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## Review

# A Review on DNA Damaging Patterns and Repair Mechanisms

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**Abstract.** Various factors and agents cause mutations and damage to DNA, such as UV radiations, alkylating agents, toxins, aromatic compounds, environmental stress and other ways, including spontaneous base DNA damage. These DNA damages could prove deleterious if left un-repaired, leading to cancer and many other unhealthy conditions. As DNA is the genomic material, repairing the damage is more critically important. However, cells have various mechanisms to cope with the damaged DNA, including DNA polymerase self-correction and proofreading, direct reversal of the chemical changes, readily repairing of double helix, base and nucleotide excision repair and mismatch repairs. This review briefly explains DNA damage and repair mechanisms and the disease states associated with them.

**Keywords:** DNA, damage, repairing, mutations, excision repair, cancer

## Introduction

DNA is one of the most critical molecules in living organisms containing all the genetic information needed for growth and cell development. It transmits genetic information from generation to generation through the process of replication. However, various agents and events cause its degradation and in this way, DNA gets mutated and leads to different types of diseases including cancer. Organisms contain enzymes and chemicals in their cells that degrade DNA in various forms, for example, during the process of apoptosis but these enzymes can also cause damage to the DNA of healthy cells (Kawane *et al*., 2014).

The genomic integrity is very important for cells, tissues and organism's survival. DNA damage is a continual threat because genetic material is chemically unstable under physiological circumstances and susceptible to bout by endogenic and external factors. To contest this, organisms have mechanisms to sense damaged DNA and repair it (Yousefzadeh *et al.*, 2021). Cells replicate millions and billions of nucleotides at every cell division and encounter changes in DNA and repair them *via* replication coupled DNA repair mechanisms (Cortez, 2019).

DNA can also get damaged as other molecules get different types of changes or mutations due to various chemical reactions. Changes in the standard structure of DNA can be very serious as linked with the process of cellular replication and inheritance. DNA damage can lead to serious genetic diseases, syndromes and many other complications including cancer. There are numerous causes of DNA damage, including mutagens, UV radiations, spontaneous mutations and incorrect base pairing during DNA replication (Nilsson and Liu, 2020). Mitochondrial reactive oxygen species damage the DNA at an exponential rate and are the cause of aging and various diseases (Huang *et al.*, 2020a). The chemical contaminants such as hazardous metals, ionic and organic contents significantly damage DNA and the level of DNA damage due to such impurities could be used for assessment of ecological risk for organisms such as fish (Bae *et al.*, 2020; Moon *et al.*, 2020).

Our data is briefed and organized from literature published in renowned journals, including research and review articles, scientific reports and books.

**Types of DNA damage.** DNA damage can be categorized into two major groups: exogenous and endogenous. Endogenous type DNA damage results from cellular replicative errors, DNA-topoisomerase complexes, DNA base mismatches, a-basic sites, spontaneous base deamination, DNA methylation and oxidative reactions. Exogenous DNA damage is mainly caused by ionizing and UV radiations. The chemical agents such as aromatic amines, alkylating agents, aromatic polycyclic hydrocarbon, toxins, reactive

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electrophiles and environmental stresses are also involved in DNA damage (Swenberg *et al*., 2011; Lindahl, 1993). Description of different types of DNA damage and their causative factors are content of our review, presented in the diagram (Fig. 1).

This DNA damage may be very harmful and lethal if not repaired in time. The mutating agents may cause base deletions, substitutions, frameshift changings, translocations, trans-lesions, transversions and even chromosome doubling or deletion (Wolters and Schumacher, 2013). Also, the DNA replication enzyme makes some mistakes, even with proofreading mechanisms. However, cells contain mechanisms that can respond to stress with damaging effects. Maintenance of genetic stability is possible in a variety of ways, including damage tolerance, cell division checkpoints, repairing of DNA mutations and structural changes but if still DNA damage cannot be repaired, the cells undergo programed death (Alhmoud *et al.*, 2020). In Fig. 2, DNA repair mechanisms are represented with little details. Prominent ones include DNA polymerase self-correcting and proofreading, mismatch repair, base excision repairs, nucleotide repair and repairing of double strand breaks (De-Almeida *et al*., 2021). Thus, the Fig. 2 representing different DNA damaging agents, their effects and possible repair mechanisms.

**DNA repair.** There are number of mechanisms to repair DNA damages, with two major classes, direct reversing the pathways responsible for generating damaged DNA and nucleotide base replacement which are damaged or mutated. The cell genome consists of DNA; therefore, its correct functioning is crucial for the organism's survival, growth and development. Mutations in the DNA sequence and changes in its structure leads to cancer and many other critical deleterious consequences (Swenberg *et al*., 2011). Therefore, their reversing or repairing is critically important.

***DNA polymerase proofreading and self-correction*.** DNA polymerases possess a high fidelity in DNA replication, which is very efficient, with only one nucleotide mispairing in $10^{10}$ nucleotides. Firstly, a correct nucleotide pairing is more attractive to the DNA polymerase process in DNA replication, as well as a correct nucleotide base pairing is energetically favourable. When a nucleotide binds to the template strand, DNA polymerase tightens its grip on the nucleotide because of a conformational change as this change and tightening occur more favourably with correctly base paired nucleotide. Also, the 3′ to 5′ exonuclease and proofreading activity repairs any mis-paired nucleotide that excised the initial fidelity mechanisms. When it finds a mis-paired nucleotide, it removes enough nucleotides until it reaches a normal 3′ OH group of a correctly paired nucleotide and start synthesizing new strand again (Fernandez-Leiro *et al.*, 2017; Reha-Krantz, 2010; Catalano and Benkovic, 1989).

***Direct reversal of damaged DNA*.** It is a DNA repair mechanism which does not need any template which is applicable to repair UV photochemical lesions/ pyrimidine dimers (caused by direct absorption of UV)

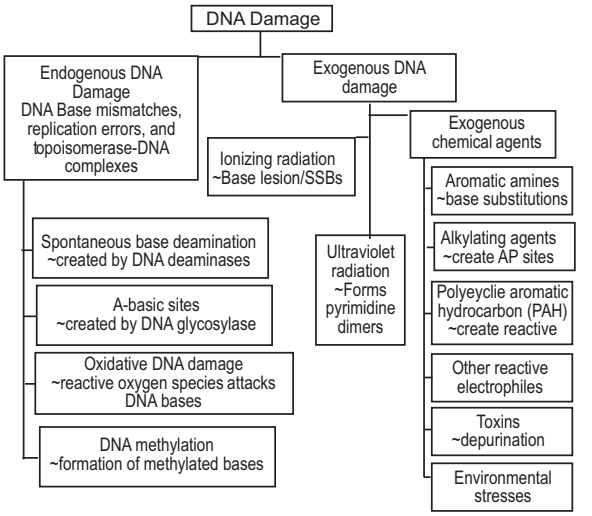


**Fig. 1.** An overview of DNA damage including its types, causative agents and effect.

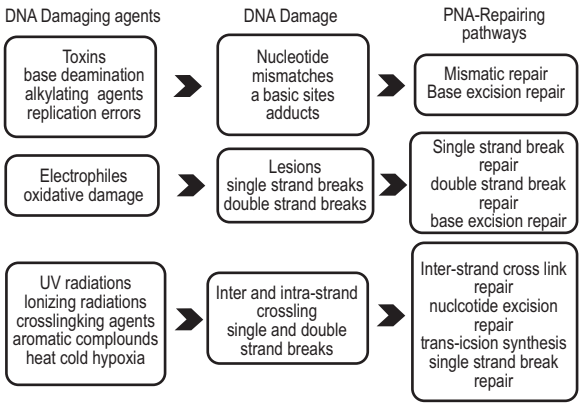


**Fig. 2.** Schematic explanation of DNA damage, agents that cause various types of damage and associated repair mechanisms.

and alkylated bases (specific bases add alkyl groups and produce alkylated products) which possess the ability to alter the structure of DNA chain by hindering transcription pathway in the nearby area of DNA damage (Chatterjee *et al.*, 2017).

*a) Photoreactivation*. It is a direct reversal DNA repair mechanism in which the utilization of visible light spectrum reverses DNA damage. Due to UV radiations, a covalent bond forms between the adjacent pyrimidine residues (T-T dimers). This dimerization results in the loss of DNA symmetry. Here photoreactivation (a DNA repair mechanism) works to remove such dimers (Banaś *et al*., 2020; Strzałka *et al*., 2020; Sutherland, 1978).

Mechanism. In this mechanism, DNA photolyase recognizes the dimer. The DNA photolyase enzyme contains two light-harvesting cofactors. One is FAD (Flavin adenine dinucleotide) and the other is MTHF (methionine tetrahydrofolate). MTHF absorbs visible light from the spectrum preferentially violet blue to the end of the spectrum. Once the MTHF gets excited, it transduces electrons and energy moves to the FAD and by accepting the electrons from MTHF, FAD is reduced to produce $FADH_2$. After this, $FADH_2$ transmits the high energy electrons towards the pyrimidine dimers and forms a dimer radical which is highly unstable and it spontaneously decomposes into its monomer and monomer radicals (Kneuttinger *et al*., 2014). Then finally, the unstable dimer radical separates into two pyrimidines, dimer breaks off and DNA damage gets fixed. This occurs in both prokaryotes (Sutherland, 1978) and eukaryotes (Kimura *et al*., 2004).

*b) DNA demethylation repair mechanism.* DNA methylation can occur by exposure to alkylating agents that cause problems in DNA, such as conversion of guanine into $O^6$-methylguanine ($O^6$-meG) (Kang *et al*., 1995; Loveless, 1969). *In vitro*, the $O^6$-meG blocks DNA elongation during DNA replication. $O^6$-meG-DNA methyltransferases (MGMT) in its active form (cys-SH) binds the methyl group (-CH3) to the $O^6$-methylguanine nucleotide. DNA demethylation repair removes methyl group (-CH3) from $O^6$-methylguanine, attaches it with itself and gets inactivated (Cys- S-$CH_3$). After removal of methyl group (-CH3), the $O^6$-methylguanine gets converted into guanine, which is normal nucleotide base of DNA (Liu and Lang, 2020; Pegg, 2011; Srivenugopal *et al*., 1996).

***Mismatch repair (MMR).*** MMR is a post-replicative repair pathway that recognizes and removes mismatched bases that have risen during insertion/deletion loops due to strand slippage and replication. The MMR also plays a significant role in various cellular processes (DNA-damage signaling, class-switch recombination, mitotic and meiotic recombination, microsatellite stability, somatic hypermutation, apoptosis and triplet repeat expansion) (D'Arcy, 2019; Jiricny, 2006; Modrich, 2006).

Mismatch repair relies on signals within the helix to direct repair to the newly synthesized strand of DNA. In the methyl-directed pathway, newly synthesized DNA is transiently unmethylated at GATC sites and it is the absence of this modification that directs repair to the new strand.

Normal bases are A, G, C and T in DNA. Sometimes bases such as U (produced due to deamination of "C"), hypoxanthine (produced by deamination of A), 5-methyladenine (produced by methylation of A) and 5-methyl-guanosine (produced by methylation of G) are inserted in DNA structure. Transition of C into U is dangerous because it creates a premutagenic U:G mis-pair. As "U" pairs with "A". So, in the next round of replication GC base pair is converted into AU (T) base pair (Krokan *et al*., 2002).

Hypoxanthine (Hx) is a major lesion generated by deamination of adenine during inflammatory conditions, which is an underlying cause of various diseases including cancer of colon, liver, pancreas, bladder and stomach (DeVito *et al*., 2017). There is evidence that deamination of DNA bases induces mutations but no study has directly linked Hx accumulation to mutagenesis and strand-specific mutations yet in human cells. Hx is a highly mutagenic lesion capable of generating A:T→ G:C transitions and large deletions with a significant variation in leading and lagging strands in human cells. Therefore, it is necessary to remove DNA mismatches by the mismatch repair system (Alberts *et al*., 2015; Bernstein *et al*., 2013).

*a) Mechanism*. The MMR process involves a complex interplay of Mut proteins (MutS, MutL, MutH) with the replication and/or recombination machinery. It is activated by the binding of the mismatch recognition factors, MutSα and MutSβ, to substrates that contain base mismatches and insertion/deletion loops that arise during recombination due to errors in DNA polymerase activity (Jiricny, 2006). Methyl-directed mismatch repair is initiated by the mismatch provoked, MutS-MutL-MutH dependent cleavage of the unmodified strand at

a hemi-methylated GATC sequence. There are four basic steps of DNA polymerase repair mechanism: recognition, removal, synthesis of new nucleotides and ligation. Normally, the parent strand is methylated at GATC containing methylated adenine, while the daughter strand is hemi-methylated. Deoxyadenosine methylase enzyme methylates the adenine in GATC sequence. This methylation marking of A is necessary to get the idea of the parent strand and the daughter strand. Strands are methylated long after replication. So, the newly synthesized DNA strand shortly after the replication remains un-methylated. They are methylated only after a particular interval of time. By this cells can easily recognize which one is parent and daughter strand. So, if there is any mis-corporation of base during replication, the daughter strand can easily be identified due to its hemi-methylation. First, MutS recognizes and binds with mismatched nucleotides. MutS recruits MutL, MutL forms a loop-like structure bringing the mismatch containing areas close together. MutH is recruited then which has endo-nuclease activity and cut DNA backbone having mismatched base sequence at two points. After this MutS, MutL and MutH are removed and UrvD (helicase-like protein) is recruited here. It simply releases mismatch containing DNA strands out. A long gap is left here having 3′OH group at the end. DNA polymerase I adds correct nucleotides and ultimately leaves a nick filled by DNA ligase (Alberts *et al*., 2015; Junop *et al*., 2003; Norbury *et al*., 2001).

Clinical conditions associated with MMR. Germline mutations in the genes of MMR can lead to:

- Lynch syndrome (which increases the vulnerability to cancer such as ovarian and colon cancer), (Duraturo *et al.*, 2019; Barnetson *et al*., 2006; Worthley *et al*., 2005; Jacob and Praz, 2002)
- Huntington's disease (Iyer and Pluciennik, 2021)

***Base excision repair (BER).*** Any change within a single base of the DNA is cleaved out by BER. DNA glycosylase cleaves the wrong base (U, hypoxanthine, 3-methyadenosine) out from the DNA strand without cleaving the DNA backbone. Glycosylases are specific according to their target bases e.g., Uracil glycosylase removes the U (unwanted base) from the DNA strand, hypoxanthine glycosylase removes hypoxanthine and 3-methyadenosine glycosylase removes 3-methyguanosine from DNA. AP sites (apurinic/apyrimidinic site) are created after the removal of mismatch bases. AP sites in the DNA are indication for DNA repair because these are not the part of normal DNA structure where the bases are paired like (A=T, C=G). AP endonucleases attach at the AP sites and make a nick in their respective backbone. Once the nick is created, the target stretch of DNA is cleaved out along with 2-3 extra nucleotides by 3′ to 5′ exo-nucleolytic activity of DNA Pol III. DNA Pol III cuts bases out of the DNA in one direction and fills the generated gap too by incorporating new nucleotides. These two processes take place simultaneously. It ultimately leads to a simple nick which is closed by an enzyme DNA ligase (Jeppesen *et al*., 2011; Wilson III *et al*., 2011; Wilson III and Bohr, 2007). Fig. 3 represents the pathway of DNA base-excision repair.

*a) Clinical conditions associated with BER.*

- Cancer predisposition (colorectal cancer and MUTYM-associated polyposis) (Wallace *et al*., 2012; Cheadle and Sampson, 2007)
- Neurological abnormalities (Wallace *et al*., 2012) and immunological defects (Stratigopoulou *et al*., 2020; Imai *et al*., 2003)

***Nucleotide excision repair (NER).*** This process removes the massive lesions created in DNA by UV radiation, environmental mutagens and DNA damage due to

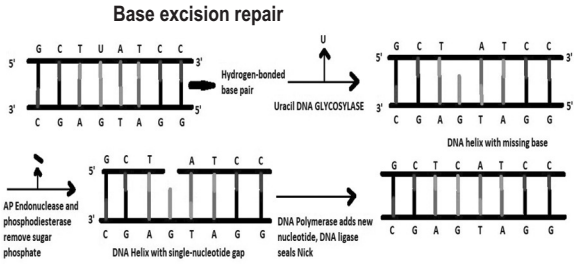


**Fig. 3.** Base-excision repair mechanism. This pathway starts with a DNA glycosylase. Here, the enzyme uracil-DNA glycosylase eliminates an accidentally aminated cytosine in DNA after the action of this glycosylase (or another DNA glycosylase that identifies a different kind of damage), the sugar phosphate with the lost base is cut out by a progressive action of AP endonuclease and phosphodiesterase. The gap of a single nucleotide is then filled by DNA polymerase and DNA ligase. The net result is that the U that was created by accidental deamination of C is restored to C.

chemotherapeutic agents which distort DNA double helical structure (Schärer, 2013). NER excises the nucleotide stretch from DNA sequence having lesions. UvrB and UvrC (proteins mainly involve in repair of DNA lesions occurred due to UV radiations) dimer proteins self-anneal and form UvrB-UvrC complex by the utilization of ATP (ATP→ADP+Pi). Then, the UvrB-UvrC complex is loaded on the actual DNA lesion site using ATP. UvrC first cuts the DNA backbone with wrong nucleotides and cleaves using its exonuclease activity (Crowley *et al*., 2006). Here, again ATP is utilized. Another protein UvrD is recruited at this site. UvrD protein cleaves the two strands of DNA and leaves a gap with free 3′OH group at one end. DNA polymerase-I fills this gap with correct nucleotides (15-20). A nick is left which is then sealed by DNA ligase (Fig. 4). Ultimately the double-stranded DNA molecule is formed with right bases (Fagbemi *et al*., 2011).

*a) Clinical conditions associated with NER.*

- Xeroderma pigmentosum: In this UV light induced the formation of T-T dimers. Person with this syndrome is sensitive to sunlight, which is observed by multiple freckles on sun-exposed skin areas and precancerous conditions (Ferri *et al*., 2020; Kraemer *et al*., 1987).
- Cockayne Syndrome (Schumacher *et al*., 2009)
- Trichothiodystrophy (TTD) (Faghri *et al*., 2008)
- Rare UV-Sensitive Syndrome (Ferri *et al*., 2020)
- Crebro Oculo-Facio Skeletal syndrome ((Ferri *et al*., 2020: Diderich *et al*., 2011; Kraemer *et al*., 2007)

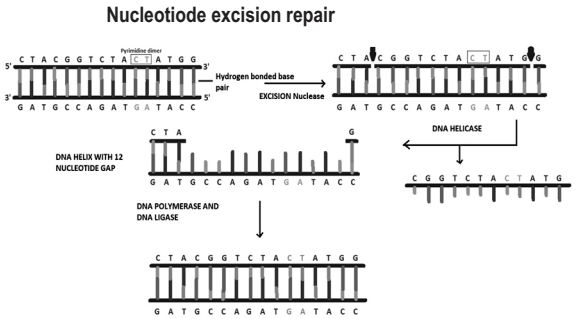


**Fig. 4.** Nucleotide-excision repair mechanism. First step is the recognition of problematic nucleotide. In the next step DNA helicase create a nick in the strand where abnormal nucleotides were found and removes them until a normal 3′ OH group is exposed. Then DNA polymerase construct that strand and ligase enzyme fills the nick.

***Single strand break repair (SSBR).*** Single strand breaks are produced due to oxidative stress, wrong action of the DNA Topoisomerase-1 and the creation of a-basic sites. Untreated SSBs stop the DNA replication, transcription and affect the poly-ADP ribose polymerase 1 (PARP1) activation (Iyama and Wilson III, 2013). Three pathways of SSBR are based on the cause of SSBs.

*a) Long patch SSBR pathway.* SSBs which are sensed by PARP1 (poly-ADP-ribose polymerase) and after detecting one PARP1 dissociates from SSB to detect the next SSB. Then end processing is done by APE1 (apyrimidinic/apurinic endonuclease 1), aprataxin and PNKP (polynucleotide kinase 3′-phosphatase. Next, flap-structure-specific endonuclease-1 (FEN1) detaches the damaged 5' ends aided by proliferating-cell nuclear-antigen (PCNA) and PARP1 leaving behind a ssDNA gap, which is filled by POL δ/ε and POL β (Abbotts *et al*., 2017). Ligation is supported by the DNA Ligase-1, which relies on the presence of X-ray repair cross complementing-1 (XRCC1) and PCNA (Klungland and Lindahl, 1997; Frosina *et al*., 1996).

*b) Short patch SSBR pathway.* APE1 recognizes the SSBs formed during BER. End processing pathway is similar to the long patch repair. POL β enzyme alone fills the gap, while ligation is completed by LIG3 (Dianov *et al*., 1992).

*c) TOP1-SSB pathway.* It is a modified form of the PARP1-dependent long-patch-repair in which the processing of ends is performed by the tyrosyl-DNA phosphodiesterase-1 (TDP1) enzyme that detaches the TOP1 from the 3'-end (Zhou *et al*., 2005). These patients consume genetic variability and high occurrence of cancers.

*d) Clinical conditions associated with SSBR.*

- Spinocerebellar-ataxia is associated with axonal neuropathy-1 (Takashima *et al*., 2002)
- Ataxia-oculomotor apraxia-1 (Moreira *et al*., 2001)

**Double strand break repair.** DNA double-strand breaks are produced when alpha and beta particles or gamma rays are deposited in our body or when we consume toxic ingredients (such as smoke, hair spray, etc.). In this case, right sequence of nucleotides is lost (O'Driscoll *et al*., 2004). This sequence might be vital for the survival of an organism. Thus, it is essential to repair it. Double-strand breaks are mortal to cells, as both strands of DNA got affected and support the loss of genomic information (Altaf *et al.*, 2007).

The double strand break repair has two mechanisms (Difilippantonio *et al*., 2002):

***Homologous recombination.*** The homologous recombination repair system uses homologous chromosome/sister chromatid as a template in order to recover the lost part of the DNA.

*a) Mechanism.* Due to exposure to UV radiations, double-stranded breaks appear in DNA with little overhangs. The sister chromatid is used as a template to repair these double-stranded breaks when there is no UV damage of the sister chromatid. A homologous chromosome is used when sister chromatids are not damaged by UV radiation. The HR repair takes place in S or $G_2$ phase. MRX (MRN complex/Mre II-Rad50-NbS1) complex in yeast comes into contact with damaged DNA (Stracker and Petrini, 2011), its function is to resect the DNA end, producing 3′ overhang (~1000bp), which is single stranded-DNA (ssDNA) - DNA is known as 3′ overhang. Different small proteins such as replication protein A (RecA) bind to ssDNA. Its function is to avoid single-stranded DNA from nucleases and re-winding. The RecA proteins form a helical nucleofilament on ssDNA (Huang *et al*., 2020b). DNA double-strand breaks (DSBs) repair by homologous recombination is carried out by a number of proteins that may act within a multi-protein complex. McIlwraith *et al*. (2000) found that hRAD51-BRCA2 protein complex replaces the RPA protein. Further, hRad51 binds to the ssDNA of tailed duplex DNA molecules and catalyzes the invasion of tailed duplex DNA into homologous covalently closed DNA (Wright *et al.*, 2018).

After searching for homologous chromosomes, a loop-like structure is formed between the DNA with the double-strand break and the homologous chromosome known as the D-loop (McIlwraith *et al*., 2005). The 3′ overhangs use the homologous chromosome nucleotides as a template and add nucleotides along with it. Once the nucleotides are added and the process is completed, the termination process starts. Here are two options for termination which are:

i. Non-crossover HR repair. In non-crossover HR repair, both the homologous chromosomes (the repaired chromosome and chromosome used as template) are the same as before the damage (Fekairi *et al*., 2009; Ip *et al*., 2008).

ii. Crossover HR repair. In this mechanism, homologous chromosomes exchange part with each other, just like crossing over during meiosis. Sometimes this exchanging part is beneficial for the individual and occasionally harmful depending upon what sequence they exchanged and the effect they will produce on the body (Heyer *et al*., 2010; San-Filippo *et al*., 2008).

***Non-homologous end-joining (NHEJ).*** The NHEJ is a pathway that repairs double-strand breaks in DNA. This DNA repair system does not utilize sister chromatids/homologous chromosomes as template to restore the missing part of the nucleotide chain (Soulas-Sprauel *et al*., 2007).

*a) Mechanism.* Due to exposure to UV radiations, double-stranded breaks appear in DNA with little overhangs. Here sister chromatid or homologous chromosomes are not present as a template. Rather than this, DNA is trimmed and joined back to recover the lost part of the DNA. Ku proteins (heterodimers having Ku-70 and Ku-80) attach with single-stranded ends and move along the few base pairs. Ku protein provides platform for other proteins to come and make complex and do their job. Now Ku protein recruits DNA-PKcs protein (DNA protein kinase catalytic site) on the single-stranded DNA along with itself (Getts and Stamato, 1994; Taccioli *et al*., 1994). Arthemis protein binds with Ku protein-DNA PKcs complex. The kinase of DNA-PKcs phosphorylates the arthemis and makes it active. Arthemis protein possessess 3' and 5' exonuclease-activity and trims the single-stranded overhang damaged DNA to create the double strand with blunt ends (Ma *et al*., 2002). These blunt ends are joined back by using DNA ligase (Andrade *et al*., 2009). Double stranded DNA is produced without any break, but this double-stranded DNA does not resemble the original DNA because the lost part of the nucleotides is not restored. The HNEJ system is more common than HR repair system.

Clinical conditions associated with DSBR.

- Lesions (blindness)
- Radiosensitivity and microcephaly (Buck *et al*., 2006)
- Severe combined immunodeficiency (SCID) phenotype and developmental delay (O'Driscoll *et al*., 2001)

**Trans-lesion DNA synthesis (TLS) and repair.** TLS is the process by which cells containing the unrepaired DNA damage (which stops the replication fork from moving) are copied. TLS polymerases carry out trans-lesion synthesis.

***In eukaryotes.*** A normal replicating enzyme (DNA polymerase III) stalls at a bulky adduct, damaged part or at lesion because the bulky adducts cannot get into the active site of normal replicating DNA polymerases. The assembly of PCNA (proliferating-cell nuclear-antigen) and polymerase δ dissociates and pol δ is replaced with ubiquitinated molecule which is now ubiquitinated PCNA. Ubiquitinated PCNA polymerase operates trans-lesion DNA synthesis on the damaged part of DNA. The TLS Polymerase continues to replicate by "bypassing" the lesions and thus the cell survives. When the TLS polymerase does not insert a nucleotide against the adducts, replication stops and the cell dies (Nayak *et al.*, 2021; Prakash *et al*., 2005; Kannouche and Lehmann, 2004; Kannouche *et al*., 2004).

***In prokaryotes.*** When the DNA Pol-III with *β-clamp* approaches at the DNA adduct (T-T dimer) replication fork stalls. Here 2 mechanisms are involved in TLS process to bypass DNA adducts/lesions.

The first studies (1984-1985) showed that RecA (recombination protein A) and UmuDC (a polymerase with two subunits that regulate mutagenesis) attach to DNA Pol III and add nucleotides opposite the adduct. It is not the DNA polymerase III but it is RecA-UmuDC complex that is adding nucleotide against the adduct. After bypassing adduct, nucleotides are added by DNA pol III (Ippoliti *et al*., 2012).

Latest studies show that UmuDC is the part or equivalent to DNA pol V (belongs to Y-family of DNA-polymerases) at the point of bulky adduct DNA Pol-III is replaced with DNA Pol V with beta-clamp by the utilization of ATP. It adds nucleotides against the adduct. After bypassing the adduct or lesions, DNA Pol III is recruited again to continue replication (Ippoliti *et al*., 2012).

*a) Clinical condition associated with TLS.* Xeroderma pigmentosum (Masutani *et al*., 1999)

**DNA damage in association with telomeres.** Telomeres are highly conserved nucleoprotein assemblies that constitute the ends of linear chromosomes. Telomeric DNA contains tandem-repetitive DNA (TTAGGG; humans). Telomerase (regulator of telomere length) is an enzyme that maintains and replicates telomeric DNA. Deprotected telomeres show responses that help to repair the DNA damage (Chakravarti *et al*., 2021), such as recruiting DSBR mechanisms that improve the unprotected ends, triggering deleterious nucleolytic degradation, chromosomal fusions, and recombination. Many environmental toxins (tobacco smoke, Obesity etc.) and genotoxic stressors (pollutants) cause telomere shortening (Sobinoff and Pickett, 2017).

*b) Clinical conditions associated with telomere shortening.* A decrease in telomerase expression leads to telomere shortening, which is associated with followed diseases:

- Tumors (Chakravarti *et al*., 2021; Martinez-Delgado *et al*., 2011)
- Aging (Zhu *et al*., 2019)
- Several bone marrow failure disorders (Savage *et al*., 2008)
- Werner syndrome, bloom syndrome, Fanconi anemia (Kong *et al*., 2013)

**Save our Soul (SOS) response system.** SOS repair or "emergency" or "bypass" repair response arises when cells are stunned by UV damage, this lets the cells to live but with a load of mutagenesis. The SOS mechanism is solitary activated when unrepaired DNA is amassed due to failure of other DNA repair systems caused by huge damage.

***Mechanism.*** It is the "response system" not the "repair system". It activates the DNA repair mechanism in case of stalled replication or extreme DNA damage due to UV radiations or oxidative stress. Normally Lex-A protein is the inhibitor of SOS operon. It binds with SOS box present on the SOS operon's promoter and keeps it inactive. Due to this, the genes involved in DNA repair remain inactive. It also blocks the promoter region of Rec-A gene operon. If there is any bulky DNA damage, Rec-A genes get activated and produce Rec-A protein which triggers the Lex-A protein to be auto cleaved. So, it breaks itself into two parts (repressor and activator) and becomes inactive. Now SOS gene's box is free from the inhibitory effect of Lex-A protein dimer. So, the DNA repair genes express themself and form repair proteins. These proteins control the expression of many genes like UvrB (used in NER; error-free repair), DNA Pol V (used in translesion bypass; error-prone repair) etc. (Maslowska *et al*., 2019; Janion, 2008).

## Conclusion

Cells are equipped naturally to repair and fight deleterious DNA mutations. Mutations are helpful from an evolutionary perspective, but some are so dangerous that they may lead to diseases that have no cure such as cancer, which have no cure and can also be inherited

across generations. The environment full of chemicals, cell-damaging and increasing pollution worsen conditions associated with DNA damage. DNA damage responses (DDR) are also used to create mutations and lesions in the structure of DNA of cancerous cells and then utilizing cellular repair mechanism, overload the cells with DNA damage attempts to death; a way to treat cancer. It is also important to find out the new mitochondrial DNA damage repair mechanisms, these mechanisms would be helpful to develop new genome editing strategies originating from eukaryotic cells rather than prokaryotic ones such as CRISPR-Cas9 gene editing system.

**Conflict of Interest.** The authors declared that they have no conflict of interest.

## References


Abbotts, R., Wilson III, D.M. 2017. Coordination of DNA single strand break repair. *Free Radical Biology and Medicine*, **107:** 228-244.

Alberts, B., Johnson, A., Lewis, J., Morgan, D., Raff, M., Roberts, K., Walter, P. 2015. *Molecular Biology of the Cell*, 6th edition, pp. 1464, Norton, W.W. & Company, New York, USA.

Alhmoud, J.F., Woolley, J.F., Al Moustafa, A.E., Malki, M.I. 2020. DNA damage/repair management in cancers. *Cancers*, **12:** 1050.

Altaf, M., Saksouk, N., Côté, J. 2007. Histone modifications in response to DNA damage. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, **618:** 81-90.

Andrade, P., Martín, M.J., Juárez, R., de Saro, F.L., Blanco, L. 2009. Limited terminal transferase in human DNA polymerase μ defines the required balance between accuracy and efficiency in NHEJ. *Proceedings of the National Academy of Sciences*, **106:** 16203-16208.

Bae, D.Y., Atique, U., Yoon, J.H., Lim, B.J., An, K.G. 2020. Ecological risk assessment of urban streams using fish biomarkers of DNA damage and physiological responses. *Polish Journal of Environmental Studies*, **29:** 1077-1086.

Banaś, A.K., Zgłobicki, P., Kowalska, E., Dziga, D., Strzałka, W. 2020. All you need is light. Photorepair of UV-induced pyrimidine dimers. *Genes*, **11:** 1304.

Barnetson, R.A., Tenesa, A., Farrington, S.M., Nicholl, I.D., Cetnarskyj, R., Porteous, M.E., Campbell, H., Dunlop, M.G. 2006. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *The New England Journal of Medicine,* **354:** 2751-2763.

Bernstein, C., Prasad, A.R., Nfonsam, V., Bernstein, H. 2013. *DNA Damage, DNA Repair and Cancer*, **vol. 1**, pp. 413-465, IntechOpen, UK.

Buck, D., Malivert, L., de Chasseval, R., Barraud, A., Fondanèche, M.-C., Sanal, O., Plebani, A., Stéphan, J.-L., Hufnagel, M., le Deist, F. 2006. Cernunnos, a novel non-homologous end-joining factor, is mutated in human immunodeficiency with microcephaly. *Cell*, **124:** 287-299.

Catalano, C.E., Benkovic, S.J. 1989. Inactivation of DNA polymerase I (Klenow fragment) by adenosine 2', 3'-epoxide 5'-triphosphate: evidence for the formation of a tight-binding inhibitor. *Biochemistry*, **28:** 4374-4382.

Chakravarti, D., LaBella, K.A., DePinho, R.A. 2021. Telomeres: history, health and hallmarks of aging. *Cell*, **184:** 306-322.

Chatterjee, N., Walker, G.C. 2017. Mechanisms of DNA damage, repair and mutagenesis. *Environmental and Molecular Mutagenesis*, **58:** 235-263.

Cheadle, J.P., Sampson, J.R. 2007. MUTYH-associated polyposis from defect in base excision repair to clinical genetic testing. *DNA Repair*, **6:** 274-279.

Cortez, D. 2019. Replication-coupled DNA repair. *Molecular Cell*, **74:** 866-876.

Crowley, D.J., Boubriak, I., Berquist, B.R., Clark, M., Richard, E., Sullivan, L., DasSarma, S., McCready, S. 2006. The uvrA, uvrB and uvrC genes are required for repair of ultraviolet light induced DNA photoproducts in *Halobacterium* sp. NRC-1. *Saline Systems*, **2:** 1-13.

D'Arcy, M.S. 2019. Cell death: a review of the major forms of apoptosis, necrosis and autophagy. *Cell Biology International*, **43:** 582-592.

De-Almeida, L.C., Calil, F.A., Machado-Neto, J.A., Costa-Lotufo, L.V. 2021. DNA damaging agents and DNA repair: from carcinogenesis to cancer therapy. *Cancer Genetics*, **252:** 6-24.

DeVito, S., Woodrick, J., Song, L., Roy, R. 2017. Mutagenic potential of hypoxanthine in live human cells. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, **803:** 9-16.

Dianov, G., Price, A., Lindahl, T. 1992. Generation of single-nucleotide repair patches following excision of uracil residues from DNA. *Molecular and Cellular Biology*, **12:** 1605-1612.

Diderich, K., Alanazi, M., Hoeijmakers, J. 2011.

Premature aging and cancer in nucleotide excision repair-disorders. *DNA Repair*, **10:** 772-780.

Difilippantonio, M.J., Petersen, S., Chen, H.T., Johnson, R., Jasin, M., Kanaar, R., Ried, T., Nussenzweig, A. 2002. Evidence for replicative repair of DNA double-strand breaks leading to oncogenic translocation and gene amplification. *Journal of Experimental Medicine*, **196:** 469-480.

Duraturo, F., Liccardo, R., De Rosa, M., Izzo, P. 2019. Genetics, diagnosis and treatment of Lynch syndrome: old lessons and current challenges. *Oncology Letters*, **17:** 3048-3054.

Fagbemi, A.F., Orelli, B., Schärer, O.D. 2011. Regulation of endonuclease activity in human nucleotide excision repair. *DNA Repair*, **10:** 722-729.

Faghri, S., Tamura, D., Kraemer, K.H., DiGiovanna, J.J. 2008. Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. *Journal of Medical Genetics*, **45:** 609-621.

Fekairi, S., Scaglione, S., Chahwan, C., Taylor, E.R., Tissier, A., Coulon, S., Dong, M.-Q., Ruse, C., Yates III, J.R., Russell, P. 2009. Human SLX4 is a Holliday junction resolvase subunit that binds multiple DNA repair/recombination endonucleases. *Cell*, **138:** 78-89.

Fernandez-Leiro, R., Conrad, J., Yang, J.-C., Freund, S., Scheres, S.H., Lamers, M.H. 2017. Self-correcting mismatches during high-fidelity DNA replication. *Nature Structural & Molecular Biology*, **24:** 140-143. https://doi.org/10.1038/nsmb.3348

Ferri, D., Orioli, D., Botta, E. 2020. Heterogeneity and overlaps in nucleotide excision repair disorders. *Clinical Genetics*, **97:** 12-24.

Frosina, G., Fortini, P., Rossi, O., Carrozzino, F., Raspaglio, G., Cox, L.S., Lane, D.P., Abbondandolo, A., Dogliotti, E. 1996. Two pathways for base excision repair in mammalian cells. *Journal of Biological Chemistry*, **271:** 9573-9578.

Getts, R.C., Stamato, T.D. 1994. Absence of a Ku-like DNA end binding activity in the xrs double-strand DNA repair-deficient mutant. *Journal of Biological Chemistry*, **269:** 15981-15984.

Heyer, W.-D., Ehmsen, K.T., Liu, J. 2010. Regulation of homologous recombination in eukaryotes. *Annual Review of Genetics*, **44:** 113-139.

Huang, Z., Chen, Y., Zhang, Y. 2020a. Mitochondrial reactive oxygen species cause major oxidative mitochondrial DNA damages and repair pathways. *Journal of Biosciences*, **45:** 1-17.

Huang, X., Lu, Y., Wang, S., Sui, M., Li, J., Ma, J., Ma, D., Jia, Q., Hu, S., Xu, C., Li, M. 2020b. Mismatch sensing by nucleofilament deciphers mechanism of RecA-mediated homologous recombination. *Proceedings of the National Academy of Sciences*, **117:** 20549-20554.

Imai, K., Slupphaug, G., Lee, W.-I., Revy, P., Nonoyama, S., Catalan, N., Yel, L., Forveille, M., Kavli, B., Krokan, H.E. 2003. Human uracil–DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. *Nature Immunology*, **4:** 1023-1028.

Ip, S.C., Rass, U., Blanco, M.G., Flynn, H.R., Skehel, J.M., West, S.C. 2008. Identification of Holliday junction resolvases from humans and yeast. *Nature*, **456:** 357-361.

Ippoliti, P.J., DeLateur, N.A., Jones, K.M., Beuning, P.J. 2012. Multiple strategies for translesion synthesis in bacteria. *Cells*, **1:** 799-831.

Iyama, T., Wilson III, D.M. 2013. DNA repair mechanisms in dividing and non-dividing cells. *DNA Repair*, **12:** 620-636.

Iyer, R.R., Pluciennik, A. 2021. DNA mismatch repair and its role in Huntington's disease. *Journal of Huntington's Disease*, **10:** 75-94.

Jacob, S., Praz, F.J. 2002. DNA mismatch repair defects: role in colorectal carcinogenesis. *Biochimie*, **84:** 27-47.

Janion, C.J. 2008. Inducible SOS response system of DNA repair and mutagenesis in *Escherichia coli*. *International Journal of Biological Sciences*, **4:** 338.

Jeppesen, D.K., Bohr, V.A., Stevnsner, T. 2011. DNA repair deficiency in neurodegeneration. *Progress in Neurobiology*, **94:** 166-200.

Jiricny, J. 2006. The multifaceted mismatch-repair system. *Nature Reviews Molecular Cell Biology*, **7:** 335-346.

Junop, M.S., Yang, W., Funchain, P., Clendenin, W., Miller, J.H. 2003. *In vitro* and *in vivo* studies of MutS, MutL and MutH mutants: correlation of mismatch repair and DNA recombination. *DNA Repair*, **2:** 387-405.

Kang, H.I., Konishi, C., Kuroki, T., Huh, N.H. 1995. Detection of O 6-methylguanine, O 4-methylthymine and O 4-ethylthymine in human liver and peripheral blood leukocyte DNA. *Carcinogenesis*, **16:** 1277-1280.

Kannouche, P.L., Lehmann, A.R. 2004. Ubiquitination of PCNA and the polymerase switch in human

cells. *Cell Cycle*, **3:** 1009-1011.

Kannouche, P.L., Wing, J., Lehmann, A.R. 2004. Interaction of human DNA polymerase η with monoubiquitinated PCNA: a possible mechanism for the polymerase switch in response to DNA damage. *Molecular Cell*, **14:** 491-500.

Kawane, K., Motani, K., Nagata, S. 2014. DNA degradation and its defects. *Cold Spring Harbor Perspectives in Biology*, **6:** a016394.

Kimura, S., Tahira, Y., Ishibashi, T., Mori, Y., Mori, T., Hashimoto, J., Sakaguchi, K. 2004. DNA repair in higher plants; photoreactivation is the major DNA repair pathway in non-proliferating cells while excision repair (nucleotide excision repair and base excision repair) is active in proliferating cells. *Nucleic Acids Research*, **32:** 2760-2767.

Klungland, A., Lindahl, T. 1997. Second pathway for completion of human DNA base excision-repair: reconstitution with purified proteins and requirement for DNase IV (FEN1). *The EMBO Journal*, **16:** 3341-3348.

Kneuttinger, A.C., Kashiwazaki, G., Prill, S., Heil, K., Müller, M., Carell, T. 2014. Formation and direct repair of UV-induced dimeric DNA pyrimidine lesions. *Photochemistry and Photobiology*, **90:** 1-14.

Kong, C.M., Lee, X.W., Wang, X. 2013. Telomere shortening in human diseases. *The FEBS Journal*, **280:** 3180-3193.

Kraemer, K.H., Lee, M.M., Scotto, J.1987. Xeroderma pigmentosum: cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Archives of Dermatology*, **123:** 241-250.

Kraemer, K.H., Patronas, N.J., Schiffmann, R., Brooks, B.P., Tamura, D., DiGiovanna, J.J. 2007. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype–phenotype relationship. *Neuroscience*, **145:** 1388-1396.

Krokan, H.E., Drabløs, F., Slupphaug, G. 2002. Uracil in DNA–occurrence, consequences and repair. *Oncogene*, **21:** 8935-8948.

Lindahl, T. 1993. Instability and decay of the primary structure of DNA. *Nature*, **362:** 709-715.

Liu, R., Lang, Z. 2020. The mechanism and function of active DNA demethylation in plants. *Journal of Integrative Plant Biology*, **62:** 148-159.

Loveless, A. 1969. Possible relevance of O–6 alkylation of deoxyguanosine to the mutagenicity and carcinogenicity of nitrosamines and nitrosamides. *Nature*, **223:** 206-207.

Ma, Y., Pannicke, U., Schwarz, K., Lieber, M.R. 2002. Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V (D) J recombination. *Cell*, **108:** 781-794.

Martinez-Delgado, B., Yanowsky, K., Inglada-Perez, L., Domingo, S., Urioste, M., Osorio, A., Benitez, J. 2011. Genetic anticipation is associated with telomere shortening in hereditary breast cancer. *PLoS Genetics*, **7:** e1002182.

Maslowska, K.H., Makiela-Dzbenska, K., Fijalkowska, I.J. 2019. The SOS system: a complex and tightly regulated response to DNA damage. *Environmental and Molecular Mutagenesis*, **60:** 368-384.

Masutani, C., Kusumoto, R., Yamada, A., Dohmae, N., Yokoi, M., Yuasa, M., Araki, M., Iwai, S., Takio, K., Hanaoka, F. 1999. The XPV (xeroderma pigmentosum variant) gene encodes human DNA polymerase η. *Nature*, **399:** 700-704.

McIlwraith, M.J., Vaisman, A., Liu, Y., Fanning, E., Woodgate, R., West, S.C. 2005. Human DNA polymerase η promotes DNA synthesis from strand invasion intermediates of homologous recombination. *Molecular Cell*, **20:** 783-792.

McIlwraith, M.J., Van Dyck, E., Masson, J.-Y., Stasiak, A.Z., Stasiak, A., West, S.C.J. 2000. Reconstitution of the strand invasion step of double-strand break repair using human Rad51 Rad52 and RPA proteins. *Journal of Molecular Biology*, **304:** 151-164.

Modrich, P.J. 2006. Mechanisms in eukaryotic mismatch repair. *Journal of Biological Chemistry*, **281:** 30305-30309.

Moon, W.-K., Atique, U., An, K.G. 2020. Ecological risk assessments and eco-toxicity analyses using chemical, biological, physiological responses, DNA damages and gene-level biomarkers in Zebrafish (Danio rerio) in an urban stream. *Chemosphere*, **239:** 124754.

Moreira, M.-C., Barbot, C., Tachi, N., Kozuka, N., Uchida, E., Gibson, T., Mendonça, P., Costa, M., Barros, J., Yanagisawa, T. 2001. The gene mutated in ataxia-ocular apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. *Nature Genetics*, **29:** 189-193.

Nayak, S., Calvo, J.A., Cantor, S.B. 2021. Targeting translesion synthesis (TLS) to expose replication gaps, a unique cancer vulnerability. *Expert Opinion on Therapeutic Targets*, **25:** 27-36.

Nilsson, R., Liu, N.A. 2020. Nuclear DNA damages generated by reactive oxygen molecules (ROS)

under oxidative stress and their relevance to human cancers, including ionizing radiation-induced neoplasia part I: physical, chemical and molecular biology aspects. *Radiation Medicine and Protection*, **1:** 140-152.

Norbury, C.J., Hickson, I.D. 2001. Cellular responses to DNA damage. *Annual Review of Pharmacology and Toxicology*, **41:** 367-401.

O'Driscoll, M., Gennery, A., Seidel, J., Concannon, P., Jeggo, P. 2004. An overview of three new disorders associated with genetic instability: LIG4 syndrome, RS-SCID and ATR-Seckel syndrome. *DNA Repair*, **3:** 1227-1235.

O'Driscoll, M., Cerosaletti, K.M., Girard, P.-M., Dai, Y., Stumm, M., Kysela, B., Hirsch, B., Gennery, A., Palmer, S.E., Seidel, J. 2001. DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. *Molecular Cell*, **8:** 1175-1185.

Pegg, A.E. 2011. Multifaceted roles of alkyltransferase and related proteins in DNA repair, DNA damage, resistance to chemotherapy and research tools. *Chemical Research in Toxicology*, **24:** 618-639.

Prakash, S., Johnson, R.E., Prakash, L. 2005. Eukaryotic translesion synthesis DNA polymerases: specificity of structure and function. *Annual Review of Biochemistry*, **74:** 317-353.

Reha-Krantz, L.J. 2010. DNA polymerase proofreading: multiple roles maintain genome stability. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, **1804:** 1049-1063.

San Filippo, J., Sung, P., Klein, H. 2008. Mechanism of eukaryotic homologous recombination. *Annual Review of Biochemistry*, **77:** 229-257.

Savage, S.A., Alter, B.P. 2008. The role of telomere biology in bone marrow failure and other disorders. *Mechanisms of Ageing and Development*, **129:** 35-47.

Schärer, O.D. 2013. Nucleotide excision repair in eukaryotes. *Cold Spring Harbor Perspectives in Biology*, **5:** a012609.

Schumacher, B., Hoeijmakers, J.H., Garinis, G.A. 2009. Sealing the gap between nuclear DNA damage and longevity. *Molecular and Cellular Endocrinology*, **299:** 112-117.

Sobinoff, A.P., Pickett, H.A. 2017. Alternative lengthening of telomeres: DNA repair pathways converge. *Trends in Genetics*, **33:** 921-932.

Soulas-Sprauel, P., Rivera-Munoz, P., Malivert, L., Le Guyader, G., Abramowski, V., Revy, P., De Villartay, J.P. 2007. V (D) J and immunoglobulin class switch recombinations: a paradigm to study the regulation of DNA end-joining. *Oncogene*, **26:** 7780-7791.

Srivenugopal, K.S., Yuan, X.-H., Friedman, H.S., Ali-Osman, F. 1996. Ubiquitination-dependent proteolysis of O 6-methylguanine-DNA methyltransferase in human and murine tumor cells following inactivation with O 6-benzylguanine or 1, 3-bis (2-chloroethyl)-1-nitrosourea. *Biochemistry*, **35:** 1328-1334.

Stracker, T.H., Petrini, J.H. 2011. The MRE11 complex: starting from the ends. *Nature Reviews Molecular Cell Biology*, **12:** 90-103.

Stratigopoulou, M., van Dam, T.P., Guikema, J.E. 2020. Base excision repair in the immune system: small DNA lesions with big consequences. *Frontiers in Immunology*, **11:** 1084.

Strzałka, W., Zgłobicki, P., Kowalska, E., Dziga, D., Banaś, A.K. 2020. The dark side of UV-induced DNA lesion repair. *Genes*, **11:** 1450.

Sutherland, B.M. 1978. Enzymatic photoreactivation of DNA. *DNA Repair Mechanisms*, 113-122.

Swenberg, J.A., Lu, K., Moeller, B.C., Gao, L., Upton, P.B., Nakamura, J., Starr, T.B. 2011. Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology and risk assessment. *Toxicological Sciences*, **120:** S130-S145.

Taccioli, G.E., Gottlieb, T.M., Blunt, T., Priestley, A., Demengeot, J., Mizuta, R., Lehmann, A.R., Alt, F.W., Jackson, S.P., Jeggo, P.A. 1994. Ku80: product of the XRCC5 gene and its role in DNA repair and V (D) J recombination. *Science*, **265:** 1442-1445.

Takashima, H., Boerkoel, C.F., John, J., Saifi, G.M., Salih, M.A., Armstrong, D., Mao, Y., Quiocho, F.A., Roa, B.B., Nakagawa, M. 2002. Mutation of TDP1, encoding a topoisomerase I-dependent DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. *Nature Genetics*, **32:** 267-272.

Wallace, S.S., Murphy, D.L., Sweasy, J.B. 2012. Base excision repair and cancer. *Cancer Letters*, **327:** 73-89.

Wilson III, D.M., Bohr, V.A. 2007. The mechanics of base excision repair and its relationship to aging and disease. *DNA Repair*, **6:** 544-559.

Wilson III, D.M., Kim, D., Berquist, B.R., Sigurdson, A.J. 2011. Variation in base excision repair capacity. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, **711:** 100-112.

Wolters, S., Schumacher, B. 2013. Genome maintenance

and transcription integrity in aging and disease. *Frontiers in Genetics*, **4:** 19.

Worthley, D.L., Walsh, M.D., Barker, M., Ruszkiewicz, A., Bennett, G., Phillips, K., Suthers, G. 2005. Familial mutations in PMS2 can cause autosomal dominant hereditary nonpolyposis colorectal cancer. *Gastroenterology*, **128:** 1431-1436.

Wright, W.D., Shah, S.S., Heyer, W.D. 2018. Homologous recombination and the repair of DNA double-strand breaks. *Journal of Biological Chemistry*, **293:** 10524-10535.

Yousefzadeh, M., Henpita, C., Vyas, R., Soto-Palma, C., Robbins, P., Niedernhofer, L. 2021. DNA damage—how and why we age? *Elife*, **10:** e62852.

Zhou, T., Lee, J.W., Tatavarthi, H., Lupski, J.R., Valerie, K., Povirk, L.F. 2005. Deficiency in 3'-phosphoglycolate processing in human cells with a hereditary mutation in tyrosyl-DNA phosphodiesterase (TDP1). *Nucleic Acids Research*, **33:** 289-297.

Zhu, Y., Liu, X., Ding, X., Wang, F., Geng, X. 2019. Telomere and its role in the aging pathways: telomere shortening, cell senescence and mitochondria dysfunction. *Biogerontology*, **20:** 1-16.