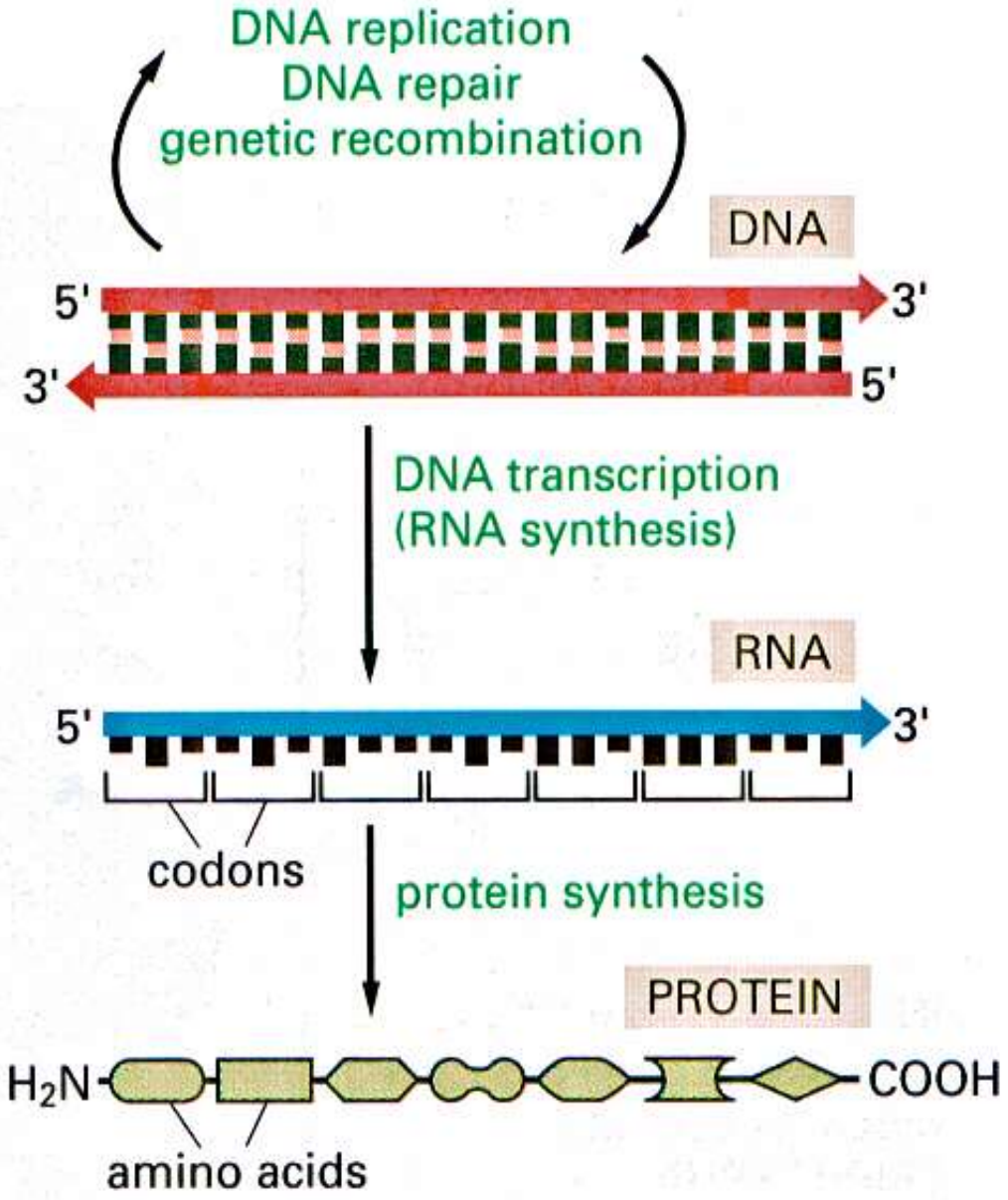
Peter Pristas

Molecular Biolgy

Mutations and DNA repair



The Central Dogma of Molecular Biology

The DNA molecule is a single biopolymer in the cell which is repaired

All other uncorrectly synthetised biopolymers (RNA, proteins) are degraded

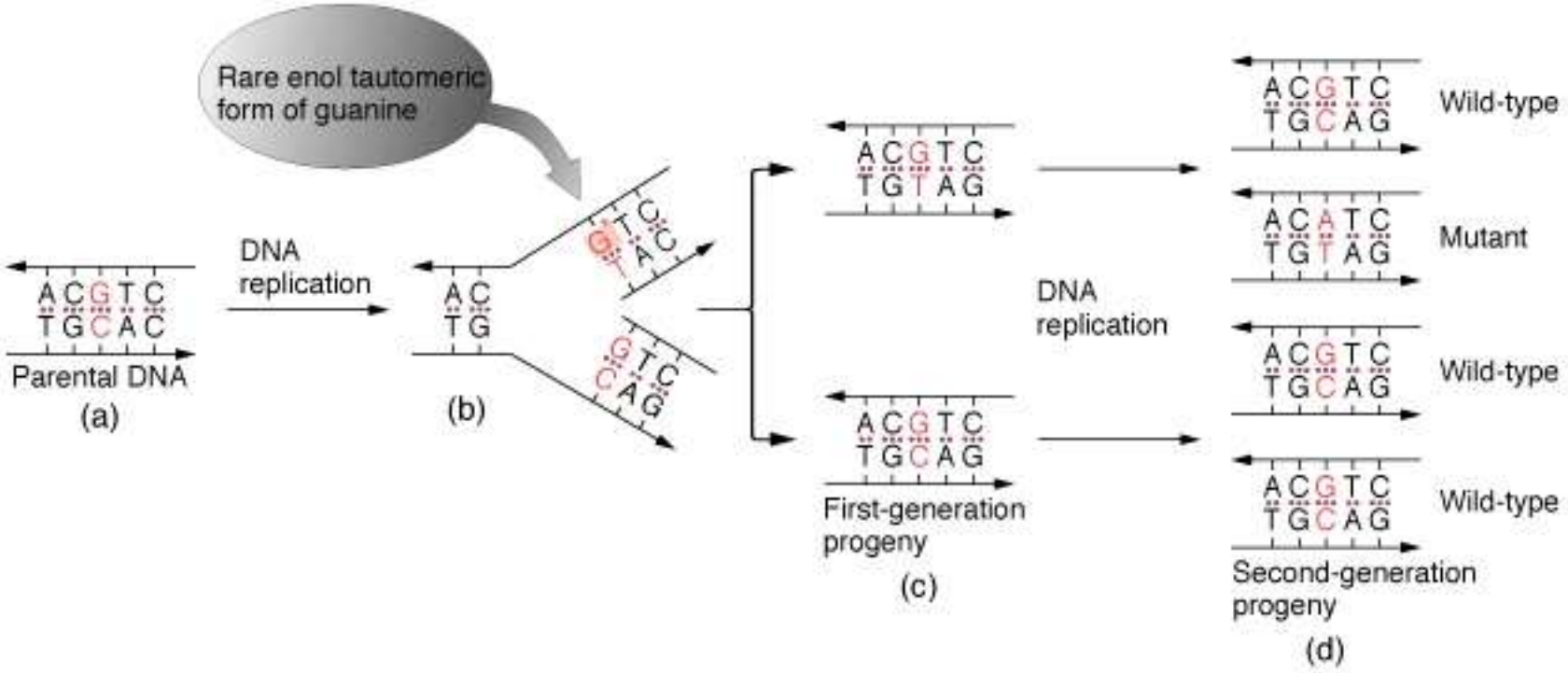
There are some 100 enzymes participating in the DNA repair in human cell

Mutation

- Change in the nucleotide sequence of the genome. Sequence changes are localized, i.e., change from an A to G, deletion of a base pair, addition of three base pairs, etc.
- By altering the DNA sequence, a modification of the instructions for a gene product may result, thus affecting the function of that gene.
- Occurrence through spontaneous means, without a known cause; or may be induced, use of chemical or physical agents that alter DNA sequences.
- May be reversible with a back mutation to the original form.

Segregation of heteroduplex DNA during replication

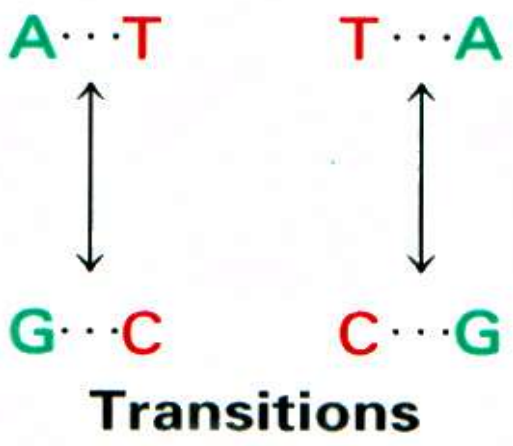
Mutations usually become apparent only after cell division yielding one wildtype and one mutant cell.



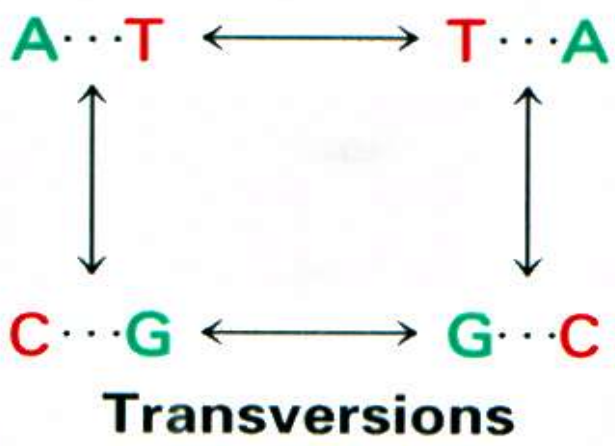
Type of mutations

A. point mutations

- **transitions**
- **transversions**



A pyrimidine is changed to another pyrimidine, or a purine to another purine.



A pyrimidine is changed to a purine, or a purine to a pyrimidine.

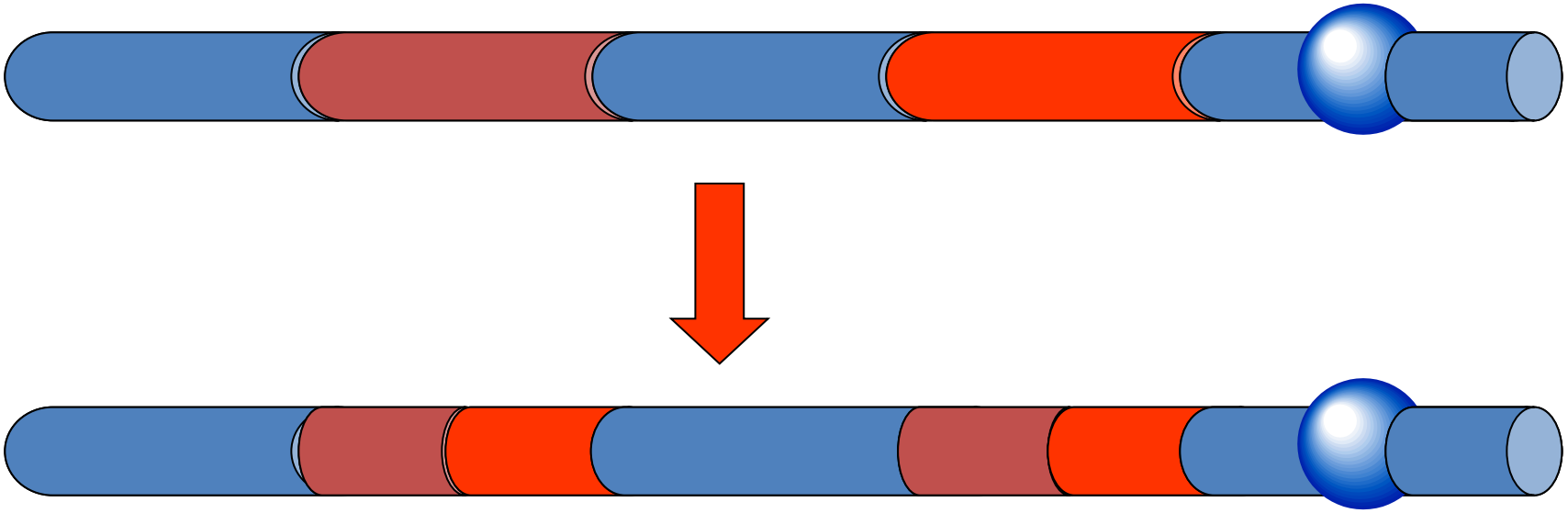
Type of mutations

B. structural mutations

- **deletions** = loss of sequence
- **inversions** = reversal of orientation
- **translocations** = displacement
- **duplications** = multiplication

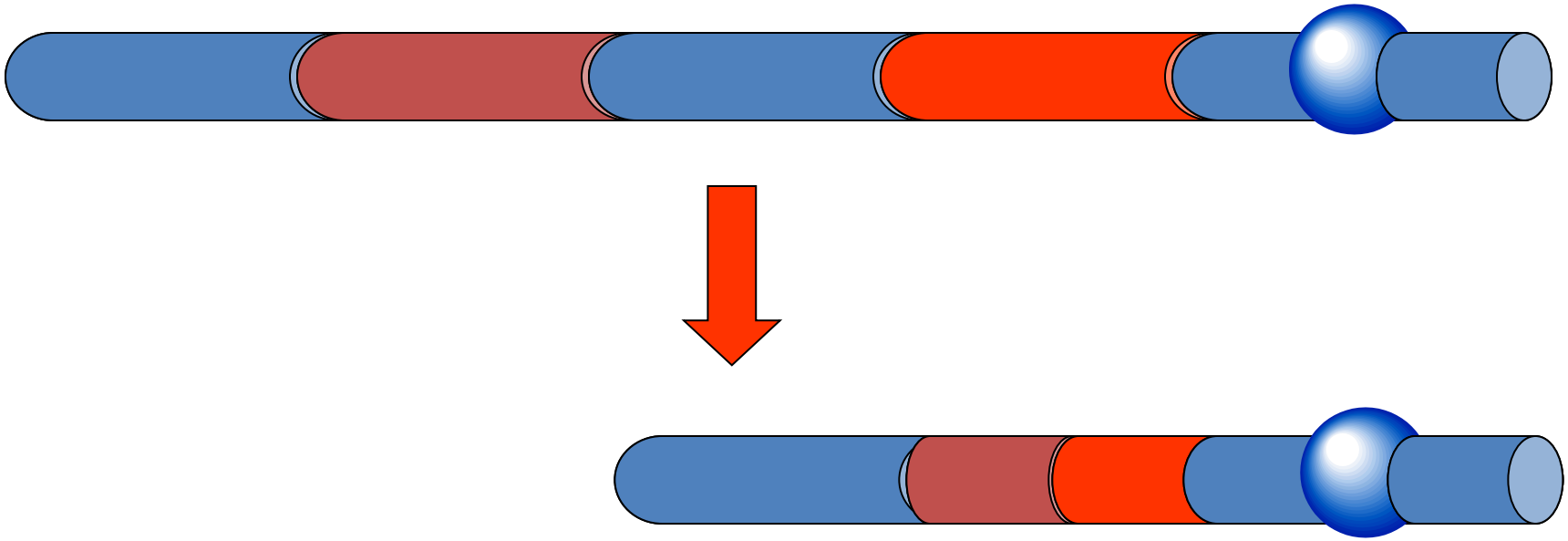
  – *main causes*: ionizing radiation, neutron radiation, UV light, recombination errors

Chromosomal Inversion



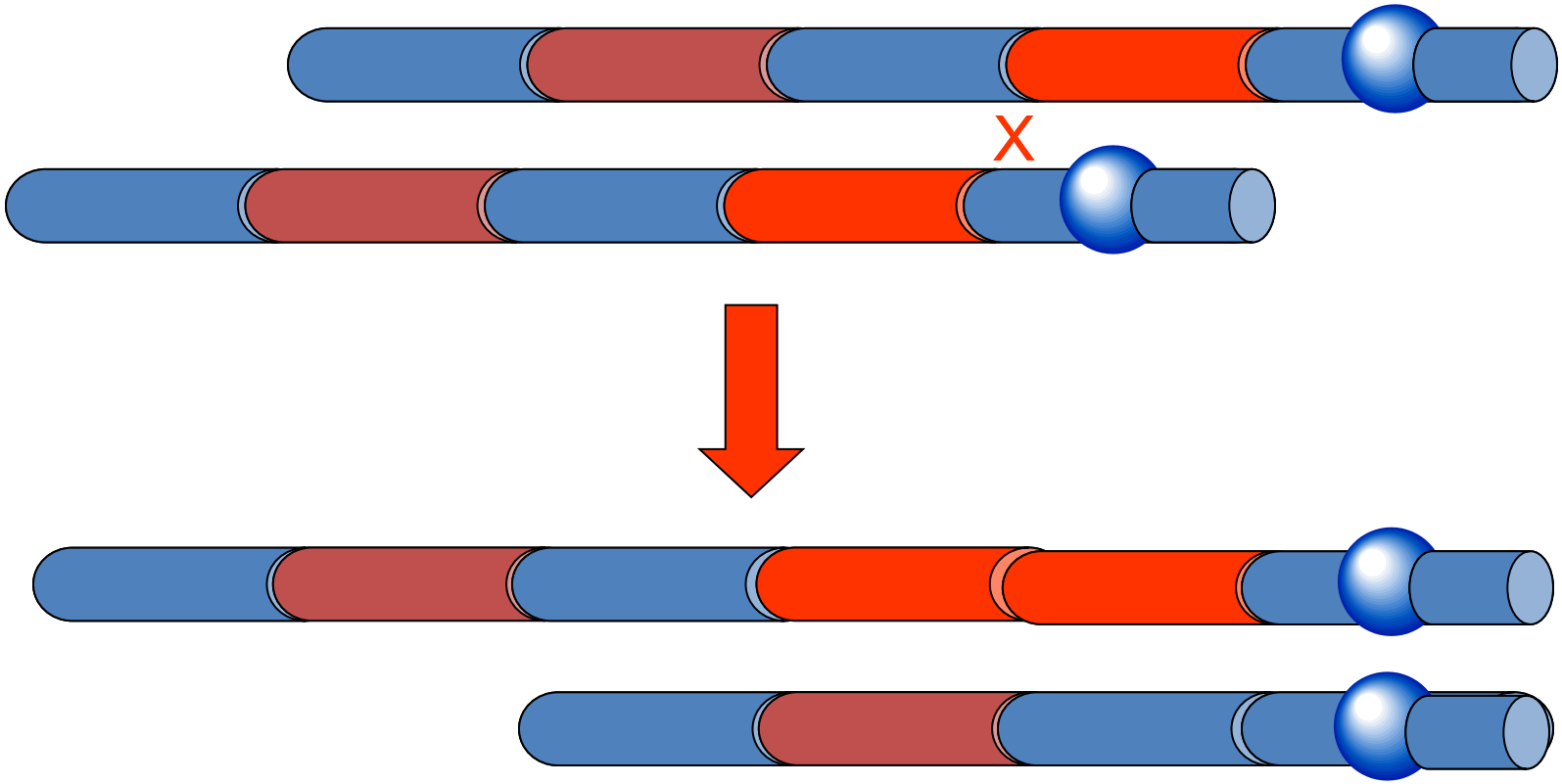
- Generation of recombinant reading frames
- generation of truncated gene products

Chromosomal Deletion



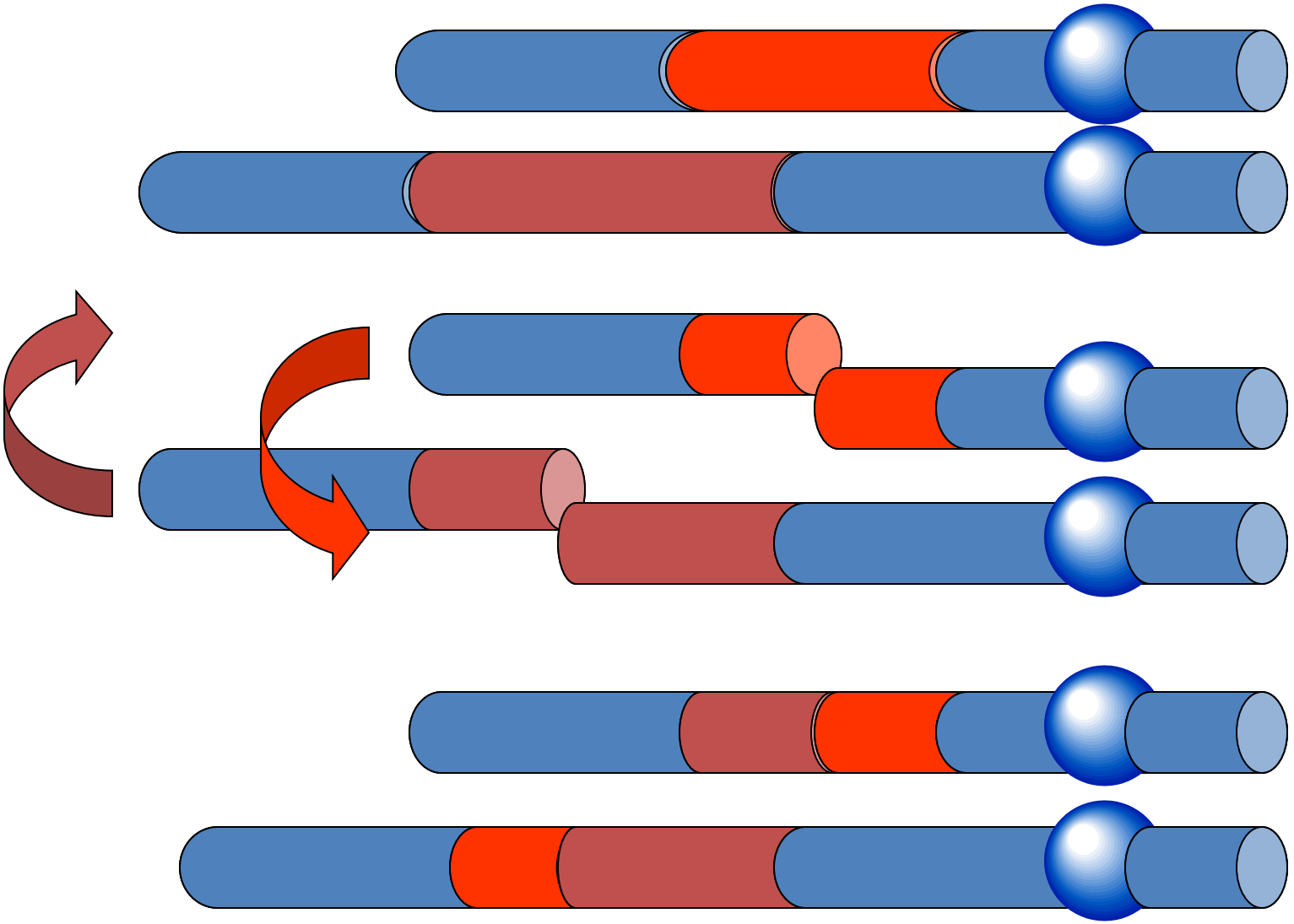
- Generation of recombinant reading frames
- generation of truncated gene products
- loss of genetic information

Duplication



•Gain of genetic information

Translocation

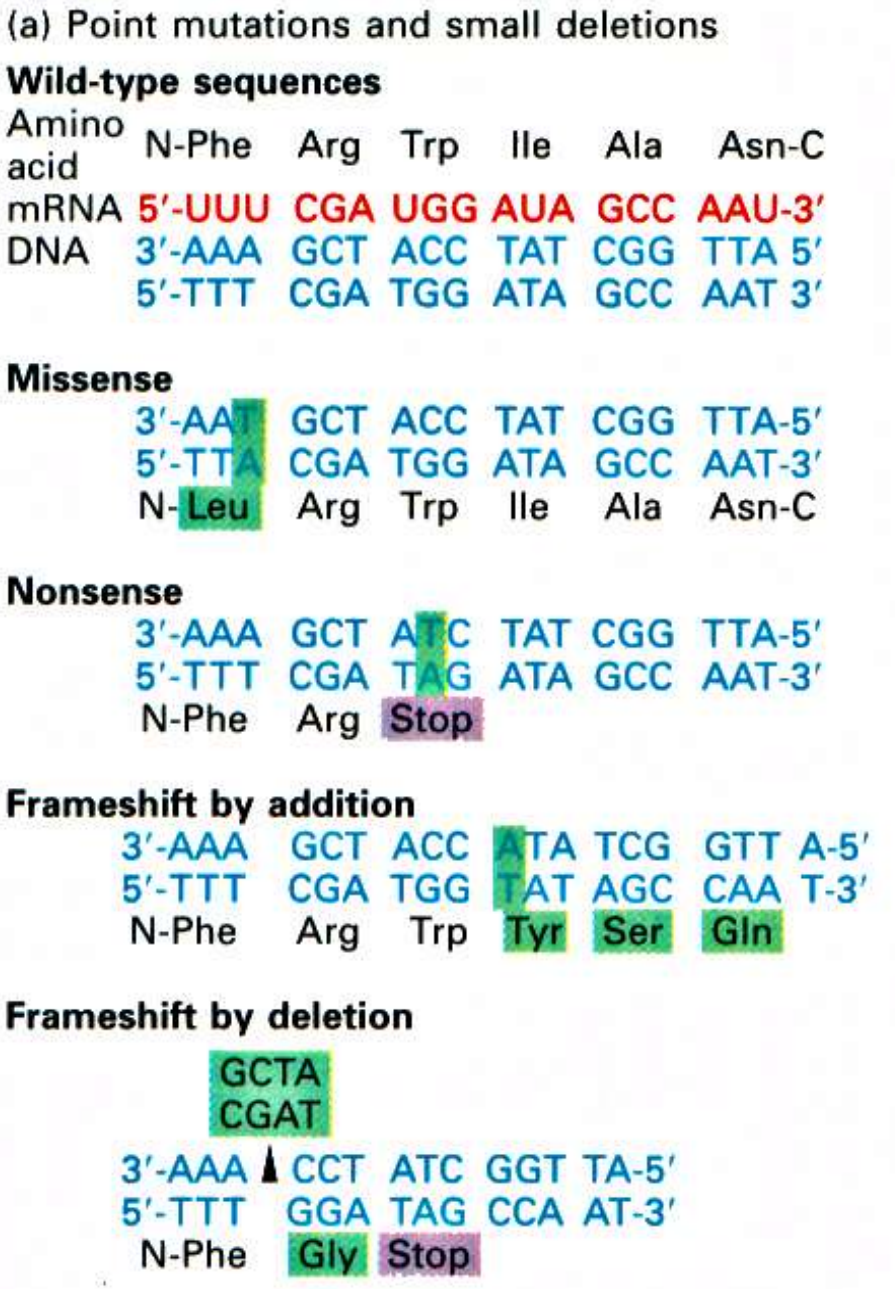


Consequences of point mutations and small deletions

Neutral mutations change a codon but the resulting amino acid substitution produces no detectable change in the function of the protein (AAA to AGA substitutes arginine for lysine. The amino acids have similar properties).

Silent mutations occur when the mutant codon encodes the same amino acid as the wild-type gene, so that no change occurs in the protein produced (e.g., AAA and AAG both encode lysine).

- no pfenotypic effect



Charakterizacia mutácií

Mutácie majúce efekt na sekvenciu aminokyselín

mutácie so zmenou zmyslu (missense mutation) - zmena kodónu spôsobí zaradenie inej, chemicky značne odlišnej aminokyseliny do polypeptidového reťazca
neutrálne mutácie - mutácie spôsobujú zámenu jednej aminokyseliny za inú aminokyselinu s podobnými chemickými vlastnosťami
tiché mutácie (silent mutation)

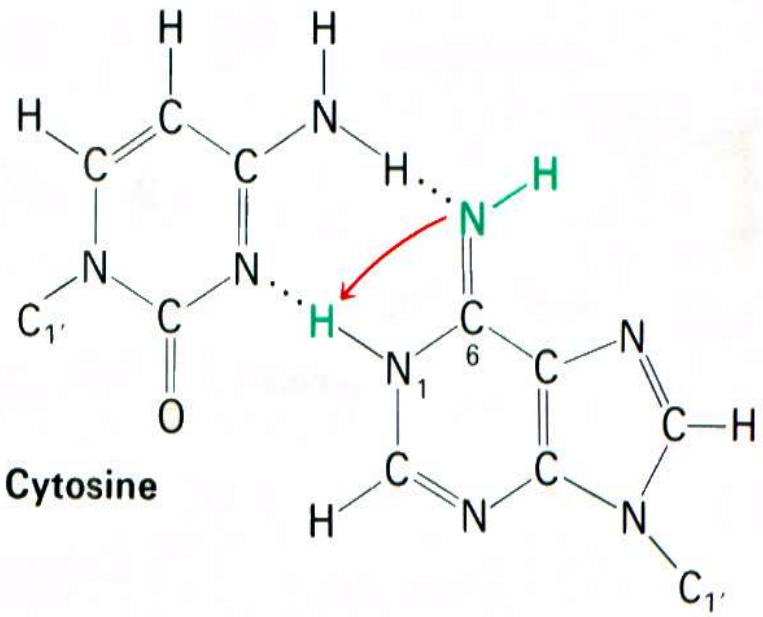
Mutácie majúce efekt na čítací rámec

mutácie bez zmyslu (nonsense mutation) - zmena kodónu pre niektorú aminokyselinu za STOP kodón (UAG, UAA alebo UGA)
posunové mutácie (frameshift mutation) - inzercia alebo delécia takého počtu nukleotidov, ktorý nie je násobkom 3, čo vedie k posunu čítania kodónov na ribozóme, následkom čoho nastáva zaradenie úplne odlišných aminokyselín od miesta mutácie

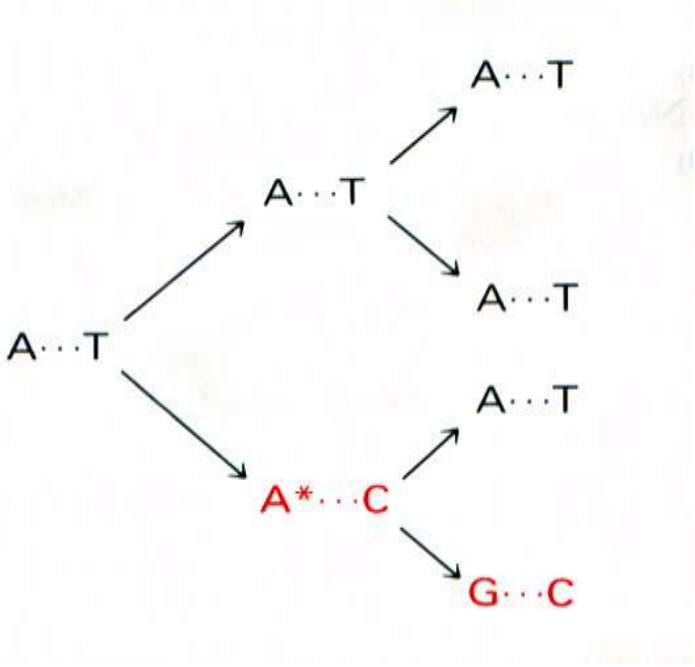
Mechanisms of Spontaneous Mutation

- Tautomeric shifts-rare isomers of each base pair incorrectly in the DNA helix.
- Polymerase errors-misincorporation of bases during DNA replication.
- Depurination-loss of purines from the DNA helix
- Deamination-loss of the amine group from cytosine (yielding uracil), and from 5-methylcytosine (yielding thymine).
- Trinucleotide repeat expansion-incorrect replication of repeated sequences in DNA.
- Transposable elements-insertions of mobile DNA

Tautomeric shift

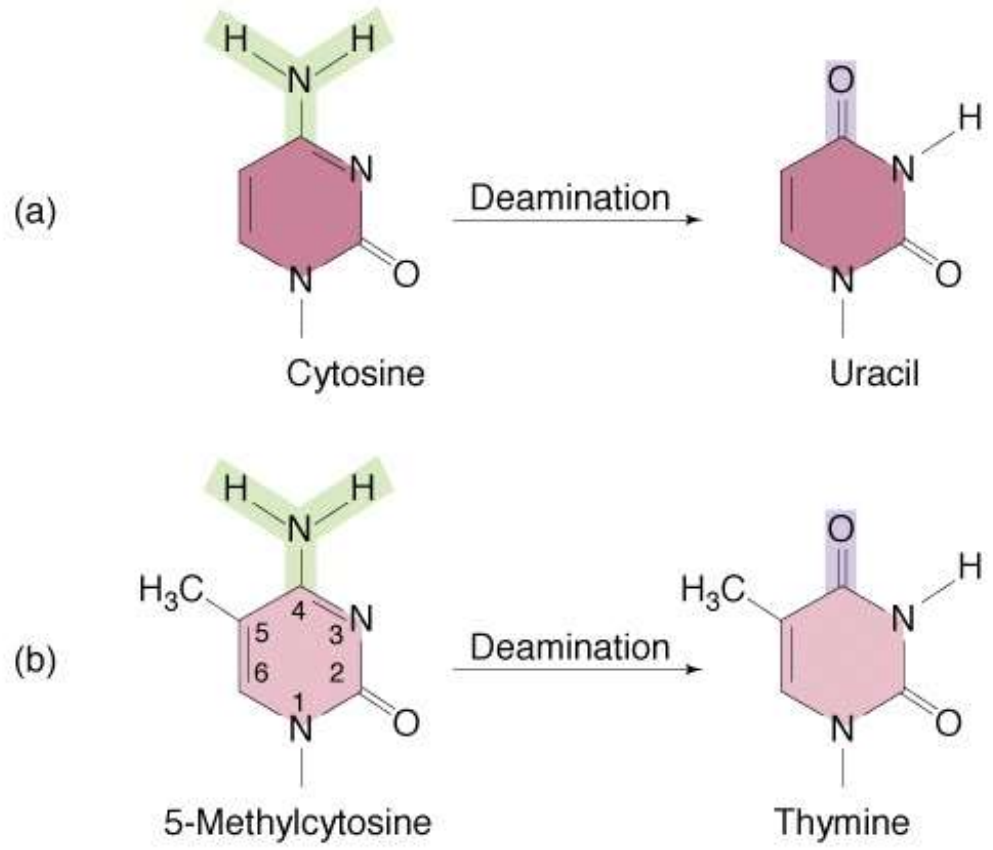


Transition mutations can arise from mispairing between adenine and cytosine during DNA replication. (The A is in its rare tautomeric form.)



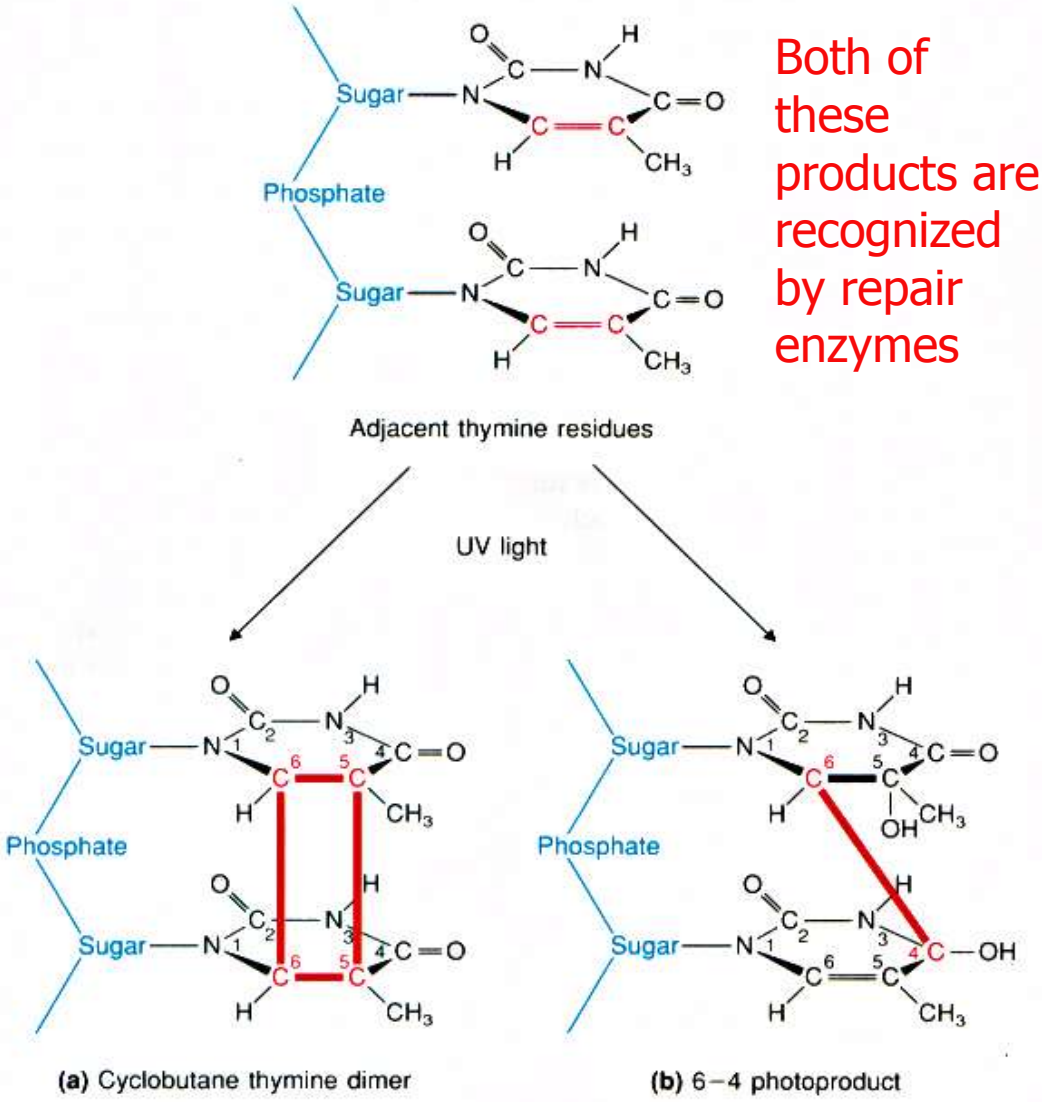
Deamination of a cytosine produces a uracil which will base-pair with adenine instead guanine, thus causing a transition mutation.

This deamination reaction occurs spontaneously or can be accelerated by nitrites, a widely used preservative of meat products.
Some C residues in human DNA are methylated at their 5 positions. A deamination
would then produce T, which is not recognized as a wrong base and thus cannot be
repaired.



Thymine dimers

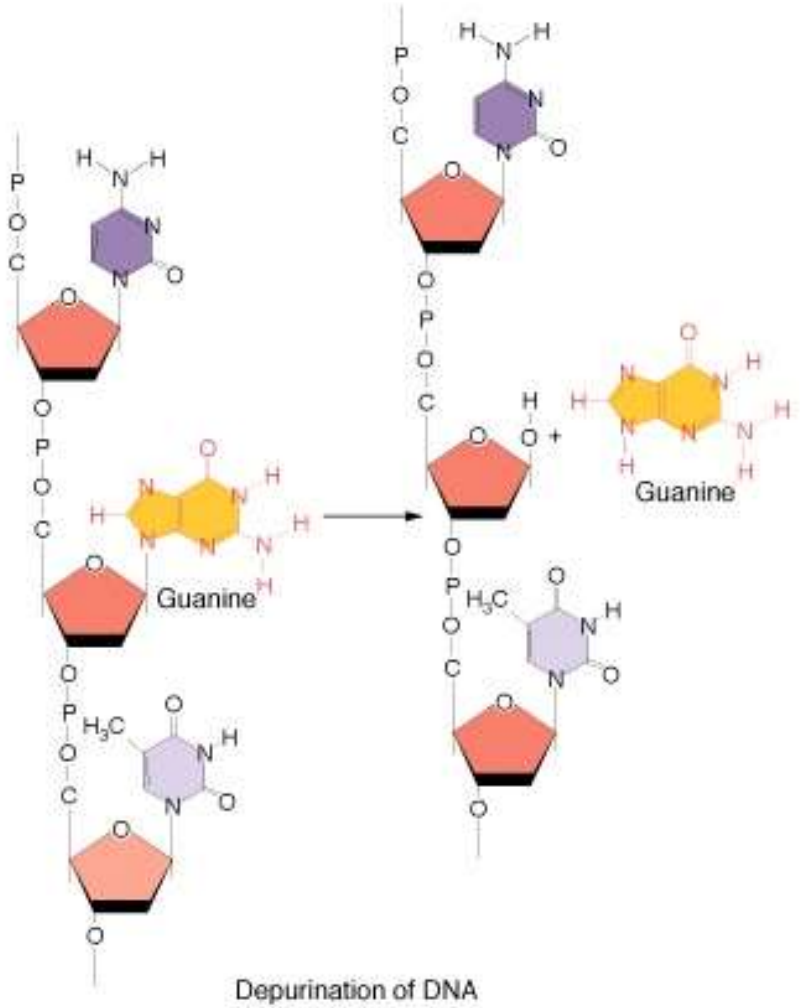
UV irradiation causes neighboring pyrimidines in the DNA to form two types of product, both of which interfere with DNA replication.



Both of these products are recognized by repair enzymes

6-4 photoproduct

Depurination: spontaneous loss of purines from DNA



Depurination of DNA

Trinucleotide repeat expansion

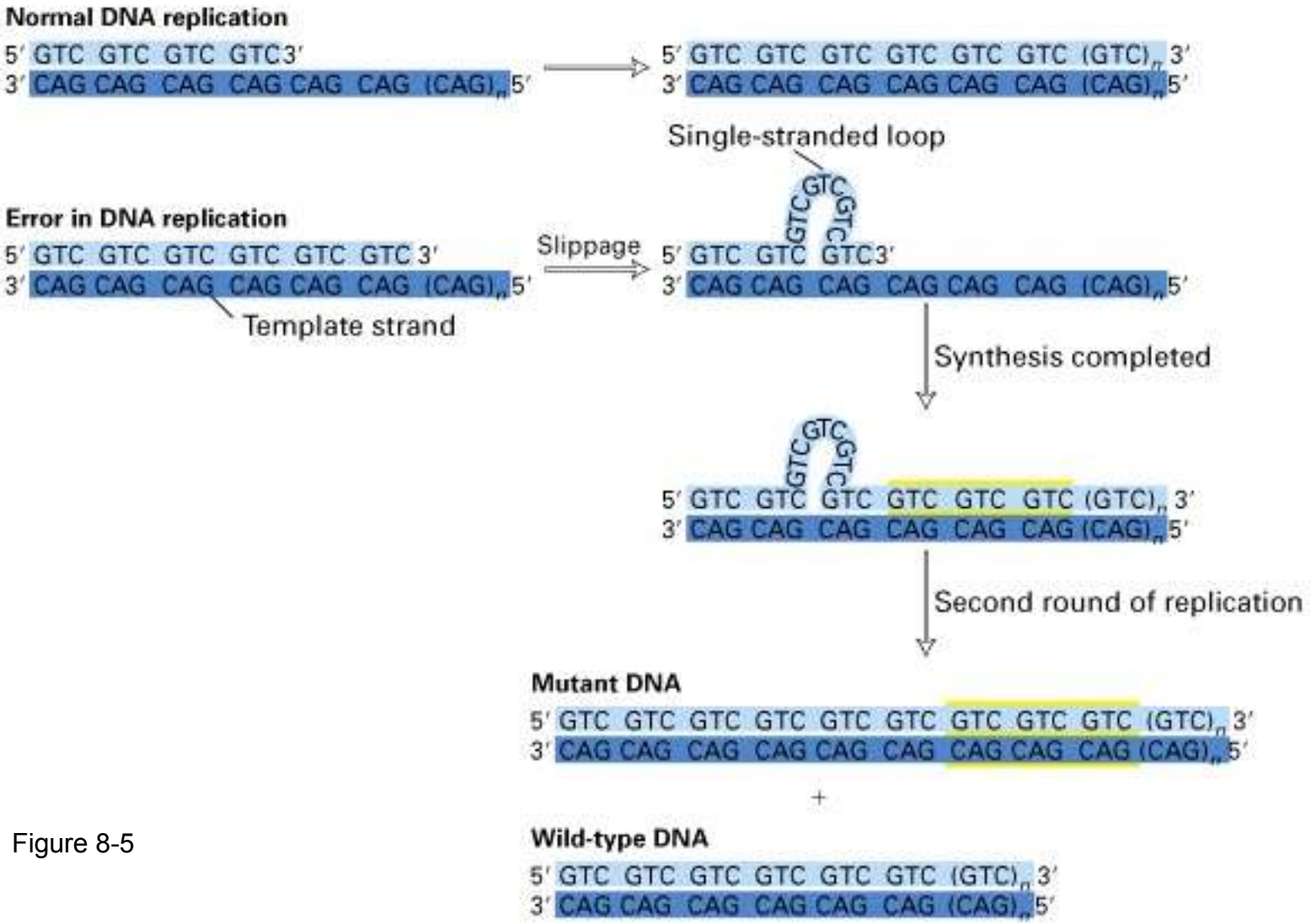
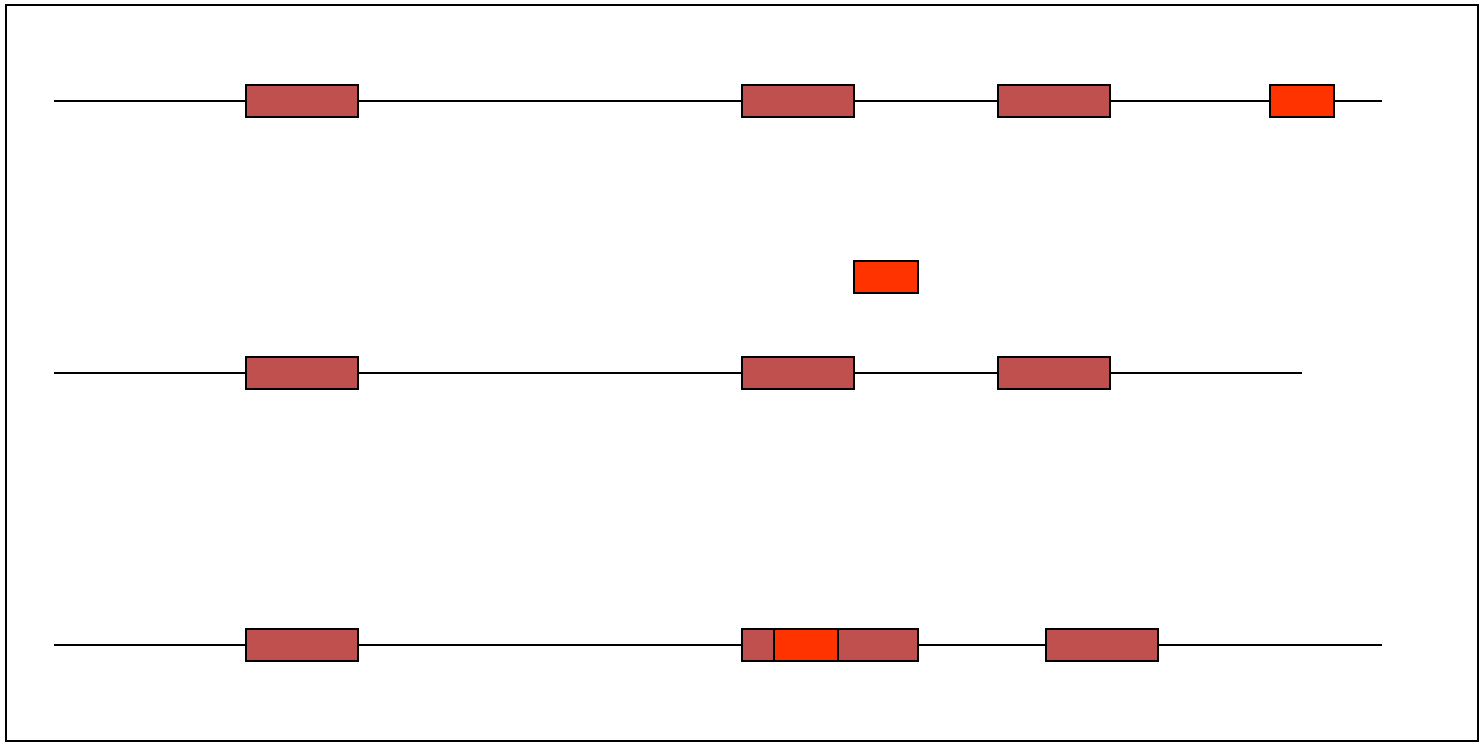


Figure 8-5

Transposable elements

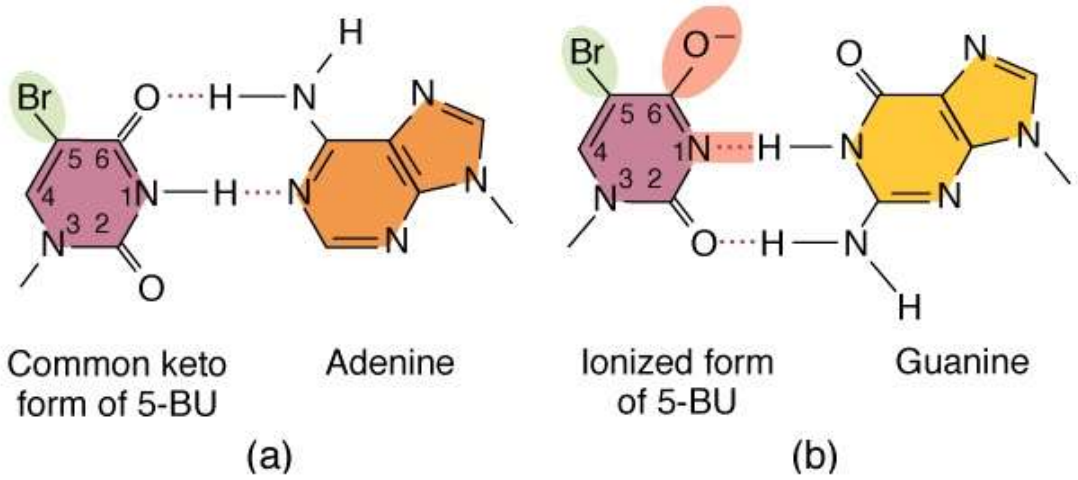


Mechanisms of Induced Mutation

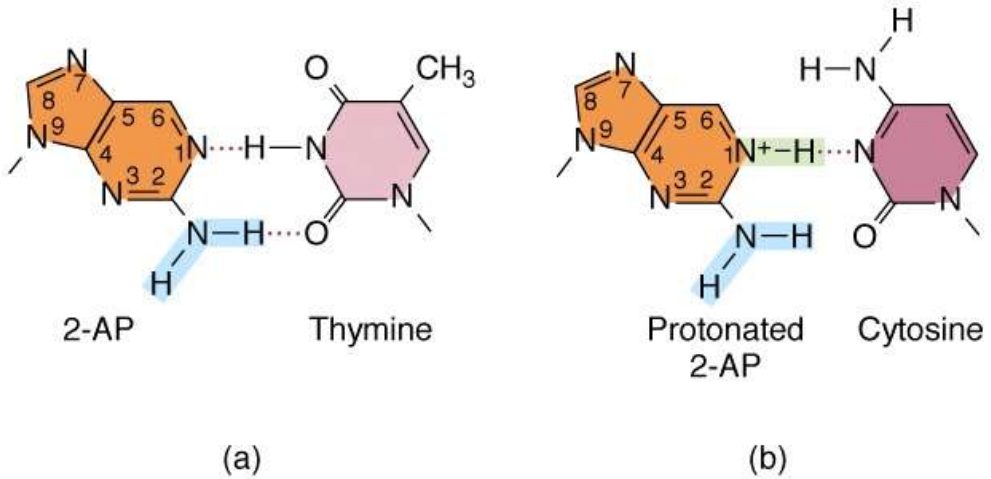
- Chemical analogs of bases-compounds similar to normal bases may be incorporated during replication, causes mispairing in subsequent replication.
- Chemical alteration of bases-structure of existing bases may be altered through chemical action, causes mispairing during replication.
- Intercalation within the DNA-binding of compound within the helix, interferes with replication.
- Radiation-modification of chemical structure within DNA, such as dimer formation, and breaks in phosphodiester backbone.

Base analogs

5-bromouracil

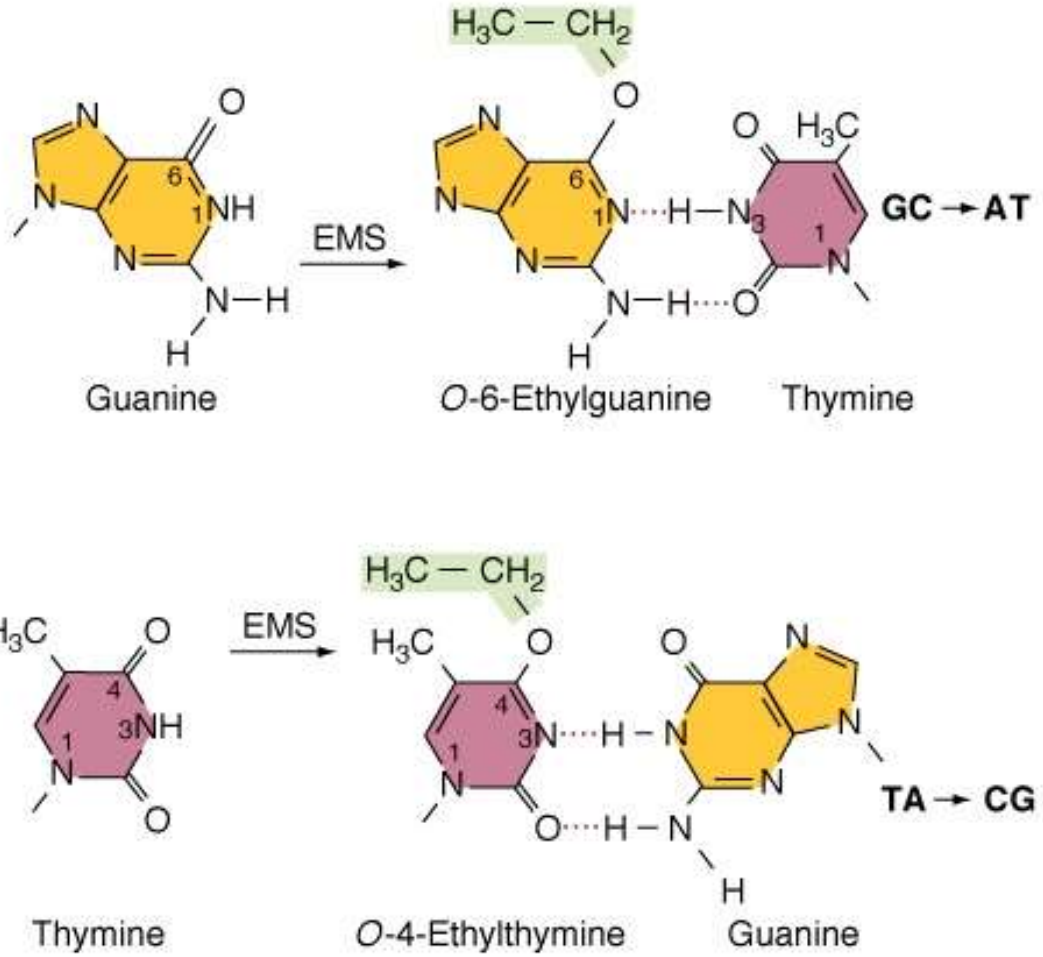


2-aminopurine

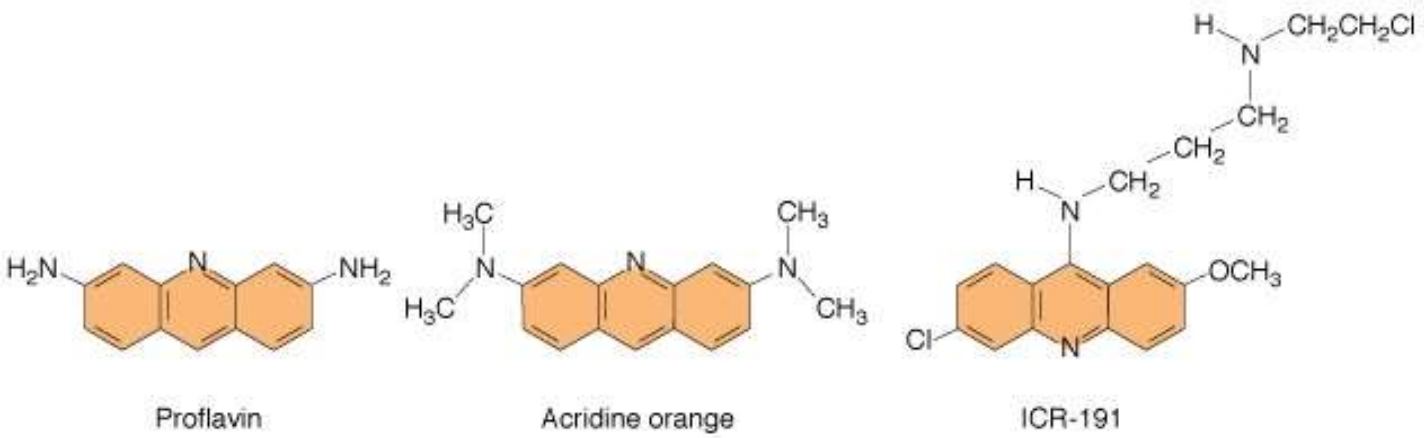


Base modification

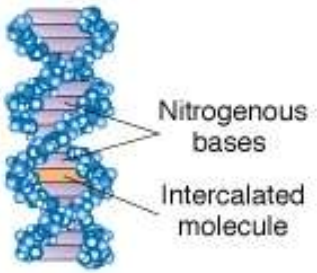
ethylmethanesulfonate



Intercalating agents

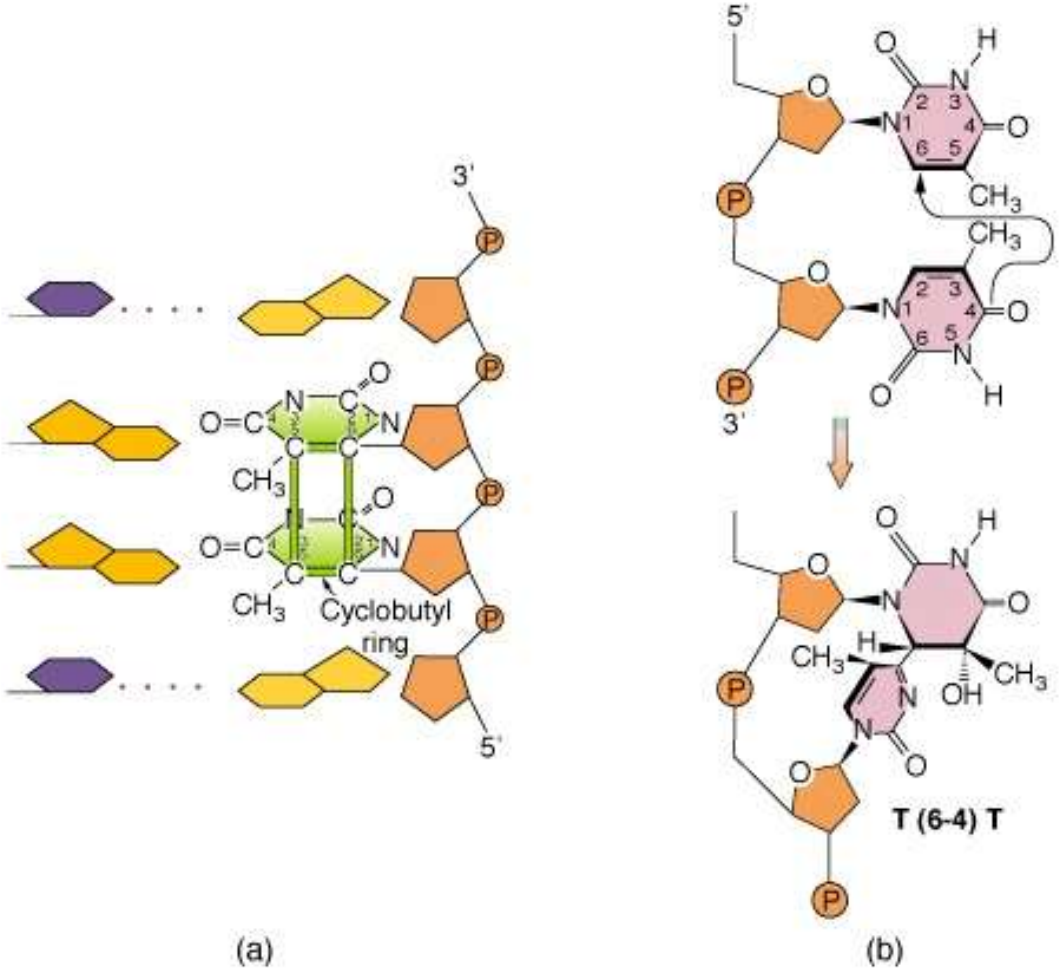


(a)



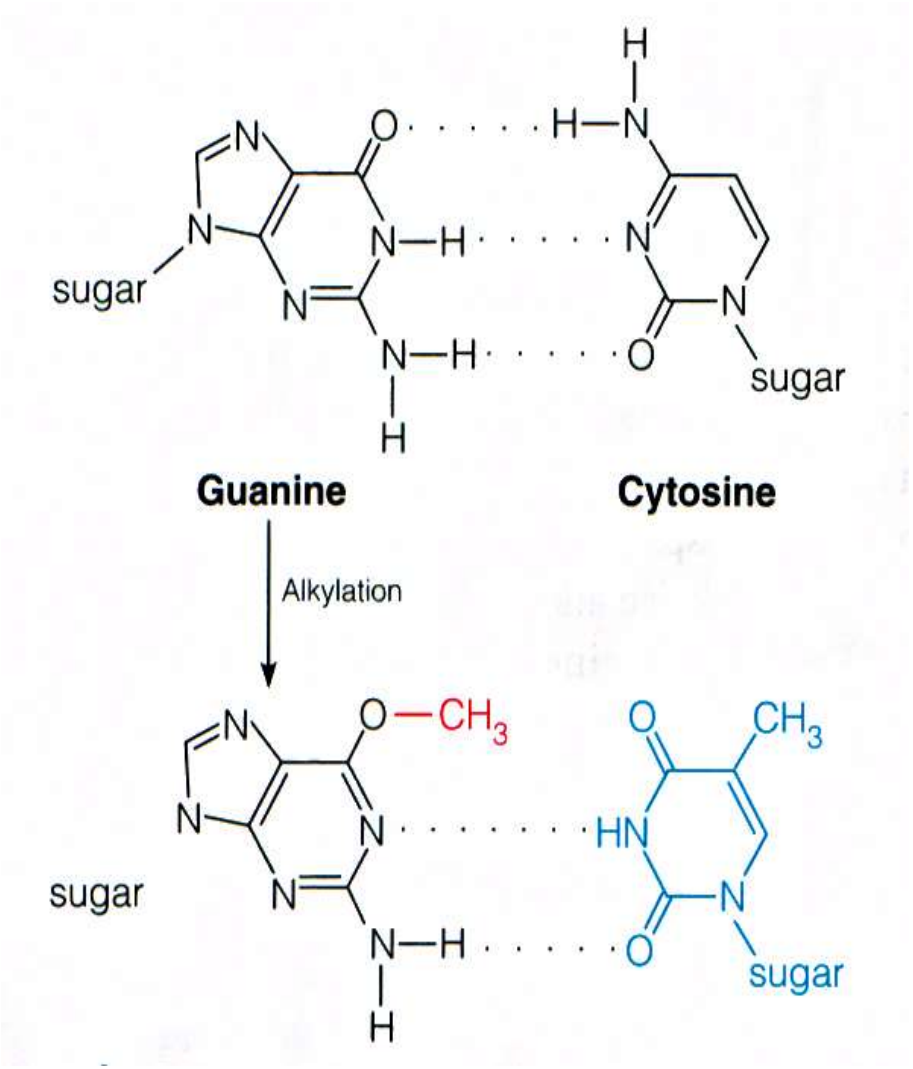
(b)

UV light – thymine dimers



Mutation by methylation

Transition mutations can arise from methylation of guanine which pairs with thymine instead cytosine



Mutation effect of ionizating radiation

Single-strand breaks - mostly sealed by DNA ligase so don't contribute to lethality

Double-strand breaks - often lethal because can't be resealed by ligase so degraded by nucleases

Alteration of bases - this type of oxidative damage is usually lethal because forms a replication barrier at that site

Mutation Rates

Table 7-2

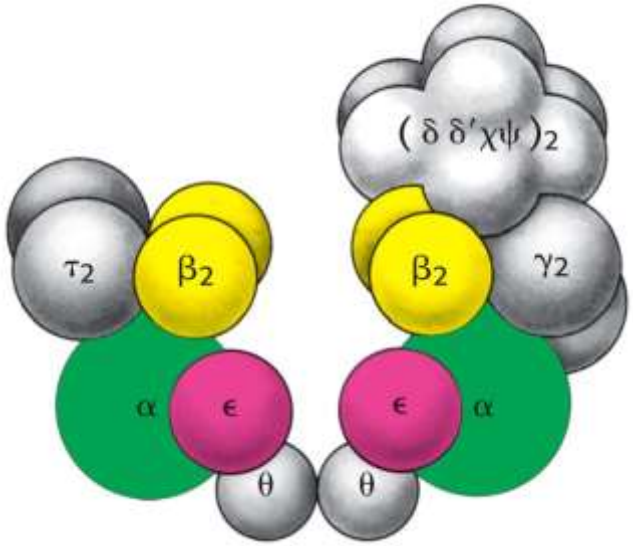
Forward Mutation Frequencies Obtained with Various Mutagens in *Neurospora*

Mutagenic treatment	Exposure time (minutes)	Survival (%)	Number of *ad-3* mutants per 10^6 survivors
No treatment (spontaneous rate)	—	100	~0.4
Amino purine (1 –5 mg/ml)	During growth	100	3
Ethyl methane sulfonate (1%)	90	56	25
Nitrous acid (0.05 M)	160	23	128
X rays (2000 r/min)	18	16	259
Methyl methane sulfonate (20 mM)	300	26	350
UV rays (600 erg/mm^2 per min)	6	18	375
Nitrosoguanidine (25 μM)	240	65	1500
ICR-170 acridine mustard (5 μg/ml)	480	28	2287

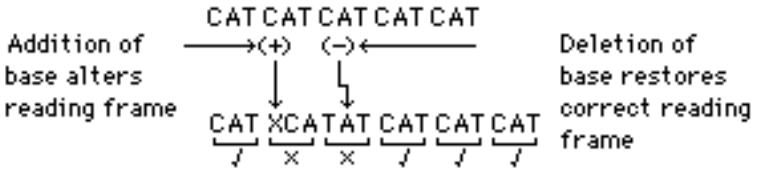
NOTE: The assay measures the frequency of *ad-3* mutants. It so happens that such mutants are red, so they can be detected against a background of white *ad*-3^+ colonies.

Mutations in certain genes can increase the mutation rate

- ***Mutator genes*** increase the mutation rate



Suppression of mutations

Type of mutation	Result and example(s)
Intragenic suppressor mutations	
Frameshift of opposite sign at second site within gene	
Second-site missense mutation	A second distortion that restores a more or less wild-type protein conformation after a primary distortion.

Type of mutation	Result and example(s)
Extragenic suppressor mutations	
Nonsense suppressors	A gene (for example, for tyrosine tRNA) undergoes a mutational event in its anticodon region that enables it to recognize and align with a mutant nonsense codon (say, UAG) to insert an amino acid (here, tyrosine) and permit completion of the translation.
Missense suppressors	Usually caused by change in tRNA anticodon. One missense suppressor in *E. coli* is an abnormal tRNA that carries glycine but inserts it in response to arginine codons. Although all wild-type arginine codons are mistranslated, the observed mutations are not lethal, probably owing to the low efficiency of abnormal substitution.
Frameshift suppressors	Very few examples have been found; in one, a four-nucleotide anti-codon in a single tRNA can read a four-letter codon caused by a single-nucleotide-pair insertion.
Physiological suppressors	A defect in one chemical pathway is circumvented by another mutation (for example, one that permits more efficient transport of a compound produced in smaller quantities owing to the original mutation).

DNA Repair

- Complex systems exist within the cell to:
  - repair DNA bases that have been damaged by environmental causes.
  - repair DNA mismatches caused by errors in DNA replication.
- Effective repair requires:
  - A system for recognizing the damage or mismatch
  - A way of telling which strand contains the correct information
  - A system for repairing the incorrect strand

Repair systems rely on the existence of an intact, complementary strand of DNA as a template

- It is important to remember that most repair mechanisms can rely on the fact that there are two complementary strands in the helix; damage to one may be repaired using the other as a template. Single-stranded genomes are generally rare and small (e.g. chi (ϕ) phage, 5000 bases).

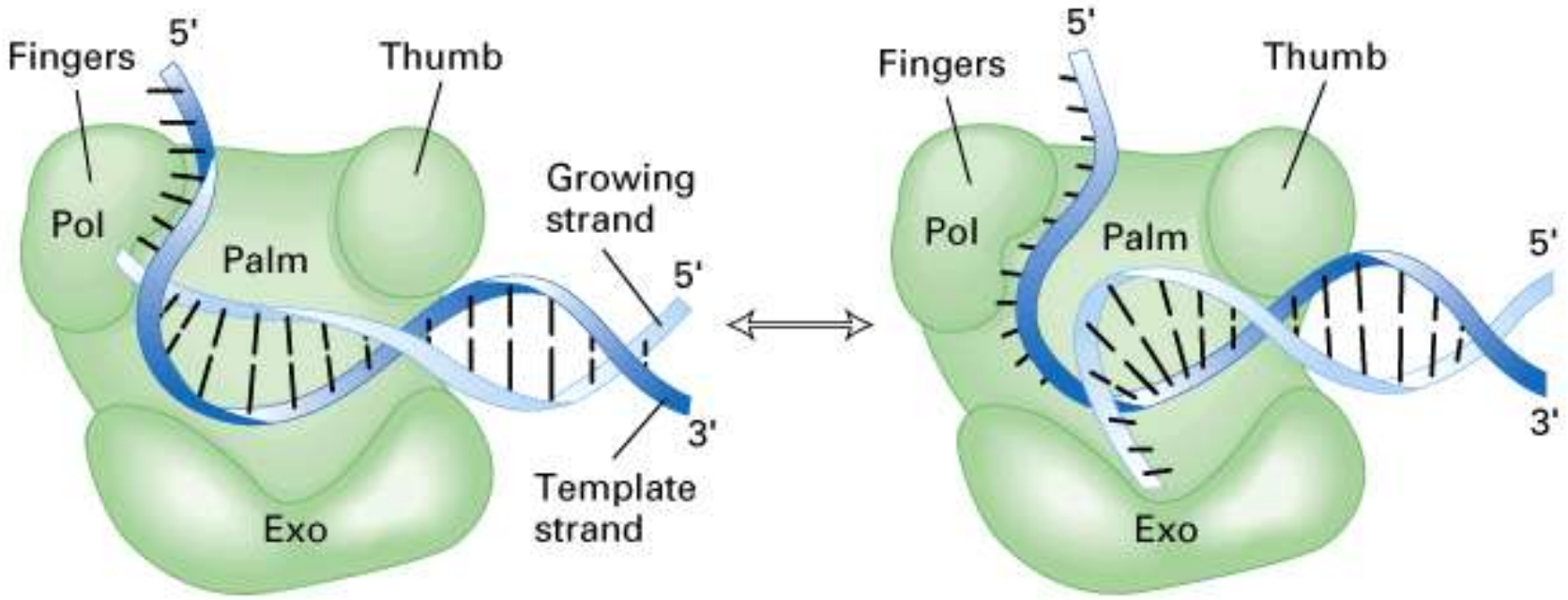
Types of DNA repair

- Direct reversal of damage
- Excision of damaged region
  - Mismatch repair
  - Base excision repair
  - Nucleotide excision repair
- Double-strand break repair
  - Pathway based on homologous recombination
  - Non-homologous end joining (NHEJ)

E. coli DNA Polymerase – proofreading activity

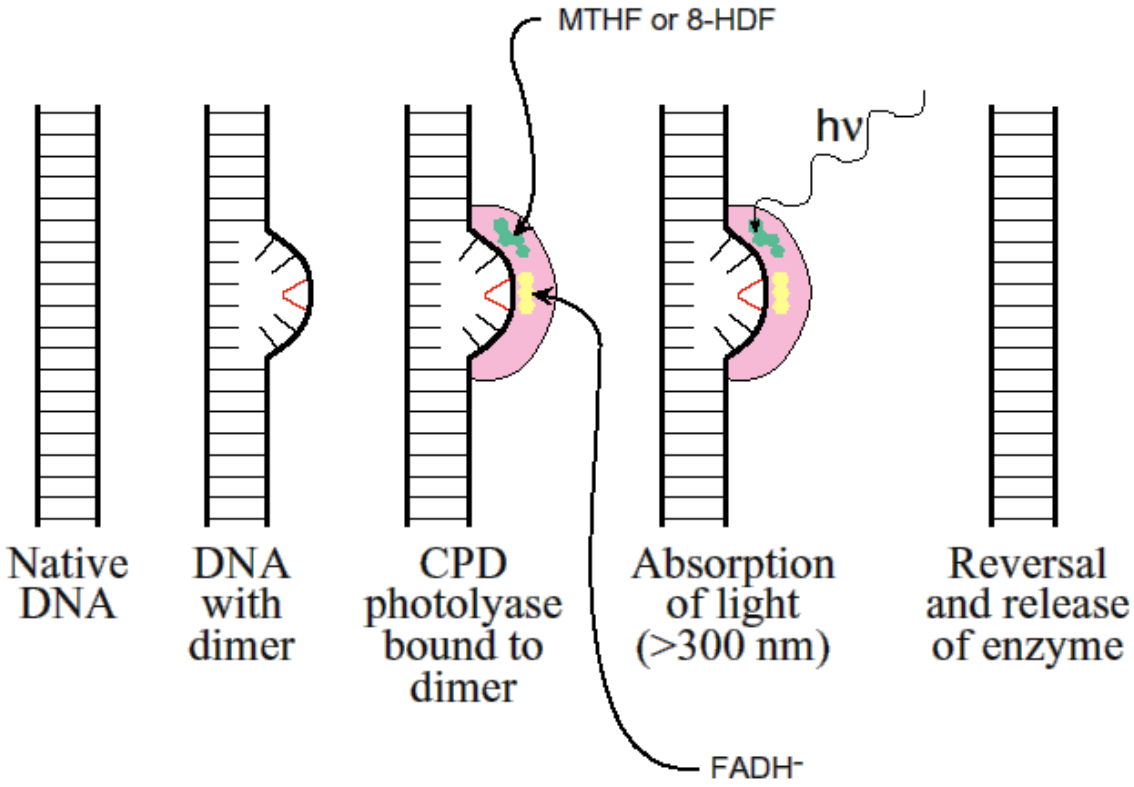
1 incorrect base in about 10^4 bases

Observed error rate : 1 in 10^9



Direct reversal of damage

Light Dependent Repair-reversal of dimers by photolyase



Photolyase: binds a pyrimidine dimers and catalyzes a photochemical reaction
Breaks the cyclobutane ring and reforms two adjacent T's
2 subunits, encoded by *phrA* and *phrB*.

Mismatch Repair

Accounts for 99% of all repairs
Follows behind replication fork.
Two ways to correct mistakes made during replication:
3'>5' exonuclease - proofreading

How does system recognize progeny strand rather than parent strand as one with mismatch?

Because of methylation.
Methylation at 5'-GATC-3' sequence in DNA at A residue.

Mismatch repair genes

mutH, *mutL*, *mutS* and *mutU* gene products Involved (*mut* for mutator because if gene is mutated, cell has increased levels of spontaneous mutations)

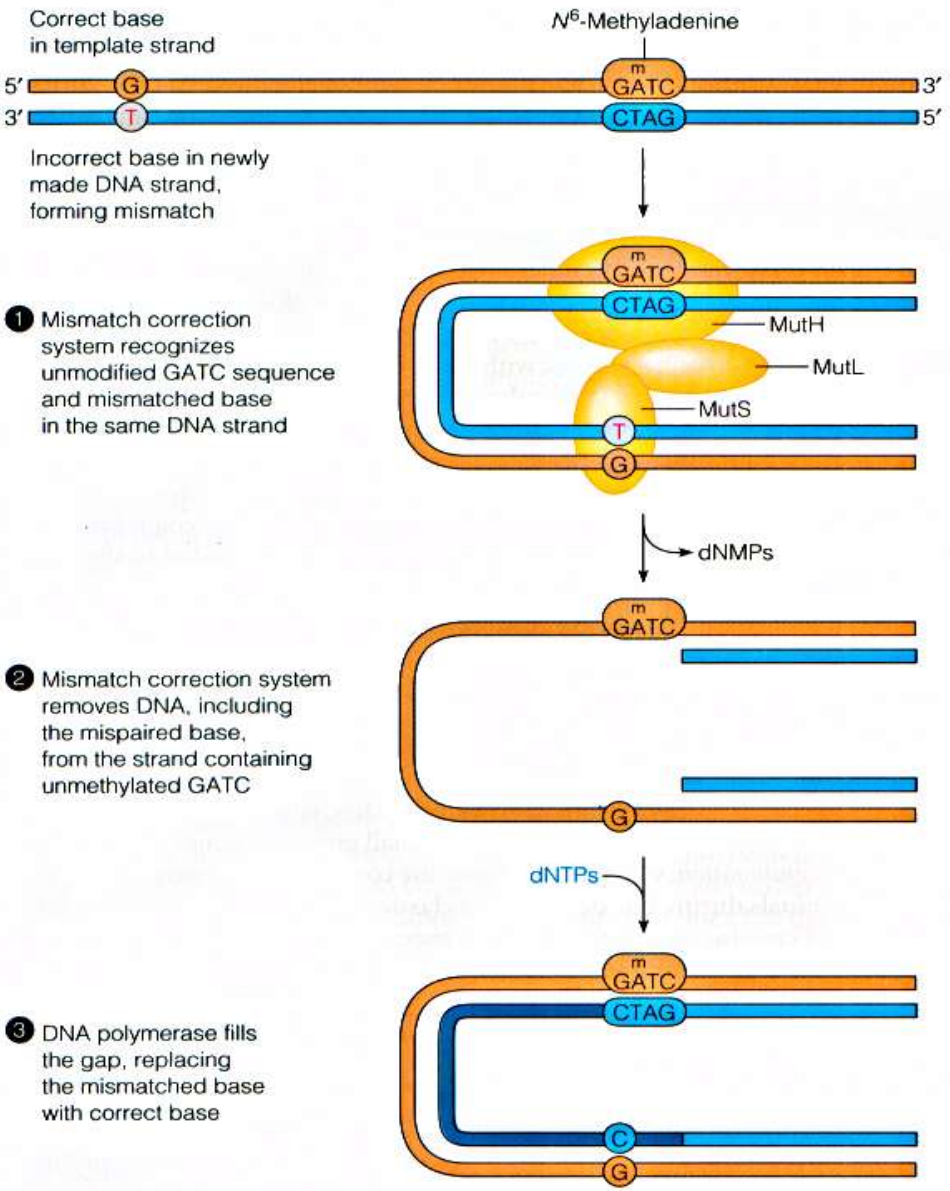
MutL and MutS: Recognize mismatch from replication

MutH: nicks DNA strand (progeny strand) on either side of mismatch.

MutU: DNA helicase II (also called UvrD) unwinds DNA duplex and releases nicked region.

Gap filled in by DNA Pol I and ligase.

Mismatch repair by the MutHLS system of *E. coli*



How does the repair system know which strand is the one that needs to be repaired?

dam methylase methylates adenine residues in the new strand of DNA but some time after the replication fork has passed through this region. Therefore, newly replicated DNA strands are not methylated yet while parental strands are.

This allows the repair to be restricted to the new strand which contains the misincorporated base.

Mismatch repair

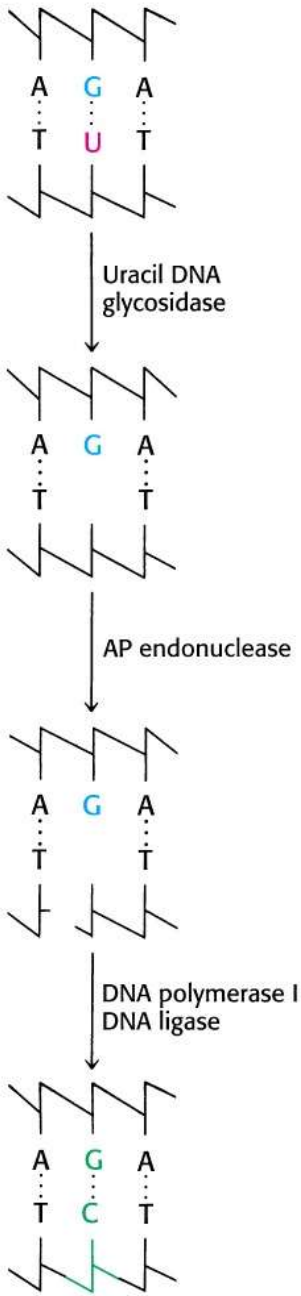
Genes Encoding Enzymes of Mismatch Repair

E. coli	*S. cerevisiae*	Human	Functions of Eukaryotic Proteins
MutS	MSH1	?	DNA repair in mitochondria
"	MSH2	MSH2	Single mismatch and small loop repair (with MSH6 to form MutSα); loop repair (with MSH3 to form MutSβ)
"	MSH3	MSH3	Loop repair (with MSH2 to form MutSβ)
"	MSH4	MSH4	Meiosis (with MLH1)
"	MSH5	MSH5	Meiosis (with MLH1)
"	MSH6	MSH6	Single mismatch and small loop repair (with MSH2 to form MSα
MutL	MLH1	MLH1	Mismatch repair
"	PMS1	PMS2	Mismatch repair (with MLH1 to form MutLα)
"	MLH2	PMS1	Not involved in mismatch repair (yeast); evidence ambiguous (humans); Interacts with MLH1 to from MutLβ.
"	MLH3	MLH3	Probably involved in loop repair (with MLH1)
MutH	?	?	?
uvrD	?	?	?
?	Exonuclease 1	Exonuclease 1	Mismatch repair (5' to 3' polarity)
?	RAD27	DNase IV FEN-1	Mismatch repair (Flap Endonuclease)

Protein	Function
dam methylase (**D**NA **a**denine **m**ethylase)	Methylates adenine to create 6-methyladenine in the sequence GATC.
MutH	Endonuclease that cleaves unmethylated strand just 5' to the G in the sequence GATC (that is, N | GATC) leaving a 3'-OH and 5'-P at the cleavage site. Requires MutL and MutS to activate latent endonuclease activity.
MutL	Adds to complex of MutS at mismatch in ATP dependent (but not hydrolysis dependent) step. Acts as a "molecular matchmaker" and uses ATP hydrolysis to bring MutS and MutH together and to stimulate MutH endonuclease activity. Also binds to and loads helicase II.
MutS	Binds to all mismatches except C-C; also binds to small insertion or deletion mismatches in which one strand contains one, two, or three extra nucleotides; heteroduplexes with four extra nucleotides are weakly repaired, but larger heterologies do not appear to be recognized.
helicase II	Also known as the mutU/uvrD gene product. Requires MutS and MutL to load on at the endonucleolytic cleavage site ("nick"). Moves along a DNA strand in the **3'-to-5' direction**. Unwinds the incised strand to make it sensitive to the appropriate single-strand specific exonuclease activity.
exonuclease VII	Also known as the xseA gene product. Hydrolyzes **single-stranded** DNA in the 5'-to-3' direction.
RecJ	Hydrolyzes **single-stranded** DNA in the 5'-to-3' direction.
exonuclease I	Also known as the sbcB or xonA gene product. Hydrolyzes **single-stranded** DNA in the 3'-to-5' direction.
DNA polymerase III holoenzyme	The replicative DNA polymerase in E. coli.
SSB	Single strand binding protein.
DNA ligase	Uses NAD^+ to form phosphodiester bonds at "nicks".

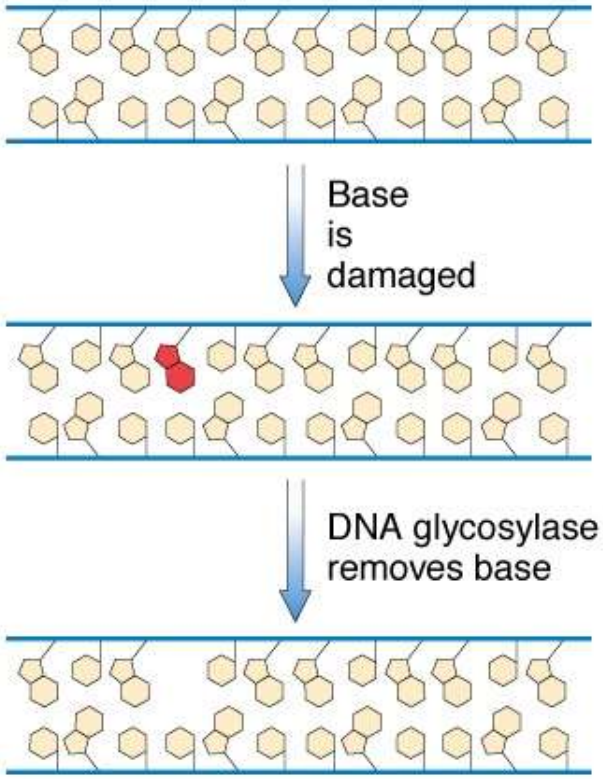
Systems for repairing DNA damage – excision systems

- **Spontaneous deamination of cytosine can be recognized by the presence of a uridine base in the strand of DNA that carries the incorrect information.**
- **This is probably why thymine rather than uracil is used in DNA.**



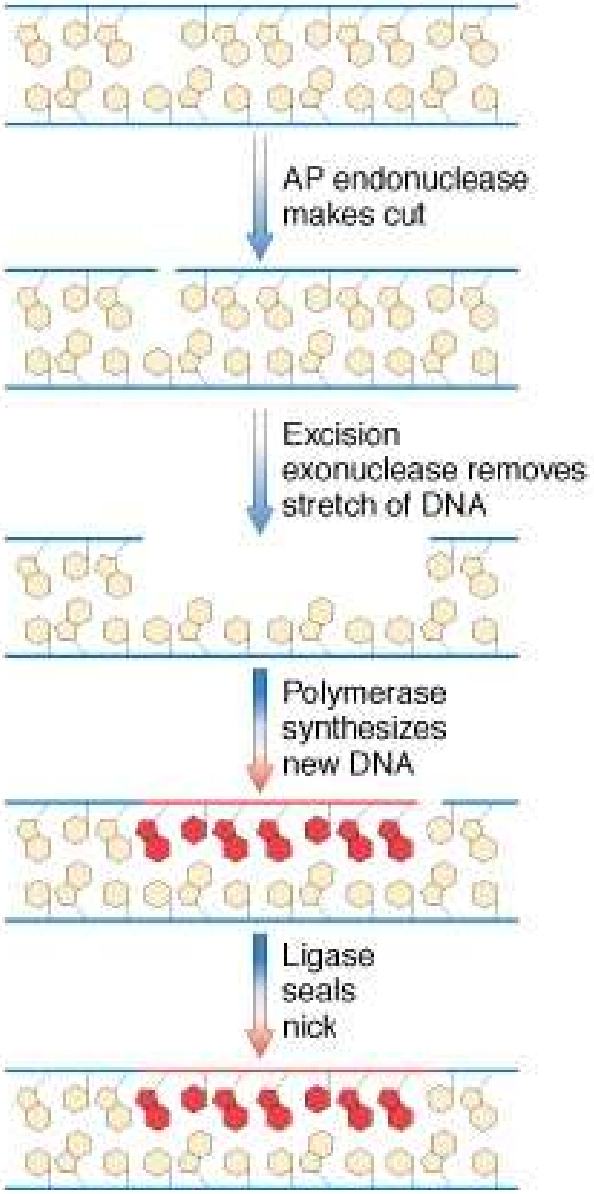
Excision pathways

- glycosylases remove unpaired bases
- AP -endonuclease cuts segment out
- DNA pol I replaces the strand 5' -> 3'
- ligase seals the nick
- special uracil-DNA glycosylase!



Base

General



Excision repair

- **Glycosylases**
  - basepair mismatch is recognized by an enzyme which hydrolyses the ester bond between the phosphate-sugar backbone and the base involved, thereby leaving a double strand with only one base. This occurs when uracil is encountered (U is the deamination product of cytosine, or any modified base)

- AP-endonuclease
  - The resulting hole is recognized by an AP-endonuclease (for *apurinic or apyrimidinic*). The AP endonuclease creates a single-stranded cut and removes a short segment of the damaged site
  - $\rightarrow$ DNA pol and ligase fill in the gap to complete the repair

Base excision repair

- Several variations, depending on nature of damage, nature of glycosylase, and nature of DNA polymerase.
- All have in common the following steps:

1. Removal of the incorrect base by an appropriate DNA N-glycosylase to create an AP site.
2. An AP endonuclease nicks on the 5' side of the AP site to generate a 3'-OH terminus.
3. Extension of the 3'-OH terminus by a DNA polymerase.

Examples of Human DNA Glycosylases

Acronym	Full Name	Size (aa)	AP Lyase	Substrates
UNG	Uracil DNA N-Glycosylase	313	No	ssU>U:G>U:A, 5-FU
TDG	Thmine DNA Glycosylase	410	No	U:G>ethenocytosine:G>T:G
UDG2	Uracil DNA Glycosylase 2	327	No	U:A
SMUG1	Single-strand-selective Monofunc-tional Uracil-DNA Glycosylase 1	270	No	ssU>U:A, U:G
MBD4	Methyl-CpG-binding Domain 4	580	?	U or T in U/TpG:5-meCpG
MPG	Methyl Purine DNA Glycosylase	293	No	3-me-A, 7-meA, 3-meG, 7-meG
MYH	MutY Homolog	535	Yes?	A:G, A:8-oxoG
OGG1	8-Oxo-Guanine Glycosylase 1	345	Yes	8-oxoG:C
NTH1	Endonuclease Three Homolog 1	312	Yes	T-glycol, C-glycol, formamidopyrimidine

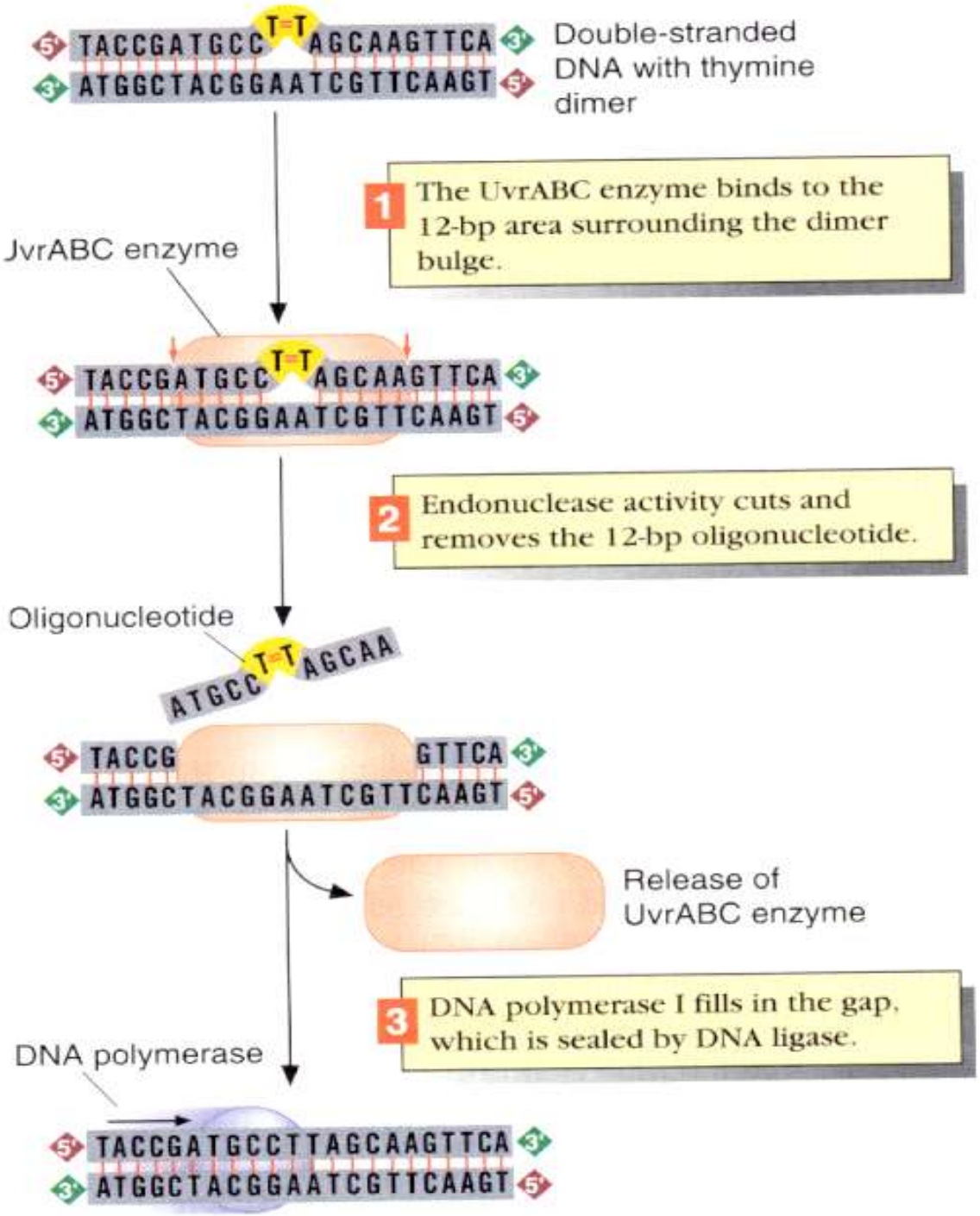
Nucleotide Excision Repair

Bacterial	Mammalian
UvrA	RPA, TFIIH
UvrB	XPA (damage recognition) *and* XPG (cleavage)
UvrC	XPF, ERCC1
UvrD	TFIIH
4 proteins	>18 polypeptides
~12 nt released	~29 nt released

The *uvr ABC* repair system

– Damage by light and by a number of mutagens in *E. coli* is repaired by the products of three genes : uvrA,B, and C. The products of these genes "feel" the shape of a helix (since, obviously, they cannot check the sequence) , and if they detect a distortion, they will produce a single-stranded cut on one strand, exactly 12 nucleotides apart (8 on the 5' side of the lesion, 4 on the 3' side).

VSP – very short patch repair

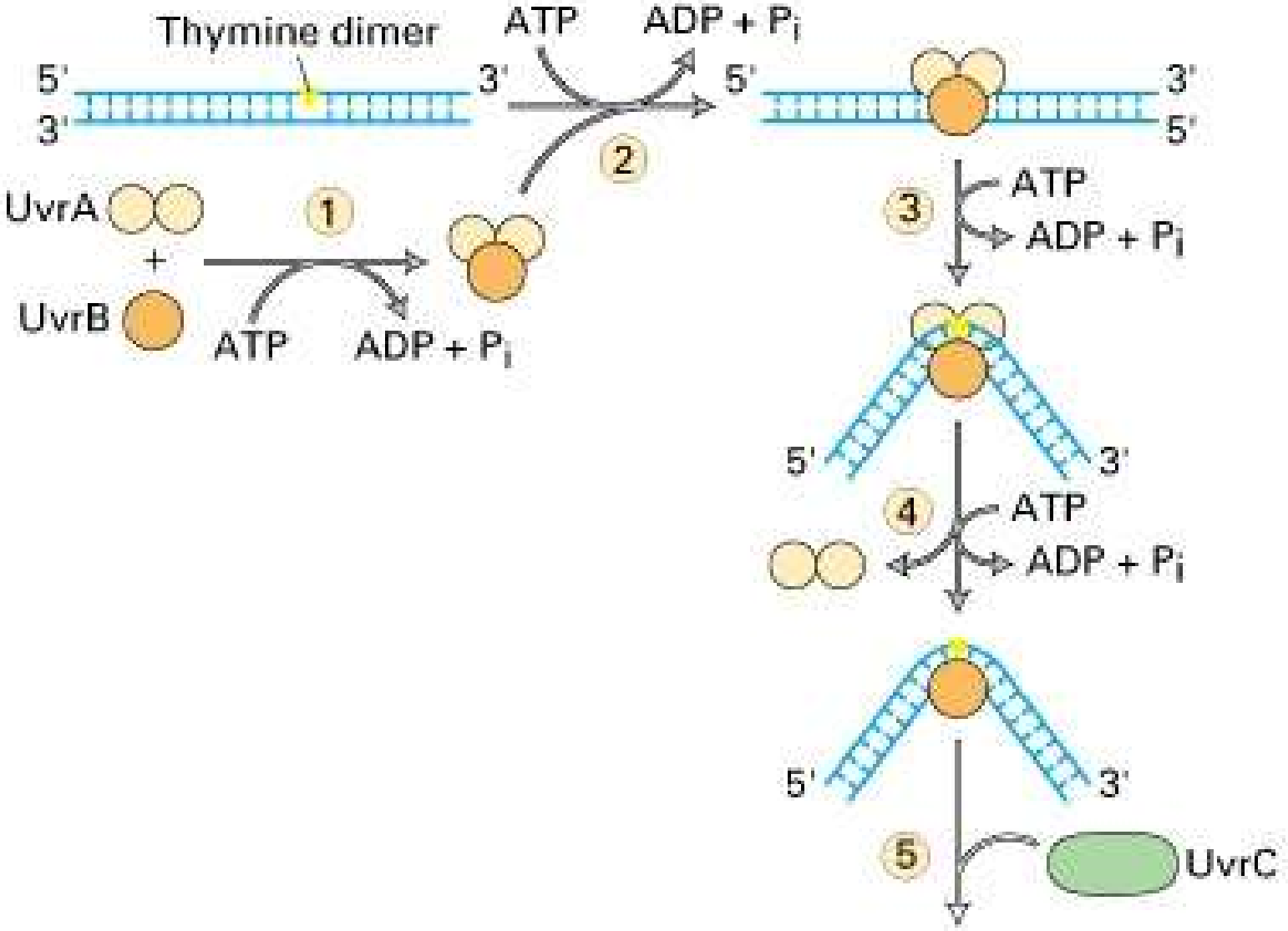


Uvr ABC

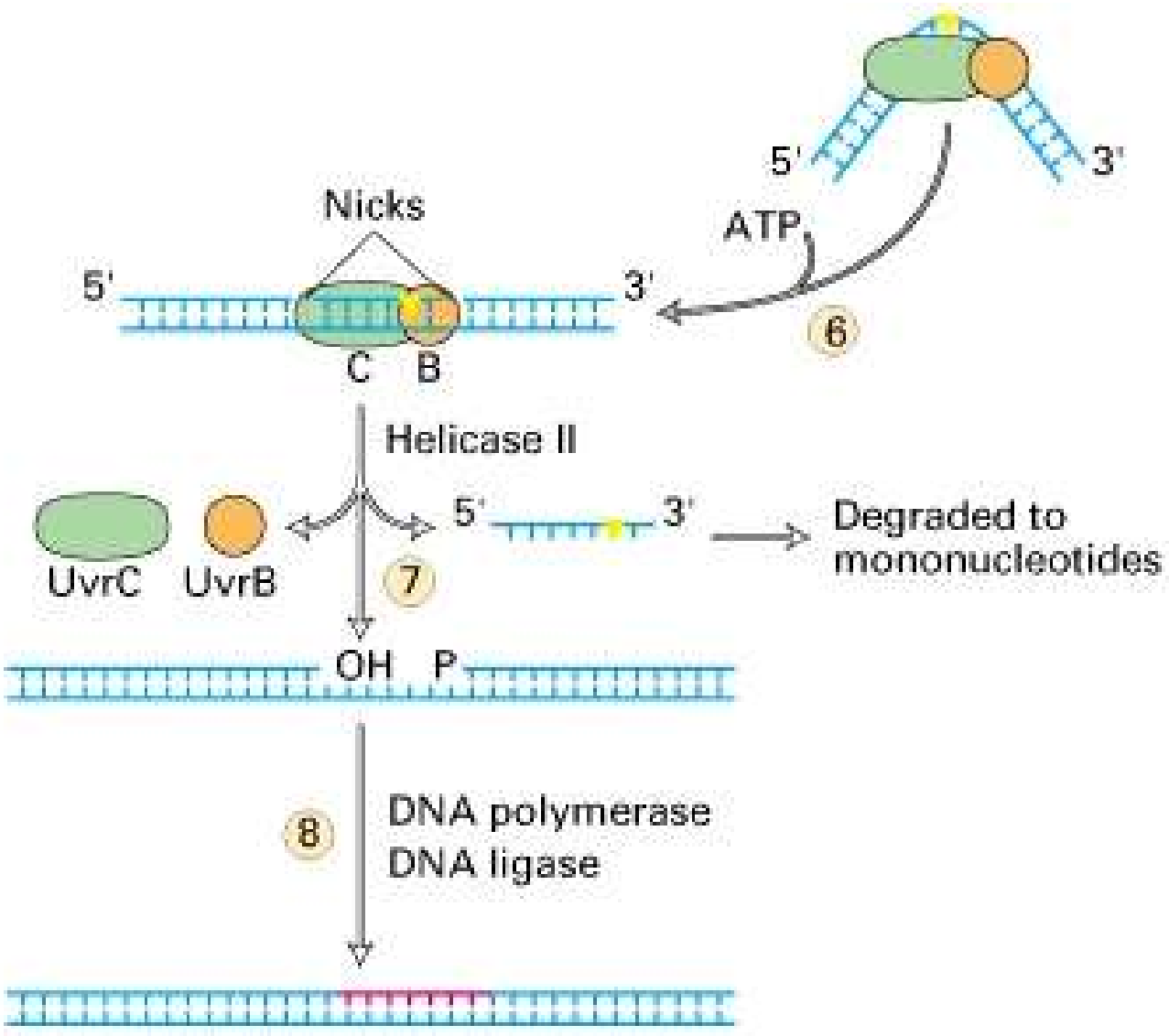
In E.coli, the enzyme that does the incision is UvrABC, an endo-nuclease with three subunits: A, B, and C.

The gap is filled by DNA Pol. I.

The *uvr ABC* repair system



The *uvr ABC* repair system



Excision Repair - *uvr* genes

uvrA

- Gene is 2820 bp long ---> 103.8 Kd protein
- ATPase activity and DNA binding activity.
- There are 3 ATPase domains in the AA sequence separated by Zn++ finger domains - thus uvrA protein ligands 2 Zn++.
- The molecule may be active in dimer form.

uvrB

- Gene is 2019 bp long ---> 76 Kd peptide (672 AA - no tryptophane)
- Has ATPase domain homology but no ATPase activity
- Monomeric
- Doesn't bind to DNA alone, only if complexed to uvrA protein -

uvrC

- Gene is 1764 bp long ---> 66 Kd peptide (588 AA)
- Monomeric
- Can bind to DNA
- C-terminus 60 base residues are homologous to human repair gene ERCC-1, some homology with uvrB sequences.

uvrD - helicase

Mutations in excision repair in eukaryotes can cause xeroderma pigmentosum (XP)

Human Gene	Protein Function	Analogous to *E. coli:*
XPA	Binds damaged DNA	UvrA/UvrB
XPB	Helicase, Component of TFIIH	UvrD
XPC	DNA damage sensor	
XPD	Helicase, Component of TFIIH	UvrD
XPE	Binds damaged DNA	UvrA/UvrB
XPF	Works with ERRCI to cut DNA	UvrB/UvrC
XPG	Cuts DNA	UvrB/UvrC

Nucleotide excision repair

Nucleotide Excision Repair

- Extremely flexible
- Corrects any damage that both distorts the DNA molecule and alters the chemistry of the DNA molecule.
- In all organisms, NER involves the following steps:

1. Damage recognition
2. Binding of a multi-protein complex at the damaged site
3. Double incision of the damaged strand several nucleotides away from the damaged site, on both the 5' and 3' sides
4. Removal of the damage-containing oligonucleotide from between the two nicks
5. Filling in of the resulting gap by a DNA polymerase
6. Ligation

Eukaryotic nucleotide excision repair

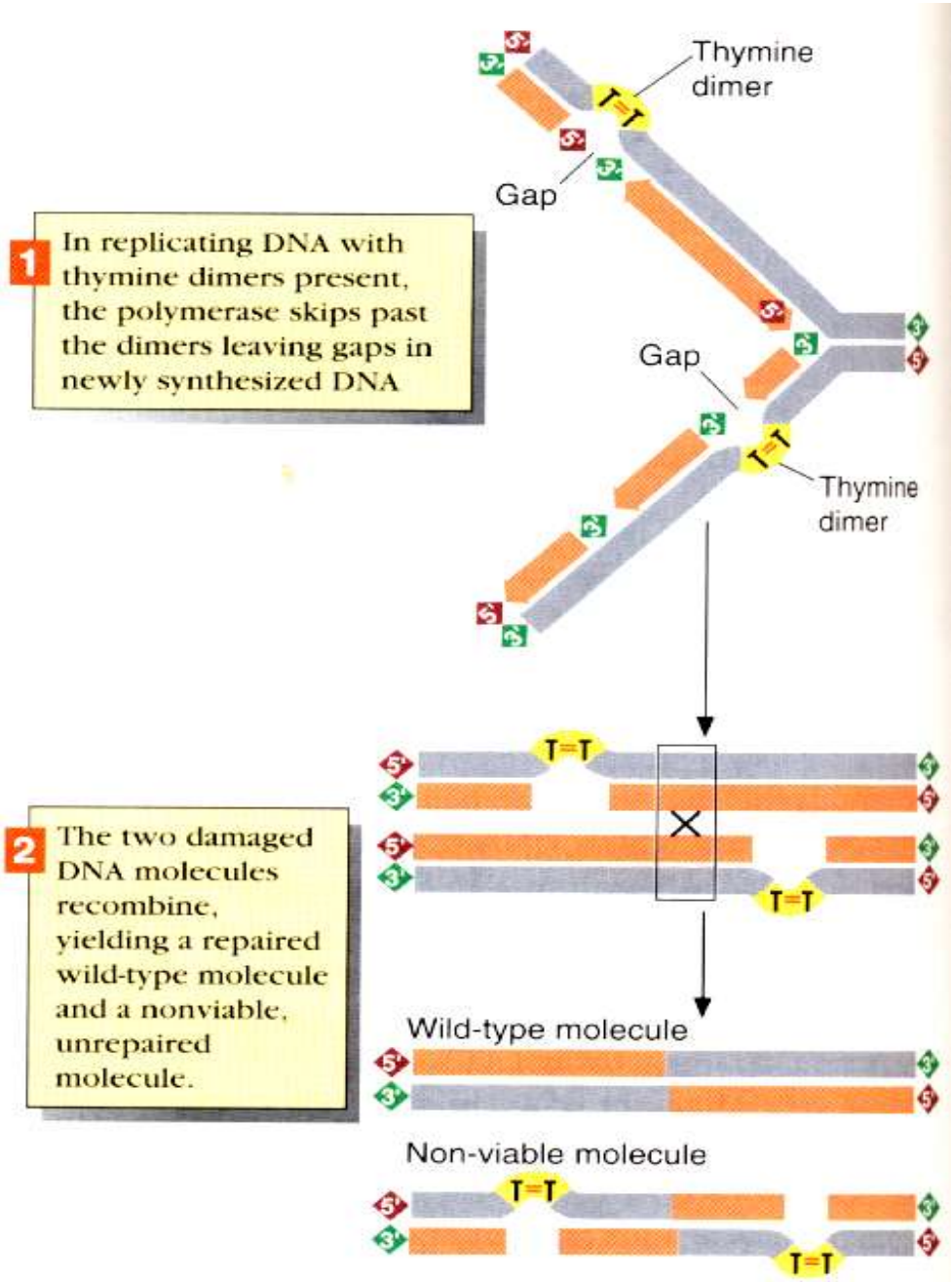
Proteins Required for Eukaryotic Nucleotide Excision Repair		
***S. cerevisiae* protein**	**Human protein**	**Probable function**
Rad4	XPC	Works with hHR23B; binds damaged DNA; recruits other NER proteins
Rad23	hHR23B	Cooperates with XPC (see above); contains ubiquitin in domain; interacts with proteasome and XPC
Rad14	XPA	Binds damaged DNA after XPC or RNA pol II; confirms DNA distortion
Rpa1, 2, 3	RPA p70, p32, p14	Stabilizes open complex (with Rad14/XPA); positions nucleases
Ssl2 (Rad25)	XPB	3' to 5' helicase
Tfb1	p62	?
Tfb2	p52	?
Ssl1	p44	DNA binding?
Tfb4	p34	DNA binding?
Rad3	XPD	5' to 3' helicase
Tfb3/Rig2	MAT1	CDK assembly factor
Kin28	Cdk7	CDK; C-terminal domain kinase; CAK
Ccl1	CycH	Cyclin
Rad2	XPG	Endonuclease (3' incision); stabilizes full open complex
Rad1	XPF	Part of endonuclease (5' incision)
Rad10	ERCC1	Part of endonuclease (5' incision)

Recombination repair

For recombination to occur, the damages on two different DNA strands have to be in different locations.

By a single crossing over, the recombination can create one good DNA molecule (chromosome) and one unrepairable DNA molecule.

In E.coli, the enzyme involved in recombination repair is recA.



RecA

The 38 kDa RecA protein has at least three distinct biological processes in *E. coli*:

1. Homologous recombination
   (and the recombinational repair of DNA damage)
2. DNA damage induced mutagenesis
3. Activation of the SOS system

A multifunctional protein with following activities:

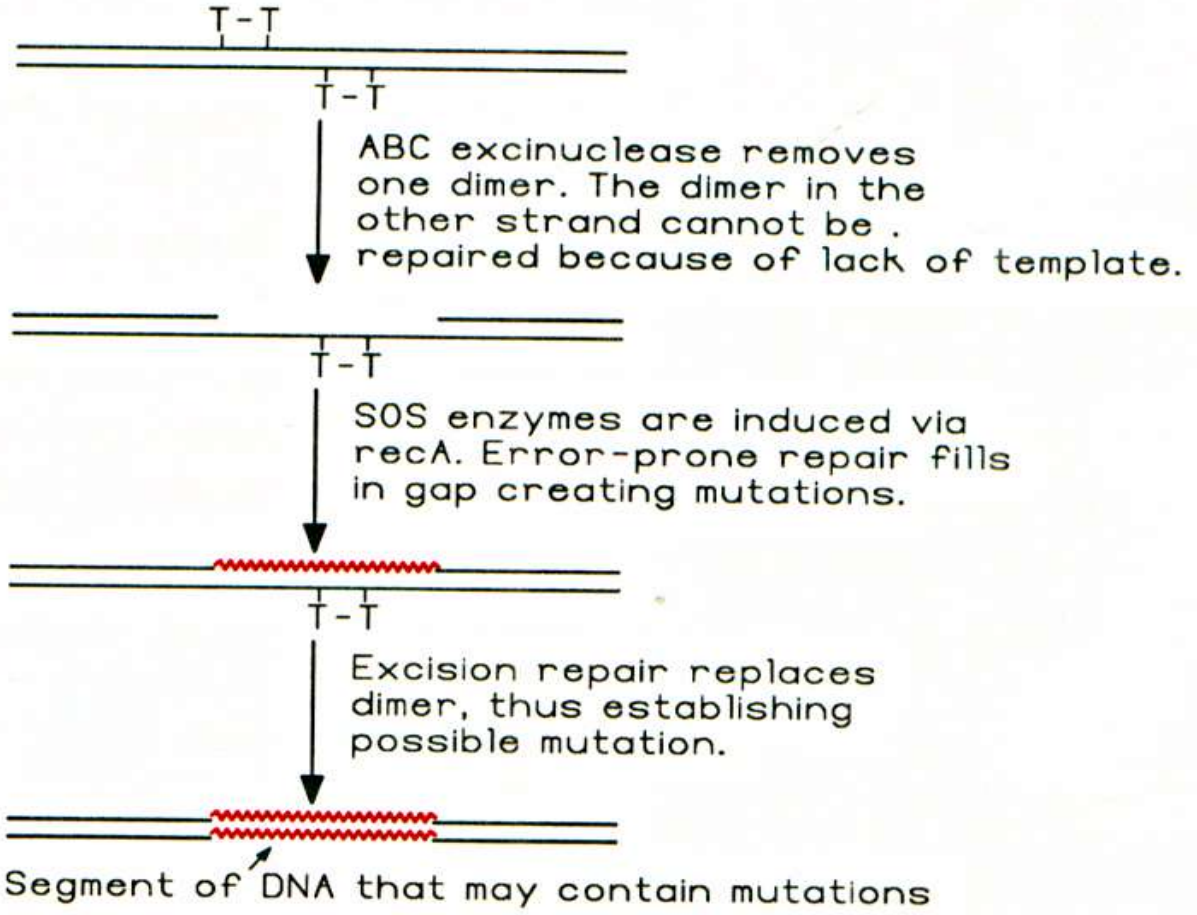
High affinity to bind to single-stranded DNA associated with a helicase activity.

Has a intrinsic protease activity which it acquires when it binds to thymidine dimers which accumulate during UV-irradiation of DNA

Interacts and inhibits the 3'-5'-exonuclease activity present in DNA polymerase and by doing so enables SOS-repair.

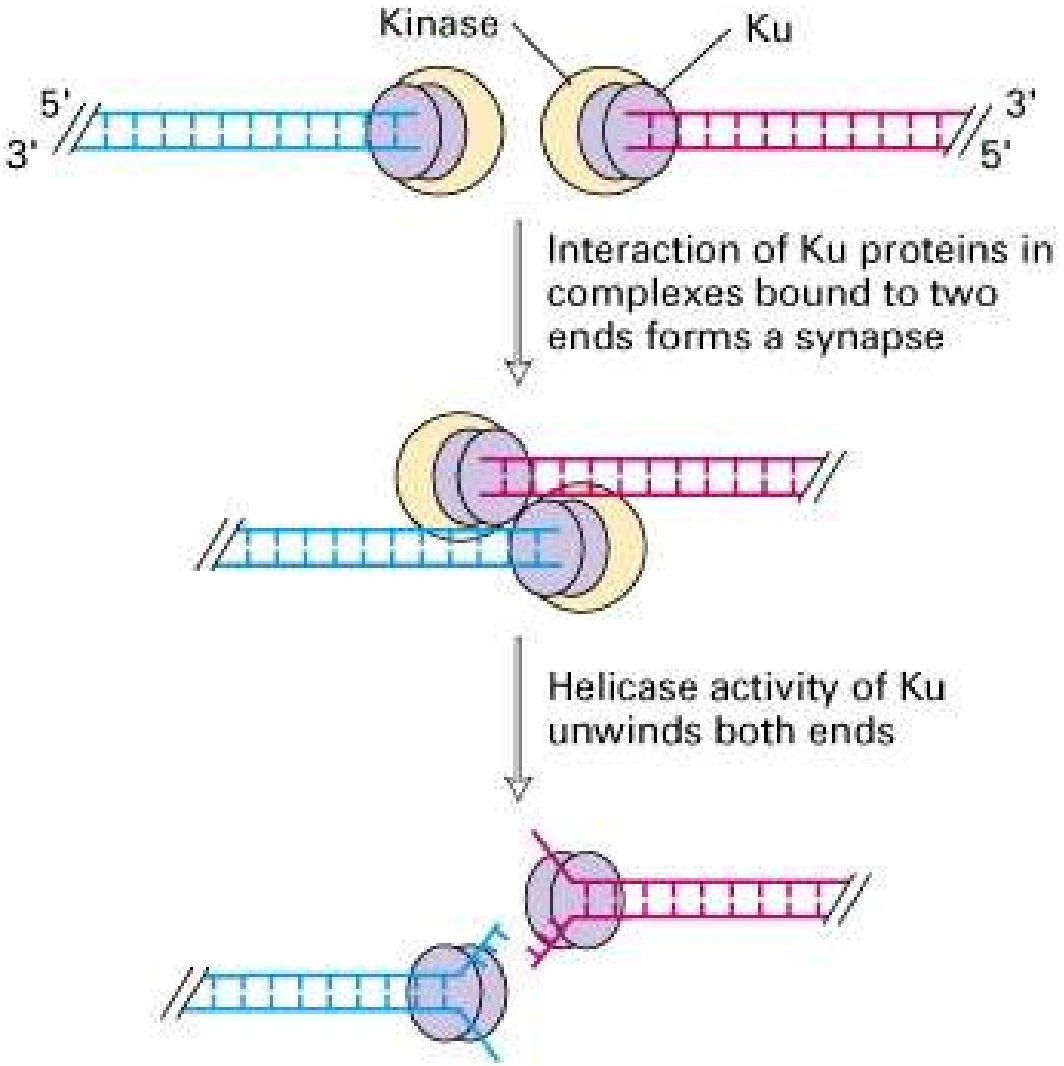
Catalyse the interaction of a variety of different DNA molecules with each other: molecules one of which as a 'nick' ie a partial single-stranded area.

Error-prone DNA repair is invoked when the excised segment of DNA cannot be repaired because of a damaged other strand.



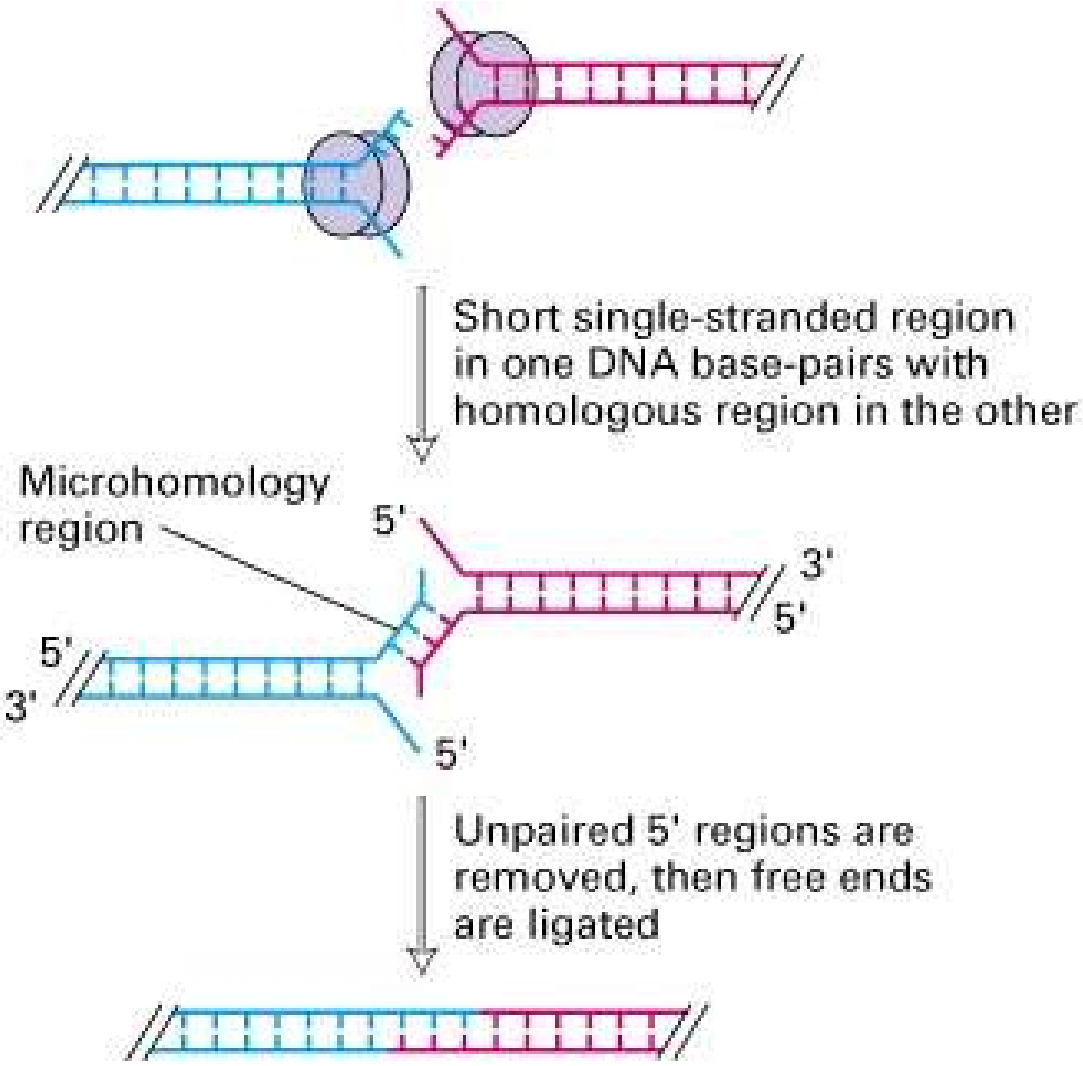
Error-prone DNA repair

Repair of double stranded breaks



Error-prone DNA repair

Repair of double stranded breaks



SOS Response

Overwhelmed damage: UV irradiation

RecA involved in increased capacity to repair damaged DNA

50X increase in RecA levels

Induction of Long-patch excision repair and the recombination repair

SOS regulon: *lexA-dinF, polB, recA, recN, rpsU-dnaG-rpoD, ssb, sulA, umuDC, uvrA, uvrB, uvrC, uvrD*

SOS Box (20 bp stretch: 5'-CTGX$_{10}$-CAG-3', where X$_{10}$ is an 10 bases) for LexA binding, LexA ((22 kDa) is the repressor that is cleaved by RecA.

The SOS system inhibit cell division in order to increase amount of time cell has to repair damage before replication.

SOS Repair genes

umuCD = involved in error-prone DNA repair system.

sulA = inhibits cell division, at least partially by increasing expression of StfZ antisense RNA which blocks translation initiation of *ftsZ* mRNA.

ssb = ss DNA binding protein.

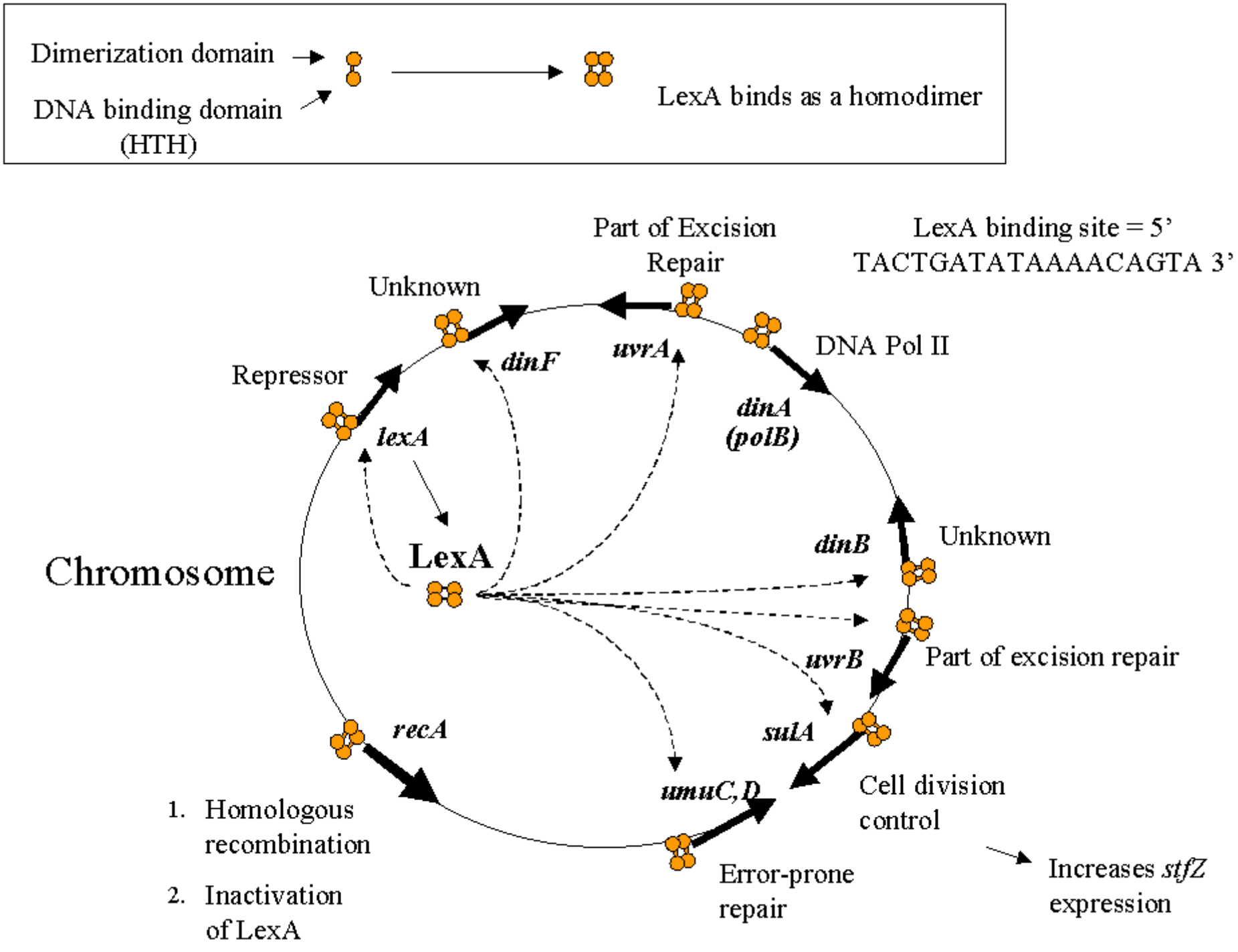
uvrA , *uvrB* and *uvrC* (Excision Repair)

dinA = polB = DNA Polymerase II

dinB, dinD, dinF = ?

lexA = LexA repressor

recA

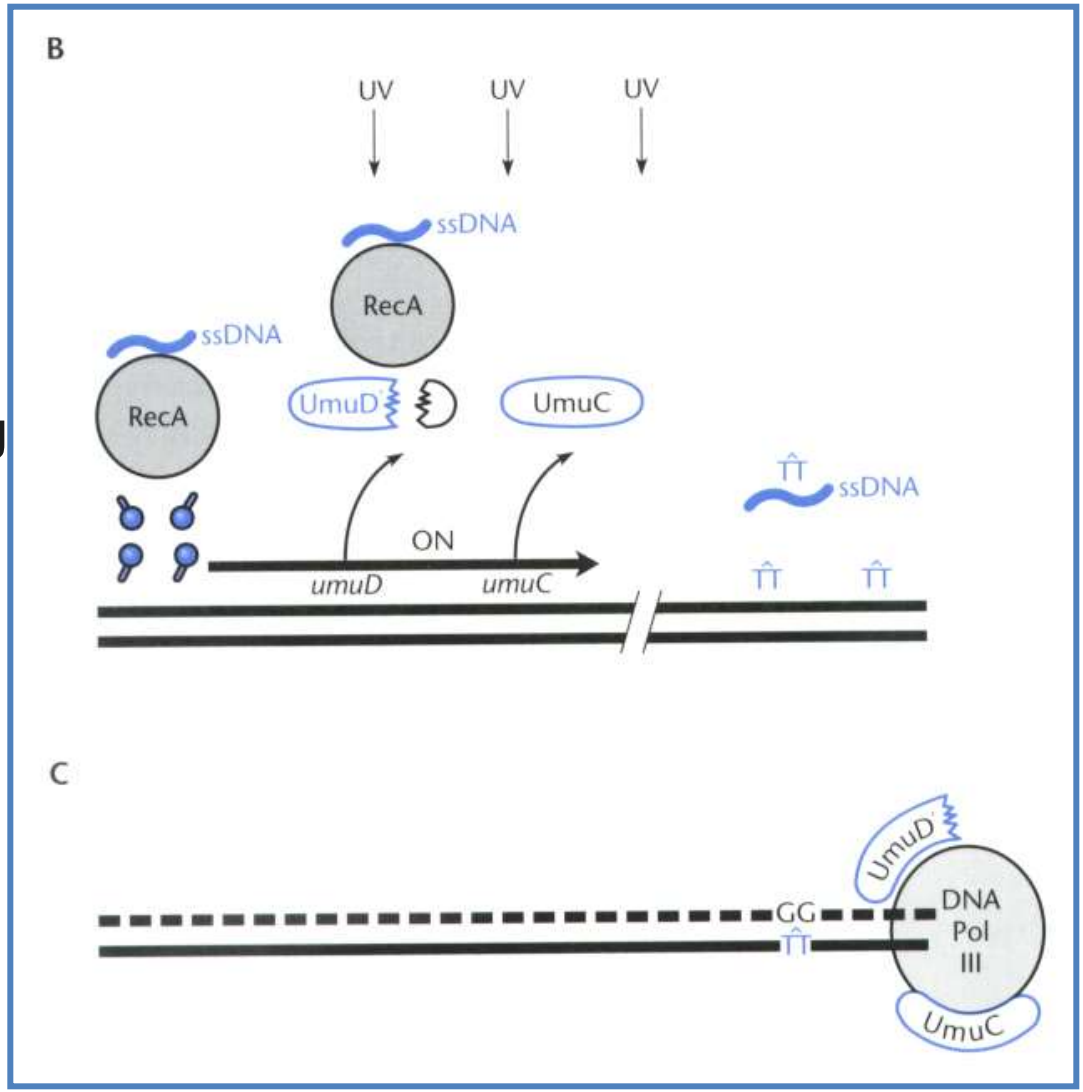

Dimerization domain
DNA binding domain
(HTH)
LexA binds as a homodimer
Part of Excision
Repair
LexA binding site = 5'
TACTGATATAAAACAGTA 3'
Unknown
DNA Pol II
Repressor
dinF
uvrA
dinA
(polB)
lexA
LexA
dinB
Unknown
Chromosome
uvrB
Part of excision repair
recA
sulA
umuC,D
Cell division
control
1. Homologous
recombination
2. Inactivation
of LexA
Error-prone
repair
Increases stfZ
expression

Effect of the SOS derepression

Bypass repair:

UmuCD enzyme adapts polymerase III to bypass lesions; error prone as editing function suppressed.

Example: 2 G's incorporated opposite
a T dimer.



LexA and RecA

LexA binds to *recA* promoter weakly

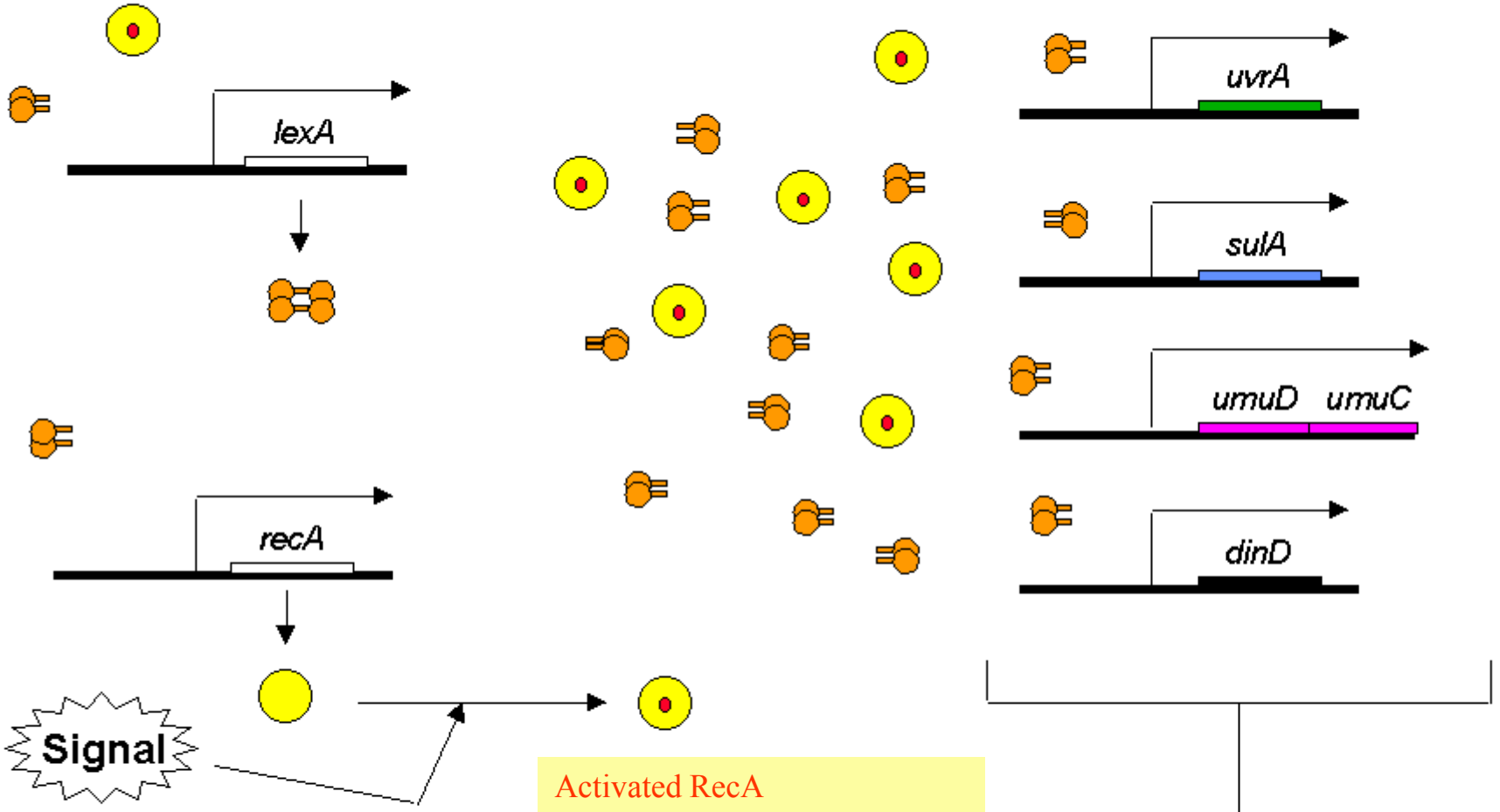
Normal levels 1000 RecA/cell - recombination and repair

RecA activation due to "ss DNA binding" induces its co-protease activity - cleaves LexA.

Weak *lexA* promoters are first to come on…..the RecA levels increase 50 X

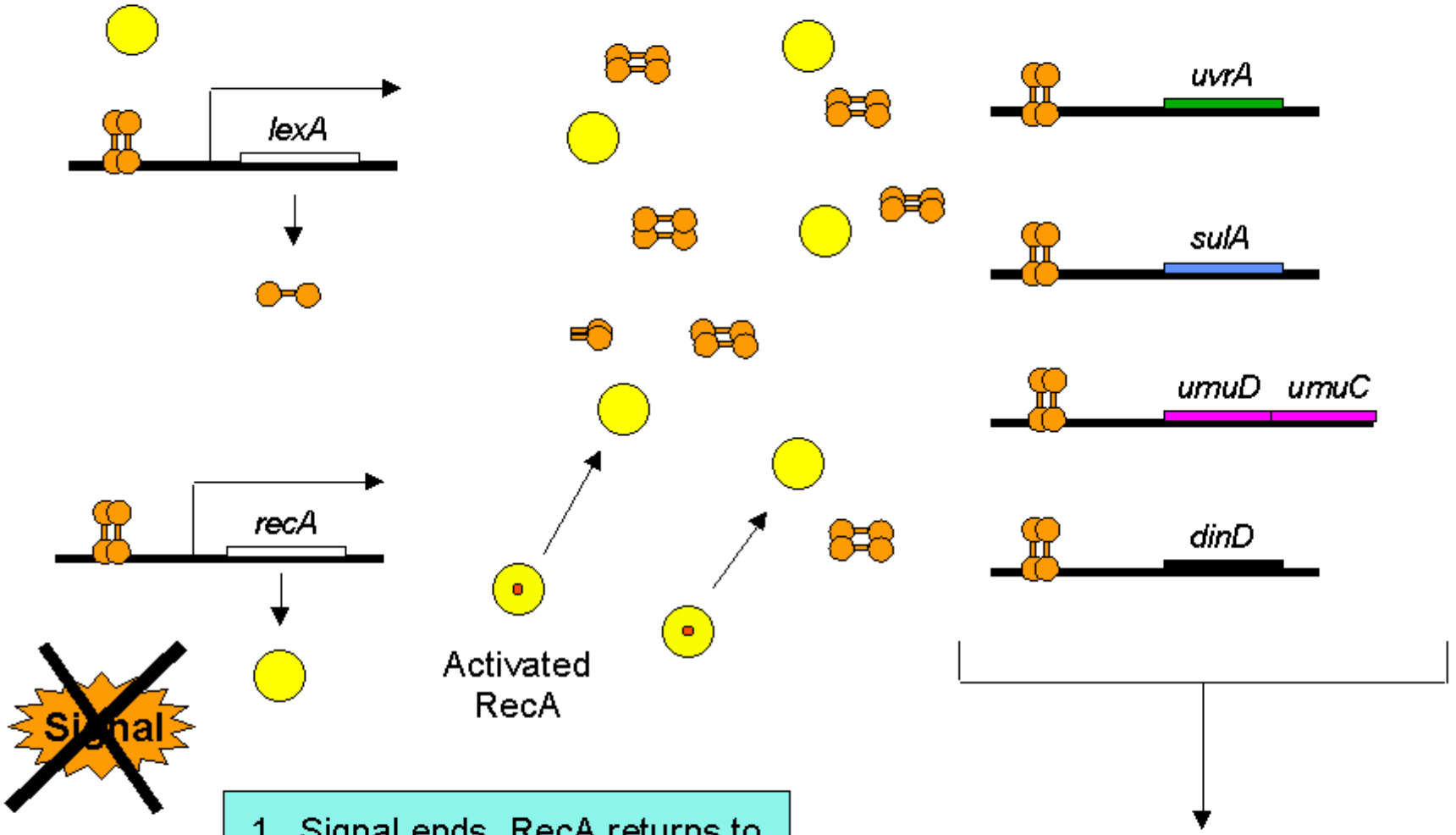
More LexA, but there is also increased amount of RecA to deal with that.

SOS Response: Induced by DNA Damage



1. RecA becomes activated.
2. RecA blocks editing function of DNA Pol III.
3. RecA bound to ssDNA causes LexA autodeavage.
4. SOS operons all activated.

SOS Response: Return to Status Quo



1. Signal ends, RecA returns to unactivated state.
2. More LexA produced.
3. LexA turns off SOS operons.

Role of *umuC* and *umuD* genes in error-prone repair

- Named for the UV ***non***mutable phenotype of mutants with defects in these genes.
- Needed for bypass synthesis; mechanism is under investigation. E.g. these proteins may reduce the template requirement for the polymerase.
- UmuD protein is proteolytically activated by LexA.

UmuC, UmuD in error-prone repair

UV damage

DNA replication

DNA Pol III

Translesional synthesis (error-prone)

UV damage, increase RecA:ssDNA

Activate protease
Induce *umuC*$^+$, *umuD*$^+$

UmuD$_2$
UmuC

beta

epsilon

DNA damage checkpoint control

UmuD'$_2$
UmuC

Pol III alpha

Polymerase for translesional synthesis