Molecular Biology : is the branch of biology that deals with the formation, structure, and function of macromolecules essential to life such as nucleic acids and proteins, especially with their role in cell replication and the transmission of genetic information.

Discovery of the Structure of DNA

1- In 1953, James Watson and Francis Crick discovered the double helical structure of DNA • The scientific framework for their breakthrough was provided primarily by: – Rosalind Franklin (X-ray diffraction) – Erwin Chargaff (chemical composition)

2- Rosalind Franklin :- She used X-ray diffraction to study wet fibers of DNA • The diffraction pattern she obtained suggested several structural features of DNA – Helical – More than one strand – 10 base pairs per complete turn

3- Erwin Chargaff's Experiment Chargaff pioneered many of the biochemical techniques for the isolation, purification and measurement of nucleic acids from living cells

4- Chargaff's rule Percent of adenine = percent of thymine (A=T) Percent of cytosine = percent of guanine (C=G) A+G = T+C (or purines = pyrimidines)

Terminology:

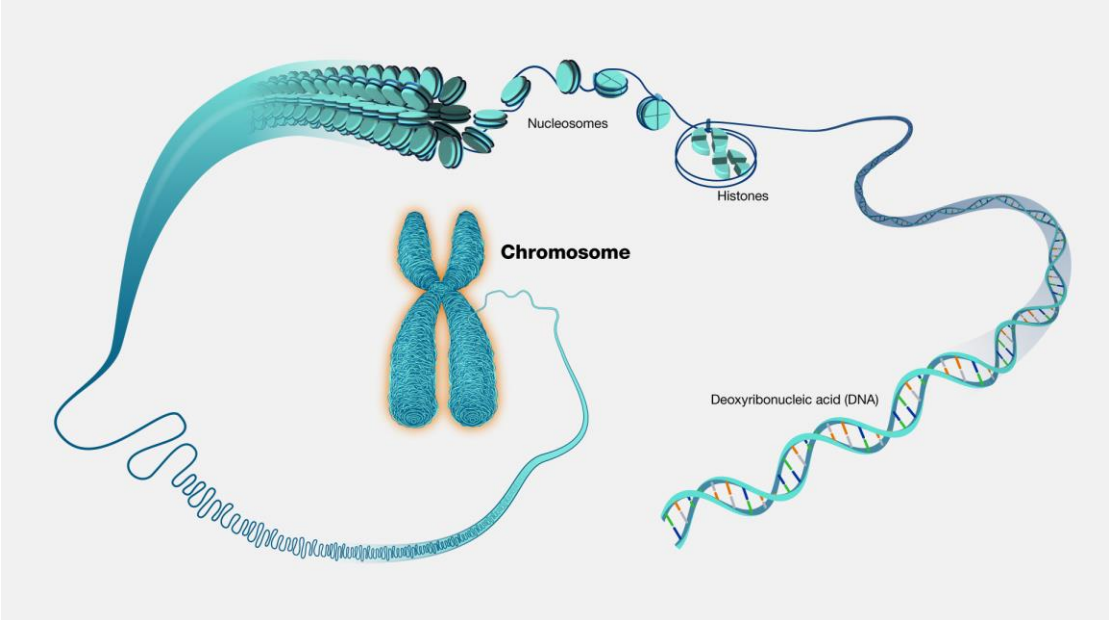
- Genome: all the genetic material in a cell
- Gene : segment of DNA that encodes a functional product , usually a protein .
- Genotype : Genes of an organism
- Phenotype : Expression of the genes.

The Genome:

- The book (genome) would contain 23 chapters (chromosomes)
- Each chapter contains 48 to 250 million letters (A,C,G,T) without spaces.
- Hence , the book contains over 3.2 billion letters total .
- At least one copy of the book (all 23 chapters) is contained in most cells of our body . the only exception in humans is found in mature red blood cells which become enuleated during development and therefore lack a genome .

Chromosomes:

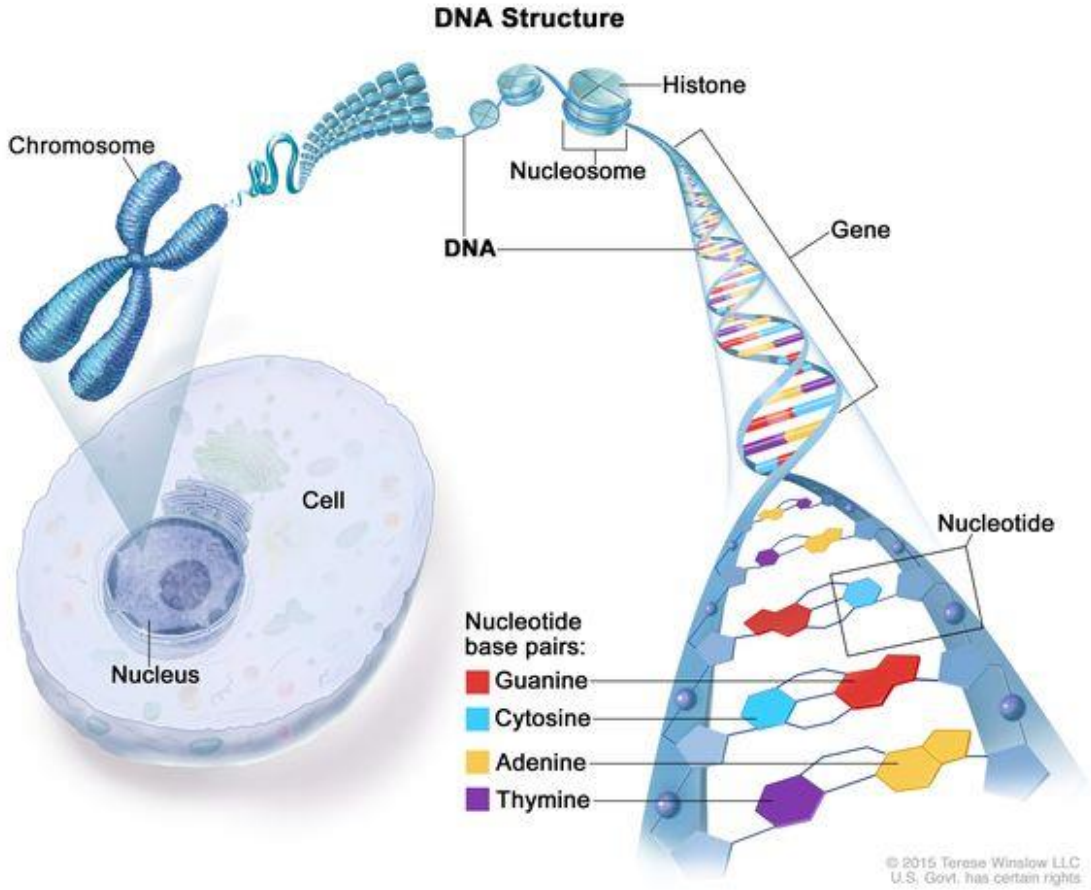
Chromosomes are large subcellular structures, that are found in the nuclei of most eukaryotic cells. Each chromosome consists of a single very long DNA molecule.Humans have 22 pairs of numbered chromosomes (autosomes) and one pair of sex chromosomes (XX or XY), for a total of 46. Each pair contains two chromosomes, one coming from each parent, which means that children inherit half of their chromosomes from their mother and half from their father.



Nucleotide:

A molecule consisting of a nitrogen-containing base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a phosphate group, and a sugar (deoxyribose in DNA; ribose in RNA).

Chromosomes have proteins called histones that bind to DNA. DNA has two strands that twist into the shape of a spiral ladder called a helix. DNA is made up of four building blocks called nucleotides: adenine (A), thymine (T), guanine (G), and cytosine (C). The nucleotides attach to each other (A with T, and G with C) to form chemical bonds called base pairs, which connect the two DNA strands. Genes are short pieces of DNA that carry specific genetic information.


DNA Structure
Chromosome
Histone
Nucleosome
DNA
Gene
Cell
Nucleotide
Nucleus
Nucleotide base pairs:
Guanine
Cytosine
Adenine
Thymine
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(Cell cycle)

The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division. The goal of the cell cycle is to produce two daughter cells, each containing chromosomes identical to those of the parent cell.

Phases of the Cell Cycle The cell cycle incorporates two principal phases: the interphase, and the M phase (mitosis).

A) Interphase: It represents continuous growth of the cell and is subdivided into three phases, G1 (gap1) phase, S (synthesis) phase, and G2 (gap 2) phase.

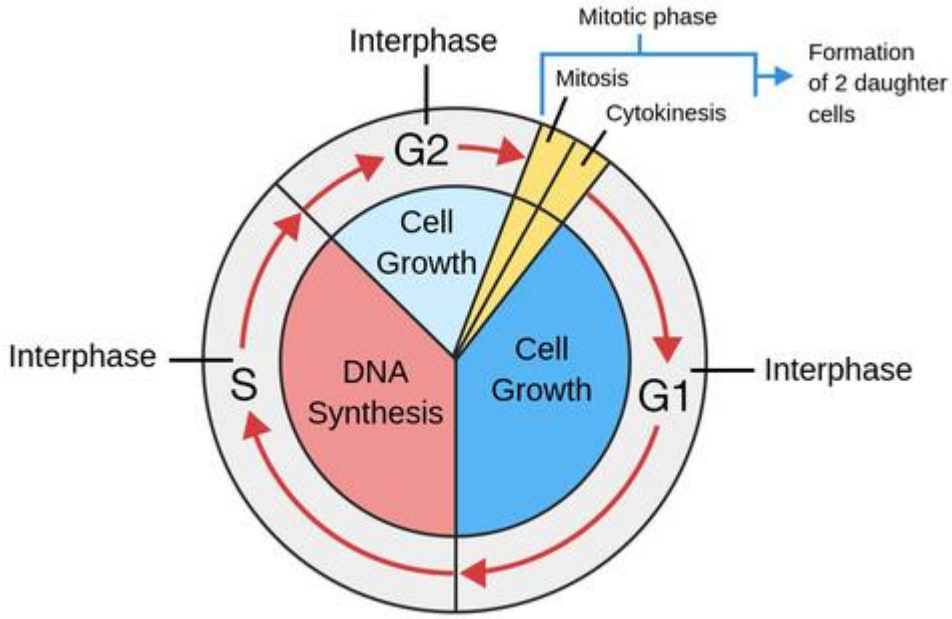
1) **The G1 phase**:- It is usually the longest and the most variable phase of the cell cycle, and it begins at the end of M phase. During the G1 phase, the cell gathers nutrients and synthesizes RNA and proteins necessary for DNA synthesis and chromosome replication.

2) **The S phase** :- (DNA replication) Initiation of DNA synthesis marks the beginning of the S phase, which is about 7.5 to 10 hours in duration. The DNA of the cell is doubled during the S phase, and new chromatids are formed.

3) **The G2 phase**:- (cell preparation for cell division) During this phase, the cell examines its replicated DNA in preparation for cell division. This is a period of cell growth and reorganization of cytoplasmic organelles before entering the mitotic cycle. The G2 phase may be as short as 1 hour in rapidly dividing cells or of nearly indefinite duration in some polyploid

cells and in cells such as the primary oocyte that are arrested in G2 for extended periods.

B) Mitosis (M) phase Mitosis nearly always includes both karyokinesis (division of the nucleus) and cytokinesis (division of the cell) and lasts about 1 hour.



Cell cycle

Cell Cycle Checkpoints :- Throughout the cell cycle, several internal quality control mechanisms or checkpoints represented by biochemical pathways control transition between cell-cycle stages.

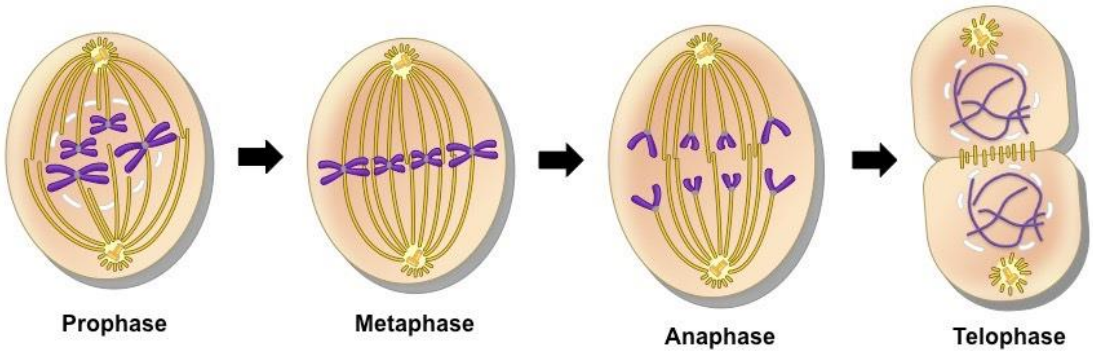
Phases of Mitosis

1. **Prophase**: The replicated chromatin condenses and become visible as chromosomes. Each chromosome can be seen to consist of two chromatids. The sister chromatids are held together by the ring of proteins at the centromere. In late prophase, the nuclear envelope begins to disintegrate, and the nucleolus completely disappears. In addition, a highly specialized protein complex called a kinetochore appears on each chromatid opposite to the centromere.

2. **Metaphase**: Formation of the mitotic spindle, consisting of three types of microtubules, that becomes organized around the centrosomes, the astral microtubules, the polar microtubules and the kinetochore microtubules.

3. **Anaphase:** Separation of sister chromatids. This separation occurs when the proteins that have been holding the chromatids together break down. The separated chromatids are pulled to opposite poles of the cell by the sliding along the kinetochore microtubules toward the centrosomes.

4. **Telophase**: Reconstitution of a nuclear envelope around the chromosomes at each pole. The chromosomes uncoil and become indistinct. The nucleoli reappear, and the cytoplasm divides (cytokinesis) to form two daughter cells.



Stage of mitosis

Meiosis

Meiosis involves two sequential nuclear divisions followed by cell divisions that produce gametes (sex cells) containing half the number of chromosomes and half the DNA found in somatic cells. ″ The zygote (the cell resulting from the fusion of an ovum and a sperm) and all the somatic cells derived from it are diploid (2n) in chromosome number (46 chromosomes in human); thus, their cells have two copies of every chromosome and every gene encoded on this chromosome. ″ These chromosomes are called homologous chromosomes because they are similar but not identical; one set of chromosomes is of maternal origin, the other is from paternal origin. ″ The gametes, having only one member of each chromosome pair, are described as haploid (1n). ″ During gametogenesis, reduction in chromosome number to the haploid state (23 chromosomes in humans) occurs through meiosis.

Phases of Meiosis I

1. **Prophase I**: It is an extended phase that is subdivided into the following five stages:

   Leptotene: chromosomes start to condense.

   Zygotene: homologous chromosomes become closely associated (synapsis) to form pairs of chromosomes (bivalents) consisting of four chromatids (tetrads).

   Pachytene: crossing over between pairs of homologous chromosomes to form chiasmata (sing. chiasma).

   Diplotene: homologous chromosomes start to separate but remain attached by chiasmata.

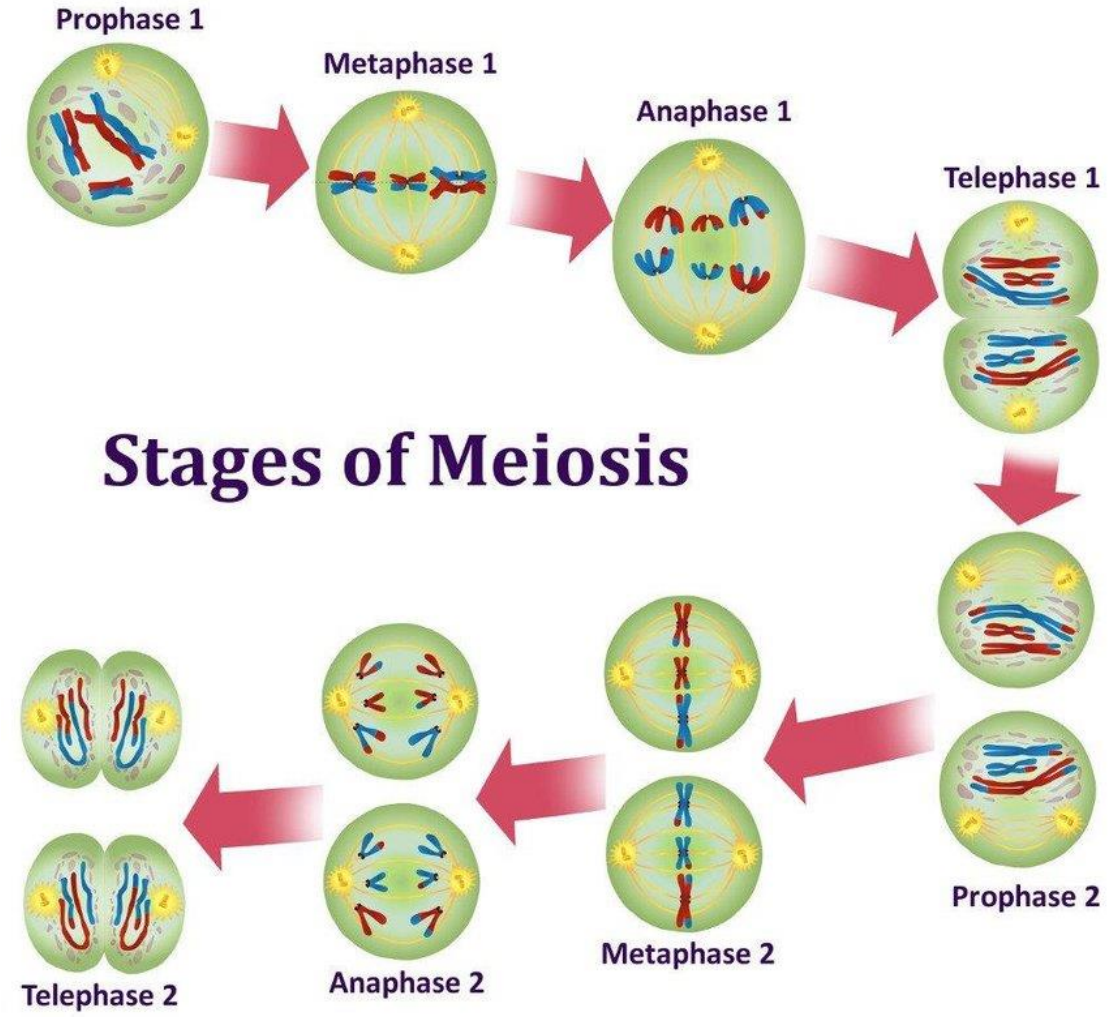
   Diakinesis: homologous chromosomes continue to separate, and chiasmata move to the ends of the chromosomes.

2. Metaphase I: Metaphase I is similar to the metaphase of mitosis except that the paired chromosomes are aligned at the equatorial plate with one member on either side. The chiasmata are cut, and the homologous chromosomes separate completely. The spindle microtubules begin to interact with the chromosomes through the kinetochore at the centromere.

3. **Anaphase I**: The sister chromatids, held together by protein complexes and by the centromere, remain together. A maternal or paternal member of each homologous pair moves to each pole.

Phases of Meiosis II: ″ After meiosis I, the cells quickly enter meiosis II without passing through an S phase. ″ Meiosis II is an equatorial division and resembles mitosis. ″ During this phase, the sister chromatids

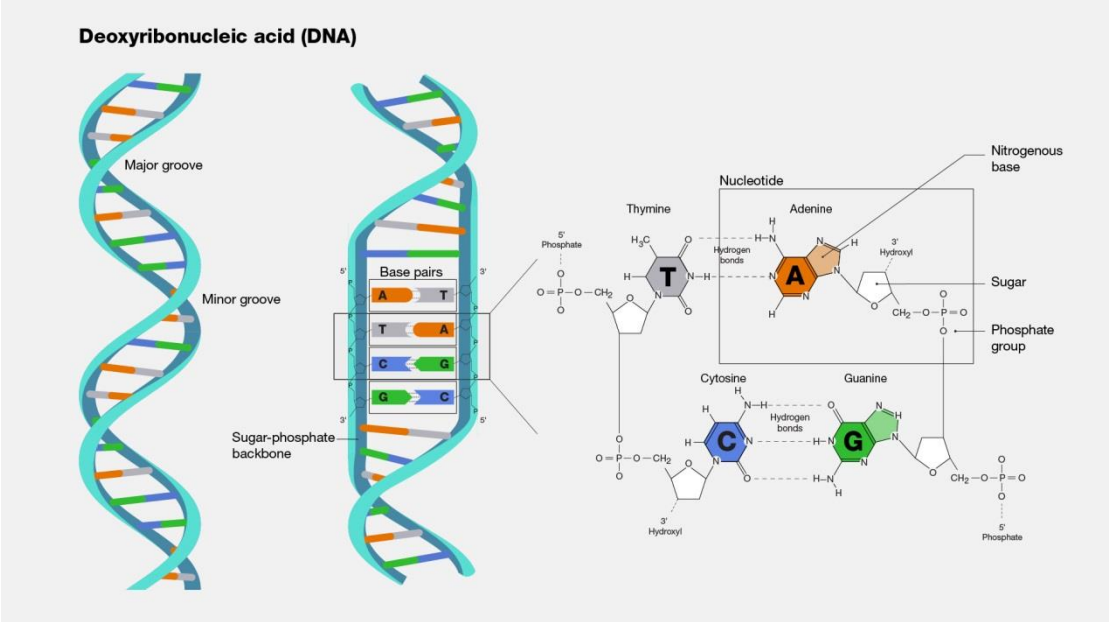
will separate at anaphase II and move to opposite poles of the cell. " During meiosis II, the cells pass through prophase II, metaphase II, anaphase II, and telophase II



Stage of meiosis

(DNA and RNA structure)

Deoxyribonucleic acid (DNA):- is a molecule composed of two chains (made of nucleotides) which coil around each other to form a double helix carrying the genetic instructions used in the growth, development, functioning and reproduction of all known living organisms and many viruses. nucleic acids are one of the four major types of macromolecules that are essential for all known forms of life.

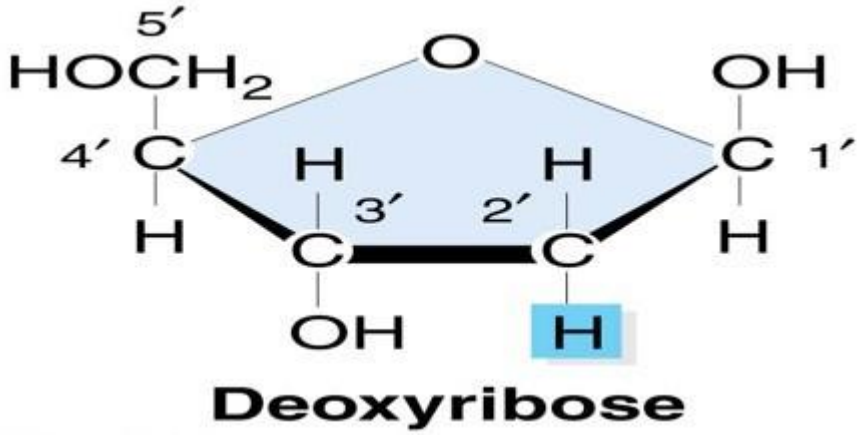


Deoxyribonucleic acid (DNA)

Components of DNA

There are three components, a pentose sugar, phosphoric acid and nitrogenous bases which combine to form monomer unit called as nucleotide. Large number of nucleotides joins to form polynucleotide chain. Each nucleotide is composed of one of four nitrogen-containing nucleobases i.e., cytosine (C), guanine (G), adenine (A) or thymine (T), a sugar called deoxyribose, and a phosphate group. The nucleotides are joined to one another in a chain by covalent bonds between the sugar of one nucleotide and the phosphate of the next, resulting in an alternating sugar-phosphate backbone. The nitrogenous bases of the two separate polynucleotide strands are bound together, according to base pairing rules (A with T and C with G), with hydrogen bonds to make double-stranded DNA. **The three components of DNA are**:

(1) Sugar: The sugar present in DNA is a pentose sugar (Fig. 5.2) called as deoxyribose sugar. Its name indicates that it is derived from ribose sugar by loss of an oxygen atom. Deoxyribose sugar joins with a nitrogenous base to form nucleoside.



Structure of deoxyribose

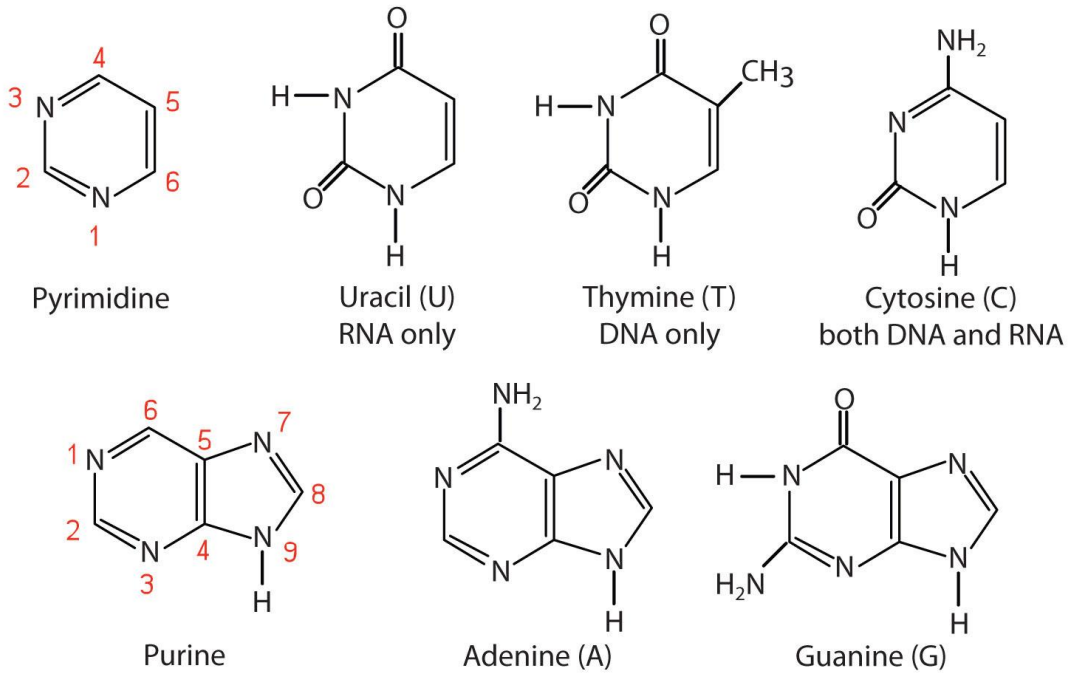
(2) Phosphoric acid:- Phosphoric acid along with sugar molecule forms the backbone of polynucleotide chain. The bond formed by a phosphate between the sugar molecules of two different nucleotides is called phosphodiester bond. In one strand of DNA helix the phosphodiester bond is formed in the direction 3'-5' direction and in the other strand of the helix phosphodiester bonds are formed in 5'-3' direction.

(3) Nitrogenous bases :-There are four nitrogenous bases present in structure of DNA which are grouped into two classes called as purines and pyrimidines. The complementary nitrogenous bases are divided into two groups, pyrimidines and purines. In DNA, the pyrimidines are thymine and cytosine; the purines are adenine and guanine.

Pyrimidines

Pyrimidines :- are simple aromatic compounds composed of carbon and nitrogen atoms in a sixmembered, heterocyclic ring system. The name also refers to a specific compound (composition C4H4N2), not found in nature that can be regarded as the parental structure of a wide range of naturally occurring chemical species. The most abundant naturally occurring pyrimidines are uracil (2, 4-dihydroxypyrimidine), cytosine (2-hydroxy-4-aminopyrimidine), and thymine (2, 4- dihydroxy-5-methyl pyrimidine). The first two are found predominantly in RNA, while the latter two are found predominantly in DNA. Small amounts of thymine are found in transfer RNA. The two pyrimidines found in DNA are usually base-paired with a purine residue on the complementary strand,

so the purine to pyrimidine ratio in DNA is unity. In RNA, which is single-stranded, this ratio varies widely



Structure of nitrogen base (pyrimidine and purine)

A purine:- is a heterocyclic aromatic organic compound that consists of a pyrimidine ring fused to an imidazole ring. Purine gives its name to the wider class of molecules Purine is water soluble, are found in high concentration in meat and meat products, especially internal organs such as liver and kidney. All purines contain a double-ringed structure that consists of a six-membered ring fused to a five-membered ring; think of a honeycomb cell attached to a pentagon.

Nucleoside and Nucleotide

A **nucleoside** is a nitrogenous base (purine or pyrimidine) bound to a pentose sugar ribose or deoxyribose. A nitrogenous base (also called nucleobase) is a nitrogen-containing compound that may form a nucleoside when they are attached to a five-carbon sugar ribose *or* deoxyribose.

A nucleotide is the basic building block of nucleic acids (RNA and DNA). A nucleotide consists of a sugar molecule (either ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base. The bases used in DNA are adenine (A), cytosine (C), guanine (G) and thymine (T). In RNA, the base uracil (U) takes the place of thymine. DNA and RNA molecules are polymers made up of long chains of nucleotides.

Structure of DNA

Primary structure

A single DNA chain is a long, threadlike molecule made up of a large number of deoxyribonucleotides. The primary structure includes all covalent bonds of the molecule similarly to the linear array of amino acids in the primary structure of proteins. The backbone of the primary structure consists of deoxyriboses linked by phosphodiester bridges. The phosphodiester bonds are formed between the 3'- and 5'-hydroxyl of the successive sugar molecules

Secondary structure

The secondary structure of DNA consists of two polynucleotide chains wrapped around one another to form a double helix. The orientation of the helix is usually right handed with the two chains running antiparallel to one another.

Tertiary structure

refers to the steric relationship of segments of DNA that are apart in the linear sequence. A circular double-stranded DNA without any folding is known as a relaxed DNA. This is the simplest and most stable tertiary structure of DNA. Viral DNAs can exist in a relaxed state in the cell

Different forms of DNA :- There are six known different morphological forms of DNA double helix. These have been named as A, B, C, D, E and Z DNA. Out of these six forms only B-DNA and Z-DNA are found to occur as cellular DNA

A-DNA A-DNA :- is a rare type of structural conformation that a DNA can adopt under dehydrating conditions. A-DNA is a double stranded helical structure almost similar to B-DNA but with a shorter and more compact structural organization. A-DNA was discovered by Rosalind Franklin

B-DNA :- The B-DNA is the most common and predominate type of structural conformation of DNA in the cells. The DNA prefers to occur in B form under the natural physiological conditions (pH and salt concentration) in the cell. The B-DNA is better described as the Watson-

Crick Model of DNA described for the first time by James Watson and Francis Crick

Z-DNA :- It is a left-handed double helical conformation of DNA in which the double helix winds to the left in a zig-zag pattern. The DNA strand with complementary nucleotides with alternating purines and pyrimidines can form Z-DNA conformation at high salt concentration. The existence of Z DNA was discovered by Andres Wang and Alexander Rich. It is one of the biologically active forms of DNA found in vivo in the cells. T

C-DNA :- This DNA is not found under normal conditions because it occurs only under condition of extreme dehydration.

RNA (Ribonucleic acid)

Ribonucleic acid (RNA) :- Is typically single stranded and is made of ribonucleotides that are linked by phosphodiester bonds. A ribonucleotide in the RNA chain contains ribose (the pentose sugar), one of the four nitrogenous bases (A, U, G, and C), and a phosphate group. The subtle structural difference between the sugars gives DNA added stability, making DNA more suitable for storage of genetic information. The key difference in RNA structure is that the ribose sugar in RNA has a hydroxyl (-OH) group which is absent in DNA. RNA plays a very crucial role in the gene expression pathway by which genetic information in DNA is coded into proteins that determine cell function.

The RNA-specific pyrimidine uracil forms a complementary base pair with adenine and is used instead of the thymine used in DNA. Even though RNA is single stranded, most types of RNA molecules show extensive intermolecular base pairing between complementary sequences within the RNA strand, creating a predictable three-dimensional structure essential for their function

Some RNA molecules play an active role within cells by catalyzing biological reactions, controlling gene expression, or sensing and communicating responses to cellular signals. One of these active processes is protein synthesis, a universal function where RNA molecules direct the assembly of proteins on ribosomes. This process uses transfer RNA (tRNA) molecules to deliver amino acids to the ribosome, where ribosomal RNA (rRNA) then links amino acids together to form proteins. Messenger RNA (mRNA) is the RNA that carries information from DNA to the ribosome, the sites of protein synthesis (translation) in the cell. The coding sequence of the mRNA determines the amino acid sequence in the protein that is produced.

Structure and composition of RNA

RNA is one of the three major macromolecules (along with DNA and proteins) that are essential for all known forms of life. The chemical structure of RNA is very similar to that of DNA, with two differences i.e., RNA contains the sugar ribose while DNA contains the slightly different sugar deoxyribose (a type of ribose that lacks one oxygen atom), and RNA has the nucleobase uracil, while DNA contains thymine (uracil and thymine have similar base-pairing properties). RNA, like

deoxyribonucleic acid (DNA), is composed of nucleic acids that are found in the nucleus of plants and animals.

Nucleic acids consist of high molecular weight macromolecules, which are made up of hundreds or thousands of smaller single unit molecules called nucleotides, Each nucleotide molecule consists of a sugar group, a phosphate group, and an amino (nitrogen containing) group. The main difference between RNA and DNA is that in RNA the sugar is ribose (a five carbon sugar); while in DNA the sugar is deoxyribose. The prefix deoxy means that one oxygen atom is missing from the ribose. RNA is built from the same nucleotides as DNA just as proteins are built up from amino acids. There are only four bases that makeup RNA: adenine, cytosine, guanine, and uracil (A, C, G, and U, respectively). DNA contains thymine (T) instead of U. Structurally; the backbone consists of alternating sugar and phosphate parts, while the amino groups stick out like branches from the backbone.

Types of RNA

(1) Ribosomal RNA (rRNA): The ribosomes are the factories of protein synthesis. The eukaryotic ribosomes are composed of two major nucleoprotein complexes- 60S subunit and 40S subunit. The 60S subunit contains around 35 different proteins and possesses three different rRNA namely; 28S rRNA (4700 bases long), 5S rRNA (12 base long) and 5.8S rRNA (160 base long) while the 40S subunit contain 50 proteins and possesses only one type of rRNA i.e. 18S rRNA, which is about 1900 bases long. 5S r-RNA has a separate gene which is transcribed to form

the RNA, whereas, all other RNA are synthesized as a single transcript, which after formation is cleaved to form other RNA molecules.

(2)Messenger RNA (m-RNA): Messenger RNA is a linear molecule formed inside the nucleus by the process of transcription from DNA. The sequence of mRNA is complementary to the template DNA strand. The nitrogenous bases on mRNA strand are arranged in form of codons, made up of three nitrogenous bases. Messenger RNA carries genetic information from nucleus (chromosomal DNA) to cytoplasm for protein synthesis.

(3)Transfer RNA (t-RNA) :- Transfer RNA (soluble RNA) molecule contains 71-80 nucleotides (mostly 75) with a molecular weight of about 25,000. There are at least 20 species of tRNA corresponding to 20 amino acids present in protein structure.

Other types of RNA

Types of RNA have been discovered besides the three classically known RNA.

(a) Small nuclear RNA (snRNA): SnRNA are found to be present in multiple copies in nucleus. Many of the snRNA are involved in the process of splicing. Small nuclear RNA is also known as U-RNA because they are rich in uridylic acid. Small nuclear RNA molecules are involved in editing of other RNA molecules.

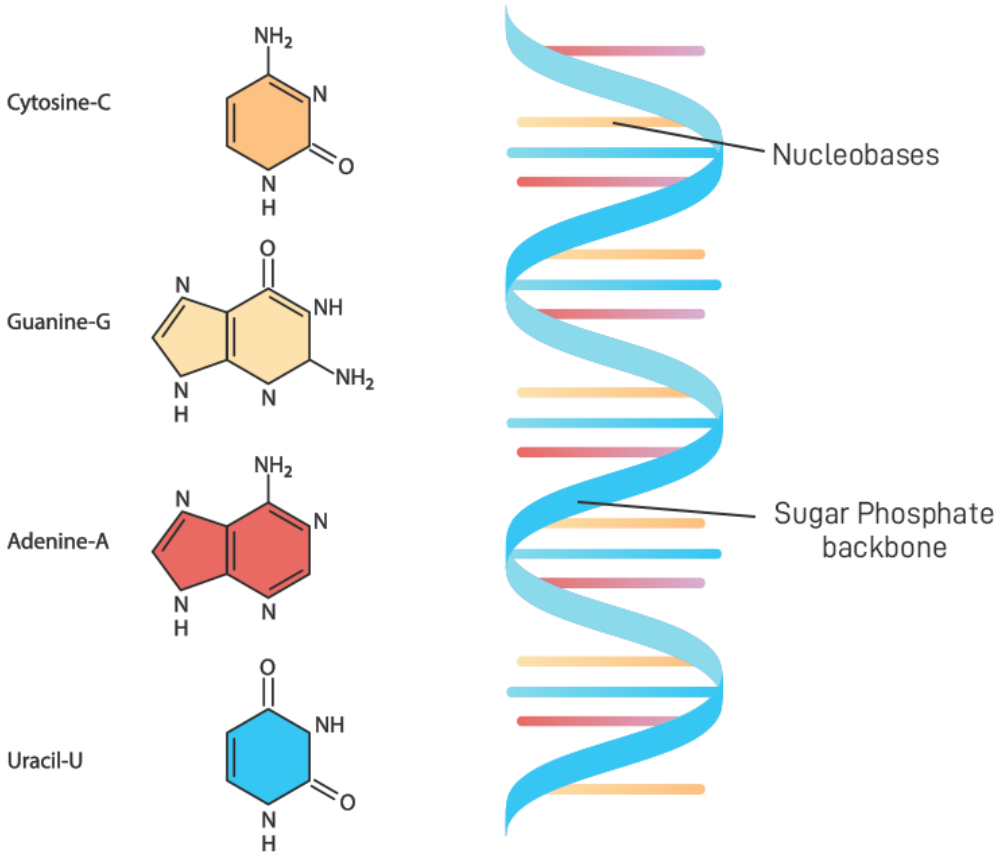
(b) Short interfering RNA (siRNA): Short interfering is double stranded RNA molecules and is involved in RNA interference. The length of such RNA is about 20-25 base pairs. It interferes with his expression of

specific genes by degrading mRNA after transcription; as a result translation of proteins is prevented.

(c) Micro RNA (miRNAs): A micro RNA (miRNA) is a small non-coding RNA molecule. It is about 22 nucleotides long. Micro RNA is found in plants, animals and some viruses that functions in RNA silencing and post-transcriptional regulation of gene expression. Micro RNAs show a base pairing with complementary sequences in mRNA molecules. As a result of this base pairing, the mRNA molecules are silenced, by one or more of the following processes.

(d) Heterogeneous nuclear RNA (hnRNA): Unlike prokaryotic mRNA, eukaryotic mRNAs are monocistronic. The primary transcript in eukaryotes is much larger than the mature mRNA and is called Heterogeneous nuclear RNA (hnRNA).

RNA (RIBONUCLEIC ACID)



DNA Replication

DNA replication is the process of producing two identical copies from one original DNA molecule. This biological process occurs in all living organisms . It is the basis for **biological inheritance**. DNA is composed of two strands and each strand of the original DNA molecule serves as template for the production of the complementary strand, a process referred to as **semiconservative replication**

Conservative Model

After DNA replication, the parental DNA remains together, and the newly formed daughter strands are together.

Semiconservative Model

The semi-conservative method suggests that each of the two parental DNA strands act as a template for new DNA to be synthesized; after replication, each double-stranded DNA includes one parental or “old” strand and one “new” strand.

Dispersive Model

Both new copies of DNA have double-stranded segments of parental DNA and newly synthesized DNA interspersed.

DNA replication process

the process of DNA replication followed by proofreading or error-checking mechanisms to ensure correct reading of the genetic code, like all biological polymerization processes (Transcription and Translation, will be discussed later), the process involve 3 stages :

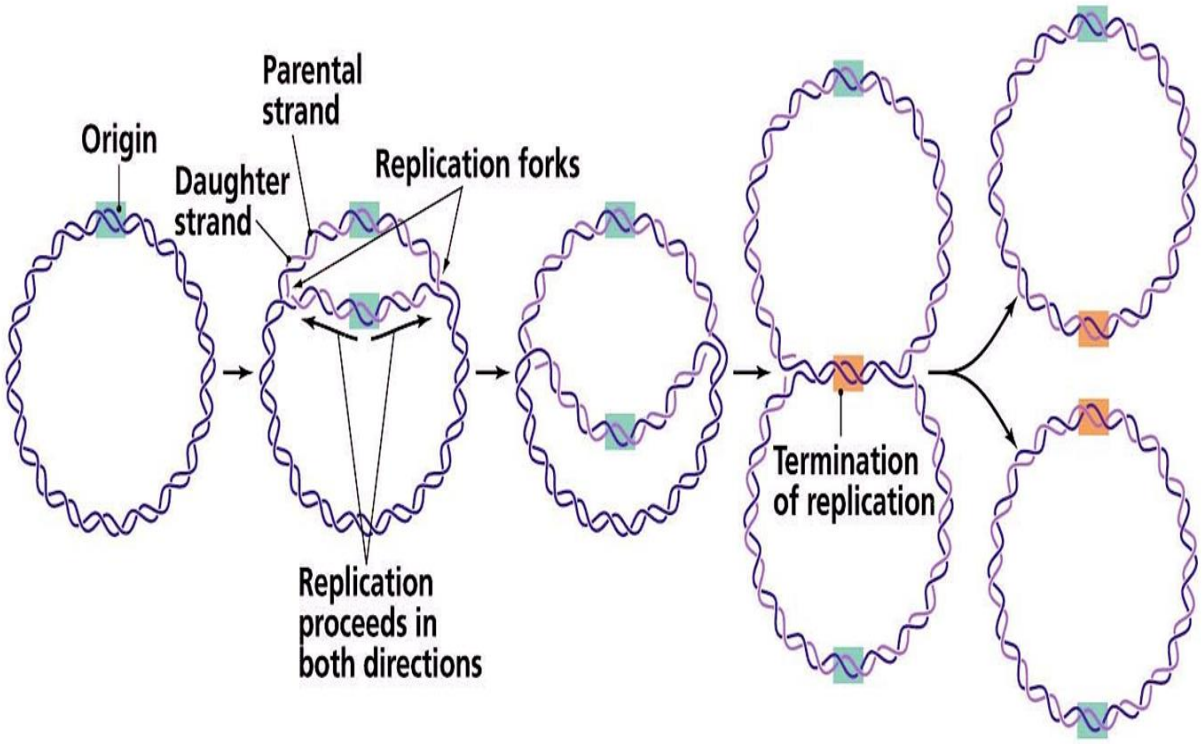
1- Initiation 2-Elongation and 3- Termination

1- Initiation

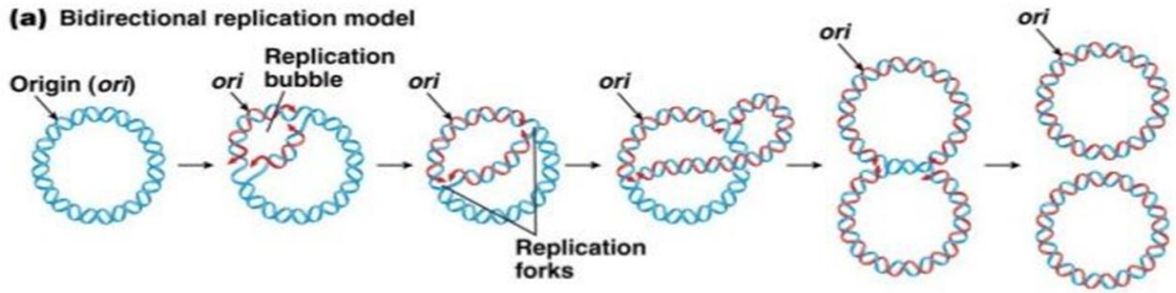
The replication of both prokaryotic and eukaryotic DNAs starts at a unique sequence called the **origin of replication**, which serves as a specific binding site for proteins that initiate the replication process.

The origin of replication (**oriC)** is recognized by certain proteins that bind to this site called Initiator proteins. These proteins (DnaA in prokaryotes, origin recognition complex in yeast) binds specifically to the AT-rich replicator sequence oriC to form a specific DnaA-oriC complex. An enzyme called **helicase** unwinds the DNA by breaking the hydrogen bonds between the nitrogenous base pairs. ATP hydrolysis is required for this process.

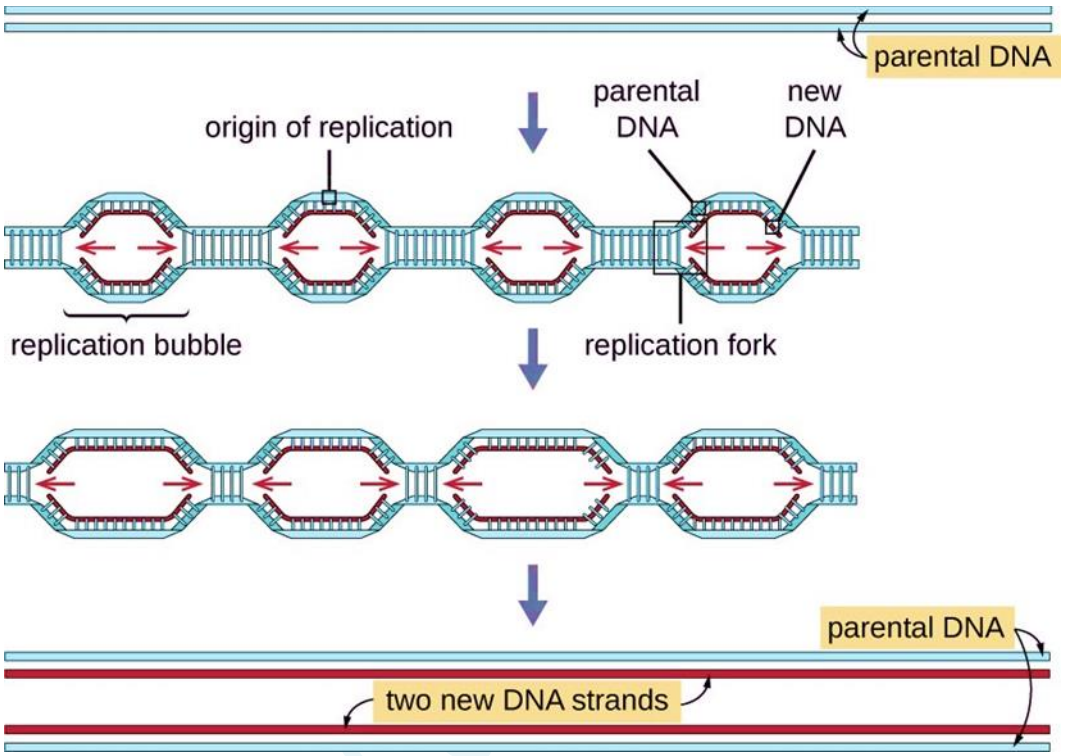
As the DNA opens up, Y-shaped structures called **replication forks** are formed. Two replication forks are formed at the origin of replication and these get extended bi-directionally as replication proceeds. (two replication forks begin at a single replication origin in bacteria and proceed in opposite directions around the chromosome forming **θ theta shape**, which look like a bubble , moving away from the origin till reaching the opposite direction in one point called Ter Terminus (**Teri**).



- In **bidirectional DNA replication**, new DNA is synthesized in both directions from the single origin, creating an expanding **replication bubble**
- At each end of the replication bubble is a **replication fork**; replication is complete when the replication forks meet



The mechanism of eukaryotic DNA replication is similar to that of prokaryotic DNA replication but it is more complex. There are multiple origins of replication on the eukaryotic chromosome so multiple replication bubbles will form.



Single-strand binding proteins (SSBPs) bind to the single strands of DNA near the replication fork to prevent the ssDNA strands from winding back into a double helix,thus maintaining the strand separation.

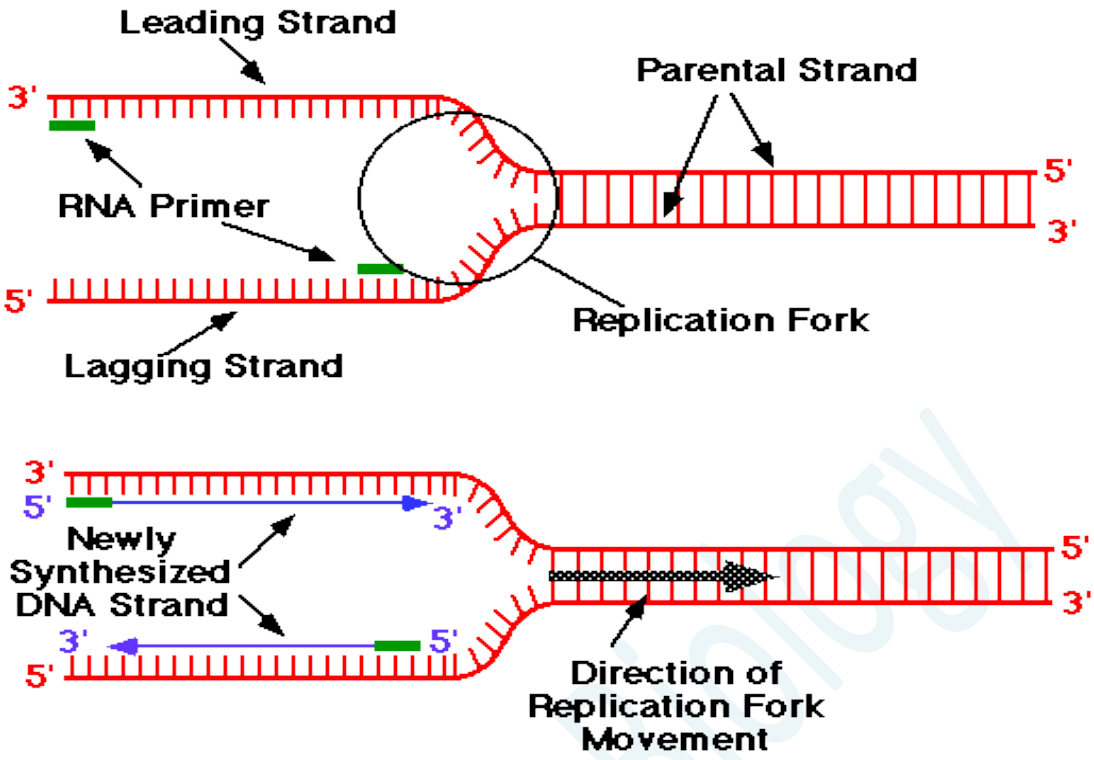
One of the key players in DNA replication is the enzyme **DNA polymerase**, also known as DNA pol (**there are many types of DNA polymerases in prokaryotes and eukaryotes**

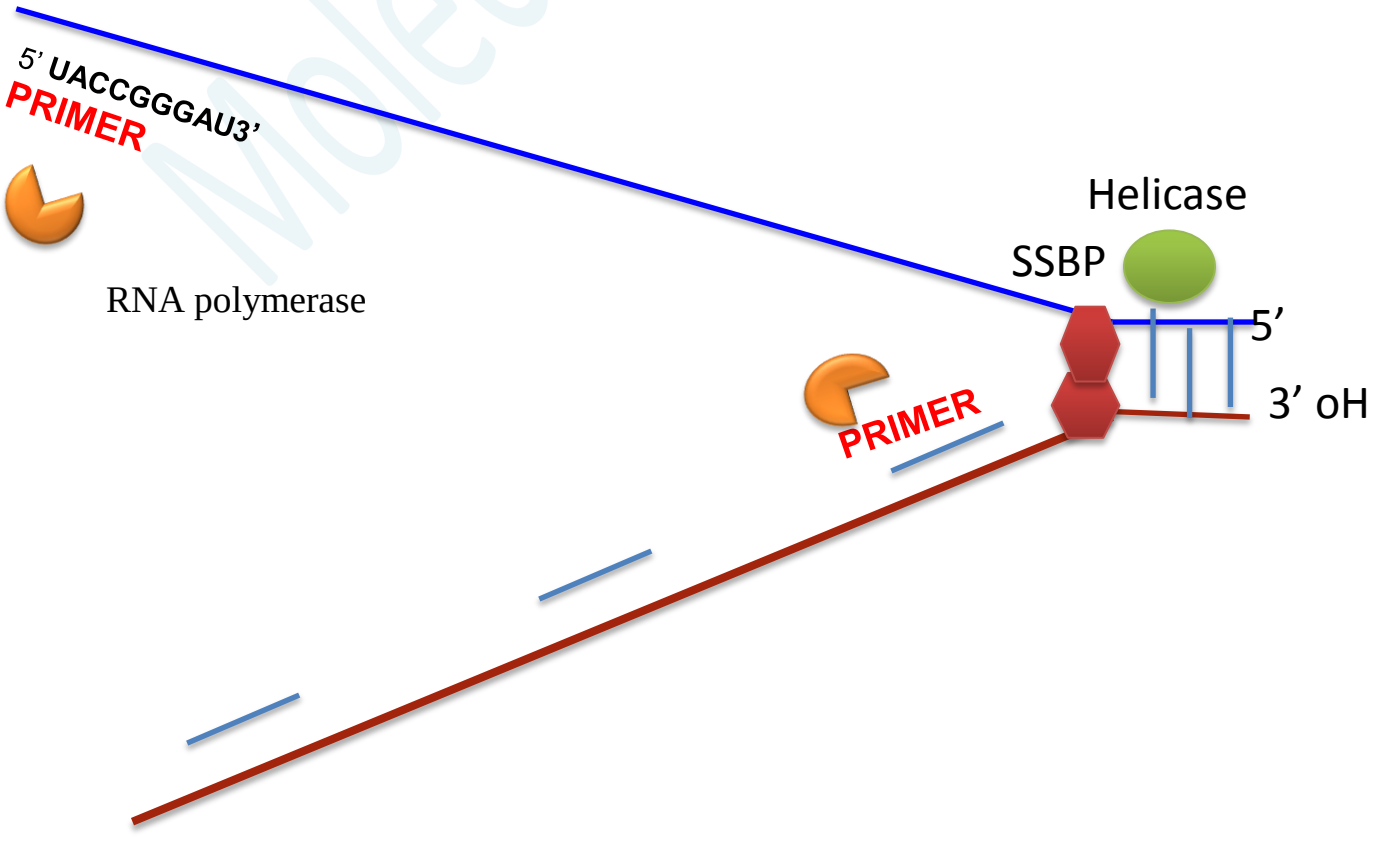
DNA polymerase is able to add nucleotides only in the 5' to 3' direction (a new DNA strand can be only extended in this direction). It also requires a free 3'-OH group to which it can add nucleotides by forming a phosphodister bond between the 3'-OH end and the 5' phosphate of the next nucleotide. This essentially means that it cannot add nucleotides if a free 3'-OH group is not available.

RNA primase, synthesizes an RNA primer that is about five to ten nucleotides long and complementary to the DNA template

DNA polymerase can now extend this RNA primer, adding nucleotides one by one that are complementary to the template strand. (example: **A** in the template strand is complement to **T** in new growing strand strand , and **G** in the template strand is complement to **C** in new growing strand strand)…

The primer is RNA rather than DNA because DNA polymerases cannot start chains de novo





2- Elongation step

During elongation, an enzyme called DNA polymerase adds DNA nucleotides to the 3′ end of the newly synthesized polynucleotide strand. The template strand specifies which of the four DNA nucleotides (A, T, C, or G) is added at each position along the new chain. Only the nucleotide complementary to the template nucleotide at that position is added to the new strand.

DNA polymerase contains a groove that allows it to bind to a single-stranded template DNA and travel one nucleotide at at time. For example, when DNA polymerase meets an adenosine nucleotide on the template strand, it adds a thymidine to the 3′ end of the newly synthesized strand, and then moves to the next nucleotide on the template strand. This process will continue until the DNA polymerase reaches the end of the template strand.

DNA polymerase cannot initiate new strand synthesis; it only adds new nucleotides at the 3′ end of an existing strand. All newly synthesized polynucleotide strands must be initiated by a specialized RNA polymerase called primase. Primase initiates polynucleotide synthesis and by creating a short RNA polynucleotide strand complementary to template DNA strand. This short stretch of RNA nucleotides is called the primer. Once RNA primer has been synthesized at the template DNA, primase exits, and DNA polymerase extends the new strand with nucleotides complementary to the template DNA.

DNA polymerase can only synthesize new strands in the 5′ to 3′ direction. Therefore, the two newly-synthesized strands grow in opposite directions

because the template strands at each replication fork are antiparallel. The **"leading strand**" is synthesized continuously toward the replication fork as helicase unwinds the template double-stranded DNA.

The "lagging strand" is synthesized in the direction away from the replication fork and away from the DNA helicase unwinds. This lagging strand is synthesized in pieces because the DNA polymerase can only synthesize in the 5′ to 3′ direction, and so it constantly encounters the previously-synthesized new strand. The pieces are called Okazaki fragments, and each fragment begins with its own RNA primer.

3-Termination

At the end of DNA replication the RNA primer are replaced by DNA by 5'-3'exonuclease and polymerase activity of DNA polymerase ε.

♣ Exonuclease activity of DNA polymerase removes the RNA primer and polymerase activity adds dNTPs at 3'-OH end preceding the primer.
♣ In case of bacteria, with circular genome, the replacement of RNA primer with DNA is not a problem because there is always a preceding 3'-OH in a circular DNA.

♣ But in eukaryotic organism with linear DNA, there is a problem. When RNA primer at 5' end of daughter strand is removed, there is not a preceding 3'-OH such that the DNA polymerase can use it to replace by DNA. So, at 5' end of each daughter strand there is a gap (missing DNA). This missing DNA cause loss of information contain in that region. This

gap must be filled before next round of replication.

Enzymes involved in DNA replication

- Primase: in fact is RNA polymerase thus the formed primer is RNA rather than DNA and it will removed latter by DNA polymerase I
- Topoisomerase I: will break the 3′ 5′ phosphodiester bond converting super coiled to relax form which opposite to ligase. **Relaxes the DNA from its super-coiled nature**
- **DNA Helicase** Also known as helix destabilizing enzyme cases formation of Replication Fork due to broken hydrogen bonds
- DNA Gyrase (and Topoisomerase IV) ; this is a specific type of topisomerase II convert relaxed form to super coiled
- DNA Ligase Re-anneals the semi-conservative strands and joins Okazak'i Fragments of the lagging strand.
- Telomerase Lengthens telomeric DNA by adding repetitive nucleotide sequences to the ends of **eukaryotic chromosomes**
- DNA Polymerase Builds a new duplex DNA strand by adding nucleotides in the 5' to 3' direction. performs proof-reading and error correction.
- DNA clamp: A protein (unit from polymerase which prevents DNA polymerase III from dissociating from the DNA parent strand.

- Single-Strand Binding (SSB) Proteins Bind to ssDNA and prevent the DNA double helix from re-annealing after DNA helicase unwinds it thus maintaining the strand separation
- **Types of DNA polymerases in Prokaryotes**
- **DNA polymerase III** is the main polymerase for DNA replication (Main enzyme that adds nucleotides in the 5'-3') . **DNA polymerase II** is involved in DNA repair.
- **DNA Polymerase I has :**
- 1- Proofreading exonuclease in (3'-5' direction)
- 2- Primer removal exonuclease in (5'-3') direction
- 3-DNA synthesis (5'-3') replaces primer with newly synthesized DNA

Types of DNA polymerase in Eukaryotic cell

- **The DNA polymerases of eukaryotes :-** Eukaryotic cells have **FIVE** polymerases: **four** major **nuclear** DNA polymerases: **DNA polymerase alpha (Pol α), DNA polymerase delta (Pol δ) and DNA polymerase epsilon (Pol ε), DNA polymerase beta (poly β),** and one found in **mitochondria: DNA polymerase Gamma (Poly γ).**

Pol α is a heterotetramer composed of two primase subunits and two polymerase subunits. The primase subunits initiate DNA replication by synthesizing short (7–12 ribonucleotides) RNA primers, which are then extended by polymerase **α**.

Pol β Beta polymerase: excision repair and it is not highly active and is not very processive.

Pol γ Gamma polymerase: polymerization the mitochondrial DNA beside repairing by its exonuclease activity 3′→5′

Pol δ delta and 5-ε epsilon polymerase :polymerization lagging (δ)and leading (ε) strand respectively 5 ′→3′.

Telomeres

To prevent the loss of genes as chromosome ends wear down, the tips of eukaryotic chromosomes have specialized DNA "caps" called telomeres. Telomeres consist of hundreds or thousands of repeats of the same short DNA sequence, which varies between organisms but is 5'-TTAGGG-3' in humans and other mammals. Telomeres need to be protected from a cell's DNA repair systems because they have single-stranded overhangs, which "look like" damaged DNA.

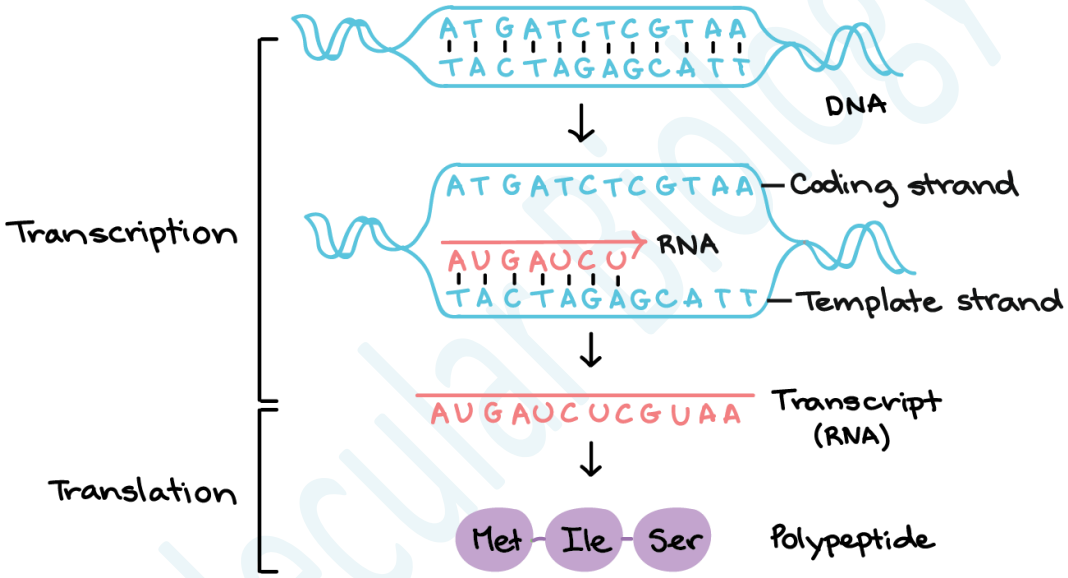
Telomerase

Telomerase is an RNA-dependent DNA polymerase, meaning an enzyme that can make DNA using RNA as a template. How does telomerase work? The enzyme binds to a special RNA molecule that contains a sequence complementary to the telomeric repeat.

(DNA Transcription)

Transcription is the first step of gene expression. During this process, the DNA sequence of a gene is copied into RNA.

Before transcription can take place, the DNA double helix must unwind near the gene that is getting transcribed. The region of opened-up DNA iscalled a transcription bubble.



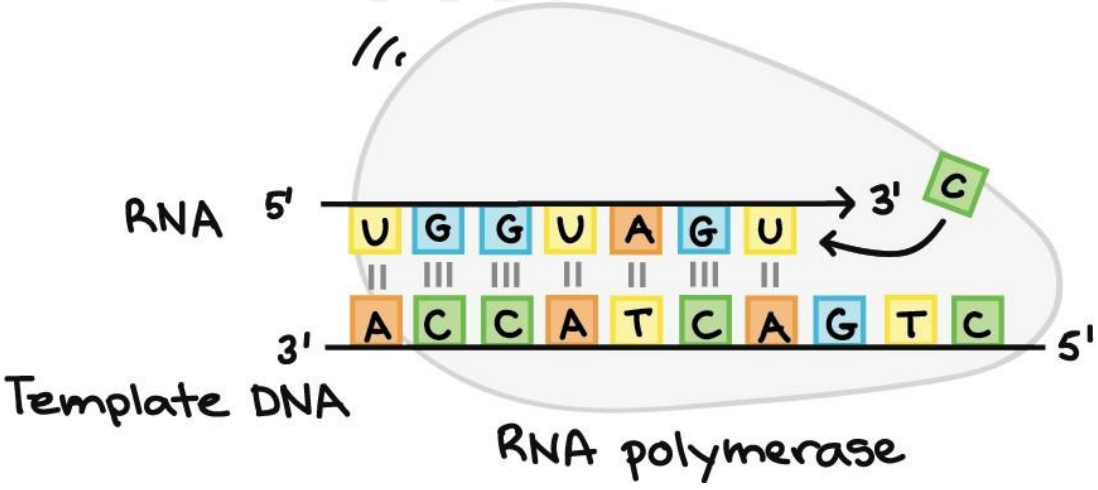
Transcription uses one of the two DNA strands as a template; this strand is called the **template strand**. The RNA product is complementary to the template strand and is almost identical to the other DNA strand, called the **non-template** (or **coding**) **strand**. However, there is one important difference: in the newly made RNA, all the T nucleotides are replaced withU nucleotides.

The site on the DNA from which the first RNA nucleotide is transcribed is called the **initiation site**. Nucleotides that come before the initiation site are given negative numbers and said to be **upstream**. Nucleotides that come after the initiation site are marked with positive numbers and said tobe **downstream**.

If the gene that's transcribed encodes a protein (which many genes do), the RNA molecule will be read to make a protein in a process called translation

RNA polymerase

RNA polymerases are enzymes that transcribe DNA into RNA. Using a DNA template, RNA polymerase builds a new RNA molecule through base pairing. For example, if there is a G in the DNA template, RNA polymerase will add a C to the new, growing RNA strand.



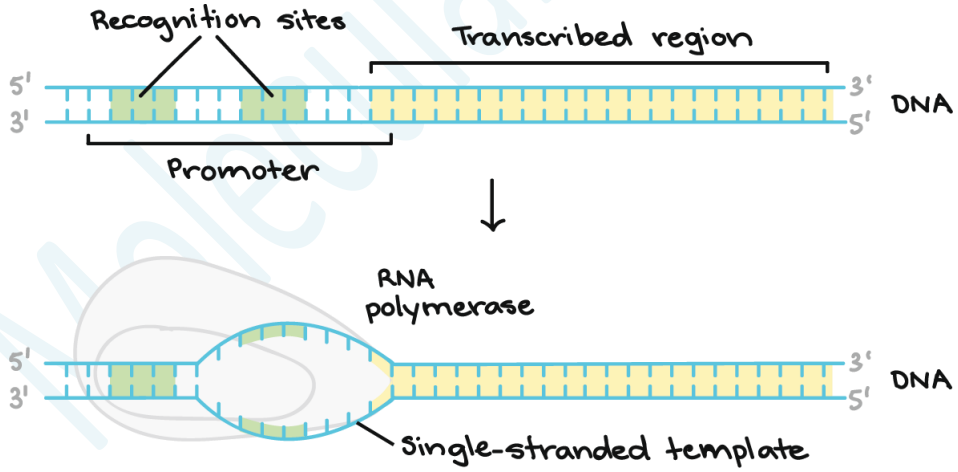
RNA polymerase always builds a new RNA strand in the **5' to 3'**

direction.That is, it can only add RNA nucleotides (A, U, C, or G) to the 3' end of the strand.

RNA polymerases are large enzymes with multiple subunits, even in simple organisms like bacteria. Humans and other eukaryotes have three different kinds of RNA polymerase: I, II, and III. Each one specializes in transcribing certain classes of genes. Plants have an additional two kinds of RNA polymerase, IV and V, which are involved in the synthesis of certain small RNAs.

Transcription initiation

To begin transcribing a gene, RNA polymerase binds to the DNA of the gene at a region called the **promoter**. Basically, the promoter tells the polymerase where to "sit down" on the DNA and begin transcribing.

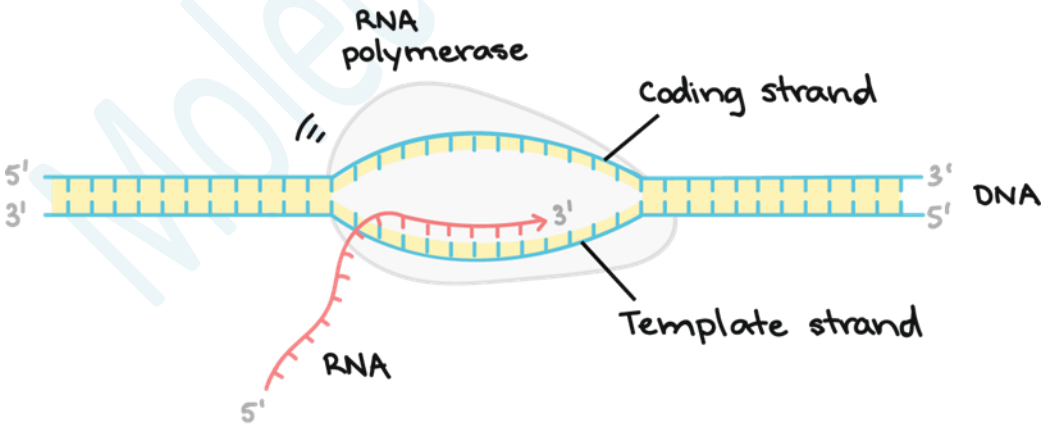


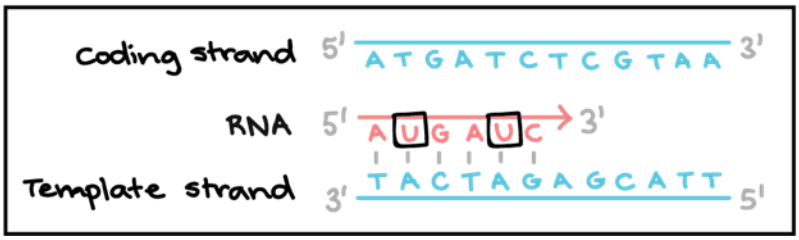
Each gene or each group of genes transcribed together in bacteria has its own promoter. A promoter contains DNA sequences that let RNA polymerase or its helper proteins attach to the DNA. Once the transcription bubble has formed, the polymerase can start transcribing.

Elongation

Once RNA polymerase is in position at the promoter, the next step of transcription—elongation—can begin. Basically, e**long**ation is the stage when the RNA strand gets **long**er, by addition of new nucleotides.

During elongation, RNA polymerase "walks" along one strand of DNA, known as the **template strand**, in the 3' to 5' direction. For each nucleotidein the template, RNA polymerase adds a matching (complementary) RNAnucleotide to the 3' end of the RNA strand.





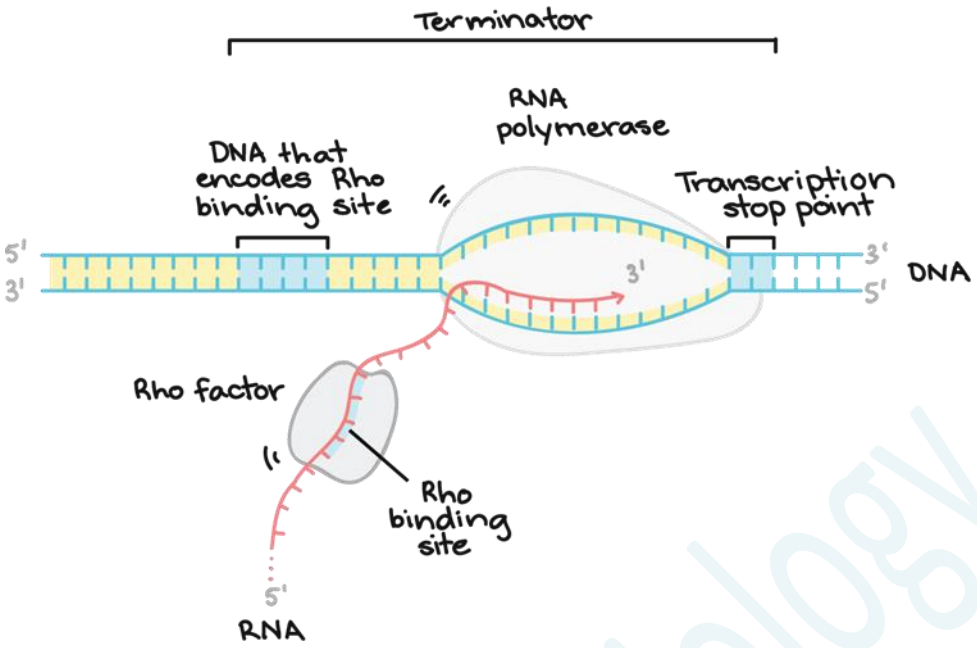
The RNA transcript is nearly identical to the **non-template**, or **coding**, strand of DNA. However, RNA strands have the base uracil (U) in place of thymine (T), as well as a slightly different sugar in the nucleotide. So, as we can see in the diagram above, each T of the coding strand is replaced with a U in the RNA transcript.

Transcription termination

RNA polymerase will keep transcribing until it gets signals to stop. The process of ending transcription is called **termination**, and it happens oncethe polymerase transcribes a sequence of DNA known as a **terminator**.

There are two major termination strategies found in bacteria: Rho-dependent and Rho-independent.

In **Rho-dependent termination**, the RNA contains a binding site for a protein called Rho factor. Rho factor binds to this sequence and starts "climbing" up the transcript towards RNA polymerase.

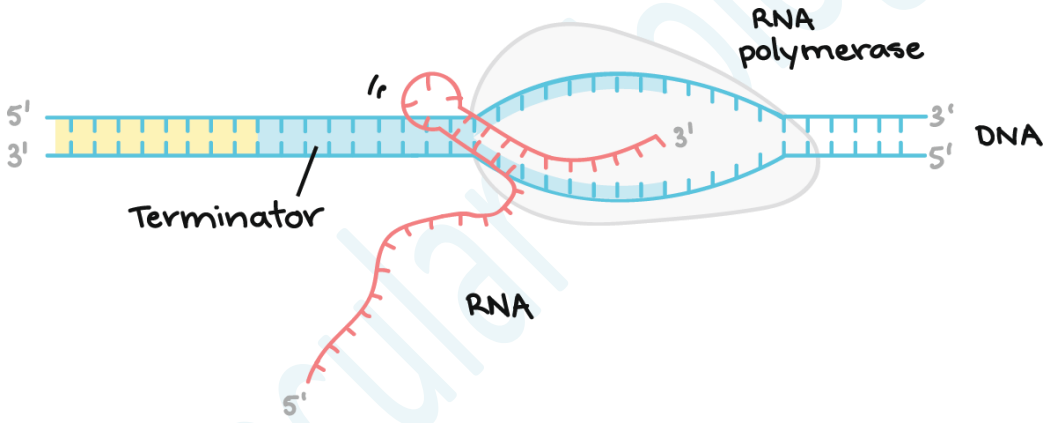


Rho-dependent termination. The terminator is a region of DNA that includes the sequence that codes for the Rho binding site in the mRNA, aswell as the actual transcription stop point (which is a sequence that causesthe RNA polymerase to pause so that Rho can catch up to it). Rho binds tothe Rho binding site in the mRNA and climbs up the RNA transcript, in the5' to 3' direction, towards the transcription bubble where the polymerase is.When it catches up to the polymerase, it will cause the transcript to be released, ending transcription.

When it catches up with the polymerase at the transcription bubble, Rho pulls the RNA transcript and the template DNA strand apart, releasing theRNA molecule and ending transcription.

Another sequence found later in the DNA, called the transcription stop point, causes RNA polymerase to pause and thus helps Rho catch up.^44start superscript, 4, end superscript

Rho-independent termination depends on specific sequences in the DNAtemplate strand. As the RNA polymerase approaches the end of the gene being transcribed, it hits a region rich in C and G nucleotides. The RNA transcribed from this region folds back on itself, and the complementary C and G nucleotides bind together. The result is a stable hairpin that causes the polymerase to stall.

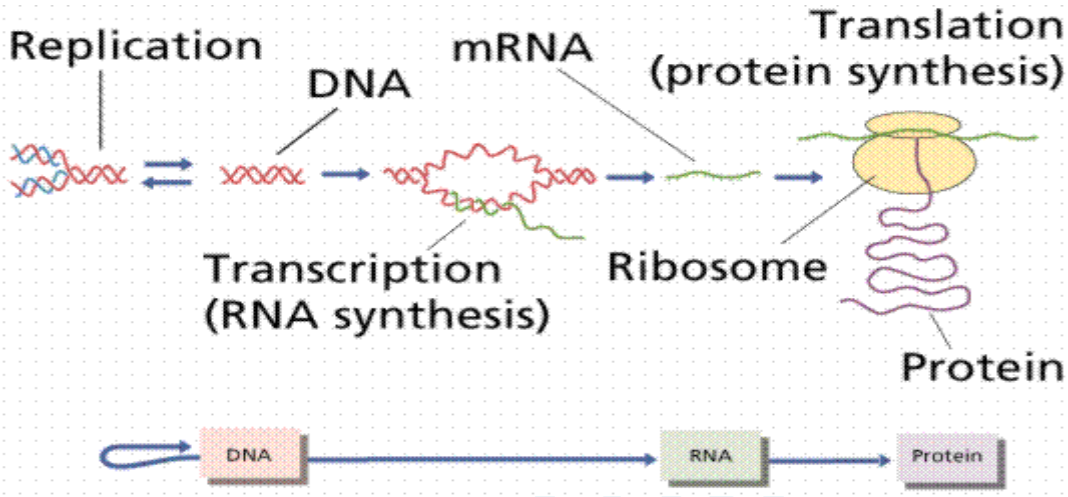


Rho-independent termination. The terminator DNA sequence encodes a region of RNA that folds back on itself to form a hairpin. The hairpin is followed by a series of U nucleotides in the RNA (not pictured). The hairpin causes the polymerase to stall, and the weak base pairing between the A nucleotides of the DNA template and the U nucleotides of the RNA transcript allows the transcript to separate from the template, ending transcription.

In a terminator, the hairpin is followed by a stretch of U nucleotides in theRNA, which match up with A nucleotides in the

template DNA. The complementary U-A region of the RNA transcript forms only a weak interaction with the template DNA. This, coupled with the stalled polymerase, produces enough instability for the enzyme to fall off and liberate the new RNA transcript.

(Translation and protein synthesis)



Codon :- Group of three mRNA nucleotides that encode one amino acid

Ribosomal Structure

- 2 subunits each made of protein and RNA:

1. Small ribosomal subunit - has mRNA binding site
2. Large ribosomal subunit

- E-site (Exit site)
- P-site (Peptidyl-tRNA binding site)
- A-site (Aminoacyl-tRNA binding site)

Prokaryotic ribosomes

Prokaryotic ribosomes have a mass of about 2500 kDa and a size of 70S (or Svedberg units: A Svedberg unit is a measure of the sedimentation rate in centrifuge and thus is representative of size). A complete ribosome (70S) can be dissociated into large subunit (50S) and a small subunit (30S)

Eukaryotic Ribosome Structure

Eukaryotic ribosomes are larger than their prokaryotic counterparts at approximately 80S (although there is some modest variation between eukaryotic species). Human cytosolic ribosomes are composed of a large subunit (60S) that contains the 28S, 5.8S, and 5S rRNAs and 47 ribosomal proteins (RPs) and a small subunit (40S) that contains the18S rRNA and 33 RPs.

translation :- is a process of protein synthesis for mRNA with the help of ribosomes. Translational unit of mRNA from 5′ to 3′ includes start codon, region coded polypeptide, a stop codon, and untranslated regions (UTRs) at 5 ‘ end & 3 ‘ end both for more efficiency of the process. The ribosome is the place where the whole machinery of translation is present. Each eukaryotic ribosome has two parts smaller 40S subunit and a larger 605 subunit. The smallest unit has a point for the attachment of mRNA. Along with the largest subunit, it forms a P-site or peptidyl transfer (Donor site).

Translation occurs in three major steps: (1) initiation. (2) elongation, and (3) termination.

Initiation

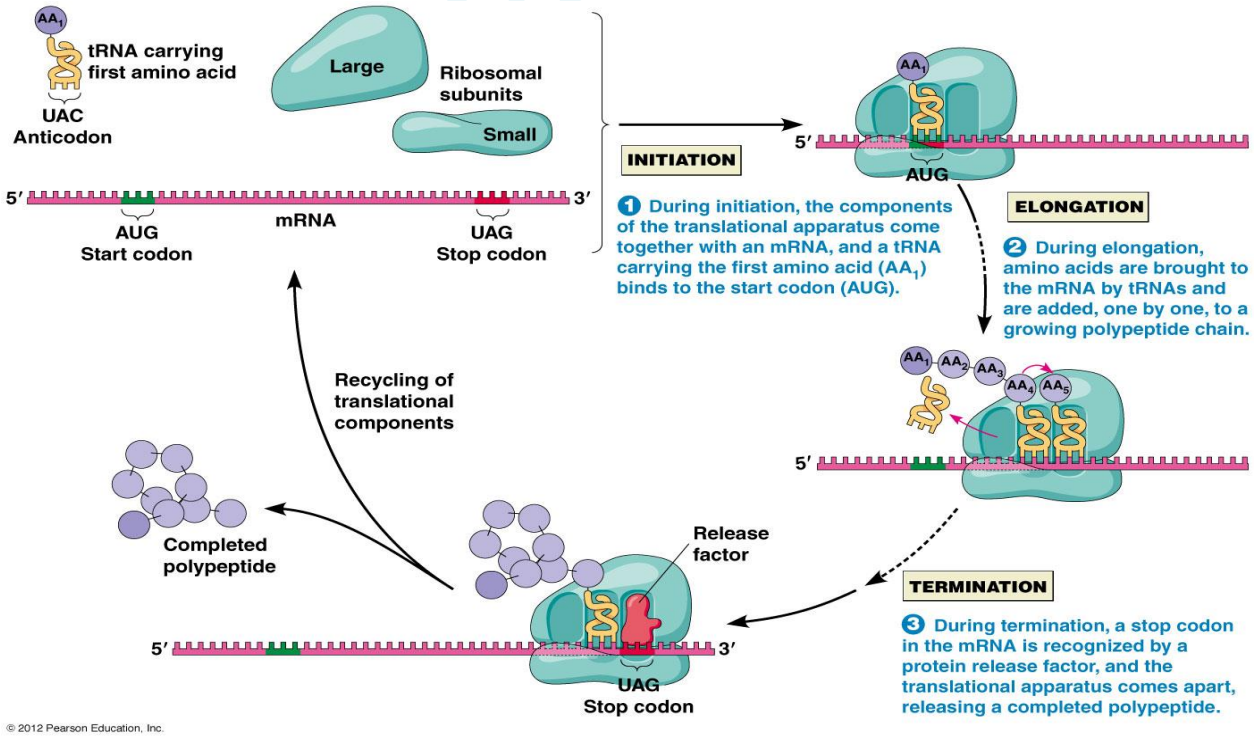
1. During initiation, a group of proteins called initiation factors assist in assembling the ribosome around the mRNA.
2. The initiation factors temporarily recognize specific sequences in the mRNA.
3. The small ribosomal subunit then recognizes the initiation factors, followed by the large ribosomal subunit.
4. The ribosome is assembled around the mRNA, much like a series of toy plastic blocks.
5. Near the beginning of the mRNA is a codon called the start codon (AUG). This codes for an amino acid called methionine.
6. Three regions are important as the ribosome is assembled around the mRNA. They are commonly called the A, P, and E sites.
7. Each site will fit a single tRNA.
8. The only tRNA that can effectively enter the site is the one whose anticodon complements the codon of the mRNA revealed within the site.
9. In initiation, the assembly of the ribosome occurs with the AUG start codon within the P site. This ends the initiation stage.

Elongation

1. The elongation stage involves the assembly of specified amino acids into a polypeptide chain.
2. The key to elongation are the E, P, and A sites within the ribosome.
3. Following initiation, the first tRNA (for methionine) is located within the P site.
4. A second codon in the mRNA is exposed in the A site.
5. Only a tRNA with an anticodon complementary to the mRNA codon exposed in the A site will correctly fit.
6. At this point there are two tRNAs in the ribosome.
7. By an enzymatic reaction, the amino acids between the P and A chains are joined together by a peptide bond.
8. As the peptide bond forms, the amino acid is released from the tRNA in the P site. The ribosome then moves one codon down the mRNA (in the 3′ direction).
9. As it does so, the tRNA that was in the P site enters into the E site and leaves the ribosome.
10. The tRNA that was in the A site, which still has the polypeptide chain attached, moves into the P site.
11. A new mRNA codon is then revealed in the A site.
12. A tRNA with an anticodon complementary to the exposed mRNA codon then enters the A site, and the process repeats itself.
13. The rate at which this reaction occurs is amazing.
14. In eukaryotic systems, the ribosome may read up to six codons per second.

Termination

1. The process of termination begins once the end of the mRNA is reached by the ribosome.
2. In place of tRNAs, proteins called release factors enter into the A site.
3. Since the release factors do not contain amino acids, the process of translation is stopped at this point.
4. The release factors also promote the disassembly of the ribosome and its interaction with the mRNA.
5. The end result of translation is a polypeptide chain. This polypeptide chain must undergo a series of folds in order to produce a functional protein.



Differences between prokaryotic and eukaryotic

Protein Synthesis: Differences Between Prokaryotes and Eukaryotes	
Prokaryotic protein synthesis	**Eukaryotic protein synthesis**
Translation occurs even before the transcription of mRNA ends	Transcription occurs followed by translation
Except in archaebacterial, bacterial mRNA formation does not include the addition of a *cap* and a *poly A tail*	mRNA formation includes the addition of 5′ cap and a poly A tail at the 3′ end of mRNA transcript
Translation begins at AUG codon	Translation begins via the 5′ cap, binding the mRNA to the ribosomal unit at the first AUG codon
Initiating factors: PIF-1, PIF-2, PIF-3	Initiating factors: eIF1-6, eIF4B, eIF4C, eIF4D, eIF4F

(DNA repair system)

DNA repair :- is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day. Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis.

Agents that Damage DNA

1- Certain wavelengths of **radiation including** ionizing radiation such as gamma rays and X-rays and **ultraviolet rays**, especially the UV-C rays (~260 nm) that are absorbed strongly by DNA but also the longer-w

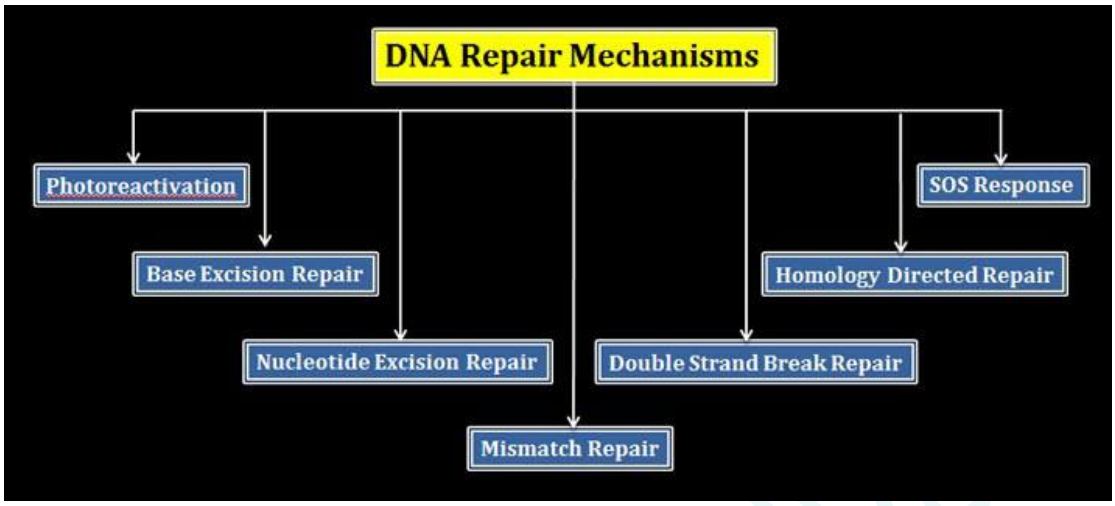
2- avelength UV-B that penetrates the ozone shield.

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

3- 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

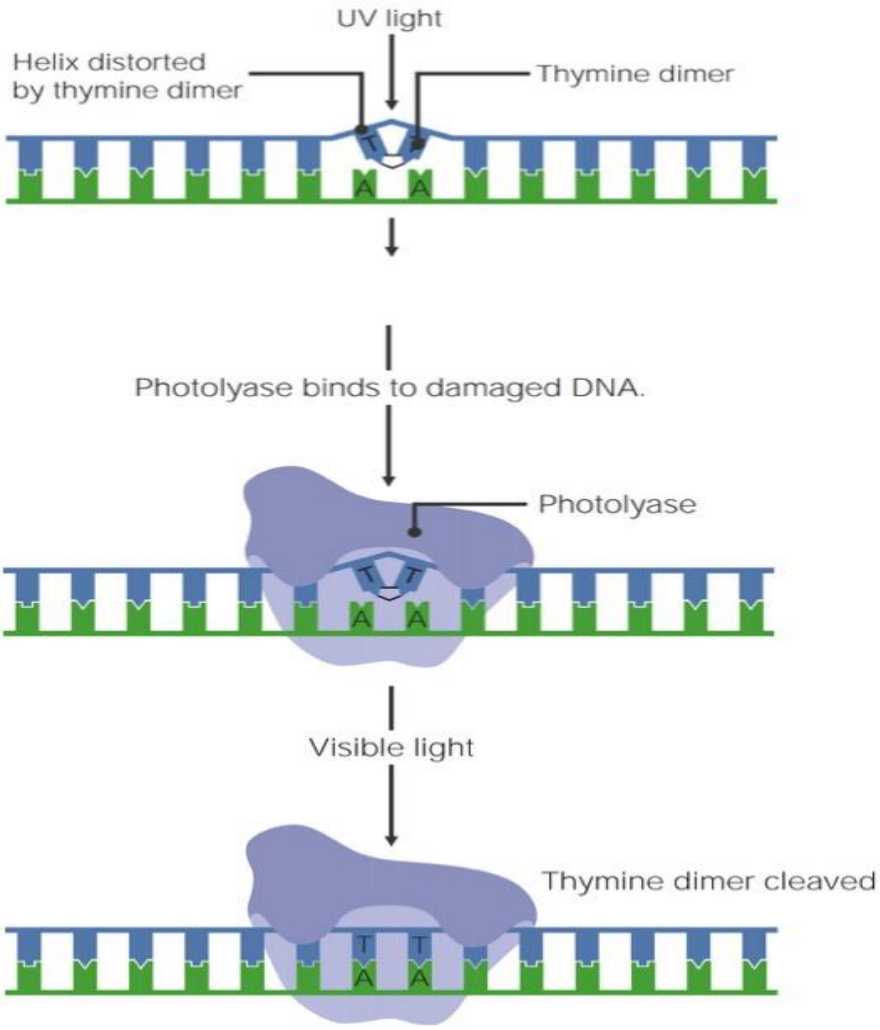
4- Chemicals used in **chemotherapy**, especially chemotherapy of cancers



Mechanism of DNA repair

1. Photoreactivation (light repair, prokaryotes only):

a) A light-dependent repair mechanism carried out by an enzyme called DNA photolyase. The enzyme repairs UV damage (largely pyrimidine-pyrimidine dimers) by binding to the dimers and using light energy to cleave dimer cross-links.



2. Excision repair (dark repair):

a) A light-independent repair mechanism that involves three steps:

(i) recognition of, binding to, and removal of damaged DNA

(ii) repair synthesis of excised region by DNA polymerase

(iii) ligation by DNA ligase to seal the break

There are two major types of excision repair:-

Base excision repair: removal/repair of abnormal or chemically modified bases; serves as another proof-reading mechanism a)

a) Base excision repair involves DNA glycosylases, enzymes that recognize abnormal bases. Different glycosylases recognize different types of abnormal bases. Removal of a damaged base is estimated to occur 20,000 a day in each cell by a DNA glycosylase and humans have at least eight genes encoding different DNA glycosylases that are responsible for identifying and removing a specific type of base damage.

b) Enzymes (DNA glycosylases):- cleave the glycosidic bond between the base and the deoxyribose sugar, leaving an apurinic or apyrimidinic site (AP site) that, in turn, is recognized by an AP endonuclease that clips out the sugar-phosphate group. Humans have at least two genes encoding enzymes with this function.

c) DNA polymerase beta fills in the missing nucleotide and DNA ligase seals the nick. There are at least two ligating enzymes – both use ATP to provide the needed energy.

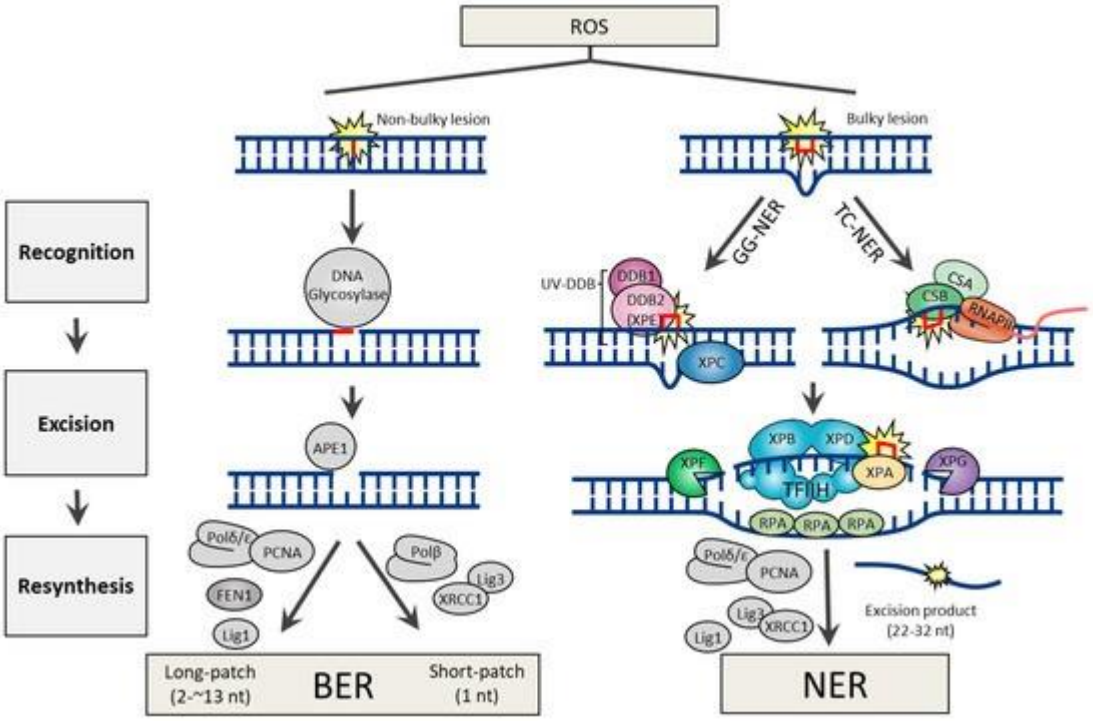
d) Base excision repair is involved in repairing bases altered by alkylation (addition of methyl and ethyl groups) and deamination (removal of amine groups) Nucleotide excision repair: removal/repair of larger fragments (≥ 2 bases) of damaged DNA

3- Nucleotide excision repair :-

involves removal of larger lesions (e.g., thymine-thymine dimers) and utilizes a special enzyme called an excinuclease that cuts on either side of the damage and excises an oligonucleotide containing the damage.

b) The damage is recognized by one or more protein factors that assemble at the damage location(s) and the damaged area removed

c) DNA polymerases delta and/or epsilon fills in the correct nucleotides using the intact (opposite) strand as a template, followed by ligation (ligase).



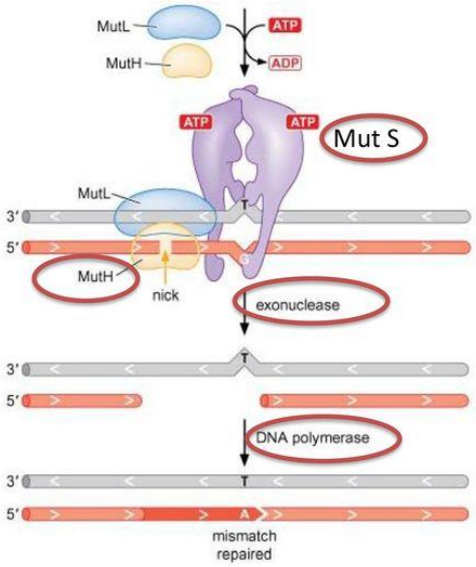
Base and nucleotide excision repair

4-Mismatch repair:

Mismatch Repair in Prokaryotes

Mismatch repair systems—removes single base pair errors that escape proofreading

- **Well studied in *E. coli***
- **Proteins are called the Mut proteins**
  - **MutS:** recognizes mismatches
  - **MutH:** nicks one strand ahead of the mutation
  - A helicase and exonuclease are recruited to remove base pairs including the mismatch
  - **DNA Pol III** fills in the gap
  - Sealed with ligase



How does the Mismatch Repair System "know" which strand has the mutation: Can you think of what is different between the parental and newly synthesized strand?

Repairing strand breaks

a) Ionizing radiation and certain chemicals can generate both single-strand and double-strand breaks in the DNA backbone Single-strand breaks: Repaired using the same enzyme systems (polymerase and ligase) used in base-excision repair

Double-strand breaks:

a) Direct joining of the broken ends (also called 'non-homologous end-joining'). This requires proteins that recognize and bind to the exposed ends and bring them together for ligating.

b) Homologous recombination – this requires information on the intact sister chromatid (available after chromosome duplication). The process is not yet well understood.

c) Two of the proteins used in homologous recombination in humans are encoded by BRCA1 and BRCA2. Inherited mutations in these genes predispose women to breast and ovarian cancers

(Mutation and chromosomal aberration)

- Mutation is the change in sequence of nucleotide of DNA.
- Change in sequence of nucleotide brings sudden change in morphological characteristics of an organism. If such change are heritable, then it is called as mutation.
- So, mutation is defined as any heritable change in the sequence of nucleotide of DNA.

Organism with mutation is called **mutant** while the organism without mutation is **wild type**.

Types of Mutation

There are three types of mutations based on genetic basis of heritable change :

• **Gene mutations** : These are produced by change in the base sequence of genes. The change may be due to base substitutions, deletion or addition.

• **Chromosomal mutation** : These arise due to change in chromosome number that may leads to polyploidy or aneuploidy or change in chromosome structure that result in deletions duplication, inversion and translocation.

• **Cytoplasmic or plasmagene mutation** : These are due to change in the base sequence of plasma genes. The plasma genes are present in mitochondria or chloroplast. Here the mutant character occurrs in buds or somatic tissues which are used for propagation in clonal crops

Based on change in genotype and phenotype, mutation are of two types

1. Point mutation
2. Frameshift mutation

1. Point mutation

- It occurs as a result of replacement of one nucleotide by other in specific nucleotide sequence of gene. Point mutation brings little phenotypic change as compared to frameshift mutation.

Point mutation are two types based on the base pair substitution

i) Transition:

- It is the point mutation occur by substitution of one purine by another purine or one pyrimidine by another pyrimidine.

ii) Transversion:

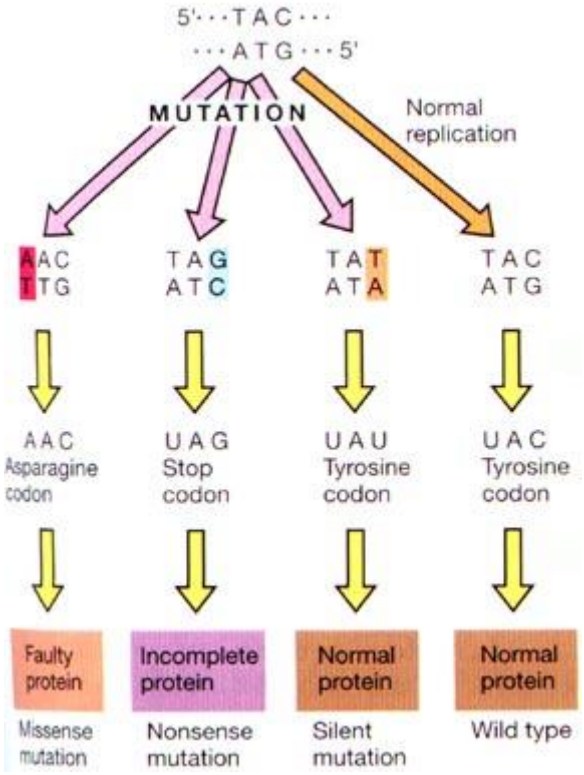
- It is the point mutation occur by substitution of purine by pyrimidine and vice versa.

Based on transcriptional property point mutation are of **three types.**

i) Silent mutation

ii) Missense mutation

iii) Non-sense mutation



i) Silent mutation:

- It is also known as neutral mutation.
- It is the mutation in which mutated codon codes same amino acids as the original codon. Since the aminoacid is same as original one, it does not effects the structure and composition of protein.
- Silent mutation causes phenotype of bacteria remain similar to that of wild type.

ii) Missense mutation:

- **I**n this mutation mutated codon codes different amino acid (other than original). Since new aminoacid coded by mutated codon is altered, the protein formed from it is also altered. Such protein can be less active or completely inactive.

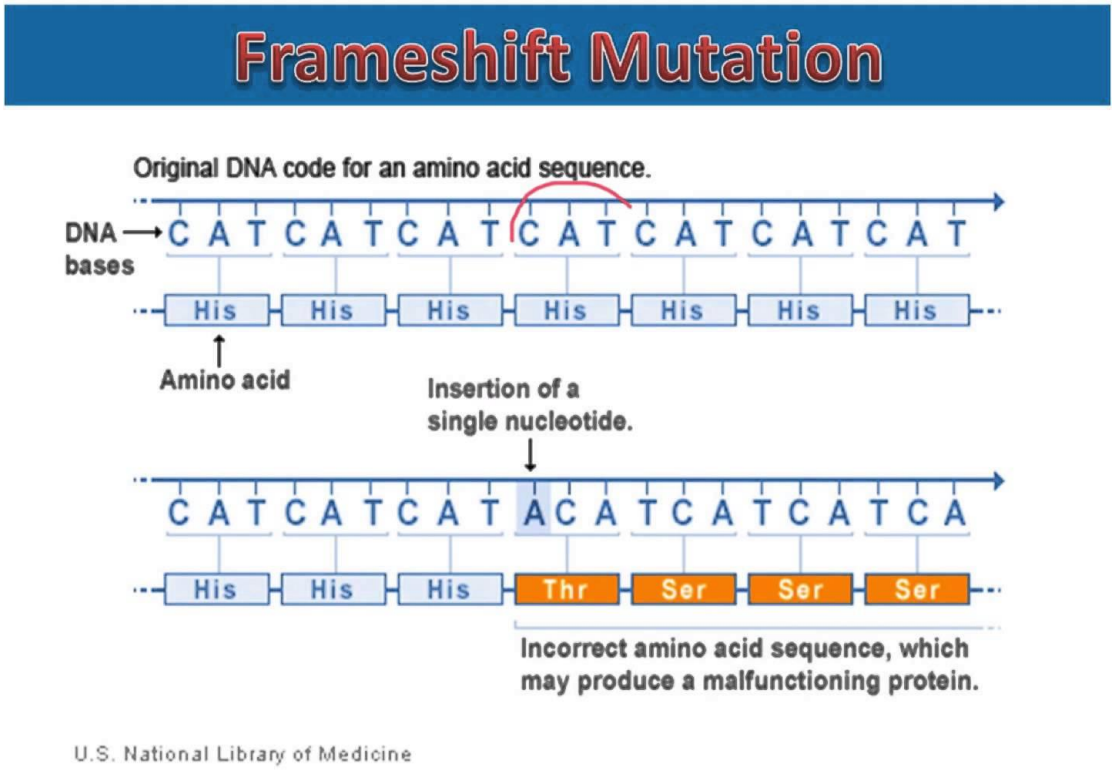
- If altered aminoacids lie on active site of protein then such protein become completely non-functional.
- The missense mutation causes phenotypic change in organism.

iii) Non sense mutation:

- Mutation in which altered codon is stop codon or chain terminating codon, such mutation is called non-sense mutation.
- Non sense mutation causes incomplete synthesis. Such incomplete protein is always non-functional.
- Non-sense mutation bring greatest change in phenotype of an organism.

2. Frameshift mutation

- It occurs as a result of addition or deletion of nucleotide in the sequence of DNA. Addition or deletion of nucleotide causes shift of the reading frame of mRNA.
- In a mRNA each codon is represented by three bases without punctuation and insertion or deletion of a nucleotide changes the entire frame. So frame shift mutation bring greater phenotypic change than point mutation.
- Insertion or deletion of one or two base pair of nucleotide causes shift in frame. However, insertion or deletion of three base pair adds or remove a whole codon, this results in addition of removal of single amino acid from polypeptide chain.



Chromosomal aberrations, or abnormalities, are changes to the structure or number of chromosomes, which are strands of condensed genetic material. Humans typically have 23 pairs of chromosomes, of which 22 pairs are autosomal, numbered 1 through 22. The last pair of chromosomes are sex chromosomes, which determine an individual's sex assignment. At birth, most people with XY sex chromosomes are assigned male, and most individuals with XX are assigned female. In general, each parent contributes one set of chromosomes to their offspring, which collectively make up the 23 pairs of chromosomes. A change to any of the chromosomes, in number or structure, creates a chromosomal aberration and may cause medical disorders.

Chromosomal aberrations can be categorized as numerical or structural aberrations. Numerical aberrations, changes to the number of chromosomes present, are referred to as aneuploidies. The most common types of aneuploidy are monosomies, when only one chromosome of a pair is present, and trisomies, when there are three copies of a chromosome instead of a pair.

The four main types of structural chromosomal aberrations are deletion, duplication, inversion, and translocation. Deletions occur when a portion of the chromosome is deleted, or taken out, which can make that chromosome less functional. For example, when part of a short arm in chromosome 5 is deleted, this causes Cri-du-chat syndrome, common symptoms of which are reduced head size and high-pitched crying in infants. In duplication, part of the chromosome is duplicated, resulting in extra genetic material. This occurs in Charcot-Marie-Tooth disease type I, which duplicates part of chromosome 17, causing muscle weakness. Inversion of a chromosome happens when the genetic material is inverted, or flipped in the opposite direction. Inversions do not often result in disease and most commonly affect chromosome 2. Translocations occur when a piece of one chromosome has broken off from its original location and attached to another chromosome. The most common example is a Robertosonian translocation, which results when two acrocentric chromosomes (chromosomes with arms of unequal lengths due to a non-centered centromere) lose the short arms of the chromosomes, and the two long arms consequently conjoin. Robertsonian translocations are one potential cause of trisomies.

What causes chromosomal aberrations?

Chromosomal aberrations are most often caused by errors during cell division. Cell division in humans occurs via mitosis or, only in sex chromosomes, meiosis. In mitosis, cells duplicate their chromosomes and produce daughter cells with an identical number of chromosomes as the original cell. In other words, a cell with 46 chromosomes will produce two cells, each with 46 identical chromosomes. Meanwhile, cell division by meiosis involves two rounds of cell division that allow for the recombination of genetic material, resulting in four sex cells with only half of the number of chromosomes. For example, a cell with 46 chromosomes undergoing meiosis will produce four unique daughter cells, each with 23 chromosomes.

Aneuploidy may result when an error occurs during meiosis. Most commonly this error is known as nondisjunction, when a set of chromosomes do not properly separate, which leaves one or two sex cells with an extra chromosome or with one less chromsome. If a sex cell affected by nondisjunction undergoes fertilization, the resulting offspring will have inherited one more or one less chromosome and may develop a chromosomal disorder.

Less commonly, structural chromosomal aberrations can result in an aneuploidy. Structural chromosomal aberrations occur when part or all of a chromosome is missing, turned upside down, duplicated, or attached to another chromosome. When this occurs after meiosis in a sex chromosome, two copies or no copies of a chromosome may be present and subsequently passed down to offspring, who will end up with a consequent monosomy or trisomy.

Sometimes, chromosomal disorders are caused by mosaicism, when there are two or more different cell lines in one person. Mosaicism can occur after nondisjunction happens in a mitotic cell division during early embryonic development. This results in one line of cells with a chromosomal aberration while other lines may stay unchanged.