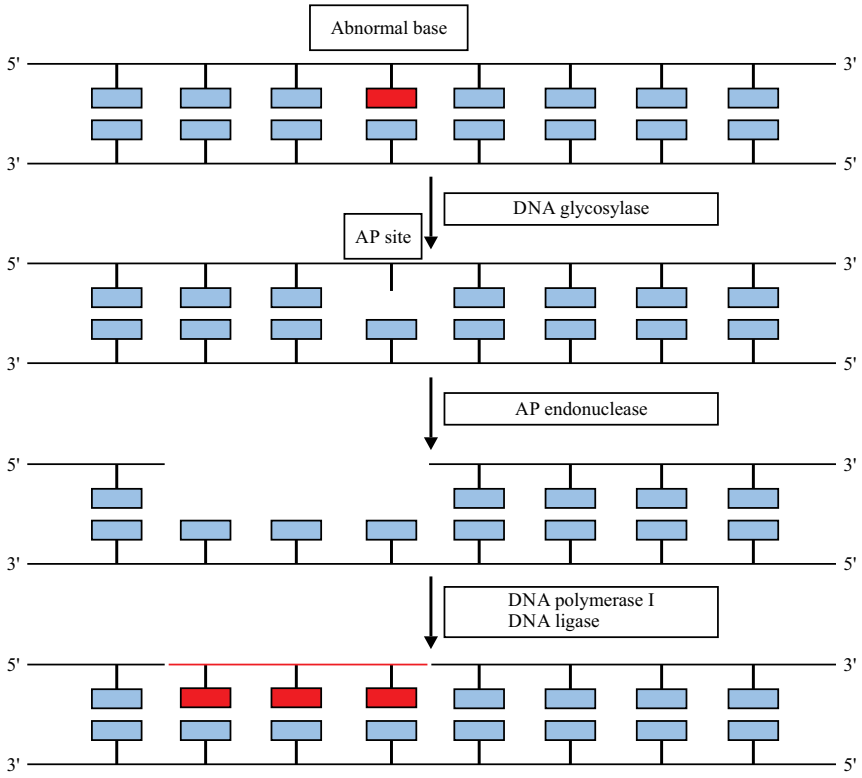

Fig. 1: Base excision repair (BER)

The DNA glycosylases are primarily used in the BER mechanism as the primary molecule to recognize DNA damage and encourage the removal of harmed nucleotides[37]. The abnormal nucleotide flips across the double strand and into the binding region of the enzyme whenever DNA glycosylases connect with the defective nucleotide. The glycosylase breaks the N-glycosidic bridge between the substrate nucleotide and the 2'-deoxyribose to form a protein-substrate complex. The harmed nucleotide is effectively removed during this process, creating an apurinic/apyrimidinic site (AP site). This region that occurs spontaneously or as a result of DNA damage is a specific location in the DNA that lacks a purine or pyrimidine nucleotide. A DNA AP endonuclease or AP lyase cleaves the DNA strand, producing a single-stranded DNA nick 5' to the AP region and a comparable nick 3' to the AP location. The DNA single-nucleotide discrepancy caused by AP endonuclease results in a 3'-hydroxyl, a 5'-phosphate and a brand-new nick. The polymerase plugs the gap in the DNA by introducing the appropriate strands and the mending procedure completes the helical DNA structure, which is then preserved until a DNA ligase shuts the nick. Clears DNA of pre-mutagenic cytosine (C) damage thanks to a human endonuclease III homolog (hNTH1)[38,39]. The 5-hydroxylysine contributes to the BER repair process by considerably raising the possibility that the adenine restoration mechanism results in C-to-T conversion alterations. A higher incidence of C to T transformation mutations has been associated with the cytosine-stable oxidation product 5-hydroxylysine (5-OHC)[40].

Nucleotide excision repair (NER): Intellectual disabilities, eating issues and hearing loss are among the symptoms. These clinical symptoms have been linked primarily to neurodegeneration, but severe growth issues like development impairment and microcephaly have been noted in certain instances. The DSC and XP, in conjunction with Cockayne syndrome (CS) are linked to these more severe conditions and this coupled illness is known as XP/CS[40]. One of the primary DNA repair processes to shield cells from DNA damage which differ in their structural and chemical makeup, is nucleotide excision repair (NER)[41]. The most common damages are caused by hefty covalent compound inclusions that are started by nitrogenous bases. They are also influenced by medicines, ionizing radiation, ultraviolet rays, electrophilic molecular genetic mutations and bioactive molecules that are chemically stable. The NER uses global genomic NER (GG-NER) and transcription-coupled NER to identify DNA damage (TC NER). Any technique for mending damaged DNA must

begin with recognizing the damage. The GG-NER subroute, which corrects both transcribed and untranscribed DNA molecules, identifies structural alterations in the entire genome[42]. The chromosome is continuously searched and any strand distortion will be found. When DNA damage impairs NER function and causes ultraviolet vulnerability and an increased prevalence of cancer, such as in xeroderma pigmentosum (XP), Cockayne syndrome (CS), neurological abnormalities and trichothiodystrophy (TTD), the TC-NER subroute is activated[38,43]. Upon determining the harm, NER is triggered to control the extent of DNA repair. If double-stranded DNA (dsDNA) appears in the genetic material, it disturbs the integrity of the genetic code and activates the NER mending process. The BER repairing mechanism substitutes NER materials for double-stranded DNA (dsDNA) when there has been significant damage to the structural system of the latter. To start NER substrates, sensitive detection is necessary to confirm breakage.

In contrast to BER, the individual specialized glycosylase essential for NER for every step simultaneously identify and remove the altered nucleotides. Additionally, many proteins are attracted to the broken structures with atypical makeup and participate in a multi-step mechanism in the NER identification of DNA abnormalities. The NER endonucleases are in charge of removing damaged segments once the pre-incision compound has been formed. The Xeroderma pigmentosum group C proteins (XPC) that are critical for detecting DNA damage and initiating the NER mechanism are the subject of much research. According to the analysis of the harmed bases, XPA and its compounds comprising RPA and XPC are among the additional elements that are thought to be harmful detectors. In the lack of XPC in cells, XPA is incapable of attaching to the defective spot in the DNA, according to research using confocal microscopy. This suggested that XPC may become inactive following UV-induced. According to molecular investigations, XPC is crucial for activating additional components required for the GG-NER pathway[44].

Mismatch repair (MMR): A method known as DNA mismatch repair is used to find and fix erroneous nucleotide insertions, deletions and integration which may happen during DNA replication and recombination. In rare cases, DNA mismatch repair is also used to repair DNA damage. Multiphase cancer results from MMR faults, which also increase the possibility of spontaneous mutations. Additionally, the MMR can fix DNA mismatches made during DNA replication. The MMR system protects cellular divisions from irreversible mutations. As a result, any MMR defect will increase the incidence of unwanted mutations[45]. The MMR is in charge of reducing the number of replications linked to defects. Most inherited or acquired cancers in humans are connected to the suppression of MMR in the cells. The MMR system must be activated for cell cycle inhibition and induced death in response to specific DNA breakage. Thus, MMR plays a significant function in the DNA damage reaction system to eliminate the destroyed cells and reduce both short-term mutagenesis and lengthy carcinogenesis. Most microsatellites (MS) are found in substantial and inherited cancers[13]. Microsatellite instability (MSI) is a hypermutator genetic marker that appears in several cancers, including stomach, urinary tract, ovarian, endometriosis, glioblastomas, lymphomas and the common inherited nonpolyposis colorectal cancer syndrome due to defects in the mismatch repair (MMR) compound. Genomic disruption leads to aneuploidy cells and aberrant chromosome structure due to increased chromosomal missegregation during mitosis. Micronuclei will consequently form in the cells as a symptom of DNA damage.

Human Exonuclease 1(hExo1) is a protein linked to MMR and it safeguards genomic stability by destroying DNA intermediates through nucleolytic cleavage. The hExo1 enzyme is a part of numerous DNA repair procedures and is a member of the exonuclease and endonuclease family that is particularly adept at working with 5' structures. The dominant exonuclease becomes active as a result of MMR. Additionally, MMR assists in eliminating the damaged DNA during Double-Strand Break Repair (DSBR). Furthermore, hExo1 is necessary to induce telomere fusion in transcription-induced telomeric complexes[36].

Genetic testing: As a component of the preliminary clinical assessment for a patient with a potential DNA repair disease that depends on the clinical symptoms and background of associated cancers, it has emerged as common practice to conduct genomic information. The differential diagnosis and, consequently, the gene expression needing additional research might be guided by the patient's medical presentation and the outcomes of functionality testing[46]. Given that these disorders are uncommon, genetic testing of people who come with a relevant tumor but no other clinical indications of a DNA repair disease is uncertain to provide a significant result[47]. Nevertheless, more research is necessary to diagnose DNA repair disorders accurately in people with associated malignancies. When conducting genetic screening, it's essential to consider the source of the sample, the definitive genetic test and any technical challenges that prevent the finding of mutations. First, peripheral blood or saliva is the most straightforward and often-used sampling source.

In contrast, the suggested germ line sample for people with advanced hematologic malignancies is skin fibroblasts or hair follicles. Specific gene testing may be a rapid technique when a certain gene is anticipated based on phenotype. A disease-specific multiple gene board is a cost-effective technique for patients with clinical traits consistent with several DNA repair defects. Clinical full exome or genotyping, frequently used after the revelation of negative results from targeted gene testing, is the current comprehensive technology.

Effects of chemotherapy or radiation in cancer treatments: By causing severe DNA damage, like DSBs, cancer chemotherapy and radiotherapy are intended to trigger apoptosis in cancer cells. Conventional treatment approaches have been devised depending on the DNA damage response characteristics of cancerous cells, which frequently exhibit unique aberrations in the process. Whenever the harm is detected and incorrectly repaired by an internal DNA repair mechanism, the aberrant expression of a specific DDR protein can be employed as an indicator of treatment failure.

Chemotherapeutic drugs cause immunogenic cell damage, apoptosis and other non-apoptotic modes of death like maturity, mitotic crisis and atrophy to cause DNA damage and cancerous cell death[3]. The immune-stimulatory effects of radiotherapy, including immune-stimulatory cell damage, inflammatory responses and the migration of T cells toward the tumor environment, are typical of this treatment. Tumor cells lyse as a result of radiotherapy and T-cells and dendritic cells are drawn to tumor-related antigens, which causes an anti-tumor therapy. In addition to ovarian failure (which can lead to fertility problems and sexual problems), excess weight, decreased bone, neurotoxicity, neurocognitive abnormalities, heart damage and recurrent tumor, exposure to chemotherapy can also lead to some premature and late protracted problems.

The level of well-being and a general health condition could mean both declines due to these impacts. It is crucial to comprehend such chemotherapy-associated side effects[28,36]. While damaging chemotherapy's implications on healthy bystander cells have received much attention, the precise impacts of therapies on tumor genes are as significant. Genomic instability can increase if DNA defects (genetic changes and genomic errors) induced into tumor cells continue to exist. Radiotherapy is often anticipated to have comparable results. Therefore, additional research is required to comprehend the protracted effects of chemotherapy and radiotherapy. Both healthy bystander and cancerous cells are capable of harboring DNA damage and disrepair, which can result in clonal evolution with other invasive traits. Among these anomalies is the development of aberrant nuclear entities known as micronuclei.

Treatment strategies: Oversensitivity to DNA-damaging chemicals, like radiation treatment utilized to kill cancerous cells, is a common trait in most DNA repair diseases. Furthermore, patients with DNA repair disorders are in greater danger of therapy-linked side effects due to the hereditary defect in repair pathway genes that underlie this condition. Due to this, special cancer care plans are created that frequently use moderate-intensity medications to manage toxicity caused by radiation treatment or chemotherapy while reaching diagnostic results which are on a level with the norm. Troublesome is the rapid prevalence of secondary cancers and treatment failures, particularly in individuals with CMMRD, NBS and AT. The impact of HSCT on patients with AT's general prognosis is still up for debate[48]. Emerging medications that target DNA repair pathways are being tested in numerous clinical testing to treat DNA repair disorder-related cancer patients effectively while limiting side effects. The usual precautions taken to prevent direct effects include reducing radiomimetic drugs like bleomycin and dactinomycin and being aware of the potential for hemorrhagic cystitis brought on by cyclophosphamide and ifosfamide happening in patients who are prone to telangiectasias[49]. The DNA repair diseases benefit from reduced strength conditioning-based transplantation of hematopoietic stem cells due to their frequent immunosuppressive symptoms and higher risk for tumors[50].

CONCLUSION

The importance of the DNA repair mechanism across the entire cancer growth life cycle. On the one side, its reasonably low possibility encourages joining the cancer process due to its ineffectiveness in eliminating DNA damage caused by carcinogens. Additionally, pro- and anti-carcinogenic effects of DNA repair were proposed depending on the level of cancer development. There is a definite dual impact of DNA repair on radiotherapy and chemotherapy. Therefore, the identical DNA repair pathway increases danger or decreases lifespan depending on the disease state. Luckily, thorough research produced techniques to control threats at every level.

SIGNIFICANCE STATEMENT

The association of DNA repair and its disorders with cancer initiation and progression. Endogenous and exogenous damaging agents such as oxidation and UV light constantly attack DNA and the damaged DNA must be repaired quickly to avoid compromising genomic integrity, leading to genomic instability, apoptosis, senescence and cancer. It was reported that around 80 % of all human cancers could be correlated to unrepaired DNA. Therefore a better understanding of the consequences of the compromised DNA repair pathways, repair disorders and their contribution to different diseases will improve cancer diagnosis and treatment.

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