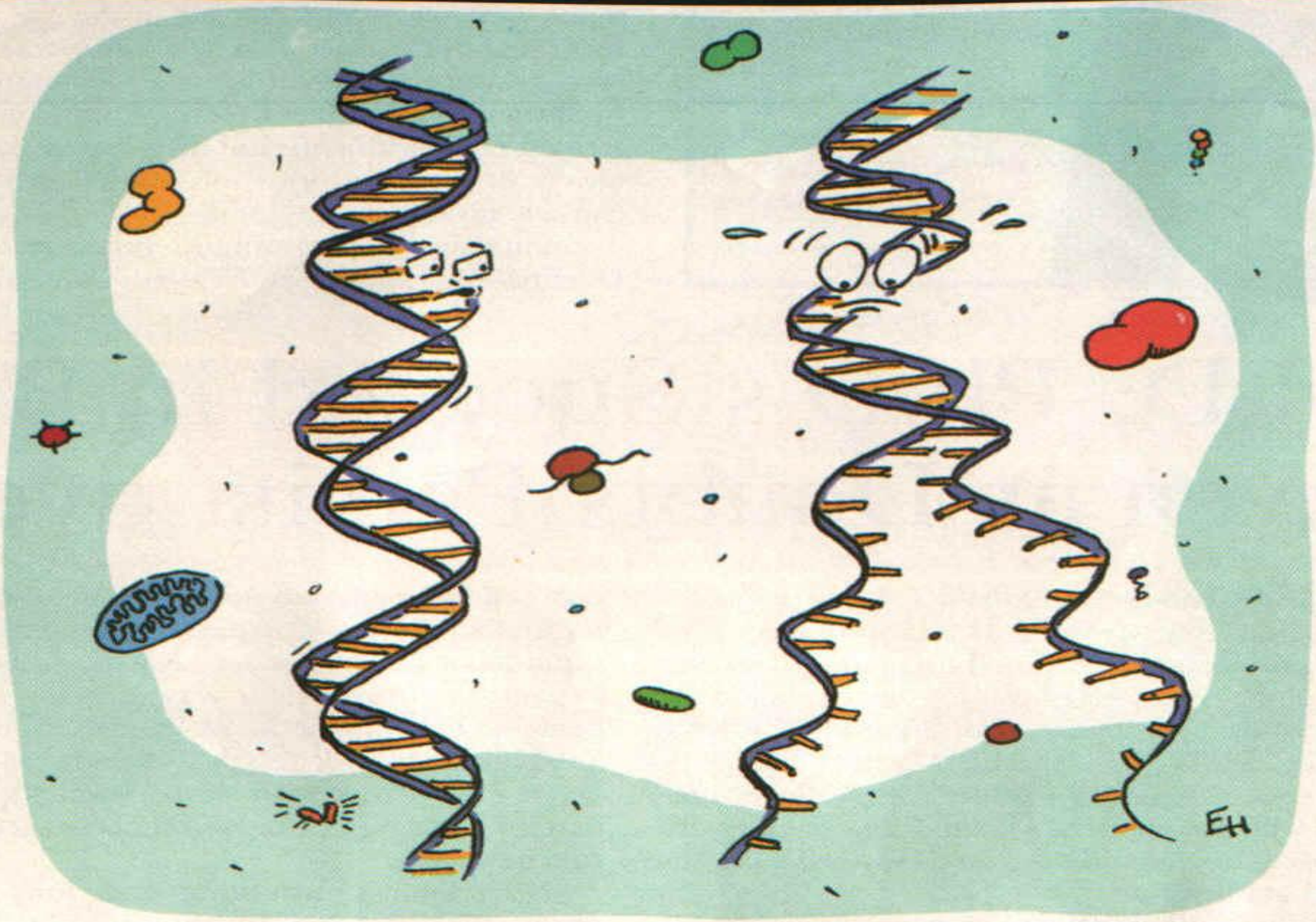
DNA Replication

Rasime Kalkan,PhD.

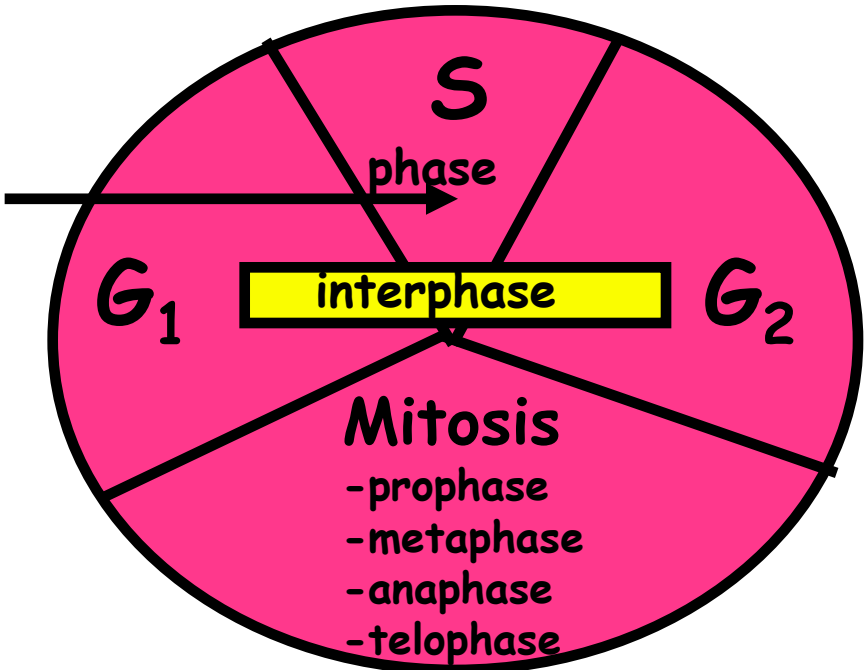


" Psst, Bob...you're unzipped"

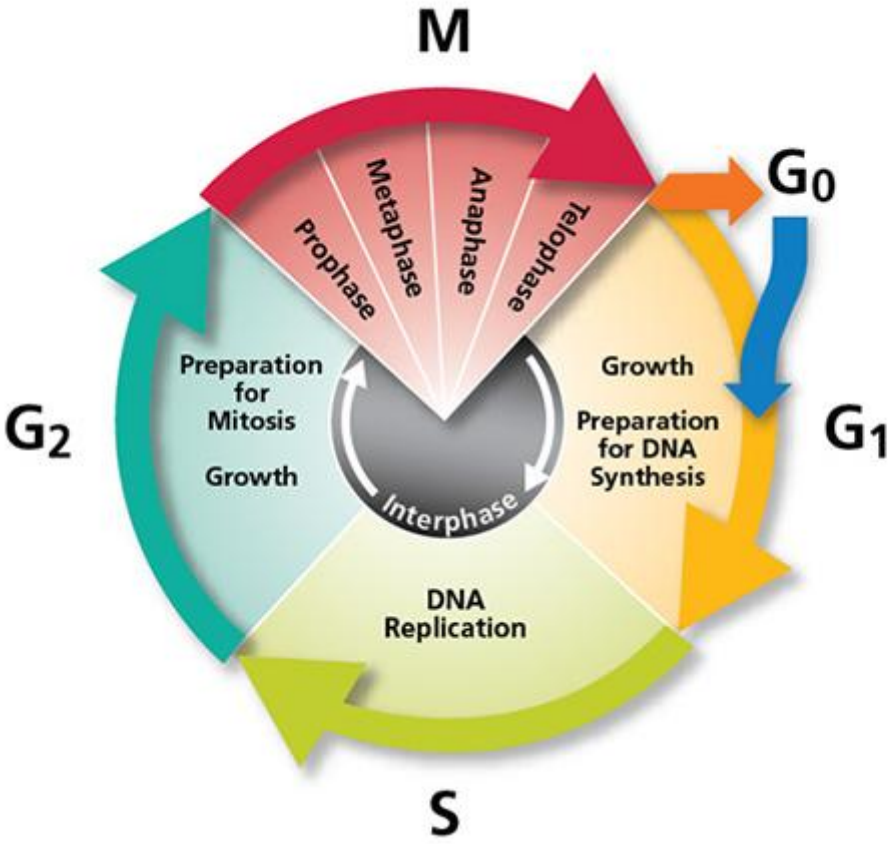
DNA Replication

- The process of copying one DNA molecule into two identical molecules is called **DNA replication**.
- DNA has to be copied before a cell divides
- DNA is copied during the S or synthesis phase of interphase
- New cells will need identical DNA strands

DNA replication takes place in the S phase.



The four standard phases of a eucaryotic cell
DNA replication occurring at S Phase (DNA synthesis phase)
G1 and G2, gap between S and M

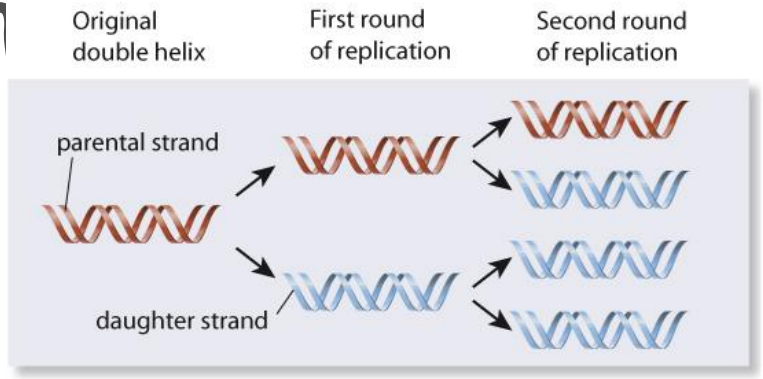


DNA Replication

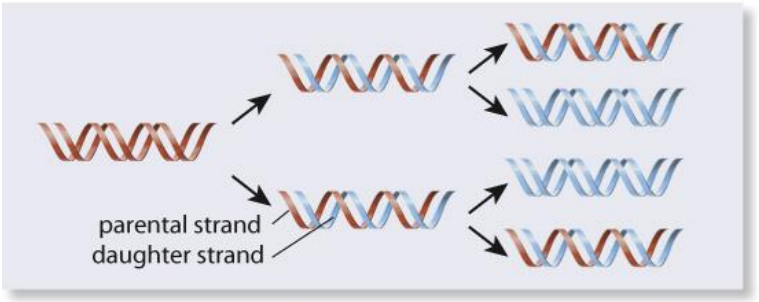
In the mid-1950s, three competing models of DNA replication were proposed:

- conservative model
- semi-conservative model
- dispersive model

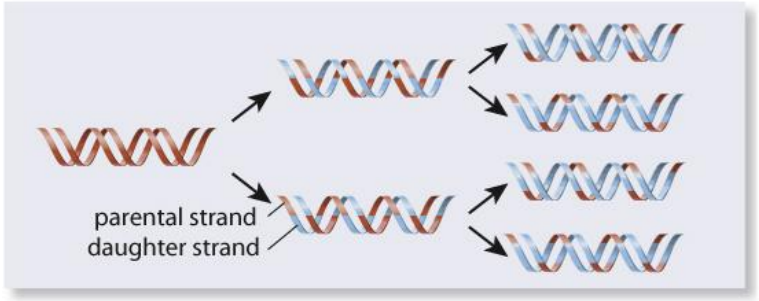
The conservative model results in one new molecule and conserves the old. The **semi-conservative replication** model results in two hybrid molecules of old and new strands. The dispersive model results in hybrid molecules with each strand being a mixture of old and new strands.



Conservative model



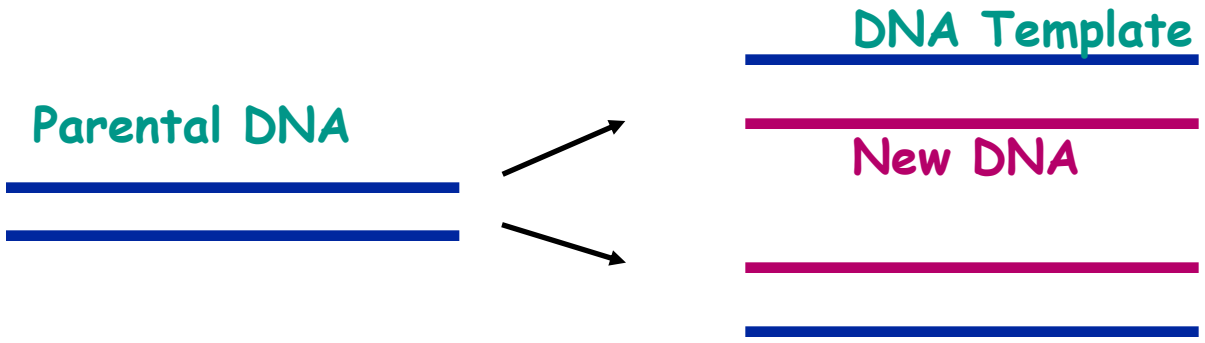
Semi-conservative model



Dispersive model

Semiconservative Model of Replication

- Idea presented by Watson & Crick
- The two strands of the parental molecule separate, and each acts as a template for a new complementary strand
- New DNA consists of 1 PARENTAL (original) and 1 NEW strand of DNA

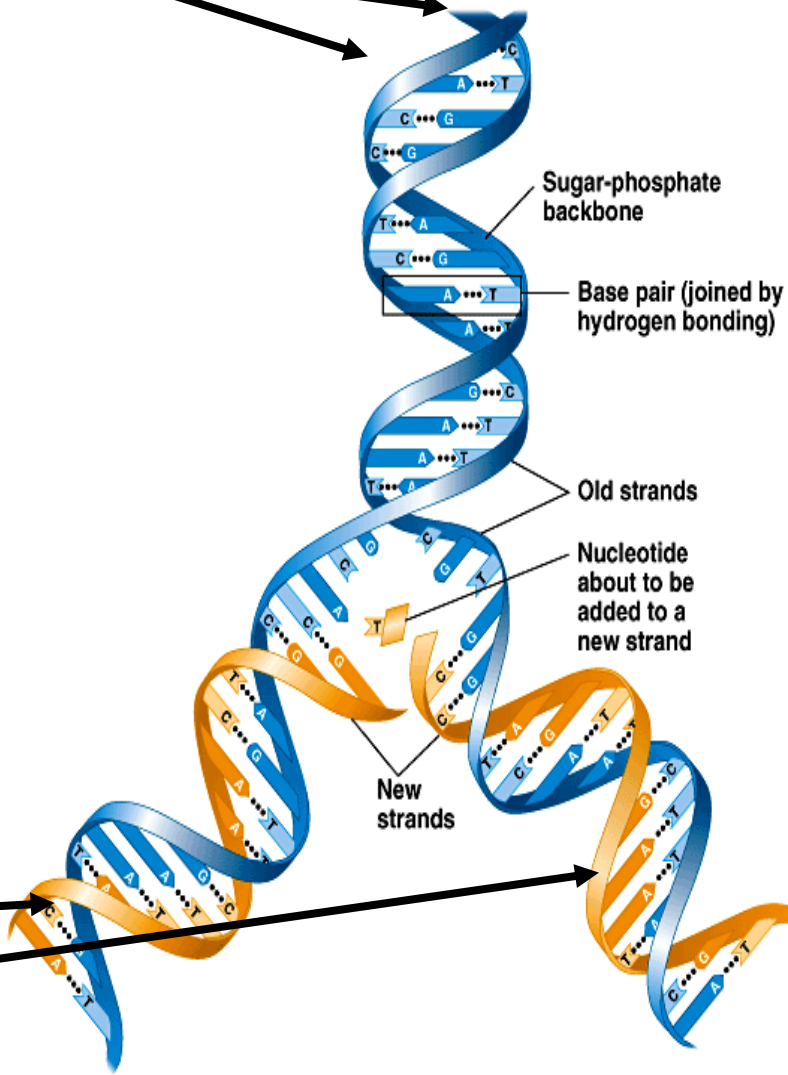


Parental DNA

DNA replication is semi conservative:

1. Parental DNA strands are used as a template for the newly replicated strands

2. Daughter DNA duplexes consist of one strand of parental DNA base paired to the newly replicated strand

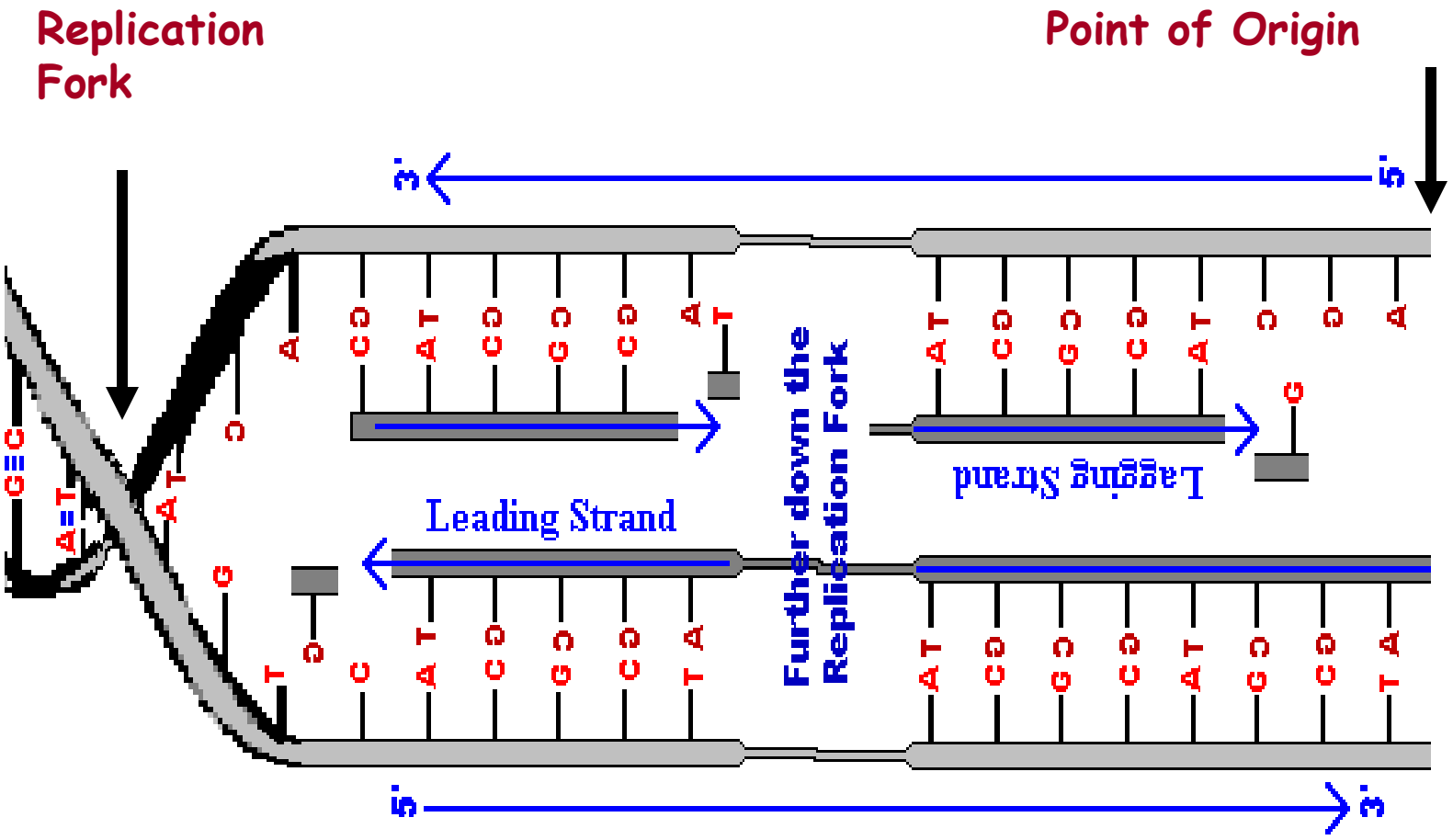


Newly replicated DNA strands

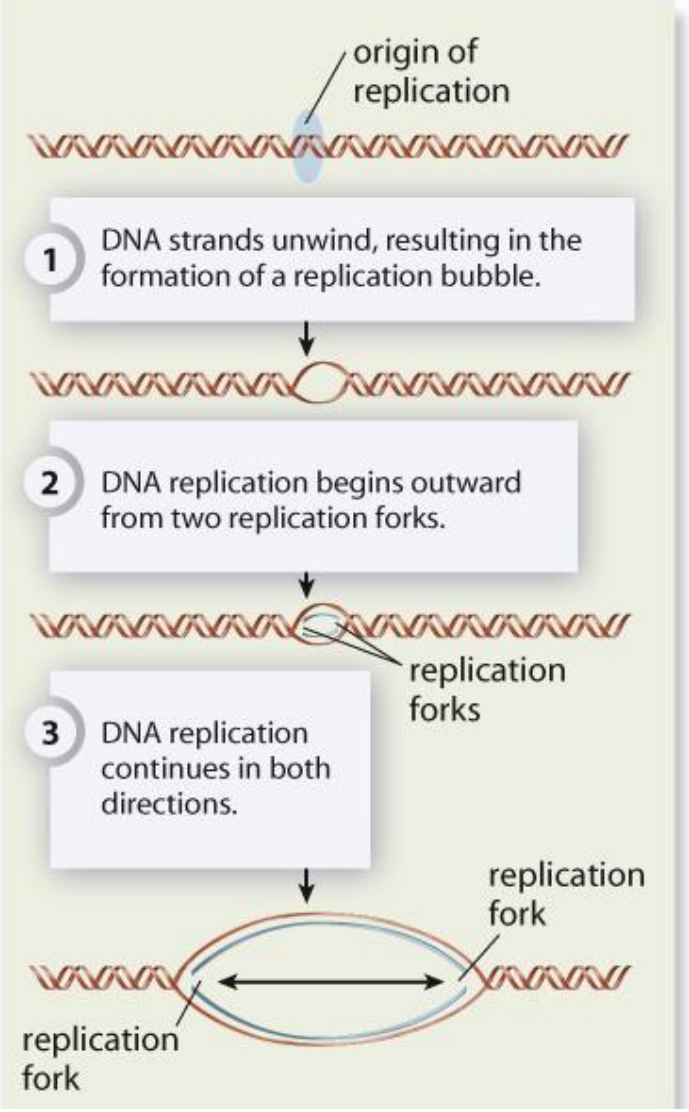
The mechanism of DNA replication

- Tightly controlled process,
- occurs at specific times during the cell cycle.
  - Requires:
- a set of proteins and enzymes,
- and requires energy in the form of ATP.
- Two basic steps:
- Initiation
- Elongation.
  - Two basic components:
- template
- primer

Replication of Strands



DNA Replication



Semi-conservative replication has three phases: initiation, elongation, and termination.

DNA Replication

Topoisomerase - unwinds DNA

Helicase – enzyme that breaks H-bonds

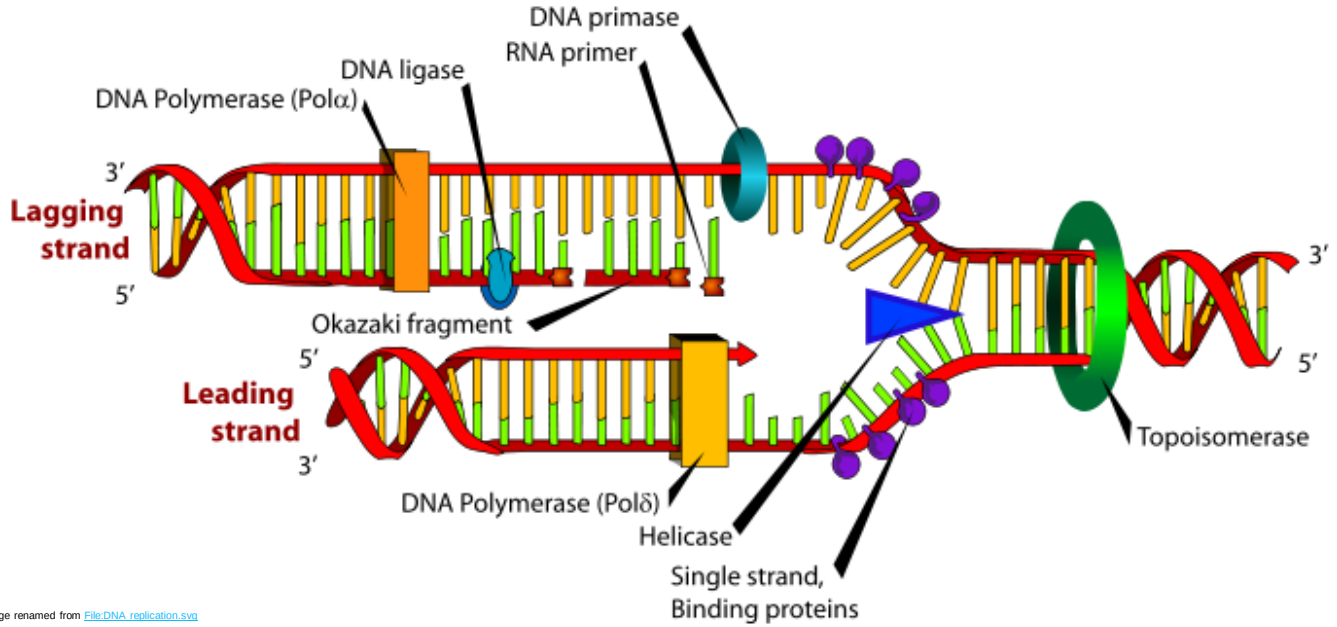
DNA Polymerase – enzyme that catalyzes connection of nucleotides to form complementary DNA strand in 5′ to 3′ direction (reads template in 3′ to 5′ direction)

Leading Strand – transcribed continuously in 5′ to 3′ direction

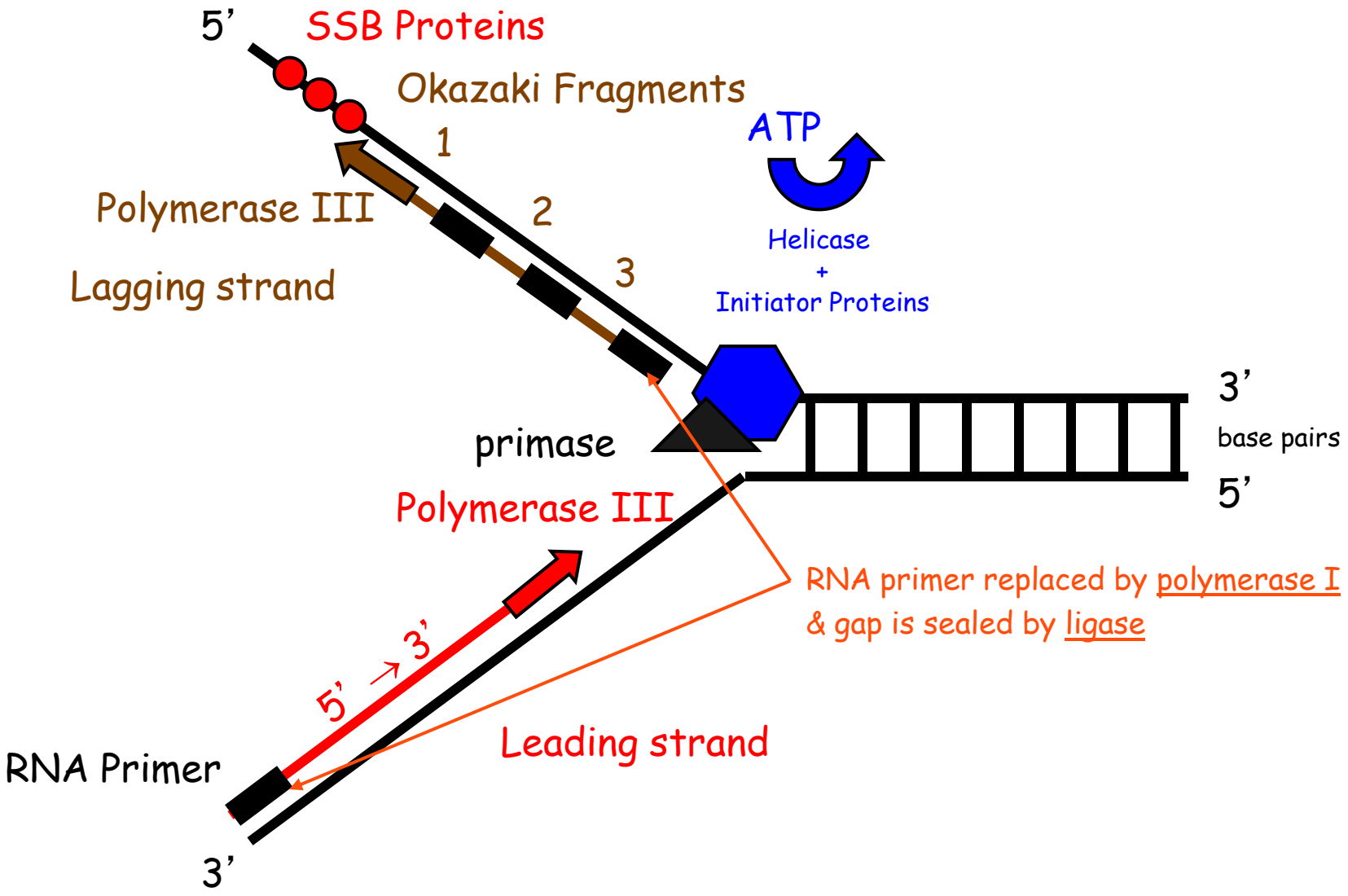
Lagging Strand – transcribed in segments in 5′ to 3′ direction (**Okazaki fragments**)

DNA Primase – enzyme that catalyzes formation of RNA starting segment (**RNA primer**)

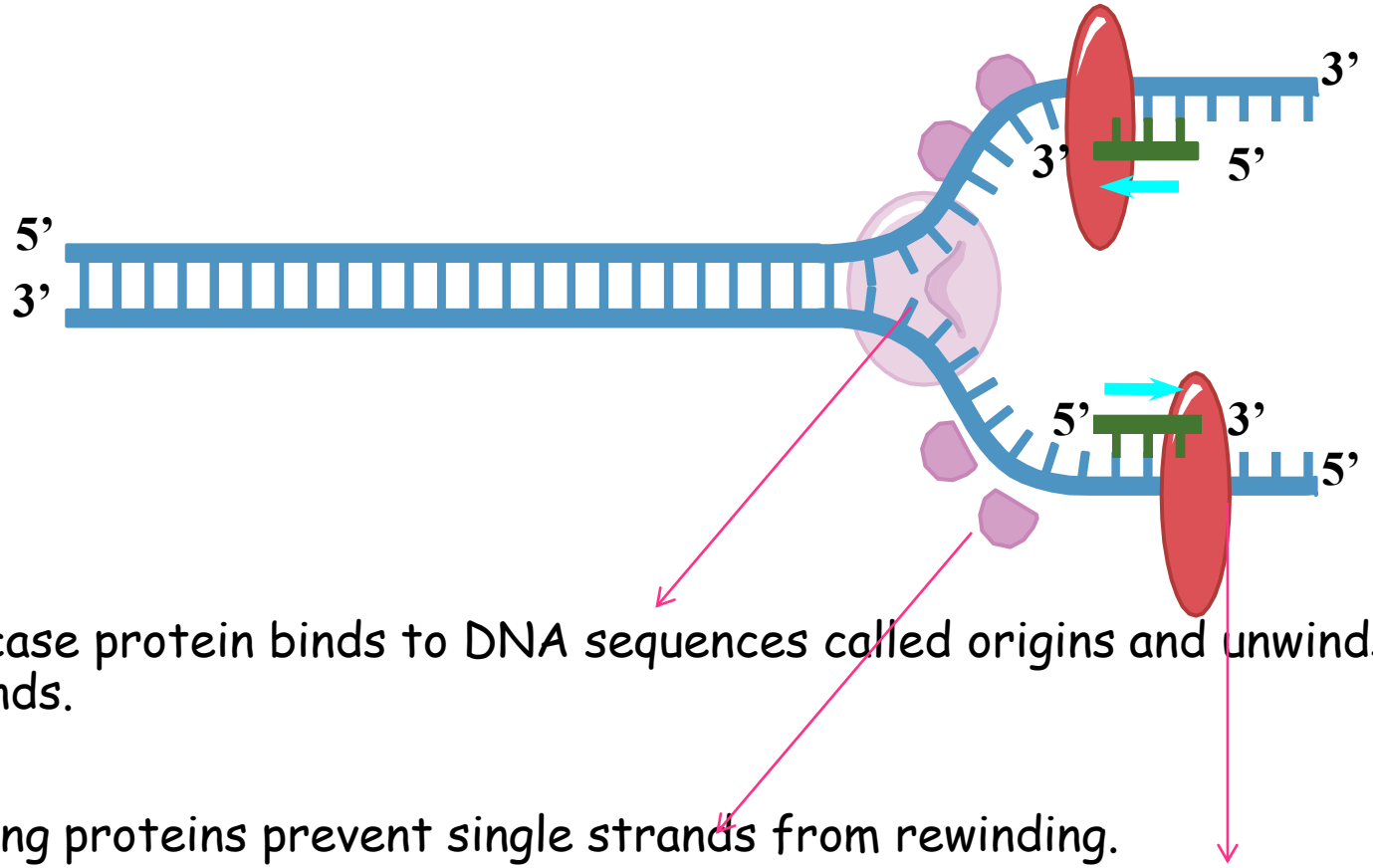
DNA Ligase – enzyme that catalyzes connection of two Okazaki fragments



Supercoiled DNA relaxed by gyrase & unwound by helicase + proteins:



Replication



Helicase protein binds to DNA sequences called origins and unwinds DNA strands.

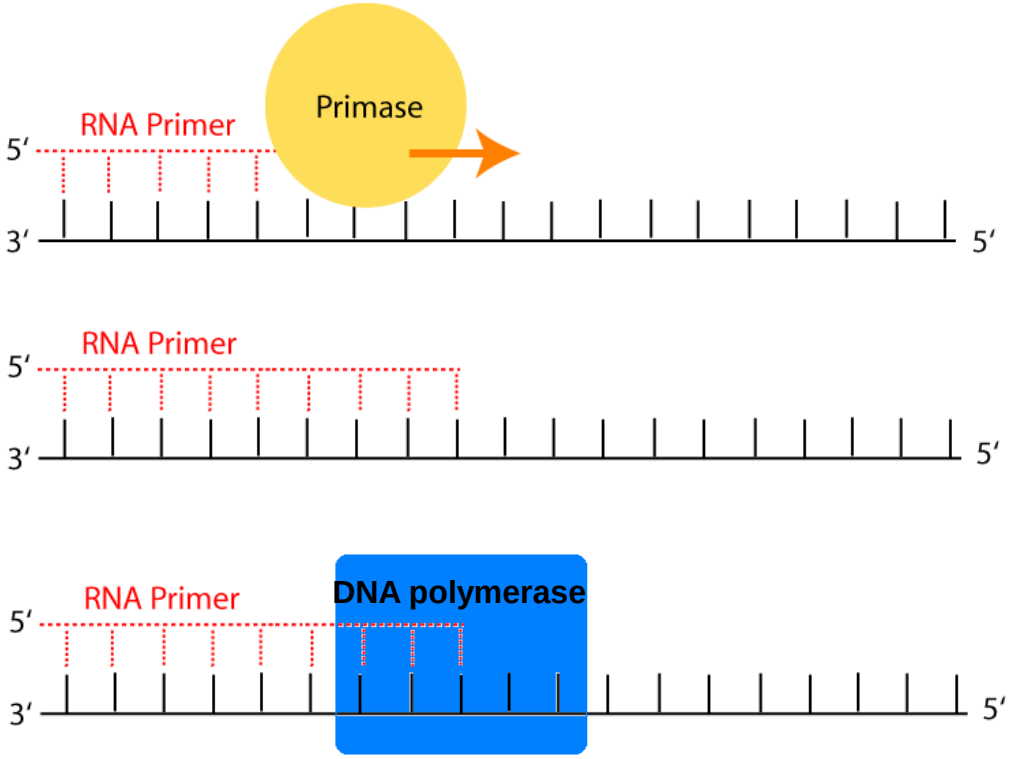
Binding proteins prevent single strands from rewinding.

Primase protein makes a short segment of RNA complementary to the DNA, a primer.

DNA Replication

Initiation

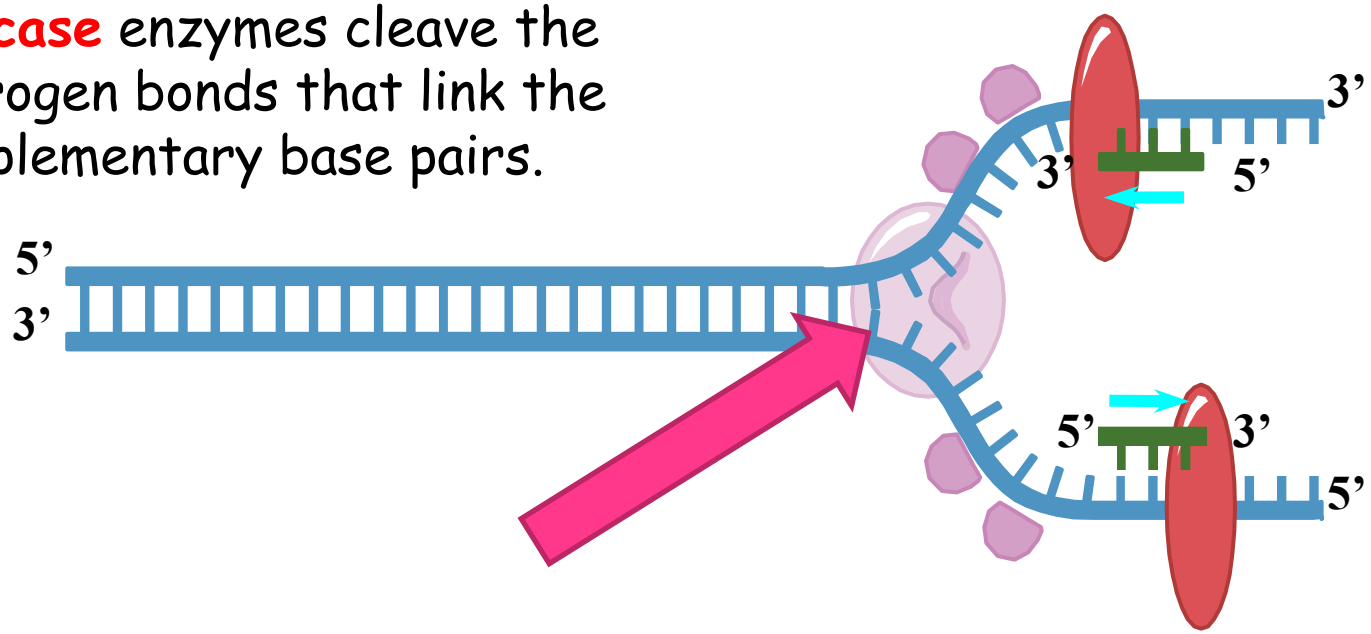
- **Primase** (a type of RNA polymerase) builds an **RNA primer** (5-10 ribonucleotides long)
- **DNA polymerase** attaches onto the 3′ end of the **RNA primer**



Initiation of DNA replication

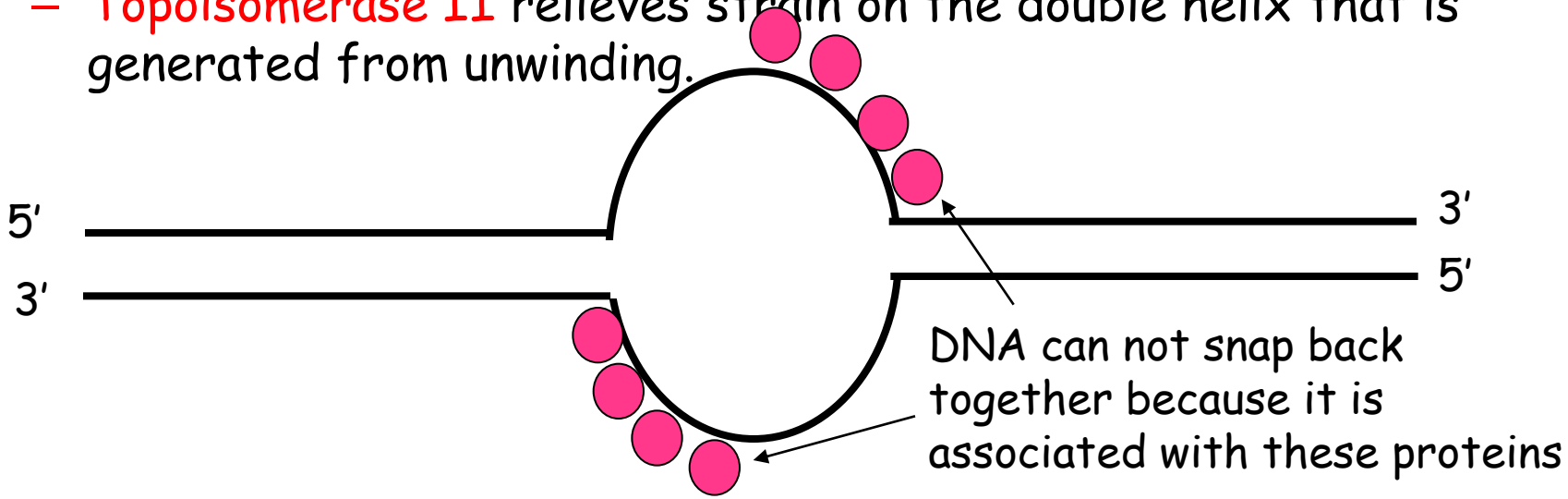
- Step 1 – opening the helix
  - Proteins bind to specific DNA sequences known as origins of replication
    - Bacteria have one
    - Eukaryotes have thousands
    - AT rich regions
      - – Why?
    - Helicases aid in the opening of the helix

- **Helicase** enzymes cleave the hydrogen bonds that link the complementary base pairs.



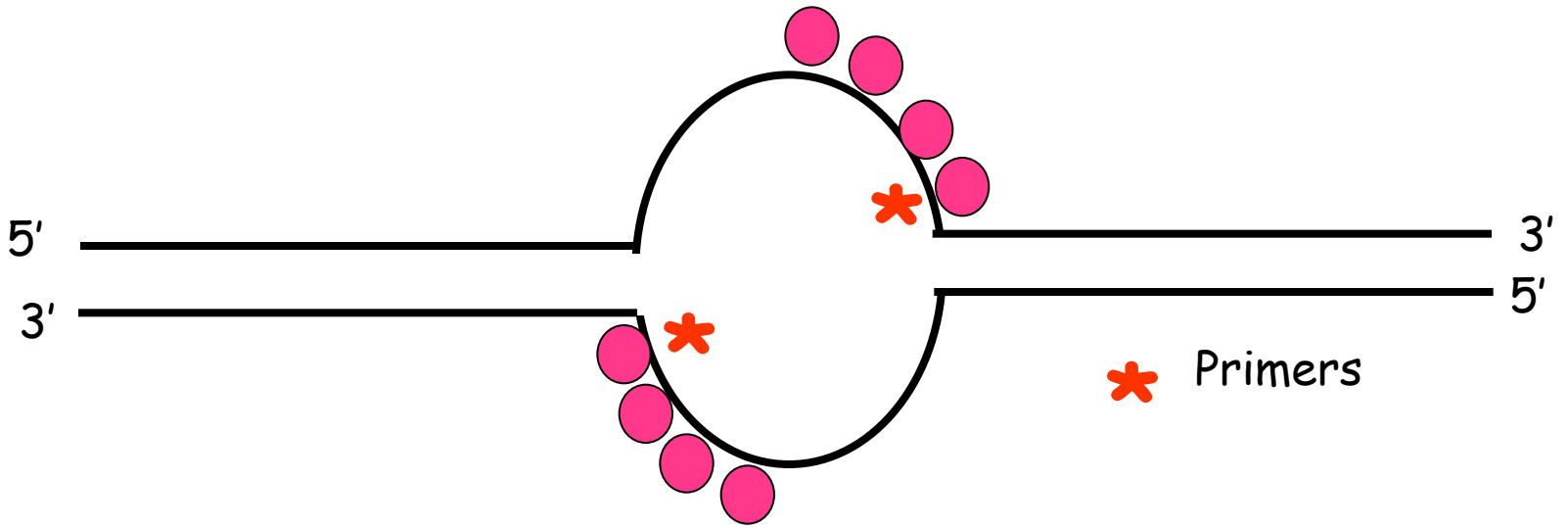
Initiation of DNA replication

- Role of SSBP
  - Single stranded binding proteins
  - After the helix has opened it is prevented from re-annealing by the action of these proteins
  - These proteins stabilize single stranded DNA
- - Single-strand-binding proteins help to stabilize the unwound strands.
  - Topoisomerase II relieves strain on the double helix that is generated from unwinding.



Initiation of DNA replication

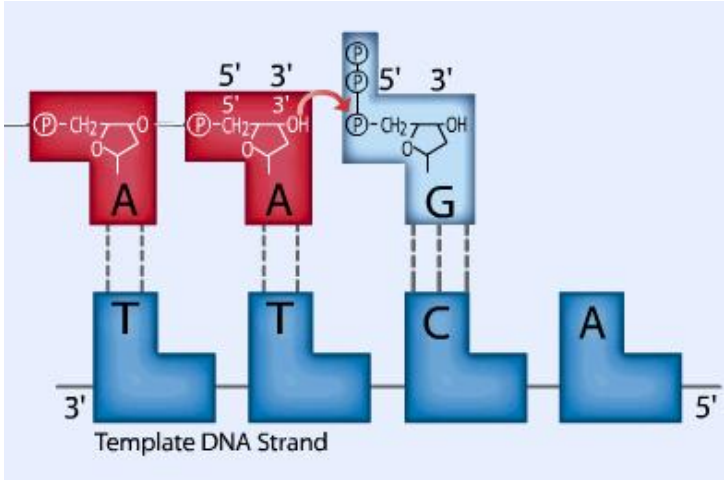
- Step 2 – binding of RNA primers
  - Primase adds short stretches of RNA primers
  - Purpose is to give DNA polymerase a 3'OH group from which to add new DNA nucleotides
  - Two primers are put down as the replication bubble opens

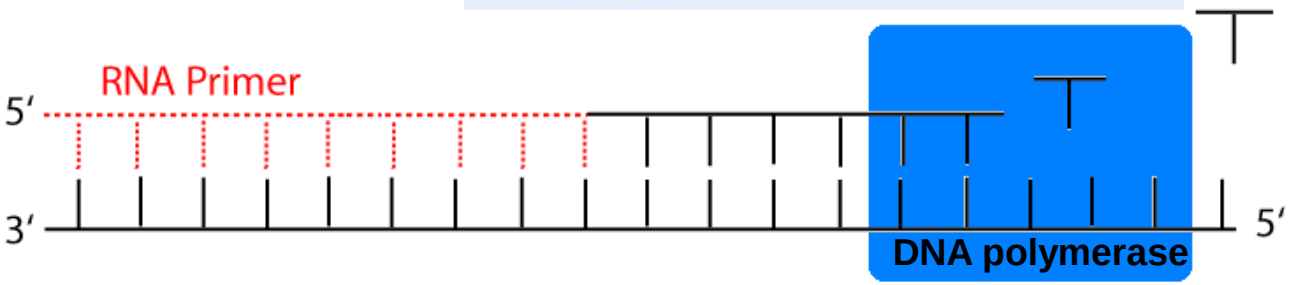


DNA Replication

Elongation

- **DNA polymerase** uses each strand as a template in the 3′ to 5′ direction to build a complementary strand in the 5′ to 3′ direction

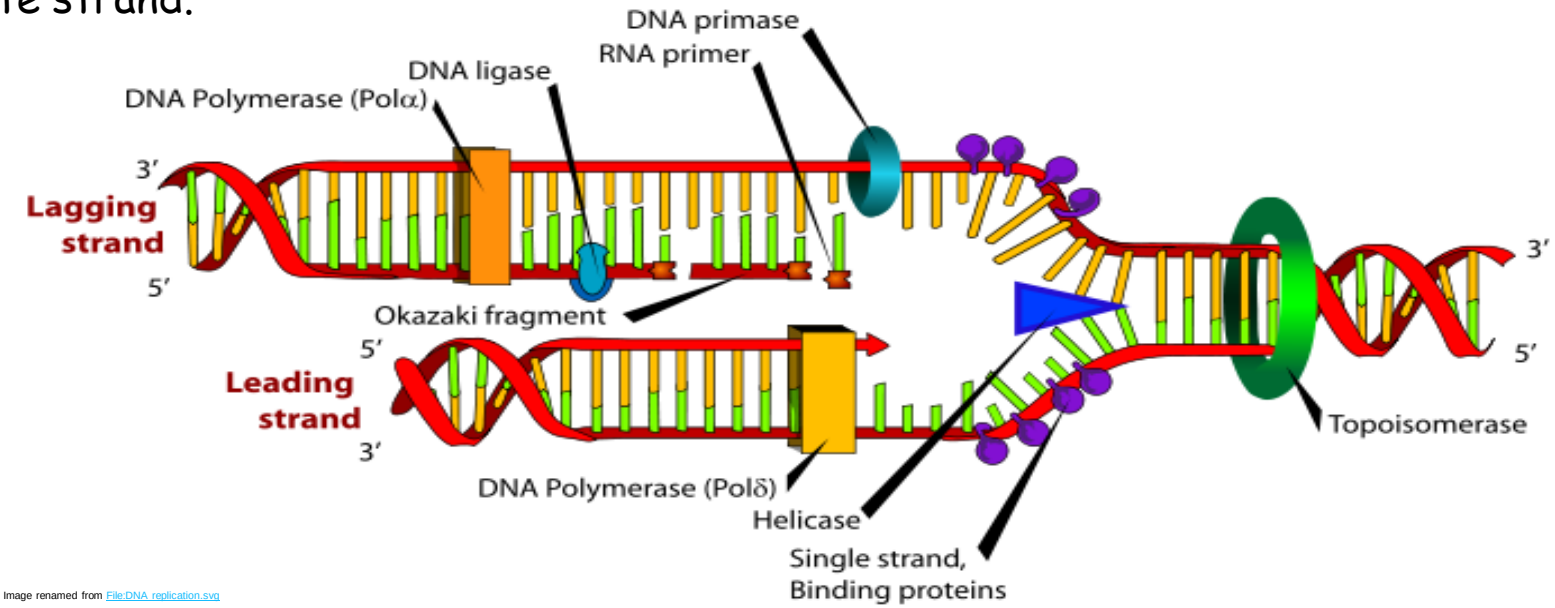


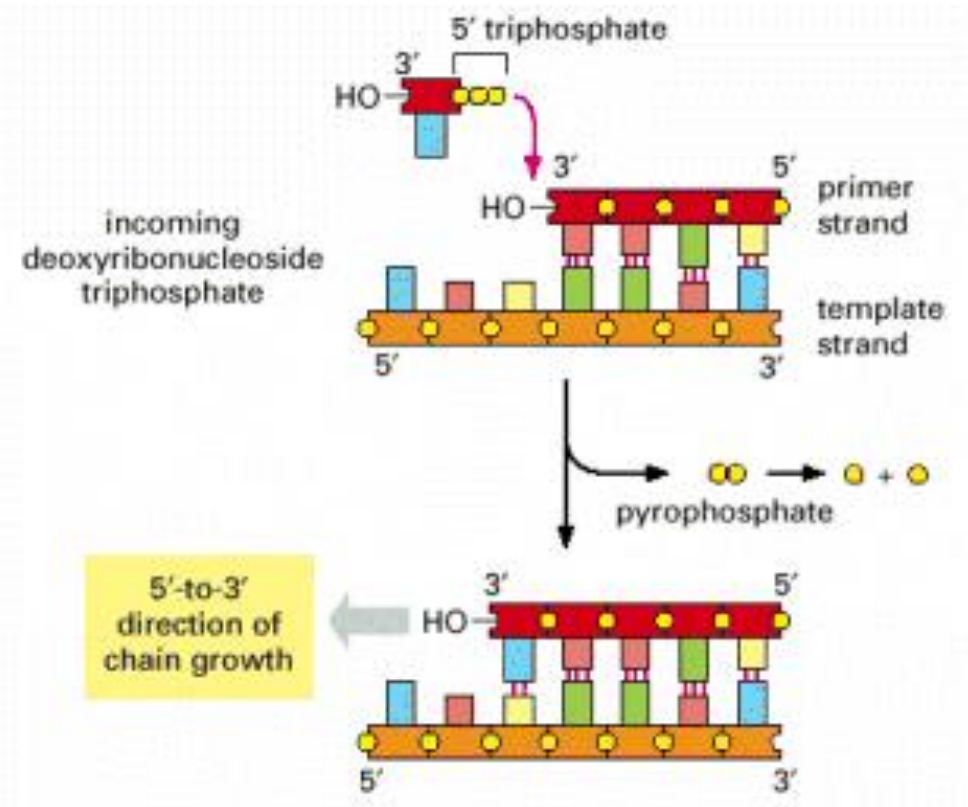


DNA Replication

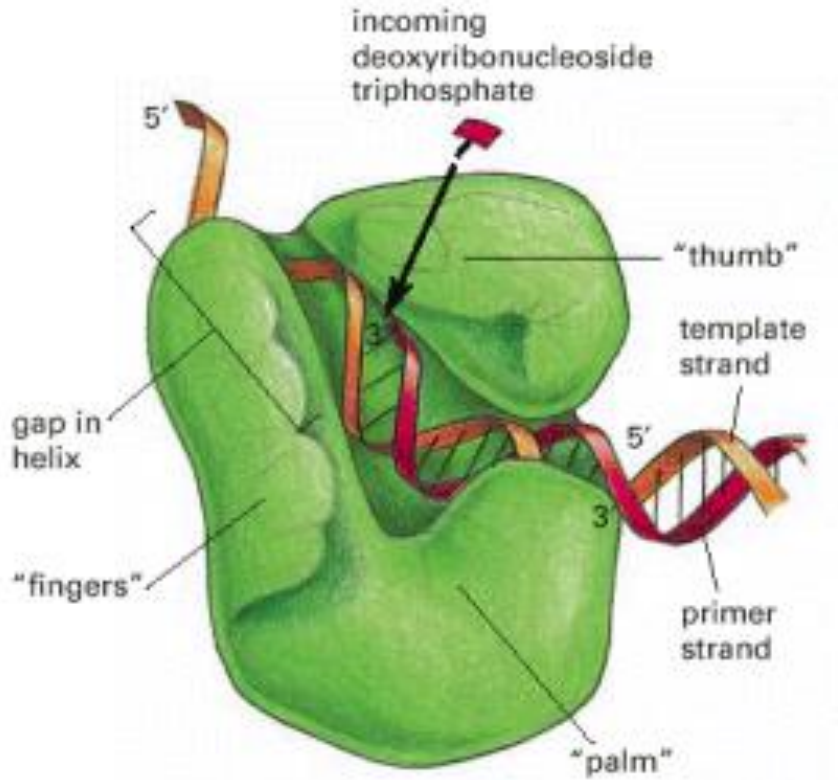
Elongation

- **DNA polymerase** uses each strand as a template in the 3′ to 5′ direction to build a complementary strand in the 5′ to 3′ direction
  - ✓ results in a **leading strand** and a **lagging strand**
- **DNA polymerase III** catalyzes the addition of new nucleotides to create a complementary strand to the parent strand. However, it can only attach new nucleotides to the free 3′ hydroxyl end of a pre-existing chain of nucleotides.
- DNA polymerase I removes the primers and fills in the space by extending the neighboring DNA fragment. DNA ligase then joins the Okazaki fragments to create a complete strand.





(A)

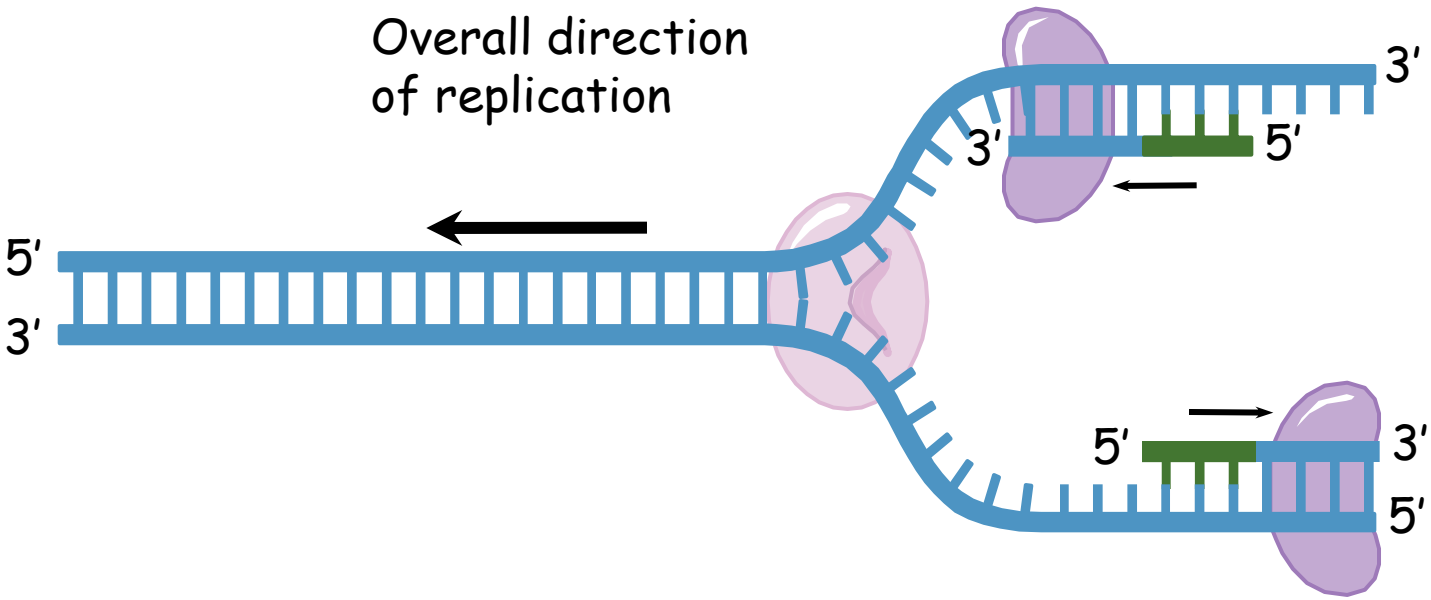


(B)

Role of DNA polymerases:

1. Polymerases catalyze the formation of phosphodiester bonds the 3′-OH group of the deoxyribose on the last nucleotide and the 5′-phosphate of the dNTP precursor.
2. DNA polymerase finds the correct complement at each step in the process. 60-90 bases per second in humans.
3. The direction of synthesis is 5′ to 3′ only.

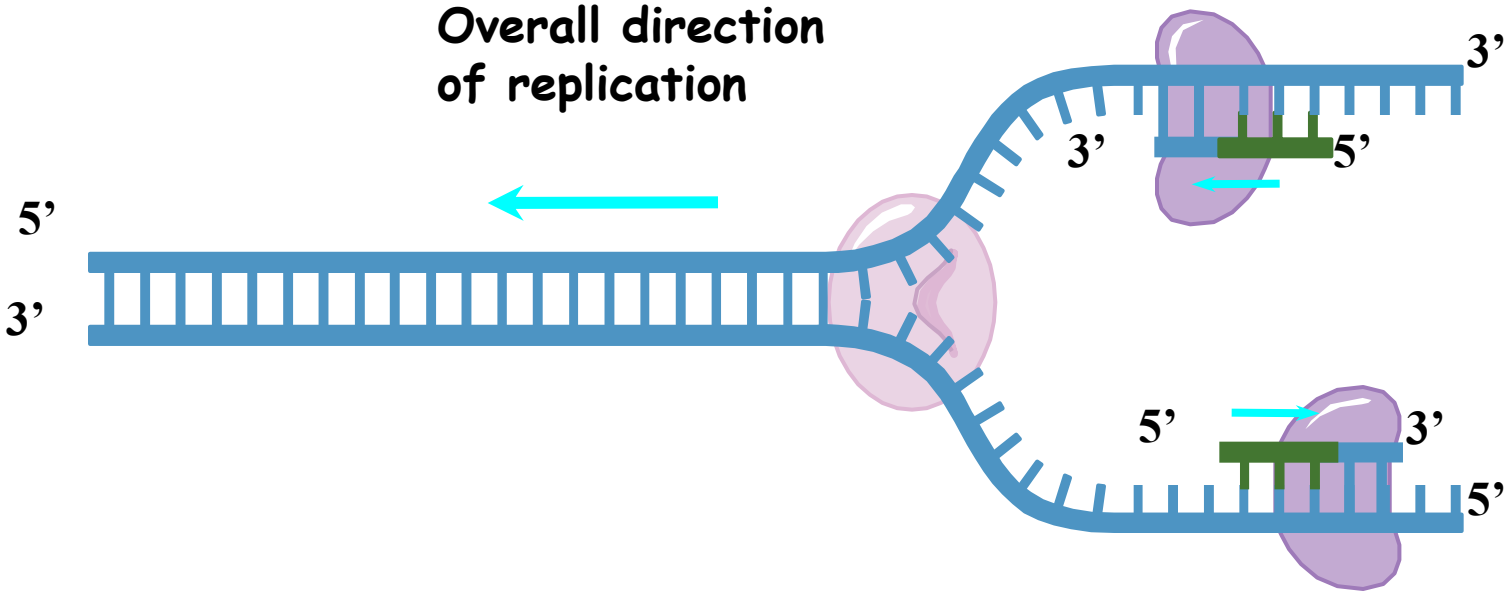
Replication



DNA polymerase enzyme adds DNA nucleotides to the RNA primer.

DNA polymerase proofreads bases added and replaces incorrect nucleotides.

Replication



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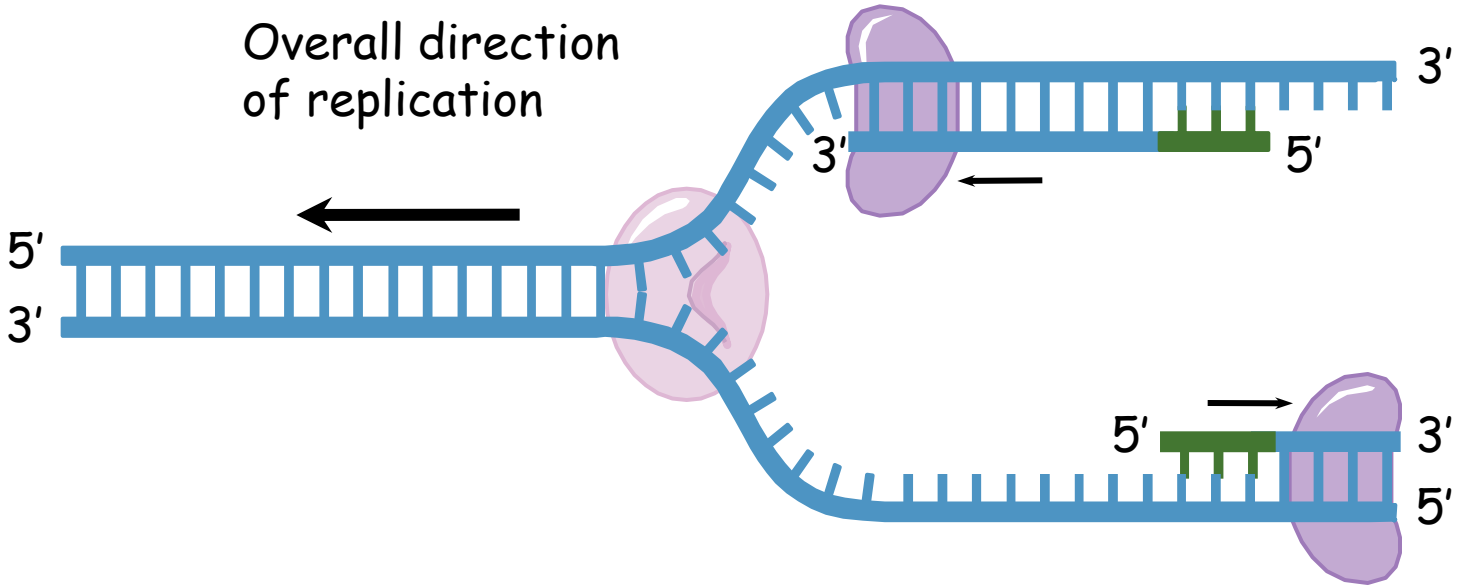
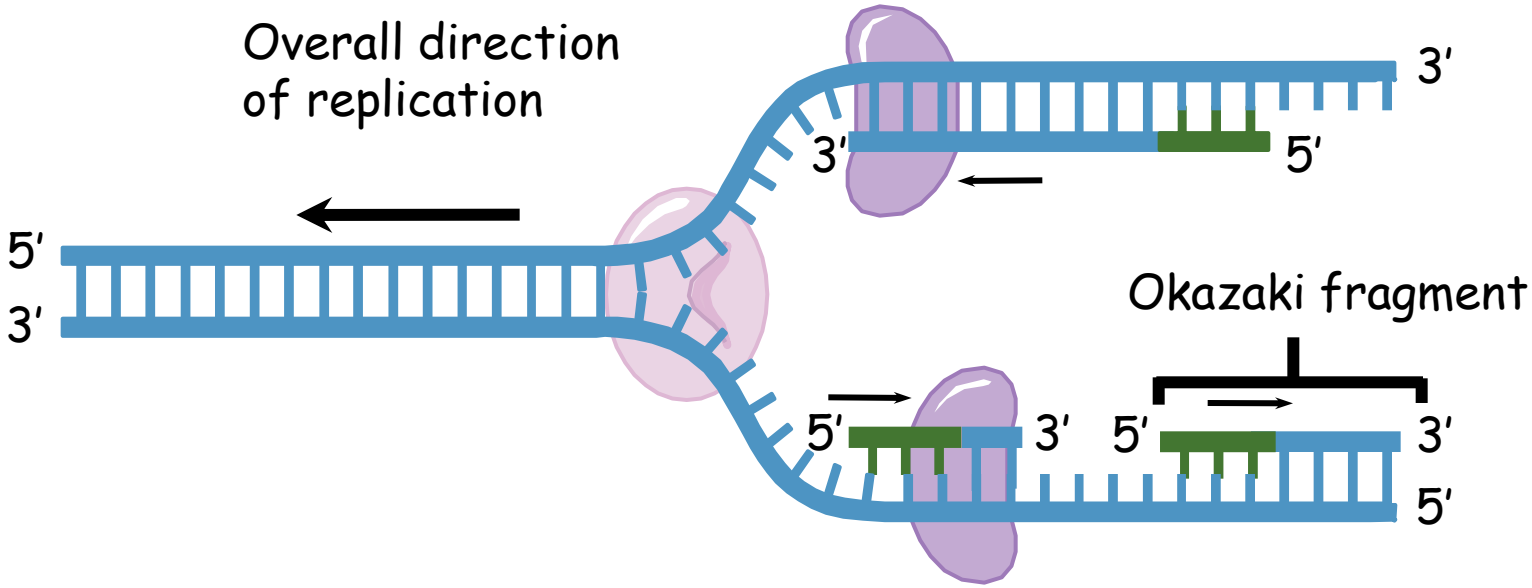


Leading strand synthesis continues in a
5′ to 3′ direction.

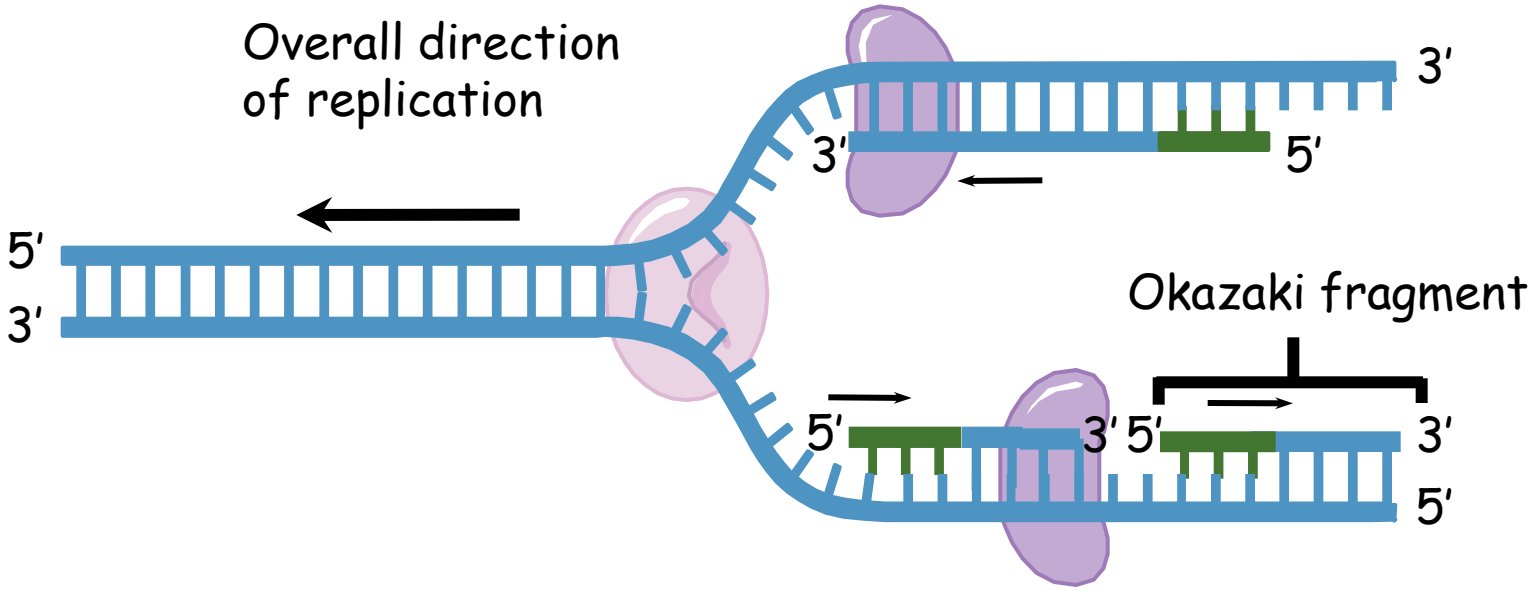
Replication



Leading strand synthesis continues in a 5′ to 3′ direction.

Discontinuous synthesis produces 5′ to 3′ DNA segments called Okazaki fragments.

Replication



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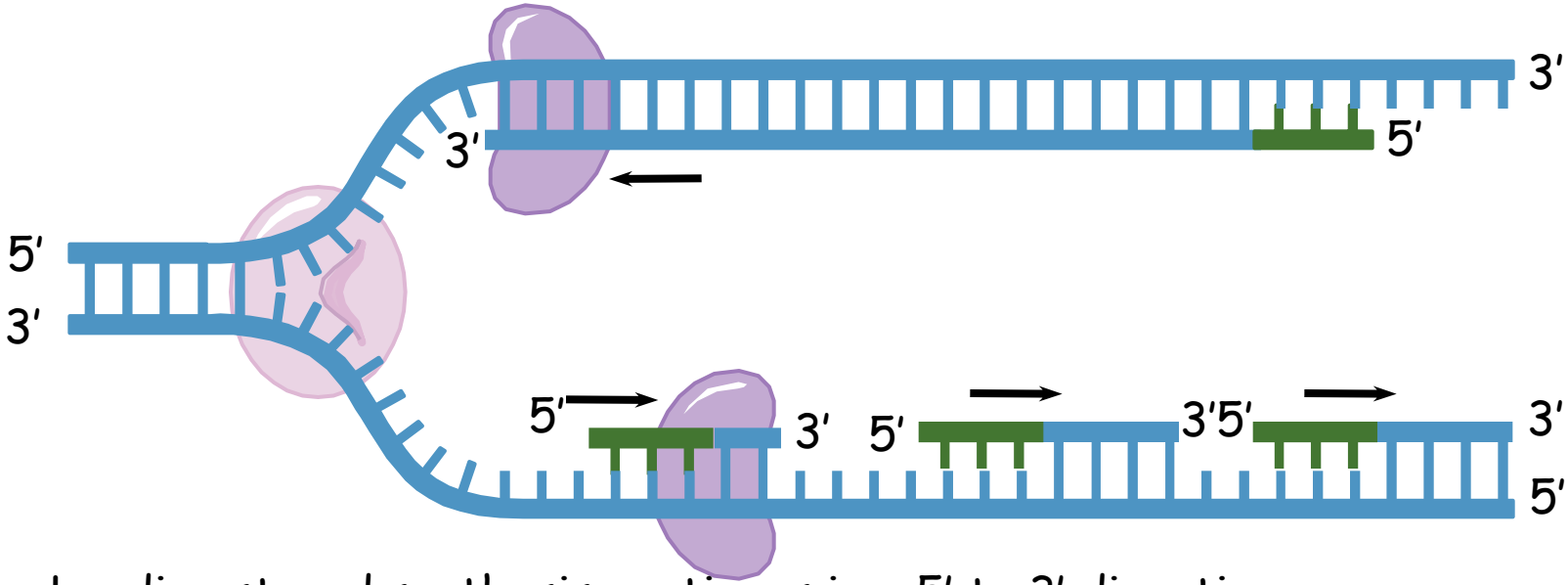

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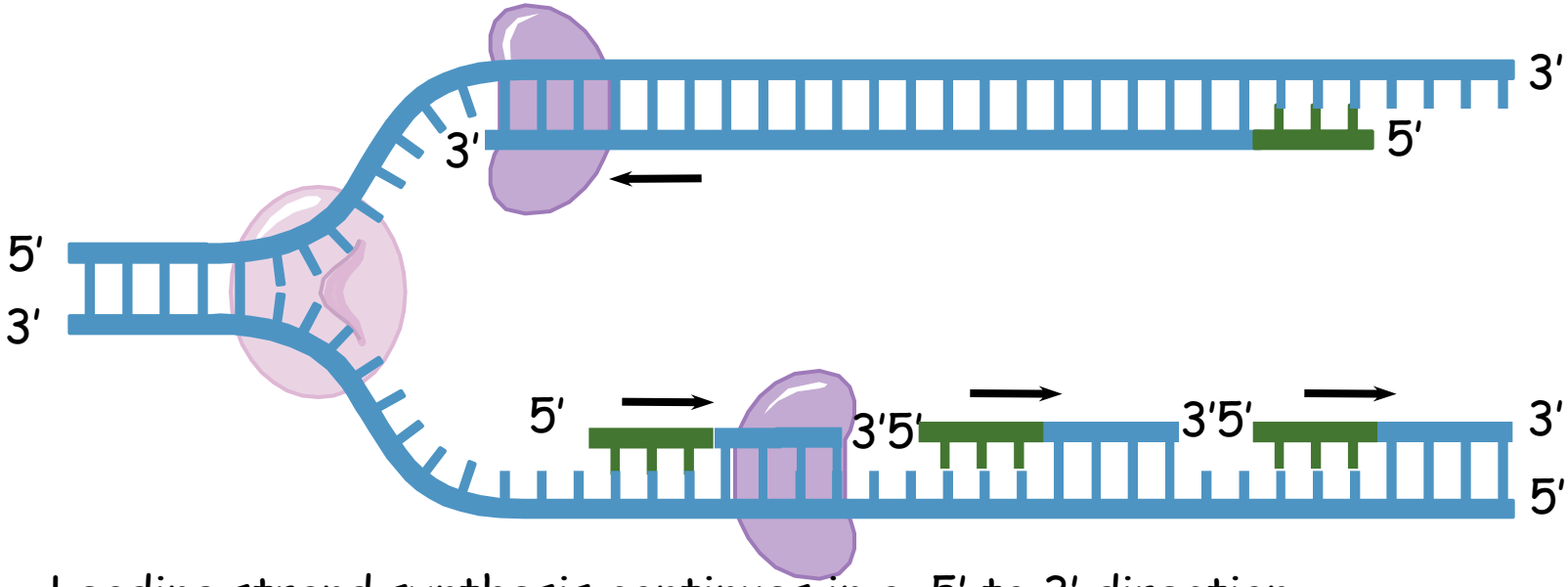

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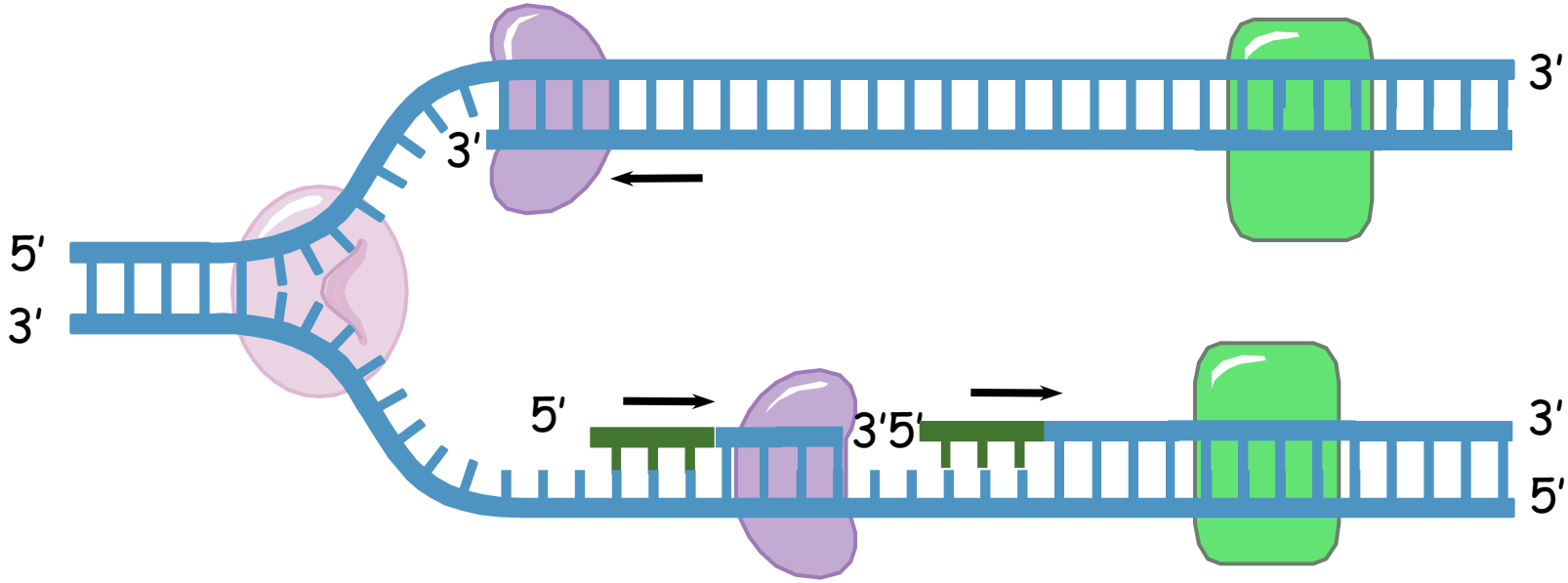
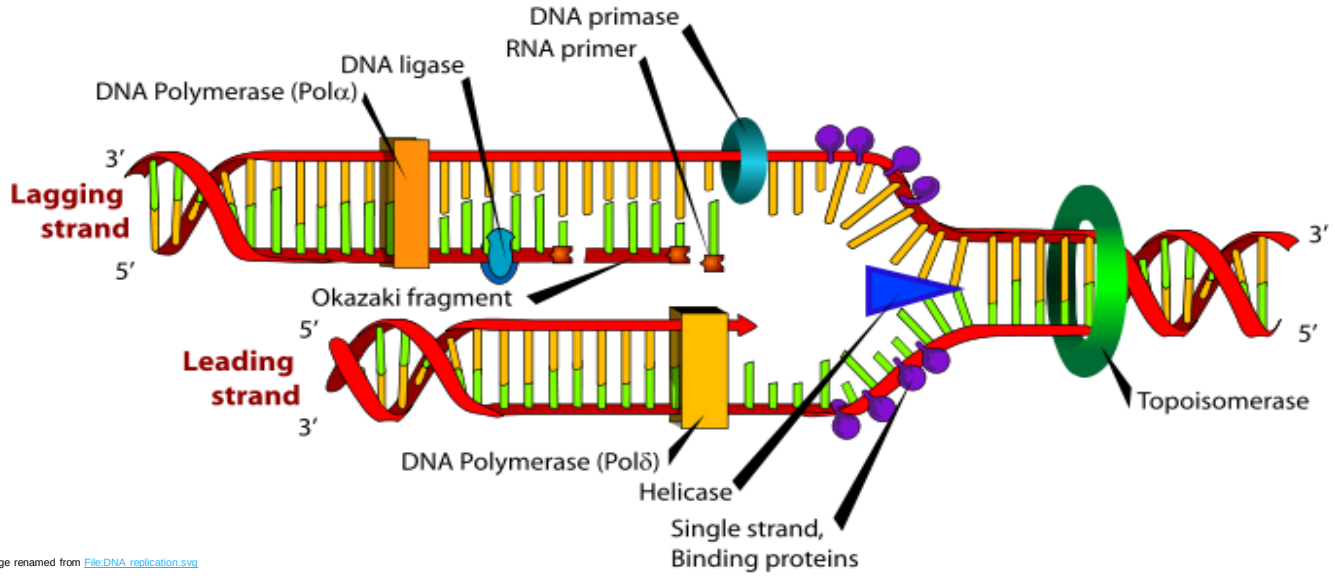


Polymerase activity of DNA polymerase I fills the gaps.
Ligase forms bonds between sugar-phosphate backbone.

DNA Replication

Leading Strand

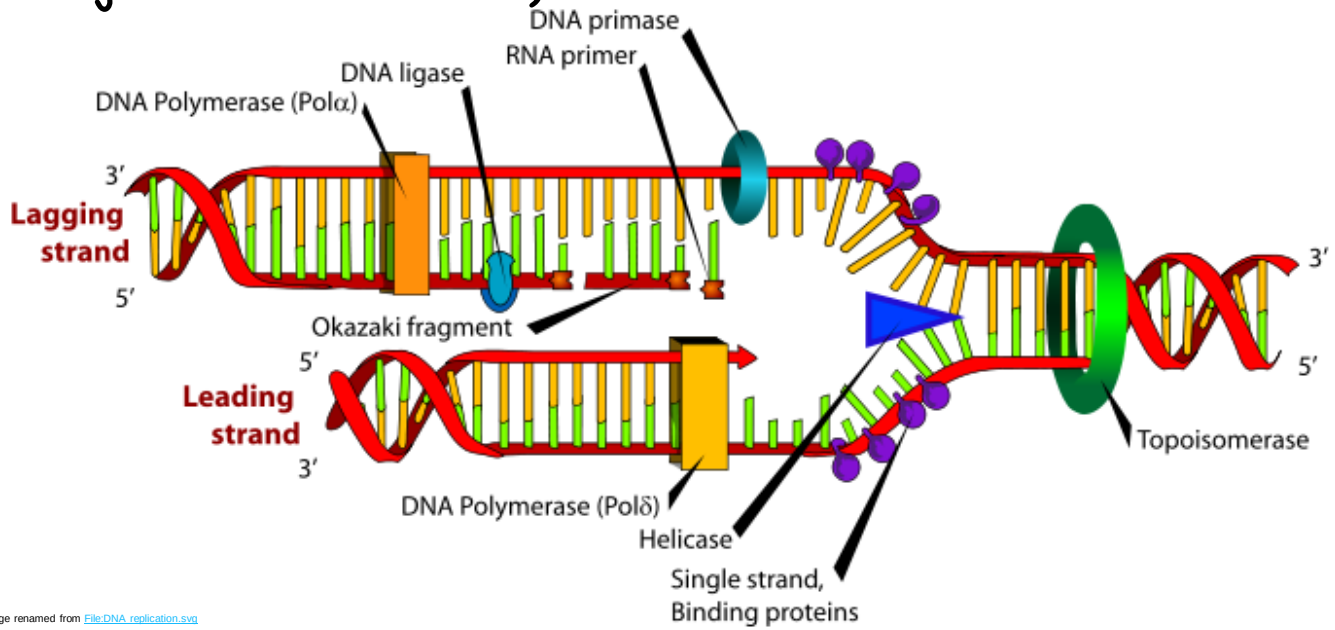
1. Topisomerase unwinds DNA and then Helicase breaks H-bonds
2. DNA primase creates a single RNA primer to start the replication
3. DNA polymerase slides along the leading strand in the 3′ to 5′ direction synthesizing the matching strand in the 5′ to 3′ direction
4. The RNA primer is degraded by RNase H and replaced with DNA nucleotides by DNA polymerase, and then DNA ligase connects the fragment at the start of the new strand to the end of the new strand



DNA Replication

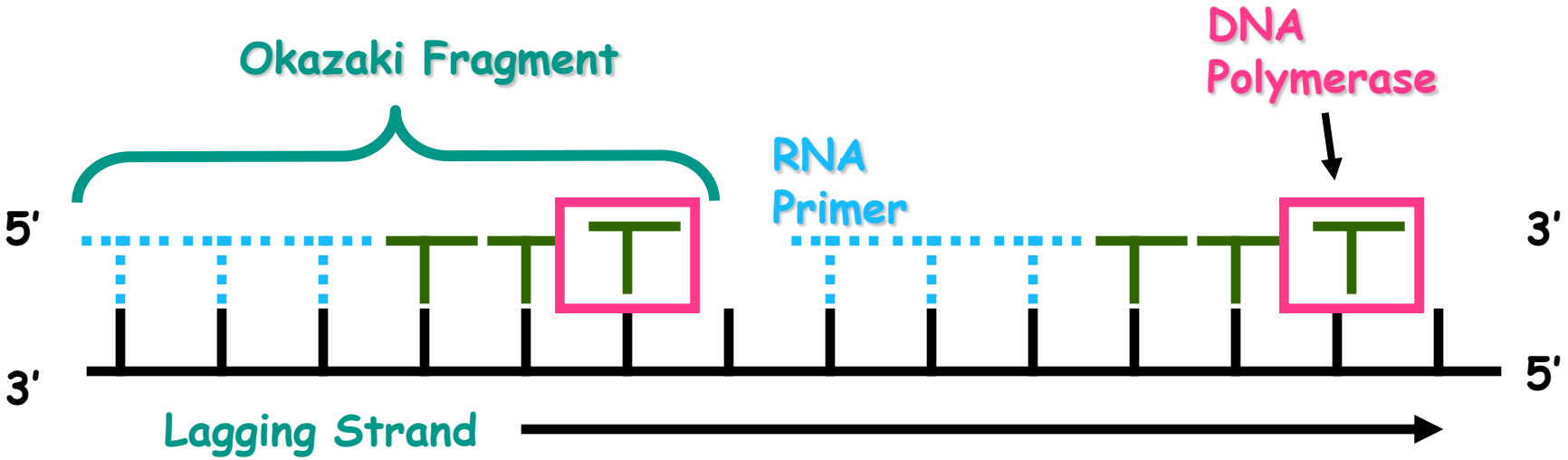
Lagging Strand

1. Topisomerase unwinds DNA and then Helicase breaks H-bonds
2. DNA primase creates RNA primers in spaced intervals
3. DNA polymerase slides along the leading strand in the 3′ to 5′ direction synthesizing the matching Okazaki fragments in the 5′ to 3′ direction
4. The RNA primers are degraded by RNase H and replaced with DNA nucleotides by DNA polymerase
5. DNA ligase connects the Okazaki fragments to one another (covalently bonds the phosphate in one nucleotide to the deoxyribose of the adjacent nucleotide)



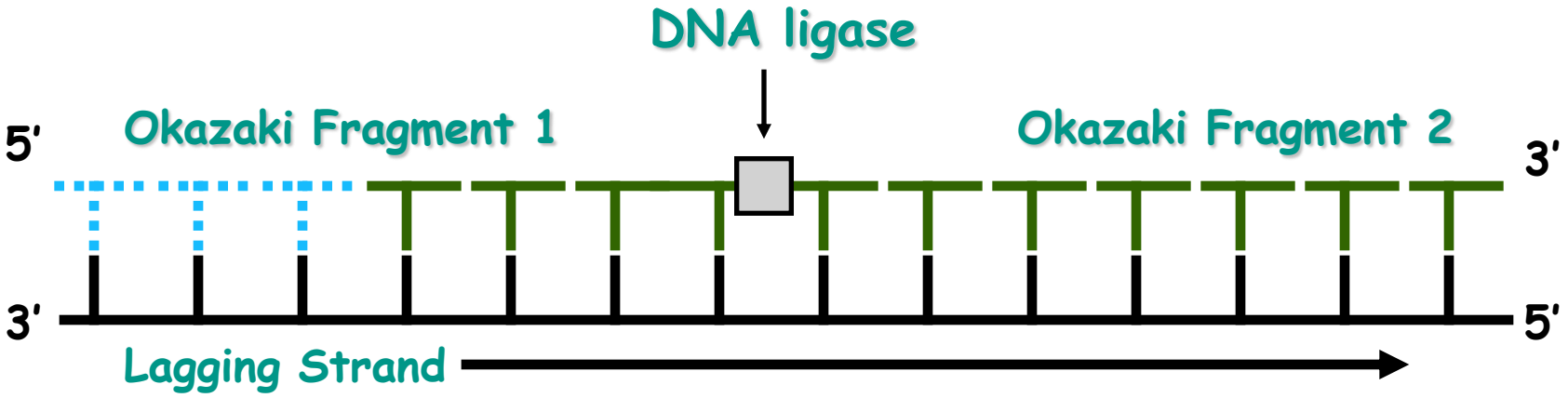
Lagging Strand Segments

- Okazaki Fragments - series of short segments on the lagging strand
- Must be joined together by an enzyme



Joining of Okazaki Fragments

- The enzyme Ligase joins the Okazaki fragments together to make one strand



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- Leading strand — synthesized 5’ to 3’ in the direction of the replication fork movement.

  continuous

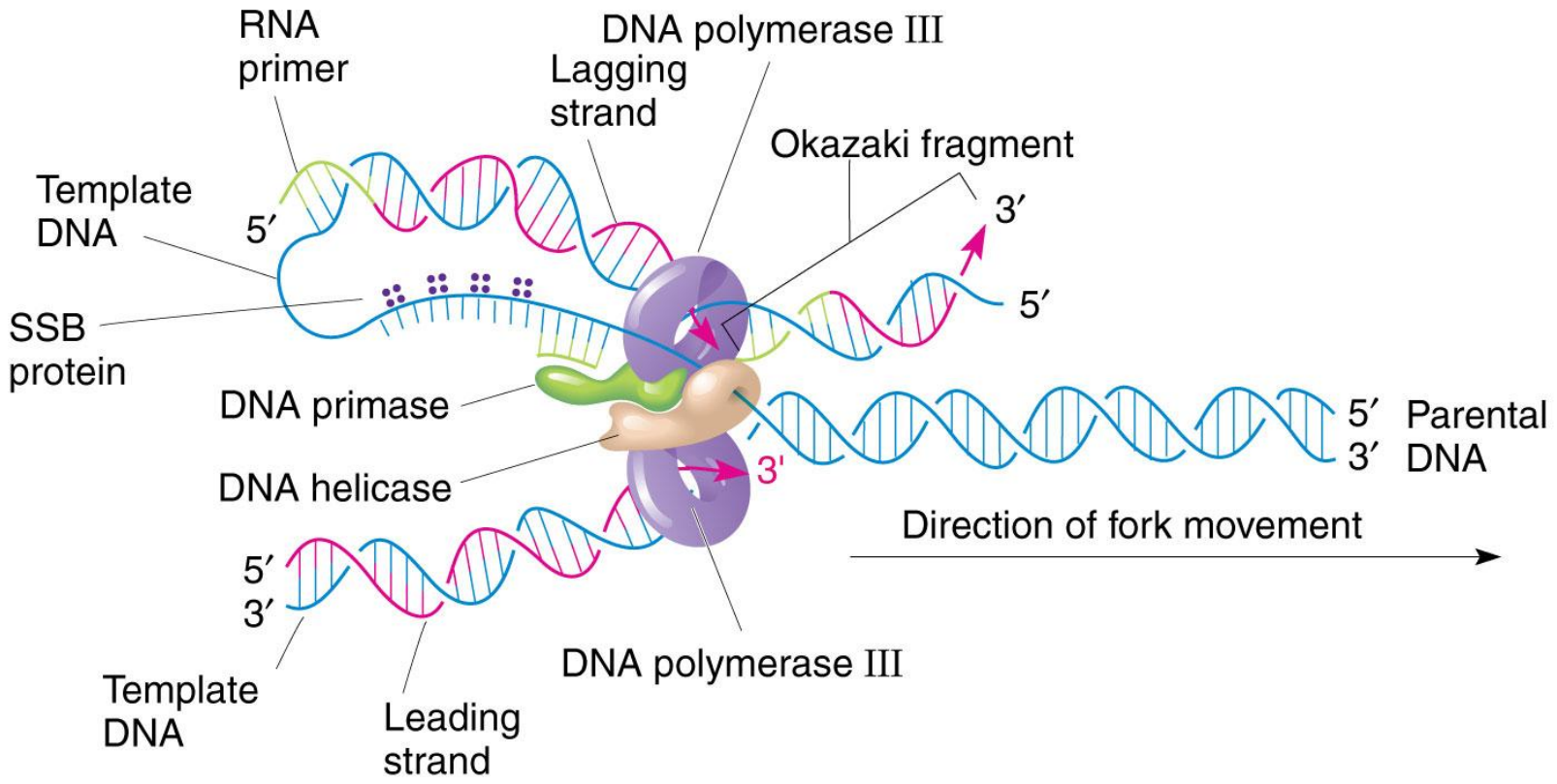
  requires a single RNA primer

- Lagging strand — synthesized 5’ to 3’ in the opposite direction.

  discontinuous (i.e., not continuous)

  requires many RNA primers , DNA is synthesized in short fragments.

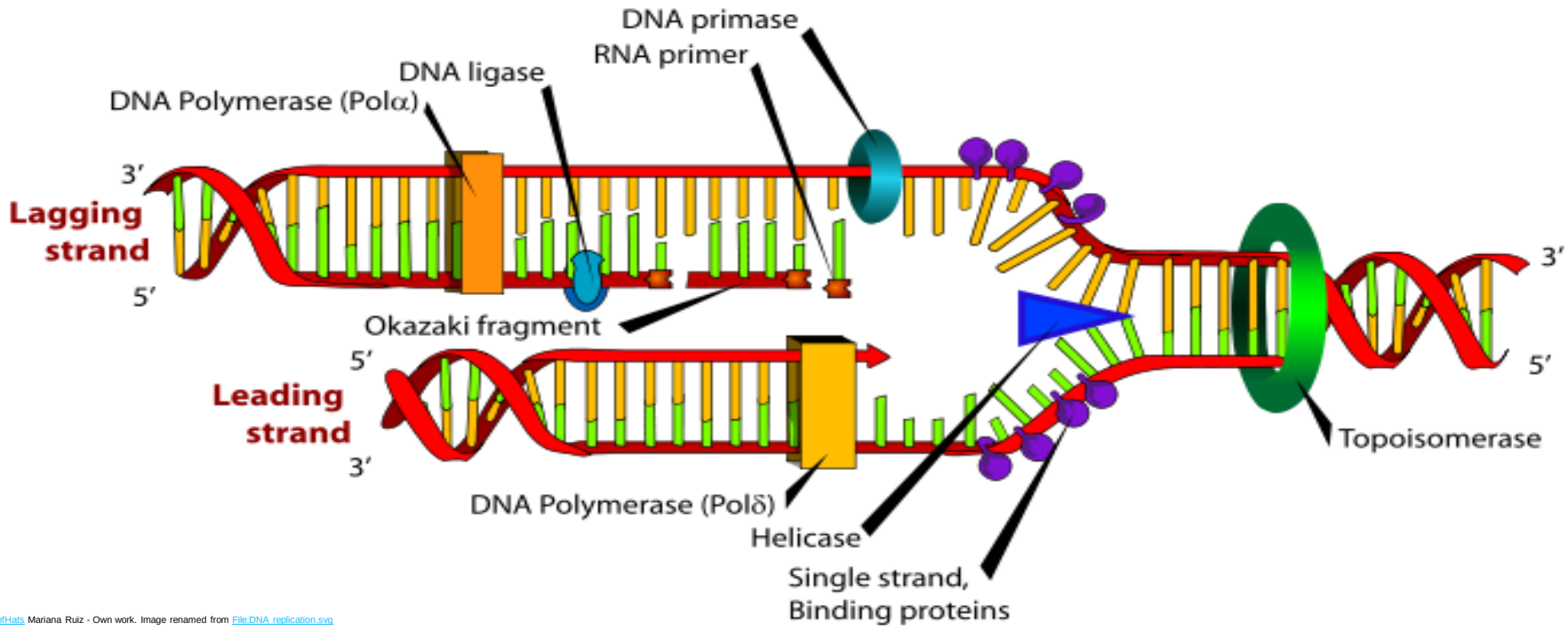
Model of DNA Replication



A General Model for DNA Replication

1. The DNA molecule is unwound and prepared for synthesis by the action of DNA gyrase, DNA helicase and the single-stranded DNA binding proteins.
2. A free 3'OH group is required for replication, but when the two chains separate no group of that exists in nature therefore RNA primers are synthesized, and the free 3'OH of the primer is used to begin replication.

3. The replication fork moves in one direction, but DNA replication only goes in the 5' to 3' direction. This paradox is resolved by the use of Okazaki fragments. These are short, discontinuous replication products that are produced off the lagging strand. This is in comparison to the continuous strand that is made off the leading strand.

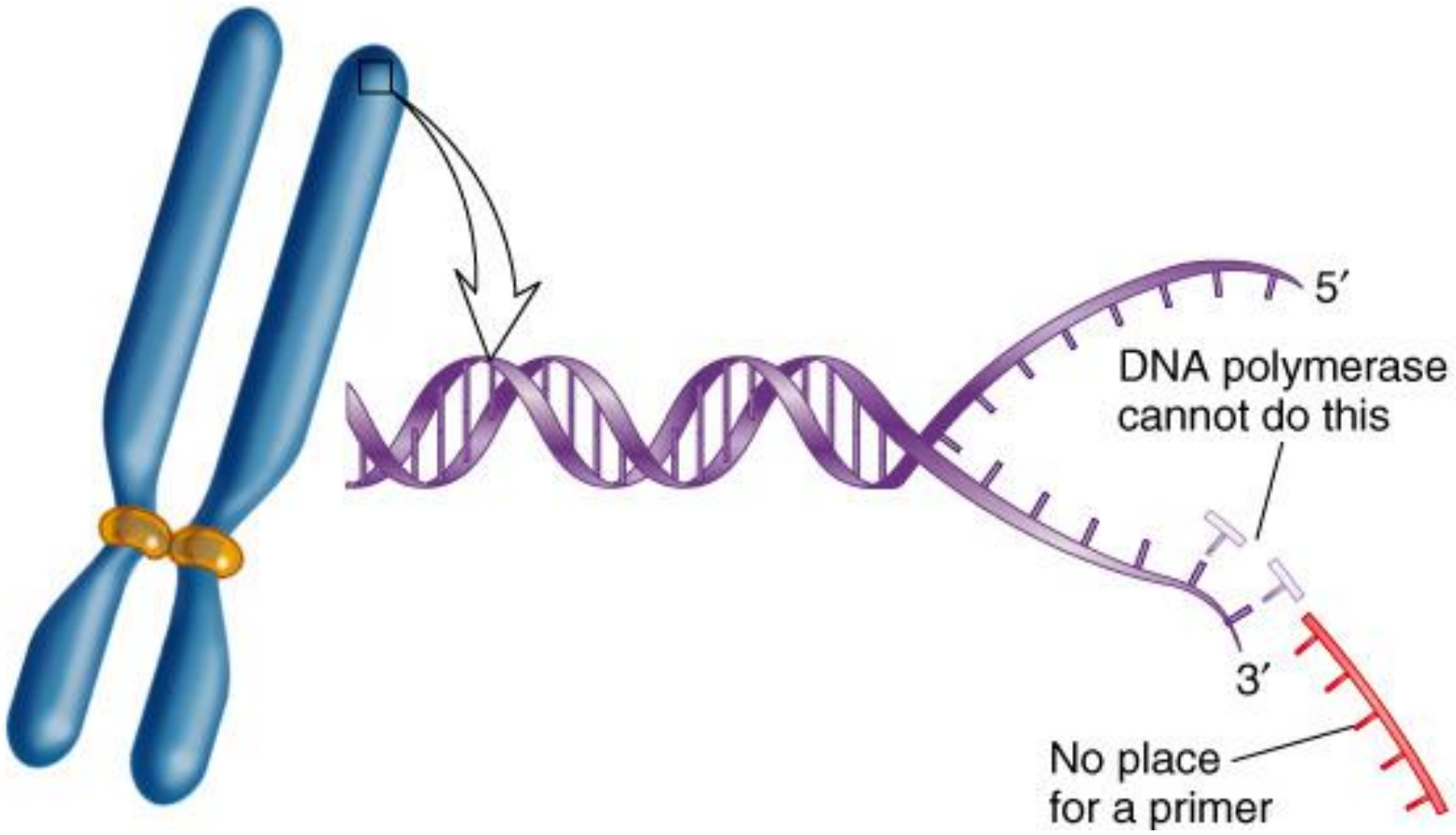


4. The final product does not have RNA stretches in it. These are removed by the 5' to 3' exonuclease action of Polymerase I.

5. The final product does not have any gaps in the DNA that result from the removal of the RNA primer. These are filled in by the 5′ to 3′ polymerase action of DNA Polymerase I.

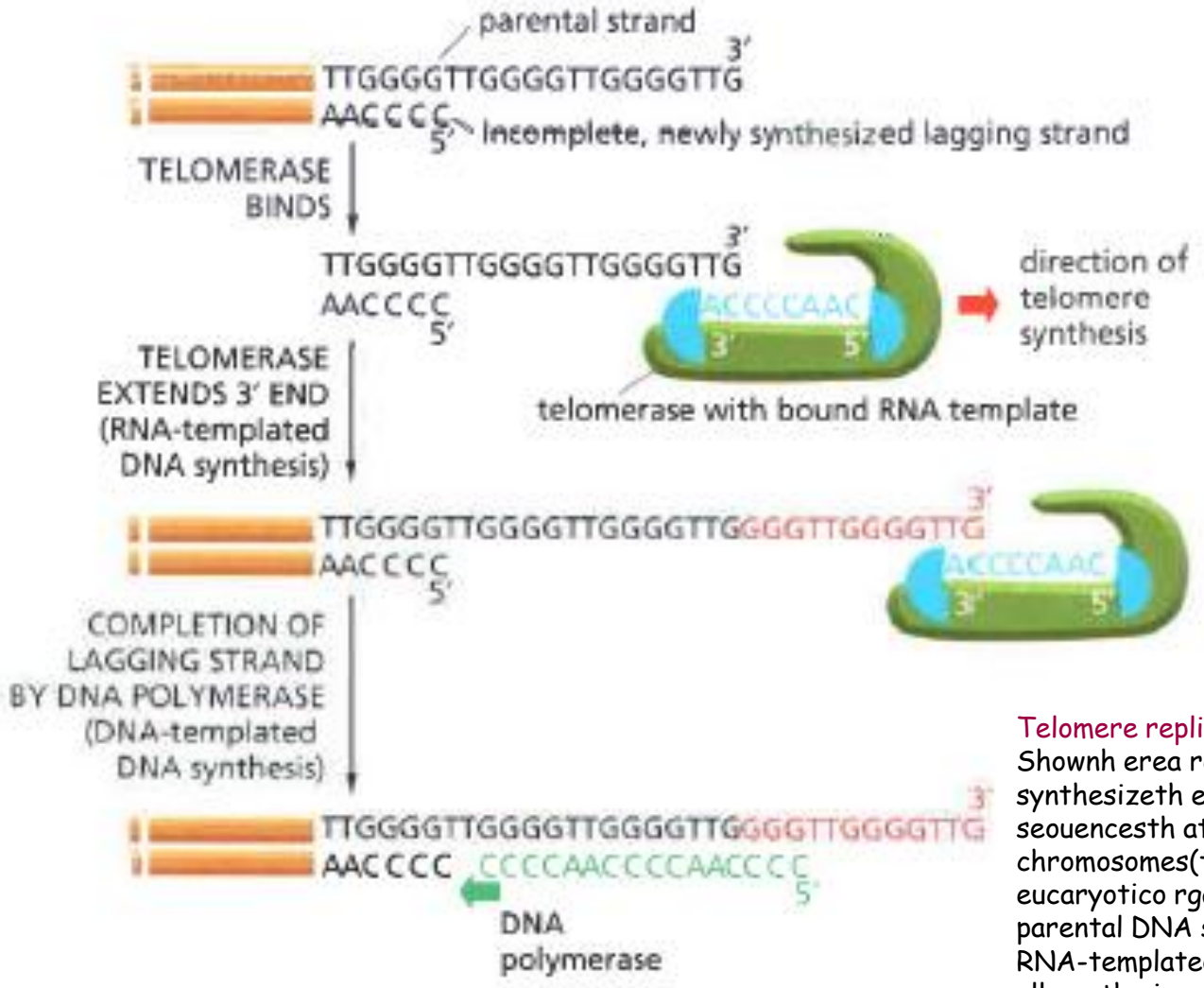
6. DNA polymerase does not have the ability to form the final bond. This is done by the enzyme DNA ligase.

- DNA polymerases can only synthesize DNA only in the 5′ to 3′ direction and cannot initiate DNA synthesis
- These two features pose a problem at the 3′ end of linear chromosomes



Problem at ends of eukaryotic linear Chromosomes

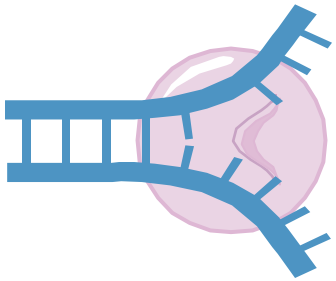
- If this problem is not solved
  - The linear chromosome becomes progressively shorter with each round of DNA replication
- The cell solves this problem by adding DNA sequences to the ends of chromosome: **telomeres**
  - Small repeated sequences (100-1000's)
- Catalyzed by the enzyme **telomerase**
- Telomerase contains **protein** and **RNA**
  - The RNA functions as the template
  - complementary to the DNA sequence found in the telomeric repeat
    - This allows the telomerase to bind to the 3' overhang



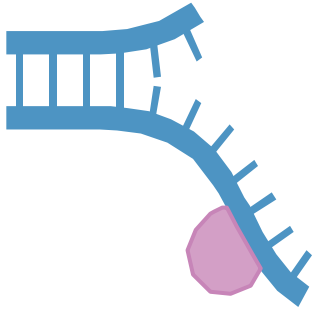
Telomere replication.

Shownh erea ret he reactionsth at synthesizeth e repeatingG -rich seouencesth at form the endso f the chromosomes(t elomereso) f diverse eucaryotico rganismsT. he 3' end of the parental DNA strand is extended by RNA-templatedD NAs ynthesist;h is allows the incomplete daughter DNA strand that is paired with it to be extendedin its5 ' directionT. his incompletel,a ggings trandi s presumed to be completedb y DNA polymeraseo , whichc arriesa DNAp rimasea so ne of its subunitsT

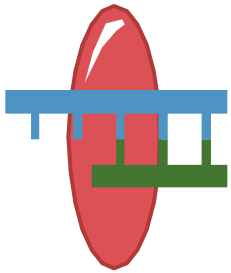
Enzymes in DNA replication



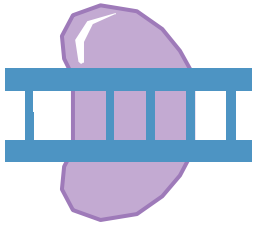
Helicase unwinds parental double helix



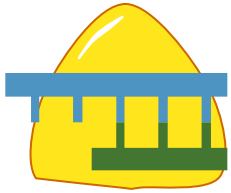
Binding proteins stabilize separate strands



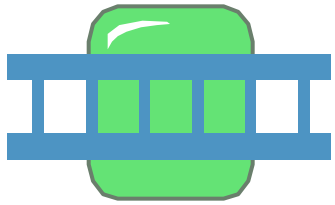
Primase adds short primer to template strand



DNA polymerase III binds nucleotides to form new strands

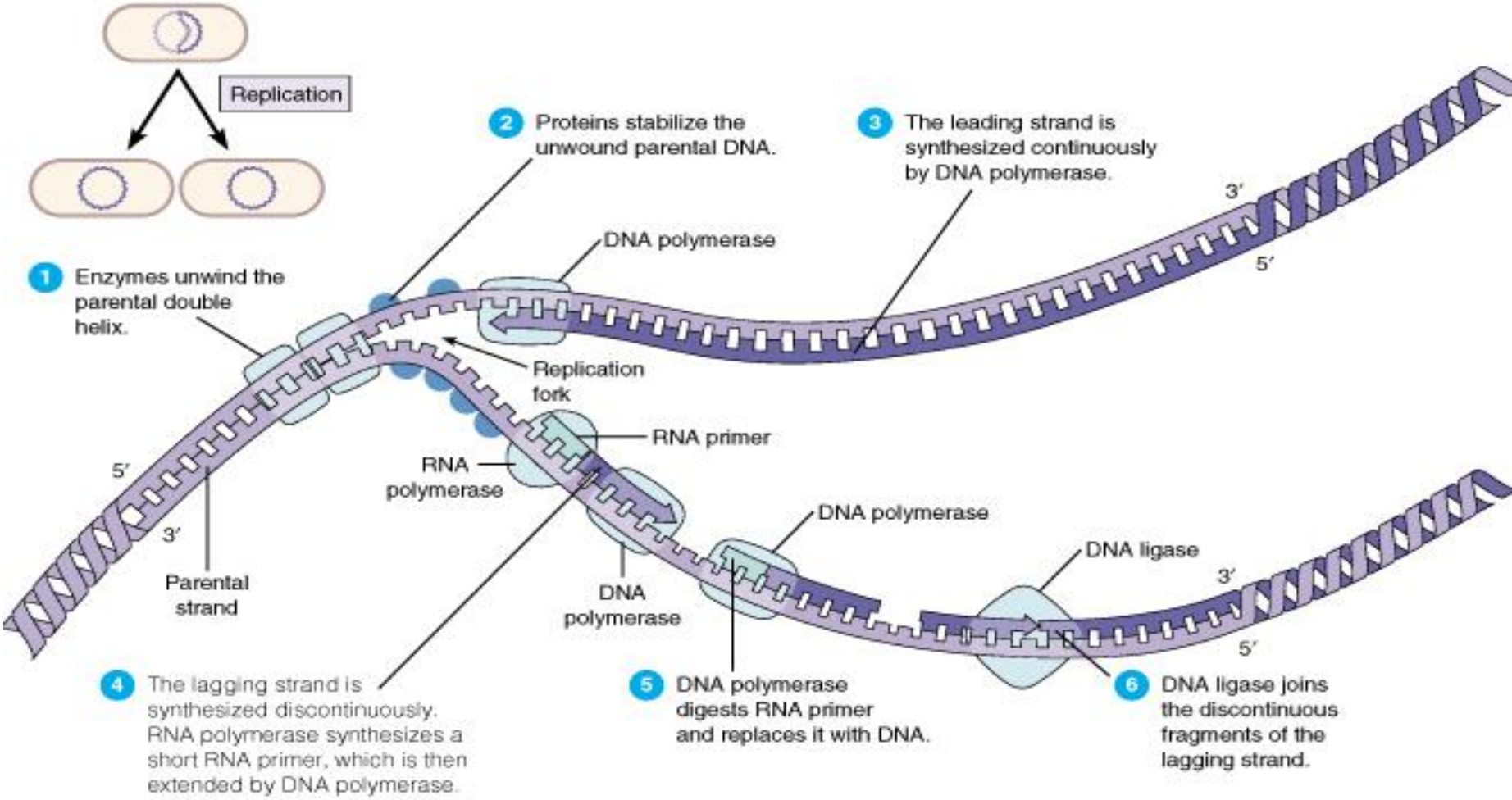


DNA polymerase I (Exonuclease) removes RNA primer and inserts the correct bases



Ligase joins Okazaki fragments and seals other nicks in sugar-phosphate backbone

Replication Fork Overview



Risks To DNA Replication

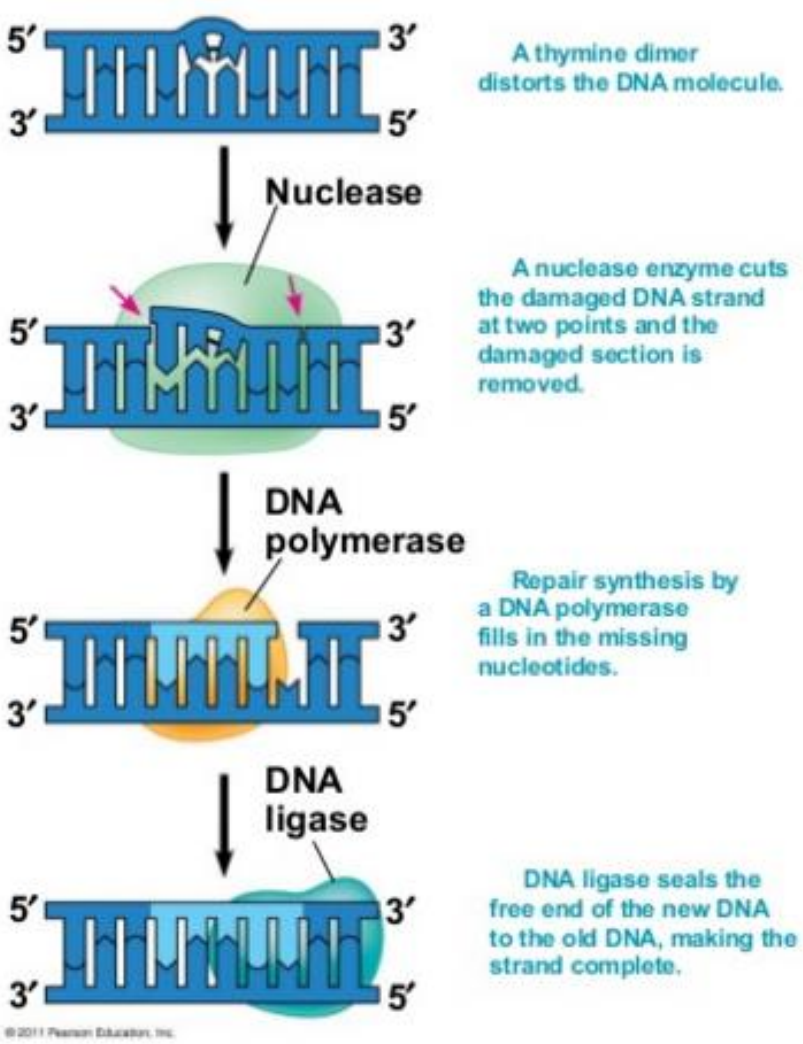
- DNA polymerase inserts the incorrect base once in every 100,000 bases
  - Error rate of 1×10^{-5}
  - At this rate your genome would be riddle with mutations
- But as it turns out DNA polymerase can proofread

Mistakes during Replication

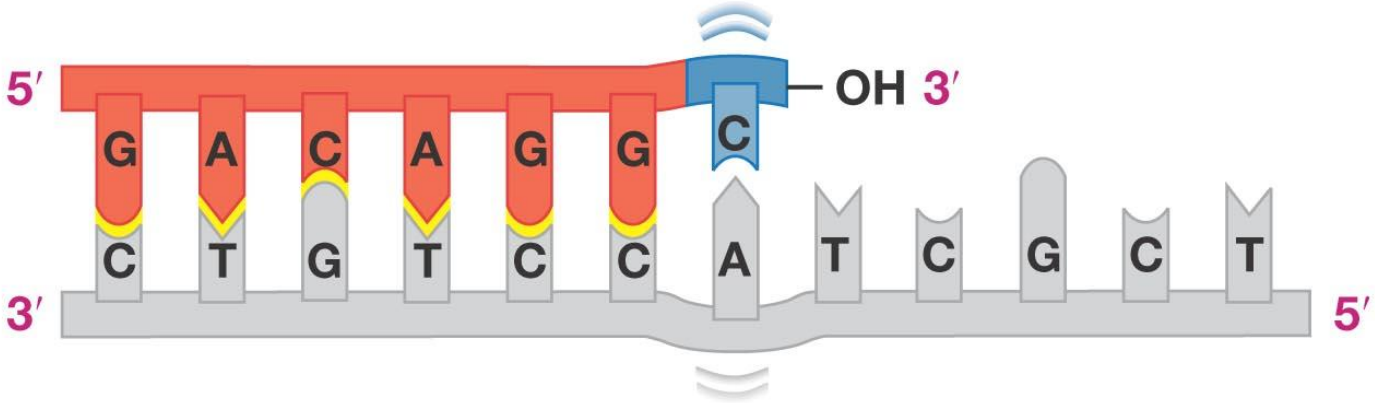
- Base pairing rules must be maintained
  - Mistake = genome mutation, may have consequence on daughter cells
- Only correct pairings fit in the polymerase active site
- If wrong nucleotide is included
  - Polymerase uses its proofreading ability to cleave the phosphodiester bond of improper nucleotide
    - Activity 3′ → 5′
  - And then adds correct nucleotide and proceeds down the chain again in the 5′ → 3′ direction

Proofreading and Repairing DNA

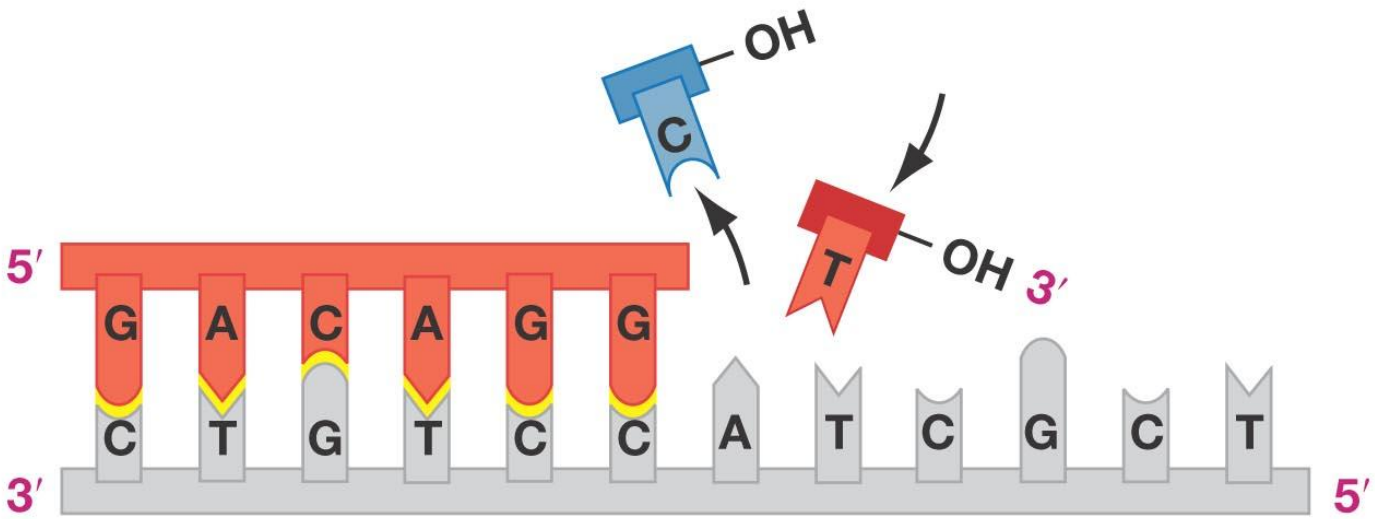
- DNA polymerases proofread newly made DNA, replacing any incorrect nucleotides
  - Mismatch repair: 'wrong' inserted base can be removed
  - Excision repair: DNA may be damaged by chemicals, radiation, etc. Mechanism to cut out and replace with correct bases



(a) Mismatched bases

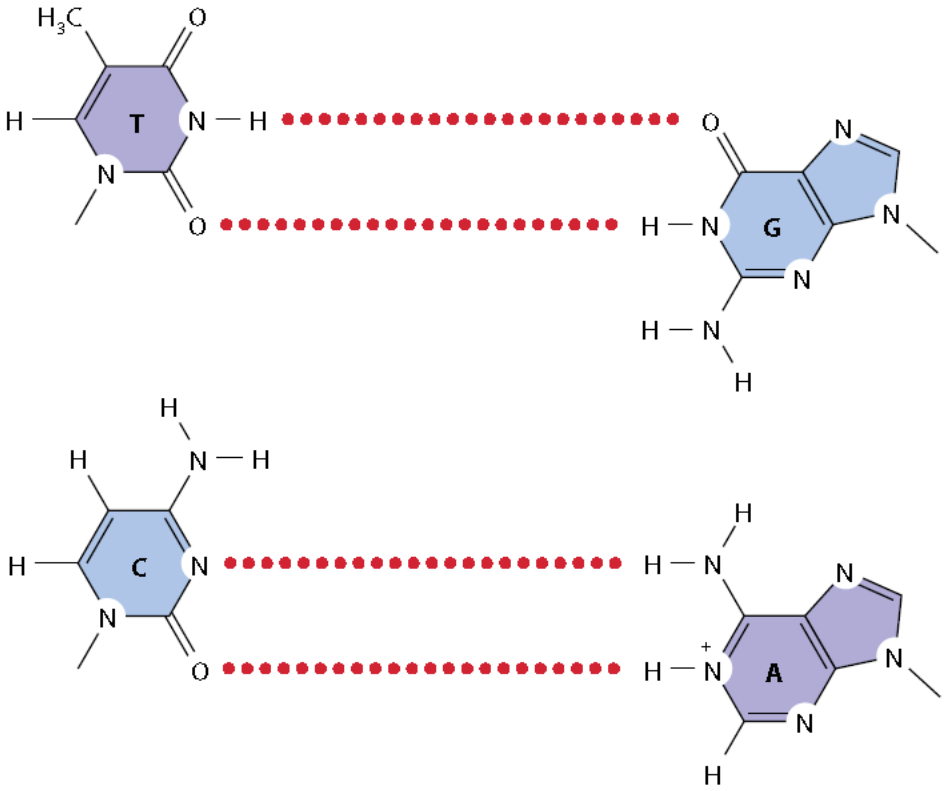


(b) DNA polymerase III can repair mismatches.



Errors During DNA Replication

A human cell can copy its entire DNA in a few hours, with an error rate of about one per 1 billion nucleotide pairs.



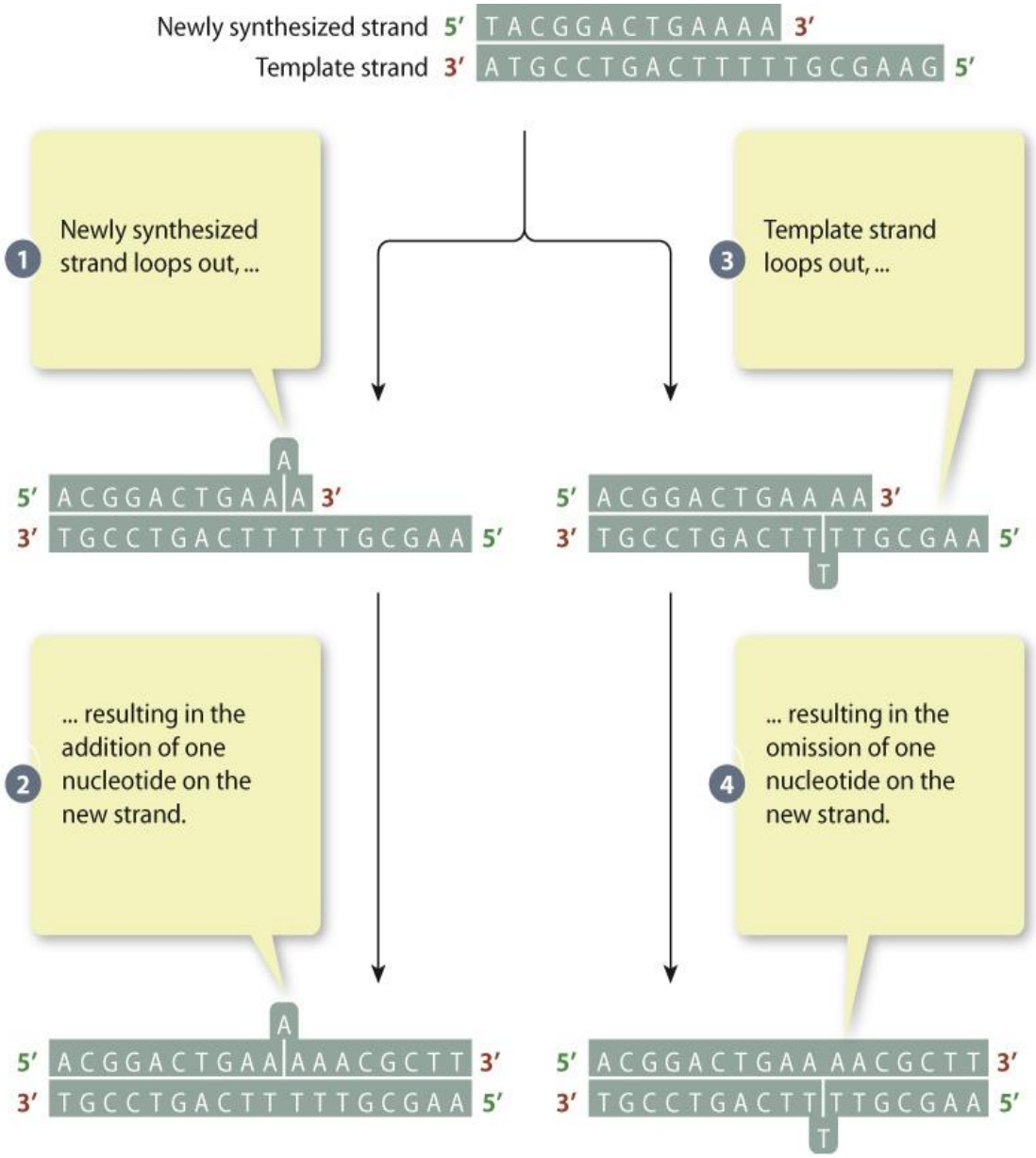
- Errors naturally occur during replication.

- Mispairing of bases and strand slippage are two types of errors that cause either additions or omissions of nucleotides.

Incorrect pairing (mispairing) of bases is thought to occur as a result of flexibility in DNA structure.

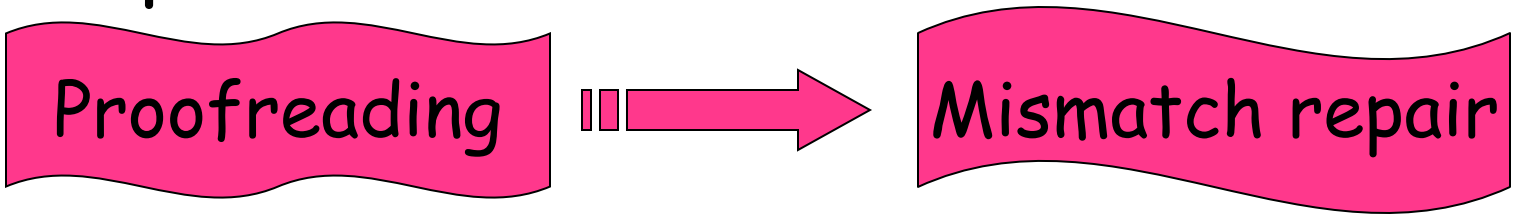
Errors During DNA Replication

Strand slippage during DNA replication can cause the addition or omission of nucleotides in newly synthesized strands, which represent errors.



Replication errors and their repair

Rapair:



Factors Influencing the Rate of Spontaneous Mutations

- Accuracy of the DNA replication machinery
- Efficiency of the mechanisms for the repair of damaged DNA
- Degree of exposure to mutagenic agents in the environment

Types of Chemical Mutagens

- Chemicals that are mutagenic to both replicating and nonreplicating DNA (e.g., alkylating agents and nitrous acid)
- Chemicals that are mutagenic only to replicating DNA (e.g., base analogs and acridine dyes)

Chemical Mutagens

Alkylating agents

$Cl—CH_2—CH_2—S—CH_2—CH_2—Cl$

Di-(2-chloroethyl) sulfide

(Mustard gas)

$CH_3—CH_2—O—SO_2—CH_3$

Ethyl methane sulfonate

(EMS)

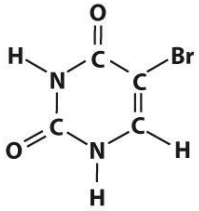
$CH_3—CH_2—O—SO_2—CH_2—CH_3$

Ethyl ethane sulfonate

(EES)

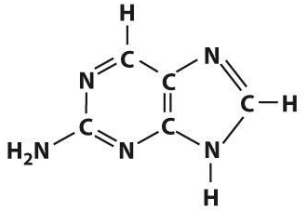
(a)

Base analogs



5-Bromouracil

(5-BU)

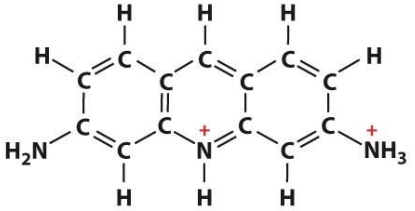


2-Aminopurine

(2-AP)

(b)

Acridines



2,8-Diamino acridine

(Proflavin)

(c)

Deaminating agent

HNO_2

Nitrous acid

(d)

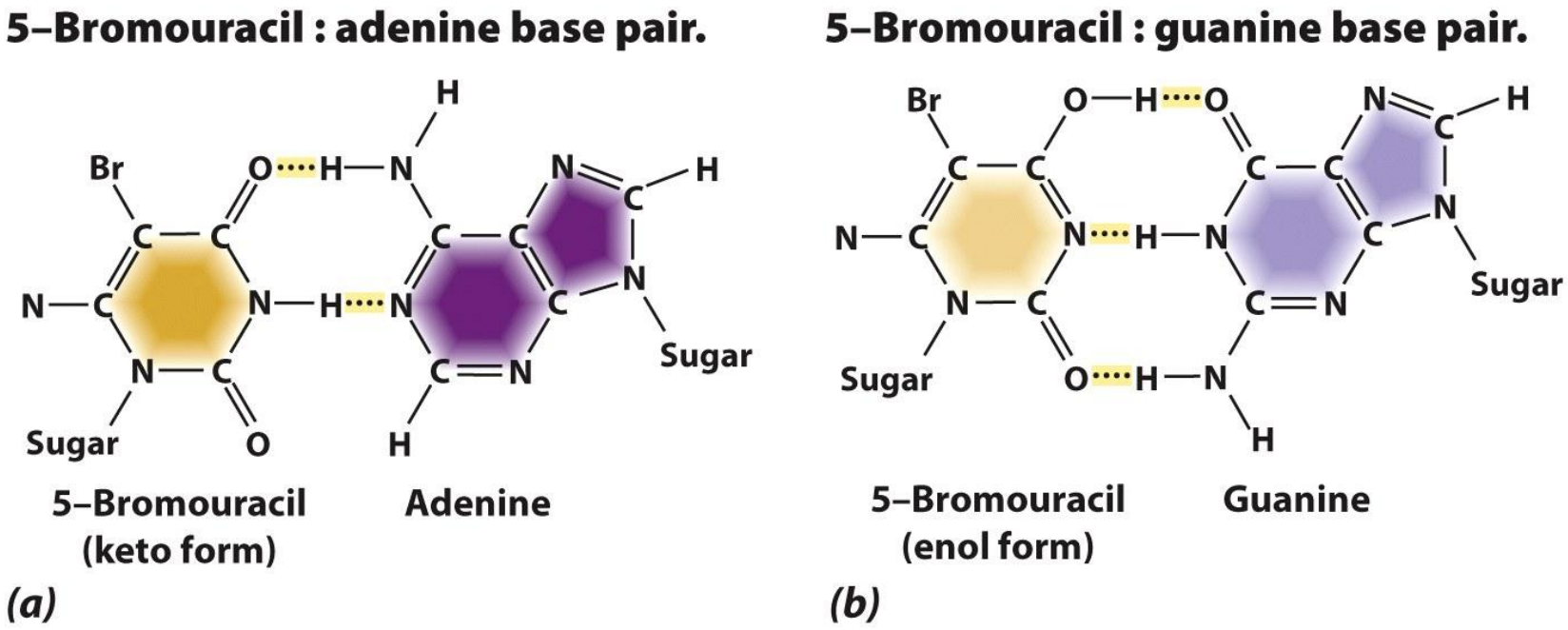
Hydroxylating agent

NH_2OH

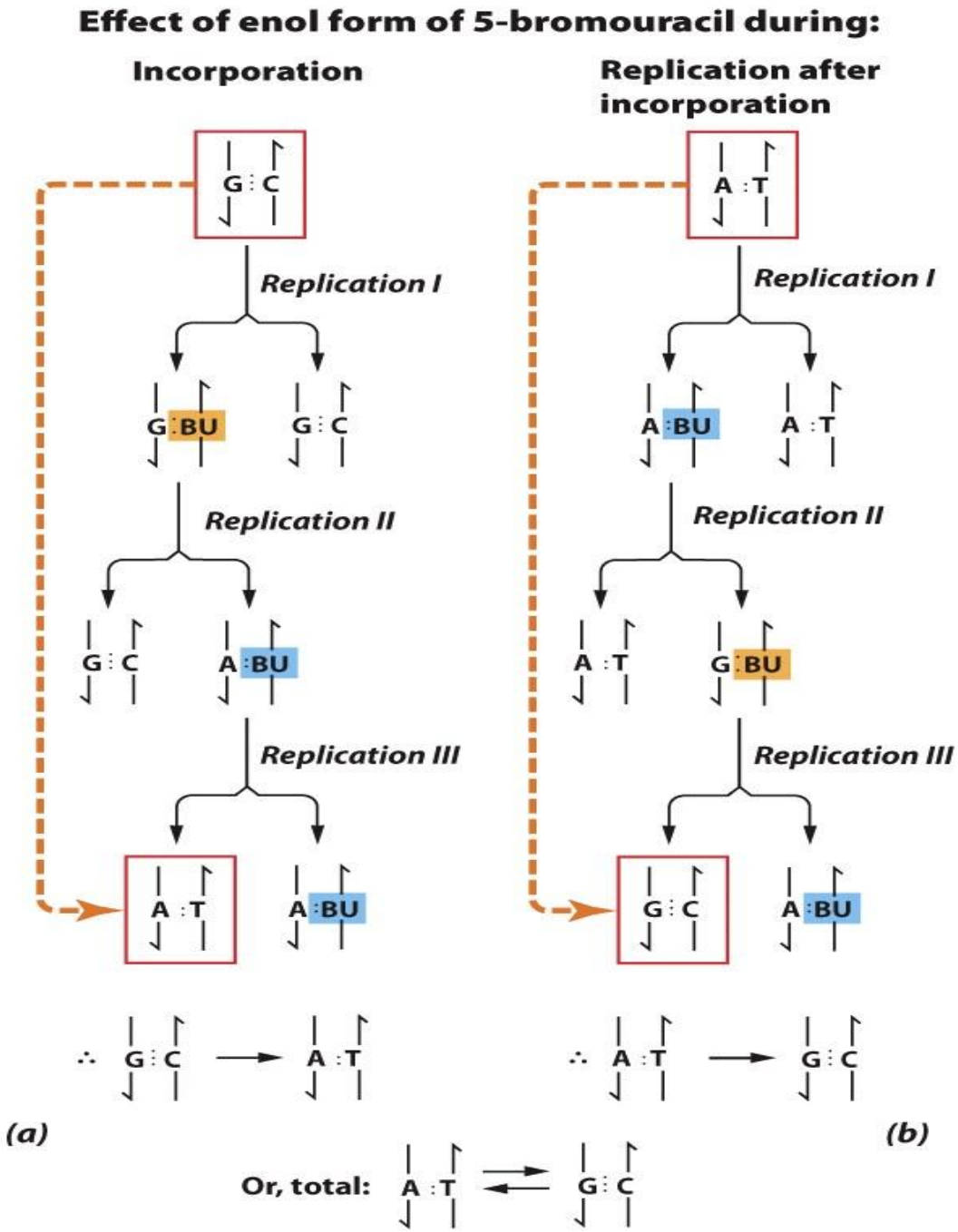
Hydroxylamine

(e)

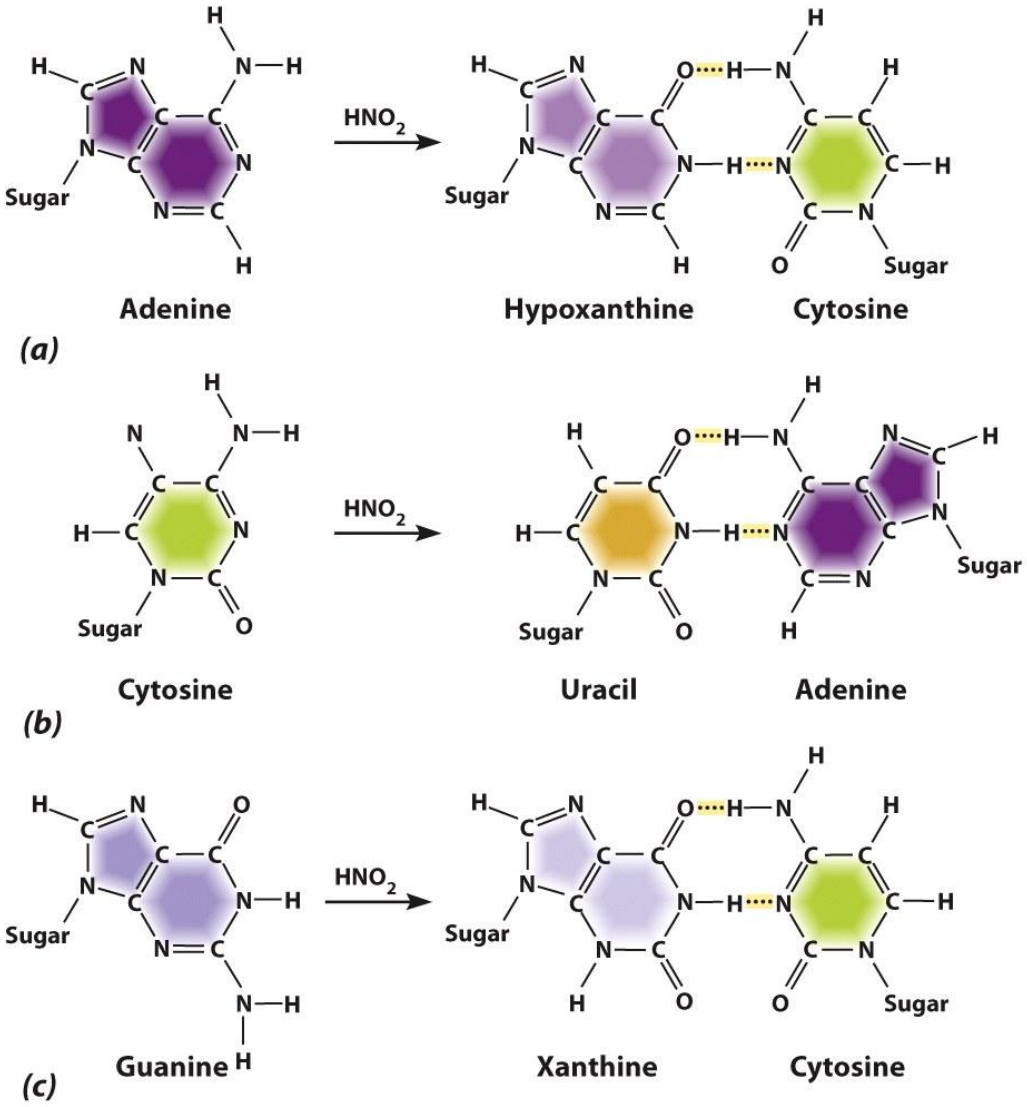
A Base Analog: 5-Bromouracil



Mutagenic Effects of 5-Bromouracil



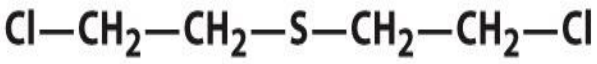
Nitrous Acid Causes Oxidative Deamination of Bases



Alkylating Agents

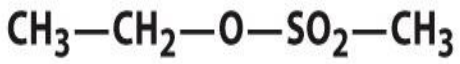
- chemicals that donate alkyl groups to other molecules.
- induce transitions, transversions, frameshifts, and chromosome aberrations.
- Alkylating agents of bases can change base-pairing properties.
- can also activate error-prone DNA repair processes.

Alkylating agents



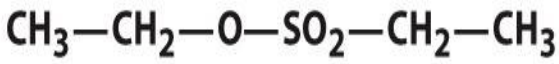
Di-(2-chloroethyl) sulfide

(Mustard gas)



Ethyl methane sulfonate

(EMS)



Ethyl ethane sulfonate

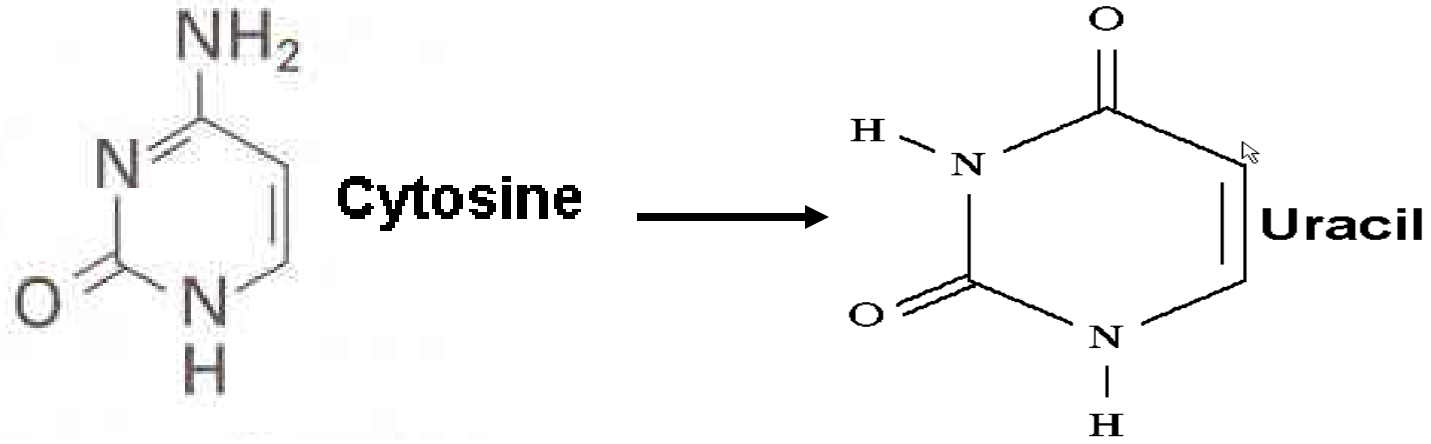
(EES)

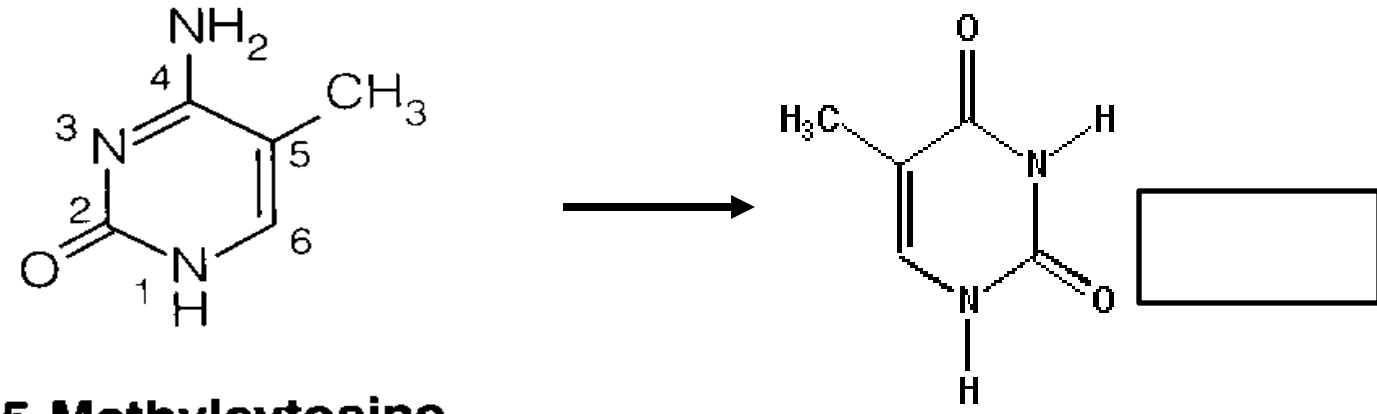
Hydroxylamine

- Hydroxylamine is a hydroxylating agent.
- Hydroxylamine hydroxylates the amino group of cytosine and leads to G:C → A:T transitions.

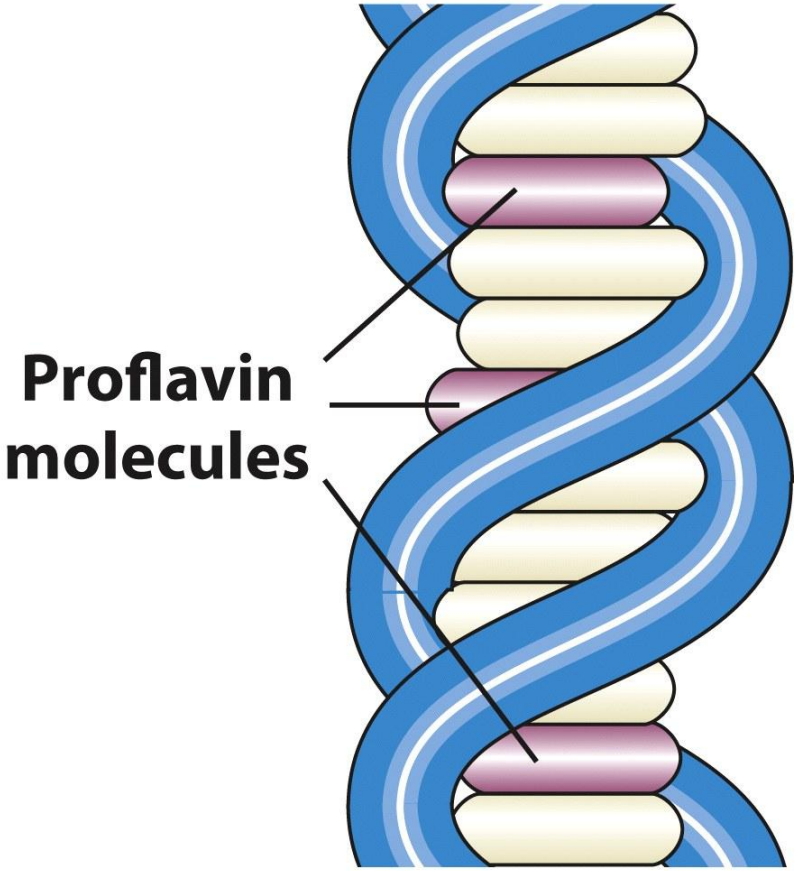
5 Methyl Cytosine Deamination

- Easily recognized and corrected
- What about 5-methyl cytosine?
- Is there a problem?
- Always remove T from a GT pair

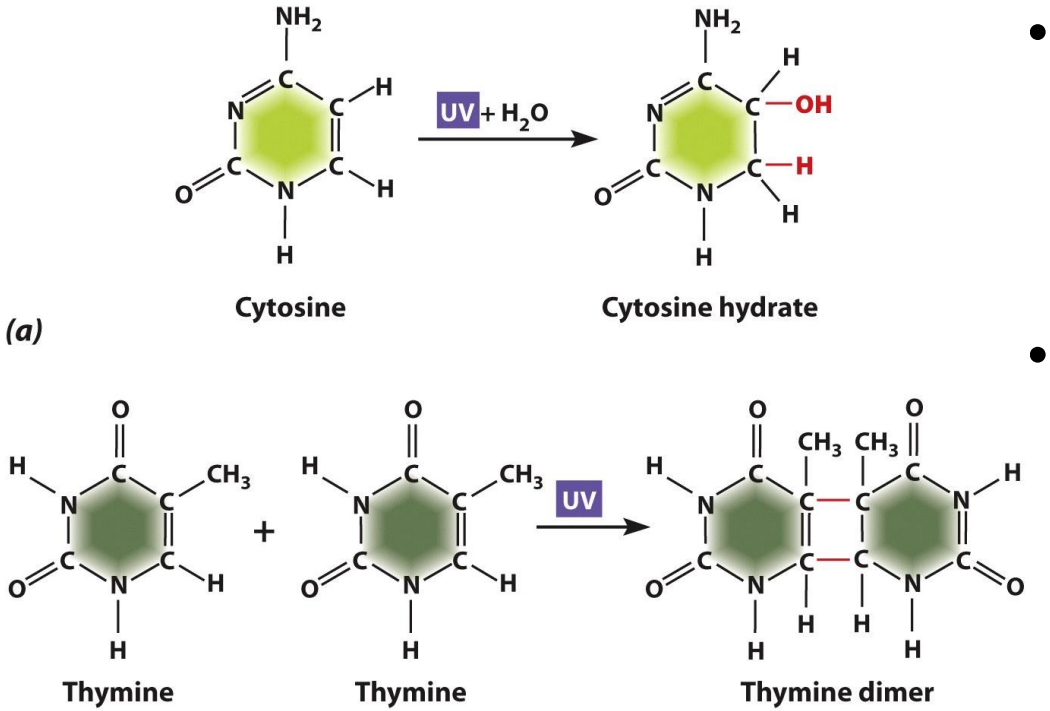




Intercalation of an Acridine Dye Causes Frameshift Mutations



Mutagenesis by Ultraviolet Irradiation



- Hydrolysis of cytosine to a hydrate may cause mispairing during replication
- Cross-linking of adjacent thymine forms thymidine dimers, which block DNA replication and activate error-prone DNA repair mechanisms.

Mutation Generation passed on to daughter DNAs

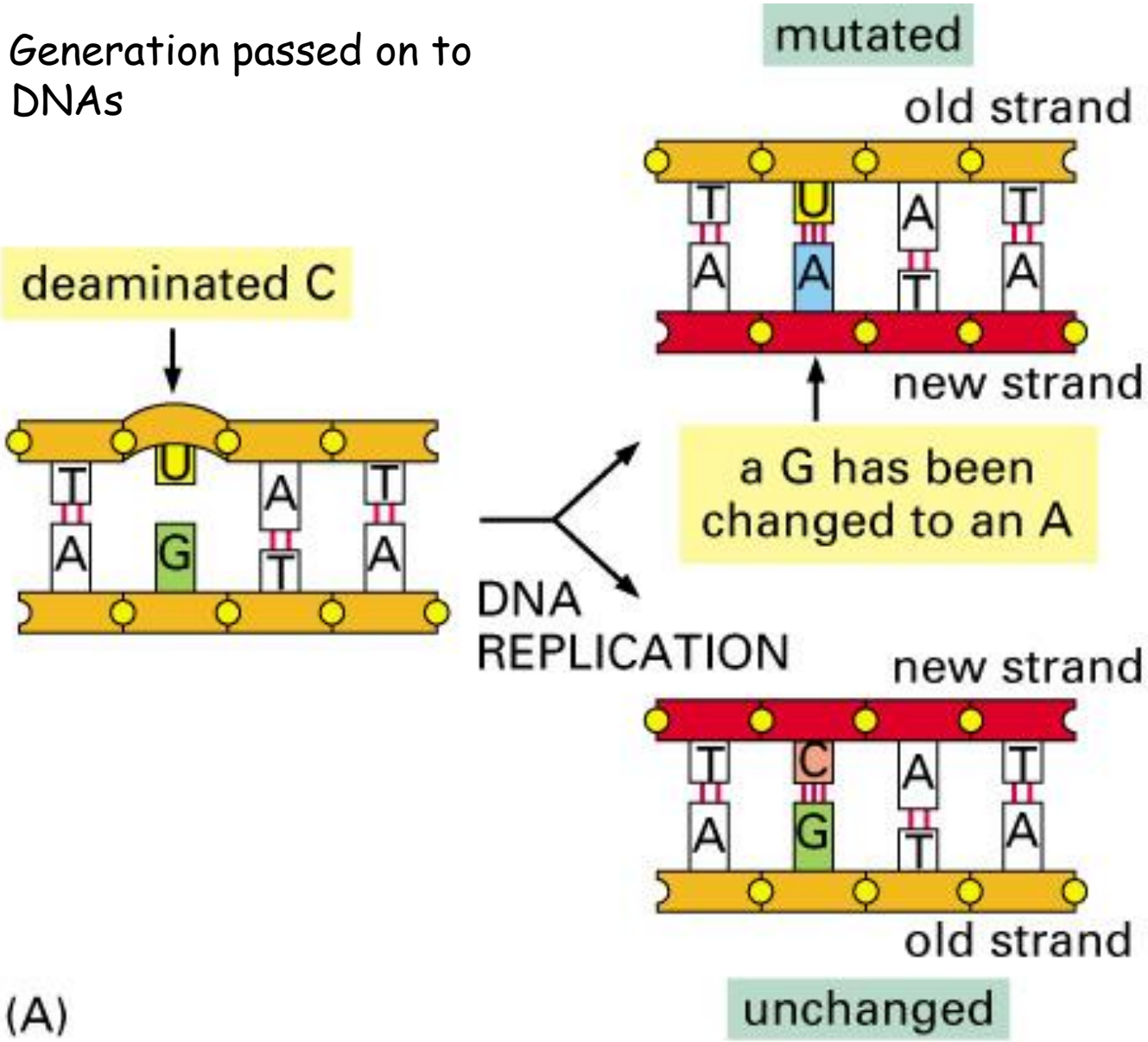


Figure 5–49 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Mutation Generation passed on to daughter DNAs

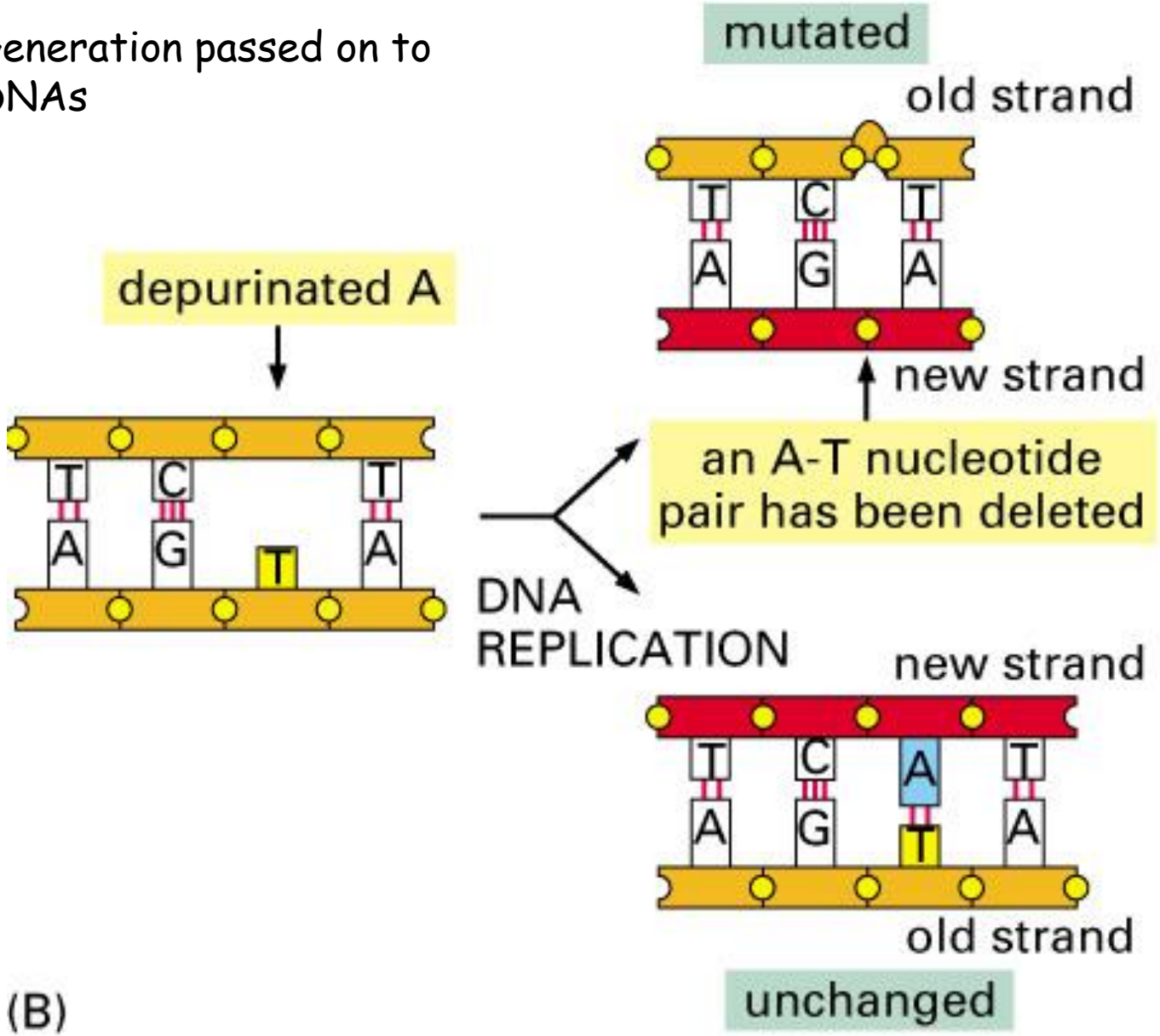


Figure 5–49 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

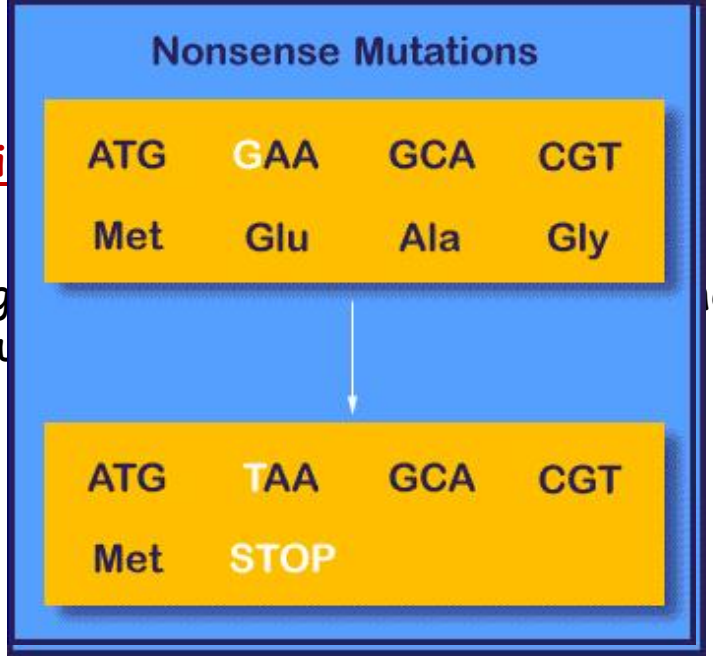
Somatic Mutations

- Occur in cells of the body, excluding the germline
- Affects subsequent somatic cell descendants
- Not transmitted to offspring

Germline Mutations

- Mutations that occur in the germline cells
- Possibility of transmission to offspring

Gene mutation (alteri

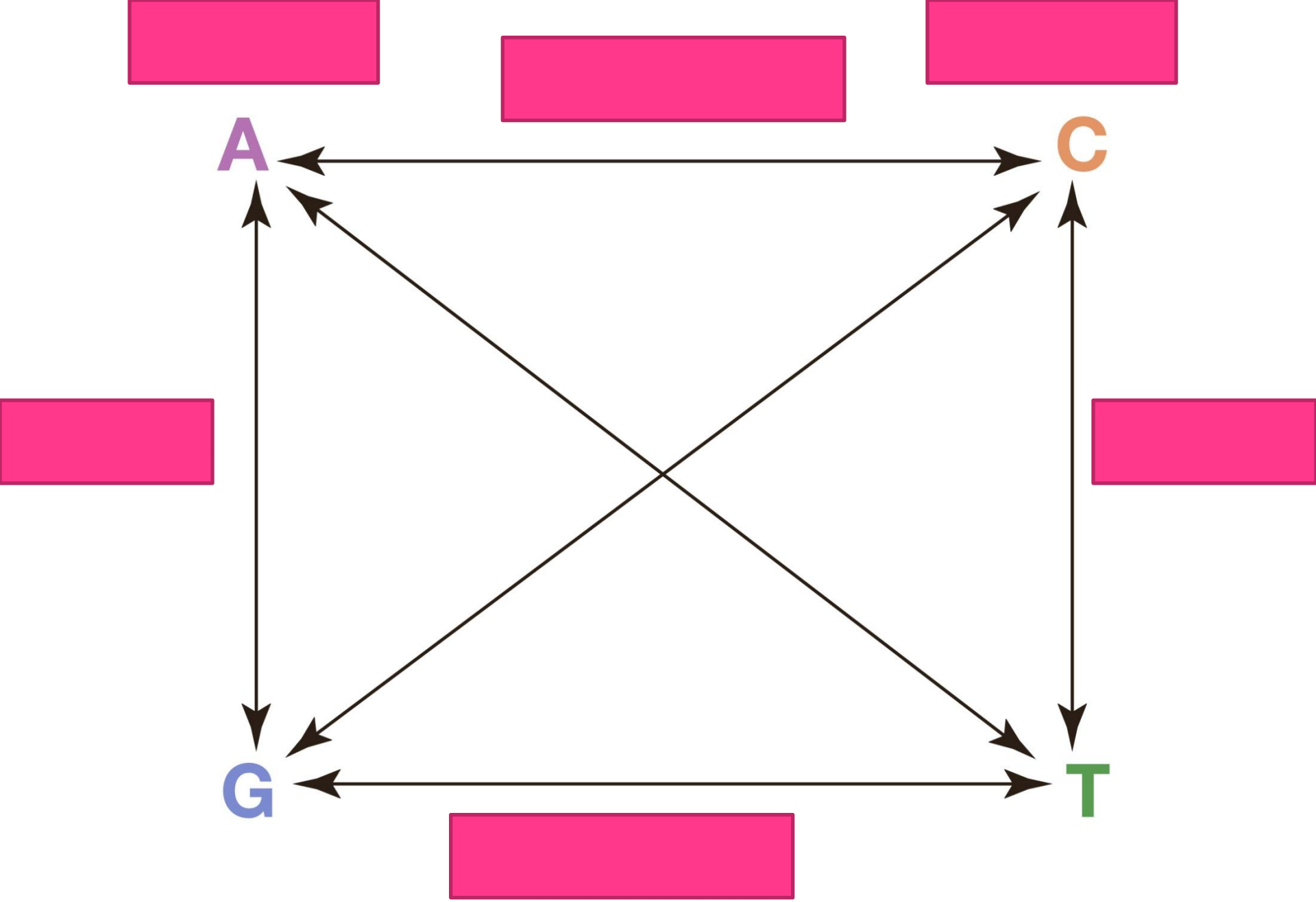


- **Point mutation:** chang e mRNA can lead to any of the following 3 resu

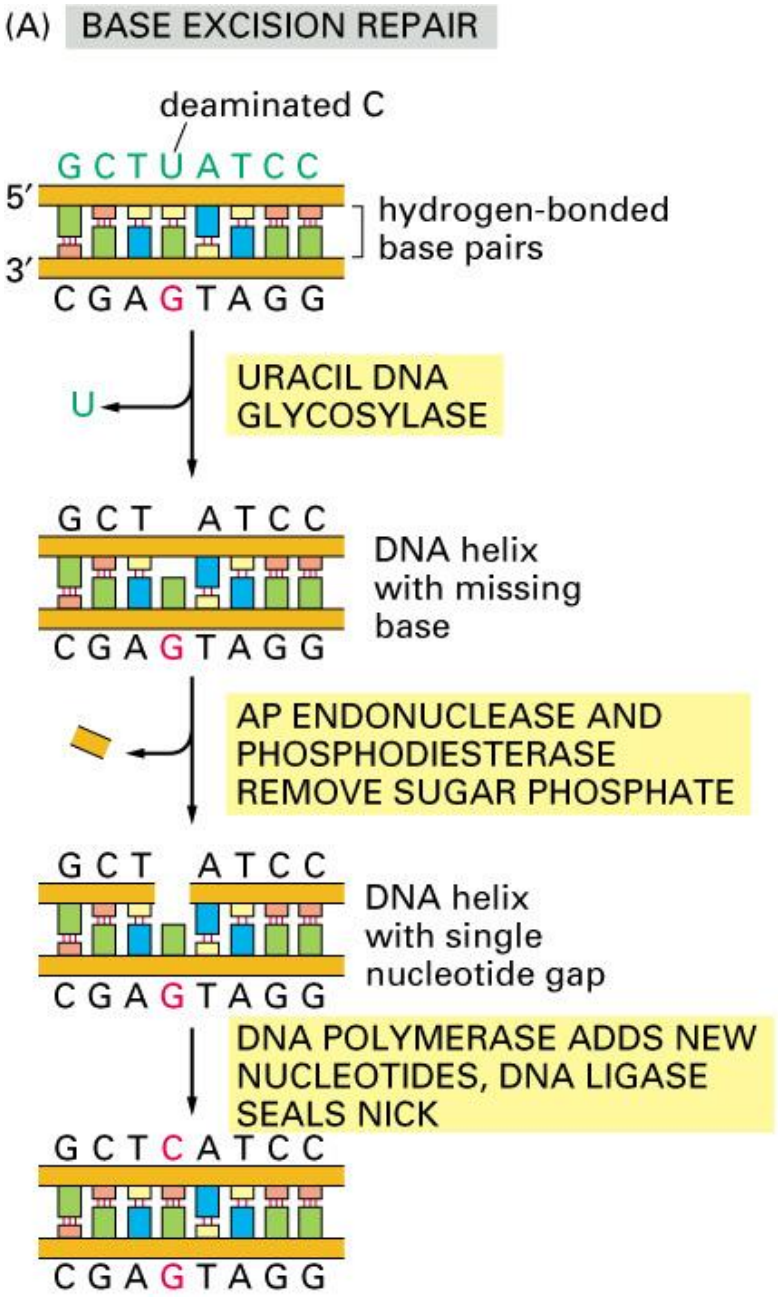
- **i- Silent mutation**: i.e. the codon containg the changed base may code for the same amino acid. For example, in serine codon UCA, if A is changed to U giving the codon UCU, it still code for serine. See table.

- **ii- Missense mutation:** the codon containing the changed base may code for a different amino acid. For example, if the serine codon UCA is changed to be CCA (U is replaced by C), it will code for proline not serine leading to insertion of incorrect amino acid into polypeptide chain.

- **iii- Non sense mutation:** the codon containing the changed base may become a termination codon. For example, serine codon UCA becomes UAA if C is changed to A. UAA is a stop codon leading to termination of translation at that point.



DNA Repair I



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DNA Repair II

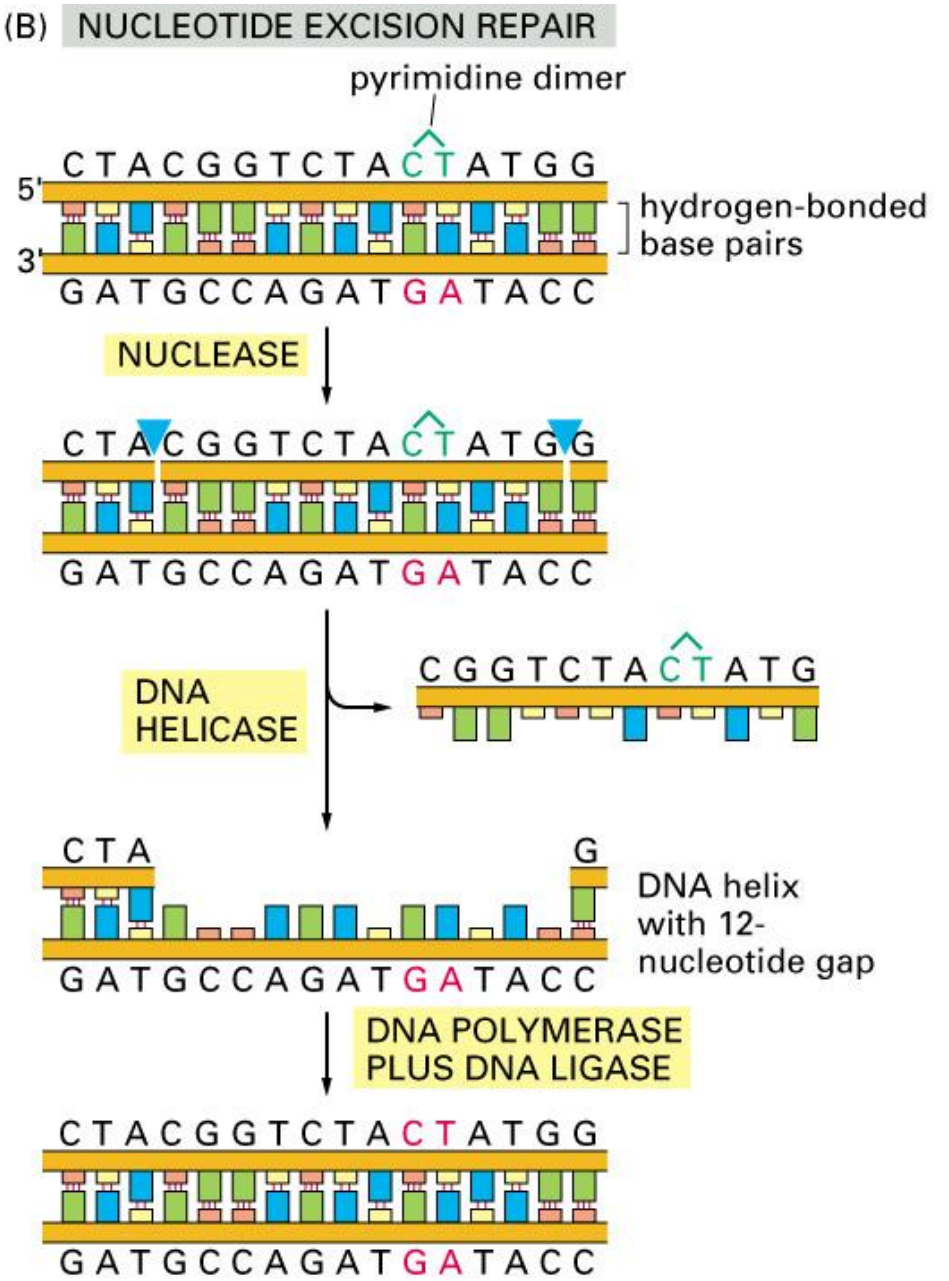

Figure 5–50 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Emergency DNA Repair for Double helix break

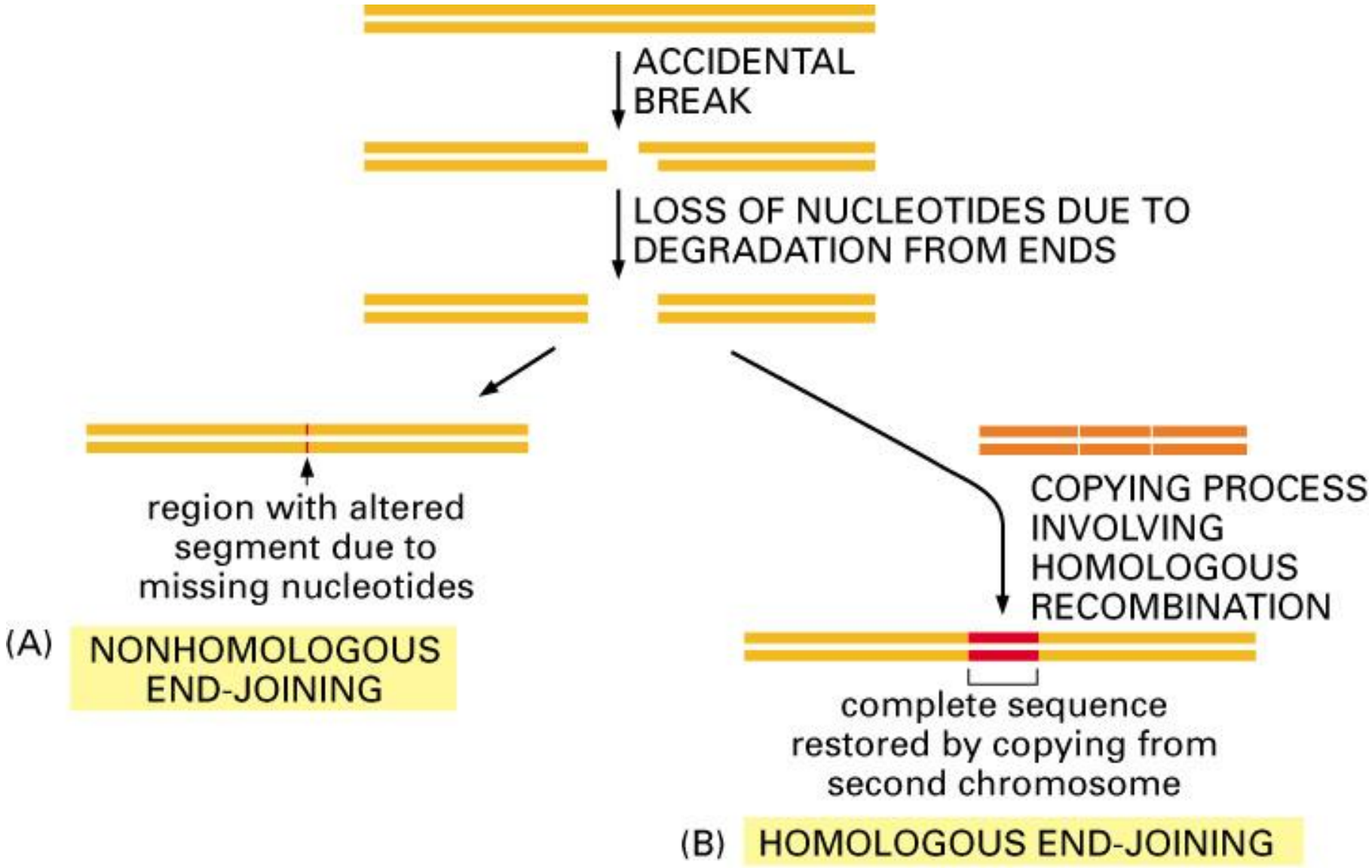

Figure 5–53. Molecular Biology of the Cell, 4th Edition.

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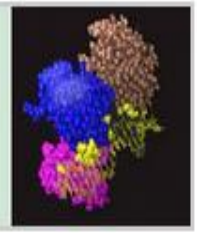

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Results: 1 to 20 of 5089

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Homo sapiens isocitrate dehydrogenase 1 (NADP+), soluble (IDH1), mRNA

1. 2,339 bp linear mRNA
   Accession: NM_005896.2 GI: 28178824
   GenBank FASTA Graphics Related Sequences

Homo sapiens nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1), transcript variant 3, mRNA

2. 1,347 bp linear mRNA
   Accession: NM_001037738.2 GI: 262331549
   GenBank FASTA Graphics Related Sequences

Homo sapiens nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1), transcript variant 2, mRNA

3. 1,362 bp linear mRNA
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Homo sapiens nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1), transcript variant 1, mRNA

4. 1,449 bp linear mRNA
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   GenBank FASTA Graphics Related Sequences

Azoarcus sp. KH32C DNA, complete genome

5. 5,081,166 bp circular DNA

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Homo sapiens isocitrate dehydrogenase 1 (NADP+), soluble (IDH1), mRNA

NCBI Reference Sequence: NM_005896.2

FASTA Graphics

Go to:

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            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 2339)
  AUTHORS   Gerardo Valadez,J., Grover,V.K., Carter,M.D., Calcutt,M.W.,
            Abiria,S.A., Lundberg,C.J., Williams,T.U. and Cooper,M.K.
  TITLE     Identification of Hedgehog pathway responsive glioblastomas by
            isocitrate dehydrogenase mutation
  JOURNAL   Cancer Lett. 328 (2), 297-306 (2013)
   PUBMED   23063752
  REMARK    GeneRIF: This study demonstrates that IDH mutation is a reliable
            surrogate marker for identifying malignant gliomas with an operant
            Hedgehog pathway.
REFERENCE   2  (bases 1 to 2339)
  AUTHORS   Jin,G., Reitman,Z.J., Duncan,C.G., Spasojevic,I., Gooden,D.M.,
```

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Articles about the IDH1 gene
Disruption of wild-type IDH1 suppresses D-2-hydroxyglutarate productio [Cancer Res. 2013]
Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and bic [Cancer Cell. 2012]
Prospective serial evaluation of 2-hydroxyglutarate, during treatme [Blood. 2012]
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Pathways for the IDH1 gene
Abnormal conversion of 2-oxoglutarate to 2-

publications that are available for this gene. Please see the Gene record to access additional publications.

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##RefSeq-Attributes-END##
COMPLETENESS: complete on the 3' end.

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Turn Off Clear
Homo sapiens isocitrate dehydrogenase 1 (NADP+), soluble (IDH1), mRNA Nucleotide
IDH (5089) Nucleotide
See more...

ORIGIN

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       61 tgggattgcc aggctgtggt tgtgagtctg agcttgtgag cggctgtggc gccccaactc
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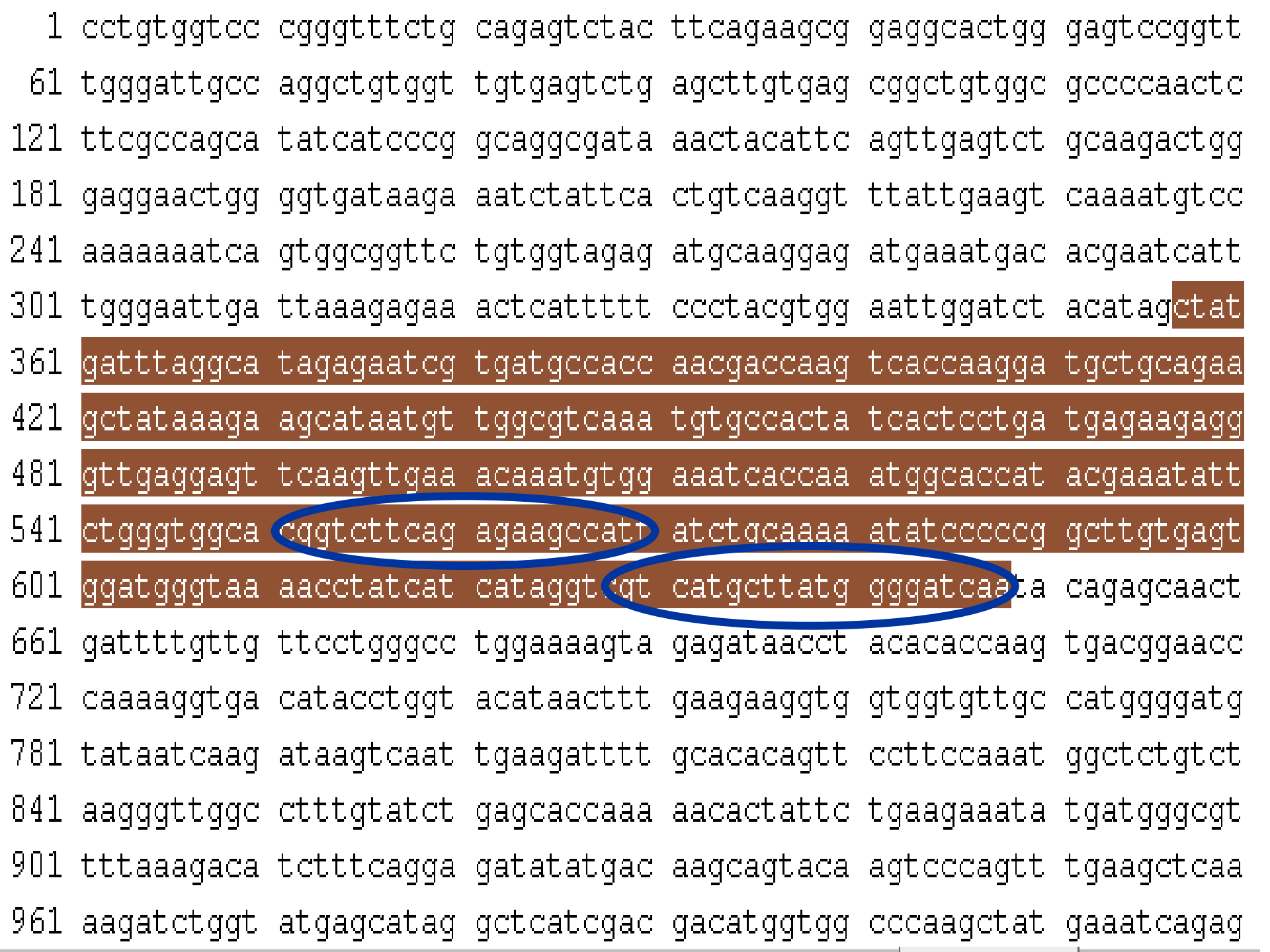
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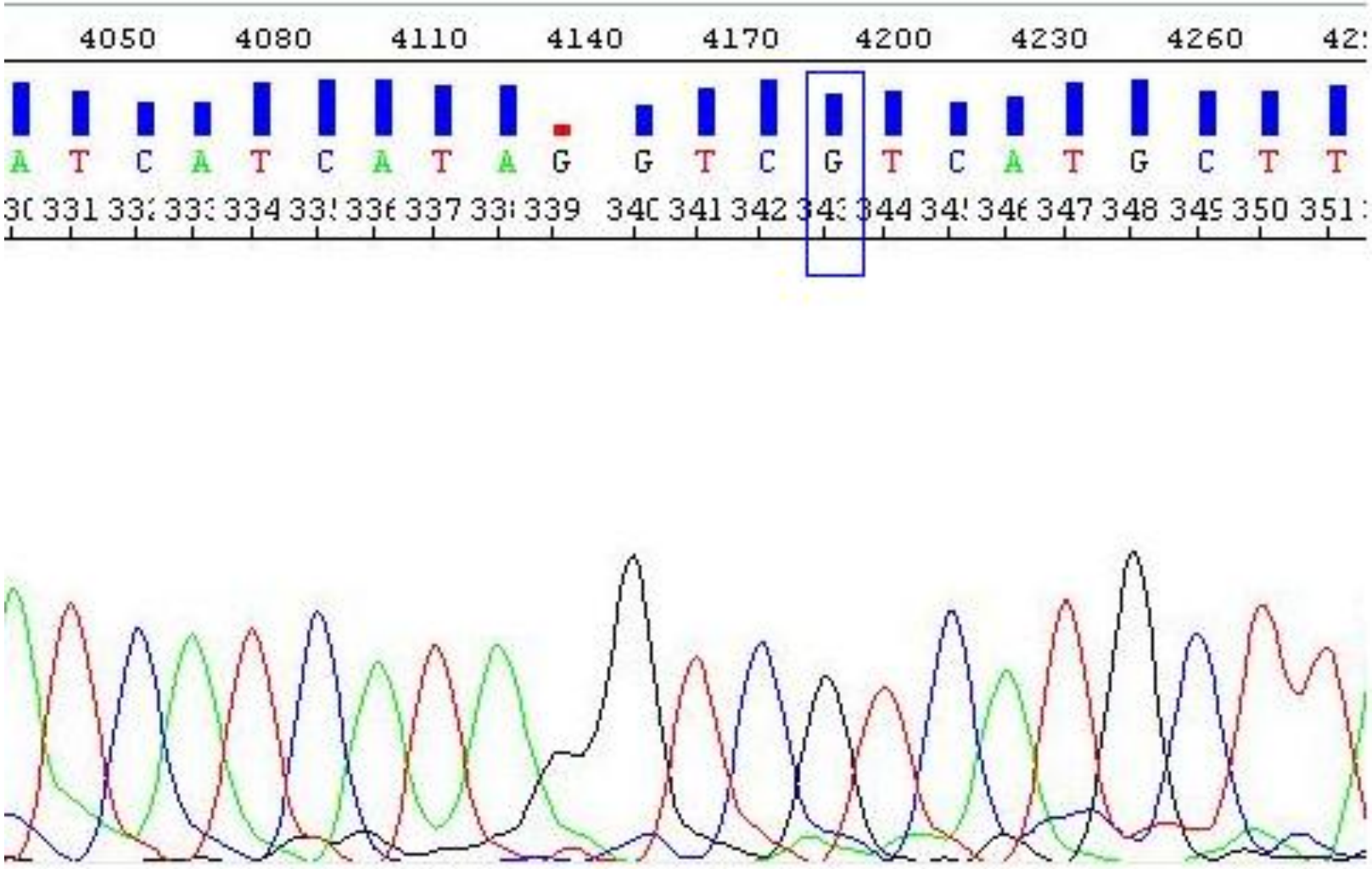

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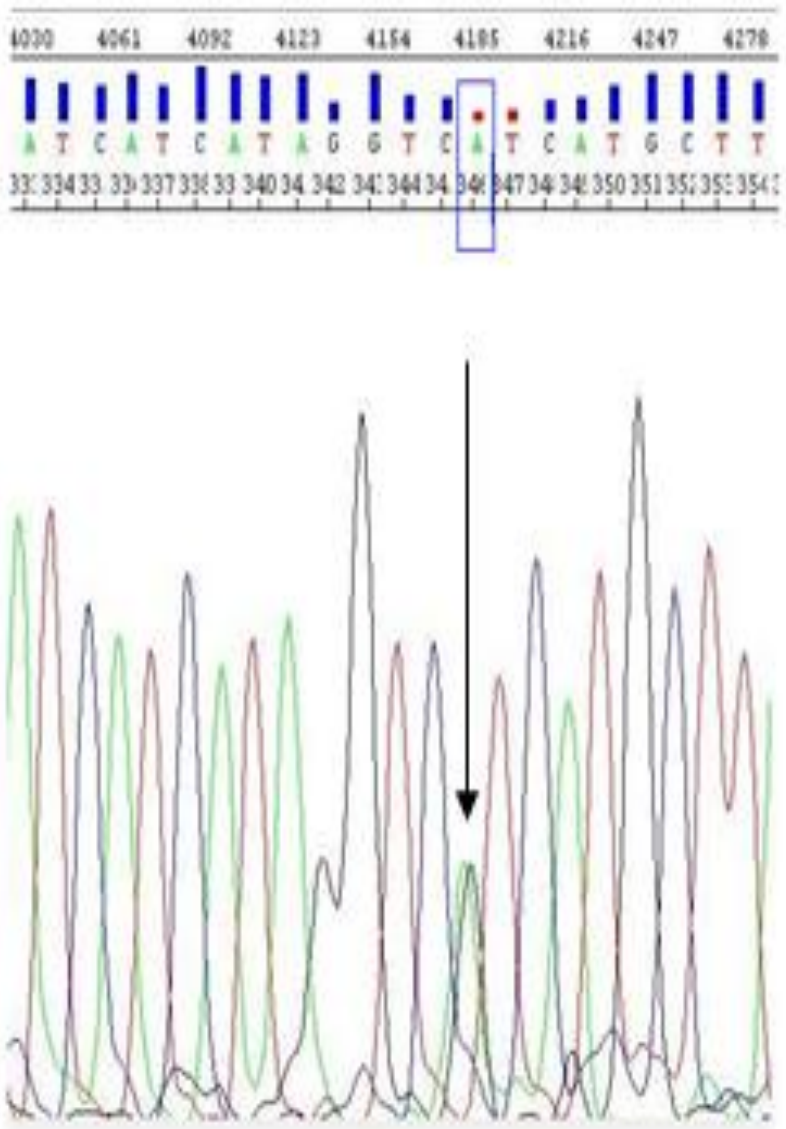

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