

DNA Damage And Repair

12/18/25

Summary of DNA replication

2

- DNA polymerases catalyze the synthesis of DNA.
- □ The reaction involves a nucleophilic attack by the 3'-hydroxyl group on the innermost phosphorous atom of the nucleotide **triphosphate**.
- Pyrophosphate is the leaving group. □
- The synthesis reaction occurs in the 5' to 3' direction - new bases are added at the 3' end of the growing chain.

Cont...

3

- **DNA polymerase I has three activities:**
 - **5'→3' DNA synthesis**
 - **3'→5' exonuclease** - used as an error corrector to check the last base of the chain to ensure accuracy.
 - **5'→3' nuclease** - used to remove bases (especially the RNA primer) ahead of synthesis occurring in the same direction.

Cont...

- DNA synthesis occurs at replication forks.
- Synthesis begins at an **origin of replication** and proceeds in a bidirectional manner. f
- DNA polymerase III is the primary enzyme for DNA replication in E. coli. f
- Leading the synthesis is the **helicase enzyme**, which unwinds the DNA strands.
- This introduces positive supercoils into the DNA which must be relieved by **DNA gyrase**.
- The single stranded DNA is protected by binding to a **Single Stranded Binding Protein**.

Cont....

5

- A **primase** synthesizes a short strand of RNA (about 5-10 nucleotides), because DNA polymerase requires a primer annealed to the template strand.
□
- The polymerase proceeds down the helix, directly synthesizing one strand in the 5'→3' direction - **the leading strand.**
- The other strand loops around and through the polymerase, and is synthesized in short, **Okazaki fragments** in the 5'→3' direction - **the lagging strand.**

Cont....

6

- **DNA polymerase I** removes the RNA primers from the **Okazaki fragments**, replacing them with DNA. f
- **DNA ligase** seals the breaks that are left after DNA polymerase I finishes

DNA damage

7

- If the genetic information encoded in the DNA is to remain uncorrupted, any chemical changes must be corrected.
- A failure to repair DNA produces a mutation.
- The recent publication of the human genome has already revealed 130 genes whose products participate in DNA repair.

Agents in DNA damage

8

□ **Certain wavelengths of radiation**

- Ionizing radiation such as gamma rays and x-rays
- Ultraviolet rays, especially the UV-C rays (~260 nm) that are absorbed strongly by DNA but also the longer-wavelength UVB that penetrates the ozone shield .

□ **Highly-reactive oxygen radicals** produced during normal cellular respiration as well as by other biochemical pathways.

Agent cont....

9

□ Chemicals in the environment

- Many hydrocarbons, including some found in cigarette smoke
- some plant and microbial products, e.g. the aflatoxins produced in moldy peanuts
- Chemicals used in chemotherapy, especially chemotherapy of cancers

Types of DNA Damage

10

- **All four of the bases in DNA (A, T, C, G) can be covalently modified at various positions.**
 - One of the most frequent is the loss of an amino group ("**deamination**") — resulting, for example, in a **C** being converted to a **U**.
- **Mismatches of the normal bases because of a failure of proofreading during DNA replication.**
 - Common example: incorporation of the **pyrimidine** U (normally found only in RNA) instead of T.

Damage cont...

11

□ Breaks in the backbone.

- Can be limited to one of the two strands (**a single-stranded break, SSB**) or
- On both strands (**a double-stranded break (DSB)**).
- Ionizing radiation is a frequent cause, but some chemicals produce breaks as well.

□ Cross links Covalent linkages can be formed between bases

- On the same DNA strand ("intrastrand")
- On the opposite strand ("interstrand")

12/18/25

Repairing Damaged Bases

12

- Damaged or inappropriate bases can be repaired by several mechanisms:
- **Direct chemical reversal of the damage**
- **Excision Repair**, in which the damaged base or bases are removed and then replaced with the correct ones in a localized burst of DNA synthesis. There are three modes of excision repair, each of which employs specialized sets of enzymes.
 1. Base Excision Repair (BER)
 2. Nucleotide Excision Repair (NER)
 3. Mismatch Repair (MMR)

Direct Reversal of Base Damage

13

- Perhaps the most frequent cause of point mutations in humans is the spontaneous addition of a methyl group (CH₃-) (an example of alkylation) to Cs followed by deamination to a T.
- Fortunately, most of these changes are repaired by enzymes, called **glycosylases**, that remove the mismatched T restoring the correct C.
- This is done without the need to break the DNA backbone (in contrast to the mechanisms of excision repair described below).

- Some of the drugs used in cancer chemotherapy ("chemo") also damage DNA by alkylation.
- Some of the methyl groups can be removed by a protein encoded by our **O⁶ alkylguanine DNA methyltransferase (MGMT gene.)**
- However, the protein can only do it once, so the removal of each methyl group requires another molecule of protein.
- This illustrates a problem with direct reversal mechanisms of DNA repair: they are quite wasteful.

- Each of the myriad types of chemical alterations to bases requires its own mechanism to correct.
- What the cell needs are more general mechanisms capable of correcting all sorts of chemical damage with a limited toolbox.
- This requirement is met by the mechanisms of excision repair

Base Excision Repair (BER)

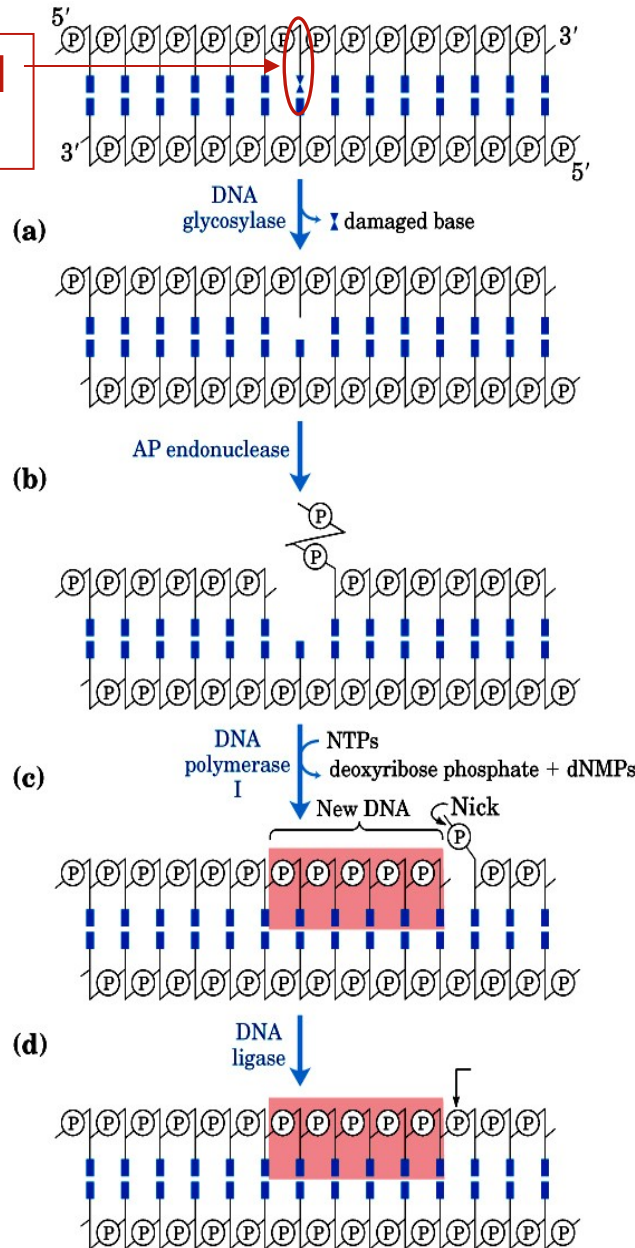
- Depurination occurs spontaneously at 37°C at a rate of 5000-10,000/cell/day due to the thermal lability of the purine N-glycosidic bond.
- **Spontaneous (hydrolytic)** or chemical or radiation-induced oxidative deamination converts **cytosine** into **uracil**, **adenine** into **hypoxanthine** and **guanine** into **xanthine**.
- Alkylated bases (mostly methylation), oxidized bases, e.g., **8-oxo-deoxyguanine** and inappropriately incorporated **adenine** opposite to it (defective repair of this damage leads to A-T mutation in place of the original G-C), and base analogs are replaced by the same mechanism.

- Since uracil, hypoxanthine, xanthine and oxidized and alkylated bases are foreign to DNA; they are recognized and removed from the DNA strand by **specific-DNA N-glycosylases** that cut the bond between the deoxyribose and the base leaving **apyrimidinic** or **apurinic** (AP) site.

- An **AP-endonuclease** cleaves the two phosphodiester bonds to remove the sugar residues.
- Then, DNA polymerase I (or β) inserts the proper nucleotide, dictated by the base on the undamaged complementary strand.
- Then, the deoxyribose-phosphate backbone is rejoined by a Ligase.
- Since this system introduces single strand break, it is also important in repair of the single strand break and is deleterious if became over-functional.
- Irreparable AP sites decay to single-strand breaks

Base excision repair

Damaged base



Base excision repair pathway (BER).

(a) A DNA glycosylase recognizes a damaged base and cleaves between the base and deoxyribose in the backbone.

(b) An AP endonuclease cleaves the phosphodiester backbone near the AP site.

(c) DNA polymerase I initiates repair synthesis from the free 3' OH at the nick, removing a portion of the damaged strand (with its 5'→3' exonuclease activity) and replacing it with undamaged DNA.

(d) The nick remaining after

AP = apurinic or apyrimidinic (a = without)

Base Excision Repair (BER)

20

- The steps and some key players:
 1. Removal of the damaged base (estimated to occur some **20,000 times a day** in each cell in our body!) by a **DNA glycosylase**.
 - We have at least 8 genes encoding different DNA glycosylases each enzyme responsible for identifying and removing a specific kind of base damage.

2. Removal of its **deoxyribose phosphate** in the backbone, producing a gap.

- We have two genes encoding enzymes with this function.

3. Replacement with the correct nucleotide.

- This relies on DNA polymerase beta, one of at least 11 DNA polymerases encoded by our genes.

4. **ligation of the break in the strand.**

- Two enzymes are known that can do this; both require ATP to provide the needed energy.

Nucleotide Excision Repair (NER)

22

- **NER differs from BER in several ways.**
 - It uses different enzymes.
 - Even though there may be only a single "bad" base to correct, its nucleotide is removed along with many other adjacent nucleotides; that is, NER removes a large "patch" around the damage.

The steps and some key players:

23

1. The damage is recognized by one or more protein factors that assemble at the location.
2. The DNA is unwound producing a "bubble". The enzyme system that does this is **Transcription Factor IIH**, TFIIH, (which also functions in normal transcription).
3. Cuts are made on both the 3' side and the 5' side of the damaged area so the tract containing the damage can be removed.

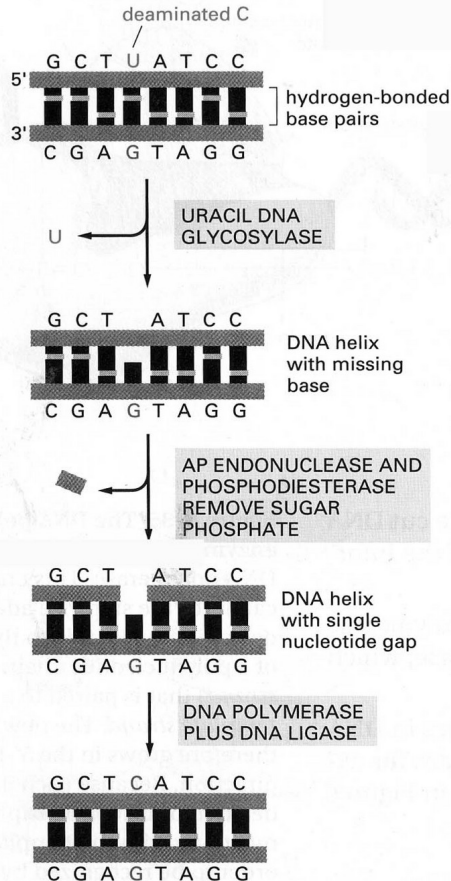
Cont...

24

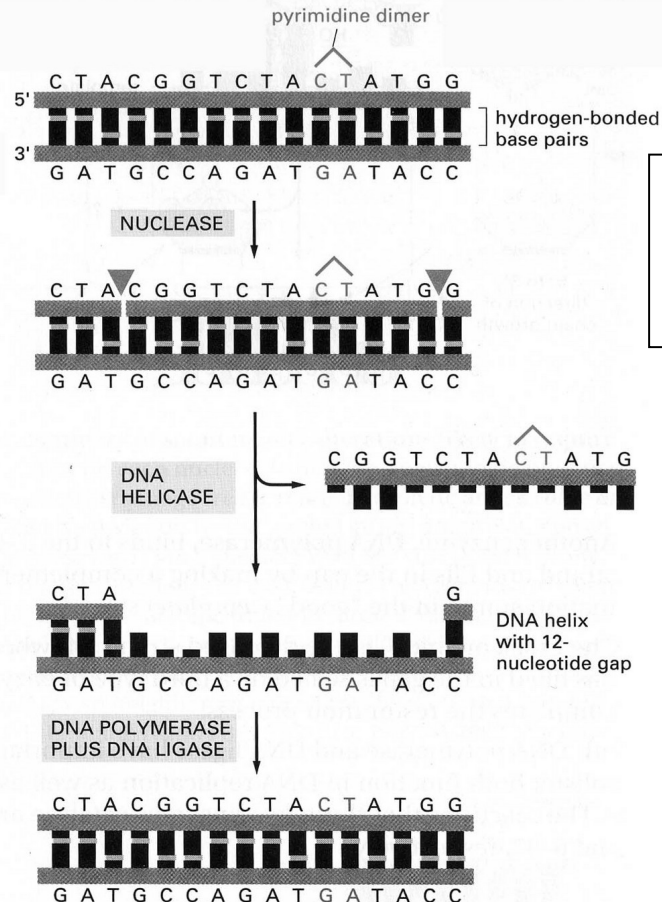
4. A fresh burst of DNA synthesis using the intact (opposite) strand as a template fills in the correct nucleotides.
 - The DNA polymerases responsible are designated polymerase delta and epsilon.
5. A DNA ligase covalent binds the fresh piece into the backbone.

Two pathways of increasing complexity

Base Excision repair



Nucleotide Excision repair



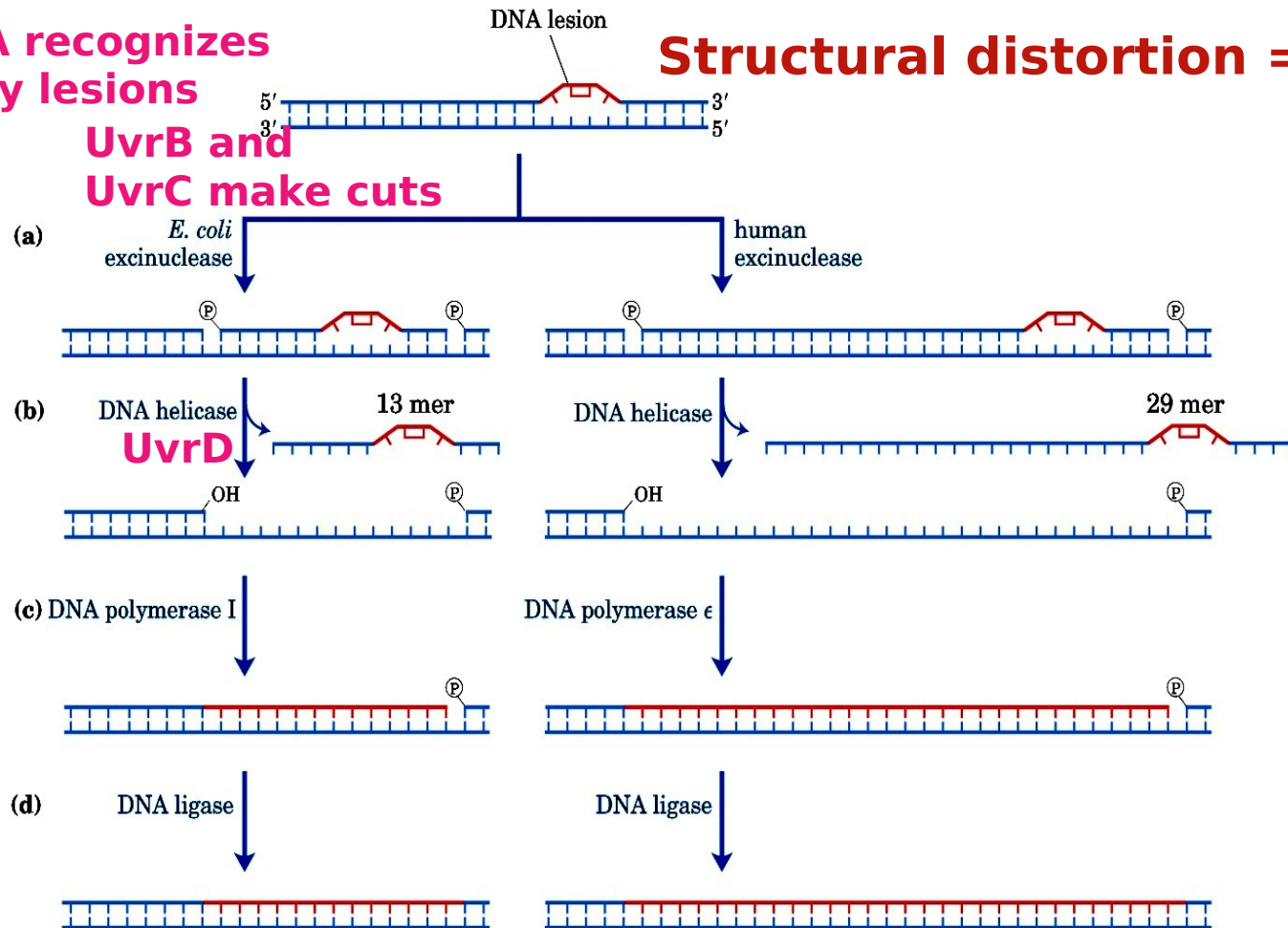
Comparison of two major DNA repair pathways. (A) *Base excision repair*. This pathway starts with a DNA glycosylase. Here the enzyme uracil DNA glycosylase removes an accidentally deaminated cytosine in DNA. After the action of this glycosylase (or another DNA glycosylase that recognizes a different kind of damage) the sugar phosphate with the missing base is cut out by the sequential action of AP endonuclease and a phosphodiesterase, the same enzymes that initiate the repair of depurinated sites. The gap of a single nucleotide is then filled by DNA polymerase and DNA ligase. The net result is that the U that was created by accidental deamination is restored to a C. The AP endonuclease derives its name from the fact that it recognizes any site in the DNA helix that contains a deoxyribose sugar with a missing base; such sites can arise either by the loss of a purine (*apurinic* sites) or by the loss of a pyrimidine (*apyriminic* sites). (B) *Nucleotide excision repair*. After a multienzyme complex recognizes a bulky lesion such as a pyrimidine dimer (see Figure 6-34B), one cut is made on each side of the lesion, and an associated DNA helicase then removes the entire portion of the damaged strand. The multienzyme complex in bacteria leaves the gap of 12 nucleotides shown; the gap produced in human DNA is more than twice this size.

Nucleotide excision repair

UvrA recognizes bulky lesions

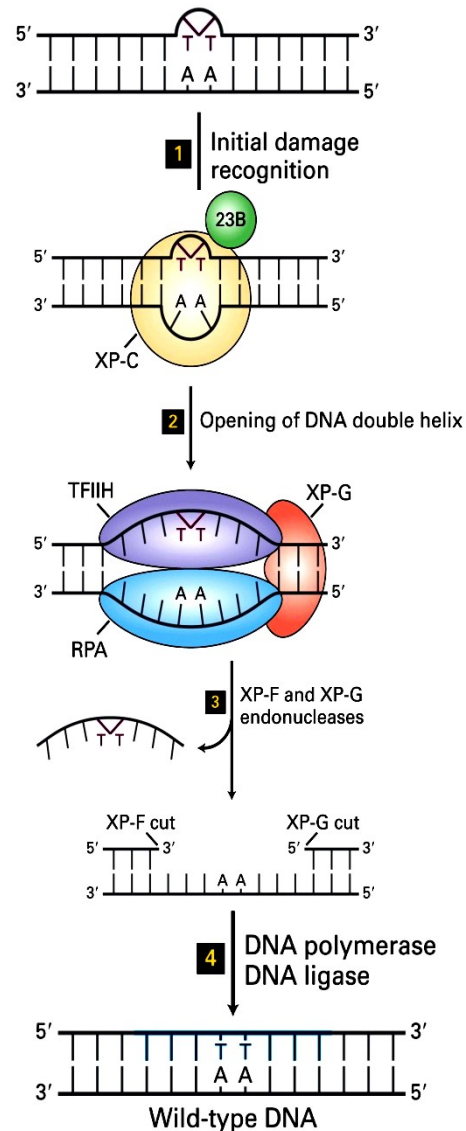
UvrB and UvrC make cuts

Structural distortion = signal



(a) Two excinucleases (excision endonucleases) bind DNA at the site of bulky lesion. (b) One cleaves the 5' side and the other cleaves the 3' side of the lesion, and the DNA segment is removed by a helicase. (c) DNA polymerase fills in the gap and (d) DNA ligase seals the nick.

Nucleotide excision repair -- eukaryotes



Mutations in any of at least seven genes, *XP-A* through *XP-G*, cause an inherited sensitivity to UV-induced skin cancer called xeroderma pigmentosum. The XP proteins are among **>30** required for

Mismatch Repair (MMR)

28

- Mismatch repair deals with correcting mismatches of the normal bases; that is, failures to maintain normal Watson-Crick base pairing (A•T, C•G)
- It can enlist the aid of enzymes involved in both **base excision repair** (BER) and **nucleotide-excision repair** (NER) as well as using enzymes specialized for this function.
 - Recognition of a mismatch requires several different proteins including one encoded by MSH2.

Mismatch Repair cont....

29

- **Mismatch**, e.g., G-T pairing, is due to copying errors during replication that may also lead to 1 to 5 bases unpaired loops due to slippage of polymerase, which can produce frameshift mutations.
- This system can correct A–C and T–C mismatches more efficiently than G–A and T–C mismatches, and is very poor correcting C–C mismatches.
- Mismatch repair plays a **significant role** in protecting against incorporation of 8–hydroxy/8–oxoguanosine into DNA.

Miss match cont...

30

- In bacteria, the mismatch is recognized by a group of proteins called **MutS**, **MutL** and **MutH** (a GATC endonuclease, plus 5 more protein in eukaryotes) that scan the newly synthesized DNA strand and identify the parent DNA strand (old) by its **methylation** at adenine in the GATC sequences (the new strand is not methylated yet and is discontinuously synthesized)
- Once they have located the mismatch or unpaired DNA sequence, they nick the defective new DNA strand at either 3' or 5' side of the defect corresponding to the old strand GATC sequence flanking the defect.

- A special exonuclease (exonuclease 1) hydrolyzes DNA in 3'=>5' or 5'=>3' direction to a few nucleotides after the defect and releases free DNA nucleotides.
- A new DNA is synthesized to fill the gap by **DNA polymerase III** and **DNA ligase** joins the 3'-end of the new DNA and the 5'-end of the DNA ahead of the defect.
- Defects in hMSH2 and hMLH1 human homologues of these MutS and MutL proteins lead to specific hereditary type of cancer, e.g., hereditary non-polyposis colorectal cancer.
- In this disease defective repair leads to failure of removal of unpaired DNA sequence and hence microsatellite expansion and instability.
- This culminates into defective cell cycle control and cancer.

Mismatch repair -- Recognition

Which strand is new and which is the parent? The mutation is in the new strand!

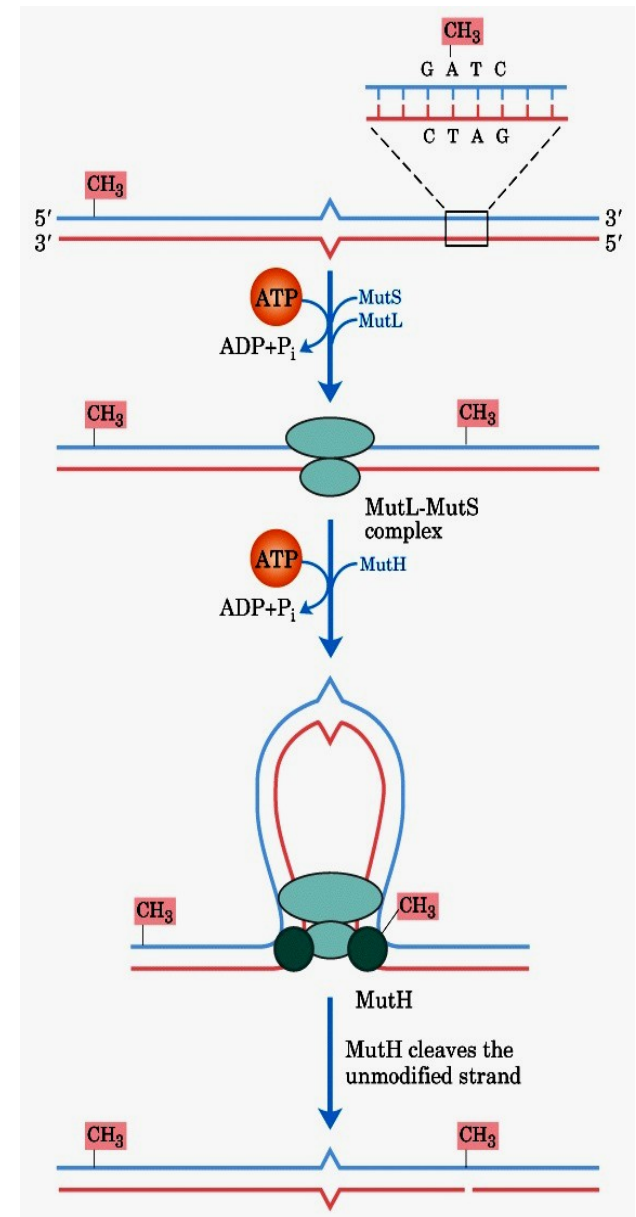
A-CH₃ marks the parental strand!

MutS - Binds mismatch

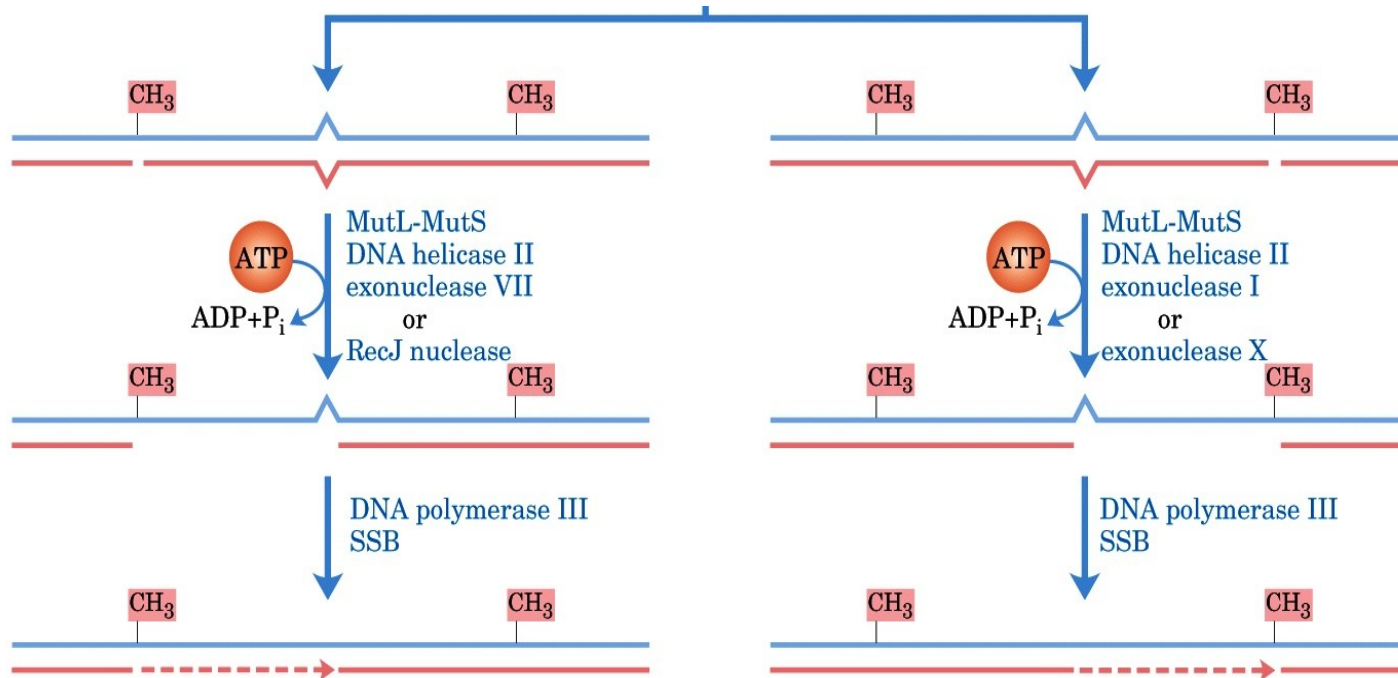
MutL - links MutH and MutS

MutH - Binds G^{me}ATC

DNA is threaded through the MutS/MutL complex. The complex moves simultaneously in both directions along the DNA until it encounters a MutH protein bound at a **hemimethylated** GATC sequence. MutH cleaves the **unmethylated** strand on the 5' side of the G in the GATC



Mismatch repair -- Resolution



1. The combined action of DNA helicase II, SSB, and one of many different **exonucleases** (only two are labeled) removes a segment of the new strand between the MutH cleavage site and a point just beyond the mismatch.
2. The resulting gap is filled in by **DNA polymerase III**, and the nick is sealed by **DNA ligase**.

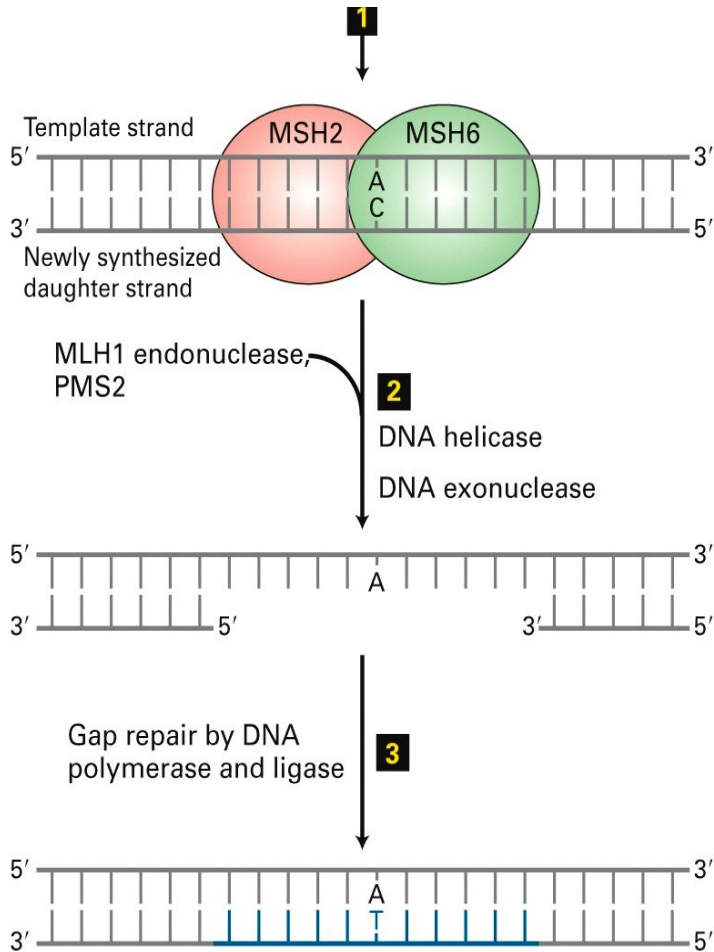
Cont...

34

- Cutting the mismatch out also requires several proteins, including one encoded by MLH1.
- Mutations in either of these genes predispose the person to an inherited form of colon cancer. So these genes qualify as tumor suppressor genes.
- Synthesis of the repair patch is done by the same enzymes used in NER: **DNA polymerase delta** and **epsilon**.
- Cells also use the MMR system to enhance the fidelity of recombination; i.e., assure that only homologous regions of two DNA molecules pair up to crossover and recombine segments (e.g., in meiosis).

Mismatch repair -- MSH proteins -- eukaryotes

Defects in mismatch excision repair lead to colon and other cancers.



1. MSH2:MSH6 complex binds the mismatch and identifies newly synthesized strand.
2. MLH1 endonuclease and other factors such as PMS2 bind, recruiting a **helicase and exonuclease**, which together remove several nucleotides including the lesion.
3. The gap is filled by Pol δ and sealed by DNA ligase.

Repairing Strand Breaks

36

- Ionizing radiation and certain chemicals can produce both **Single-strand Breaks** (SSBs) and **Double-strand Breaks** (DSBs) in the DNA backbone.
- **Single-Strand Breaks (SSBs):**
 - Breaks in a single strand of the DNA molecule are repaired using the same enzyme systems that are used in Base-Excision Repair (BER).
- **Double-Strand Breaks (DSBs):**
 - There are two mechanisms by which the cell attempts to repair a complete break in a DNA molecule:

- Although double-strand breaks are rare, they are difficult to repair and can be very injurious for dividing somatic cells.
- Repair of double-strand damage in mammals can best occur during meiosis division of germ cells when homologous pairs of chromosomes line-up, where as, complementary pairs don't typically line-up very well in somatic cells

Double strand breaks are repaired by two mechanisms:

38

I. **Non-Homologous End-Joining,**

- the simplest but is the least accurate due to rejoining the two broken ends without regard to deletions or rearrangements.

II. **Homologous Recombination (or Recombinational Repair),**

- Which is less frequently used but more accurate by exactly reconstituting the original sequence because the homologous chromosome or sister **chromatid** is used as template.

- **In direct joining of the broken ends** requires proteins that recognize and bind to the exposed ends and bring them together for **ligating**.
- They would prefer to see some complementary nucleotides but can proceed without them so this type of joining is also called **Nonhomologous End-Joining** (NHEJ).
- Errors in direct joining may be a cause of the various translocations that are associated with cancers.
- **Examples:**
 - Burkitt's lymphoma
 - the Philadelphia chromosome in chronic myelogenous leukemia (CML)
 - B-cell leukemia

- **Homologous recombination** is the dominant method used in the S and G2 phases of the cell-cycle, after a sister chromatid has been created.
- Homologous pairing of the sister chromatids is often mediated by Rad51 protein, which is normally necessary for cell proliferation and survival.
- Rad52 protein recognizes the double strand breaks and adheres to the free ends of the break while Rad51 searches the undamaged sister chromatid for a homologous repair template.
- The tumor suppressor protein BRCA2 co-localizes with Rad51 during homologous recombinational repair, and contributes significantly to its activity.
- Homologous recombination could be a basis for telomerase-independent telomere lengthening in mammals.
- .

Diseases related to defective repair of DNA damage

41

- **Xeroderma Pigmentosum:** It is an autosomal recessive disease.
 - It is due to defective repair of **nucleotide excision repair** caused by mutation of at least 7 genes called XPA –XPG with helicase, recognition and excision activities, which also are subunits in the basic transcription machinery.
 - Patients are highly sensitive to sunlight or UV light and their skin is damaged and is liable for multiple cancer, immunodeficiency, atrophy and scarring of eyelids, ulcerated cornea, and/or progressive neurological degeneration and may lead to premature death.

12/18/25

- **Ataxia Telangiectasia:** it is caused by autosomal recessive mutations in the ATM gene (for ataxia-telangiectasia mutated), a protein kinase known to be an 'early responder' to double-stranded DNA breaks leading to increased sensitivity to X-ray-induced damage.
- In presence of such DNA damage, normal ATM protein (mainly acting through p53 protein) blocks progression through the cell cycle to induce repair or apoptosis. Cells of AT patients are resistant to apoptosis and do not undergo cell cycle arrest when subjected to ionizing radiation.
- Cerebellar degeneration, immunodeficiency, sterility, increased risk of cancer of the reticulo endothelial system and genomic instability are the characteristics of the disease. Patients have a life span of only about 20 years

□ **Fanconi's Anemia:**

- It is an autosomal recessive anemia associated with increased susceptibility to malignant neoplasms and chromosomal instability. It is due to failure of correction of cross-linkage damage.

□ **Hereditary Non-polyposis Colorectal Cancer (HPPC) and Other Types of Cancer:**

- It is Lynch syndrome in which patients develop cancer in the colon along with cancer of stomach and/or uterus.
- It is due to defective DNA mismatch repair due to mutations in two genes, hMSH2 and hMLH1 (human analogs of MutS and L).
- It has an autosomal dominant pattern of inheritance with cancer at early age that also affects ovary

Mutation

44

- Mutation is the alteration of DNA sequence, whether as small as the alteration of a single base pair, or as gross event as the gain or loss of an entire chromosome.
- Therefore, mutation could be a **gene mutations** (sequence alteration); **chromosome mutations** (structural aberrations in the chromosomes) and/or genome mutations (numerical aberrations in the chromosomes).

- It is mostly due to **damaging chemicals or radiation, faulty replication** ($\sim$ one mutation/ 10^6 bp), **repair of DNA**; and **abnormal recombination** and **segregation of the chromosomes**.
- The fate of these alterations include: **an altered gene product** (function and/or amount) and/or regulation, or a change in gene copy number and dose due structural or numerical abnormality in chromosomes and genomic instability.

- **Germ cell mutation** is vertically heritable,
- **Somatic cell mutation** affects daughter cells within the organism (horizontal transmission) and is not heritable.
- Inborn errors are due to heritable mutations whereas; other diseases like cancer and aging are due to vertically and horizontally acquired mutations.

Factors that increase the natural rate of mutation

47

- A. Physical (most common) such as: UV, X and γ radiations.
- B. Chemical carcinogens such as anticancer base analogs and alkylating agents. Of chemicals known to be mutagenic in bacteria 85% are carcinogenic (cancer-causing) in animals - the basis of the Ames test for carcinogenicity.
- C. Environmental pollutants-derived oxidative free radical such as nitrous acid.
- D. Genetic genomic instability, errors of DNA replication and defective repair.
- E. Viral infections such as retroviruses and oncogenic viruses.

Types and Mechanism of DNA mutations:

48

- DNA mutations can be divided into five categories depending upon the number of nucleotides or the type of defect.

a) Single base alteration (point mutation):

49

1. **Deamination**, e.g., adenine into hypoxanthine and cytosine into uracil.
2. **Depurination or depyrimidination**, i.e., removal of a purine or a pyrimidine base from the nucleotide leaving an exposed deoxyribose attached to the sugar-phosphate backbone. It is due to hydrolysis or thermal disruption or carcinogens such as aflatoxins.
3. **Alkylation** of a base (mostly guanine) by covalent addition of an alkyl radical (e.g. - CH₃).

Cont..

50

3. Oxidative conversion of deoxyguanosine into 8-hydrox- rearranged into 8-oxodeoxyguanosine, which base pairs with A leading to GC-AT conversion.

4. Insertion or deletion of a nucleotide.

5. Base-analog incorporation

b) Two bases alteration:

- UV-induced thymine-thymine dimer.
- Cross linkage caused by **bifunctional alkylating** agent.

C. Strand breakage:

51

- **Single-strand breaks** are less harmful than **double strand breaks** in the **phosphodiester** backbone. The strand breaks are generally caused by:
 1. Ionizing radiation.
 2. Radioactive disintegration of incorporated element(s).
 3. Oxidative free radical formation.
 4. Very high doses of alkylating carcinogens such as nitrogen mustards.
 5. DNA-strand breaking chemotherapeutic agents, e.g., cisplatin.

D. Cross-linkage:

52

1. Two bases in same strand or opposite strands.
2. DNA cross-linkage to histones or other proteins.

E. Chromosomal structural and number abnormalities:

- Due to faulty segregation; recombination or gross damage.
- These gross chromosomal changes are out of the scope of this book.

Point mutations:

- **Definition and types:**

- Change/alteration of a **single base** in DNA is known as **point mutation**. These mutations are either of three types:

1. **Homologous** i.e. **Transitions**: where a purine base is changed to another purine base e.g. adenine into guanine or a pyrimidine base to another pyrimidine base e.g. thymine into cytosine. Or,
2. **Heterologous** i.e. **transversion**: a purine base is changed into a pyrimidine base and vice versa.
3. **Shift in the trinucleotide reading frame**, i.e., frame shift mutation is due to deletion or insertion of a number of nucleotides not divisible by three.

Fate (or effect) of point mutation:

54

□ **Silent mutation**

- the changed base leads to a codon, which produces the same amino acid due to degeneracy of the genetic code.
- In this case, the change lies in the **third base** of the codon, which differs among codon synonyms for the same amino acid.

No change

Normal gene

GGTCTCCTCACGCCA



CCAGAGGAGUGCGGU
Codons



Pro-**Glu**-Glu-Cys-Gly
Amino acids

Substitution mutation

GGTCT**T**CTCACGCCA



CCAGA**A**GAGUGCGGU



Pro-**Glu**-Glu-Cys-Gly

□ Missense mutation

- the change occurred either in first or second base of the codon producing a different amino acid.
- The effect of missense mutation on the protein produced is dependent on the position and nature of the replacement amino acid.
- The protein could be normally functioning (i.e., an **acceptable** miss-sense mutation) such as **hemoglobin Milwaukee**, which has **glutamic acid** at position 67 of β -chain in stead of the normal **valine**; **hemoglobin Bristol**, which has instead an aspartic acid.
- Or, the mutation could be **partially acceptable** because the product will be partially functioning, e.g., **Sickle cell anemia**.

- **Sickle cell anemia or hemoglobin S** - an autosomal recessive disease with two normal β -chains but two abnormal β -chains, where an abnormal valine replaces the normal glutamate position 6.
- It is partially accepted because HbS binds and releases O_2 , although inefficiently and become misfolded, sticky, polymerizes and precipitate as long fibers when deoxygenated and at low O_2 concentrations

- **missense** mutation could be **unacceptable** because it produces a **non-functioning protein** or leads to complete loss of the protein because of defective RNA processing
 - Example is **methemoglobinemia** (Hb M or Boston) due to replacement of histidine 58 (F8) with tyrosine of the α -chains with Fe^{3+} and inability to bind O_2 .
 - Methemoglobinemia is caused also by hereditary deficiency of the NADH-dependent methemoglobin reductase that reduces Fe^{3+} into Fe^{2+} and by oxidizing agents such as sulfonamides.

Mutations: Substitutions

Normal gene

GGT CTC CTC ACG CCA



CCAGAGGAGUGCGGU
Codons



Pro-Glu-Glu-Cys-Gly

Amino acids

Substitution mutation

GGT C**AC** CTC ACG CCA



CCAG**U**GGAGUGCGGU



Pro-**Arg**-Glu-Cys-Gly

Substitutions will only affect a single codon
Their effects may not be serious unless they affect an amino acid that is essential for the structure and function of the finished protein molecule (e.g. sickle cell anaemia)

Non-sense mutation

60

- the altered base results in a “**non-sense**” or termination codon.
- This leads to pre-mature stopping of protein synthesis thus releasing a truncated protein or no protein is produced at all.
- Example of truncated protein is c-erbB2 oncogene.

Normal gene

GGTCTCCTCACGCCA



CCAGAGGAGUGCGGU

Codons



Pro-Glu-Glu-Cys-Gly

Amino acids

Substitution mutation

GGTCTCCTCAC**T**CCA



CCAGAAGAGUG**A**GGU



Pro-Glu-Glu-**STOP**

Frame shift mutation

62

- Is reported in the Hb genes causing β -thalassemia and BAX gene in ovarian cancer. Shifting results:
- **Intron-exon splice junction mutations**, e.g., β -globin gene leading to some types of β -thalassemia.
- **Truncated protein** if a non-sense codon is developed due to the shift.
- **Garbled translation** into totally different protein downstream the shift.
- A protein may not be produced at all because mRNA is degraded.

12/18/25

- Insertion or deletion of a number of nucleotides divisible by three produces a protein with an extra or lacking an amino acid(s).
- It has a moderate effect on the produced protein. However, the most common mutation in cystic fibrosis is deletion of amino acid number 508 (deltaF508, a phenylalanine).

Frameshift Mutation

64

- Original:
 - The fat cat ate the wee rat.
- Frame Shift (“a” added):
 - The fat caa tat eth ewe era t.

Mutations: Additions

A frame shift
mutation

Normal gene

GGTCTCCTCACGCCA



CCAGAGGAGUGCGGU

Codons



Pro-Glu-Glu-Cys-Gly

Amino acids

Addition mutation

GGT**G**CTCCTCACGCCA



CCA**C**GAGGAGUGCGGU



Pro-**Arg-Gly-Val-Arg**

Mutations: Deletions

A frame shift
mutation

Normal gene

GGTCTCCTCACGCCA



CCAGAGGAGUGCGGU

Codons



Pro-Glu-Glu-Cys-Gly

Amino acids

Deletion mutation

GGT**C/C**CTCACGCCA



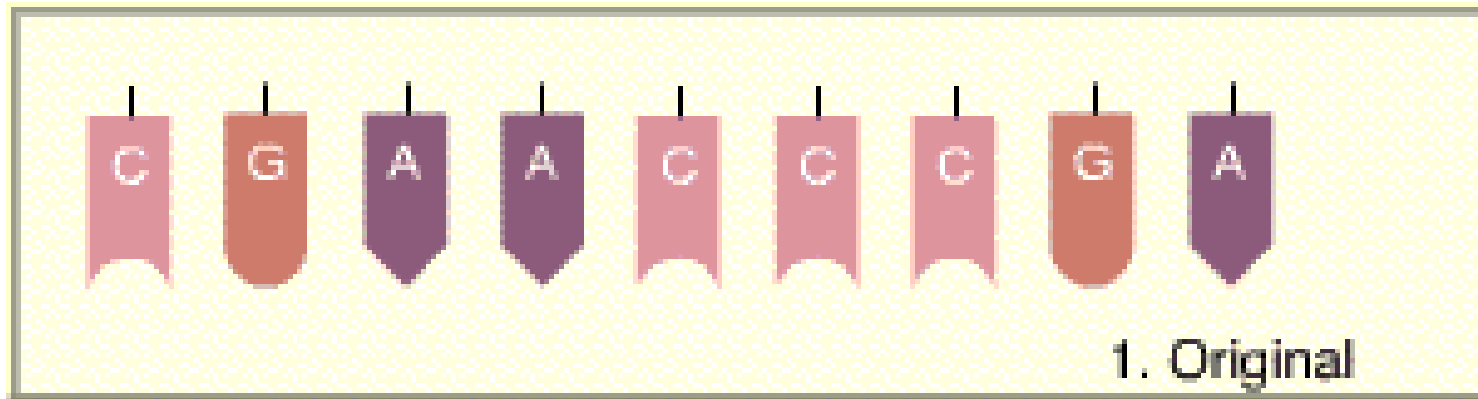
CCA**GG**GAGUGCGGU



Pro-**Gly-Ser-Ala-Val**

Gene Mutation Animation

67



First Base in Codon	Second Base in Codon				Third Base in Codon
	A	G	T	C	
A	phenylalanine phenylalanine leucine leucine	serine serine serine serine	tyrosine tyrosine stop stop	cysteine cysteine stop tryptophan	A G T C
G	leucine leucine leucine leucine	proline proline proline proline	histidine histidine glutamine glutamine	arginine arginine arginine arginine	A G T C
T	isoleucine isoleucine isoleucine methionine	threonine threonine threonine threonine	asparagine asparagine lysine lysine	serine serine arginine arginine	A G T C
C	valine valine valine valine	alanine alanine alanine alanine	aspartate aspartate glutamate glutamate	glycine glycine glycine glycine	A G T C

END