DNA Repair

By
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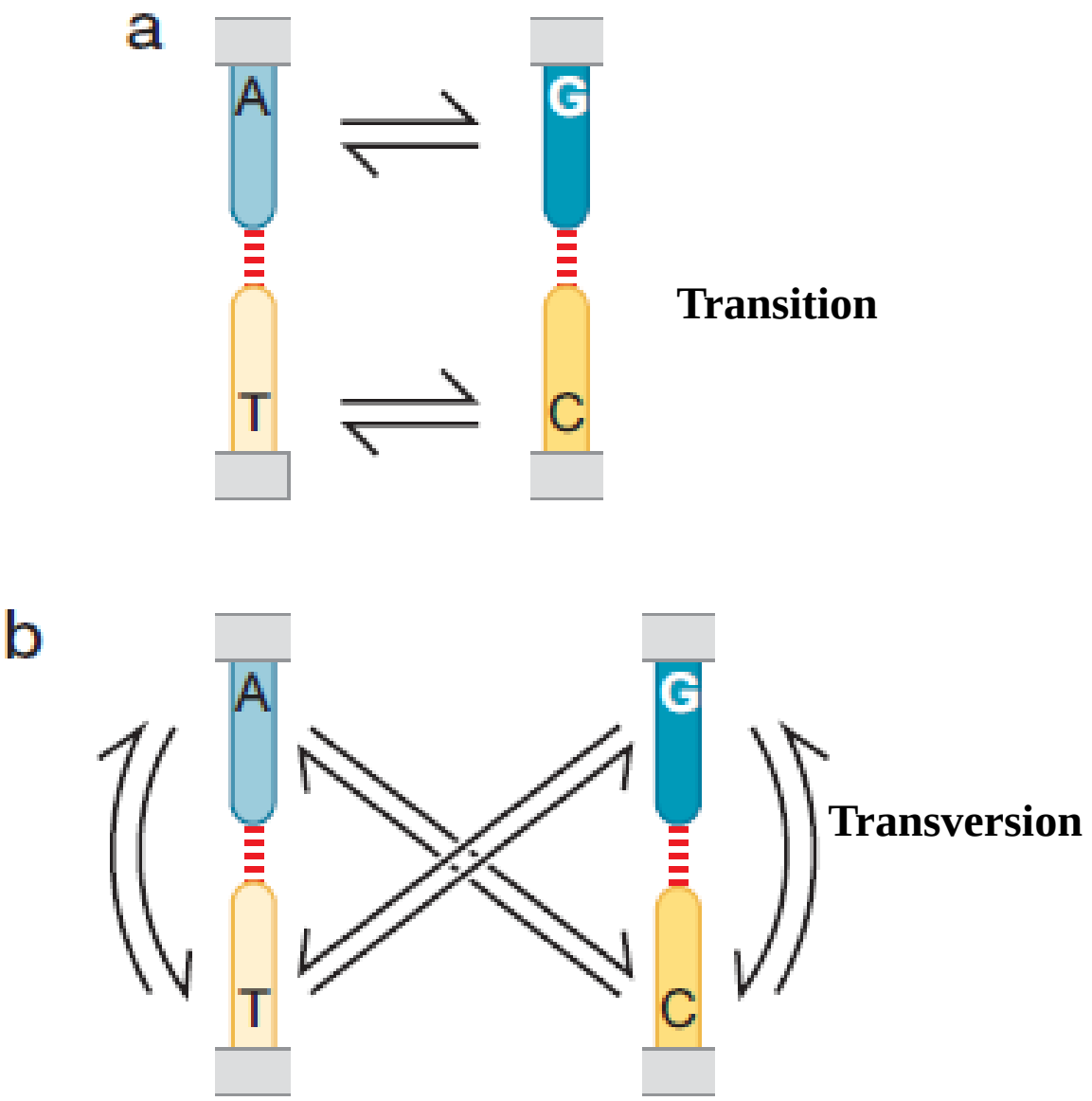
MUTATION



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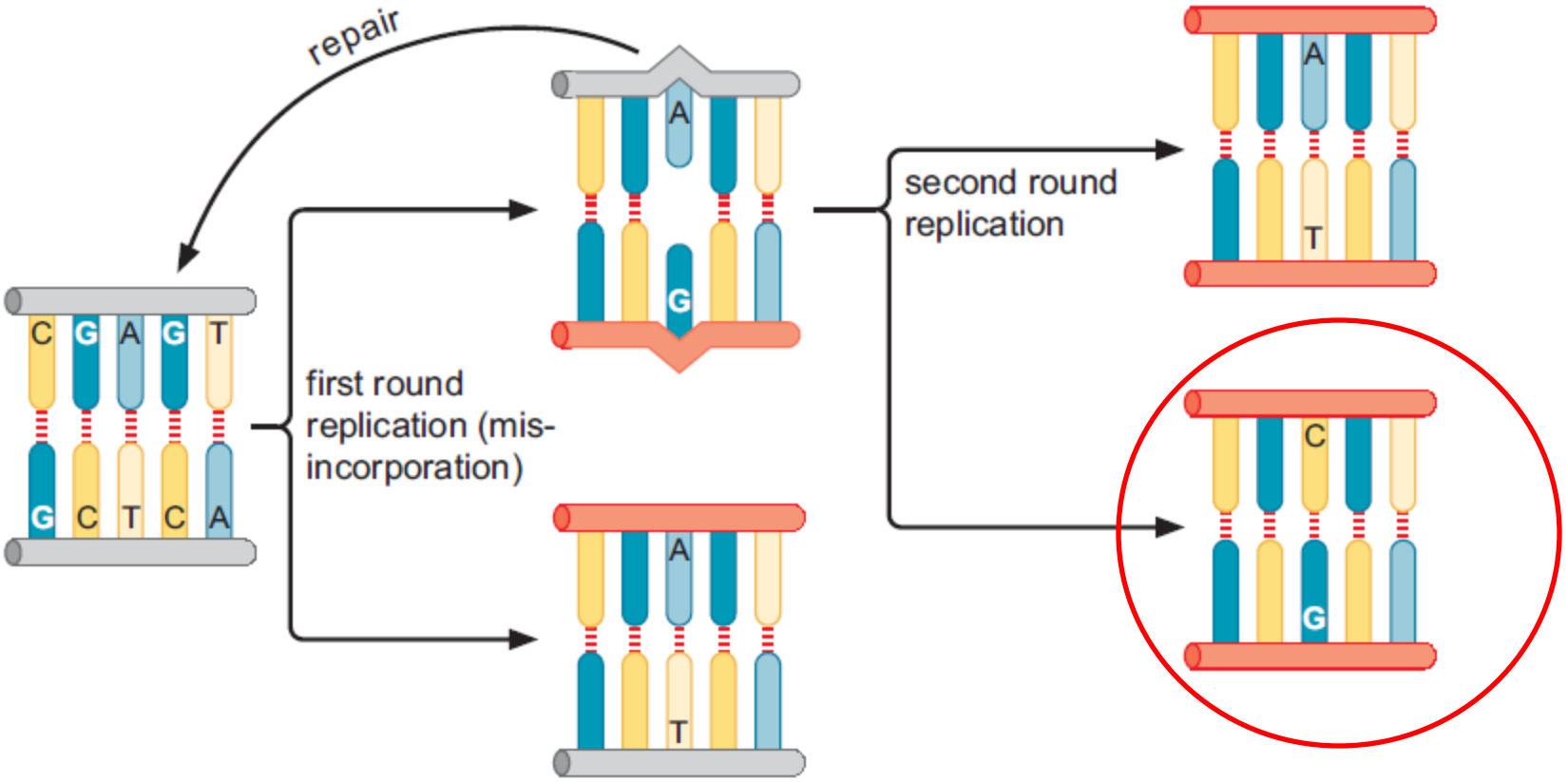
Replication can change a misincorporated base into a permanent mutation.



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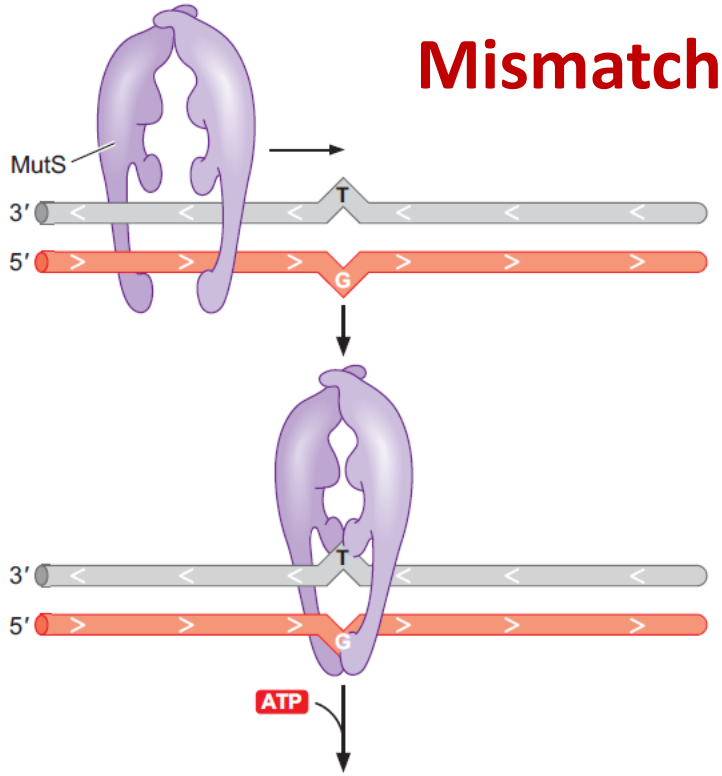
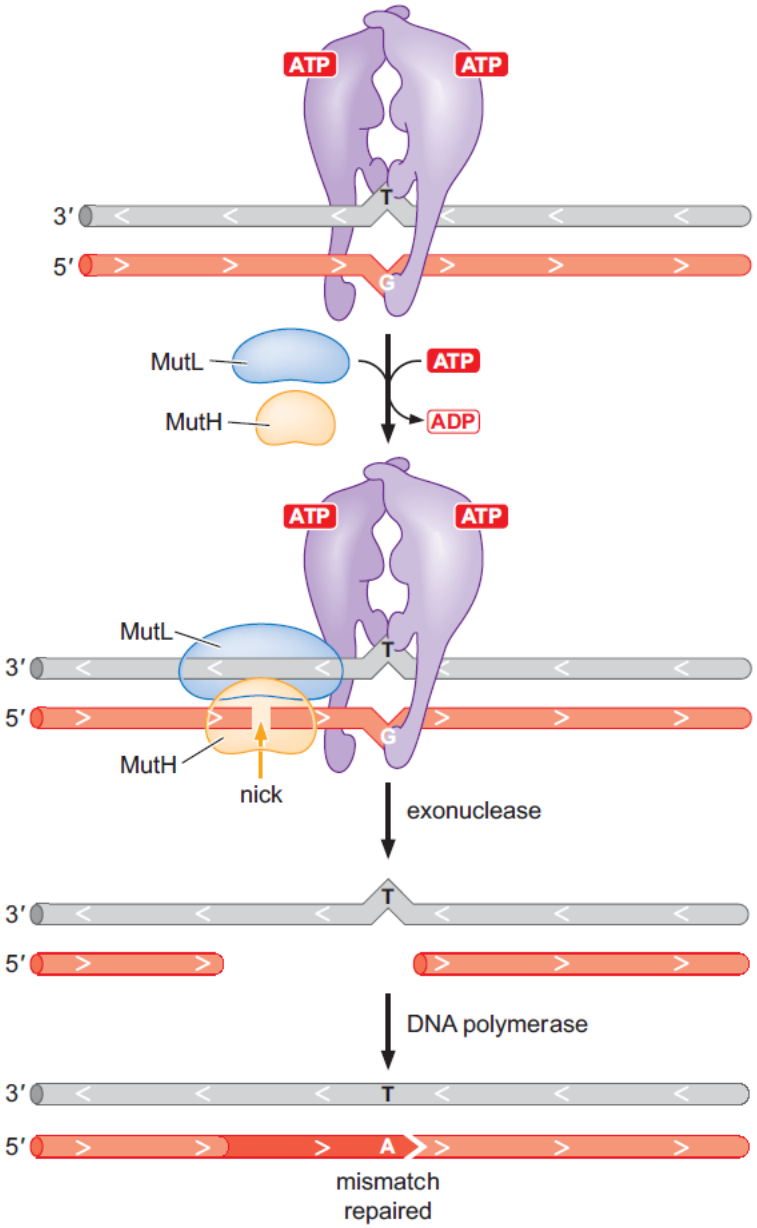
Mismatch Repair System



MutS embraces mismatch-containing DNA, inducing a kink. In subsequent steps, MutS recruits MutL and MutH, and the ATPase activity of MutS catalyzes the hydrolysis of ATP. MutH is an endonuclease that creates a nick in the DNA near the site of the mismatch. Next, an exonuclease digests the nicked strand moving toward and beyond the mismatch. Finally, the resulting single-strand gap is filled in by DNA polymerase, eliminating the mismatch.



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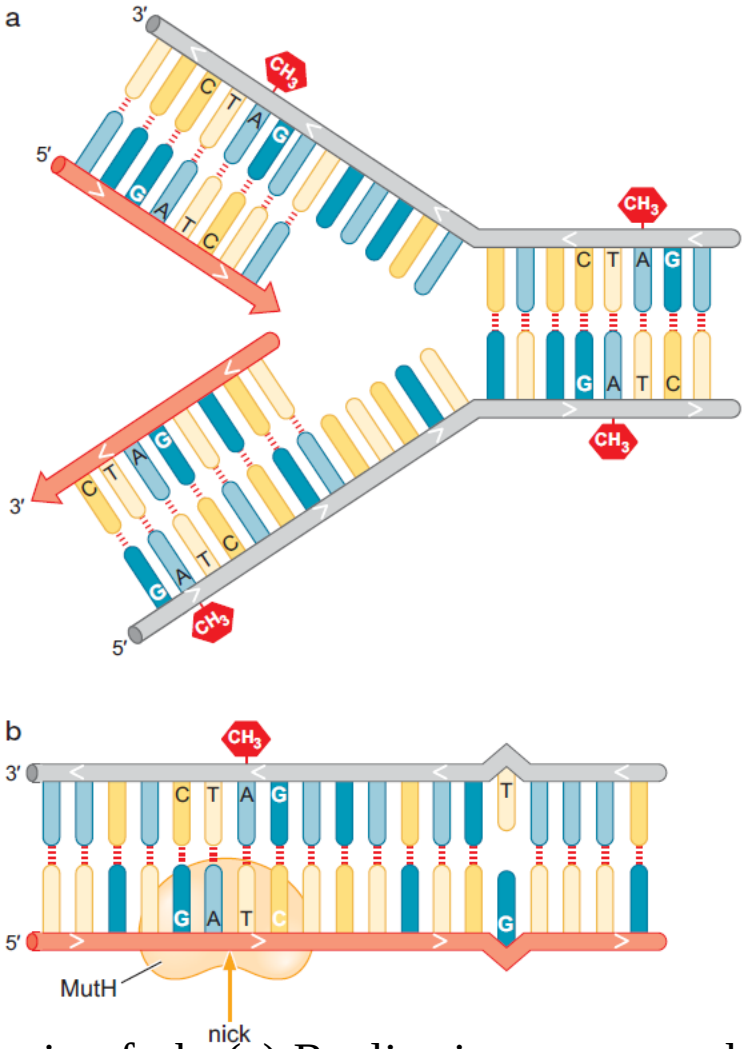
Mismatch Repair System



Dam methylation at replication fork. (a) Replication generates hemimethylated DNA in E. coli. (b) MutH makes incision in unmethylated daughter strand.

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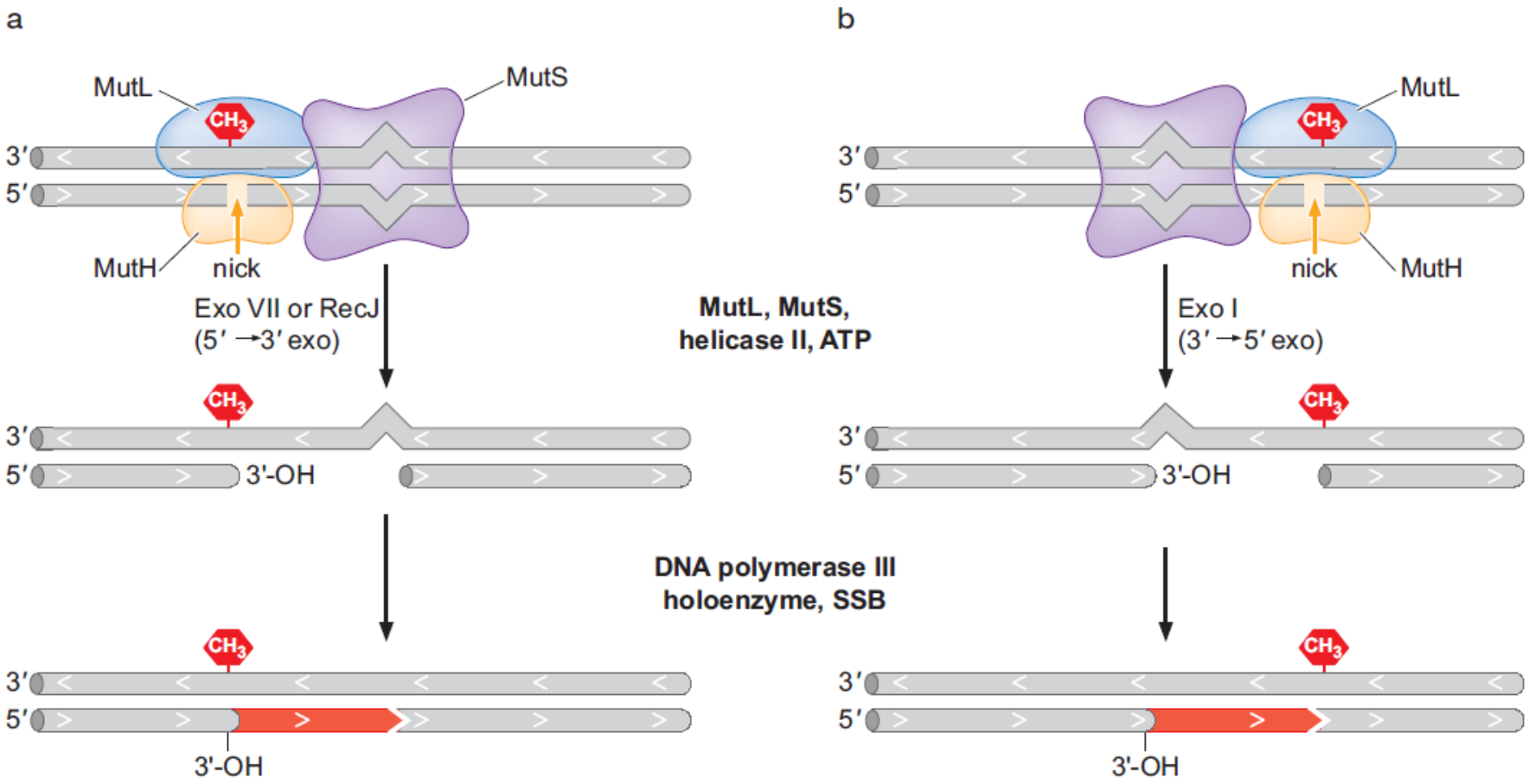
Mismatch Repair System



Directionality in mismatch repair: exonuclease removal of mismatched DNA.
For simplicity, DNA-bound MutH is shown as being immediately adjacent to MutS at the mismatch. (a) Unmethylated GATC is 5' of mutation. (b) Unmethylated GATC is 3' of mutation.

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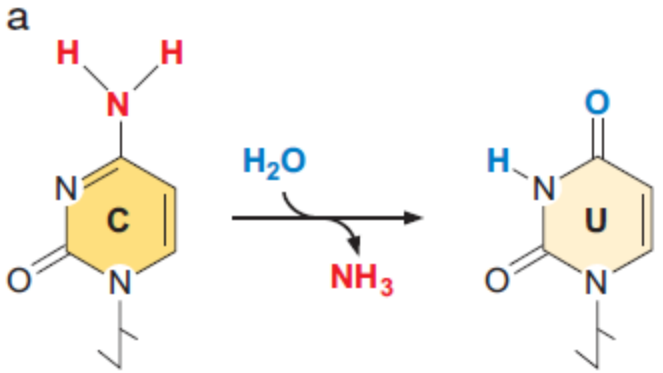
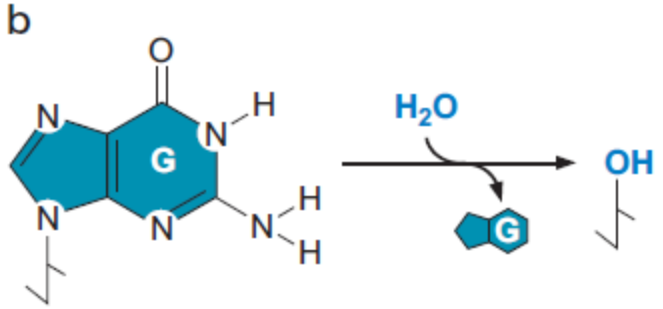
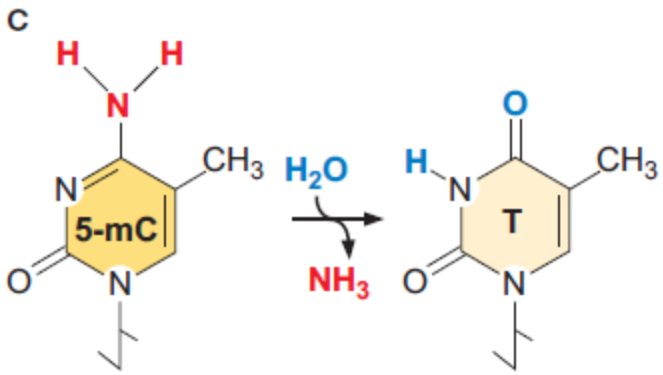
Common types of hydrolytic DNA damage



Deamination of cytosine create Uracil



Depurination of Guanine by hydrolysis create apurinic deoxyribose



Deamination of 5-methyl cytosine create thyamine

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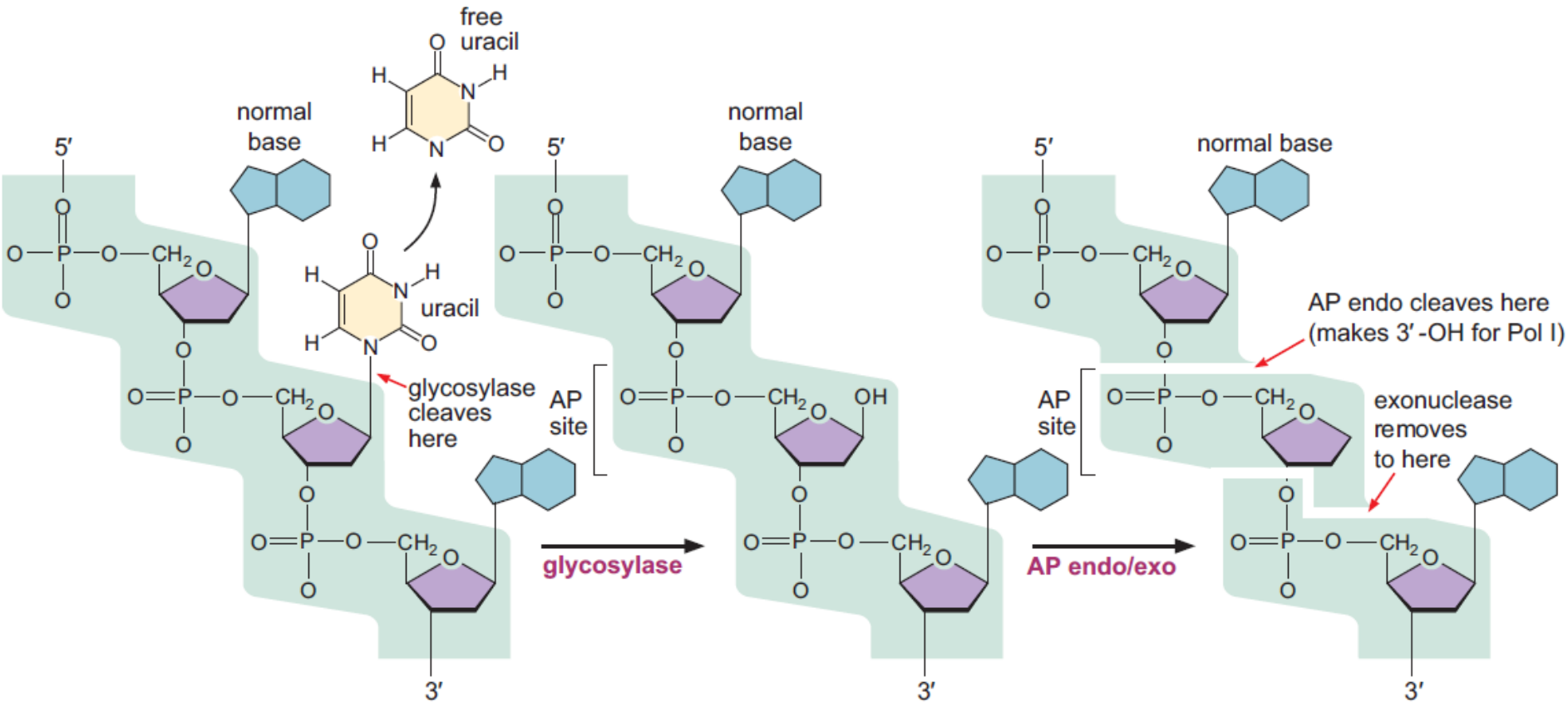
Base excision Pathway



The uracil glycosylase reaction: Uracil glycosylase hydrolyzes the glycosidic bond to release uracil from the DNA backbone to leave an AP site (apurinic or, apyrimidinic site). AP endonuclease cuts the DNA backbone at the 5' position of the AP site, leaving a 3'OH; exonuclease cuts at the 30'position of the AP site, leaving a 5'-phosphate. The resulting gap is filled in by DNA Pol I.

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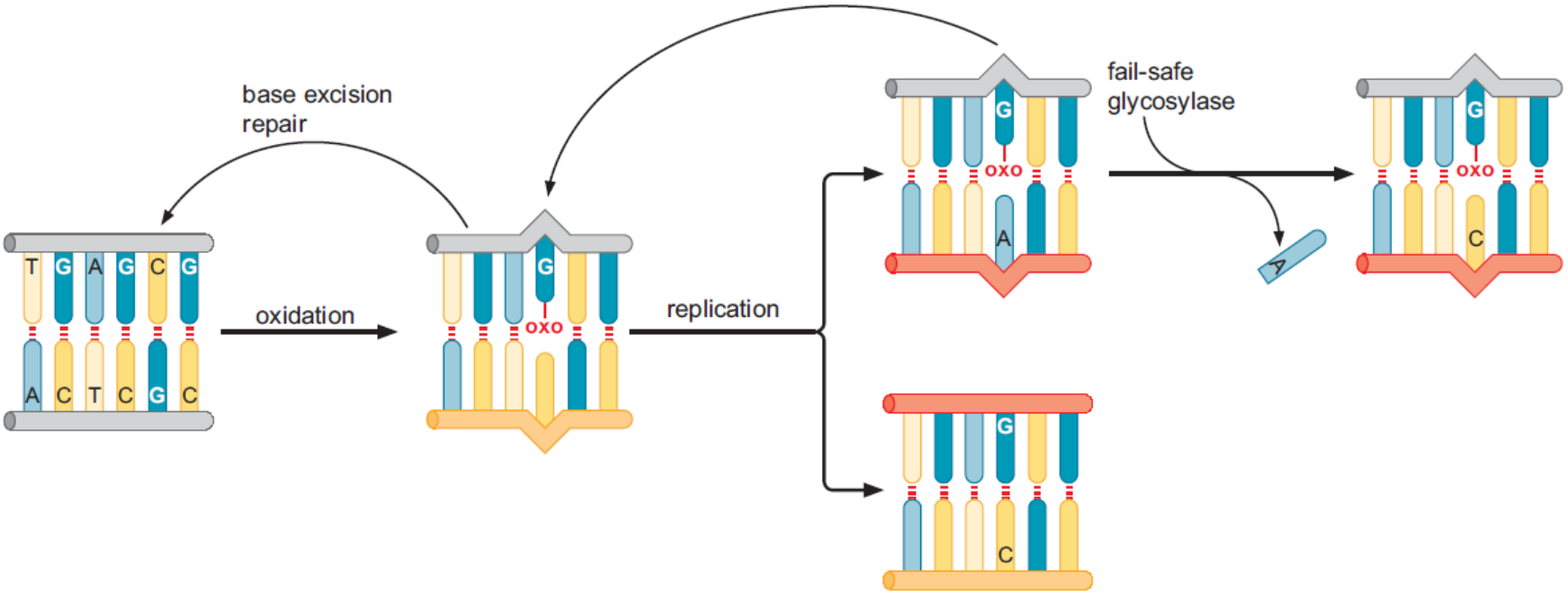
oxoG:A repair.



Oxidation of guanine produces oxoG. The modified base can be repaired before replication by DNA glycosylase via the base excision pathway. If replication occurs before the oxoG is removed, resulting in the misincorporation of an A, then a fail-safe glycosylase can remove the A, allowing it to be replaced by a C. This provides a second opportunity for the DNA glycosylase to remove the modified base.

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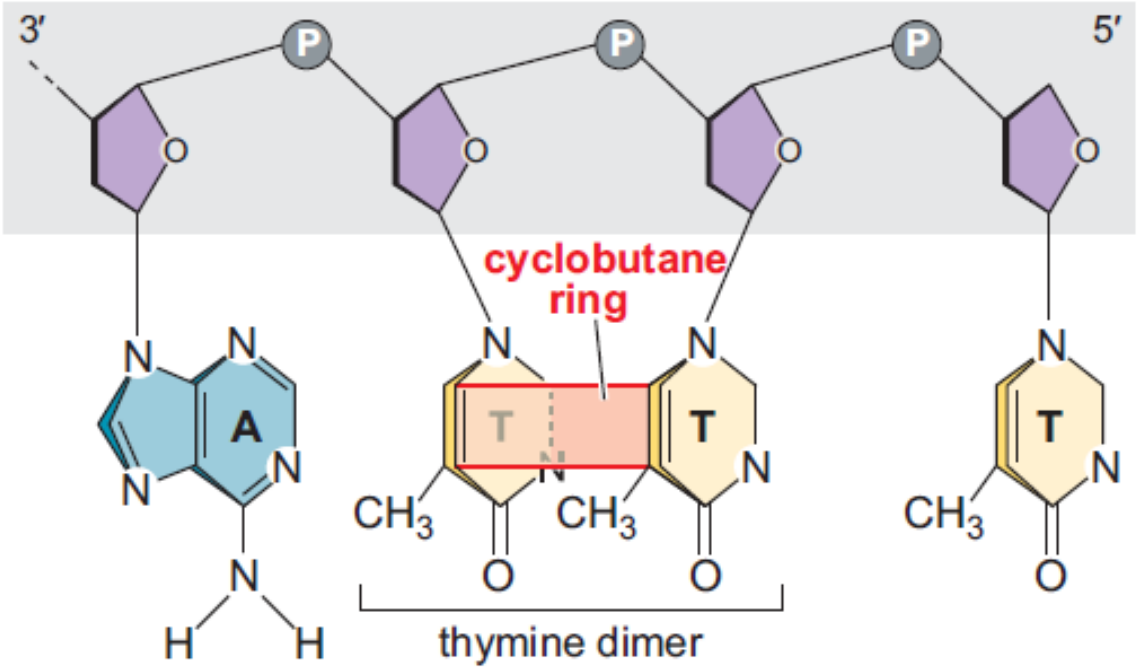
Thymine dimer



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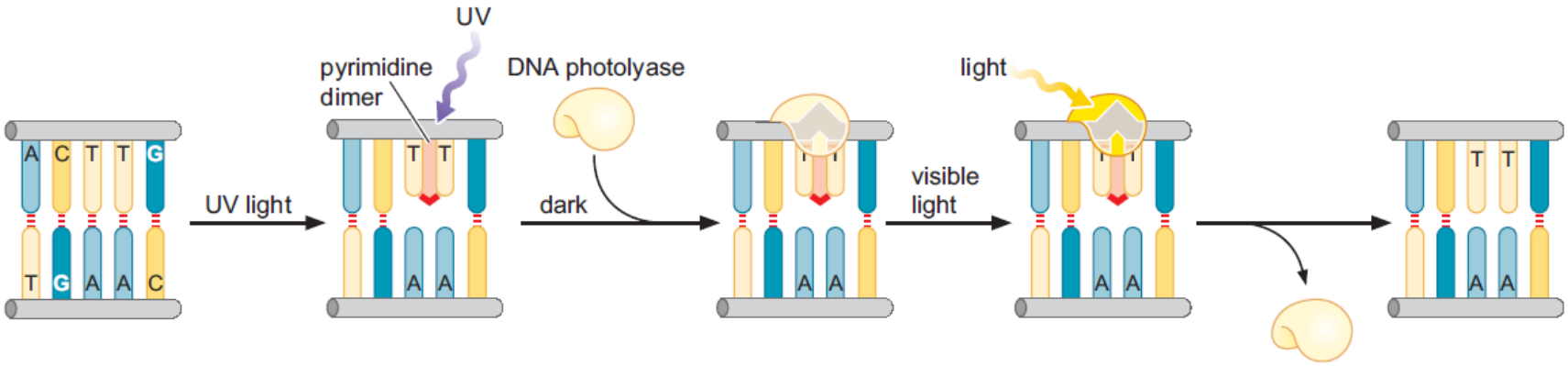
Direct Repair

Photoreactivation



Photoreactivation. Ultraviolet irradiation causes formation of thymine dimers. Upon exposure to light, DNA photolyase breaks the ring formed between the dimers to restore the two thymine residues.

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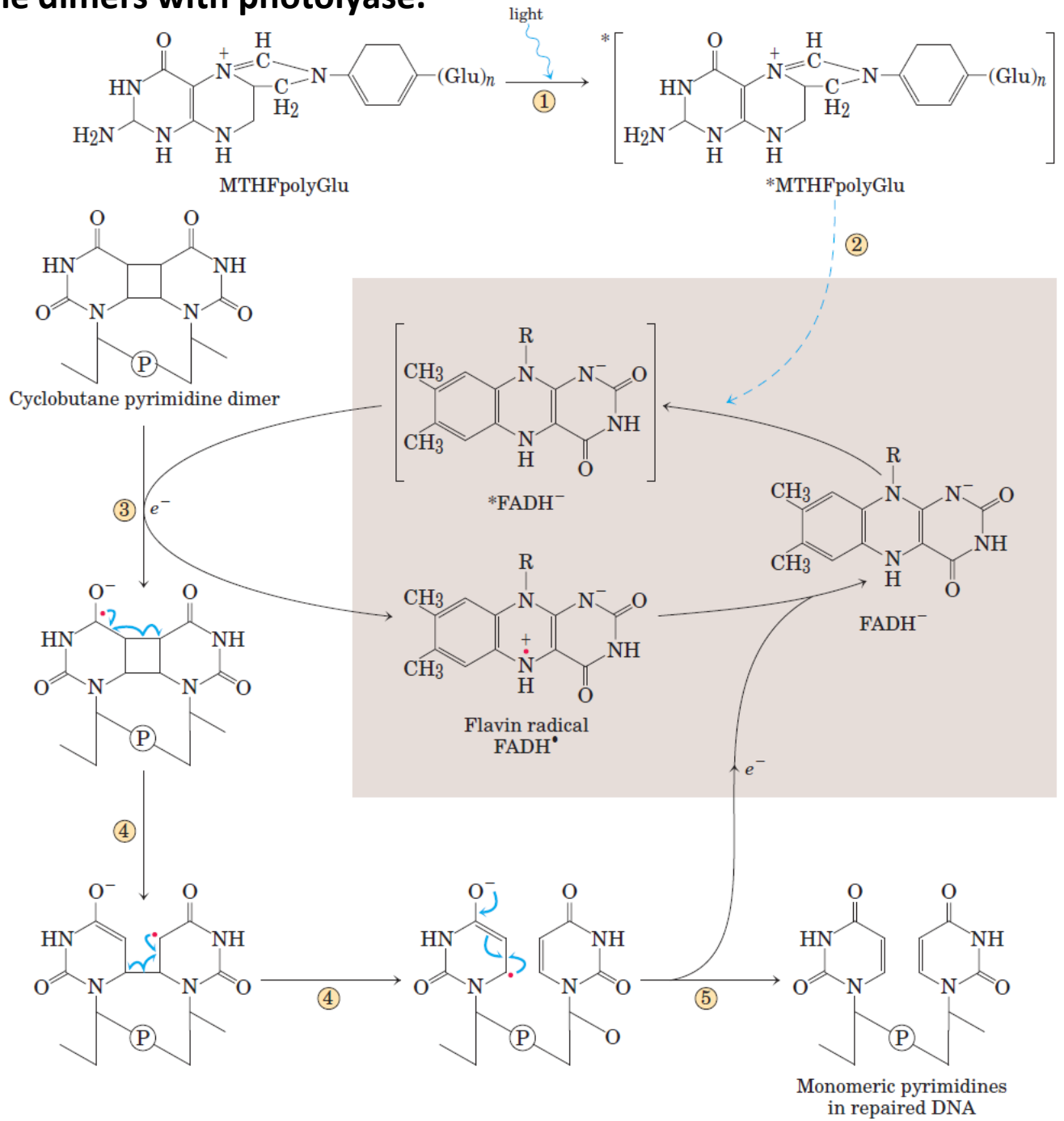
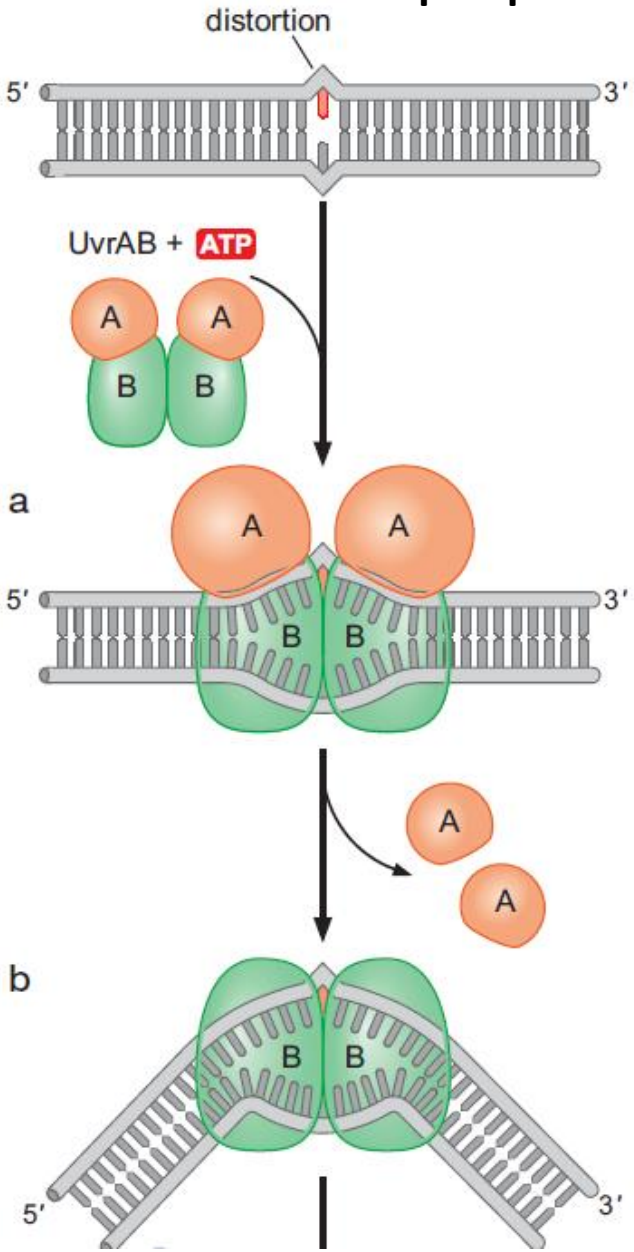
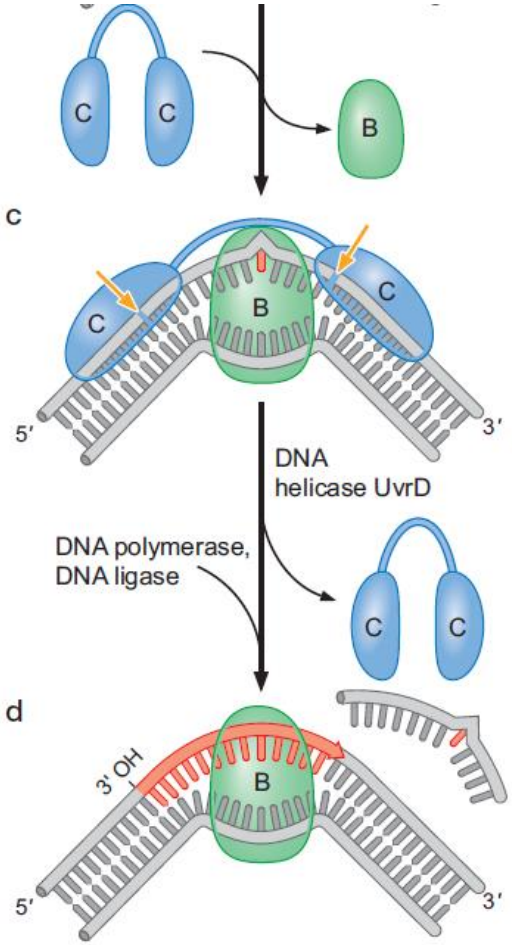
Repair of pyrimidine dimers with photolyase.



Nucleotide excision repair pathway





(a) ATP hydrolysis promotes dimer formation by UvrA, which forms a complex with a dimer of UvrB. The UvrA and UvrB complex scans DNA to identify a distortion.

(b) UvrA leaves the complex, and the remaining UvrB dimer melts DNA locally around the distortion.

(c) UvrC forms a complex with UvrB and creates nicks 3’ to the lesion and 5’ to the lesion.

(d) DNA helicase UvrD releases the single-strand fragment from the duplex, and DNA Pol I and ligase repair and seal the gap.

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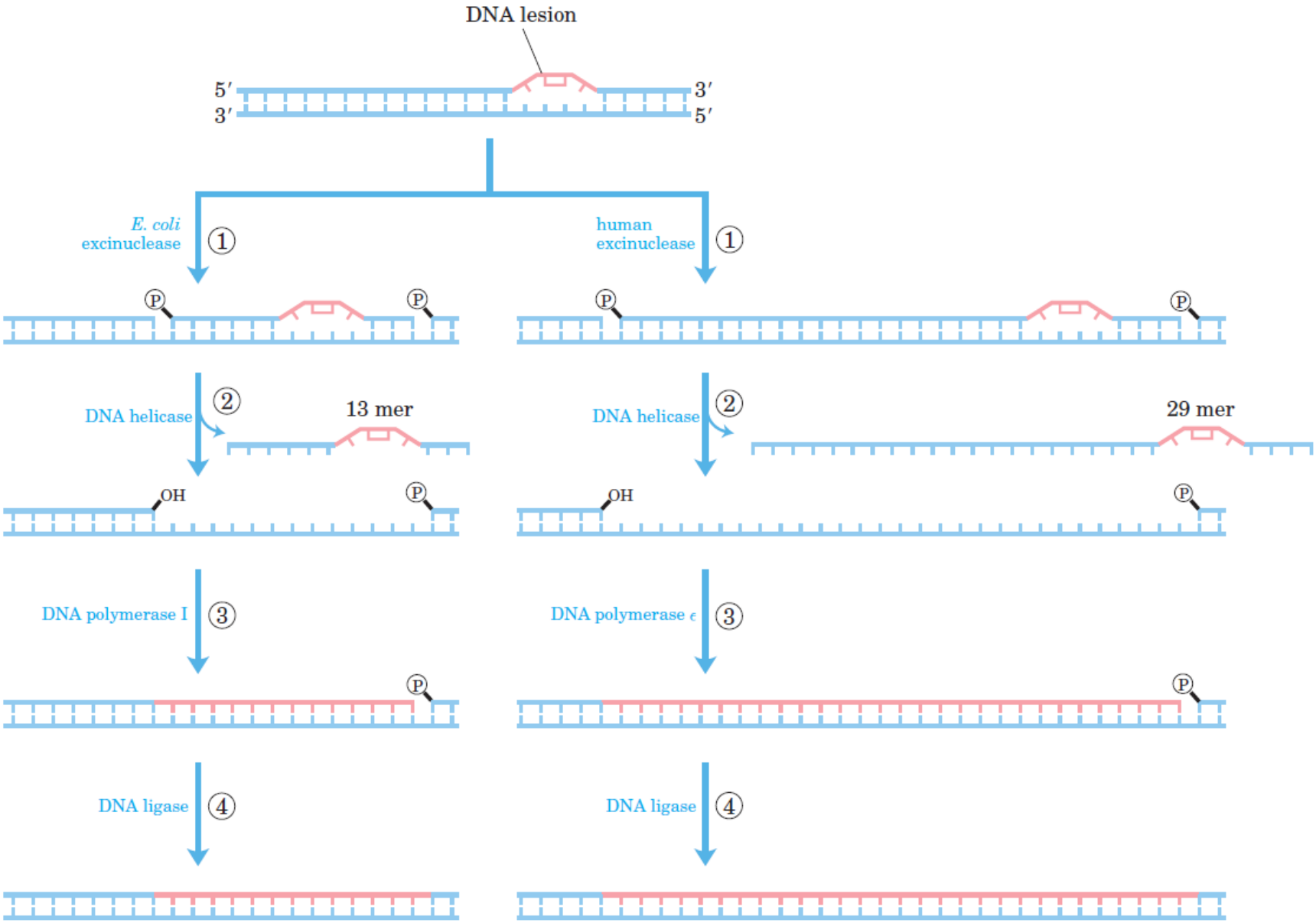
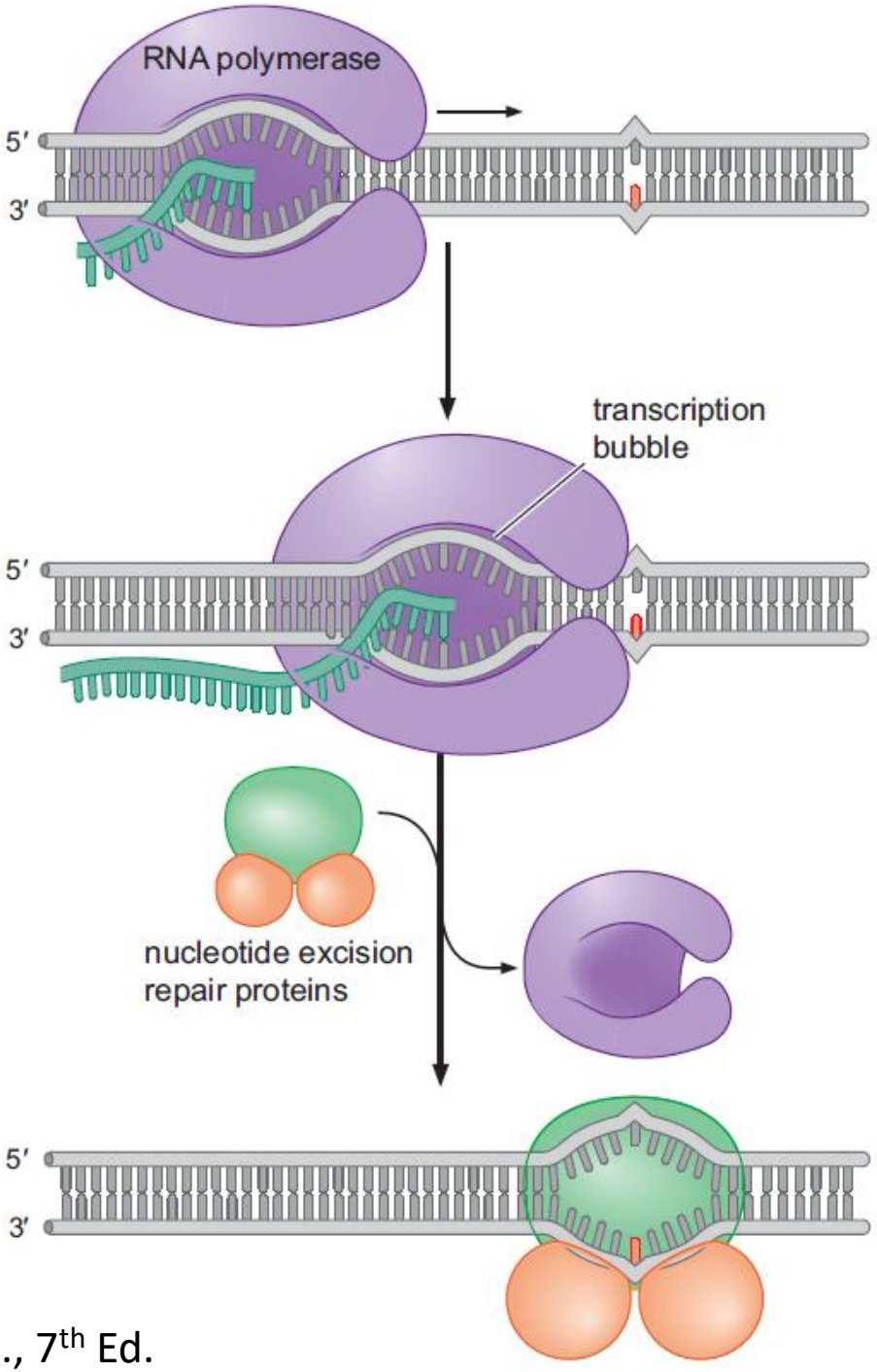
Nucleotide-excision repair in *E. coli and humans*



Transcription-coupled DNA repair.

RNA polymerase transcribes DNA normally upstream of the lesion. Upon encountering the lesion in DNA, RNA polymerase stalls and transcription stops. RNA polymerase recruits the nucleotide excision repair proteins to the site of the lesion, and then it either backs up or dissociates from the DNA to allow the repair proteins access to the lesion.



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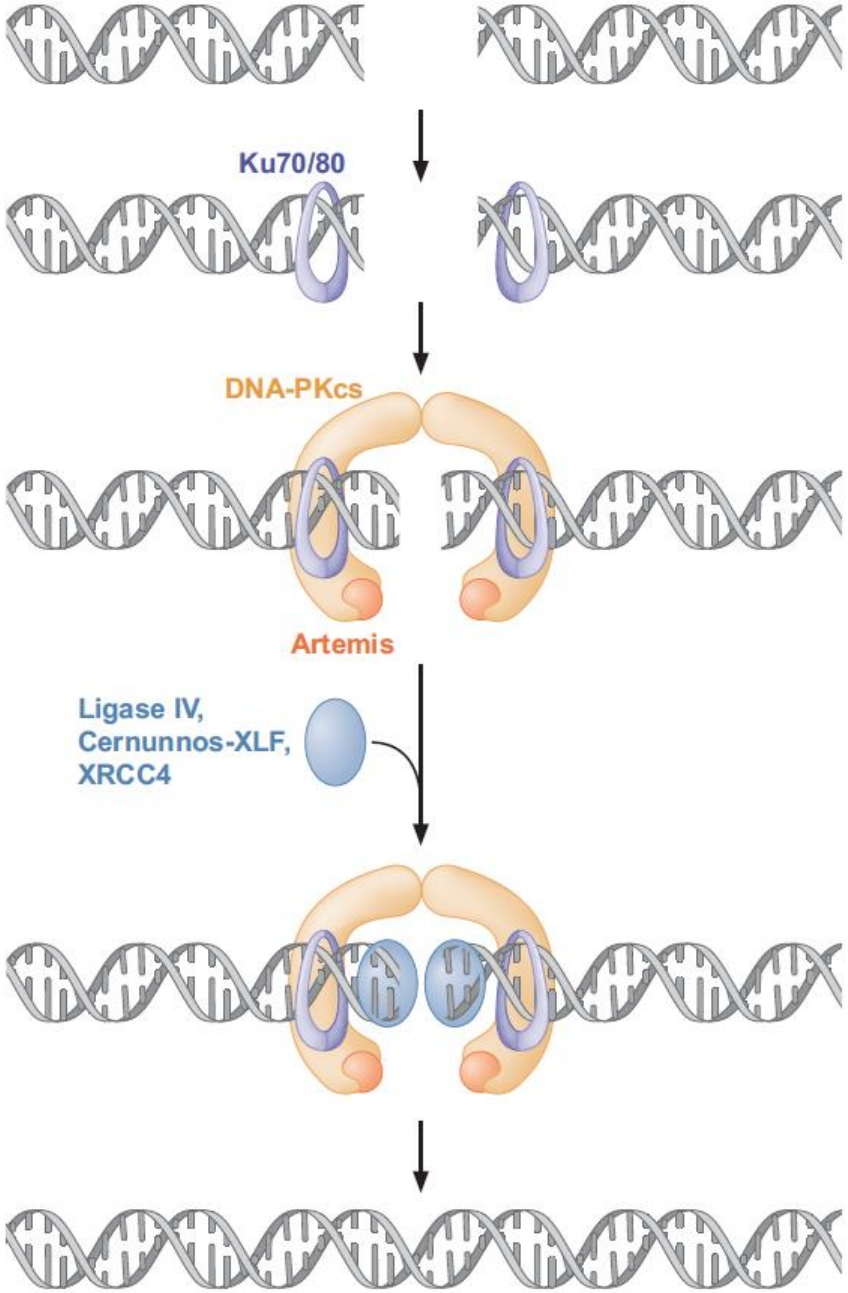
Mammalian pathway for NHEJ.

A heterodimer of Ku70 and Ku80 binds to broken DNA ends and recruits the protein kinase DNA-PKcs. DNA-PKcs, in turn, recruits Artemis, an enzyme having exonuclease and endonuclease activities, which processes the broken ends. Finally, a complex of Ligase IV with XRCC4 and Cernunnos- XLF joins the broken ends to each other.



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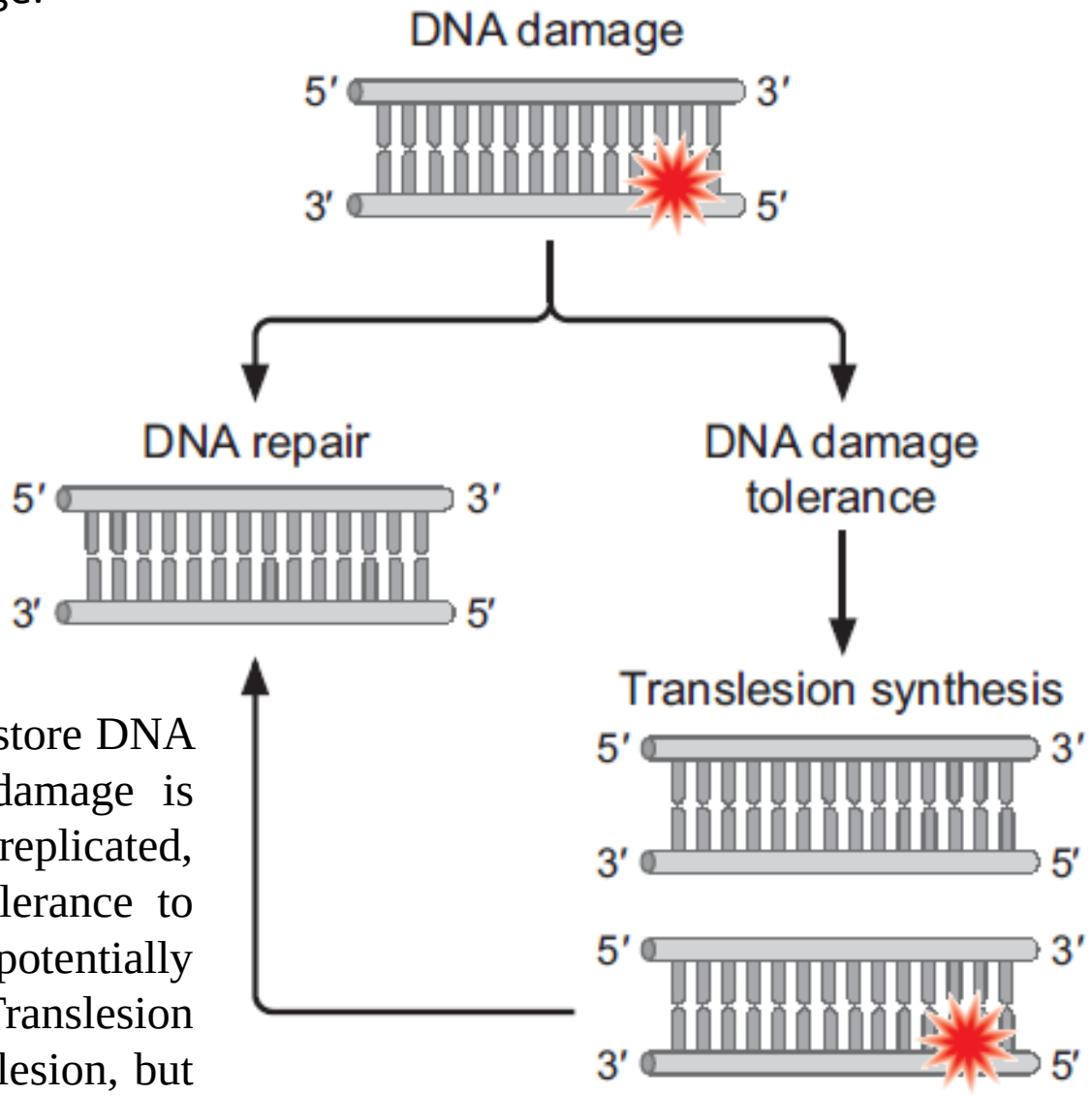
Cellular defenses against DNA damage.



Cells use DNA repair pathways to restore DNA to its undamaged state. If DNA damage is present when the genome is being replicated, the cell must use DNA damage tolerance to avoid a block in replication and a potentially lethal double-strand break. Translesion synthesis replicates across the DNA lesion, but the lesion remains in the genome until a DNA repair pathway can subsequently correct the damage.

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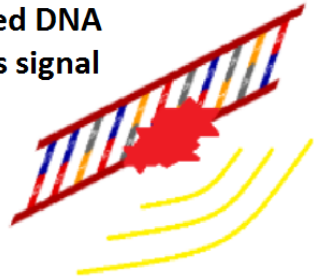
SOS Repair System

Damaged DNA releases signal



Inactive RecA

Repressor removed

Active RecA

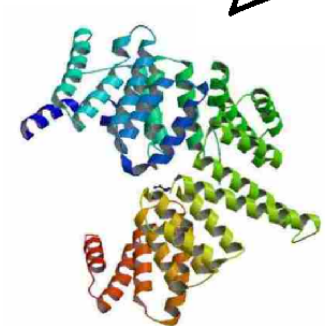
LexA

LexA

LexA

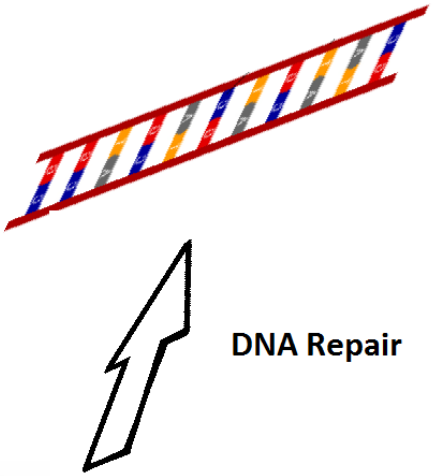
Various DNA operons with LexA repressor

Broken LexA dimers

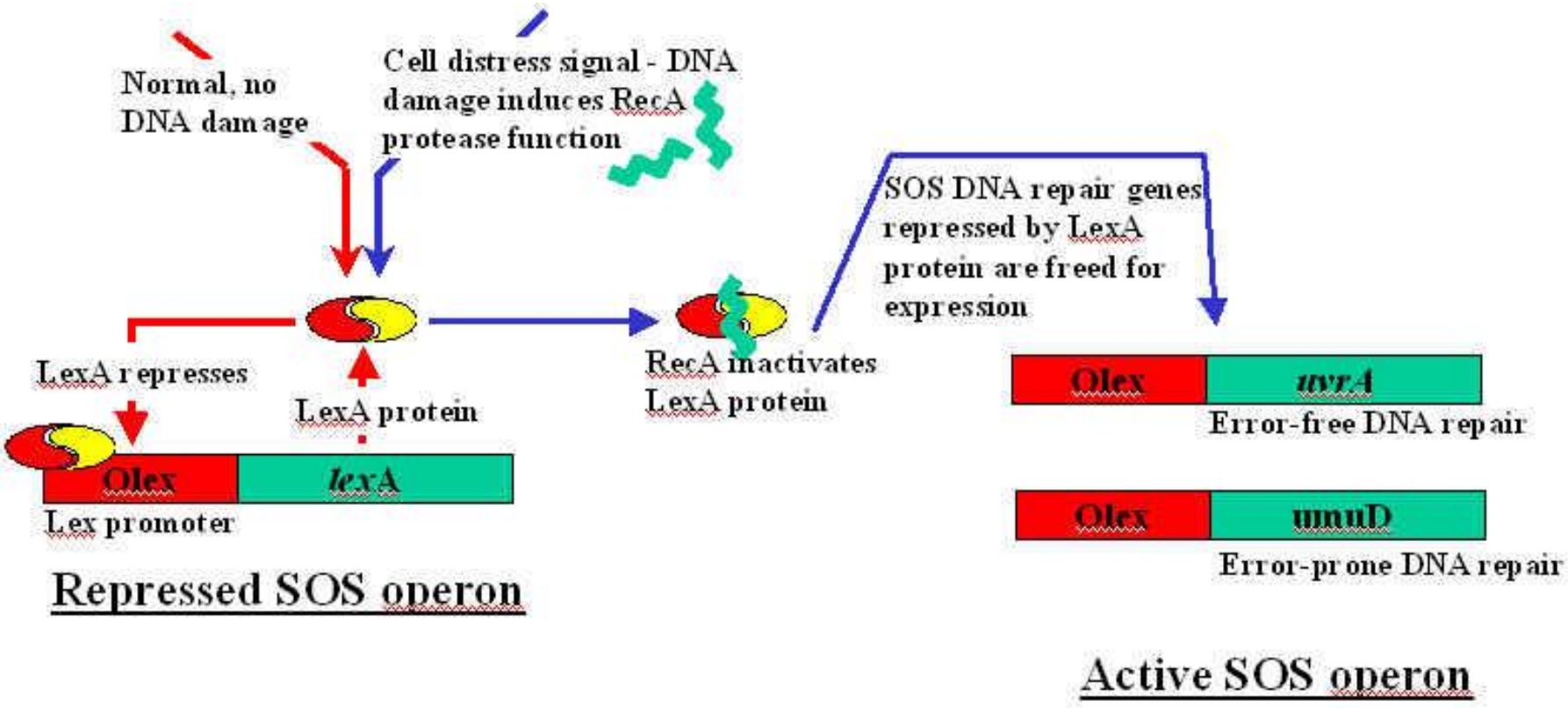


Transcription of DNA repair proteins

DNA Repair

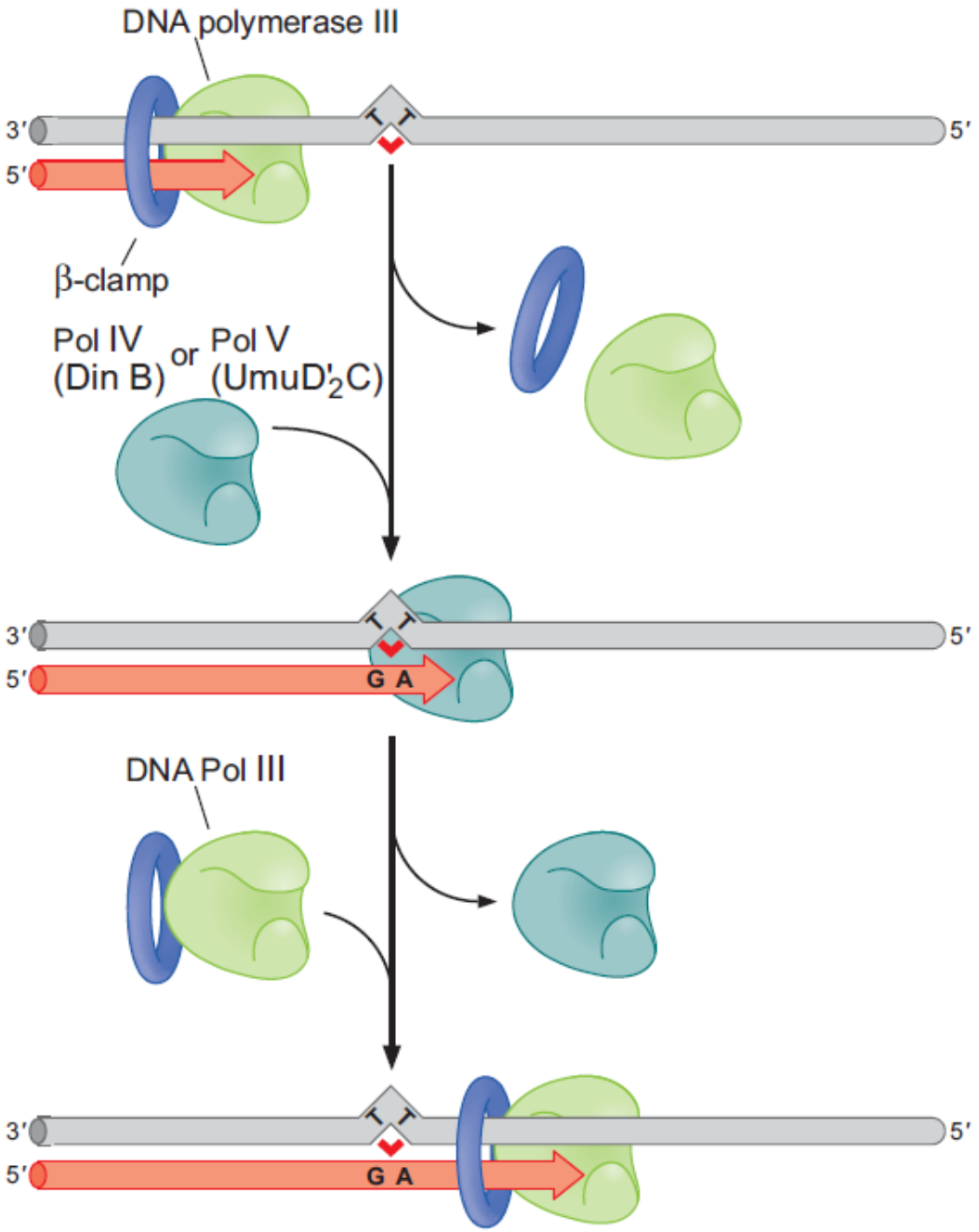


Lex A Target Genes	
uvrA	Excision repair
uvrB	Excision repair
umuC	Mutagenesis; repair
sfiA	Cell division inhibitor
himA	site-specific recombination
dinA, dinB, dinC	Unknown


Normal, no DNA damage
Cell distress signal - DNA damage induces RecA protease function
SOS DNA repair genes repressed by LexA protein are freed for expression
LexA represses
LexA protein
RecA inactivates LexA protein
Olex
lexA
Lex promoter
Repressed SOS operon
Olex
uvrA
Error-free DNA repair
Olex
umuD
Error-prone DNA repair
Active SOS operon

Translesion DNA synthesis

Upon encountering a lesion in the template during replication, DNA Pol III with its sliding clamp dissociates from the DNA and is replaced by the translesion DNA polymerase, which extends DNA synthesis across the thymine dimer on the template (upper) strand. The translesion polymerase is then replaced by the DNA polymerase III.



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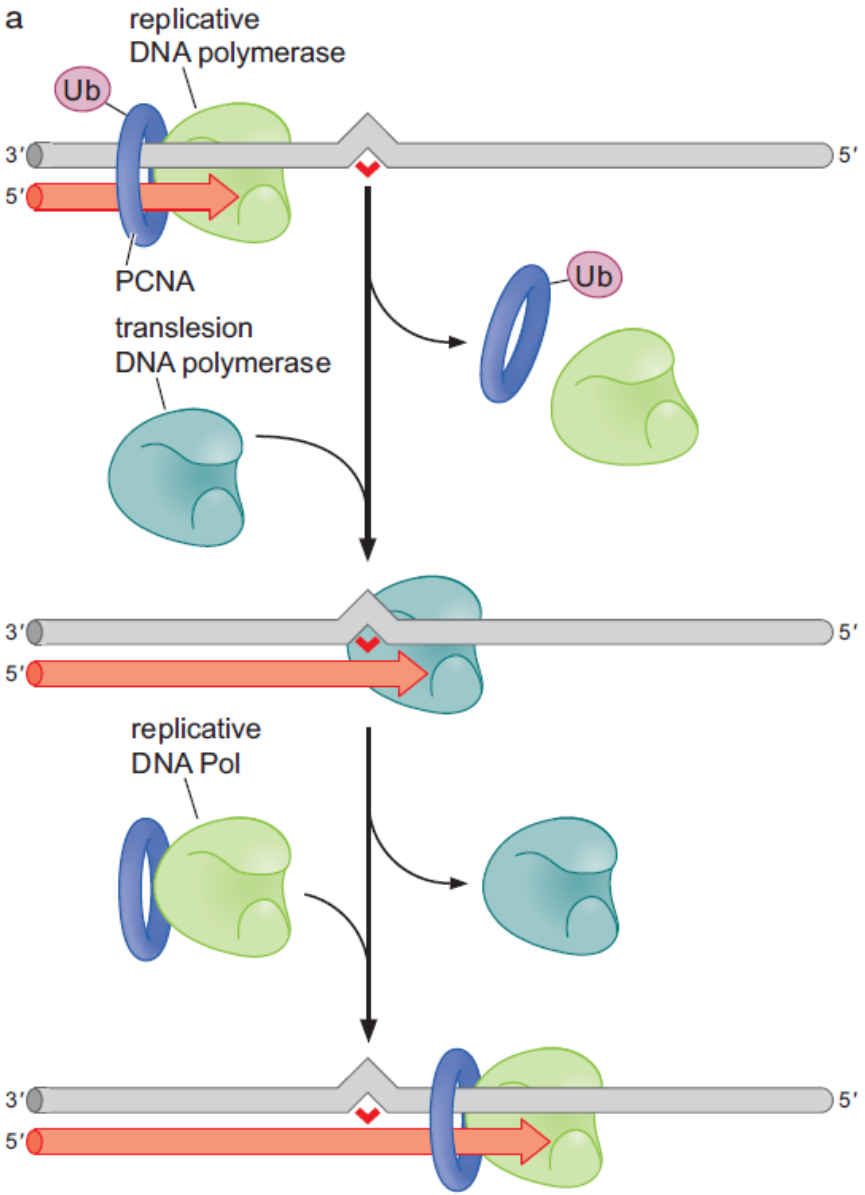
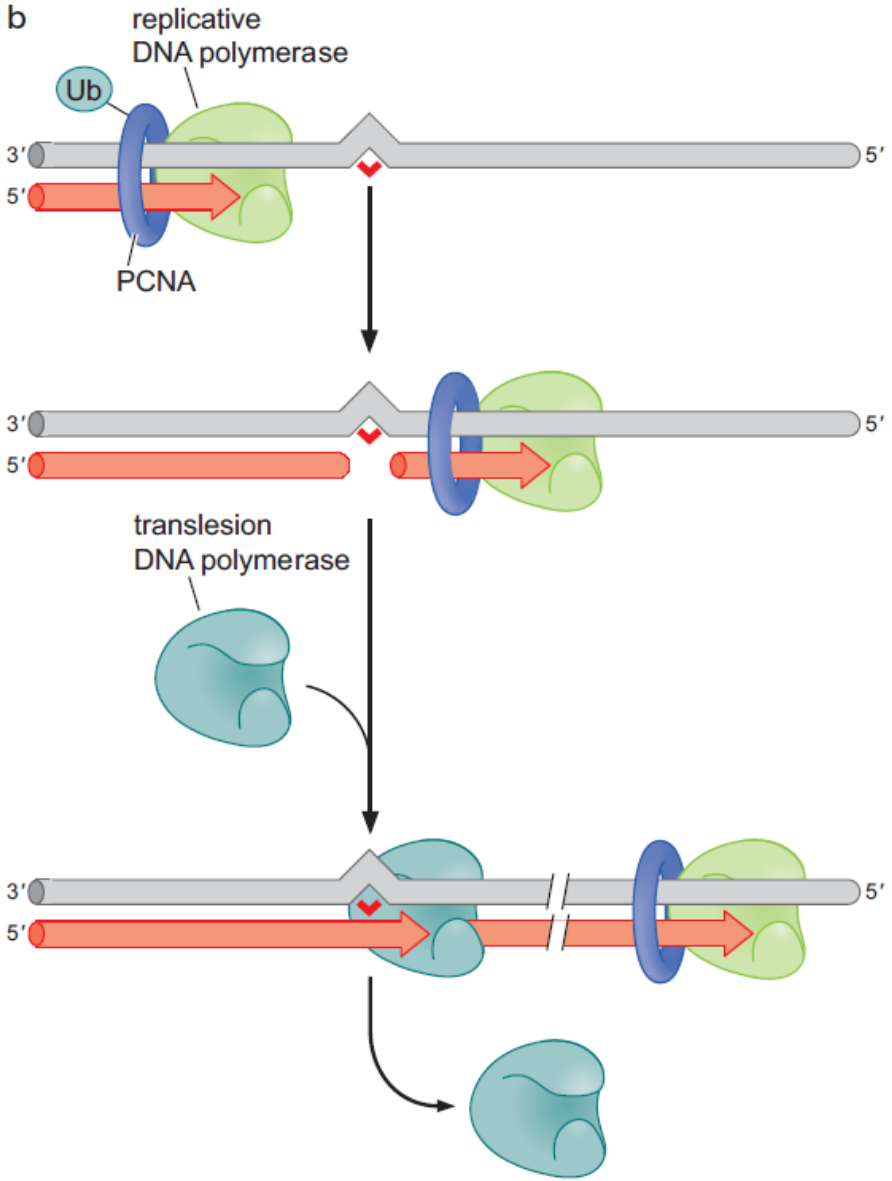
Alternative models for translesion synthesis





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Thank You