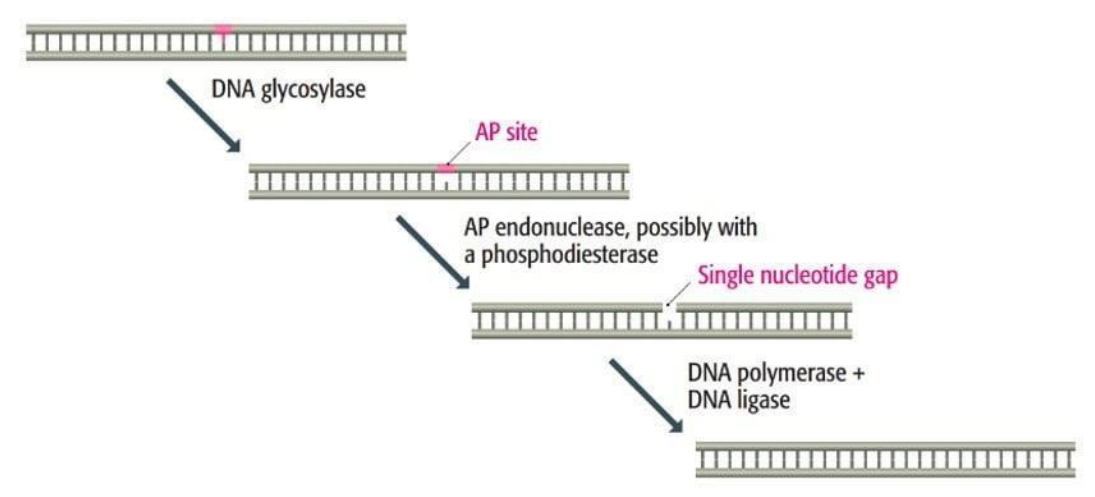
DNA REPAIR

Base excision repair

Base excision repair (BER) is a DNA repair mechanism that removes and replaces damaged bases. It involves the action of various DNA glycosylases such as 8-oxoguanine DNA glycosylase (OGG1). These enzymes recognize and remove damaged bases. BER includes both short patch repair, where an abasic site is processed and filled by specific enzymes, and long patch repair, where gaps are tailored and DNA synthesis occurs followed by ligation. One example of BER is the repair of uracil-containing DNA. In this process, a DNA glycosylase recognizes and removes the uracil base, creating a gap in the DNA called AP site. The gap is then cleaved by an enzyme called AP endonuclease. After that, the remaining sugar is removed, and the gap is filled using DNA polymerase and sealed with ligase.



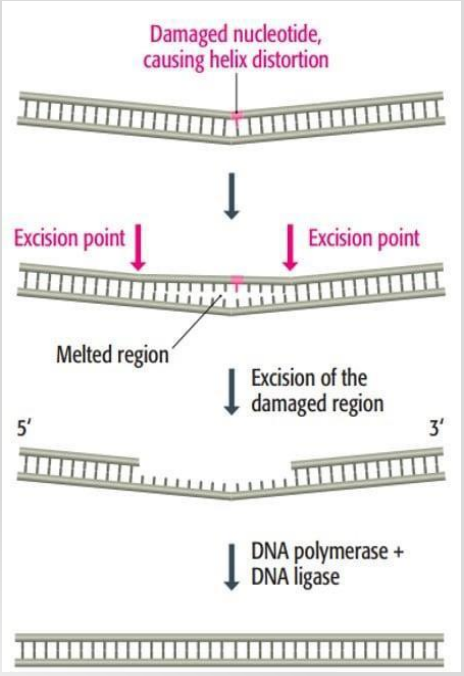
BASE EXCISION REPAIR

Nucleotide excision repair

Nucleotide excision repair (NER) deals with bulky adducts and cross-linking lesions caused by UV radiation or chemical exposure. NER removes a fragment of nucleotides containing the damaged lesion and synthesizes a new DNA strand using the undamaged strand as a template.

NER consists of two pathways:
Global Genome NER (GG-NER) repairs bulky damages throughout the entire genome, including regions that are not actively transcribed.
Transcription-Coupled NER (TC-NER) repairs damage that occurs on the transcribed DNA strand.

Mutations in NER pathway genes can lead to disorders such as xeroderma pigmentosum (XP) and certain other neurodegenerative conditions.



NUCLEOTIDE EXCISION REPAIR

Double-strand break repair

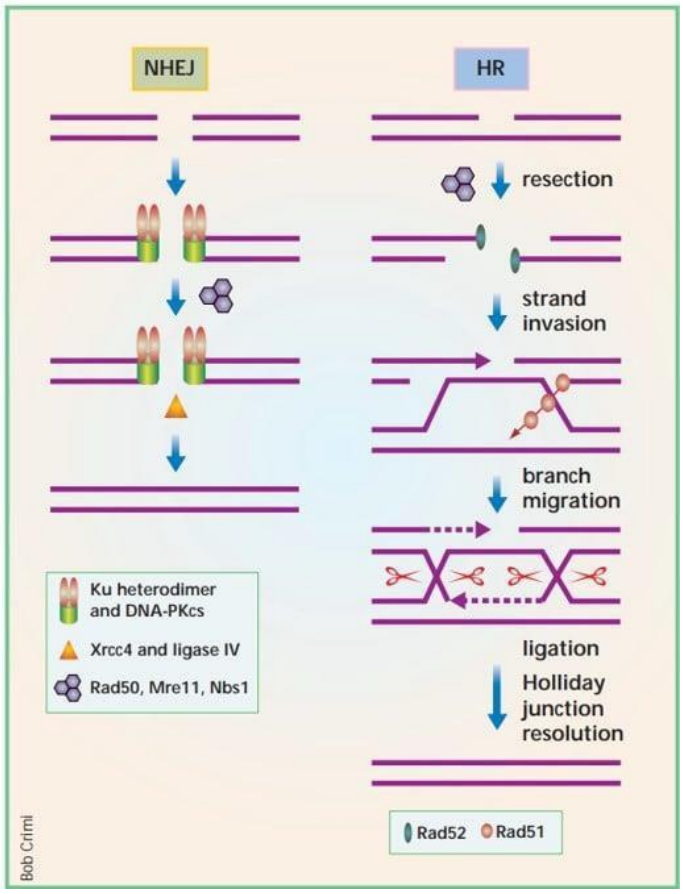
Double-strand breaks (DSBs) in DNA can be repaired through two pathways: homologous recombination (HR) and non-homologous end joining (NHEJ).

Homologous recombination (HR)

HR is a precise repair pathway that requires a matching DNA sequence as a template. It primarily uses the sister chromatid, a copy of the damaged DNA, for repair. HR is most active during the S, G2, and M phases of the cell cycle when sister chromatids are present. The HR process involves creating single-stranded DNA (ssDNA) by degrading one strand of the DNA break and coating it with proteins like RPA. Rad51 replaces RPA and pairs the ssDNA with a homologous DNA template for repair.

Non-homologous end joining (NHEJ)

NHEJ is a simple and widely used mechanism that directly seals the broken ends of DNA without the need for a homologous DNA template. It can occur throughout the cell cycle. Proteins like Ku70/Ku80, DNA-PKcs, and LIG4/XRCC4 are involved in NHEJ. Ku70/Ku80 protects the DNA ends and prevents recombination, while DNA-PKcs and LIG4/XRCC4 help with end joining. The NHEJ pathway is faster but can be more error-prone compared to HR.



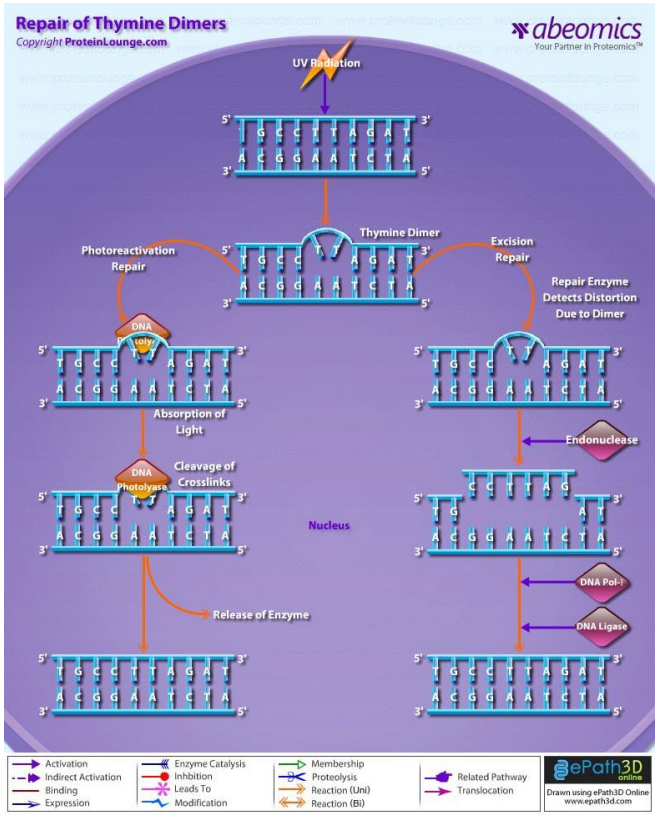
DOUBLE STRANDED BREAK REPAIR

THYMINE DIMER REPAIR

Irradiation of DNA by UV causes lesions, such as cyclobutane-pyrimidine dimers or 6-4PPs (6-4 pyrimidine pyrimidone). The most common covalently linked adjoining pyrimidines are T-T (thymine dimers), T-C (thymine-cytosine dimers) and C-C (cytosine-cytosine dimers). T-T dimers cause kinks in the DNA strand that prevent both replication and transcription of that part of the DNA. Because they block DNA replication (and therefore prevent cells from reproducing), T-T dimers and other forms of UV damage cannot be inherited, and thus do not constitute mutations. Such kinds of DNA damage are known as premutational lesions because they prevent both transcription and replication of the genes in which they are present, and these lesions are fatal if they go uncorrected.

Several mechanisms are available for the removal or correction of T-T dimers from DNA depending upon the circumstances of the cell. Certain organisms possess a photoreactivating enzyme called photolyase, which contains chromophores capable of capturing photons of blue light. Photolyase first detects and binds to the damaged DNA site. Then it uses light energy absorbed from the visible range to oxidize the cyclobutane ring and convert the dimer into monomers without disrupting the double strands. Finally, the enzyme dissociates from the DNA and the damage is repaired. Recognition of cyclobutane-pyrimidine dimers by photolyase is structure specific and the enzyme is not influenced by the nucleotide content surrounding the dimer. Photoreactivation, however, is affected by the nucleotide content of the pyrimidine dimers. The cyclobutane-pyrimidine dimers photolyase is found in prokaryotes, lower and higher eukaryotes, but their existence in placental mammals is still unknown. Hence, the repair of T-T dimers in humans takes place through an excision repair mechanism. This repair mechanism does not require light and instead of just breaking the bonds of the T-T dimer as was done by photolyase, it excises the region of damaged nucleotides. A protein complex recognizes the distortion in the DNA

caused by the T-T dimers and a pair of endonucleases makes nicks in the DNA strand on either side of the T-T dimer. Generally, the nicks are 12 nucleotides apart and the DNA between the nicks is removed. DNA polymerase I fills in the gaps left behind, and DNA ligase seals the final nick in the DNA. In addition, other mechanisms such as mutagenic repair or dimer bypass, recombinational repair, cell-cycle checkpoints, apoptosis, and certain alternative repair pathways are also operative in various organisms for the removal or correction of T-T dimers.



THYMINE DIMER REPAIR