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Review article:

Overview of DNA Damage and Various Genetic Repair Mechanisms "DNA Damage and Repair Mechanisms"

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Abstract

Nucleic acids (DNA and RNA) carry the genetic information of living organisms in the form of units called genes. Each gene consists of a specific sequence of buildings units called nucleotides that code for making proteins that are essential for our general growth, development and reproduction. Therefore, any disruption in genetic materials will lead to serious complications and diseases that may lead to the death of the organism. Disruption in the genetic material of most living organisms (DNA) can occur by two main types of factors: exogenous factors such as environmental agents (chemicals, radiation and pollutants) and endogenous factors such as highly reactive molecules that are produced within body during metabolic processes. Either exogenous or endogenous factors can damage DNA but the endogenous factor is the most dangerous factors. Fortunately, various induced DNA can be distinguished and repaired by different repair mechanisms that try to fix induced exogenous or endogenous DNA damage. Consequently, the different types of induced DNA damage and various mechanisms of DNA repair will be discussed in the manuscript.

Keywords: DNA damage; Repair mechanisms; Nucleic acids; Genes

1. Genes.

Genes are basic physical and functional unit of heredity that passed from parents to offspring in both sexual and asexual reproduction; it is called coded information because some genes act as instructions and coded to make molecules called proteins. However, many genes do not code for proteins. The coded information is different from species and another. So, Genes vary greatly from one to another **(Torpy, 2008).**

Genes are found inside cell (Figure 1). In Eukaryotes (especially human), every cell

contains about 20000 to 25000 genes and in prokaryotes (only one cell), cell contain approximately 800 genes **(Ghai et al., 2013)**.

All genes are represented in a structure called DNA (deoxyribonucleic acid) which consider hereditary material in all prokaryotic and eukaryotic cells and in many viruses. In Eukaryotes most DNA is long and linear and located in the cell nucleus (where it is called nuclear DNA) which is packaged with ribonucleic acid and proteins into compact structures called chromosomes, but there are a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA). In prokaryotes, DNA is contained in central area of the cell called the nucleoid, which is not surrounded by a nuclear membrane (found in cytoplasm), and also carry small, circular DNA molecules called plasmids, which are distinct from the cytoplasmic DNA and can provide genetic advantages in specific environments **(Torpy, 2008; Libretexts, 2022).**

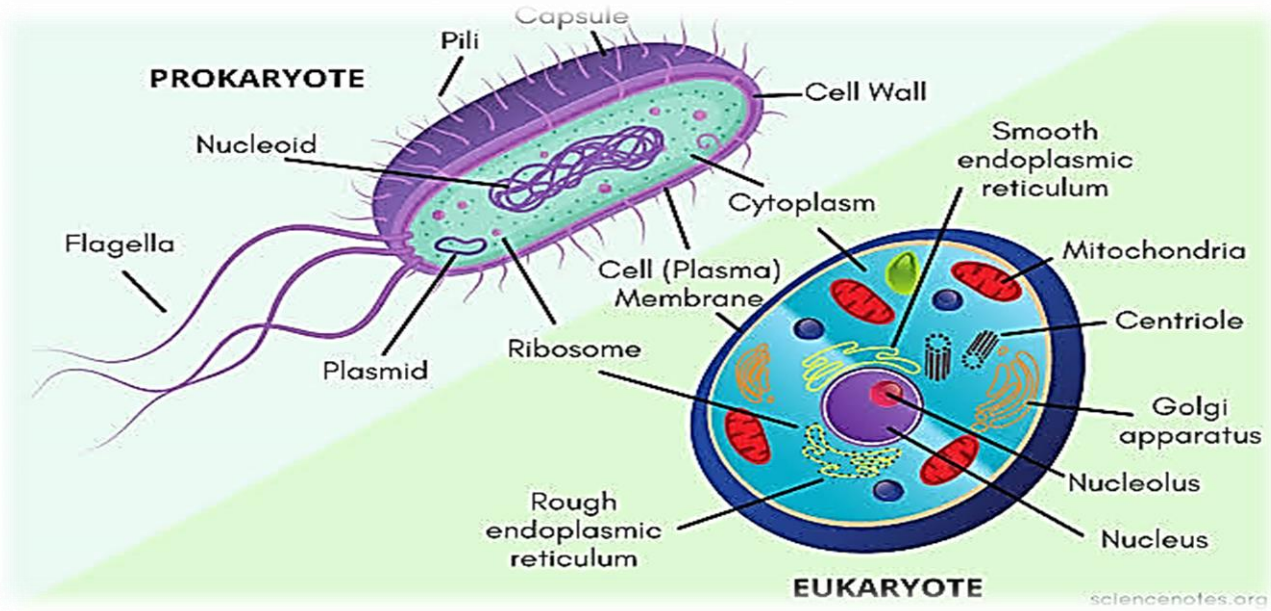

Figure 1: The difference between Prokaryotic and Eukaryotic cell **(Libretexts, 2022)**

2. Structure of DNA

Deoxyribonucleic acid (DNA) is made up of two antiparallel strands that are twisted around each other to form a right-handed helix, called α double helix. The building blocks of DNA are nucleotides, which are made up of three parts:

1) A deoxyribose (5-carbon sugar).
2) A phosphate group.
3) A nitrogenous base.

The nucleotide is named according to the nitrogenous bases, and thus there are four types of nucleotides based on the contained nitrogenous base in DNA (Figure 2): Adenine (A) and guanine (G) are double-ringed

purines nucleotides, while cytosine (C) and thymine (T) are smaller, single-ringed pyrimidines nucleotides **(Alberts *et al.*, 2002)**.

The phosphate group of one nucleotide (which is attached to the 5′ carbon of the) binds covalently with the sugar molecule of the next nucleotide (At 3′ carbon of the next nucleotide) and so on, forming a long polymer of nucleotide monomers (Figure 2). Thus, the single strand of DNA consists of the sugar–phosphate groups line up in a "backbone", and the nucleotide bases stick out from this backbone. The two single strands of DNA held together along their length with hydrogen bonds between the bases. Base-pairing takes place between a purine and pyrimidine nucleotides: namely A pairs with T by two hydrogen bonds, and G pairs with C by three hydrogen bonds **(Alberts *et al.*, 2002).**

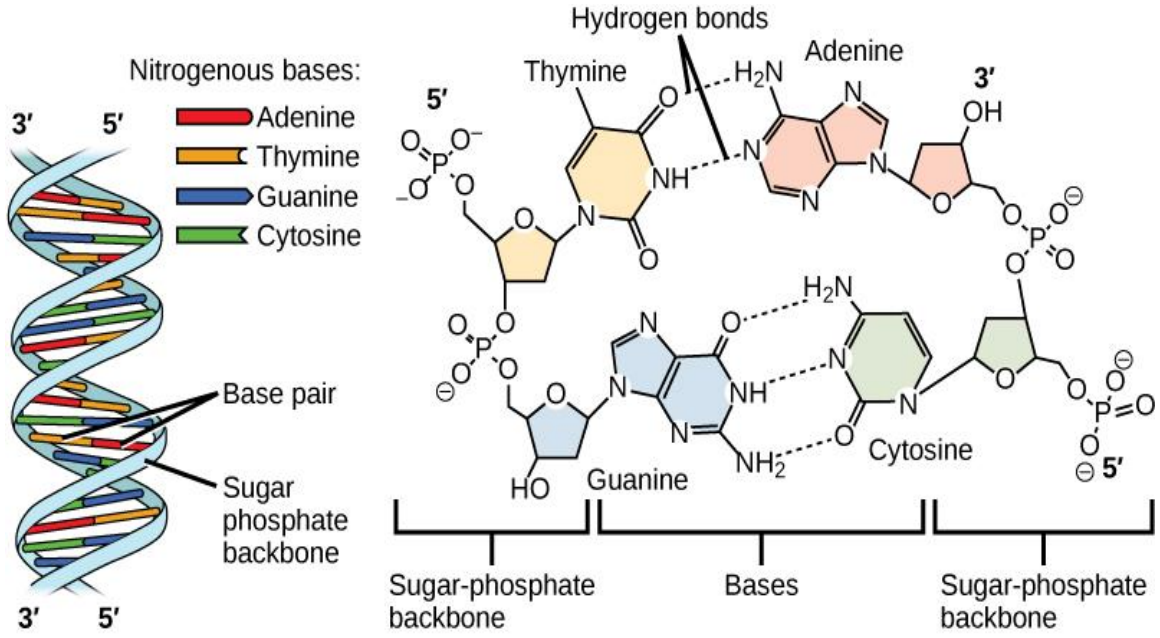

Figure 2: Chemical structure of DNA **(Alberts *et al.*, 2002)**

3. Importance of DNA

DNA carries the genetic information which is specific for each one. The structure and function of DNA has opened up many areas of research, such as genetic engineering, which is an area of study of increasing interest. Forensic science and genealogy also rely heavily on DNA fingerprinting and sequencing for information **(Alberts *et al.*, 2002; Eric Bank, 2019).** It also contains the instructions necessary for life. These instructions exist within the sequence of nucleotide base pairs. The sequence of nucleotide base pairs gives codes that provide directions on how to make proteins that are vital for our growth, development, Reproduction overall health.

This happens by two steps. First step is called transcription step which enzymes read the information in a DNA molecule and transcribe it into an intermediary molecule called messenger ribonucleic acid, or mRNA. Second step is called translation step which the information contained in the mRNA molecule is translated into the "language" of amino acids, which are the building blocks of proteins. This language tells the cell's protein-making machinery the precise order in which to link the amino acids to produce a specific protein. This is a major task because there are 20 types of amino acids, which can be placed in many different orders to form a wide variety of proteins. So, any damage in DNA or any mutation in one nucleotide in DNA has adverse effects on the health and well-being of an individual **(Eric Bank, 2019)**.

4. DNA damage

4.1 Main differences between DNA damage and mutation.

There are distinctly differences between DNA damage and mutation. DNA damage is a change in the basic structure of DNA that is not itself replicated when the DNA is replicated. Also DNA damage can be a chemical addition or disruption to a base of DNA or a break in one or both chains of the DNA strands. DNA damage occurs in both replicating, proliferative cells (such as those forming the internal lining of the colon or blood forming “hematopoietic” cells), and in differentiated, non-dividing cells (such as neurons in the brain or myocytes in muscle) **(Bernstein *et al*., 2013).**

While mutation occurs when DNA carrying a damaged base is replicated, an incorrect base can often be inserted opposite the site of the damaged base in the complementary strand, leading to mutation in the next round of replication. Also, when DNA double-strand breaks may be repaired by an inaccurate repair process leading to mutations. A mutation prevents a gene from carrying out its function, or it causes a gene to be translated into a protein that functions abnormally. Mutations can activate oncogenes, inactivate tumor suppressor genes, or cause genomic instability in replicating cells. So, if DNA damages in proliferating cells are not repaired due to inadequate expression of a DNA repair gene, this increases the risk of cancer. In contrast, when DNA damages occur in non-proliferating cells and are not repaired due to inadequate expression of a DNA repair gene, the damages can accumulate and cause premature aging **(Bernstein *et al*., 2013)**.

4.2 Type of DNA damage

Tens of thousands of DNA damages occur per day per cell, on average, naturally (endogenous) or via environmental factors (exogenous). DNA damage caused by the action of endogenous factors may be more serious and more extensive than the effect of the exogenous DNA damaging factors **(De Bont, 2004).**

4.2.1 Exogenous DNA damage

In exogenous, DNA can be damaged via environmental agents such as short-wavelength electromagnetic energy such as ultraviolet (UV) radiation light, ionizing radiation, and genotoxic chemicals **(De Bont, 2004; Flatt, 2019).**

4.2.2 Endogenous DNA damage.

In endogenous, DNA damage occur due to reactive molecules such as reactive oxygen species, reactive nitrogen species, reactive carbonyl species, lipid peroxidation products and alkylating agents, that produced by metabolism or by hydrolytic reactions in the warm aqueous cellular replication. So, we can divide endogenous damage to several types: (A) oxidative processes, (B) alkylation process, (C) bulky adduct formation, (D) base loss or hydrolysis of bases, (E) base pair mismatched (F) DNA crosslinking, and DNA strand breaks, including single and double stranded breaks **(Flatt, 2019).**

A) Oxidative damage.

Reactive oxygen species (ROS) Such as Hydroxyl radicals (•OH) is the most reactive and electrophilic of the ROS (Figure 3). The •OH can cause the formation of 8-oxo-7,8-dihydroguanine (8-oxoG) from guanine residues because guanine is the most easily oxidized of the nucleic acid bases, due to having the lowest ionization potential among the DNA bases. It has been estimated that up to 100,000 8-oxo-dG lesions can occur daily in DNA per cell. So, the 8-oxo-dG is one of the most abundant DNA lesions, and it considered as a biomarker of oxidative stress and a lot of diseases as shown in Figure 4 **(Flatt, 2019; Poetsch, 2020)**.

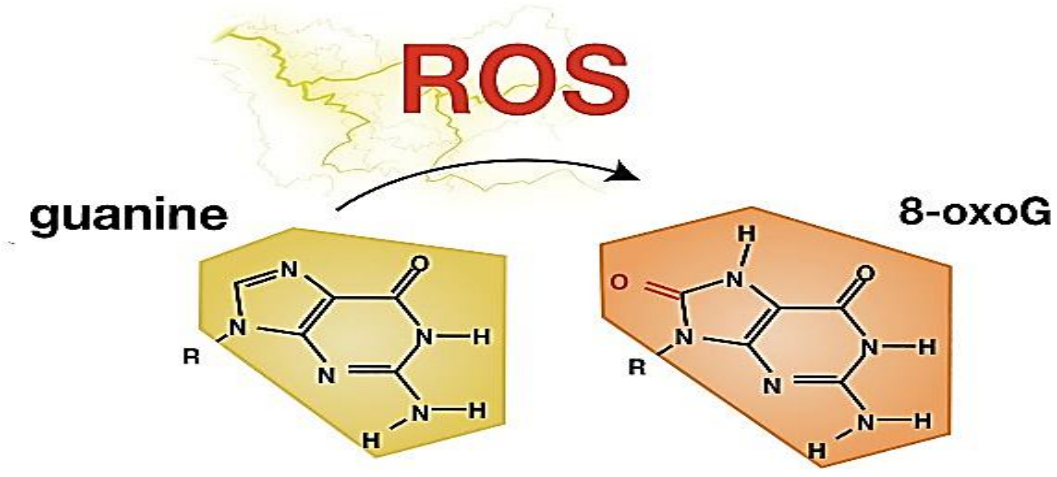

Figure 3: 8-oxoG is the result of reactive oxygen (ROS) modifying a guanine **(Poetsch, 2020)**

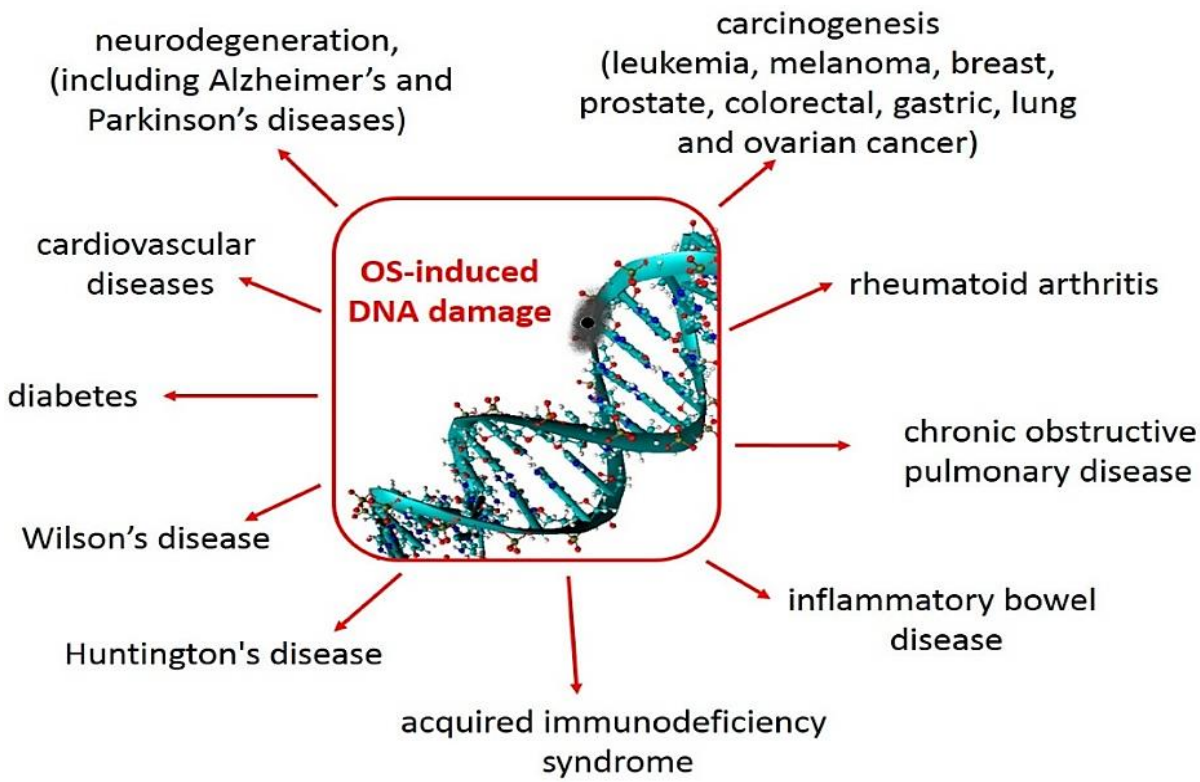

Figure 4: DNA damage caused by oxidative stress has been associated with many human disease states (Flatt, 2019)

B) Bases alkylation

Alkylating agents are produced by-products of cellular metabolism such as methylation process (The most common type of alkylation). Simple methylating agents form adducts at O – N and -atoms causing several changes for DNA because alkylating agents are generally electrophilic compounds that have an affinity for the nucleophilic centers in organic macromolecules and react in either a mono- or bifunctional manner for example N7-methylguanine (7meG), N3-methyladenine (3meA), and O6-methylguanine (O6meG). A particularly important type of damage is methylation of the O6 position of guanine, because the product, O6-methylguanine, forms complementary base pairs with thymine instead of cytosine (Figure 5). Also, smaller amounts methylation occurs on other DNA bases, including the formation of N1-methyladenine (1meA), N3-methylcytosine (3meC), O4-methylthymine (O4meT), and methyl phosphotriesters (MPT). Interestingly, O-alkylation are more mutagenic and harmful than N-alkylation, which may be more cytotoxic, but not as mutagenic **(Flatt, 2019; Kondo *et al.*, 2010).**

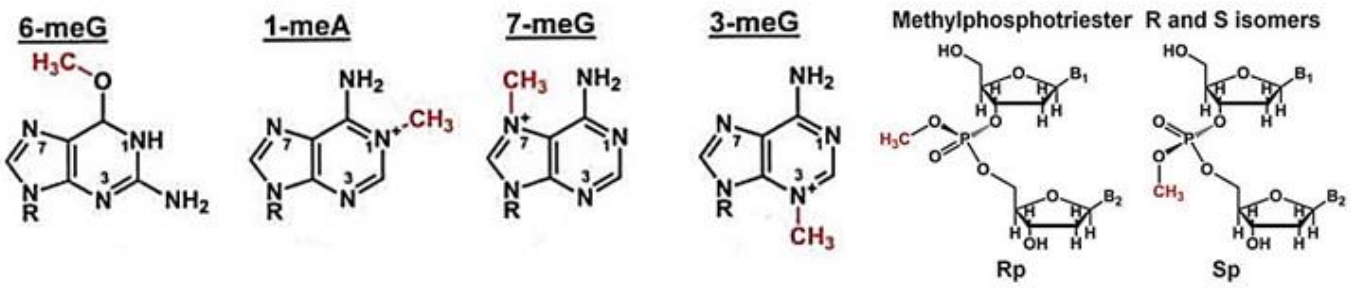

Figure 5: The diagram shows DNA modified by small alkylating agents (methyl) and Phosphotriester formation indicated by the presence of methyl groups, along with the Rp and Sp isomers **(Flatt, 2019)**

C) Bulky adducts formation

Bulky adducts are chemicals are biologically reactive and will form covalent linkages with biological molecules such as DNA. The best example of bulky adducts is f benzo[a]pyrene (Cigarette smoke is a source of benzo[a]pyrene). When body is exposed to these molecules, it will start a metabolic process that makes the molecule more hydrophilic and easier to remove as a waste product. Unfortunately, in the case of benzo[a]pyrene, the resulting metabolite is a highly reactive epoxide that forms a bulky adduct preferentially with guanine residues in DNA (Figure 6). DNA adducts play a central role in chemical carcinogenesis **(Flatt, 2019; Hang, 2010)**.

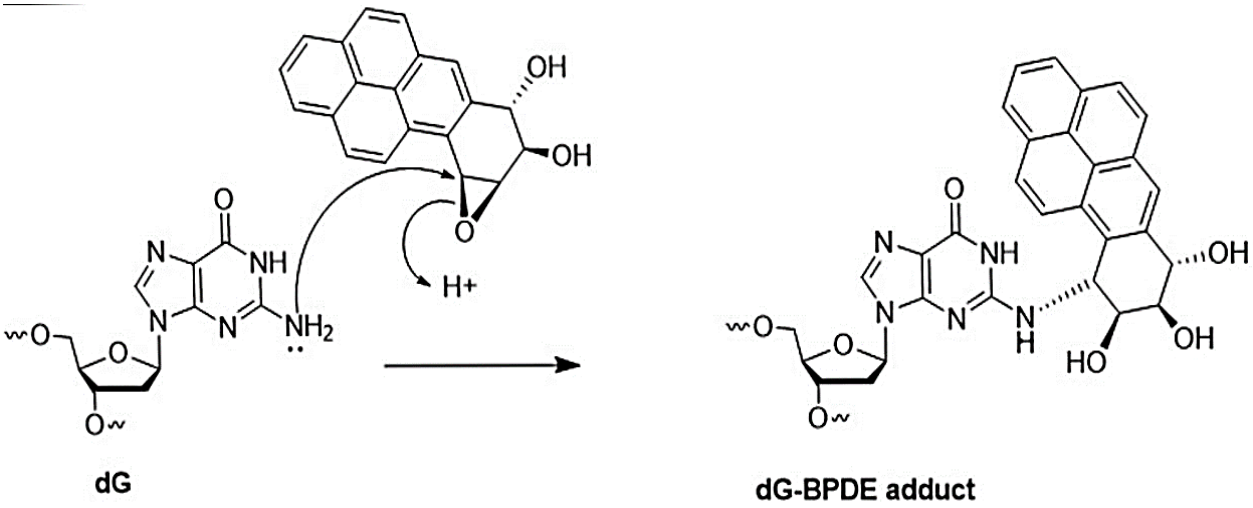

Figure 6: Activated benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide can form a DNA adduct with guanine residues (Flatt, 2019)

D) Bases Loss

Bases loss is a process caused by hydrolysis of bases known as depurination (loss of purine bases) or depyrimidination (loss of pyrimidine bases) and leading to an empty site called the abasic AP site (also called an apurinic or apyrimidinic site). Purine losing is more common than pyrimidine (Figure 7). The formation of abasic sites in a human cell has been estimated at ~18,000 per day. Abasic sites occur because alkylated purines (N7-alkyl guanines and N3-alkyl adenines) have labile glycosidic bonds (glycosidic bonds are bonds binding nitrogen bases with sugar–phosphate backbone. So, they can be released from DNA by heating for 30 min at ~90° C at neutral pH **(Guengerich, 2018).**

We can say that abasic site is non-informational site that give rise to miscoding by DNA polymerases. Depurination can play a major role in cancer initiation **(Hang, 2010)**.

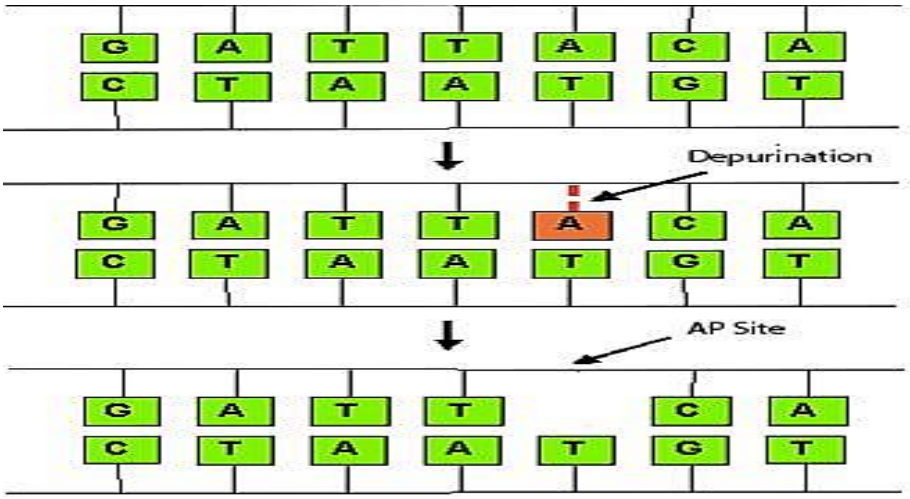

Figure 7: Depurination process (Flatt, 2019)

E) Base pair mismatch

The presence of a non-homologous base in double-stranded DNA results from spontaneous deacetylation of cytosine or adenine, mismatches during homologous recombination, or errors during DNA replication that are not removed by DNA error correction. Multiple, sequential mismatches in base pairs lead to the formation of a DNA heteroduplex **(Flat, 2019).**

F) DNA crosslinking and DNA breaks

i. **DNA Crosslinking**

Crosslinking of DNA occurs when various exogenous or endogenous agents react with two nucleotides of DNA, forming a covalent linkage between them. This crosslink can occur within the same strand (intra-strand) or between opposite strands of double-stranded DNA (inter-strand). The best example for crosslinking agent, nonionizing radiation UV light which cause molecular crosslinks to between two pyrimidine residues, commonly two thymine residues, that are positioned consecutively within a strand of DNA

(intra-strand) making Thymine Dimer Formation. This leads to formation of a cyclobutane ring resulting from saturation of the double bonds or pyrimidine pyrimidones (6–4) photoproducts **(Flatt, 2019; Huang and Li, 2013).**

Inter-strand crosslinking is more harmful than intra-strand because it causes an absolute block to DNA strand separation interrupting essential DNA metabolic processes such as replication and transcription. Left unrepaired inter-strand crosslinks can be extremely toxic especially in dividing cells, stalling DNA replication and leading to cell death. This type of crosslinking has useful merit in chemotherapy and targeting cancerous cells for apoptosis **(Huang and Li, 2013).**

***ii.* DNA breaks**

Ionizing radiation from radioactive decay or cosmic rays such as X-rays and gamma rays has enough energy to cause single and double breaks in the DNA backbone (Figure 8). Also, chemical agents that form crosslinks within the DNA, especially inter-strand crosslinks, can also lead to DNA strand breaks. Indeed, if the damaged DNA undergoes DNA replication this crosslinked DNA can cause topoisomerase enzymes to stall in the transition state when the DNA backbone is in the cleaved state. Instead of relieving supercoiling and resealing the backbone, the stalled topoisomerase remains covalently linked to the DNA in a process called abortive catalysis. This leads to the formation of a single stranded break in the case of Topoisomerase-1 enzymes or double stranded breaks in the case of Topoisomerase-2 **(Flatt, 2019; Huang and Li, 2013)**

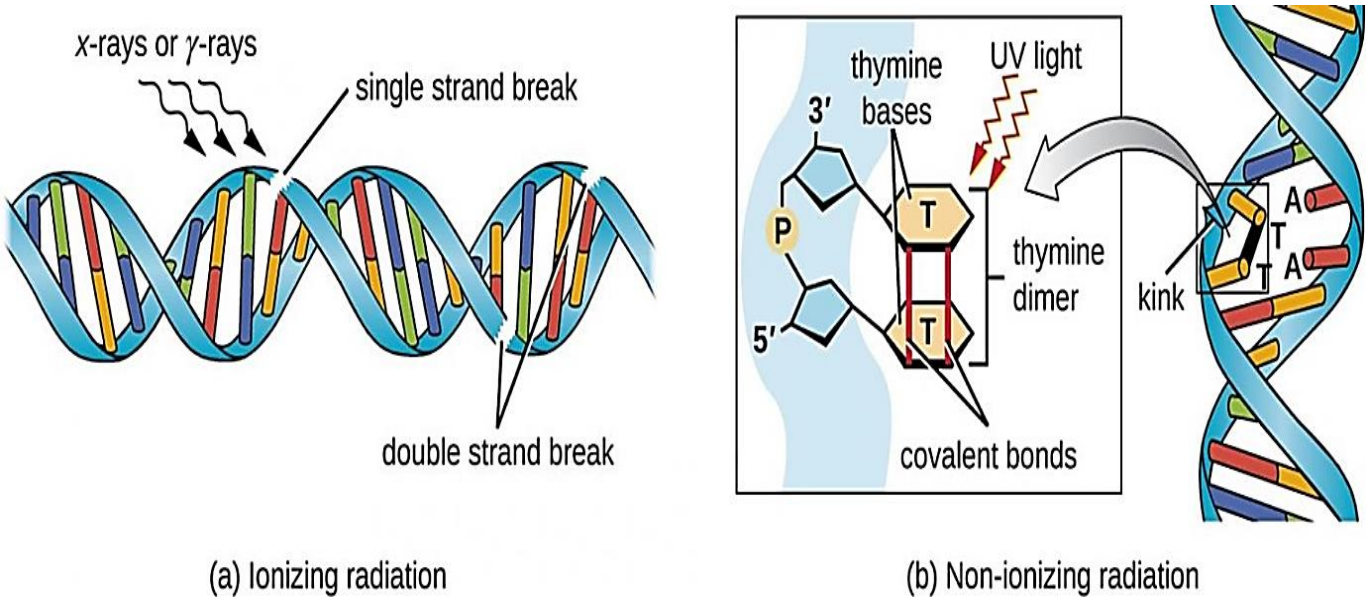

Figure 8: The difference between ionizing and non-ionizing radiation (Flatt, 2019)

5. DNA repair.

All above mentioned types of DNA damage can be avoided it if accurate DNA repair systems recognize DNA damages as abnormal structures and repair the damages prior to replication. Fortunately, the organisms have evolved checkpoint mechanisms and facilitate cells respond to DNA damage by activating a complex DNA-damage-response pathway that includes cell-cycle arrest, the transcriptional and post-transcriptional activation of a subset of genes including those associated with DNA repair. If damage is too extensive to be repaired, apoptotic pathways will be elicited **(Ma & Dai, 2018).**

5.1. General mechanism of DNA repair.

The general reconized mechanisms of DNA repair **(Cooper and Hausman, 2000)** are:

(1) Direct reversal of the chemical reaction responsible for DNA damage.

(2) Removal of the damaged bases followed by their replacement with newly synthesized DNA.

(3) Repair of Double-Stranded DNA Breaks

(4) Postreplication Repair

5.1.1. Direct Reversal of DNA Damage.

Direct reversal of DNA damage is a mechanism of repair that does not require a template. Only eliminates some DNA modifications without using excision, re-synthesis, and ligation. It is a more efficient way of dealing with specific types of DNA damage that occur frequently. Only a few types of DNA damage are repaired in this way, particularly Alkylation damage and pyrimidine dimers resulting from crosslinking **(Cooper & Hausman, 2000; Ahmad *et al.*, 2015)**.

In Alkylation damage repaired by two enzymes, the first one is called Xn alkylguanine alkyltransferase (x: O or N/ alkyl: methyl or ethyl) which have cysteine residue on its active site. This enzyme is found in prokaryotes, archea, and many eukaryotes and also found in human. For example: O6-methylguanine damage repair by O6-methylguanine methyltransferase that transfer the methyl group from O6-methylguanine to a cysteine residue in its active site converting cysteine to S-methylcysteine. The second one is called ALKBH α-ketoglutarate Fe (II) dioxygenases (FeKGDs). The family of FeKGDs encompasses nine proteins with conserved active site domains, but removal of alkyl damage in DNA has only been established for four family members, ALKBH1 – ALKBH2-ALKBH3 and obesity associated gene FTO. This enzyme is found in prokaryotes, and many eukaryotes (especially in mammals ALKBH2-ALKBH3). Unlike repair by MGMT, each ALKBH can catalyze numerous repair reactions to eliminate N or o-modifications of cytosine, adenine, thymine and guanine residues. These reactions are known as oxidative demethylation that results releasing of the hydroxylated methyl group as formaldehyde. The repair reaction consists of four steps with various intermediates.

The first step of this mechanism involves a reaction between the active site Fe (II) and O2 which produces a superoxo anion (O2-) bound to Fe (III). The second step Involves the superoxide attacks the α-keto carbon of the α-ketoglutarate, resulting in a bridged peroxotype intermediate. The third step Involves the intermediate is decarboxylated releasing succinate and CO2 and undergoes a heterolytic cleavage of the O–O bond to form the high-valence ferryl-oxo intermediate. The fourth step Involves oxo intermediate hydroxylates the alkyl adduct on the DNA producing an unstable intermediate that decomposes in water, with release of formaldehyde for methylated bases **(Cooper and Hausman, 2000; Ahmad *et al*., 2015)**.

In pyrimidine dimers resulting from crosslinking, direct reversal of the dimerization reaction occurs this process is called photo-reactivation because energy derived from visible light or near UV is utilized to break the cyclobutane ring structure or pyrimidine pyrimidones (4-6) photoproduct. That lead to the original pyrimidine bases remain in DNA, now restored to their normal state. All of this occurs by a single enzyme, is called photolyase. Photolyase is present in bother prokaryotes and eukaryotes. Photolyases are flavoproteins and contain two light-harvesting cofactors. The first one is present in all photolyases which is called flavin adenine dinucleotide (FAD) which fully reduced in the influence of visible light from the violet/blue end of the spectrum to $FADH^-$ (it is catalytically competent), then initial electron-transfer step from $FADH^-$ to the lesions, a dimer-splitting process, and a final electron-transfer step from the pyrimidine monomer radical back to FADH· occur, thus regenerating $FADH^-$. The second one binds to N-terminal domain of photolyases. The second cofactor is variable, it may be either the pterin methenyltetrahydrofolate (MTHF) in folate photolyases or the deazaflavin 8-hydroxy-7,8-didemethyl-5-deazariboflavin (8-HDF) in deazaflavin photolyases (Figure 9). It is important for accelerates reaction rate in low-light conditions. This mechanism of DNA repair lacks in human **(Cooper & Hausman, 2000; Yi and He, 2013)**.

5.1.2. Removal of the damaged bases

This process called excision repair, when the damaged DNA is recognized and removed, either as free bases or as nucleotides. The resulting gap is then filled in by synthesis of a new DNA strand, using the undamaged complementary strand as a template. Excision repair is a more general means of repairing a wide variety of damage DNA **(Cooper and Hausman, 2000).**

There are three types of excision repair mechanism **(Cooper & Hausman, 2000)**; A) base-excision repair, B) nucleotide-excision repair, and C) mismatch repair:

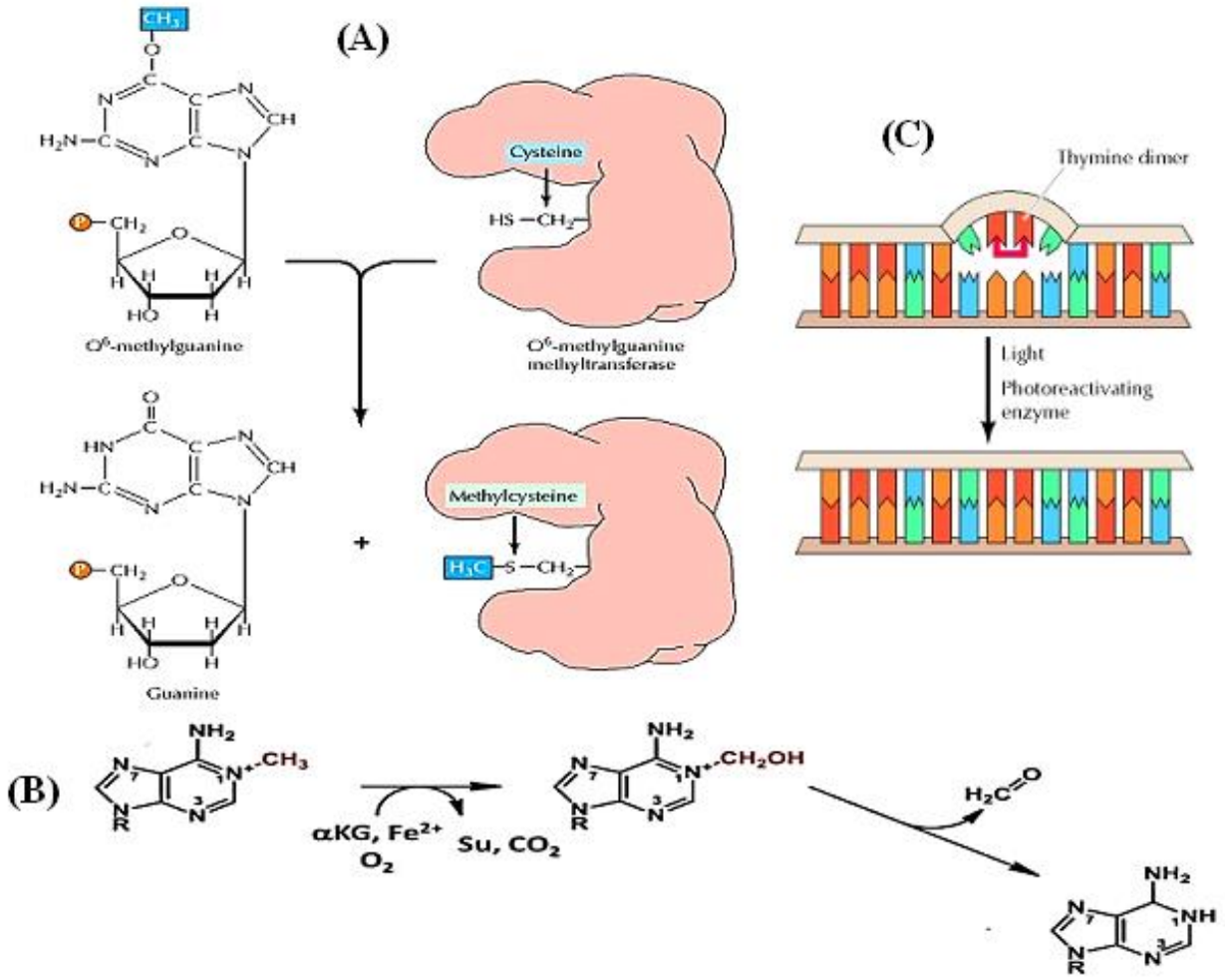

Figure 9: Direct repair of A) O6-methylguanine damage by O6-methylguanine methyltransferase B) 1-meA by ALKBH α-ketoglutarate Fe (II) dioxygenases (FeKGDs) C) thymine dimers by photo-reactivation, in which energy from visible light is used to split the bonds forming the cyclobutane ring (Cooper & Hausman, 2000; Ahmad *et al.*, 2015)

A) Base excision repair (BER) mechanism

***i*. Base excision repair (BER) mechanism in prokaryotes**

It occurs when one base is modified into incorrect base making impairing with another based on complementary leading to DNA (this damage due to oxidative processes, alkylation process, bulky adduct formation). Once cell recognized this problem, the excision mechanism activated by specific enzyme called DNA glycosylase, an enzyme that cleaves the bond linking the base to the deoxyribose of the DNA backbone (N-N-glycosidic bond). This reaction

yields free base leaving a sugar with no base attached and formation of an apyridiminic or apurinic site (generally called an AP site) in DNA. Then removing backbone by AP endonuclease which cleaves the DNA backbone 5′ to the abasic site, thus generating 3′-OH and 5′-deoxyribose-5-phosphate (5′-dRP) (if DNA glycosylase monofunctional), or AP lyase activity, usually associated with a subset of DNA glycosylases which catalyzes 3′ incision to the AP site by β-elimination, generating 3′-α, β unsaturated aldehyde (3′-PUA), and 5′-hydroxyl (OH) termini then unconventional ends generated by AP lyases (3′-PUA) need to be processed to conventional 3′-OH and 5′-P termini, respectively, to allow DNA polymerization and ligation preforming its action . Cleaning of 3′-PUA ends is performed by the 3′-phosphodiesterase activity of AP endonucleases, (All of this happen if DNA glycosylase bifunctional). The result is the single nucleotide gap which processed further into 1) direct addition of correct nucleotide restoring the original structure by the action of polymerase and ligase (this path is short patch also is called "single-nucleotide BER) or 2) single strand breaks via backbone by Flap endonuclease which cleaves adjacent to the AP site. The remaining deoxyribose moiety is then removed, and the resulting gap (2–10) nucleotides are filled by DNA polymerase and ligase (long patch) **(Cooper and Hausman, 2000; Krokan and Bjoras, 2013)**.

So, the subsequent steps are incision, end processing, repair synthesis, and ligation "common steps" but in reality, take place by different mechanisms, depending on the type of polymerase and physiological state of the cell. In Short-patch BER requires several repair-specific proteins that do not participate in replication and is equally efficient in proliferating and nonproliferating cells while long-patch require replication proteins mainly occurs in proliferating cells for treatment after glycosylase action and strand cleavage by APE. (Krokan & Bjoras, 2013)

For example, uracil can arise in DNA by two mechanisms: (1) Uracil as deoxyuridine triphosphate (dUTP) is occasionally incorporated in place of thymine during DNA synthesis, and (2) uracil can be formed in DNA by the deamination of cytosine. Once a single damaged DNA base is recognized, the excision of uracil in DNA will be activated **(Cooper & Hausman, 2000)**. This mechanism is also useful in repair DNA damage result from base loss and single strand DNA break **(Flatt, 2019)**.

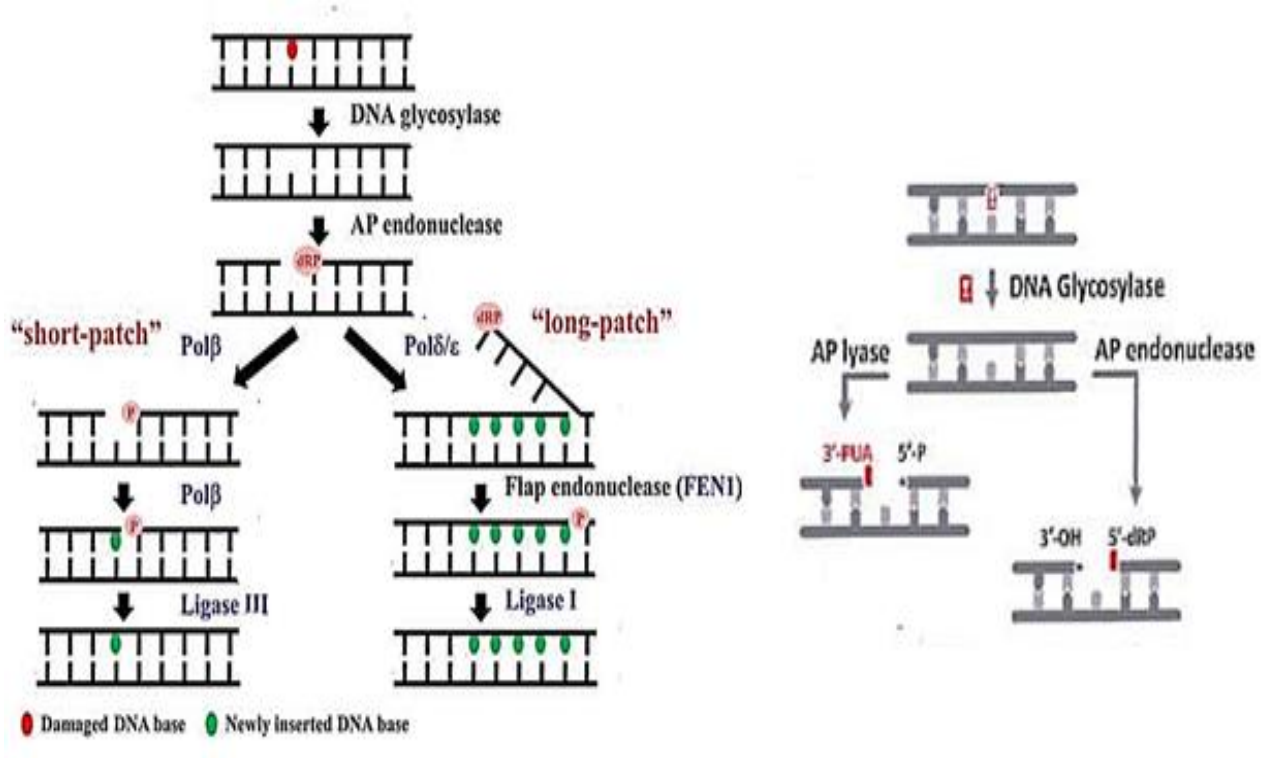

Figure 10: Base excision repair generally (A) and the difference between AP endonuclease and AP lyase (B) (Krokan and Bjoras, 2013)

ii. **Base excision repair (BER) mechanism in eukaryotes**

It occurs in the same way in prokaryotes, but it takes place in eukaryotic nuclei or mitochondria, largely using different isoforms of proteins or genetically distant proteins such as 1) one of at least 11 distinct DNA glycosylases, depending on the type of lesion, 2) AP endonuclease 1 (APE1) is highly enriched in nuclei or AP endonuclease 2 (APE2) is enriched in mitochondria and 3) DNA polymerase b (Pol β), and DNA ligase I or III (LIG1/3, 1 in nuclease 3 in mitochondria) in short patch or DNA polymerase δ/ε, PCNA, flap endonuclease FEN1, and LIG1 in long patch **(Krokan and Bjoras, 2013).**

B) Nucleotide excision repair (NER) mechanism

It is happened by removing part of an oligonucleotide (nucleotide strand containing at least 2 bases) containing the lesion. That is happened by serval steps first recognition the damage then cleave on the 3′ and 5′ sides of the damaged site by specific proteins, respectively, thus excising an oligonucleotide by helicase which have ability to directly excise an oligonucleotide. Then the action of a exonuclease or endonuclease, is required to remove and degrade the damage-containing oligonucleotide from the

double-stranded DNA molecule, and the resulting gap is filled by DNA polymerase. Finally reparative synthesis is occurred by using the undamaged strand as a template, followed sealing by ligase. This damage recognition step can occur in two manners: Global genome nucleotide excision repair (GG-NER) or transcription-coupled nucleotide excision repair (TC -NER) **(Cooper and Hausman, 2000; Vaughn and Sancar, 2020)**.

For Global genome nucleotide excision repair (GG-NER): it occurs detects and eliminates damages in the entire genome, including the untranscribed regions and silent chromatin (independent of transcription). It is activated by a specialized protein factor that reveals the damage **(Vaughn and Sancar, 2020)**.

For transcription-coupled nucleotide excision repair (TC -NER): it only occurs for damage on the transcribed strand of actively transcribed genes. It i s activated by the stalling of RNA polymerase II at the damaged sites of a transcribed strand **(Vaughn and Sancar, 2020).**

The process of recommendation is recognized by coordinated action of approximately 30 proteins that successively form complexes with variable compositions on the DNA unlike BER, where a damaged base is simultaneously recognized by a single specialized glycosylase **(Cooper & Hausman, 2000)**. This mechanism is very specific for crosslinking DNA damage that forms pyrimidine dimers. It is unique mechanism to repair the formation of pyrimidine dimers from UV light within humans **(Cooper and Hausman, 2000)**

***i.* Nucleotide excision repair (NER) mechanism in prokaryotes**

Global genome nucleotide excision repair is carried out by three key proteins UvrA (100 kDa), UvrB (85 kDa), and UvrC (66 kDa), with additional accessory proteins to help recognition and release of the excised oligodeoxynucleotides (Figure 11). Specifically, damage is recognized by UvrA, an ATPase. The UvrA homodimer then recruits a second ATPase, UvrB, to the site and a stable UvrB–DNA complex is formed by an ATP hydrolysis-dependent reaction. Once this stable complex is formed, UvrA is released and UvrC is recruited to the complex by UvrB. UvrC creates both the 5′ and 3′ incisions using its two nuclease active sites. These incisions are made seven nucleotides from the 5′ end and three nucleotides from the 3′ end of the adduct to create a 12-base long oligodeoxynucleotide (12mer). UvrD, an accessory NER protein, is a helicase and through this activity causes the release of both the excised oligodeoxynucleotides and UvrC. the excised oligodeoxynucleotide is degraded by exonucleases (Exo I, Exo VII, and RecJ). The gap is then filled in through repair synthesis by polymerase I. If DNA polymerase I is not present, repair synthesis can be conducted by DNA polymerase II or DNA polymerase III. This repair patch is then ligated by

DNA ligase to complete the repair process **(Cooper and Hausman, 2000; Vaughn and Sancar, 2020).**

In transcription-coupled nucleotide excision repair: damage recognition can be accelerated when RNA polymerase stalls after encountering a DNA lesion. The stalled RNA polymerase then forms a stable complex with the damaged DNA. The stimulating effects of this complex on repair in cells are through another accessory repair protein, the 130 kDa Mfd translocase, The Mfd protein helps displace RNA polymerase to make the damaged DNA accessible to repair factors and helps recruit the UvrA, B, and C, to the damaged site. These actions accelerate damage recognition and, in turn, repair by polymerase I This repair patch is then ligated by DNA ligase to complete the repair process **(Vaughn and Sancar, 2020)**.

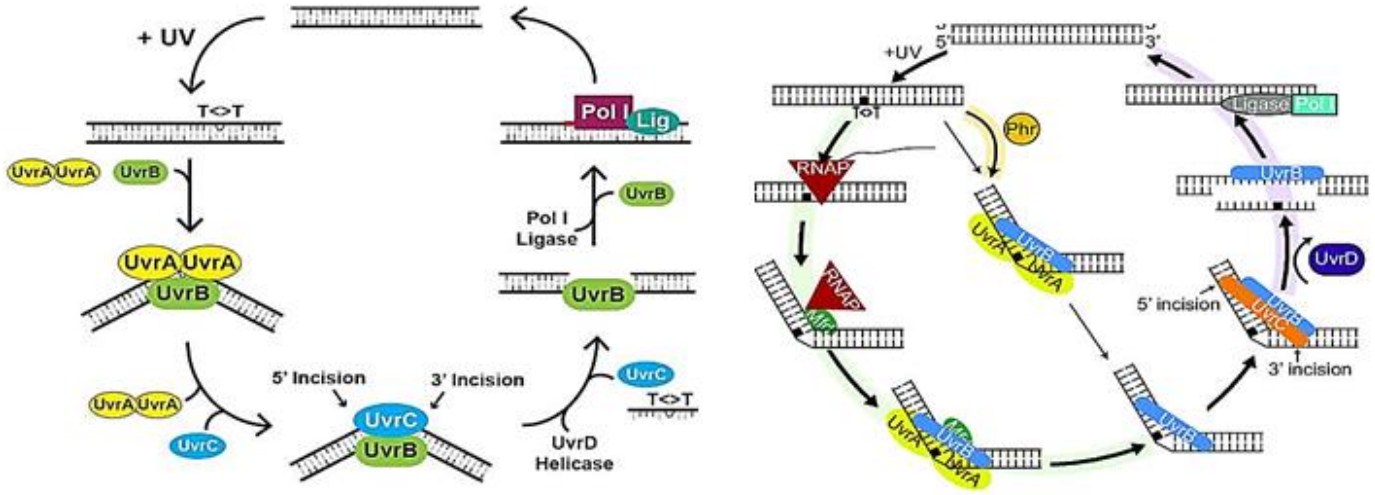

Figure 11: Nucleotide excision repair in prokaryotes (Vaughn & Sancar, 2020)

ii. Nucleotide excision repair (NER) mechanism in eukaryotes

In higher eukaryotic cells, NER excises 24-32 nucleotide DNA fragments containing the damaged lesion with extreme accuracy. Over sixteen proteins are involved in the NER pathway in mammalian cells, including XPA, XPChHR23B, replication protein A (RPA), transcription factor TFIIH, XPB and XPD DNA helicases, ERCC1-XPF and XPG, Polδ, Polε, DNA ligase I or the XRCC1- ligase3, and RNA polymerase **(Flatt, 2019; Vaughn and Sancar, 2020)**.

In Global genome nucleotide excision repair: It is initiated by XPC, RPA, and XPA recognizing damage and recruiting the TFIIH repair complex (Figure 12). The TFIIH repair complex includes the helicase XPB and XPD which help with damage recognition and unwinding DNA to create a repair bubble of about 25 base pairs surrounding the DNA lesion (25mer). XPC then dissociates

from the repair complex. This is followed by the recruitment of XPF and XPG which create 5′ and 3′ incisions using the SMX family structure-specific endonuclease active site. The excised oligodeoxynucleotide is then released in complex with TFIIH. Once TFIIH dissociates from the excised oligodeoxynucleotide, the oligodeoxynucleotide is then degraded by nucleases. Following the release of the damaged DNA, DNA polymerases fill in the gap in the DNA with repair synthesis by DNA polymerase. The type of DNA polymerase depends on the cell cycle stage. In proliferating cells, DNA pol δ/ε δ or ε (in association with RFC and PCNA) fill in the gap, while in non-proliferating cells, other polymerases such as DNA pol κ/λ complete this task. After this, ligation of the repaired patch occurs by either DNA ligase I or the XRCC1- ligase3 complex, the process of NER is complete **(Cooper and Hausman, 2000; Vaughn and Sancar, 2020)**.

In transcription-coupled nucleotide excision repair: damage recognition can be accelerated when RNA polymerase II forms a stable RNA pol II-DNA complex. Then recruit repair factors to the stalled RNA polymerase one of two translocases, CSB or CSA. The binding of CSB to RNA polymerase II facilitate the recruitment of NER factors and promote subsequent repair of the damaged DNA. Like global genome mechanism but XPC is not involved in the repair process **(Vaughn and Sancar, 2020)**.

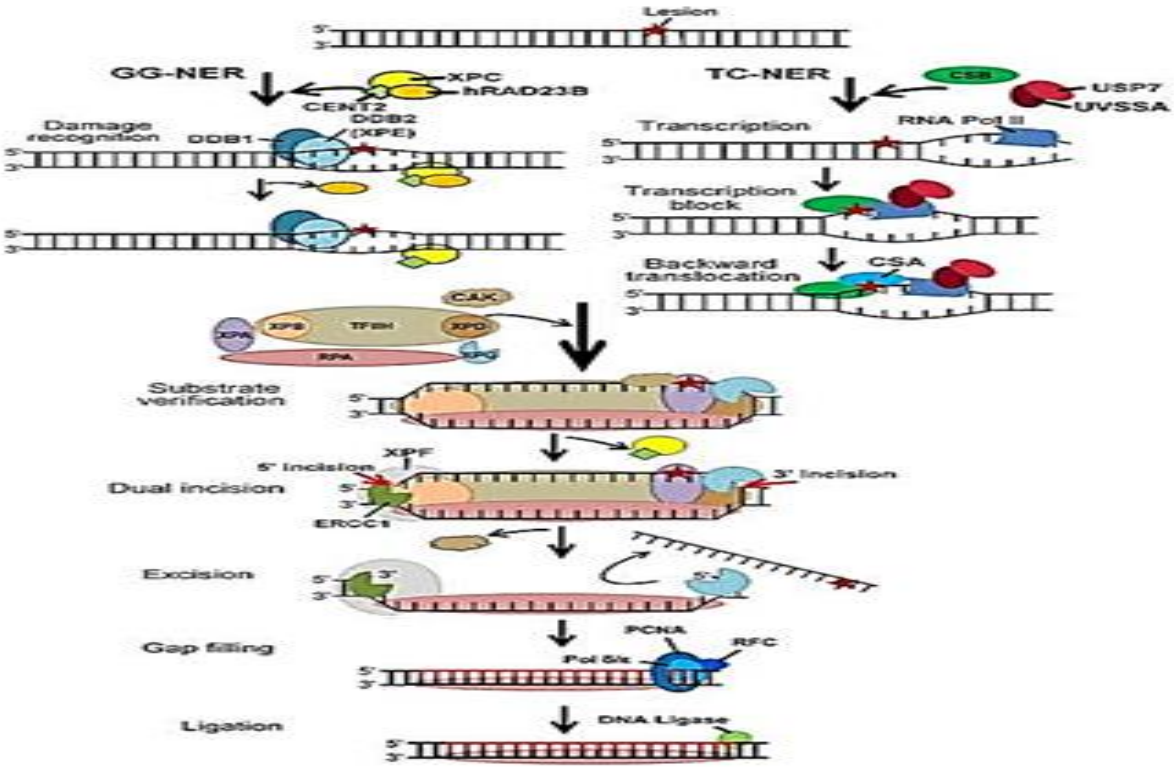

Figure 12: Nucleotide excision repair in Eukaryotes (Cooper and Hausman, 2000)

C) Mismatch repair (MMR) mechanism

DNA mismatch repair (MMR) is a highly conserved DNA repair system that greatly contributes to maintain genome stability. The mechanism is activated when base pair mismatched occur during replication and are not removed by proofreading DNA polymerase. The ones that are missed are subject to later correction which scans newly replicated DNA. So, if a mismatch is found, the specific proteins of this repair system are able to identify the mismatch base and make a nick at 3' or 5' of strand following excise the part of strand including mismatch base by exonuclease activity. Finally, specifically the newly replicated DNA strand form by the action of DNA polymerase and ligase, allowing the error to be corrected and the original sequence restored **(Cooper and Hausman, 2000; Li, 2007)**.

***i.* Mismatch repair (MMR) mechanism in prokaryotes**

The Mismatch base occurred in hemimethylation strand during replication from parent strand (methylation strand). key players of MMR in prokaryotes are many proteins such as MutS, MutL, MutH, DNA helicase II (MutU/UvrD), four exonucleases (ExoI, ExoVII, ExoX, and RecJ), single-stranded DNA binding protein (SSB), DNA polymerase III holoenzyme (Figure 13), and DNA ligase **(Li, 2007).**

MutS has been called the "mismatch recognition" protein because it is responsible for recognizes base-base mismatches. It has ATPase/dimerization domain. Once the recognition is occurred MutS binds to a mismatch as a homodimer. Then MutL interacts physically with MutS, enhances mismatch recognition, and recruits and activates MutH. Then the strand-specific nick generated by MutH which has endonucleases activity. But by MutS and MutL complex, the site 5′ or 3′ to the mismatch is cleaved because it stimulates the loading and the processivity of MutU helicase II (or UvrD) at the MMR initiation site. Depending on the position of the strand break relative to the mismatch, ExoI or ExoX (3′→5′ exonuclease), or ExoVII or RecJ (5′→3′ exonuclease) excises the nicked strand from the nicked site. That is generating single-strand DNA, which is rapidly bound by single-stranded DNA-binding protein (SSB) to protect it from nuclease attack and undergoes repair DNA resynthesis and ligation by DNA polymerase III holoenzyme, SSB, and DNA ligase **(Li, 2007; Graham *et al.*, 2018).**

***ii.* Mismatch repair (MMR) mechanism in eukaryotes**

The main proteins require are human homologs of MutS, MutL, EXO1, single-strand DNA-binding protein RPA, proliferating cellular nuclear antigen (PCNA), DNA polymerase δ (pol), and DNA ligase. There are similarities between MMR in eukaryotes and MMR in prokaryotes such as 1) absence of MutH and 2) MutS and MutL proteins in prokaryotes are homodimers but in

Eukaryotes MutS and MutL are heterodimers (Figure 14).

MutS is present in two forms hMutSα or hMutSβ and plays a critical role in mismatch recognition and initiation of repair. hMutSα preferentially recognizes base-base mismatches and ID mispairs of 1 or 2 nucleotides, while hMutSβ preferentially recognizes larger ID mispairs. MutL is present in three forms hMutLα, hMutLβ, or hMutLγ. hMutLα regulates termination of mismatch by possessing a PCNA/replication factor C (RFC)-dependent endonuclease activity which plays a critical role in 5′ nick and cleavage the nucleotide mismatch. hMutLγ plays a role in meiosis, but no specific biological role has been identified for hMutLβ. A 5' Nick excises by EXO1, a 5′→3′ exonuclease, in the presence of MutSα or MutSβ. the ssDNA gapped region generated during excision is protected by single-strand DNA-binding protein RPA,l and high mobility group box 1 protein (HMGB1) (they have DNA-unwinding activity) so facilitates DNA resynthesis by and DNA pol δ and ligation by DNA ligase **(Li, 2007; Pećina-Šlaus *et al.*, 2020).**

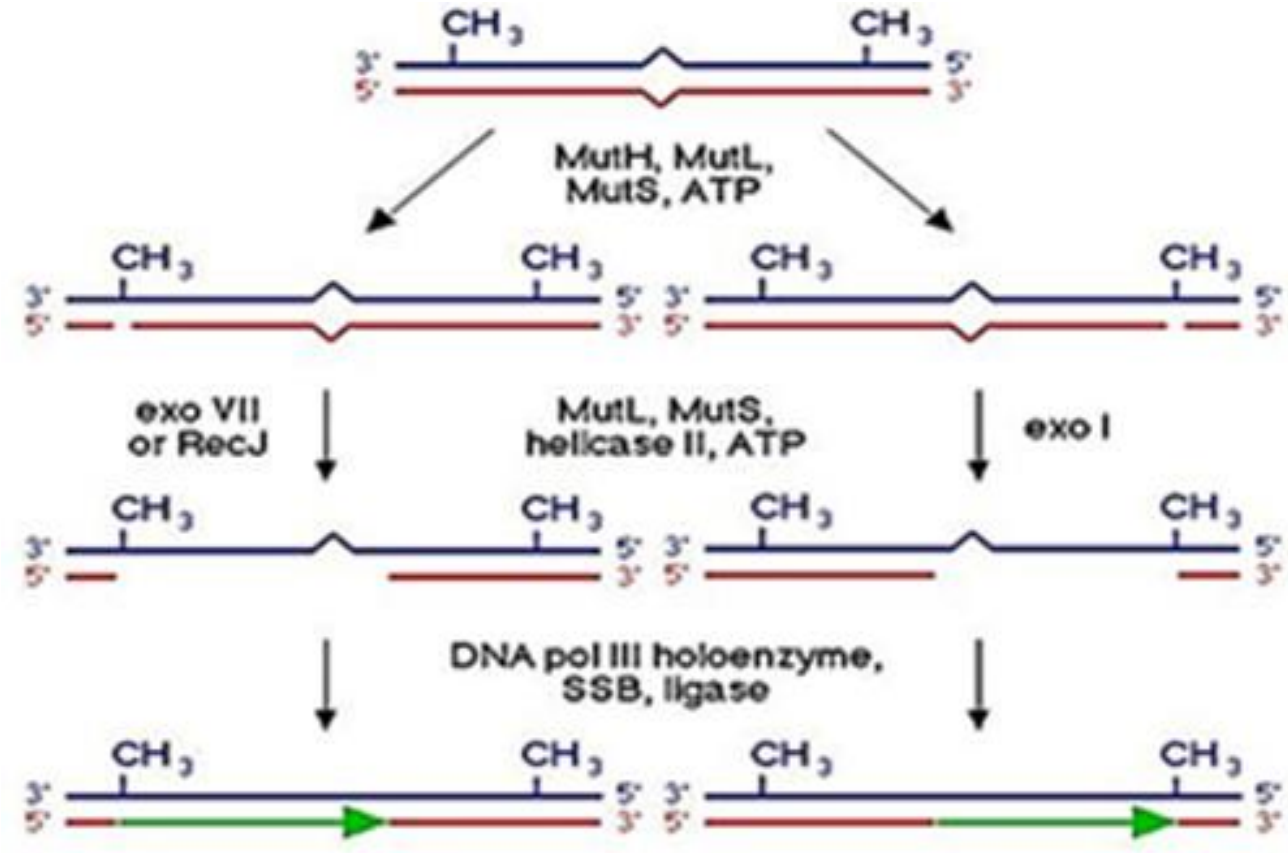

Figure 13: Mismatch repair mechanism in prokaryotes (Li, 2007)

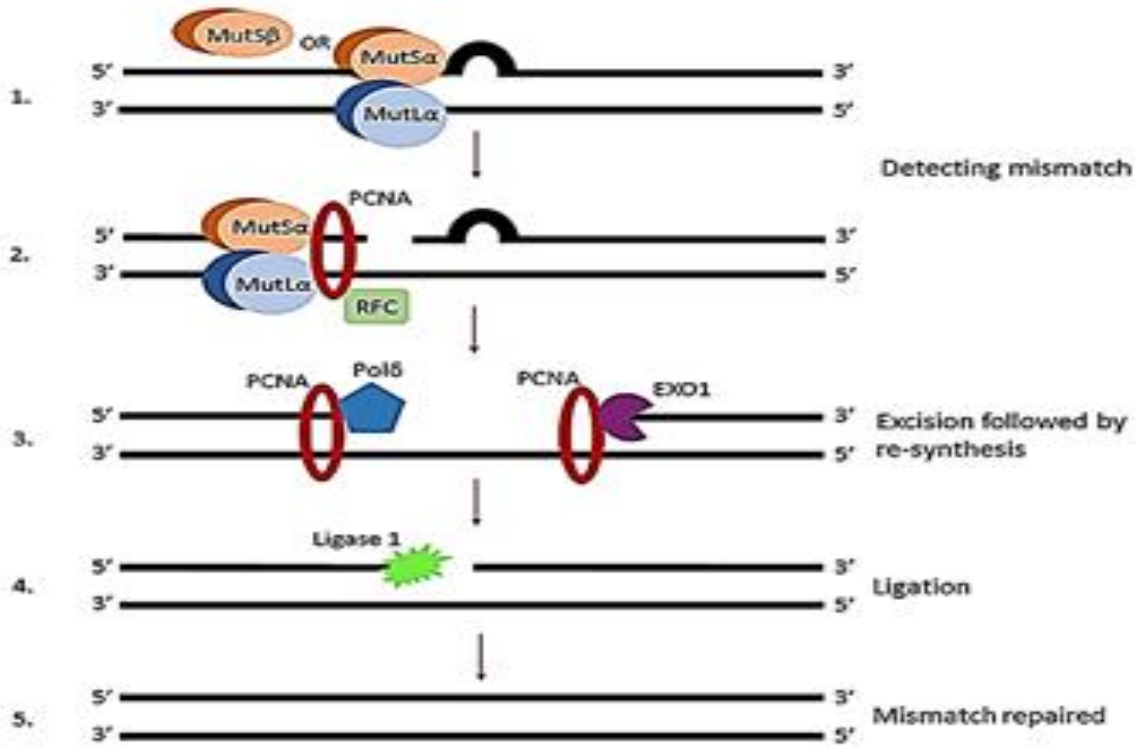

Figure 14: Mismatch repair mechanism in Eukaryotes (Pećina-Šlaus *et al.*, 2020)

5.1.3. Double-strand break repair (DSBR)

Cells also have two major mechanisms for repairing Double-Strand-Breaks (DSBs): A) non-Homologous End-Joining (NHEJ) and B) Homologous Recombination (HR) **(Flatt, 2019)**.

A) Non-homologous end-joining (NHEJ)

It is the simplest and most widely utilized mechanism to repair double strand DNA breaks. Repair by NHEJ involves direct resealing of the two broken ends independently of sequence homology (not need to template), and thus it is referred to as "non-homologous". The process of NHEJ depends on the main Ku protein to thread onto each broken DNA end and acting as a 'tool belt. Then depending on the degree of microhomology between the ends (Microhomology is short homologous sequences present in single-stranded DNA overhangs on the ends of double-strand breaks and used to guide end joining), the mechanism passes in one way of three ways: direct ligation, insertion or deletion. So the ku protein recruits the enzymes and complexes that are needed for DNA repair such as DNA ligase 4 to direct ligation of the two DNA ends or if DSBs have two incompatible DNA ends that preclude direct ligation so need to (nucleases) to trim or (polymerases) to fill the ends to make them optimally ligatable by the DNA ligase IV complex **(Flatt, 2019; Chang *et al.*, 2017)**.

When NHEJ is absent owing to a lack of Ku protein or the DNA ligase complex, alternative end joining (a-EJ) can join the ends using microhomology by DNA polymerase θ (Pol θ) **(Chang et al., 2017).**

i. **Non-homologous end-joining (NHEJ) in prokaryotes.**

Many species of prokaryotes, including Escherichia coli, lack the non-homologous end joining pathway and thus rely completely on homologous recombination to repair double-strand breaks. But it is utilized in little organisms depending on two main proteins: a Ku homodimer protein which binds to DNA double strand breaks and the multifunctional LigD protein which preforms three functions polymerase/nuclease and ligase functions **(Chang *et al*., 2017; Cahill, 2006).**

ii. **Non-homologous end-joining (NHEJ) in eukaryotes**

The NHEJ Repair in eukaryotes occurs throughout the cell cycle during S and G2 phases by four major protein complexes (Figure 15): a) highly conserved Ku70/Ku80 heterodimeric complex, b) DNA-dependent protein kinase catalytic subunit (DNA-PKcs), and c) polymerase (Pol μ and λ) and DNA Ligase IV (LIG4) in complex with XRCC4 (XLF). By directly binding ends to DNA, Ku70/Ku80 ensures protection against exonucleases and, as such, acts as an inhibitor of DNA end excision (5′–3 exo) so it prevents homologous recombination. One parameter affecting the DNA end-joining mechanism is the amount of transient base-pairing that can occur between the two ends of the DNA before joining, or in other words, the degree of microbiology between the ends. Some DNA ends (blunt) can be linked together using a ligase-complex only, but other DNA ends (Microhomology overhangs) require the action of polymerases or nucleases, which together form different NHEJ (deletion or insertion) sub-pathways **(Flatt, 2019; Cahill, 2006).**

The NHEJ repair of blunt DNA ends lacking microhomology relys on Ku protein for efficient joining and promote the binding of XRCC4–DNA ligase IV to the DNA ends. The Ku–XRCC4–DNA ligase IV complex promotes the ligase to directly ligate to the blunt ends **(Cahill, 2006; Sharma and Raghavan, 2016).** In Nuclease-dependent subpathways (deletion process). DNA-PKcs is recruited in complex with the endonuclease Artemis. Once DNA-PKcs undergoes auto-phosphorylation and activates the Artemis exonuclease activity, both the 5′ and 3′ overhangs of DNA degrades to make the two ends compatible, and splicing occurs finally by the XRCC4–DNA ligase IV complex **(Cahill, 2006; Sharma and Raghavan, 2016).**

In Polymerase-dependent subpathways (insertion process): DNA polymerase μ (Pol μ) and Pol λ (two members of the Pol X family

polymerases) interact with Ku protein. This interaction make polymerase enzyme active and add some nucleotides without an actual template generating regions of microhomology for subsequent base pairing and ligation by DNA XRCC4–DNA ligase IV complex **(Cahill, 2006; Sharma & Raghavan, 2016).** NHEJ repair mechanism protects genetic integrity by rejoining broken strands of DNA that may otherwise be lost during DNA replication and cell regeneration but in general it is more error prone than homologous recombination **(Flatt, 2019; Cahill, 2006).**

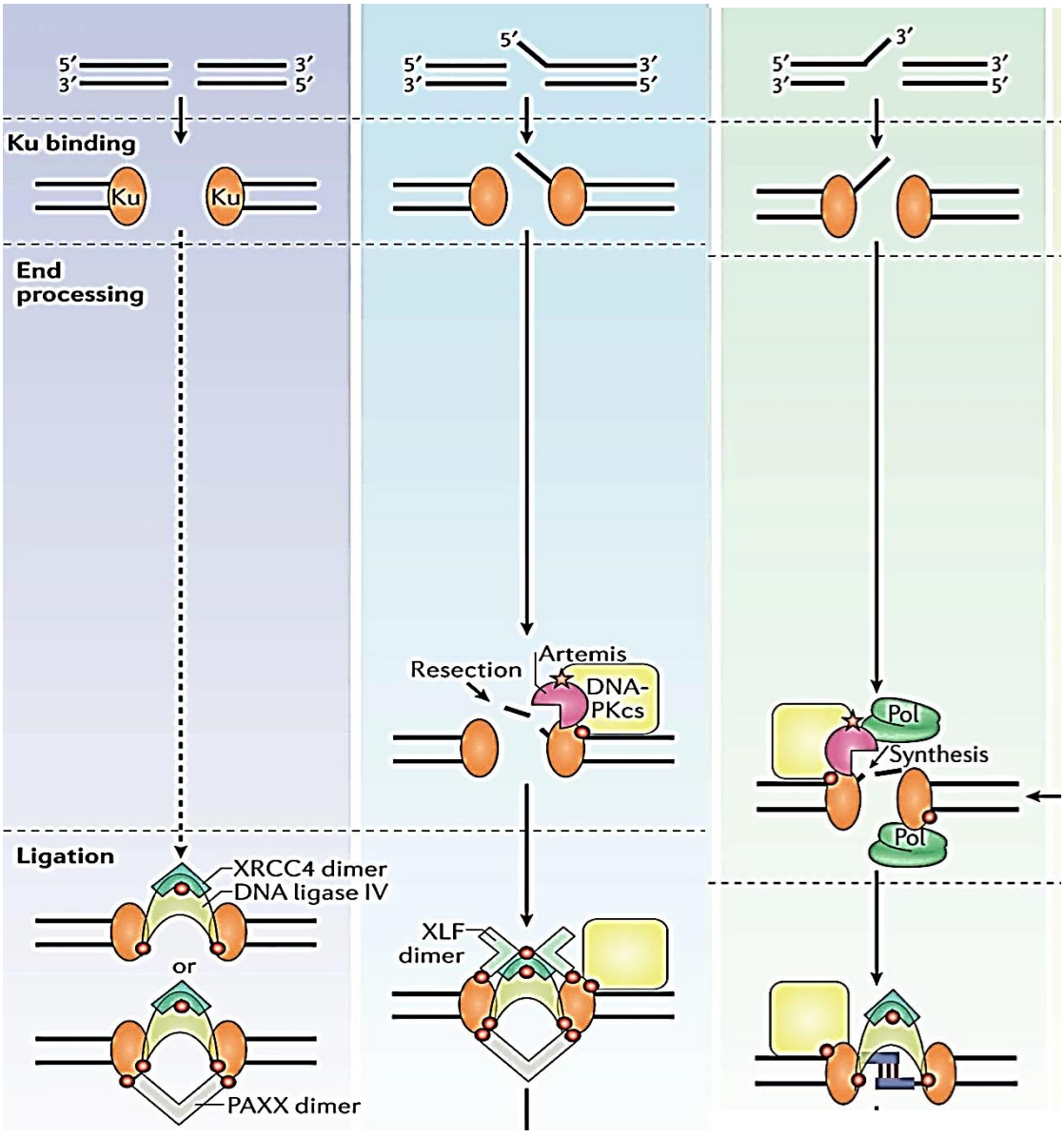

Figure 15: The three subpathways of non- homologous end-joining (NHEJ) in eukaryotes (Cahill, 2006)

B) Homologous Recombination (HR)

Homologous recombination (HR) is a dynamic pathway with multiple metastable and reversible intermediates designed to achieve DNA repair with high fidelity in somatic cells (Figure 16-17). It predominantly uses the sister chromatid as a template for double strand break repair, or the homologous chromosome, because the sister chromatid contains homologous DNA sequence to serve as a template for DNA-synthesis-dependent repair and involves extensive DNA-end processing. HR is largely inhibited while the sister chromatid has not yet been replicated. So, it occurs in the late S and G2 phases of the cell cycle, when the sister chromatid becomes available. Now, we can say that HR is extremely accurate, as it leads to precise repair of the damaged locus. The common early step of HR-dependent mechanisms is the formation of single strand DNA. For this to occur, 5′-single-stranded DNA (ssDNA) with terminal 3′-OH (3' Overhang) is generated by nucleolytic degradation of the 3′-strands releasing a terminal 5′-ending oligonucleotide and catalyzing DNA resection. Then the single strand DNA is coated by specific recombinase and mediator proteins that facilities invasion of these 3′ ssDNA overhangs into a homologous sequence forming the junction by ssDNA transitioning to dsDNA at the resection boundary and DNA synthesized at the invading end. Depending on the next step, homologous recombination is divides into two subpathways, including synthesis-dependent strand annealing (SDSA) and double Holliday junction resolution **(Wright *et al*., 2018; Sung and Klein, 2006).**

Both SDSA and double Holliday junction resolution depend on the strand invasion and on nucleoprotein scaffolds to direct their own and play a central role in HR because it has specific filaments that is stretched as much as half the length of dsDNA This stretching is essential for fast and efficient homology search and invasion **(Wright *et al*., 2018; Sung and Klein, 2006).**

But there is difference between them: SDSA occurs by disruption of the extended D-loop and strand displacement, annealing of the extended single-strand end to the ssDNA on the other break end. So, the end result of the repair is always a non-crossover outcome avoiding loss of heterozygosity produced by crossovers. Finally, the gap is filled by polymerase and ligase activity **(Wright *et al.*, 2018; Sung and Klein, 2006).** While double Holliday junction depends on D-loop formation and extended D-loop undergo second-end capture or invasion to form an intermediate two Holliday junction. The resolution of Holiday junctions is achieved through the action of nicking endonucleases, a type of restriction endonuclease which cuts only one DNA strand leading to non-crossover outcome or a crossover (by the action of helicase activity) and gaps are filled by polymerase and ligase enzymes **(Wright et al., 2018; Sung & Klein, 2006)**

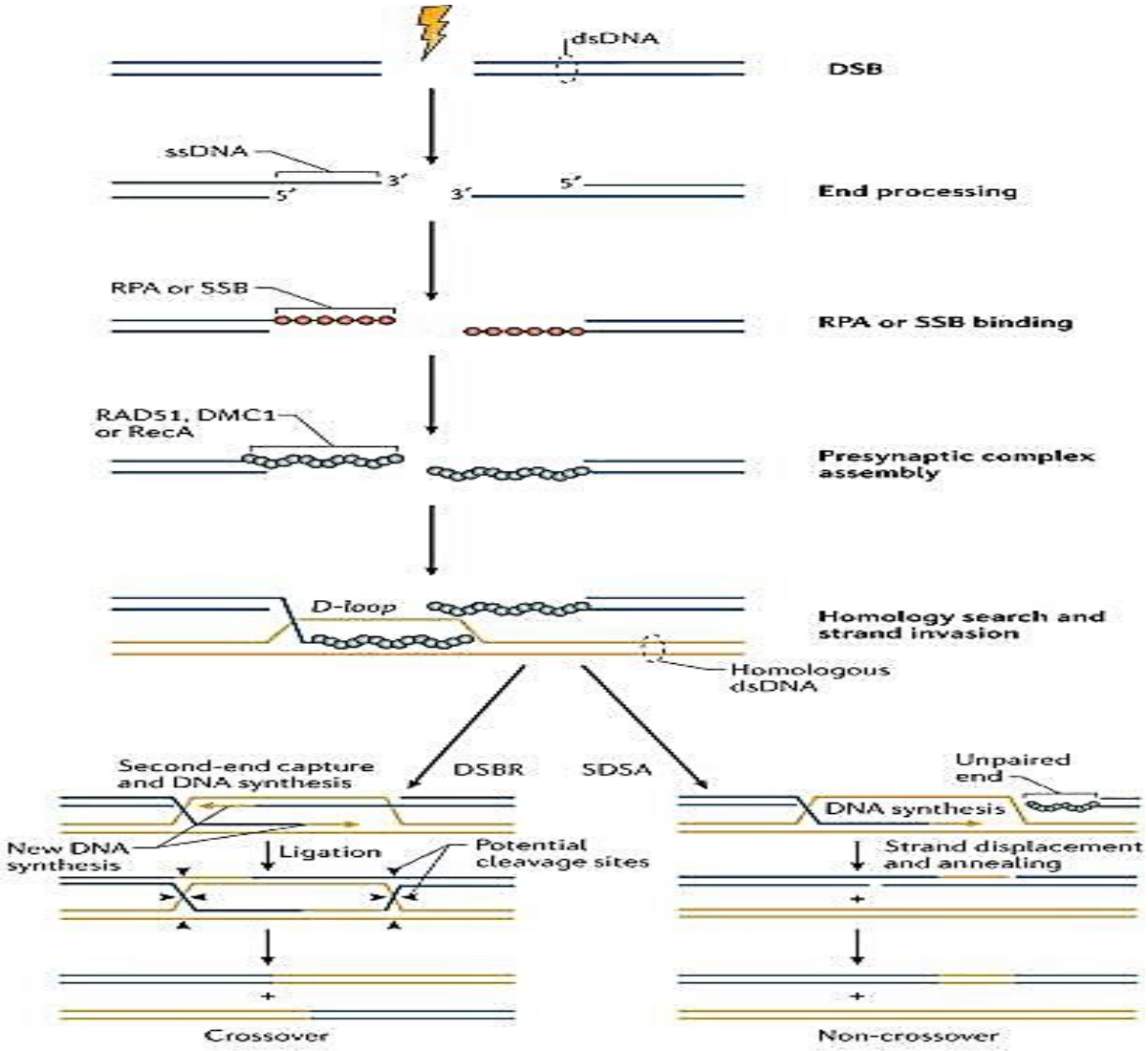

Figure 16: s Homologous Recombination mechanism and its subpathways (Wright et al., 2018)

i. **Homologous Recombination (HR) in prokaryotes**

The 3′-strands is produced by the action of endonuclease/helicase complex called RecBCD, and the 3′-strands is coated by SSB to prevents single-stranded DNA (ssDNA) from winding back on itself or from forming secondary structures. Then RecN, RecF, RecO, and RecR act as mediator proteins and bind to ssDNA promoting RecA to do its action (invasion) leading to either synthesis-dependent strand annealing (SDSA) or double Holliday junction resolution pathways. The resolution of Holiday junctions is achieved through the action of RecG or RuvABC helicase **(Sung and Klein, 2006)**.

ii. **Homologous Recombination (HR) in eukaryotes**

The 3′-strands is produced by the action of MRX (Mre11–Rad50–NBSI) complex, and the 3′-strands is coated by replication protein A (RPA) to prevents single-stranded DNA (ssDNA) from winding back on itself or from forming secondary structures. Then, Rad52 (epistasis group of HR proteins) and Rad55/57 mediator proteins bind to ssDNA promoting the formation and stability of Rad51 to do its action (invasion) leading to either synthesis-dependent strand annealing (SDSA) or double Holliday junction resolution pathways. The resolution of Holiday junctions is achieved through the action of nicking endonucleases, a type of restriction endonuclease which cuts only one DNA strand. This may lead to non-crossover outcome or a crossover by the action of helicase Rad 54 **(Wright *et al.*, 2018; Sung and Klein, 2006).**

In eukaryotes, there is a unique mechanism If a double strand break occurs between closely repeated sequences, it can also be repaired by the HR process and called single-strand annealing (SSA). Single-strand annealing (SSA) pathway, it occurs by double strand break ends that are processed to form ssDNA tails and thus can anneal with each other. So, it does not require the full repertoire of HR genes and also do not require strand invasion and therefore it does not depend on DNA sequence that serve as a template. It is distinguished by presence of small flap that remove by the Rad1 – Rad10 endonuclease, before gap-filling and ligase completes the repair mechanism **(Flatt, 2019; Sung and Klein, 2006).**

5.1.4. Post-replication Repair (PRR)

The direct reversal, excision repair and double strand break systems act to correct the DNA damage before replication but the cell has alternative mechanisms dealing with the damaged DNA such as pyrimidine dimers and other types of lesions that cannot be copied by the normal action of DNA polymerases at the replication fork. The general route of this mechanism is replication block at the sites of such damage, and then polymerase reinitiates replication at a site downstream of damage by the synthesis of an Okazaki fragment proceeding along the damaged template strand. That results in a gap opposite the damage in the newly synthesized DNA, and this gap is then filled by: re-combinational repair or error-prone repair **(Cooper and Hausman, 2000)**.

Re-combinational repair depends on the fact that one strand of the parental DNA was undamaged and therefore was copied during replication to yield a normal daughter molecule. The undamaged parental strand can be used to fill the gap opposite the site of damage in the other daughter molecule by recombination between homologous DNA sequences. Because the resulting gap in the previously intact parental strand can be filled in by DNA polymerase-ligase, using the intact daughter strand as a template. Two intact DNA molecules are thus formed, and the

remaining damage eventually can be removed by excision repair **(Cooper and Hausman, 2000)**

In error-prone repair, a gap opposite a site of DNA damage is filled by the newly synthesized DNA. Since the new DNA is synthesized from a damaged template strand, this form of DNA synthesis is very inaccurate and leads to frequent mutations **(Cooper and Hausman, 2000).**

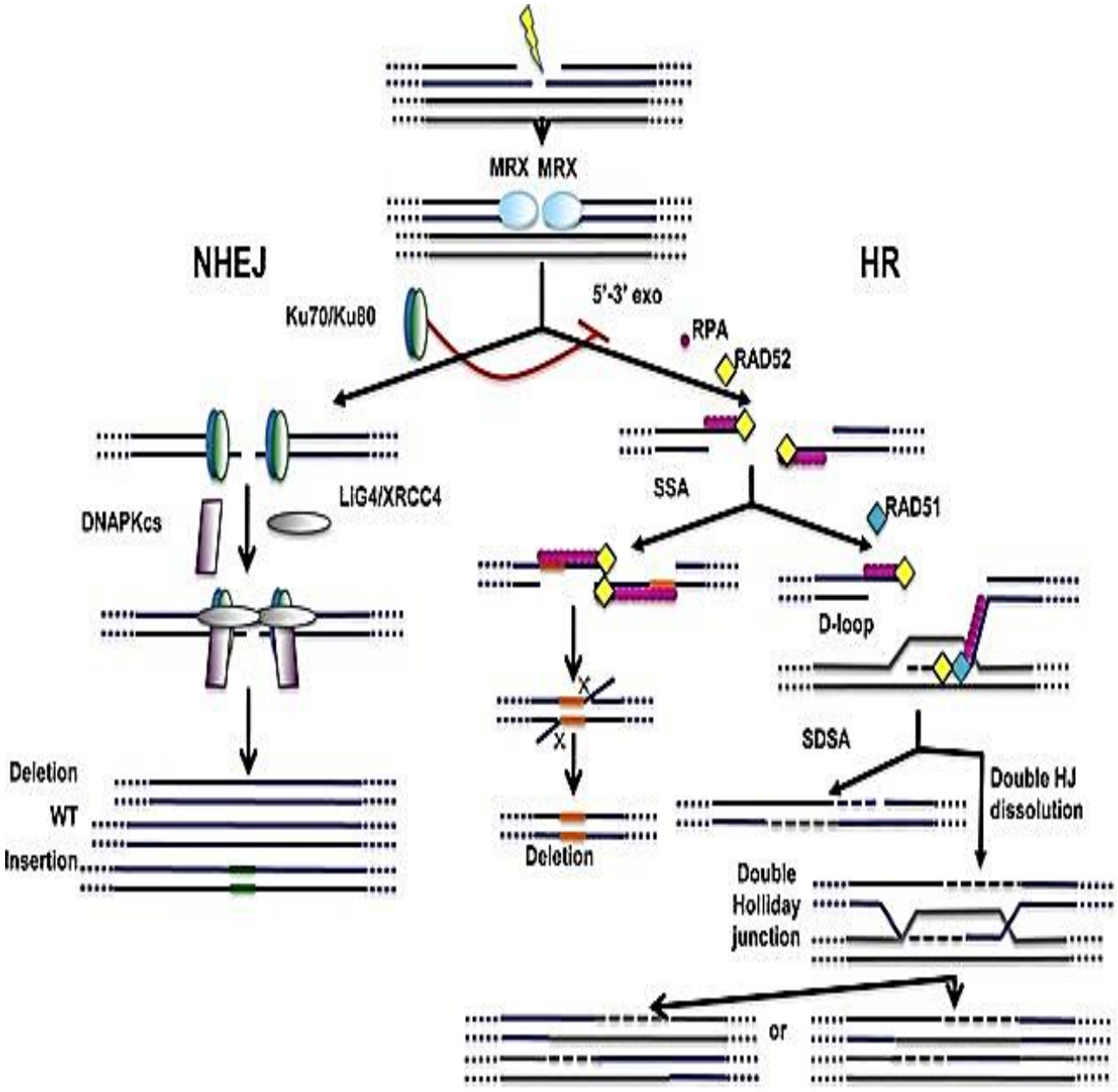

Figure 17: Two main Pathways of DNA Double-Stranded Break Repair: Non-homologous end-joining (NHEJ), homologous recombination (HR) and single strand annealing pathways in eukaryotes (Flatt, 2019)

6. Conclusion

Deoxynucleic acids (DNA) represent the genetic material of most living organisms and store the genetic information in a particular sequence of nucleotides called genes. Therefore, a disturbance in the nucleotides sequences of genes is dangerous and may cause the death of living organism. Disturbance in the DNA nucleotides sequence may occur by exogenous or endogenous factors. Endogenous factors are the most dangerous DNA factors because large number of reactive molecules produced by metabolism or by hydrolysis reactions in the warm aqueous cellular replication such as 1) reactive oxygen species that bind to nitrogen bases especially guanine base causing oxidative processes, 2) alkylating agents are highly electrophilic agents and have an affinity for the nucleophilic centers in organic macromolecules such as nitrogen bases in DNA molecule causing DNA alkylation, bases loss, DNA crosslinking and DNA single and double-strands break, and 3) bulky molecules that have high ability to bind to DNA molecule, and also can make defect in DNA during replication process leading to mismatch base pairing problem. But fortunately, a powerful system in living organisms can distinguish DNA damage and fix it as soon as possible through different DNA repair pathways. These pathways are divided into two main categories: The first category depends on the direct removal of the source that causes the DNA defect as in case of DNA damage induction by alkylating agents. Whereas, the second category starts its function when damaged DNA base, base mismatch, base loss or DNA breakage is detected. Therefore, damaged DNA or mismatched base pairs can be removed and replaced with another, loss of bases can be repaired by adding new bases or broken DNA can be repaired by synthesizing a new short stand instead of the damage DNA part. All these processes depend on the operations of excision, re-synthesis and ligation reaction. The second category is also the most important because it repairs many DNA defects with great precision before these defects reach the replication state. In general, there are six general mechanisms for DNA repair: 1) Base excision repair (BER) mechanism which the damage base is replace by new one or the gap results from bases loss repair by specific molecules (DNA glycosylase, AP endonuclease, DNA polymerization and ligase), 2) Nucleotide excision repair mechanism by which a number of nucleotides including the damage bases are removed and replaced with new ones by the action of helicase, endonuclease, DNA polymerase and ligase, 3) Mismatch repair mechanism by which the mismatched base is removed and replaced with another one match with the completely base by the action of exonuclease, DNA polymerase and ligase, 4) Non-homologous end-joining mechanism

is a specific mechanism for repair DNA strand breaks by resealing of the two broken ends by the action of ku protein, nucleases or polymerases and DNA ligase IV complex, 5) Homologous Recombination (HR) mechanism is a specific repair mechanism for DNA strand breaks by using sister chromatid as a template to generate new short stand that ligated with the broken strand, and this occurs by the action of DNA resectase, specific recombinase and mediator proteins, DNA polymerase and ligase, and 6) Post-replication Repair mechanism which occurs through replication process by the action of polymerase and ligase.

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