DNA Repair Mechanisms

Since many mutations are deleterious, DNA repair systems are vital to the survival of all organisms– Living cells contain several DNA repair systems that can fix different type of DNA alterations!

- Cells have a variety of mechanisms to prevent **mutations**, or permanent changes in DNA sequence.
- During DNA synthesis, most DNA polymerases "check their work," fixing the majority of mispaired bases in a process called **proofreading**.
- Immediately after DNA synthesis, any remaining mispaired bases can be detected and replaced in a process called **mismatch repair**.
- If DNA gets damaged, it can be repaired by various mechanisms, including **chemical reversal**, **excision repair**, and **double-stranded break repair**.

DNA repair mechanisms fall into 2 categories –

- Repair of damaged bases
- Repair of incorrectly base paired bases during replication

In most cases, DNA repair is a multi-step process –

1. An irregularity in DNA structure is detected

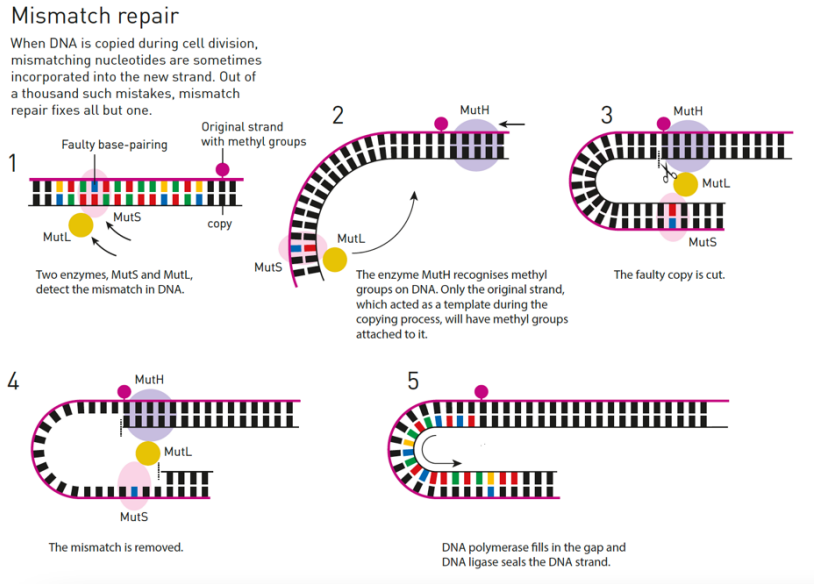
2. The abnormal DNA is removed

3. Normal DNA is synthesized

The Basic Pathway of DNA Repair

Repair mechanisms that include nucleotide removal utilize a common four-step pathway:

1. Detection: The damaged section of the DNA is recognized. **2. Excision:** DNA-repair endonucleases nick the phosphodiester backbone on one or both sides of the DNA damage and one or more nucleotides are removed. **3. Polymerization:** DNA polymerase adds nucleotides to the newly exposed 3′-OH group by using the other strand as a template and replacing damaged (and frequently some undamaged) nucleotides. **4. Ligation:** DNA ligase seals the nicks in the sugar–phosphate backbone. The primary differences in the mechanisms of mismatch, base excision, and nucleotide-excision repair are in the details of detection and excision. In base-excision and mismatch repair, a single nick is made in the sugar–phosphate backbone on one side of the damage; in nucleotide-excision repair, nicks are made on both sides of the DNA lesion. In base-excision repair, DNA polymerase displaces the old nucleotides as it adds new nucleotides to the 3′ end of the nick; in mismatch repair, the old nucleotides are degraded.



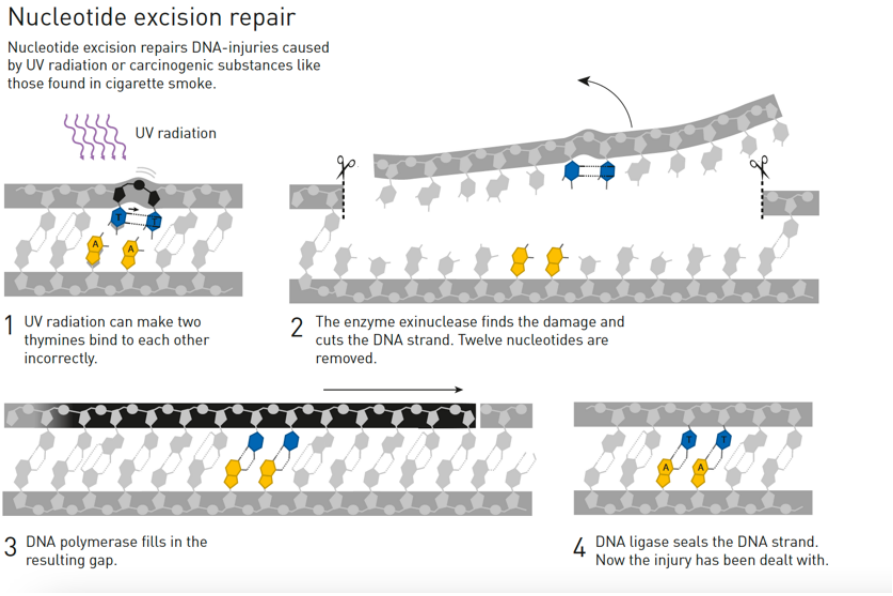
Mismatch Repair

- In DNA replication, a mismatched base was added to the new strand.
- Methylation at GATC sequences allows old and newly synthesized nucleotide strands to be differentiated: a lag in

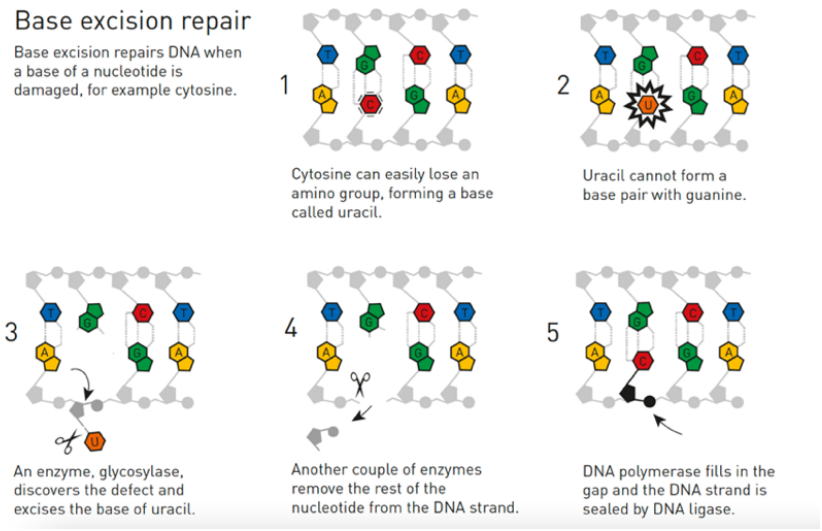
methylation means that, immediately after replication, the old strand will be methylated but the new strand will not.

- The mismatch-repair complex brings the mismatched bases close to the methylated GATC sequence, and the new strand is identified.
- Exonucleases remove nucleotides on the new strand between the GATC sequence and the mismatch.
- DNA polymerase then replaces the nucleotides, correcting the mismatch, and DNA ligase seals the nick in the sugar–phosphate backbone.

Nucleotide Excision Repair (NER)



- In nucleotide excision repair mechanism, the defective nucleotide is cut out and replaced.
- Unlike base excision repair, the enzymes in nucleotide excision repair recognizes the distortion in shape of double stranded DNA structure caused by thymine dimers or intercalating agents.
- The multi subunit **enzyme excinucleases** (endonuclease and exonuclease activity) hydrolyses two phosphodiester bond one on either side of distortion caused by lesion creating **3'-OH** group and **5'-P** group.
- The excised nucleotide is removed, and the resulting gap is filed by DNA polymerase-I in *E. coli* and DNA polymerase E in Human and finally joined by DNA ligase.



Base Excision Repair

- In this mechanism modified bases are recognized and cut out. Mutation causes alkylation and deamination of bases which are recognized by special **DNA glycosylase enzyme.**
- Glycosylase recognizes and remove the damaged bases by hydrolyzing the glycosidic bond and cut out the damaged base creating **AP site (a purinic or pyrimidinic site).**
- The AP site is recognized by AP endonucleases which split the phosphodiester bond on DNA strand at AP site and removes the AP sugar.
- After the damaged nucleotide is removed, the gap is repair by **DNA polymerase I** and ligated by **DNA ligase**.

References

- www.biologydiscussion.com
- www.npr.com
- Pierce, Benjamin A. Genetics: A Conceptual Approach. New York: W.H. Freeman, 2012.

[The information, including the figures, are collected from the above references and will be used solely for academic purpose.]