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Review

DNA repair mechanisms: DNA repair defects and related diseases

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ABSTRACT

The deoxyribonucleic acid (DNA) of living organisms is damaged by exogenous and endogenous agents. These damages are repaired by a series of repair mechanisms. These repair mechanisms function both directly and indirectly. Photoreactivation, repair by O6-methylguanine-DNA-methyltransferase, base-excision repair, nucleotide-excision repair, DNA double-strand break repair, homologous recombination repair, non-homologous end-joining, and mismatch repair are some examples of these mechanisms. Many damages, such as DNA strand breakage in the genome and base-base mismatches during replication, are repaired by various repair systems. There are some anomalies and disorders that develop when damage cannot be repaired or when the repair processes are impaired. These include xeroderma pigmentosum, Cockayne syndrome, Bloom syndrome, Werner syndrome, Huntington's disease, ataxia-telangiectasia, Nijmegen breakage syndrome, and Fanconi anemia. The functioning of DNA repair systems and the diseases caused by their defects are discussed in this review.

Keywords: Base excision repair, cockayne syndrome, DNA repair, homologous recombination, nucleotide excision repair, xeroderma pigmentosum.

The fundamental purpose of life is the transmission of genetic material from generation to generation without degradation or alteration.[1] It is critical for living organisms to preserve genomic sequence information in order to continue their generations. There are, however, several agents that can alter the lives of living organisms, generate disease states, and damage deoxyribonucleic acid (DNA).[2]

The cytotoxic and mutagenic effects of DNA-damaging substances pose a persistent threat to cells. These agents include different substances found in foods or as airborne and waterborne agents, such as ultraviolet (UV) rays and ionizing radiation (IR).[3] Environmental factors such as UV radiation, X-rays, and chemical compounds induce various DNA damage to endanger the integrity and existence of human genomic DNA. Examples of DNA damage include double and single chain breaks, insertions and deletions, abasic sites, and DNA-protein cross-link formation.[4]

Endogenous and external factors contribute to the stability of human genomic DNA.[5] Endogenous factors include spontaneous DNA mutations, reactive oxygen species (ROS) and lipid peroxidation products, endogenous alkylation agents, estrogen and cholesterol metabolites, and reactive carbonyl species generated as a byproduct of cellular metabolism.[3,5] While ROS produced as a result of exposure to UV light or IR might be helpful for intercellular communication, an excessive accumulation can cause a variety of diseases. This condition is frequently related to DNA damage.[6] Exogenous factors include UV light, ionizing radiation, heavy metals, air pollution, cigarette smoke, and chemotherapy drugs.[5] Every day, approximately 10,000 lesions accumulate in the DNA of each cell. This damaged DNA must be removed or repaired in order for the DNA code to be correctly read.[7,8] Cells have developed a variety of DNA repair mechanisms to maintain the integrity and stability of genomic DNA over time in order to resist DNA damage from both endogenous and external causes.[9] Due to the numerous different types of damage, a single mechanism cannot deal with them all. Therefore, each repair system has a distinct

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function, a spectrum of damage that it can detect and repair.[7]

The repair of more complex lesions is regulated by the DNA damage response (DDR). It is regarded to be an effective repair for difficult-to-treat lesions.[8] The genome, which has a complex network of DDR systems, includes a set of DNA repair mechanisms, damage tolerance processes, and cell-cycle checkpoint pathways to deal with damage issues. A functional DDR is crucial for human health. Hereditary defects in DDR factors, cause a variety of diseases that have substantial effects such as immunological insufficiency, neurological degeneration, accelerated aging, and a high risk of cancer. These DNA repair systems, each with its unique damage specificity, serve as the foundation of cellular defense against DNA lesions. As a result of their collaboration, they will be able to erase the great majority of injuries from the DNA.[10]

Repair mechanisms can occur either directly or indirectly. Direct repair occurs in two ways photoreactivation and repair by O6-methylguanine-DNA-methyltransf erase (MGMT). Indirect repair includes base-excision repair (BER), nucleotide-excision repair (NER), DNA double-strand break (DSB) repair, homologous recombination (HR) repair, non-homologous end-joining (NHEJ), and mismatch repair (MMR).[5,9]

DIRECT REPAIR

Photoreactivation

Kelner[11] and Dulbecco[12] of Cold Spring Harbor Laboratory by chance found a DNA repair mechanism. They found abnormal survival rates when cells and bacteriophages (viruses that infect bacteria) were accidentally exposed to long wavelengths of light while utilizing UV radiation as an experimental tool at their University lab. These findings led to the discovery of photoreactivation, which is the repair of DNA damage caused by UV light exposure by a light-dependent enzyme reaction.[13] The enzyme photolyase removes lesions of DNA damaged by UV-induced cyclobutane pyrimidine dimers and photoproducts in this system.[14] Although the photoreactivation repair mechanism is prevalent in bacteria, fungi, plants, and most vertebrates, it is not considered a universal repair system since it is absent in other eukaryotic species, including humans.[5]

O6-Methylguanine-DNA Methyltransferase

A protein called MGMT, which is involved in DNA repair, reverses the damage caused by protecting cells from the toxic effects of methylation and chloroethylation agents.[15] After the protein is separated from the repaired DNA, the enzyme caused by the catalytic event is inactivated and is therefore referred to as the MGMT suicide enzyme.[16] It has been demonstrated that MGMT binds to the estrogen receptor and influences growth rate. It is also assumed that high levels of MGMT expression inhibit stem cell proliferation, but no research has been done on this.[15] High levels of MGMT in tumor cells are frequently regarded as a significant factor since they represent therapeutic resistance to alkylating drugs. When MGMT was depleted in tumors, cells became vulnerable to alkylating agents, making this protein a therapeutic target.[17]

INDIRECT REPAIR

Base-excision repair

Endogenous-induced DNA damage, such as oxidative stress, hydrolysis, or deamination, is removed by BER.[18] This repair process is also in charge of repairing DNA single-strand breaks caused by ROS-induced blocked termini.[19] Bases with simple chemical alterations that do not significantly impair the DNA double-helix structure are BER substrates.[10] The base-excision repair mechanism has four major steps: Damages or groups of lesions are targeted by lesion-specific DNA glycosylases, which recognize the damaged base and remove it from the sugar-phosphate backbone. The resulting abasic region is subsequently removed by apurinic/apyrimidinic (AP)-endonucleases and filled with BER-specific DNA polymerase (Pol)-beta (β) by processing the base area to leave a single nucleotide cavity. It is finally sealed by a DNA ligase complex.[9,10] A single nucleotide exchange occurs in the short-patch (SP) BER pathway, whereas the nucleotide cutting and removal process occur in the long-patch (LP) BER pathway in the mechanism with two distinct sub-pathways. Repair is initiated in the first step of both by single-function (such as uracil-DNA

glycosylase and N-methylpurine-DNA glycosylase) or multifunctional DNA glycosylase (8-oxoguanine DNA glycosylase, mutY homolog, etc.) that are specific to the error.[5] Proliferating cell nuclear antigen (PCNA) and Flap endonuclease 1 (Fen1) cut off the damaged area.[6] In the SP-BER pathway, the gaps are filled by DNA Pol-β, but in the LP-BER pathway, they are filled by Pol-epsilon (ε) or Pol-delta (δ). As illustrated in Figure 1, the SP-BER ligation process is carried out by the XRCC1 and ligase III complexes, whereas the LP-BER is carried out by PCNA and ligase I enzymes.[5,6]

Nucleotide-excision repair

The nucleotide-excision repair mechanism is involved in the repair of the damaged helix structure of double-stranded DNA, particularly in the repair of UV radiation damage and damage caused by induced pyrimidine dimers or mutagenic agents.[5,9] Humans and most other eukaryotic animals have NER systems. Despite having different amino acid sequences from prokaryotic species, the proteins involved in eukaryotic NER perform similar functions.[14]

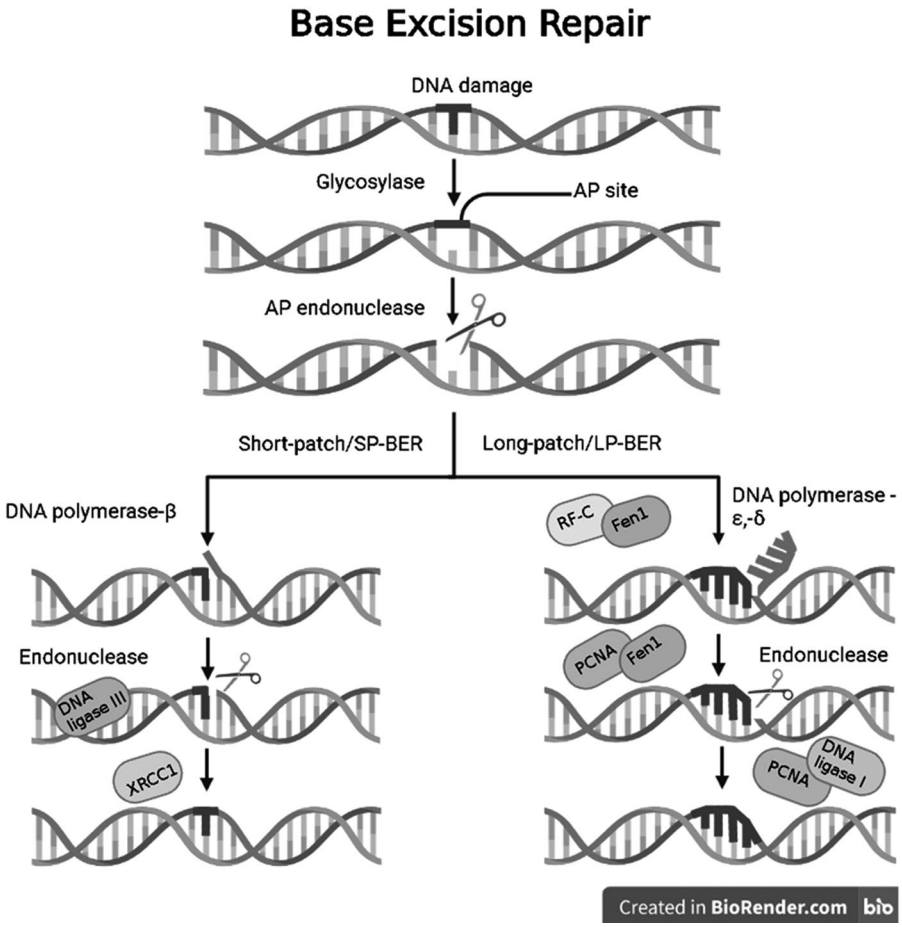

Figure 1. Schematic representation of BER mechanism. Base-excision repair consists of two main pathways; SP-BER and LP-BER. DNA glycosylase recognizes damaged lesions. The AP endonuclease cleaves the damaged base. Followed by gap-filling step in SP-BER is executed by Pol-ß and X-ray repair cross-complementing protein 1 (XRCC1). For Long-patch BER, the gap filling and strand displacement are performed by Pol-ε, Pol-δ, PCNA, and Fen1. The last ligation step is carried out by DNA ligase III and XRCC1 in SP-BER. In LP-BER, the ligation step is completed by DNA ligase I and PCNA.

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In contrast to the BER pathway, the NER pathway is more complex. A specific nuclease activity called excision nuclease participates in NER. This enzyme creates double incisions across the damaged thread of the DNA lesion to form fragments that are 12-13 nucleotides long in prokaryotes and 24-32 nucleotides long in eukaryotes. The damaged DNA is therefore separated from the oligonucleotide structure for removal. DNA polymerases properly fill the resultant cavity, and ligation completes the process.[4,9,16]

Global genome (GG)-NER and transcription-coupled (TC)-NER are the two subpathways of NER. The pathways are shown in Figure 2.[5,18]

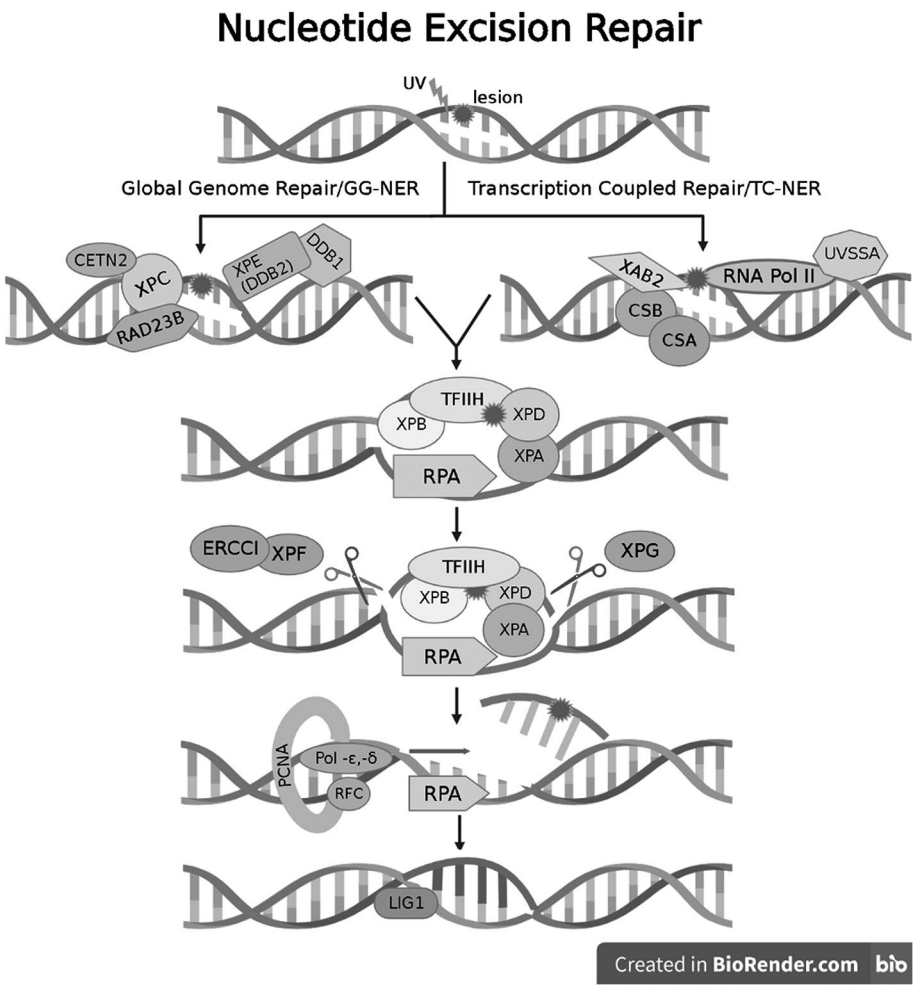

Figure 2. Schematic representation of NER mechanism which can be specified into two subpathways, GG-NER and TC-NER. Xeroderma pigmentosum (XP) complementation group E protein (XPE/DDB2) and DDB1 initiate the recognition of the damage. The Cockayne syndrome (CS) groups B and A (CSB, CSA) proteins are required to initiate the TC-NER process. Regardless of the damage recognition mechanisms, the downstream events are conserved in both NER mechanisms. Helix unwinding is carried out by TFIIH (complex with the XPB and XPD helicases). The lesion is interrupted by XPF and XPG endonucleases. XPF-excision repair cross-complementation group 1 (ERCC1), is directed to the damage by replication protein A (RPA) and makes a strand break, and XPG then makes a cut on the opposite side to the damage. The PCNA is loaded onto XPF-ERCC1 and recruits DNA Pol δ/ε to fulfill the gap and DNA ligase I or III seals the nick.
These figures were drawn using BioRender.

The only difference between the GG-NER and TC-NER mechanisms is the point at which damage is recognized. While GG-NER identifies and eliminates DNA damage from the genome, TC-NER repairs genes.[5] Only the UvrABC endonuclease system, which is used by bacteria and some archaea, is involved in the detection and removal of DNA lesions in the prokaryotic NER system.[14,20]

In GG-NER, the initial-stage repair response begins with the identification of DNA lesions by UvrA, whereas in TC-NER, it begins with the termination of ribonucleic acid (RNA) polymerase. When RNA polymerase encounters DNA damage during transcription, polymerase stalling. The stalled RNA polymerase is released from the DNA and replaced with UvrA by the transcription-repair coupling factor, and subsequent events proceed as in GG-NER.[14]

DNA double-strand break repair

The primary cytotoxic lesion for IR and radiomimetic substances is the DNA double-strand break (DSB), although it can also result from mechanical stress on chromosomes, when a replicative DNA polymerase comes into contact with a DNA single-strand break, or from other types of DNA lesions.[3,21,22] Double-strand breaks induce cell death and chromosome breakage if not repaired appropriately, and chromosome translocation and cancer if repaired improperly.[4,5]

There are two primary mechanisms for repairing DSBs: HR and NHEJ pathways. Both mechanisms are found in eukaryotic cells.[23] Due to the distribution of responsibilities controlled by the cell cycle, various repair systems differ from one another. Since it requires a sister chromatid, HR occurs only in stages S and G2. On the other hand, NHEJ controls the DSBs of cells that are in the G1 phase and after the mitotic phase.[10]

Homologous recombination repair

A homologous DNA sequence, preferably a sister chromatid, is used as a template for error-free repair in HR of DNA DSBs. This occurs during the cell cycle's S and G2 phases.[5] In meiosis I, HR is also critical in maintaining chromosomal distribution, replication forks, and telomeres of meiotic cells, resulting in recombination between homologous chromosomes.[5,24]

The HR process consists of three steps: DNA strand invasion, branch separation, and formation of the Holliday junction. Endonucleases in the structure cleave the Holliday junction into two duplexes, whereas strand invasion and branch separation are triggered by the Rad51 protein in eukaryotes and the RecA protein in prokaryotes. Although Rad52, Rad54, Rad55, Rad57, breast cancer type 1 susceptibility protein 1 (BRCA1), and BRCA2 are all involved in homologous recombination in eukaryotes, the precise roles of these proteins are unknown.[16] Mutations in the BRCA1 and BRCA2 genes, on the other hand, have been linked to breast and ovarian cancer.[4]

The MRN complex, which consists of Mre11/Rad50/Nbs1 proteins and acts as a fracture sensor, detects DSBs in the first stage of HR.[5,16] The MRN complex binds to the DNA around the lesion and cuts it in the 5'-3' direction, functioning as a signal to activate other damage-recognition proteins. The Rad51 protein forms a nucleoprotein filament along a single strand of DNA, and the other intact homologous region of DNA is invaded. The final stage of DNA, which is elongated by DNA polymerase, is completed by ligation.[5] One of the most essential characteristics of HR is that the information lost due to the broken chain can be recovered from the other homologous. Gene transformation occurs when the two chains are not exactly homologous.[16]

Non-homologous end-joining

The NHEJ works for both cells that divide and cells that do not divide independently of the cell cycle, with the G1 phase being the phase where it functions most actively. Non-homologous end-joining regulates and connects the broken ends of two strands of DNA. Unlike the HR system, this repair mechanism performs DNA repair with the deletion of several nucleotides, being aware of the error without the need for an undamaged DNA template.[5] The NHEJ process facilitates mammalian cells' survival after being exposed to damaging agents, even if it produces alterations in breaking points in the DNA sequence and the merging of previously unattached DNA molecules. Although eukaryotes and some prokaryotes have an NHEJ repair pathway, most DSBs are repaired by HR in these organisms.[25]

In humans, heterodimer structures such as Ku70 and Ku80, as well as DNA ligase IV

and the protein complex XRCC4 (DNA repair protein), are critical for NHEJ.[3] The Ku70 and Ku80 heterodimers are activated by attaching to the broken ends of the DNA and act as a bridge for other proteins to reach the site of damage.[2,4] In mice, disruption of the Ku80 gene causes immunodeficiency and chromosomal abnormalities, as well as gamma-ray sensitivity. In mice, disrupting the XRCC4 or DNA ligase IV protein complexes results in embryonic mortality. XRCC4 and ligase IV heterodimeric complex is bound to DNA ends by the Ku complex.[3] The crucial stage of NHEJ involves the physical juxtaposition of DNA ends and the binding of specific proteins to broken ends. Thus, the bridge formed by sequencing the ends side by side can occur via protein-protein interactions between the end binding factors linked to the DNA ends. The activity of the DNA ligase, which is the final to finish the repair process, occurs if the DNA ends lined up adjacent to each other may be connected directly. Since they lack connectable ends, the bulk of DSBs created by exposure to DNA-damaging agents must be processed before ligation.[25]

Mismatch repair system

As long as DNA damage is not repaired, mutations in the body and reproductive cells might arise, resulting in phenotypic abnormalities and disease. Cells have a mechanism called MMR that removes damaged cells and prevents both short-term mutagenesis and long-term tumor growth from preventing such damage and protecting the integrity of the genome.[26] Witkin and Sicurella,[27] and Holliday[28] proposed mismatch repair as a repair mechanism that interrupts the fault-containing chain and then resynthesises the defective DNA strand.[29]

The DNA damage that results during DNA replication is repaired by the MMR, which also guards against irreversible mutations in proliferating cells. According to the types of DNA damage that take place, the MMR is crucial for either causing programmed cell death (apoptosis) response or stopping the cell cycle as a result of a possible error in the cell.[26] The mismatch repair system is dependent on the energy source adenosine triphosphate (ATP).[5]

Inactivation or restriction of MMR might result in several circumstances. Since MMR contributes to a variety of DNA processes, its inactivation can have both positive and negative biological consequences for organisms. The rise in point mutations that occur during DNA synthesis is one example of the results. This mistake in DNA, caused by the lack of MMR function, initiates multi-stage carcinogenesis in mammals.[30]

In humans, at least six different proteins are involved in MMR. To determine the mismatch, the heterodimer structure formed by the MSH2 protein with MSH6 forms MutS-alpha (α), and the heterodimer structure formed by MSH3 forms MutSβ.[5] In the event of a mismatch, the MutS complex recognizes the lesion and attaches to it.[6] MutSα detects base-base mismatches and insertion-deletion mistakes in several nucleotides, while MutSβ can detect insertion-deletion errors in larger forms. The heterodimer complexes formed by MutL-related proteins; MLH1 with PMS2, MLH3, and PMS1 are referred to as hMutL, hMutL, and hMutL, respectively, in Figure 3. These protein complexes regulate the interaction of proteins such as PCNA, exonuclease 1 (EXO1), DNA Pol, and replication protein A (RPA), which is essential for MMR.[5]

DISEASES ASSOCIATED WITH DEFECTIVE DNA REPAIR

DNA lesions have a significant impact on processes including transcription and replication.[10] Gene damage has serious immediate and long-term consequences.[7] Replication of damaged DNA induces mutations that can initiate and spread cancer. Thus, it arises when lesions inhibit transcription, causing cellular aging or apoptosis, which causes accelerated aging owing to damage.[10]

Mutations that alter the genetic information are quite likely to occur when a damaged DNA template is duplicated during the DNA replication. These mutations cause cancer, innate abnormalities, and overall cell degradation.[7] Cancer is also caused by defects in the DSB repair pathway.[21]

A proportion of autosomal recessive diseases (including XP, and CS) are hereditarily associated with defects in NER. These diseases, which are

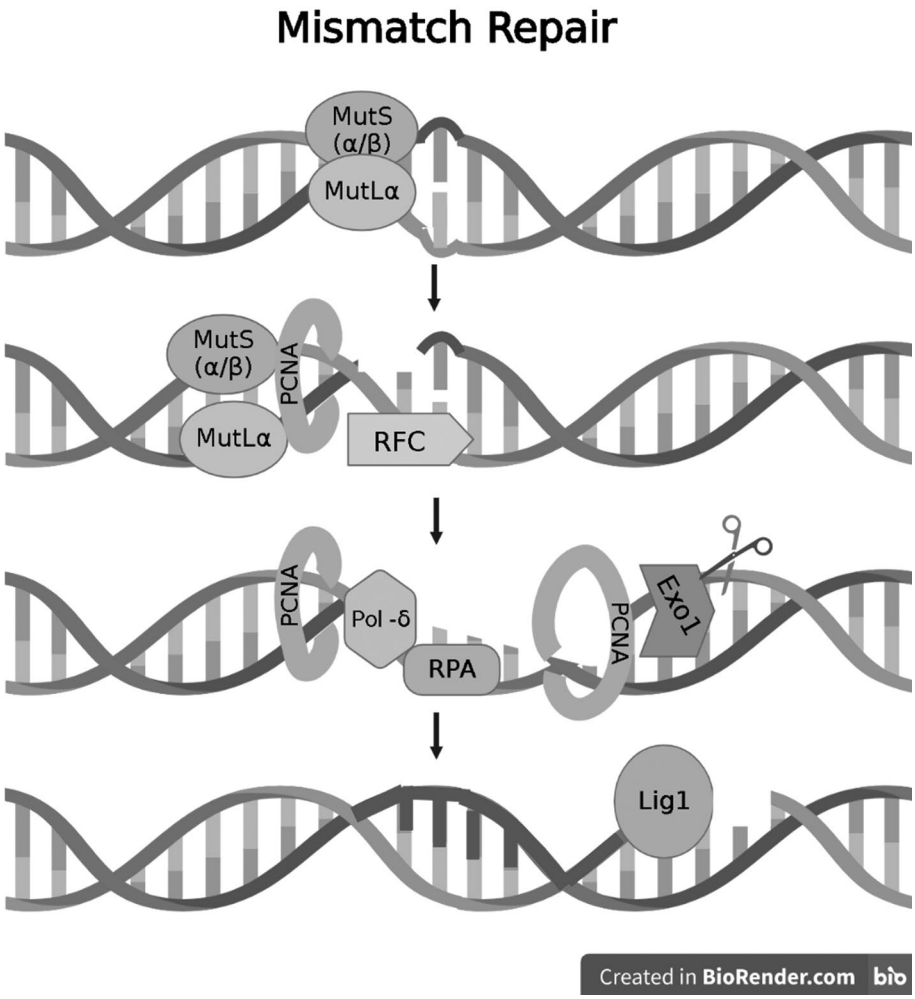

Figure 3. Schematic representation of MMR system. MutSβ (heterodimer MSH2-MSH6 complex) or MutSβ heterodimer complex starts DNA repair by recognizing and binding to mismatches. MutLα (heterodimer MLH1-PMS2), PCNA and replication factor C (RFC) are recruited to the complex. Excision by EXO1 leads to the formation of an RPA-coated single-strand gap. Resynthesis by Pol-δ and ligation restore the integrity of the duplex.

These figures were drawn using BioRender.

susceptible to UV light, can cause neurological problems in some individuals.[5]

Xeroderma pigmentosum

Some diseases originate in DNA as a result of UV light acquired by mammals and environmental mutagens.[31] In humans, hypersensitivity to sunlight can result in XP, which has been related to cancer, due to the loss of NER function.[18] People with XP often acquire deadly skin cancer as a result of their sensitivity to the sun. Some of the XP patients also exhibit anomalies brought on by severe neurological conditions in addition to these symptoms. The disruption of the NER pathway is responsible for the increase in significant damage in XP patients.[9,31]

Cockayne syndrome

Cockayne syndrome is an inherited autosomal recessive disorder. Premature aging, brain growth retardation due to numerous organ deteriorations, disruption of neurological development, and hypersensitivity to sunlight are the most visible symptoms of the disorder.[32,33]

Patients with CS also develop retinal dystrophy.[34] The condition is caused by mutations in the CSB gene. Aside from growth disorders, research is being conducted on the deterioration process induced by defective DNA repair.[32] Patients with CS have a deficiency or error in the TC-NER pathway, which corrects DNA damage. Furthermore, several studies suggest that BER damage may play a crucial role in CS.[35,36]

Bloom syndrome

In the primary clinical findings of Bloom syndrome (BS), it was determined that the individuals' intelligence levels were normal, growth retardation before and after birth, rashes in the sun-exposed areas, the fertility level of the female was normal, and the males were infertile. Bloom syndrome is an inherited autosomal recessive disorder.[37] The cytogenetic findings of BS show chromosomal changes and a rise in chromosomal abnormalities. According to one study, BS is caused by the endogenous synthesis of agents that induce DNA damage.[38] Bloom syndrome is caused by a deficiency in the BLM helicase, which is crucial in the management of the DNA replication fork that is disrupted due to lesion accumulation, hence increasing chromosome stability.[39]

Werner syndrome

Werner syndrome (WS) is an inherited disorder characterized by somatic stunting, premature aging, and the early onset of degenerative and neoplastic diseases. It is thought that the WRN protein, a RECQ-like helicase, takes involved in DNA DSB repair through either HR or NHEJ.[35,40] The homologous recombination function has been associated with the expression of SMRAD51, the Rad51 protein. Activation of SMRAD51 has been shown to suppress HR in WRN and control cells while improving WRN cell survival after DNA damage.[41]

Huntington's disease

Individuals suffering from Huntington's disease (HD) have involuntary movements, dementia, altered personality, and motor abnormalities as a result of cognitive and memory impairment.[42] The mismatch repair system corrects base/base mismatches that occur during replication, but oxidative DNA damage causes multiple repeats, leading to HD.[35]

Human disorders such as ataxia-telangiectasia (AT) and Nijmegen breakage syndrome (NBS) emerge as a result of errors in HR or NHEJ repair pathways, and these diseases result in the formation of individuals with neurological, immunological, and developmental problems.[5] Mutations in the AT and NBS genes cause chromosomal instability disorders. These genes play a key role in cellular resistance to the formation of DSBs and IR, both of which damage DNA.[39]

Ataxia-telangiectasia

In the clinical manifestations of AT, neurodegeneration, and immunodeficiency are observed. Motor delay manifests itself in children up to the age of five.[37] The ataxia-telangiectasia mutated (ATM) gene is one of the proteins that function in the region of protein complexes that initiate DNA damage signaling, and AT is brought on by nonsense and frameshift mutations in this gene. One of these protein complexes, the MRN complex, functions in DSB repair. Due to cerebellar degeneration, patients with AT had considerable DSB accumulation in their genomes. The ATM protein has a critical function in DNA repair. Alternative repair mechanisms can reduce the disease's lethality in AT cases caused by ATM protein mutations by repairing the damaged DNA.[43]

Nijmegen Breakage Syndrome

Individuals with NBS show indications of growth and mental retardation, microcephaly, facial dysmorphism, immunodeficiency, and cancer predisposition due to increased malignancy.[44,45] The lymphocytes and fibroblasts of NBS patients have been found to be hypersensitive to IR. After patients were exposed to X- or gamma radiation, abnormal cell death and higher DNA damage were observed.[46] Mutations in the NBS1 gene cause the disease. The NBS1 gene encodes the nibrin protein, which interacts with other repair proteins to form the MRN complex, which resides in DNA damage sites and performs DNA repair.[44] Thus, it was found that the clinical findings of NBS were similar to those of AT. The Mre11 and Rad50 complex induced a mutation in the NBS1 gene in this manner.[47]

Fanconi anemia

Fanconi anemia (FA) is an autosomal recessive inherited disorder with a variety of symptoms.[48] Examples include bone marrow failure and cancer caused by a predisposition to cancer.[49] Some FA genes collaborate with the BRCA1, BRCA2, and RAD51 genes to repair the DNA interstrand cross-links formed in replication forks by activating FANCD2, a component of the common DNA repair signaling pathway.[44,50] According to recent research, the Fanconi-associated nuclease 1 protein exhibits nuclease activity during the repair of DNA interstrand cross-links. There is additional evidence that the proteins involved in FA have other functions besides DNA repair in cell damage, or that they contribute to these processes.[50]

In conclusion, many events occur in order for living organisms to form and develop. The key to the genome, DNA, is at the core of these processes. DNA carries out a range of tasks utilizing diverse processes and going through distinct stages. Despite the orderly succession of these events, DNA abnormalities can occasionally arise for a variety of reasons. These abnormalities are repaired by distinct repair processes. Since a single mechanism cannot repair multiple damages, numerous DNA repair mechanisms with distinct functions are implicated in such circumstances. Most disorders that emerge when DNA cannot be repaired are understood by hereditary transmission or the presence of distinct findings in the individual. Therefore, the activity of DNA repair mechanisms is critical not only for managing the proper occurrence of events but also for avoiding the emergence of diseases caused by their inactivity.

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