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DNA REPAIR AND RECOMBINATION PATHWAYS: MOLECULAR MECHANISMS, REGULATION, AND IMPLICATIONS FOR HUMAN DISEASE

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Abstract

Genomic integrity is essential for healthy cellular function. Although cellular processes are highly sophisticated and have numerous checkpoints, there are many points where our DNA gets damaged, which can lead to the development of several disorders. To combat this, cells have created a variety of repair processes that focus on various forms of DNA damage. DNA is damaged when its bases or nucleotides are mismatched; in such cases, mismatch repair (MMR) is the pathway primarily responsible for correcting replication-associated base-base mismatches and insertion/deletion loops. While there are certain situations in which the DNA phosphodiester backbone is damaged, either one strand or both. Such breaks are repaired by mechanisms like non-homologous end joining, microhomology-mediated end joining, and homologous recombination. These pathways, including the HR sub-pathways, are discussed in this review. We also explore how disorders like dementia and immunological dysfunction relate to DNA repair and recombination, and we briefly touch on mitochondrial DNA damage and repair.

Introduction

Genome carries genetic information and has the capability to transfer this information to daughter cells. But this information changes even if single nucleotide base pair is changed and will lead to different types of disorders, for instance, cancer. DNA repair and recombination are such critical processes that play a crucial part in maintenance of genomic stability [1]. Both internal mechanisms, like as errors made during replication and exposure to oxidative stress, and external influences, such as UV radiations or toxic chemicals, can undermine the integrity of DNA. This may lead to DNA damage, which may have a variety of biological repercussions [2]. As a result, cells have created sophisticated mechanisms that can recognize and repair various types of DNA damage. The preservation of genomic integrity and the avoidance of cellular malfunction depend on these repair pathways.

Chromosome rearrangements and genetic instability can result from double-strand breaks (DSBs), when both strands of DNA break at phosphodiester backbone [3]. These types of breaks are repaired by two main processes named as Non-homologous end joining (NHEJ) and homologous recombination (HR) [4]. Directly joining the broken ends of the DNA, or NHEJ, is a quick and effective procedure, but it has the potential to introduce mutations at the repair site. Contrarily, HR is a more complex mechanism that properly repairs the DSB using homologous sequence on sister chromatid, but it is also a longer and more laborious process [5].

There are several alternative DNA repair mechanisms outside DSB repair, including mismatch repair (MMR), base excision repair (BER), and nucleotide excision repair (NER) [6]. Single-strand breaks, bulky adducts, and base mismatches are among the specific forms of DNA damage that each of these pathways is intended to repair.

In general, repairing and reconstitution of DNA plays a key role in maintaining genetic stability as well as limiting the incidence of genetic diseases and cancer. To that end, understanding the molecular mechanisms of such processes and their regulation are essential to developing new therapeutic strategies for combating these diseases.

Understanding the Types and Origin of DNA Damage

A significant portion of DNA lesions involves alterations to DNA bases, such as methylation, oxidation, or the formation of abasic sites, which do not affect the sugar-phosphate backbone. Other types of damage disrupt the backbone, affecting only one DNA strand. While SSBs typically do not harm double-stranded DNA, an unrepaired SSB encountered during DNA replication can convert into a one-ended DNA double-strand break (DSB). Ionizing radiation (IR) can cause both SSBs and DSBs either through a direct mechanism or indirectly through the production of ROS(reactive oxygen species) [7]. Moreover, the nature of DNA ends resulting from double-strand breaks (DSBs) can vary based on the mechanism of their formation. Some DNA ends are considered "clean" because, apart from the break in the phosphodiester

backbone, they have typical DNA chemistry. While, some DNA breaks have certain chemicals or even proteins attached to their backbone, they are called as "dirty" DNA ends. DNA nucleases creates clean ends while ionization radiation creates dirty ones [8].

To minimize the loss of genetic material, our cells employ several mechanisms for repairing double-strand breaks (DSBs). If double strands break are not corrected it may cause chromosome mutations and reorganizations, resulting in anomalous cell growth, cancer growth, or even apoptosis [9].

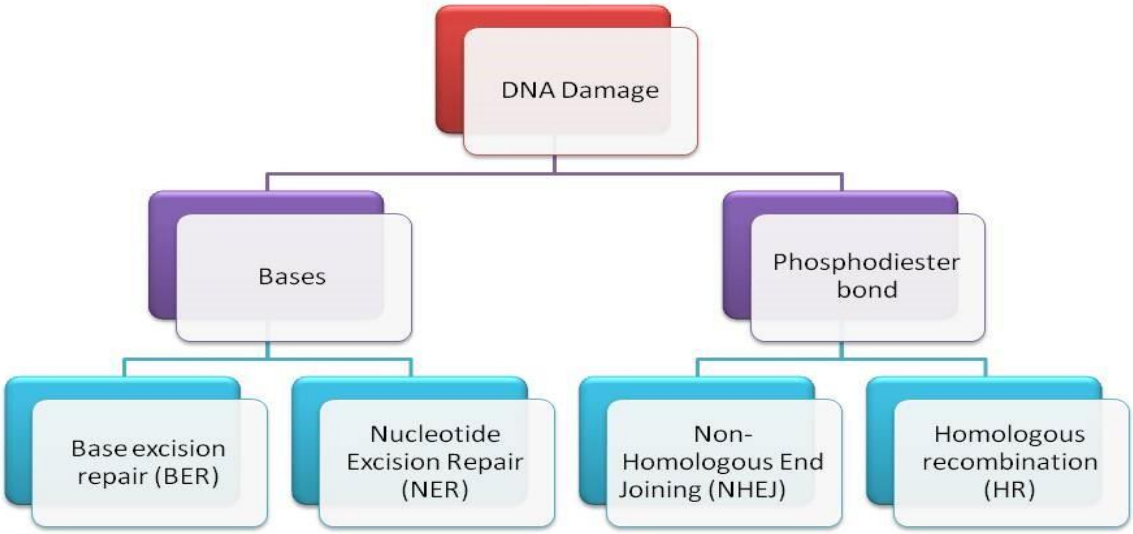


Figure 1. DNA damage overview

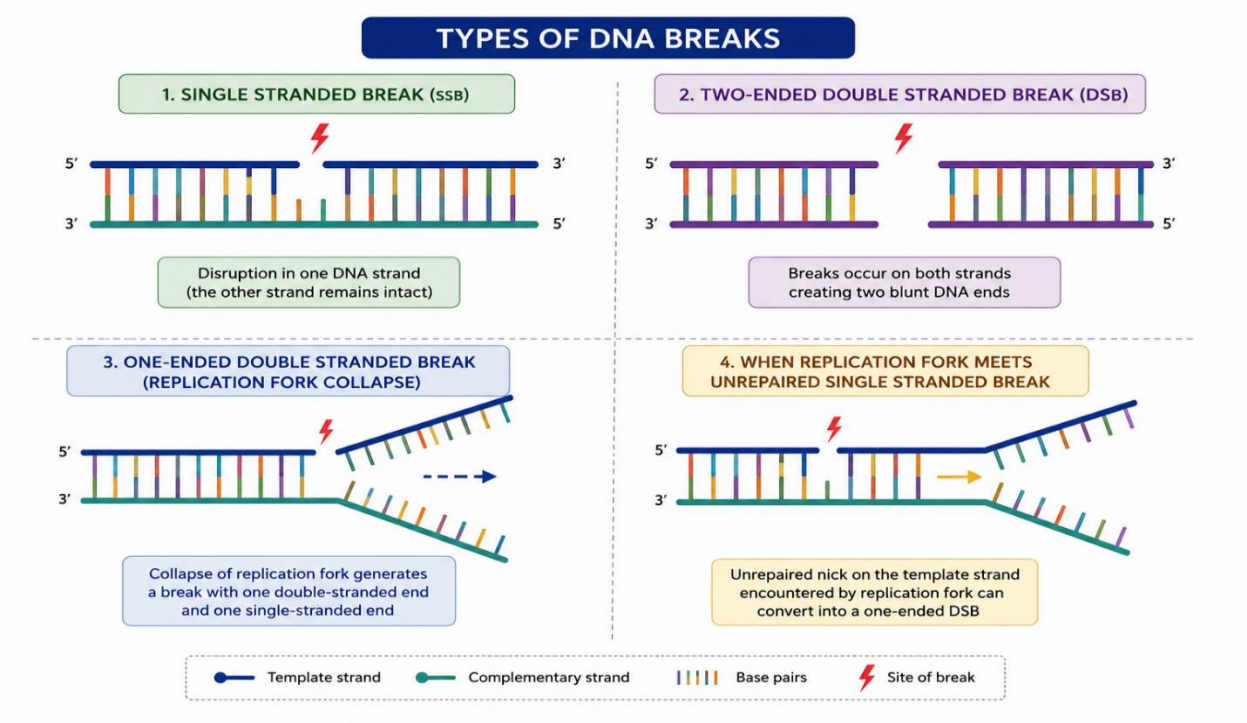


Figure 2. Types of DNA Breaks

Repair pathways

Base excision repair (BER)

As its name implies this process involves repair of that DNA in which either wrong or damaged nitrogenous bases are present. This type of damage is caused by alkylating agents, oxidative stress, and spontaneous deamination. In this pathway, firstly damaged bases is recognized by DNA glycosylase enzyme and then it is removed with the activity of same enzyme. Now, this site is called as apurinic/apyramidic site as nitrogenous base is removed but its sugar moiety is still present in the DNA backbone. Now this sugar moiety is cut from DNA backbone by AP endonuclease and it creates single strand break. Now, this sugar moiety is removed by another enzyme called as dRP lyase. As removal of damaged base created a space, DNA polymerase beta fills this gap by reading sequence on undamaged complementary DNA strand. Finally, nick is filled by DNA ligase [10]. This pathway is mostly regulated by post-translational modification of the proteins involved in this pathway and by DNA binding proteins [11].

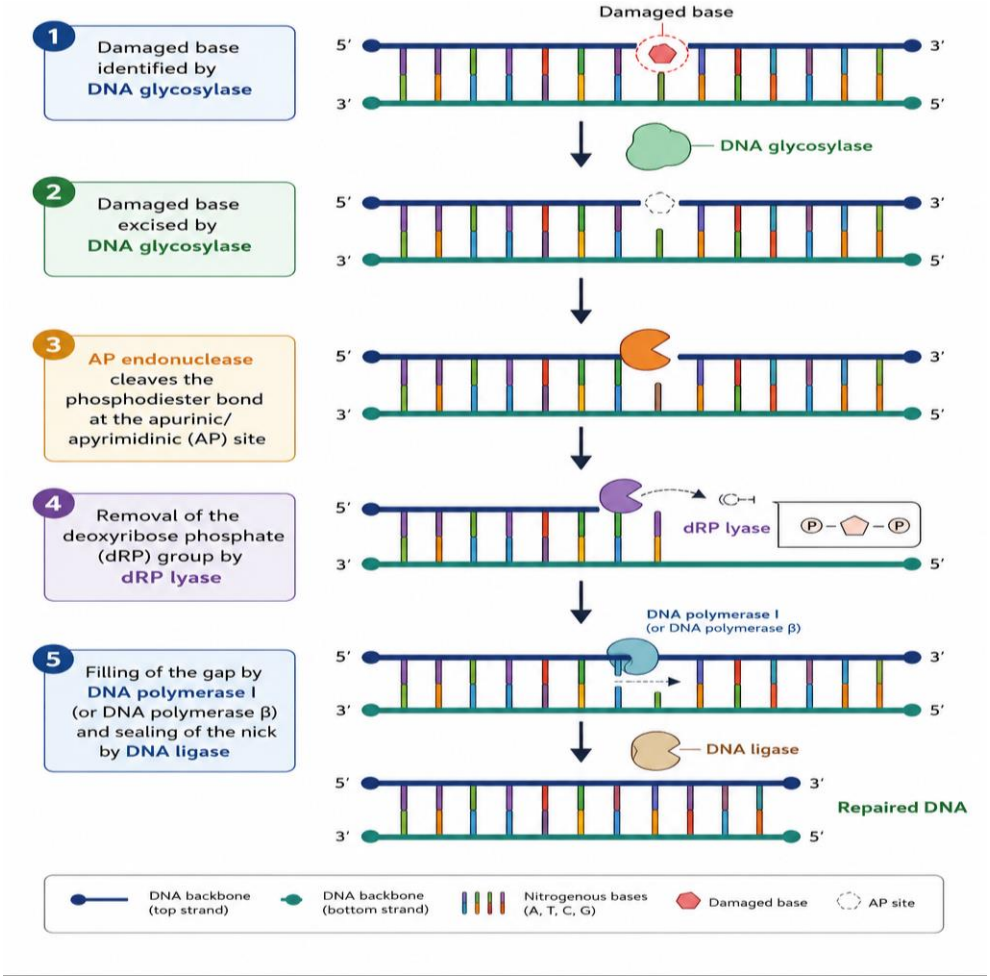


Figure 3. Base Excision Repair Pathway

Nucleotide Excision Repair (NER)

It is a one of the main processes that are involved in repair of damaged DNA including those brought on by UV radiation and chemical carcinogens [12]. As its name implies the procedure involves removal of whole nucleotide which is then replaced by fresh, undamaged one. The process starts with the XPC-RAD23B protein complex's attachment to damaged DNA triggers the start of NER by luring the TFIIH complex to the damaged site [13]. Purpose of TFIIH is to cut the damaged DNA with the help of other proteins including XPA, XPG, RPA and ERCC1-XPF [14]. Now removal of this damaged strand caused a break which is filled by DNA polymerase eta and finally nick is sealed by DNA ligases [15].

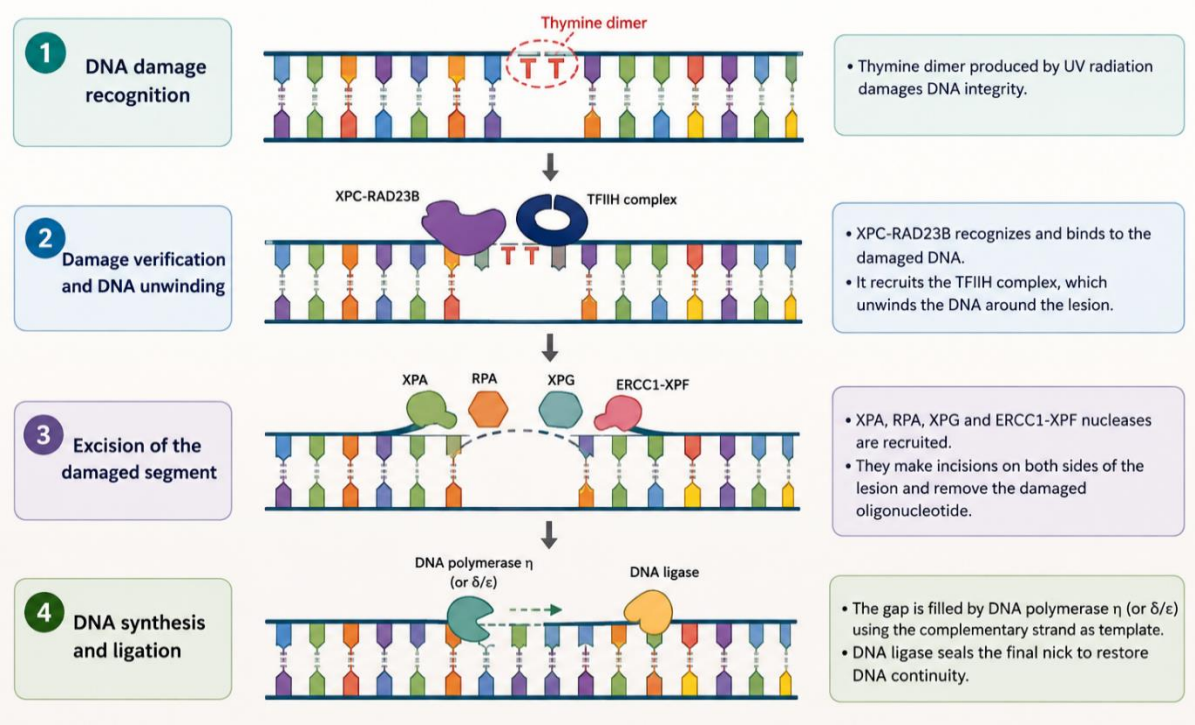


Figure 4. Nucleotide Excision Repair Pathway

This repair pathway is very important as its dysregulation may result in different kind of pathologies. Cockayne syndrome, xeroderma pigmentosum, and trichothiodystrophy are some of the diseases caused by malfunctioning of this repair process [4].

Mismatch repair (MMR)

Although DNA replication is highly sophisticated process and DNA polymerase is very efficient, in addition it has proof reading capability as well. But there are certain situations in which wrongly incorporated base by DNA polymerase skips the poof reading activity. In order, to remove this mismatch base our cell has unique process of mismatch repair. Main players of this process are MSH2-MSH6 and MSH2-MSH3. These protein complexes identifies the mismatch base pairs and removes them by them help of EXO-1 or other enzymes. And then new strand is synthesized with the help of DNA polymerases. This process is highly regulated and if its function is effected it might cause Lynch syndrome which is a kind of cancer [16].

Non-Homologous End Joining (NHEJ)

As its name implies this type of repair process repairs double-stranded DNA lesion that do not requires any sequence homology. It means it does not generate single-stranded overhangs at the site of damage; rather it directly ligates the broken ends.

The process begin with the Ku70/Ku80 complex's attachment to the damages DNA ends, the NHEJ process draws in other proteins such DNA-PKcs, XRCC4, and Ligase IV. In order to repair the DNA structure, the NHEJ machinery processes the broken ends by removing any damaged or projecting DNA, bridging any gaps with nucleotides with the help of polymerase λ or polymerase μ, and ligating the ends [17].

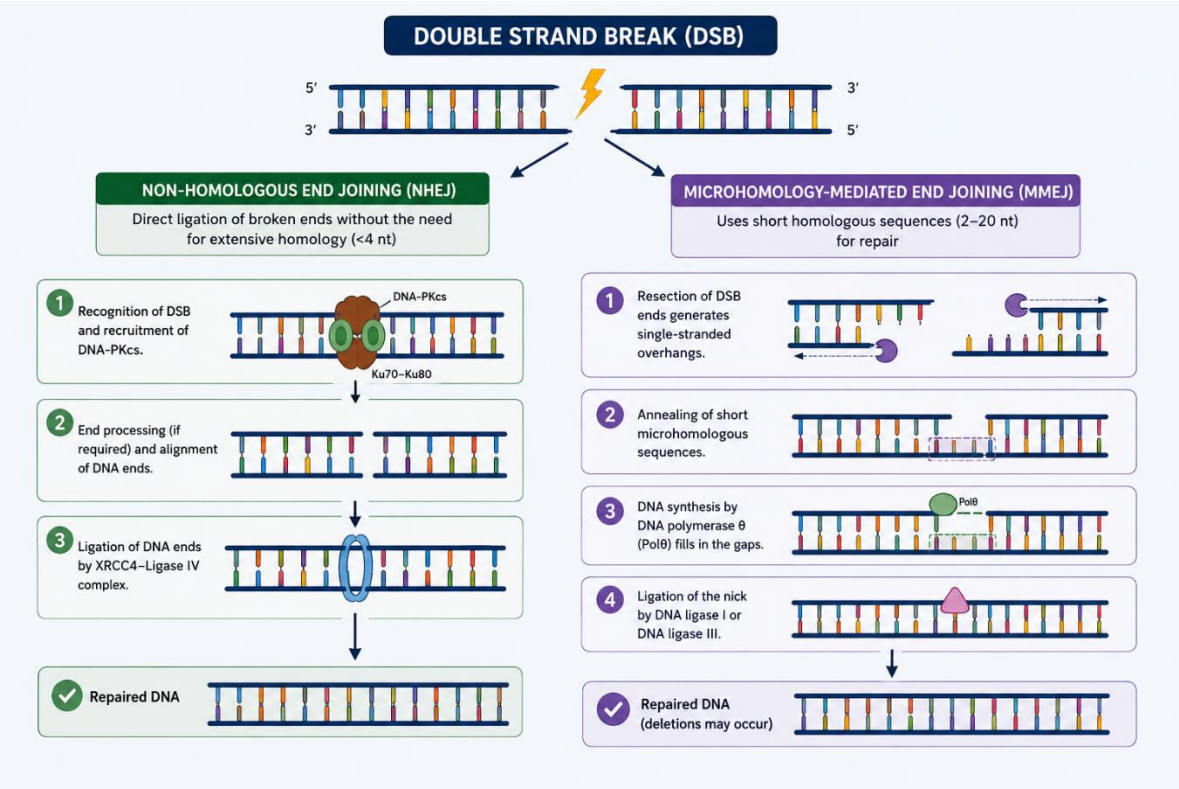


Figure 5. NHEJ and MMEJ Repair pathways

Microhomology-mediated end joining (MMEJ)

MMEJ, also called as Alternative end joining (Alt-EJ), serves as an additional mechanism for mending DNA DSBs as opposed to the traditional NHEJ process. MMEJ fixes DSBs by joining the frayed ends of the DNA with brief homologous sequences that typically have a length of 2 to 20 nucleotides [18].

The process starts with removal of damaged site's blunt ends that creates single-stranded DNA (ssDNA) overhangs, usually 5' to the break site. The short homologous sequences on the other strand that the ssDNA overhangs anneal with create a DNA intermediate called a "flap" as a result. DNA polymerase theta (Polθ) repairs the remaining DNA gap using the complementary strand as a template after MRE11's endonuclease activity eliminates the flap. Once the gap is filled, DNA ligase I/III seals the nick [19].

Homologous recombination (HR)

In contrast to NHEJ and MMEJ, Homologous recombination (HR) is most effective and sophisticated process of double strand break. As this process utilizes the homologous sequence on sister chromatid to synthesize damaged strands, it doesn’t causes any sequence change after repair.

This repair mechanism is capable of effectively fixing one- and two-ended double-stranded breaks (DSBs), as well as “dirty” DNA breaks that have proteins covalently attached to them. HR is a more complex process when compared to NHEJ in terms of its mechanism, involving a greater number of enzymes, which can lead to a slower but more precise repair process [20].

The process is started with the detection of double strand break by the protein complex called as MRN complex. This complex is made up of three proteins Mre11, Rad50, and Nbs1 [21]. Once this complex detected double strand break it attaches itself to the damaged site and recruits other enzymes such as ExoI or BLM complex. These enzymes cleaves the single strand from site of damage and produce 3’ overhangs single strands. Now in order to protect these single stranded overhangs another protein called as RPA (replicative protein A) is coated over it. It is a three-subunit protein complex that binds to single-stranded DNA (ssDNA) and participates in a variety of DNA processing operations. Now BRAC1 will be loaded on damaged site along with PALB1. This complex will recruits BARCA2. BARCA2 will exchange RPA on single stranded over hang with another enzyme called as RAD51 [22]. This is the main player of homologous recombination. It will search out for sequence homology on sister chromatid. The RAD51 filament then invades the homologous sequence, forming a DNA intermediate known as a “D-loop”. The D-loop is extended by copying genetic information from the homologous sequenc. This process of DNA synthesis leads to the formation of an intermediate that is eventually resolved, completing the repair of the double-stranded DNA break [23].

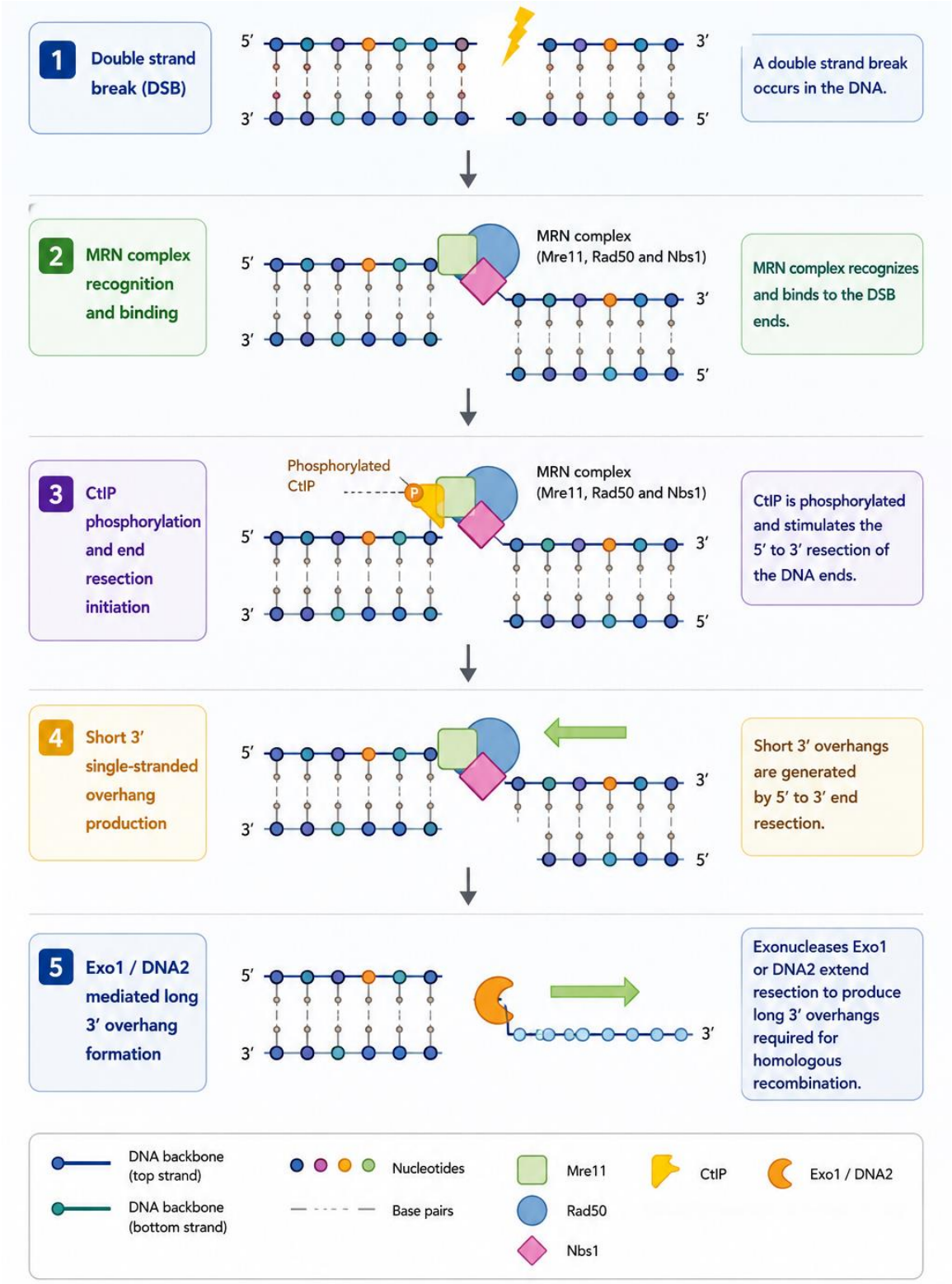


Figure 6. Processing of ds break

The presence of a homologous template, the degree of HR protein production, and competition from other DSB repair pathways are some of the variables that control HR. Since HR is mostly active during the "S"

and "G2 phases" of the cell cycle, the control of HR is likewise closely correlated with the course of the cell cycle. Recent research has uncovered novel HR regulatory mechanisms, including the role of chromatin alterations and the regulation of RAD51 nucleofilament stability [24].

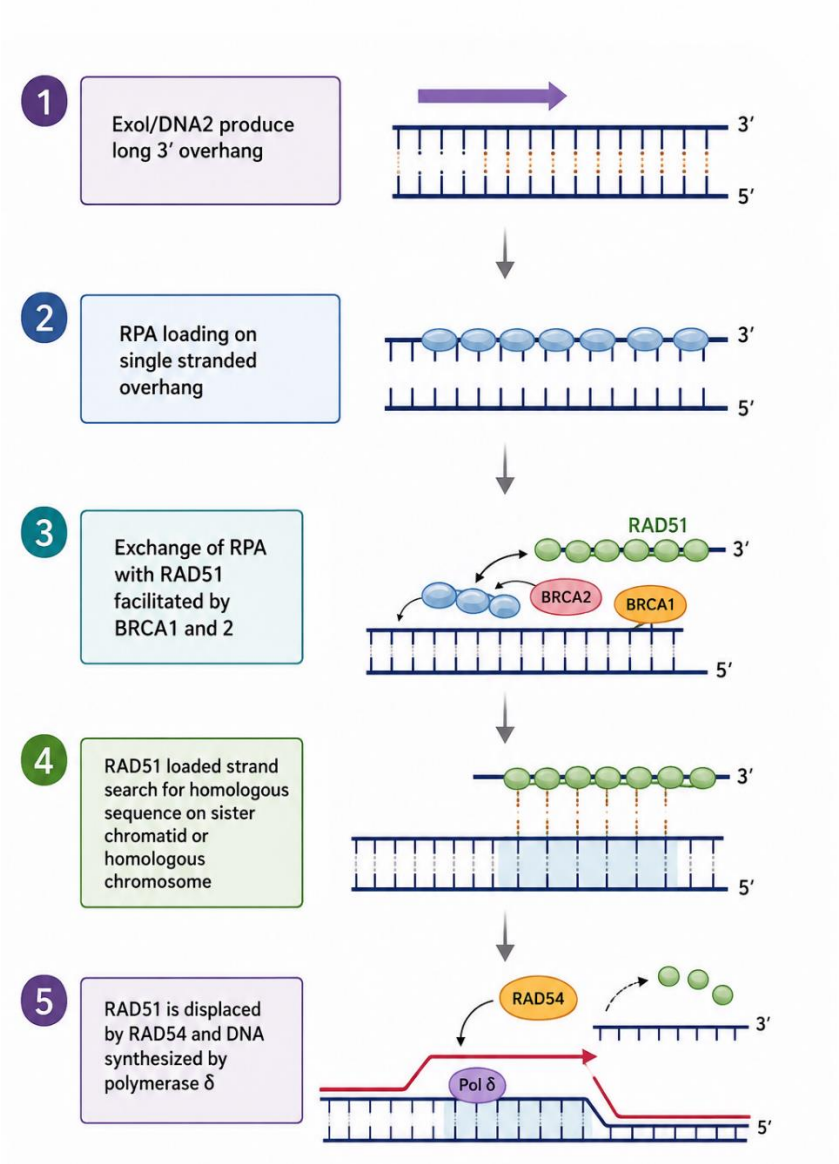


Figure 7. Homologous Recombination

HR Sub pathways

There are multiple pathways of homologous recombination (HR) exist, each corresponding to different outcomes of the synapse mediated by RAD51. First sub pathway is SSA pathway that repairs double-strand breaks (DSBs) independently of RAD51 and involves the fusion of two homologous 3′ single-stranded DNA ends, such as those found in tandem repeats, through annealing [25]. This process results in the removal of the “intervening sequence” between the repeats, making SSA an inaccurate sub pathway [25]. Extensive DNA end resection and displacement of RPA are necessary for exposing complementary

homologous sequences [26]. RAD52 and its paralogue RAD59 are essential for SSA in yeast, while in mammals, RAD52 is also involved, but there are additional redundant annealing factors present [27].

Second sub pathway is SDSA (Synthesis-dependent strand annealing). It can be considered the simplest and most efficient HR pathway, as it requires only a short region of similarity between the damaged DNA and the template strand [27]. Moreover, it doesn't involve the creation of a double Holliday junction, which has the potential to cause chromosome abnormalities and genetic instability. This pathway involves the pairing of the 3' end of a damaged DNA strand with a "homologous sequence"[28]. DNA synthesis then proceeds along the template until the broken strand is fully repaired. This repair mechanism is considered conservative, as it preserves the genetic information without exchanging it with the homologous chromosome [29].

Third sub pathway is the most unique pathway as in this process of the DNA molecule that has been invaded is held in place, and synthesis of DNA proceeds through a bubble-like structure along the entire length of the template DNA, ultimately reaching the end of the chromosome [29]. The process is called as break-induced replication (BIR) as it involves the catalysis of polymerase δ, including the helicase (Pif1) that facilitates polymerase δ's ability to displace the template strand while synthesizing a new complementary strand [30]. It is worth noting that DNA synthesis during BIR is conservative and differs significantly from canonical DNA replication [23]. The precise mechanism by which the complementary strand synthesis is accomplished remains unclear. BIR is used as a repair mechanism only when there is no other option available, for example, in situations where the second DNA end is absent, and is associated with increased mutagenesis [30]. .

Lastly, pathway is called Canonical recombinational DSBR Pathway [31]. This pathway is referred to as "canonical" because it is the most widely studied and understood form of homologous recombination in eukaryotic cells [32]. This pathway is different from other sub pathway in a sense that the after the formation of double Holliday junctions (dHJs), they can undergo further processing that results in either "crossovers or non-crossovers". The type of processing pathway utilized determines which outcome occurs [31].The double Holliday junctions (dHJs) that arise in the canonical recombinational DSBR pathway can be processed in several ways [31]. In vegetative cells, they can be processed through either resolution or dissolution mechanisms [31]. Dissolution involves the action of helicase-coupled topoisomerase, while resolution involves cleavage of junctions using nucleases [33]. On the other hand, in meiotic cells of most organisms, there is a preference for a specific pathway that promotes crossovers, along with some involvement of nucleases that are shared between meiotic and mitotic cells [31]. The complete role of nucleases in meiotic cells of humans or mice is still not completely understood. .However, in yeast S. cerevisiae cells, a specialized pathway for creating crossovers is utilized that involves a complex consisting

of Exo1, Mlh1, and Mlh3, as well as structure-specific nucleases like Slx1-Slx4, Mus81-Mms4, , and Yen1 [34].

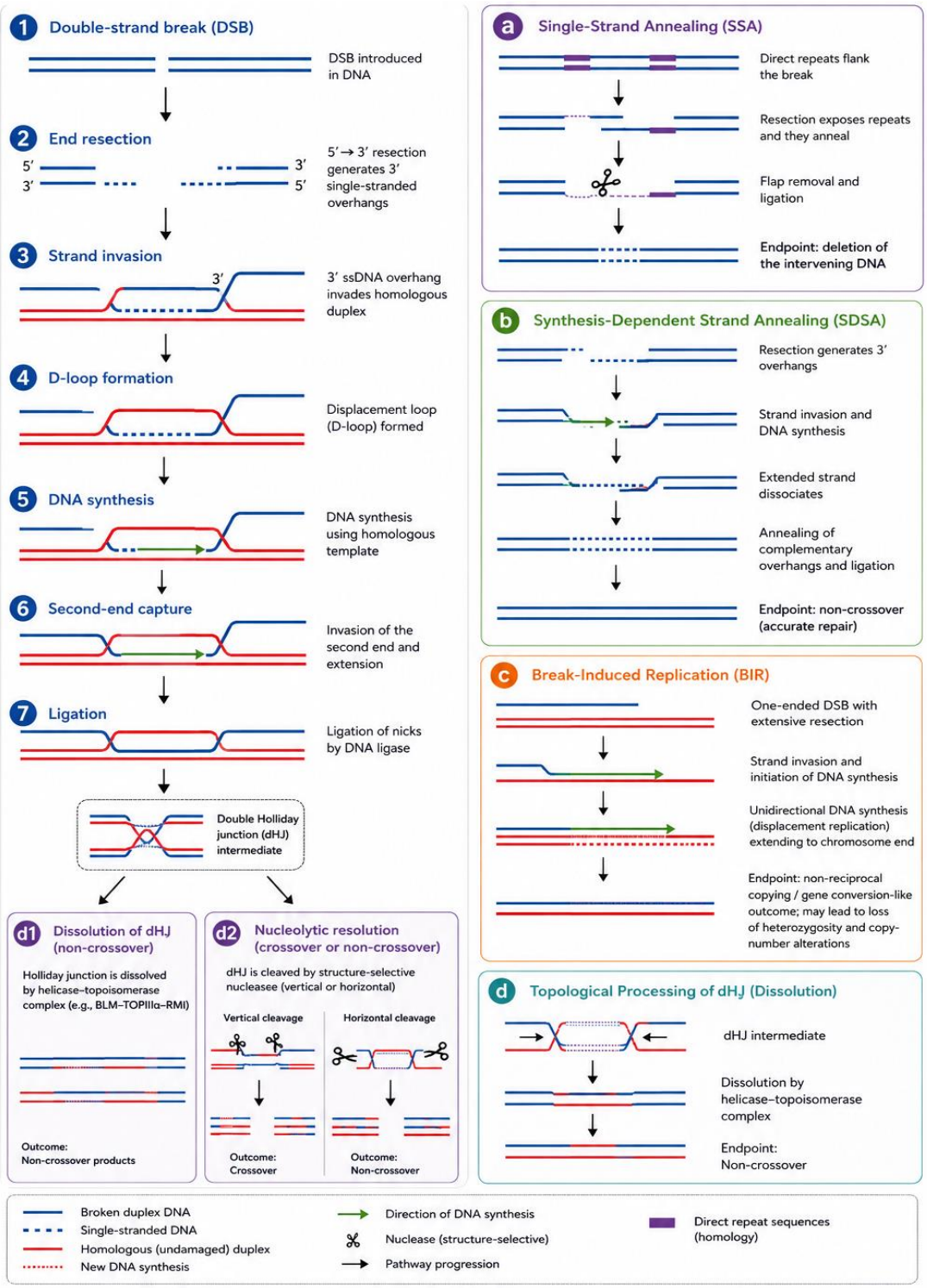


Figure 8. Major sub-pathways of homologous recombination-mediated DNA double0strand break repair

Master Transducers OF DNA Repair Signal Transduction Pathway

The signaling pathway of DNA repair is predominantly directed by a group of Serine/Threonine protein kinases known as phosphatidylinositol 3-kinase-like protein kinase (PIKK) family [35]. This family includes Ataxia Telangiectasia Mutated (ATM), ATM-related (ATR), and DNA-dependent protein kinase (DNA-PK) [36]. When a DNA double-strand break (DSB) occurs, ATM and DNA-PK are called to the position, and the stimulation of every enzyme directs different repair mechanism [37]. The DNA-PK controls proteins responsible for NHEJ, ATM is responsible for regulating molecules that eventually lead to homologous recombination (HR) and cell cycle arrest [38]. On the other hand, ATR, in conjunction with its partner ATRIP, becomes active upon being summoned to single-stranded DNA (ssDNA) coated with replication protein A (RPA) that arises during stalled replication forks or processing of double-strand breaks (DSBs) [39]. ATM, ATR, and DNA-PK utilize phosphorylation to modify hundreds of substrate proteins at S/T-Q motifs composed of serine/threonine residues, which can trigger subsequent phosphorylation events by activating other kinases, such as Chk1 and Chk2 [40]. The catalytic subunit of DNA-PK, known as DNA-PKcs, exhibits a tendency towards phosphorylating serine/threonine residues located within S/T-Q motifs [41]. Additionally, hydrophobic or acidic amino acids surrounding the S/T-Q motifs promote phosphorylation, whereas basic residues inhibit it. These kinases have similar targets and are the primary mediators of DDR, making them the "master transducers" of this pathway [42] [43].

Role of DNA repair and recombination in disease

DNA repair and recombination are essential processes for preserving the stability of the genome and preventing the accumulation of mutations and chromosomal abnormalities. Dysregulation of these processes can lead to a various disease such as cancer, neurodegenerative disorders, as well as immune dysfunction. Disruptions or malfunctions in DNA repair pathways can result in the buildup of DNA damage and mutations, which are major drivers of cancer development. For example, mutations in genes involved in the HR pathway, such as BRCA1 and BRCA2, are allied with increased susceptibility to different types of cancer such as ovarian and breast cancer [44]. Similarly, mutations in the nucleotide excision repair (NER) pathway are linked with xeroderma pigmentosum (XP), a disorder that predisposes individuals to skin cancer [45].

DNA damage and genomic instability can also contribute to progressive neurological conditions, such as Parkinson's disease and Alzheimer's disease [46]. Buildup of DNA lesions and impaired DNA repair pathways have been observed in postmortem brain tissue from patients with these diseases, as well as in animal models of neurodegeneration. For example, mutations in the DNA repair genes FANCJ and XPA has been associated to increased risk of developing neurodegenerative disorders [47]. DNA recombination is crucial in the formation and operation of the immune system, especially in creating a broad range of

antigen receptor genes using V(D)J segments of immunoglobulin genes [48]. Dysregulation of this process can lead to immune dysfunction and predisposition to autoimmune diseases and immunodeficiency disorders [49].

Emerging areas of research in DNA repair and recombination

Research on DNA repair and recombination is a rapidly evolving field, and there are several emerging areas of research that hold promise for advancing our understanding of these processes. Latest findings in single-cell sequencing technology have enabled researchers to study DNA repair and recombination events at the individual cells level. This approach has the possibility for alternative interpretations into the dynamics and heterogeneity of these processes within complex tissues and across different cell types. For example, single-cell sequencing has been used to identify subpopulations of cells with distinct DNA repair profiles in the brain and to track the repair of DNA damage in real time in reaction to external factors or conditions [50].

DNA repair and recombination pathways are regulated by epigenetic modifications, including DNA methylation and histone modifications. Recent findings have shown that changes in the epigenetic landscape can impact the efficiency and fidelity of these processes, and that dysregulation of epigenetic regulators can contribute to genome instability and disease. For example, loss of the DNA demethylase TET2 has been linked to defects in homologous recombination repair and higher likelihood of developing leukemia [51].

A new window of opportunity has been created by the discovery of genome editing tools, such as CRISPR/Cas9, for investigating DNA repair and recombination processes and for creating cutting-edge treatments for genetic illnesses. The ability of cells to mend specific DNA breaks by NHEJ or homology-directed repair is a prerequisite for these technologies. However, the context of the break and the particular repair route involved can affect how effective and precise these repair mechanisms are. Recent research has investigated methods to modify DNA repair mechanisms to improve the effectiveness and specificity of genome editing [52].

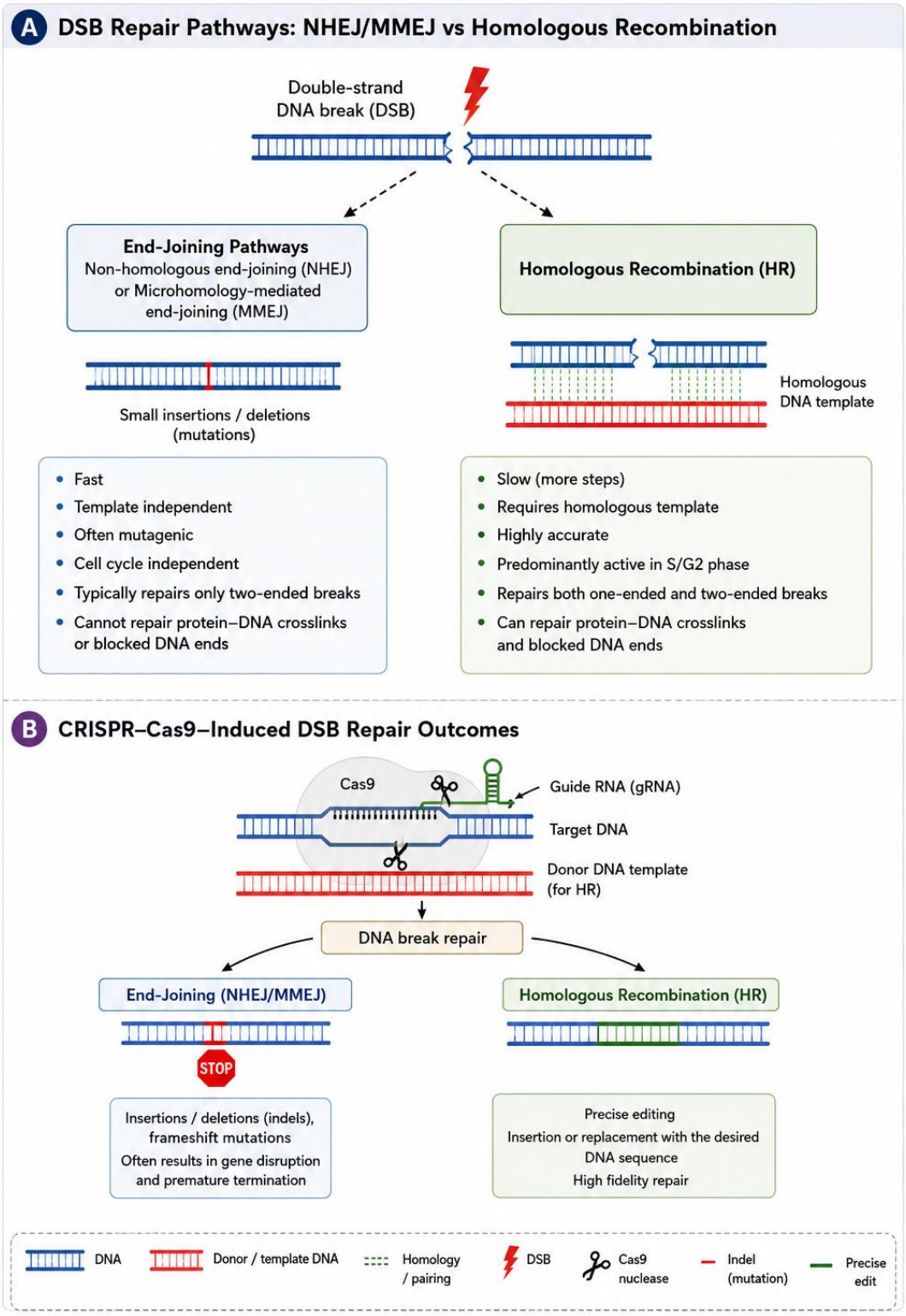


Figure 9. Comparison of DNA repair pathways and outcomes following CRISPR-Cas9-induced DSBs

Mitochondrial DNA (mtDNA) damage and repair:

A double-stranded circular DNA molecule called mitochondrial DNA (mtDNA) may be discovered in the mitochondria of eukaryotic cells. It encodes numerous crucial proteins that are necessary for the process of oxidative phosphorylation, which produces ATP, the cellular energy currency. MtDNA is vulnerable to oxidative stress, replication mistakes, and environmental pollutants because of its closeness to the electron transport chain and lack of protecting histones.

Cells have a number of DNA repair mechanisms, such as BER (base excision repair), NER (nucleotide excision repair), and MMR (mismatch repair), to maintain the integrity of mtDNA .The base excision repair (BER) mechanism is primarily responsible for repairing mtDNA damage brought on by oxidative stress. Through the use of a particular DNA glycosylase, damaged bases are identified and removed from this route [53].

Another DNA repair system that can fix mtDNA damage brought on by environmental chemicals and UV radiation is called NER [14]. This route entails identifying and removing a brief section of DNA that contains the broken base, after which a DNA polymerase and DNA ligase fix the hole. MMR has a role in fixing mistakes made during DNA replication and is crucial for preserving the integrity of mtDNA [2].

In addition to the aforementioned processes, it has been shown that mtDNA uses homologous recombination (HR) to help in DSB repair, replication, and segregation, notably in yeast mitochondria and plants [54]. Animal mtDNA recombination, on the other hand, appears to occur seldom [55]. However, it has been shown that RAD51 and a few other nuclear HR mediators are present in mitochondria, suggesting that this mechanism may also take place in animal mtDNA. To further understand HR repair in mtDNA, more study is required [55].

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