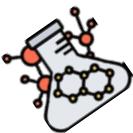


A Happy
Easter



MB L9: Nucleotide structure, DNA

Nucleoproteins :-They are one of the conjugated proteins they are formed of non-protein prosthetic group (nucleic acid) attached to one or more molecules of a simple protein, this simple protein is usually basic protein as histone or protamine. -These conjugated proteins are found in all animals and plant tissues (in all cell nuclei and protoplasm), but are most easily isolated from yeast or from cells whose nuclei are densely packed e.g. thymus cells.

There are TWO types of Nucleic Acids:

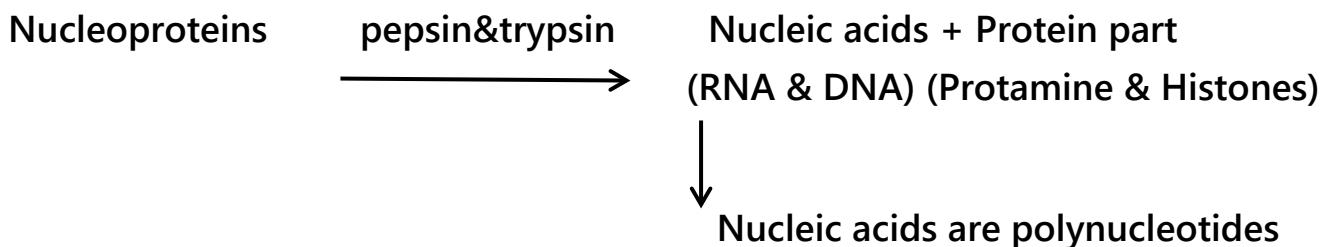
1-Ribonucleic acid (RNA)

2-Deoxyribonucleic acid (DNA)

- Our diet contains nucleic acids in the form of nucleoproteins which are responsible for: **Storage & passage** of information needed for the production of proteins.

Digestion of Nucleoproteins:

-In the small intestine



Nucleic Acids:

-Nucleic acids can be hydrolyzed either by acids or by use of enzymes producing a number of nucleotides.

Nucleic acids are therefore polynucleotides.

- Each nucleotide can be further hydrolyzed into nucleoside and phosphoric acid molecule.
- Further hydrolysis of nucleosides yields a nitrogenous base (purine or pyrimidine) in addition to pentose sugar (ribose or deoxyribose); as can be seen the diagrammatic representation.
- Pentose of nucleic acids are ribose and deoxyribose; both are present as beta and furanose form:

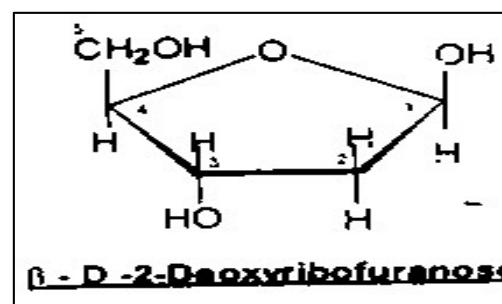
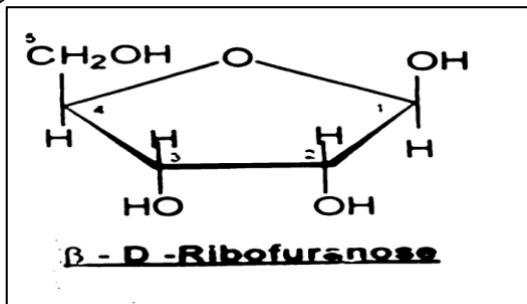
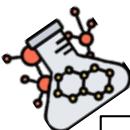
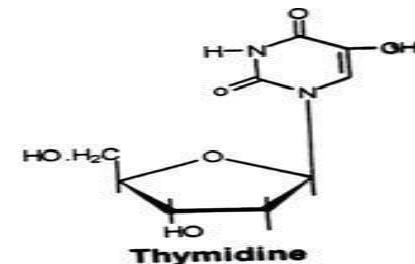
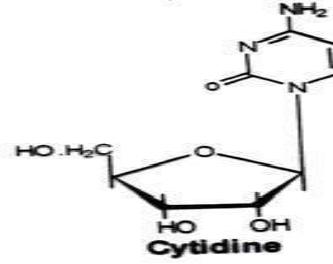
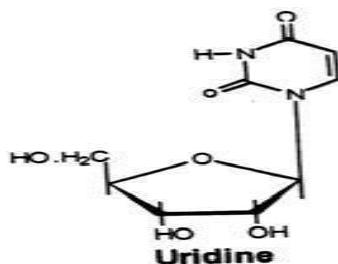
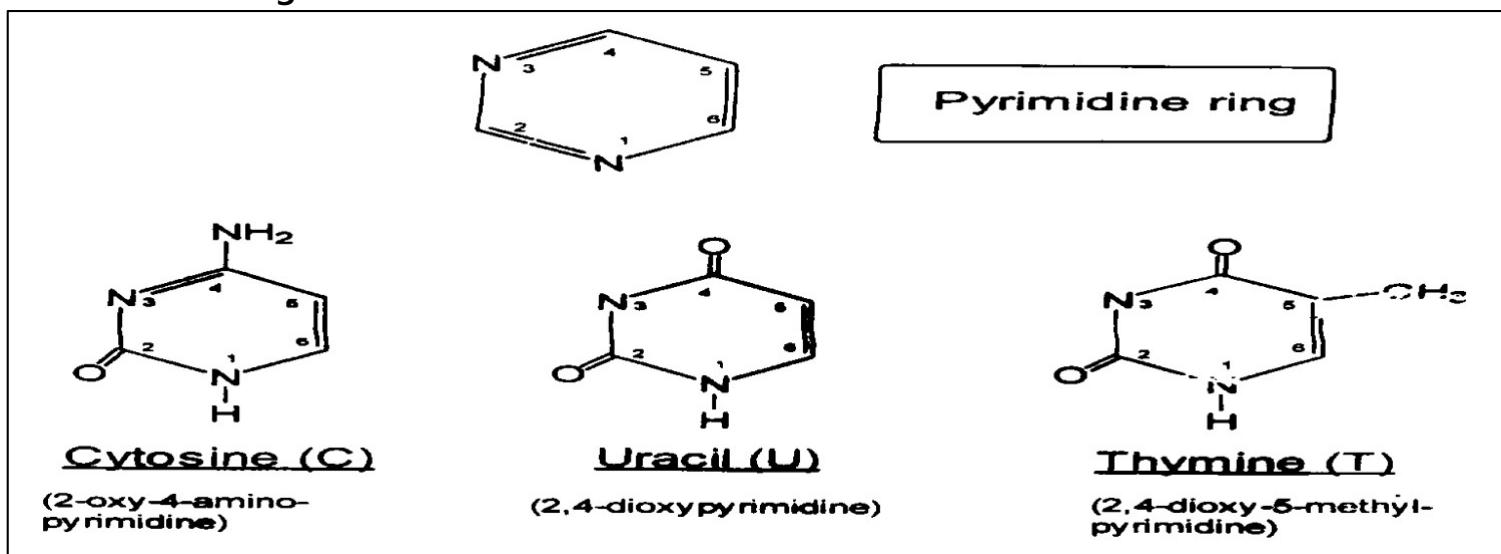


Figure (1): Pyrimidine Bases

Pyrimidine Bases:



-They are bases which contain the pyrimidine ring a **6-membered ring**; the numbering is clockwise:



- Purine bases:** Purine bases are bases that contain ring, **an aromatic heterocyclic** 9 - membered ring: the numbering is counterclockwise.
- Purine bases include: adenine and guanine:

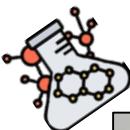
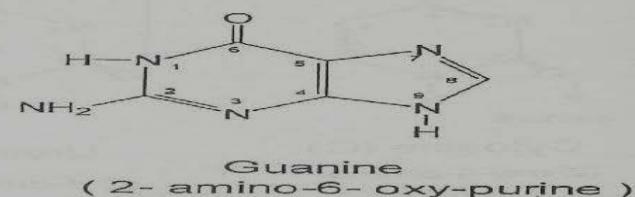
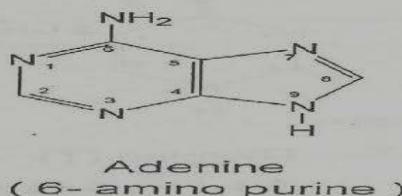


Fig.: Purine ring

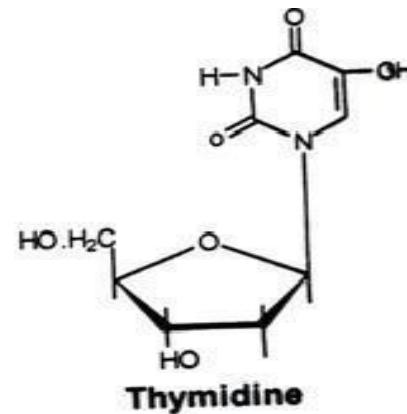
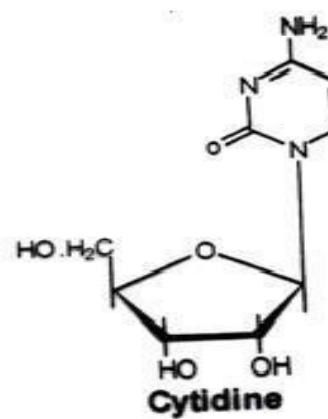
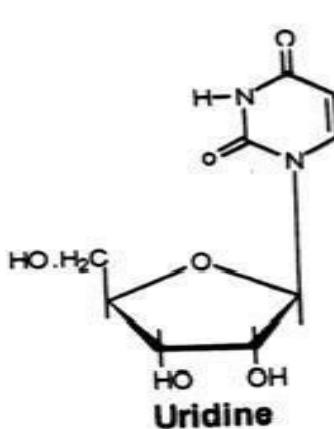
Purine bases include: adenine and guanine;



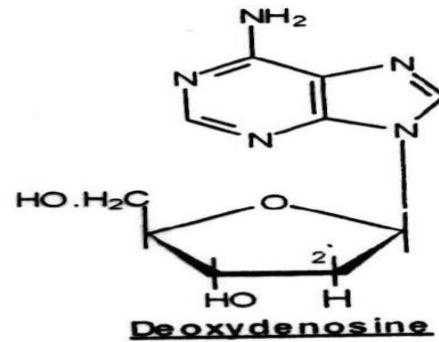
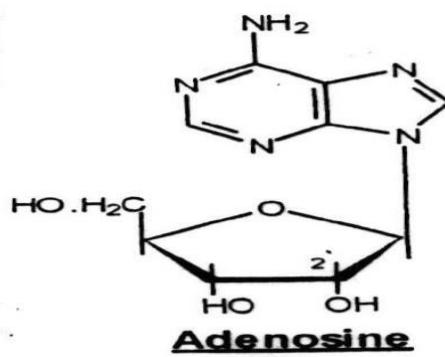
Nucleosides :

- They are formed by connecting C-1 of pentose, in Glycosidic linkage to N-1 of pyrimidine base or N-9 of purine base.

Structure of Pyrimidine Nucleosides :

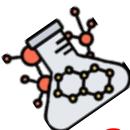


Structures of Purine Nucleosides

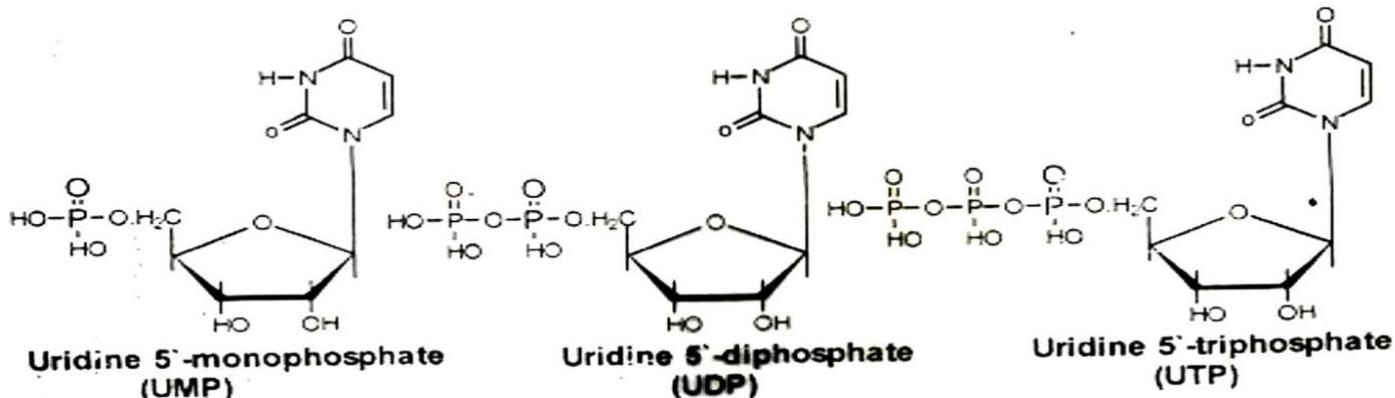


Nucleotides:

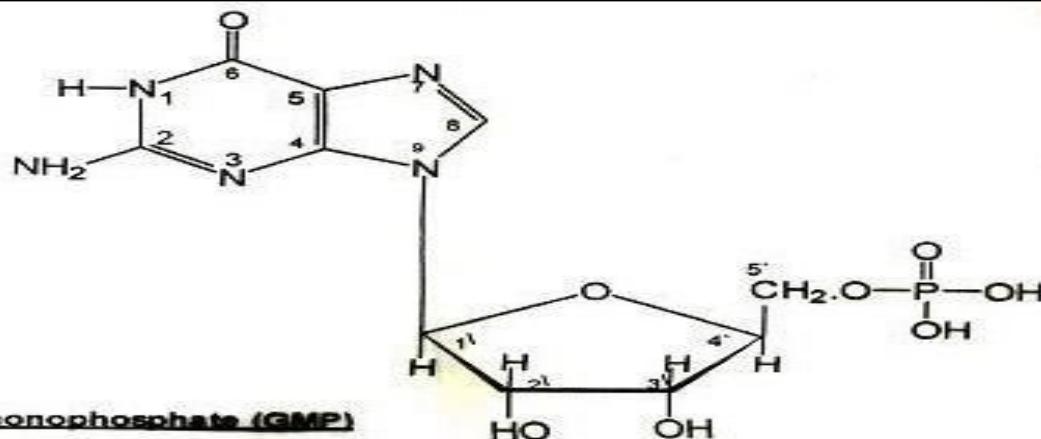
- They are phosphorylated nucleosides; formed by esterification of phosphoric acid to the -OH of C-5' of the pentose of the nucleoside.
- Mononucleotides are nucleosides singly phosphorylated. For example, AMP (adenosine monophosphate) is adenine + ribose phosphate.



Structure of Pyrimidine Nucleotides

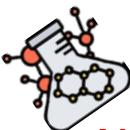


Structure of Purine Nucleotides



BASE	NUCLEOTIDE	
	NUCLEOSIDE	
•Adenine (A)	Adenosine(A)	Adenosine monophosphate(AMP);Adenylic acid (AA)
•Guanine (G)	Guanosine(G)	Guanosine monophosphate(GMP);guanylic acid (GA)
•Xanthine (X)	Xanthosine(X)	Xanthosine monophosphate(XMP);Xnothonylic acid(XA)
•hypoxanthine(i)	Inosine(I)	Inosine monophosphate(IMP);inosinic acid(IA)
•Uracil(U)	Uridine(U)	Uridine monophosphate(UMP);uridylic acid(UA)
•Thymine (T)	Thymidine(T)	Thymidine monophosphate(TMP);Thymidylic acid (TA)
•Cytosine (C)	Cytidine(C)	Cytidine monophosphate(CMP);cytidylic acid(CA)

Table (1): The Major Purines And Pyrimidines and Their Nucleosides and Nucleotides.



Nucleotide functions:

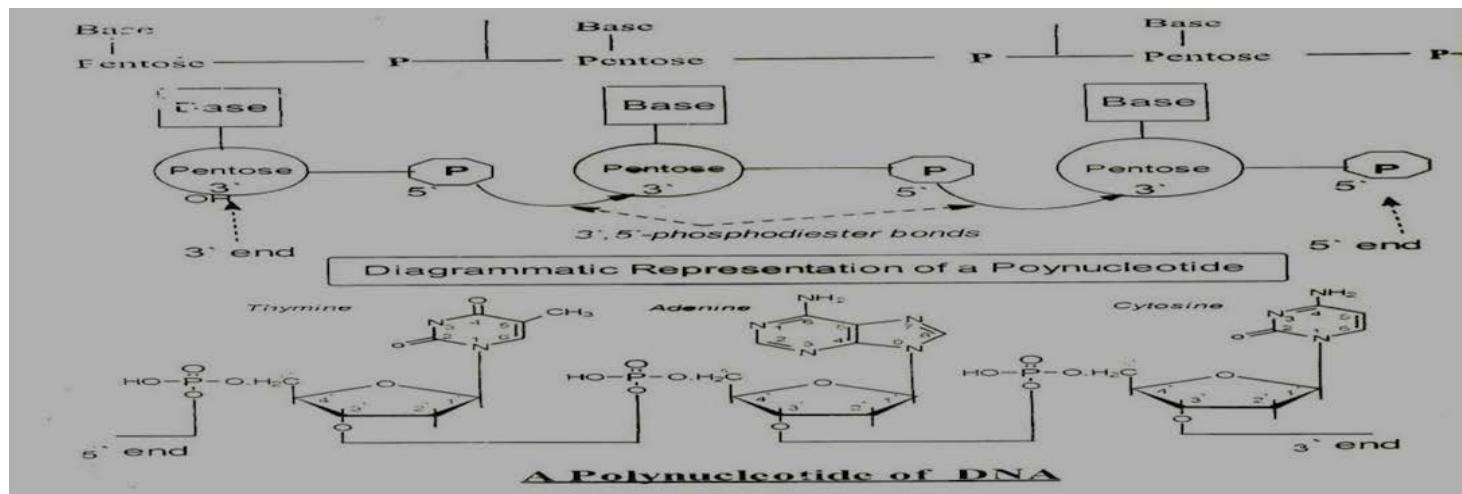
- Serve as energy stores (ATP).
- forms portions of several co-enzymes (NAD⁺).
- Serves as signaling intermediates (cAMP- cGMP).
- Is an allosteric modifier of certain modulated enzymes.
- conveys genetic information (DNA- RNA).

NUCLEIC ACIDS STRUCTURE

The polynucleotide structure of nucleic acids is obtained by esterification of the 5 phosphate of each nucleotide with – OH group of C3 of the pentose of the adjacent nucleotide forming a phosphodiester linkage.

Nucleic acid has 2 ends:

- The 5` end has a free 5 phosphate group.
- The 3` end has a free 3` free hydroxyl group.



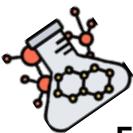
DNA Structure:

-DNA: Mostly found in nucleus forming chromatin & little of DNA, found n Mitochondria.

-DNA: is organized into genes, which is the fundamental unit of genetic information.

-DNA: is very long polynucleotide (1 M).

Many nucleotides covalently - linked by 5`→3` Phosphodiester bond.



-Each nucleotide in DNA composed of 3 elements:

- 1-Sugar (Pentose) is Deoxy Ribose.
 - 2-Base (Adenine, Guanine, Cytosine and Thymine)
 - 3-Phosphate.

- The sugar is linked to base forming Nucleoside, the phosphorylated nucleoside called nucleotide.
- According to **Watson** and **Crick** Model structure 1953 DNA exists a double strand molecule, where the two strands twisted around each other forming double helix.
- In the double helix chain are coiled around a common axis.
- The chains are paired in an anti-parallel manner that is the '5- end of one strand is paired the '3- end of the other strand .

The most common type of DNA "B" (Right handed twisted)

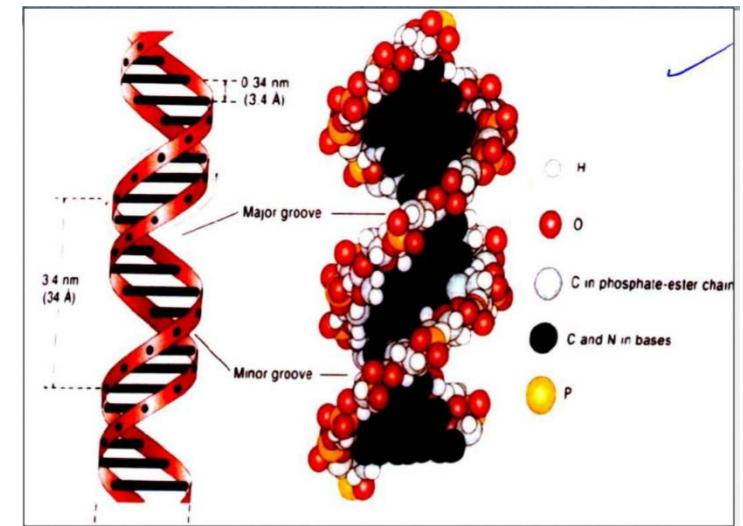
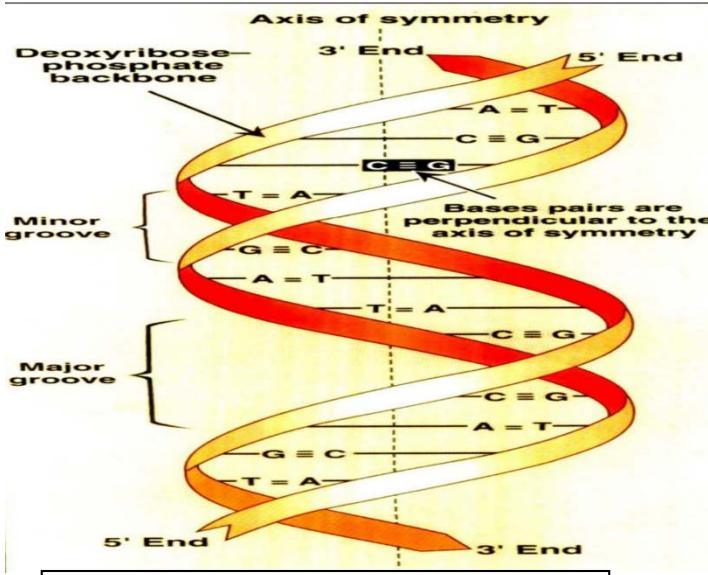
- The hydrophilic (polar) **Deoxyribose -phosphate** backbone of each chain is on the outside of the molecule, whereas the hydrophobic (non-polar) bases are stacked inside perpendicular to the axis of the helix.

The overall structure resembles a twisted ladder

- **Base Pairing Role:** the bases of one strand are paired with the bases of the second strand. So, an Adenine is always paired with Thymine, whereas Cytosine is always paired with Guanine. Therefore one polynucleotide chain of the DNA double helix is always **complementary** of the other.

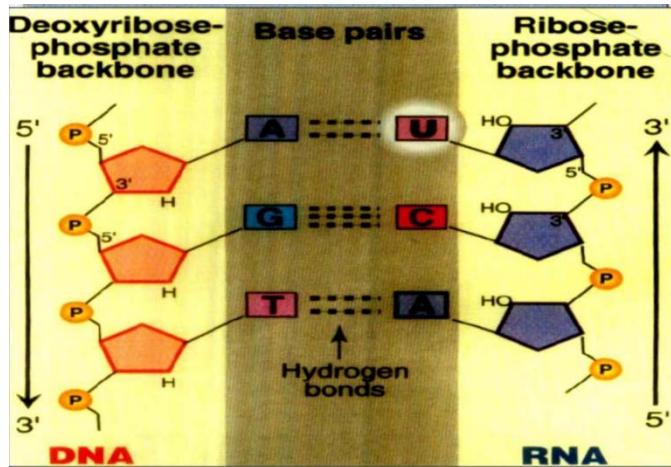
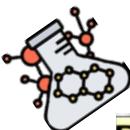
- The base pairs are held together by H bonds; Two Hydrogen bonds between A and T ($A = T$) and three Hydrogen bonds between G and C ($G \equiv C$).

These **Hydrogen** bonds plus **hydrophobic** interactions between the stacked bases stabilize the structure of the double helix.

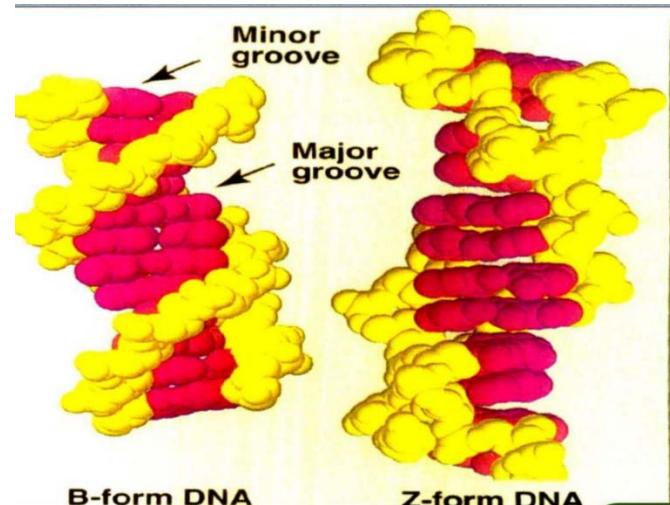


The most common form of the Double – Helix DNA

DNA double helix, illustrating some of its major structural features.

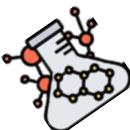


Anti parallel, Complementary base pairs between DNA and RNA.



Structures of B-DNA and Z-DNA.

- According to the base-pair rule the A always paired with T (some thymine present in t RNA) and C is always paired to G. The two chains in such DNA are said to have **Complementary Structure**.
 - The proportion of the bases in a given DNA can be characterized by (A+T / G+C Ratio) which are constant for each type of DNA. However, this ratio varies widely between organisms.
 - The two strands of DNA are anti-parallel i.e. running in opposite directions: one strand runs 5' → 3', the other runs 3' → 5'. Each turn of the double helix contains 10 base-pairs. The helix is (2nm) in diameter and makes a complete turn (run) every (3.4 nm).
 - The special relationship between the two strands in the helix creates a major groove (wide) and a minor (narrow) groove; these grooves are of different size due to the asymmetry of the base pairs.
 - The total length of all DNA in a single human cell is about (1 meter long).
 - An adult human body contains approximately (10¹⁴) cells and thus the total (10¹¹) length of (1 × 10) 11 km. This compare with circumference of earth (4 × 10⁴ km) or the distance between the earth and the sun (1.5 × 10⁸ km), if one nucleotide is added per second, it will take 250 years to synthesize the whole DNA of a human cell.
 - The length of a DNA molecule is compressed to 10,000 fold to generate the chromosomes.
- A dramatic illustration of the extraordinary degree of DNA compaction in our cells.
- Microscopically observation of nuclei in dividing eukaryotic cells has shown that the genetic material is sub-divided into **Chromosomes**, their diploid number



depending upon the species.

(There are 46 Chromosomes in every normal human somatic cell). Each Chromosome of eukaryotic cell contains a single very large duplex DNA molecule, which may be (4- 100) times longer than that of an E. coli.

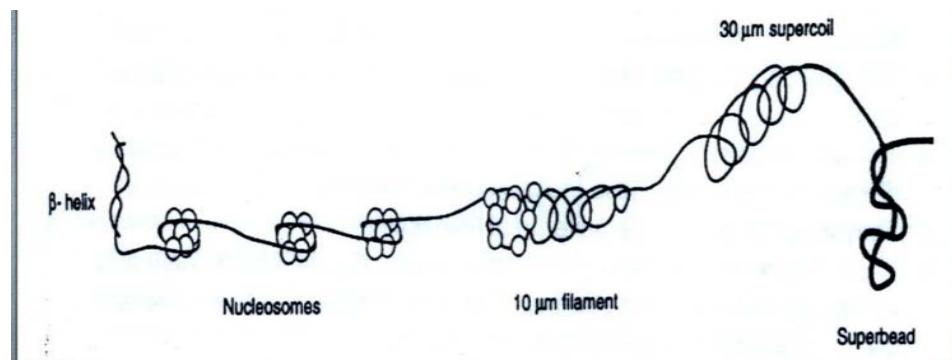
- The DNA molecules have the 24 different types of human chromosomes (22 matching - pairs plus the x & y sex chromosomes), vary in length.
- Each type of the chromosomes in eukaryotes carries a characteristic set of genes.

DNA ORGANIZATION Chromatin and Chromosomes

- Free eukaryotic cell DNA (one meter) is too long to fit into cell nucleus ($5.8\mu\text{mol}$) . It must be condensed or compacted into **chromosome**; the term is used to refer to nucleic acid molecule that repository (stored) for genetic information in all organisms.

The chromosomal material called chromatin, Long stretch DNA with histones (The combination of **DNA** and **protein** on chromosome), it is further & further condensed (10,000 fold) to form chromosomes.

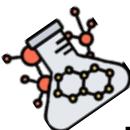
The fundamental unit of organization in the chromatin of eukaryotes cell called **nucleosome**.



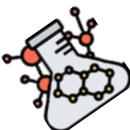
Higher orders of structure found in eukaryotic chromosomes.

These include Nucleosomes, 10mm filament, and proposed 30 mm super coil and rosettes or super beads.

- Almost all nuclear DNA in eukaryotes is bound to Histones in the nucleosomes.
- Nucleosome consists of Histone and 200 base- pair segment of DNA.
- Histone is basic protein as a result of high lysine & arginine it is synthesized in the cytoplasm migrate to the nucleus and is modified by acetylation , mythylation and phosphorylation



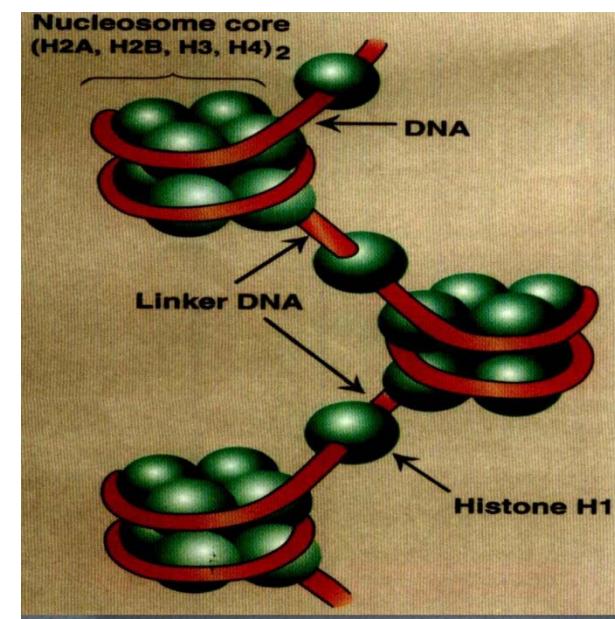
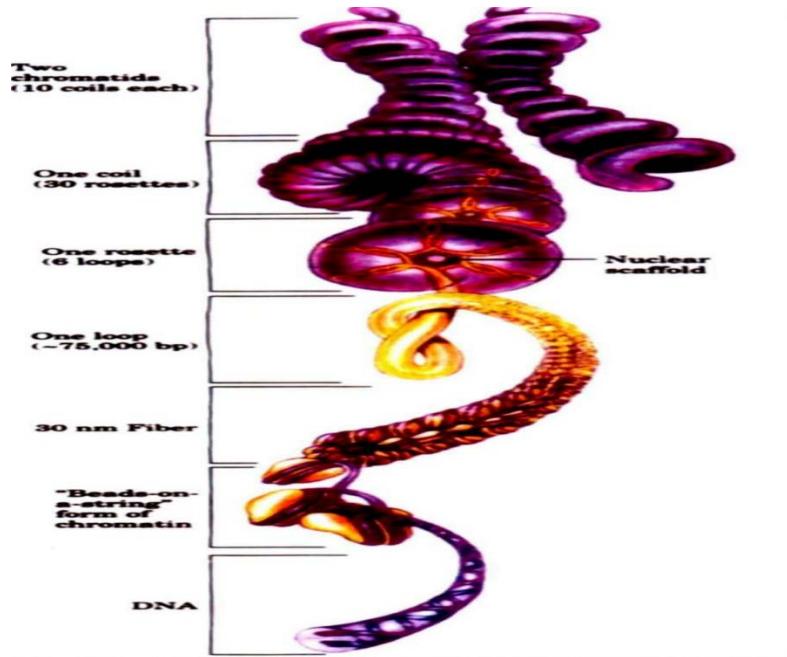
- There are **5 types of Histone** (H1, H2A, H2B, H3 and H4).
Histones account for nearly half of weight of eukaryotic chromosomes.
- **Nucleosomes** consist of DNA core and a linking region.
- The core is composed of 140 base –pairs of DNA encircling a Histone octamer i.e. two molecule of each (H2A, H2B, H3 and H4) thus Histone occupies the center of the nucleosomes core with DNA wrapped around The outside (left handed).
- The linking region of nucleosomes consisting of 60 basepairs of DNA bound to 1 mole of Histone (H1).
- Chromatin arranged like beads on string form.
- Nucleosomes are organized into (30 nm) fibers (nucleosome core); the 30 nm fiber in a second level of chromatin organization (an approximately 100 fold).
- As the nucleosomes are formed, they stack together in regular cylindrical arrangement, solenoidal coiling of 30 nm fiber, the stacking of nucleosomes is mediated by H1 Histone.
- 30 nm fiber themselves are extensively folded to provide 10,000 fold.
Additional packing of solenoid (30 nm fiber) into twisted looped structure attached to nuclear protein called **Scaffold protein** within the chromosomes.
- **Scaffold protein** contains large amount of Histone H1 & non Histone protein (Topo -isomerase).
- Each twisted loop can be coiled & super coiled then packing these loops in the form of stacked helical coils i.e. (stacked on each other into two chromatids fibers), these packing to fit a typical eukaryotic chromosomes into the nucleus as two chromatids fiber.
- So, it is speculated that the chromatids of metaphase chromosomes consists of helical packed 30 nm fibers.
- Human cells, with exception of germ cells, each contain two copies of chromosomes are inherited from the mother and father.



- The maternal & paternal chromosomes of a pair are called **homologous chromosome**.

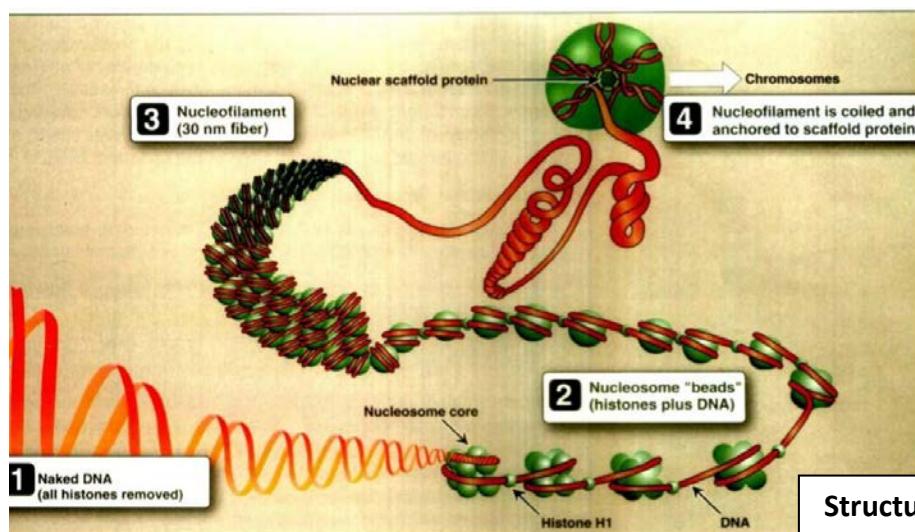
The only non homologous chromosomes pairs are the sex chromosomes in males, where Y chromosomes inherited from the father and X chromosome is inherited from the mother.

- In human normal somatic cell, 46 chromosomes (22 matches pairs + plus X & Y sex chromosomes), each type of chromosomes carries a characteristic set of genes.

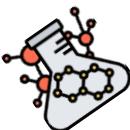


Model for levels of organization that could provide DNA compaction in eukaryotic chromosome. The levels take the form of coils upon coils. In cells, the higher-order structures

Organization of human DNA, illustrating the structure of nucleosomes



Structural organization of eukaryotic DNA



L12&13 MB: DNA replication

DEFINITION: Replication is the formation of daughter DNA molecules from the parent DNA. This process of DNA synthesis occurs during the S phase of cell cycle and catalyzed by a complex of proteins that includes the enzyme **DNA polymerase**.

- ⦿ Each strand of the parent DNA acts as a template for the synthesis of each complementary strand, this occurs prior the cell division.
- ⦿ The DNA strand copies the template strand in 3` to 5` direction and synthesized the newly strand in the 5` to 3`direction, using deoxyribose nucleoside triphosphate **as precursor**.
- ⦿ Errors that occur during replication are corrected by enzyme associated with the replication complex.

MECHANISM OF REPLICATION:

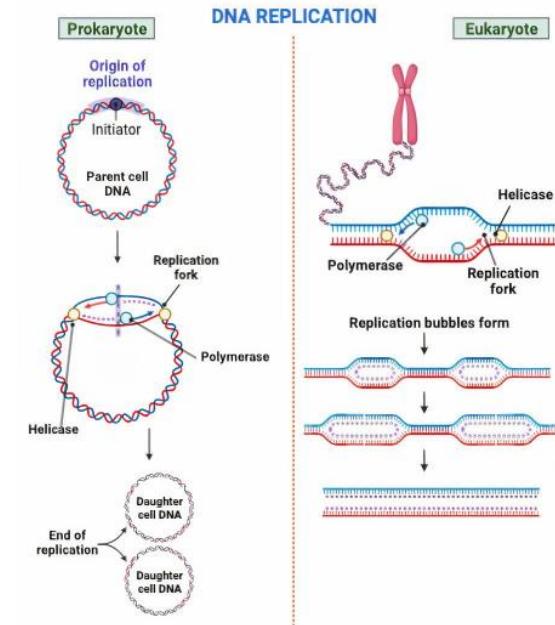
Replication is bidirectional and semi-conservatives: -

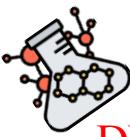
- Bidirectional** means that replication begins at a site of origin simultaneously moves out in both directions from this point:
 - Prokaryotes have one site of origin on each chromosome.
 - Eukaryotes have multiple sites of origin on each chromosome.
- Semi-conservative**: means that, following replication, each daughter molecule of DNA contains one intact parental strand and one newly synthesized strand joined by base pairs.

Replication forks: -

The forks are the sites at which DNA synthesis is occurring. The parental strands of DNA separate and the helix unwind at a head of replication fork.

- Helicases**: unwind the helix and single-strand binding proteins hold it in a single-a strand (DNA binding protein)
- Topoisomerase**: act to prevent the extreme super coiling or twisting of the parental helix that would result of un-circling at the replication fork (at the site at which DNA synthesis occurring)
 - ✓ Topoisomerase breaks and rejoin DNA strand.
 - ✓ DNA Gyrase: it is the topoisomerase of prokaryotes.





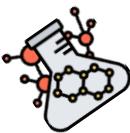
DNA Polymerases: catalyzes the synthesis of DNA

Prokaryotes have three DNA polymerases	Pol is involved in DNA repair. Poll PolIII is the replication enhancement.
Eukaryotes have four to five DNA polymerases	α It contain primase that initiate DNA synthesis. β Is involved in repair of molecule of DNA with ε γ Initiate the replication of the mitochondrial DNA. δ Involve in elongation of leading strand & Okazaki fragment. ε Involve with β in the repair of DNA molecule

- DNA polymerase can only copy DNA template in 3` to 5` direction and production of the newly strand in the 5` to 3`direction.
- Deoxytrinucleoside triphosphate (dATP, dTTP, dCTP) are precursors of the DNA chain:
 - ≡ Each one pair with corresponding base on the template strand forms a phosphodiester bond with OH gp. on the 3` carbons of the sugar at the end of the growing chain.
 - ≡ Pyrophosphate is produced and cleaved to two inorganic phosphates, releasing energy that drives the reaction.

DNA polymerase requires a primer

- DNA polymerase cannot initiate the synthesis of new strand, RNA serves as a **primer** for DNA polymerase.
- RNA primer contains **10 or fewer nucleotides** which formed by copying of the parental strand in reaction catalyzed by primase.
- DNA polymerase adds deoxyribonucleotides to the OH of C 3`of RNA primers and subsequently to the ends of the growing DNA strand.
- DNA parental (template) strands are copied simultaneously at replication forks, although they run in opposite direction.
- The leading strand is formed by continuous copying of the parental strand, that runs 3` to 5` towards one replication fork.
- The lagging strand is formed by discontinuous copying of the parental strand that runs 5` to 3` away from the replication fork:
 - As more the helix unwinded; synthesis of the lagging strand begins another primer.
 - The short fragment formed by this process are known as - Okazaki fragment: short segment of single strand DNA containing RNA primers.
 - RNA primer is removed by RNA polymerase I and the gaps are filled with appropriate -deoxyribonucleotides by another DNA polymerase I.



- ❑ Finally, the Okazaki fragments are joined by polynucleotide ligase (DNA ligase) that enzyme catalyzed the formation of phosphodiester bond between the two polynucleotide chains.
- ❑ In eukaryotic cells about 100 – 200 nucleotides are added to lagging strand in each round whereas in prokaryotes about 1000 – 2000 nucleotide are added.

THE FIDELITY OF REPLICATION

is very high with an overall error rate 10^{-4} to 10^{-10}

- ❖ an error (insertion of inappropriate nucleotide that occur during replication) may be corrected by editing during replication this performing by a 3` to 5` nucleosidase (exonuclease) associated with poly III in prokaryotes and by DNA polymerase β and ξ in eukaryotes.
- ❖ Post replication repair process also increase the fidelity of replication.

DNA Replication

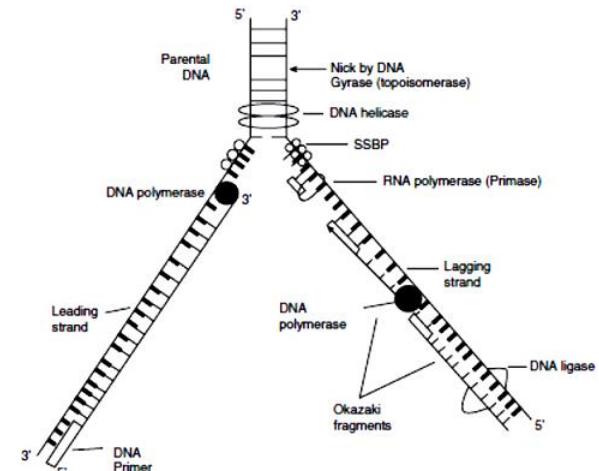
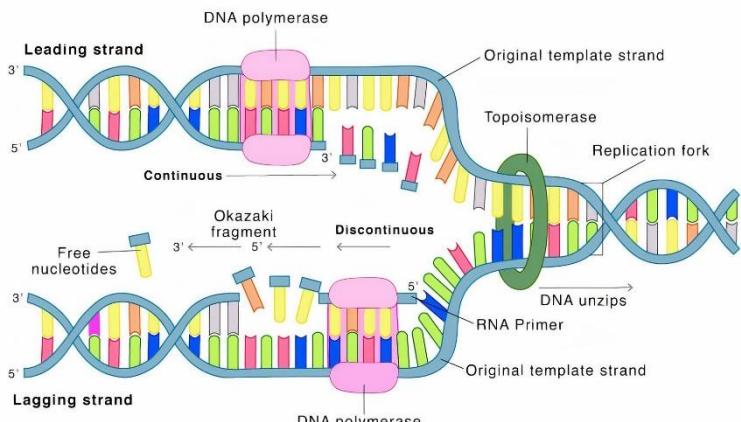
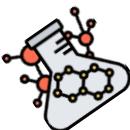


Fig. Replication of DNA

To summarize the events in DNA replication:

- Helicase: unwind DNA double helix & DNA binding protein hold it in a single strand.
- Topoisomerase: act to prevent the super coiling or twisting of parental helix that would be results from unwinding at replication fork (DNA gyrase in prokaryotes).
- Primase: form RNA primer for each strand of DNA.
- DNA polymerase III: at replication fork synthesizes DNA in a 5` to 3` direction. The leading strand can be synthesized continuously; however, the lagging strand must be synthesized discontinuously in the form of Okazaki fragment.
- DNA polymerase I: removes the RNA primer and fills the gaps between Okazaki fragments in lagging strand and also the gaps due to the removal of the primer on the leading strand of DNA.
- DNA ligase: join DNA fragments (lagging & leading strands) forming a single DNA molecule.



L14 : RNA structure and types, gene, genome and genetic code

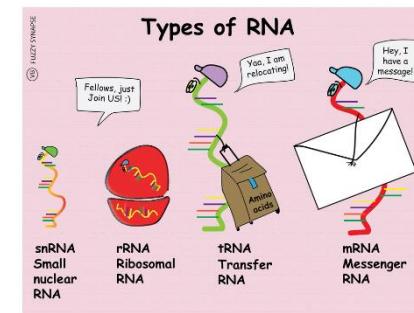


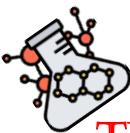
RNA STRUCTURE

- RNA is polynucleotide structure similar to that of DNA except that RNA contains sugar ribose instead of deoxyribose in DNA.
- It usually contains Uracil (U) instead of Thymine (T); (some thymine in t RNA).
- It is present **mainly in cytoplasm** but **little in mitochondria**.
- About 50% cellular RNA is distributed in the ribosomes and endoplasmic reticulum, 25% in cytoplasm, 15% in mitochondria and the rest 10% in nucleus.
- It consists of 75 to several thousands of ribonucleotides (AMP, GMP, CMP and UMP).
- Generally, RNA is single stranded, which may be loop-back (folding-back) on itself and the bases on the opposite side of the same strand base-pairing with each other.

THERE ARE 4 TYPES OF RNA:

1. Transfer RNA (t RNA).
2. Messenger RNA (m RNA).
3. Ribosomal RNA (r RNA).
4. Small nuclear RNA (sn RNA).





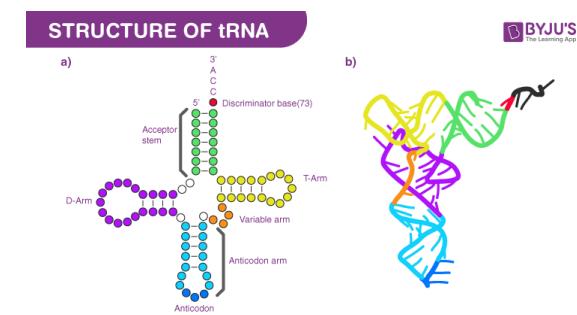
TRANSFER RNA (TRNA OR SRNA) :

- It presents in the soluble part of the cytoplasm (**cytosol**).
- It represents 15-30 % of total cellular RNA.
- It consists of 75 – 85 ribonucleotides which arranged in single strand which is folded- back on itself like (**hair-pin**) having a clover leaf appearance.
- This shape is maintained by formation of hydrogen bonds between the bases of the same strand **A=U, C≡G**.

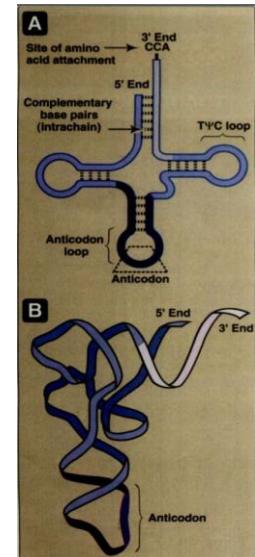
Structure:

It has **3 loops & lump** with **3' CCA arm** :

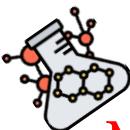
- ❖ The first loop is **D arm** (dihydrouracil loop) (DHU).
- ❖ The second is the **anti-codon loop or arm** which contains sequence of the 3 bases the anti-codon that base-pair with the codon of mRNA.
- ❖ The third loop is **TΨC arm** (thyamidine-pseudouridine – cytocine) contain pseudouridine.
- ❖ **CCA arm** : the base sequence contain cytosine –cytosine adenine, it present at the 3' end . it is an acceptor arm for the attachment of amino acid to form amino acyl- tRNA.



tRNA function

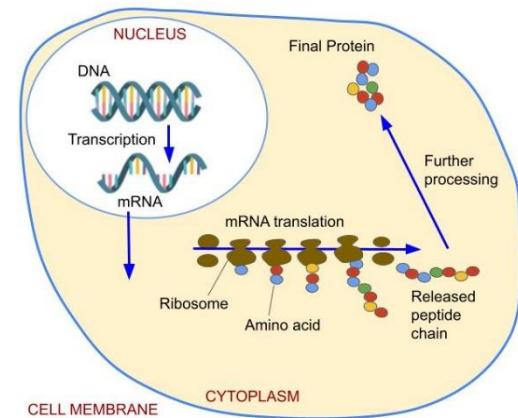


- is to carry amino acids during protein synthesis (ensure amino acid is properly position in the protein being synthesized).
- The -COOH group of amino acid is connected by ester linkage with OH group of ribose at C3 of nucleotide at the 3' terminal adenosine and the sequence is ACC
- Each amino acid has at least one tRNA , so there are at least 20 tRNA differ in the sequence of the bases especially the 3 successive bases found in middle loop (Anti- Codon loop).
- Guanosine at the 5' terminal and the sequence ACC at the 3' terminal



MESSENGER RNA (M RNA)

- Messenger RNA is so called because it carries genetic information from the DNA for protein synthesis.
- mRNA has a precursor form called **heterogeneous nuclear RNA(hnRNA)** which is further processed to form mature RNA. It account 5-10 % of total RNA.



- It is synthesized in the nucleus as complementary strand to the sense strand of chromosomal DNA, then sent to the ribosomes in the cytoplasm carrying a message, from DNA where it is going to direct the synthesis of specific protein.
- The letters of the message are the nitrogenous bases and the sequence of which is possible for arranging the amino acids in polypeptide chains.
- Each 3 successive bases in the mRNA are called **Codon** as they code for specific amino acid. mRNA contains 4 different bases (A, G, U and C) that interchange with each other (in 3 forms) in 3 successive bases give $(4)^3 = 4 \times 4 \times 4 = 64$ different codons for **20 amino acids**.
- The informational codons are **61 codons**

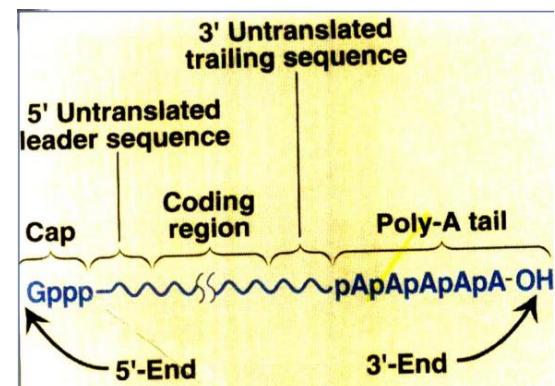


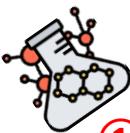
The first codon is called Initiating codon at the 5' terminus AUG



The last codon is called Terminating codon at the 3' terminus UGA
UAG, UAA.

- Eukaryotic mRNA structure includes:
 1. Cap
 2. 5' UTR un translated region
 3. coding region
 4. 3' UTR untranslated region
 5. polyadenylate tail.





① Cap is an inverted 7- methyl GTP attached to 5' end.

Its functions include:

1. Inhibits nuclease digestion of mRNA from 5' end.
2. Helps the stabilization of the mRNA.
3. Facilitates the binding of mRNA to ribosomes (initiation of translation).

② 5' UTR (5' untranslated region in at the 5' end).

③ Coding region contains 3 types of codons.

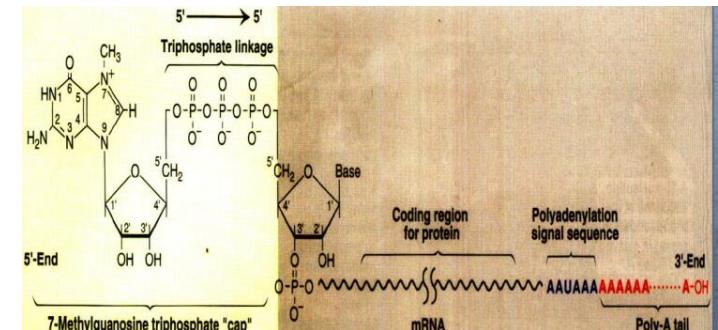
- Initiating codon which is always AUG for methionine.
- Specific codons for different amino acids.
- Terminating codons which are UGA, UAA and UAG.

④ 3'UTR (3'' untranslated region in at the 3' end.)

⑤ Polyadenylate tail (poly A tail) consist of 200-300 adenylate residues at the 3' end.

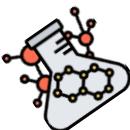
Its functions include:

1. Helping stabilization of mRNA
2. Facilitating their exit from the nucleus.



✓ Bacterial & mitochondrial mRNA lacks of caps and tails.

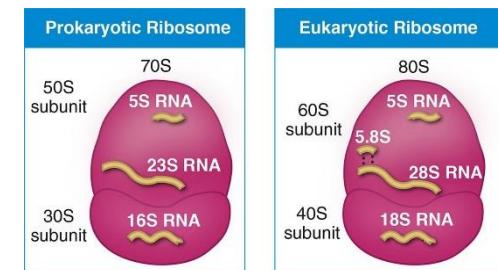
- The 5'end contains a cap structure, followed by untranslated region after that the coding or translated region (it is a portion of the molecule that specifies the amino acid sequence of the protein for which mRNA codes) after the translation region, there is another untranslated segment, followed by a poly A tail at the 3' end.



RIBOSOMAL RNA (rRNA)

- Ribosomal RNA (rRNA) is found in ribosomes.
- In ribosomes it is associated with different ribosomal proteins.
- It is 60-80% of total cellular RNA. O It is synthesized in the nucleus as a complementary strand to the nuclear DNA. It is present in the cytoplasm & broken into few pieces differs in sedimentation coefficients (S)
- They associated with proteins to form **ribosomes**.

- Prokaryotic rRNA has 3 types of rRNA: 16S, 23S and 5S.
- Eukaryotic rRNA has 4 types of cytoplasmic rRNA: 18S, 28S, 5S, and 5.8S.

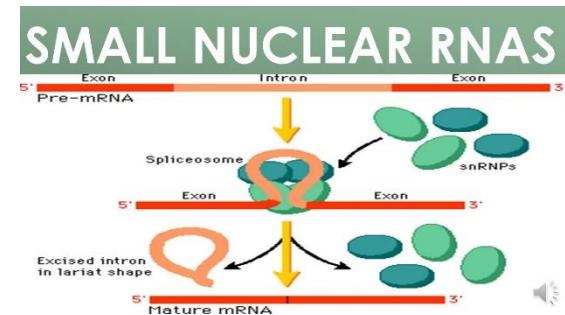


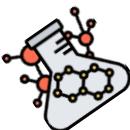
- The RNA ribosome consists of 2 subunits, they are characterized by sedimentation co-efficient (S), in ultra centrifugation which measured by Svedberg unit(S).
- The rRNA acts as a machinery for protein synthesis i.e. **it is responsible for protein synthesis.**

- The 40S or 30S subunits responsible for binding of tRNA and mRNA.
- The 60S or 50S subunits contain enzymes responsible for connecting amino acids together to form poly-peptides chain.

SMALL NUCLEAR RNAs (sn RNAs)

- Their size ranges from 90-300 nucleotides they are name as U1, U2, U4, U5, U6 and U7. All of them are located in the Nucleus.
- snRNPs associated with precursor mRNA (hnRNA) at the exon-intron junction form spliceosomes that catalyze the splicing or removal of introns of mRNA precursors.
- It is absent in **prokaryotes**.



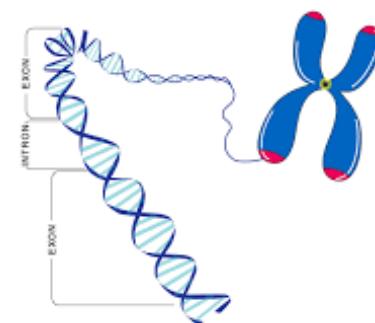
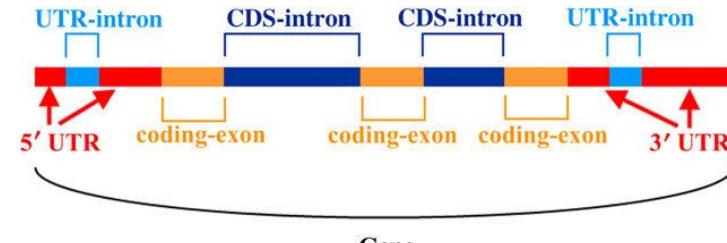


NUCLEOPROTEINS AND NUCLEIC ACIDS

GENE STRUCTURE:

- The genes of prokaryotes are **continuous** DNA sequences, in contrast, few human gene are continuous DNA sequences.
- Continuous human genes include those for most tRNA molecules and Histones.
- Most human genes are - **discontinuous**, with it two or more expressed sequence called "**Exons**" separated by untranslated region called "**Introns**".
- The total length of introns far exceeds that of exons.
- Introns often spliced out of RNA prior to Translation (maturation).
- Exons often code for specific portion of protein, hence new proteins can be built from - duplication of previous exon.

GENES

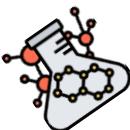
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GENETIC CODE:

- The genetic code: is the collection of codons that specify all the amino acid found in protein.
- Each DNA strand codes for the synthesis of many polypeptides.
- A segment of DNA that codes for one polypeptide is termed a "**gene**".
- Each mRNA can code for one or several polypeptide.

CODON:

- A codon is a sequence of three bases (**triplet**) in mRNA (**5' to 3'**) that specifies or corresponds to, a particular amino acid.
- Each codon leads to the addition of one particular amino acid during translation, or protein synthesis, the successive codon in mRNA determine the sequence in which amino acids added to the growing polypeptide chain.



- There (4^3) or 64 possible trinucleotide sequence of the four nucleotides in mRNA. - The three codons — UAA, UAG and UGA near the 3`end, do not represent amino acids, but rather they signal the point of chain termination.
- The genetic code is degenerate (redundant) there is at least one codon for each of the 20 common amino acids, many amino acids have several codons, so called degenerated code.

■ **Genetic code:** is un-overlapping, i.e. each nucleotide is used only once beginning with a start codon AUG near the 5`end of mRNA (the only codon for Methionine) is the chain initiation codon for protein of higher organisms.

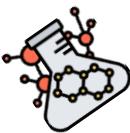
- We have 40.000 genes (approximately) of human genome translate into 100 to 1000 of proteins.

■ **The codons** is commaless i.e. there are no breaks or markers to distinguished one codon from the next.

- Universal, the codons are the same for the same amino acid in all species, the same for Elephant and E.coli.
- The start codon AUG sets the reading frame.
- Any change in the DNA base sequence will transmitted in both DNA replication and RNA transcription.
- Thus the codon determines the so-called "Reading frame", the shifting of this frame by one or more nucleotides leading to the formation of polypeptide which are composed of completely different amino acids (different from the original).

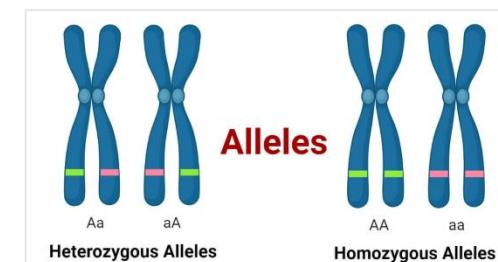
BASIC PRINCIPLES OF HEREDITY GENOME AND GENOMICS:

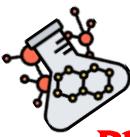
- Human cells: with exception of germ cells each contain two copies of chromosomes are paired, one inherited from the mother and one inherited from the father.
- Heredity is transmitted from parent to offspring as individual characters.
 - Y chromosome is inherited from the father.
 - X chromosome is inherited from the mother.
- In human normal somatic cell there are 46 chromosomes (22 matching pairs plus X, Y sex chromosomes).
- Each type of chromosomes in eukaryotes carries a characteristic set of genes.



- **Chromosome:** is the term that used to refer to the nucleic acid molecule that respiratory for genetic information in all organisms.
- The chromosomal material called **chromatin**; the fundamental unit of organization in the chromatin of eukaryotic cell is **the nucleosome**; the nucleosome are organized into 30 nm fibers, this 30 nm is the second level of chromatin organization provide approximately 100 fold.
- The fiber themselves are extensively folded to provide 10,000 fold to fit a typical eukaryotic chromosome into cell nucleus.
- The genes are linearly distributed on chromosomes at fixed positions (**loci**).
- Genes that may replace one another at the same locus are called all elomorphic genes or alleles.

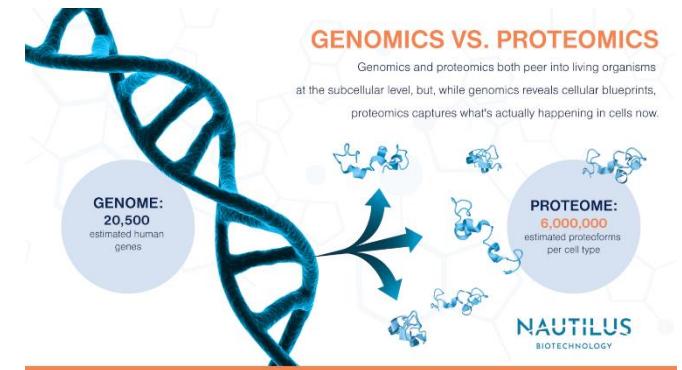
- **ALLELES** are genes responsible for alternate or contrasting characters. (usually one allele is inherited from father and the other from mother).
 - When both alleles carry the same defect, it is said to be **homozygous**.
 - When one allele is normal, and the counterpart is defective; it is called **heterozygous**.
- Genes on the same chromosome are linked; and the linkages are more pronounced in the nearby genes. The observed character expressed by the gene is called phenotype.
- The genotype represents the set pattern of genes present in the cell.
- **GENOME OF A CELL** is the total number of genes within one mature cell of an organism (9×10^4) nucleotide pairs organized as 23 chromosomes, and it accounts millions of genes.
- Only 10% are functioning, i.e. can be expressed and synthesize polypeptide, while the functions of the other 90% are not known.
- Now 30,000 to 25000 of human genome translate to 100 - 1000 of proteins.
- **Genomics:** is the study of the genome and its actions involves analysis of DNA sequence of the organism.



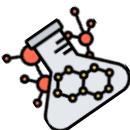


PROTEOME AND PROTEOMICS

- **Proteome** is the sum of all proteins expressed by the genome of an organism, thus involving the identification of the proteins in the body and determination of their role in physiological and pathological functions.
- While the genome remains largely unchanged, the proteins of a particular cell change dramatically as genes are turned on and off in response to the environment.
- **Proteomics:** It directly addresses the protein complement of the genome. It has been defined as the study of protein properties (expression level, post-translational modification, interaction, etc.) on a large scale to obtain a global, integrated view of disease processes, cellular processes, and networks at the protein level.
- The study of all proteins by a cell type of an organism (all proteins expressed by genome) is called 'proteomics'.

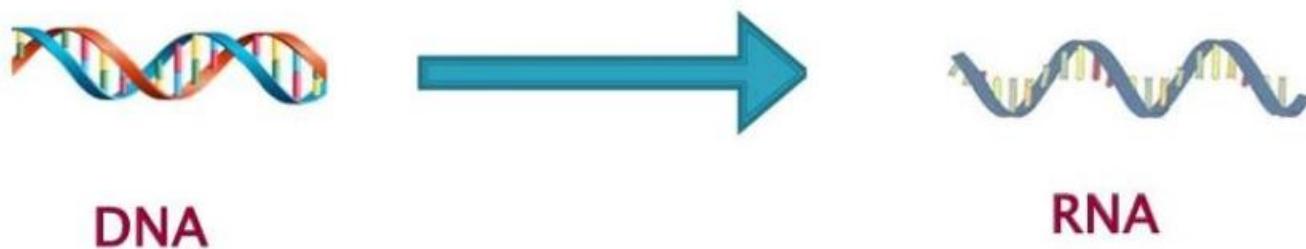


أَللّٰهُمَّ نَصْرٌ لِّلّٰهِ قَوْبَتْ



L18 : Transcription and post transcriptional modification

Definition: Cellular process in which RNA is synthesized using DNA as a template known as **TRANSCRIPTION**.



Features of transcription

In transcription: the 2 strands of DNA are:

- Template strand (antisense strand)
- Coding strand (sense strand)

The sense strand is the strand of DNA that has the same sequence as the mRNA, which takes the antisense strand as its template during transcription.

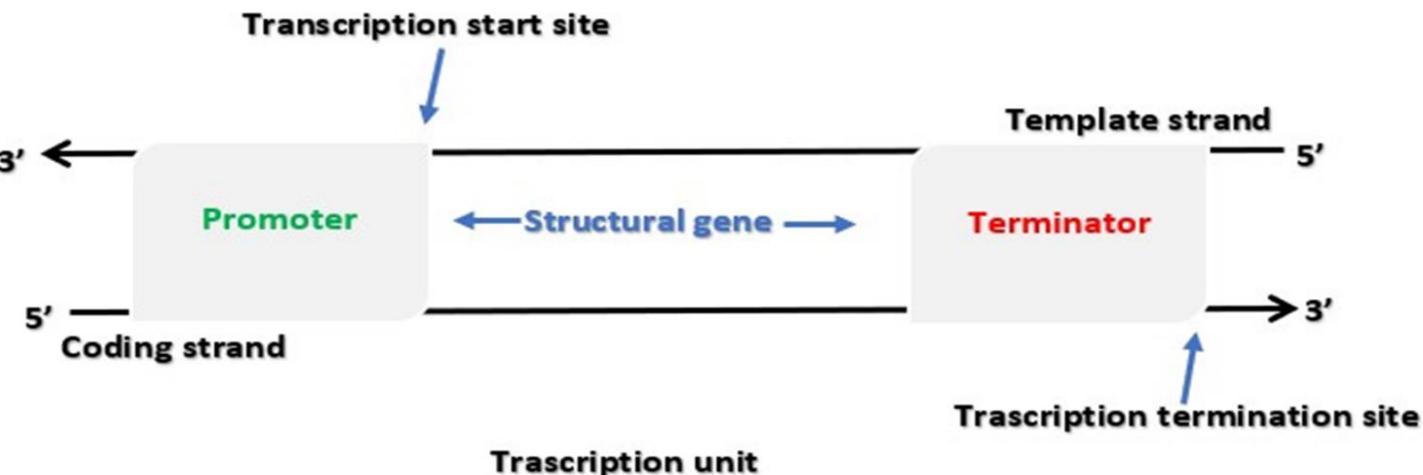
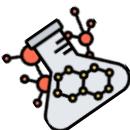
Only one of the 2 strands can be the template.

Transcriptional unit:

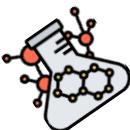
Definition : A transcription unit is a segment of DNA that takes part in transcription. It has three components –

- (i) a promoter
- (ii) a structural gene and
- (iii) a terminator.

Promoter is located upstream of structural gene.



- Upstream means
- Downstream means
- Upstream is toward the 5' end of the coding strand and downstream is toward the 3' end.
- A promoter. A terminator the start point
- Promoters and terminators are stretches of DNA upstream and downstream (respectively) of genes that control both the rate at which the gene is transcribed
- The first base of a gene to be transcribed by an RNA polymerase, corresponding to the 5'-most base of the resulting transcript, is referred to as the transcription start site (TSS)(+1)
- starting at the initiation site and receive positive values to the right and negative values to the left.
- The nucleotide in the promoter adjacent to the +1 nucleotide is designated -1. Adjacent nucleotides are given negative numbers that increase as we go upstream the promoter.



Difference between replication & transcription

REPLICATION

- New DNA is formed
- DNA-DNA hybrid complex
- DNA polymerase enz.
- Primer is required
- Deoxyribonucleotides used
- Entire genome is copied.
- Proofreading
- Genetic information is inherited.

TRANSCRIPTION

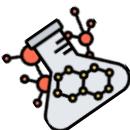
- New RNA is formed
- DNA -RNA hybrid complex
- RNA polymerase enz.
- Primer not required
- Ribonucleotides used
- Very small portion of genome transcribed
- No proofreading.
- Information is transferred from gene to protein.

❖ Differences between transcription in eukaryotes and prokaryotes

Polycistronic: The gene encodes multiple separate gene products. **Monocistronic:**

The gene encodes one gene product.

	prokaryotes	eukaryotes
mRNA	Polycistronic RNA	Monocistronic RNA
RNA polymerase (RNAP)	One type	3 nuclear RNAP 1 mitochondrial RNAP
Inhibitors of RNAP	Rifampicin Actinomycin D	Alpha amanitin

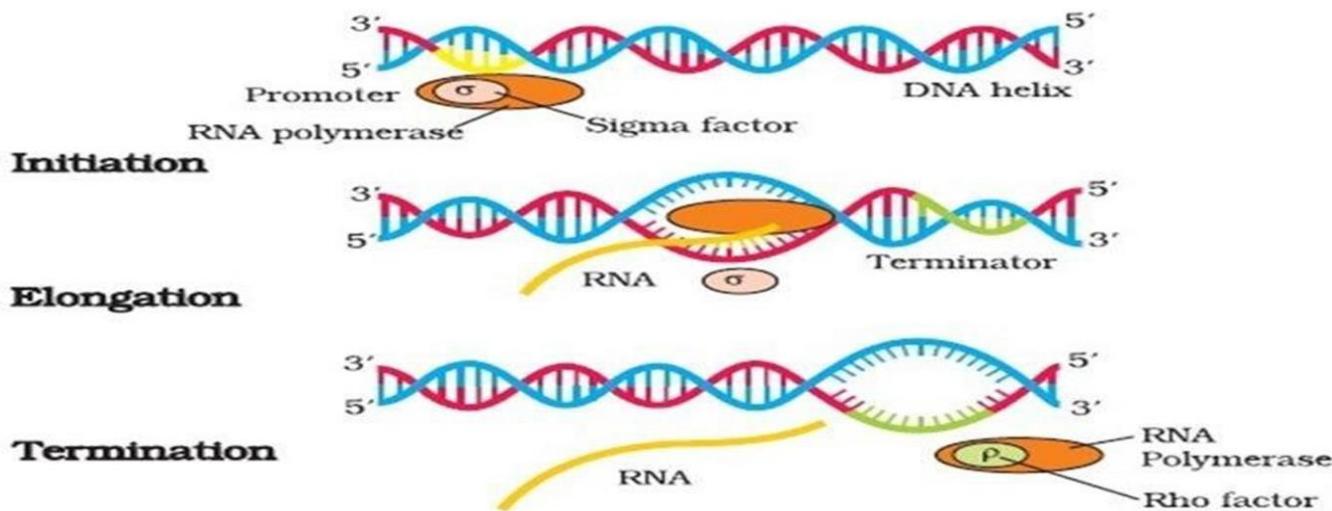


RNA polymerases and their function

- RNA polymerases transcribe the information in DNA into RNA molecules that have a variety of functions, including messenger RNA (mRNA; codes for proteins), and non-coding RNAs such as transfer RNA (tRNA; transports amino acids to the ribosome for protein synthesis), ribosomal RNA (rRNA; helps catalyze protein synthesis ...)
- RNA Polymerase I is an enzyme that transcribes ribosomal RNAs. RNA Polymerase II is an enzyme that transcribes precursors of mRNAs. RNA Polymerase III is an enzyme that transcribes tRNAs. It transcribes all rRNAs except the 5S rRNA component.

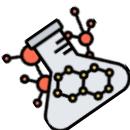
Steps of transcription :

- (1) initiation
- (2) elongation
- (3) termination

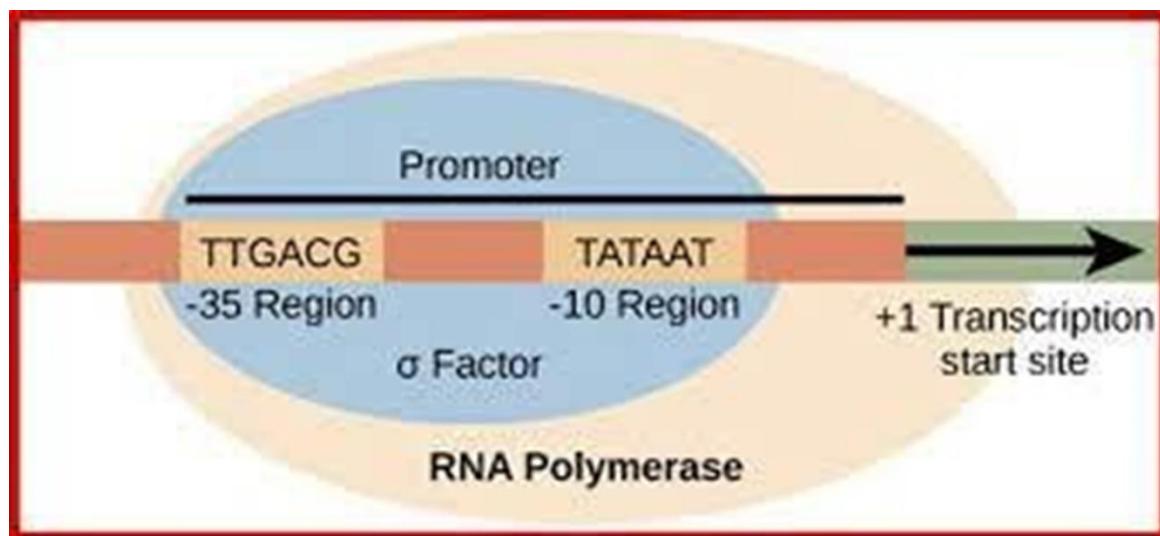


1- Initiation

Involves binding of the RNA polymerase to the promoter region of the genes to be transcribed.



promoter region in prokaryotes



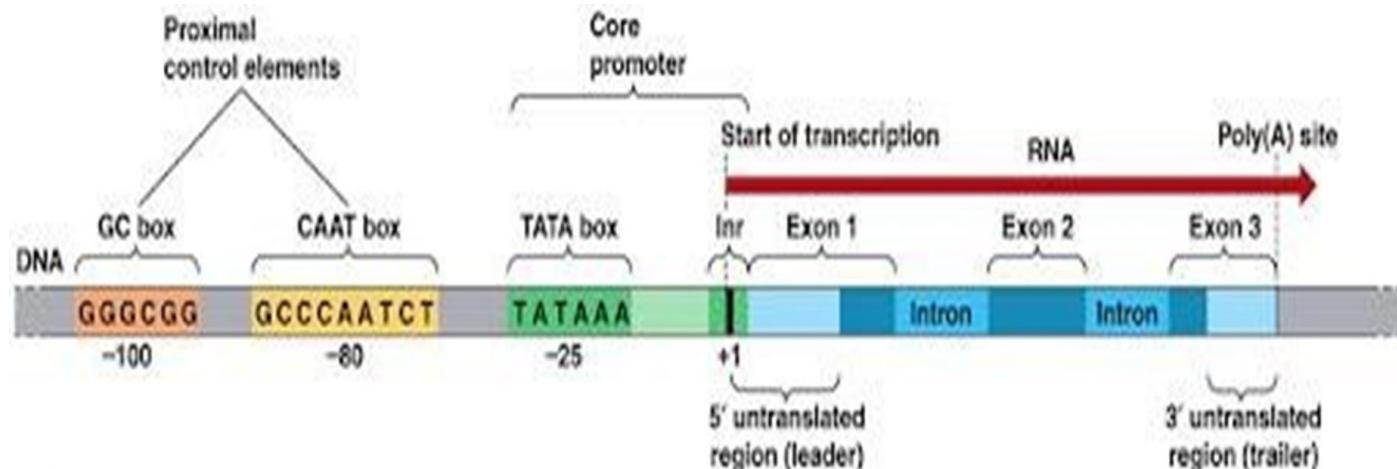
Prokaryotic promoters

In prokaryotes, the promoter consists of two short sequences at -10 and -35 positions upstream from the transcription start site.

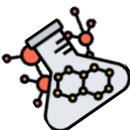
The sequence at -10 is called the Pribnow box, or the -10 element, and usually consists of the six nucleotides TATAAT. The Pribnow box is absolutely essential to start transcription in prokaryotes.

The other sequence at -35 (the -35 element) usually consists of the six nucleotides TTGACA. Its presence allows a very high transcription rate.

promoter region in eukaryote:

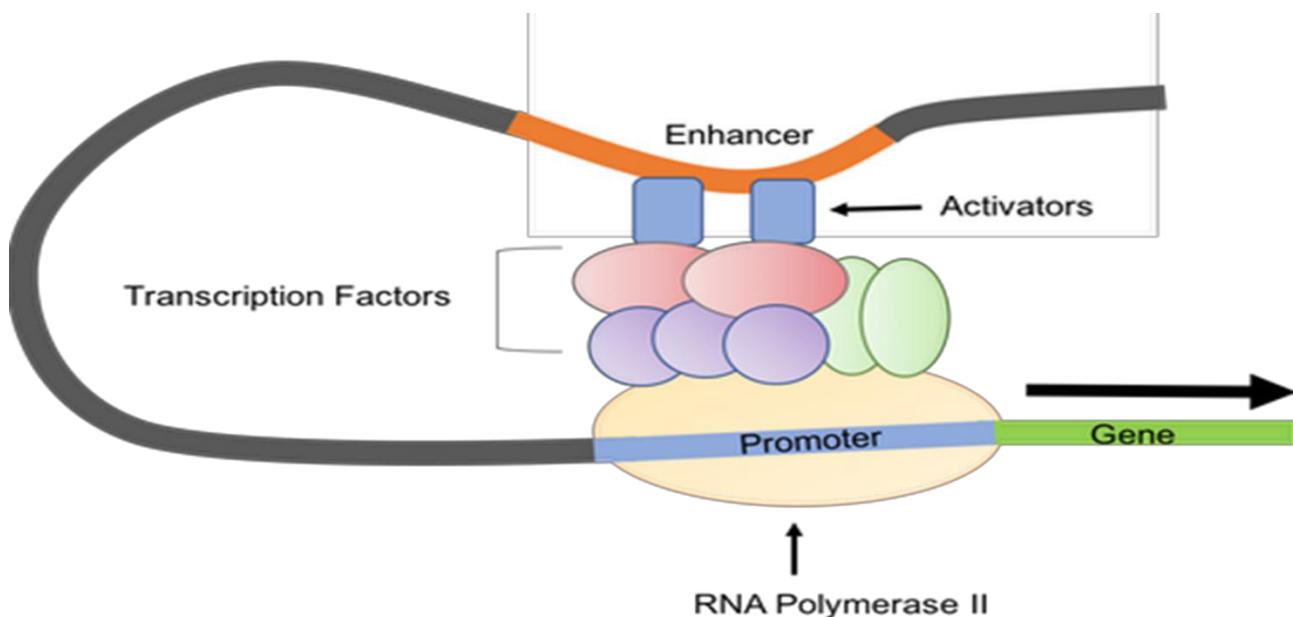


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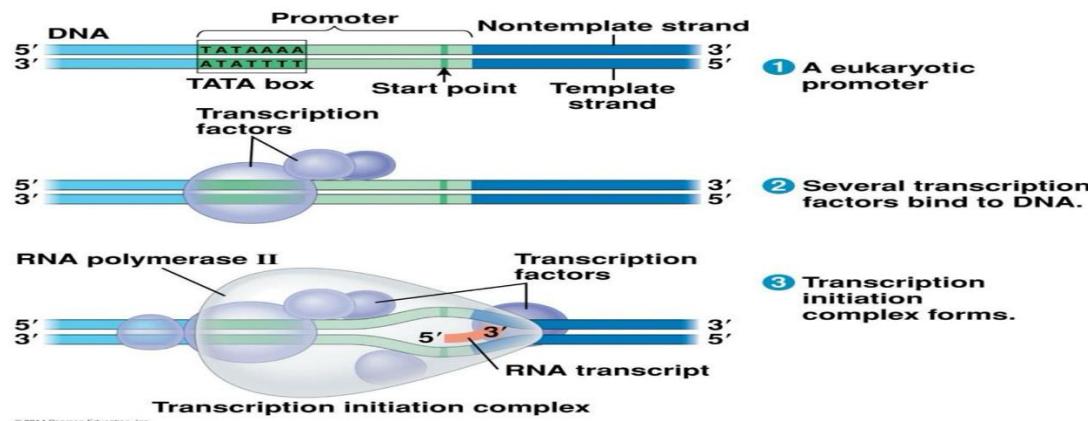
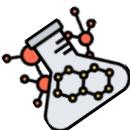
Eukaryotic promoters

Eukaryotic promoters are much more complex and diverse than prokaryotic promoters. Eukaryotic promoters span a wide range of DNA sequences. It is not unusual to have several regulatory elements such as enhancers several kilobases away from the TSS. Eukaryotic promoters are so complex in structure that the DNA tends to fold back on itself which helps to explain how many physically distant DNA sequences can affect transcription of a given gene. The TATA-binding protein binds the TATA box and helps in the subsequent binding of the RNA polymerase. A transcription complex is constructed from the RNA polymerase and several transcription factor proteins.



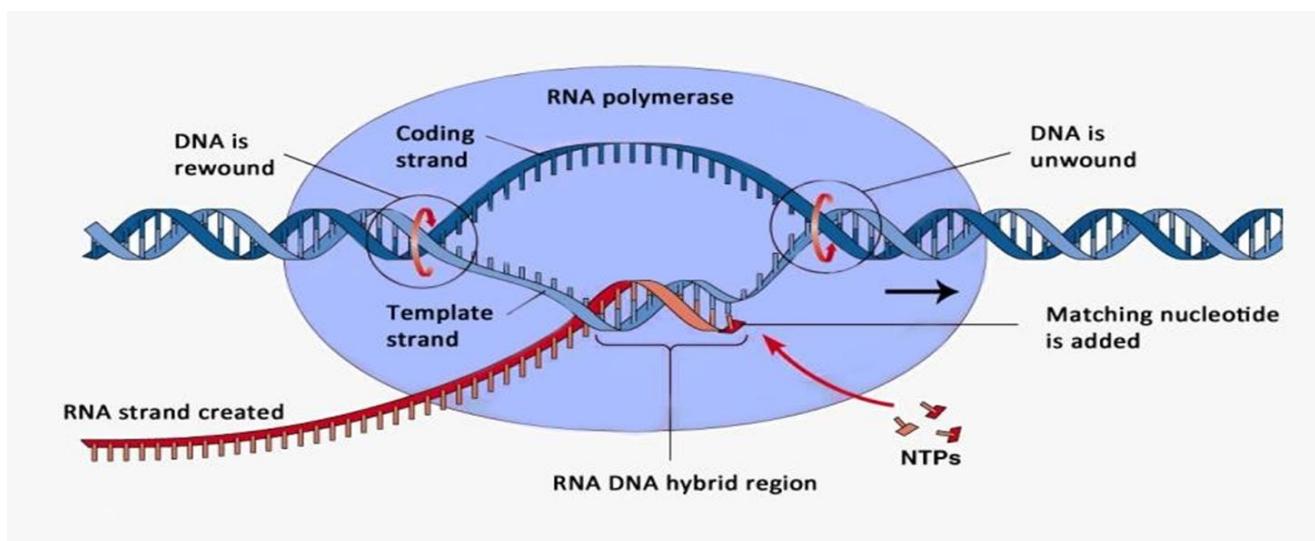
Binding of Transcription factors II in eukaryotes (Sigma factor in prokaryotes) to the

TATA box → Binding of DNA polymerase to the promotor →
transcription initiation complex → activation of the enzyme →
unwinding of the DNA → RNA polymerase incorporates the 1st
nucleotide



2- Elongation:

RNAP uses ribonucleotide triphosphate (ATP, GTP, CTP & UTP) (with release of pyrophosphate) to elongate the RNA strand in the 5' to 3' direction

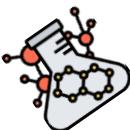


-sigma factor

-rho factor

Explain:

Mechanism of Transcription is different for prokaryote and eukaryote



Transcription in Eukaryotes and Prokaryotes

1. In prokaryotes, transcription and translation occur within the same cellular compartment
2. In fact translation of bacterial mRNA begins during transcription.
3. In eukaryotic cells, transcription and translation occurs in different cellular compartment, transcription occurs within the nucleus and translation occurs outside the nucleus.
4. Human mitochondrial DNA is an exception to the general rule; mitochondrial DNA is transcribed within the mitochondria.
5. Another difference, prokaryotes translate primary transcripts (the RNA synthesized by RNA polymerase) whereas eukaryotes extensively process primary transcripts prior to translation.
6. In eukaryotic cells, promoter sites generally have the base sequence TATAA .additional promoter sequence are required such as GC and CAAT located further from the start of transcription.
7. Eukaryotic cells have 3 types of RNA polymerase, in contrast to the single type found in prokaryotes.

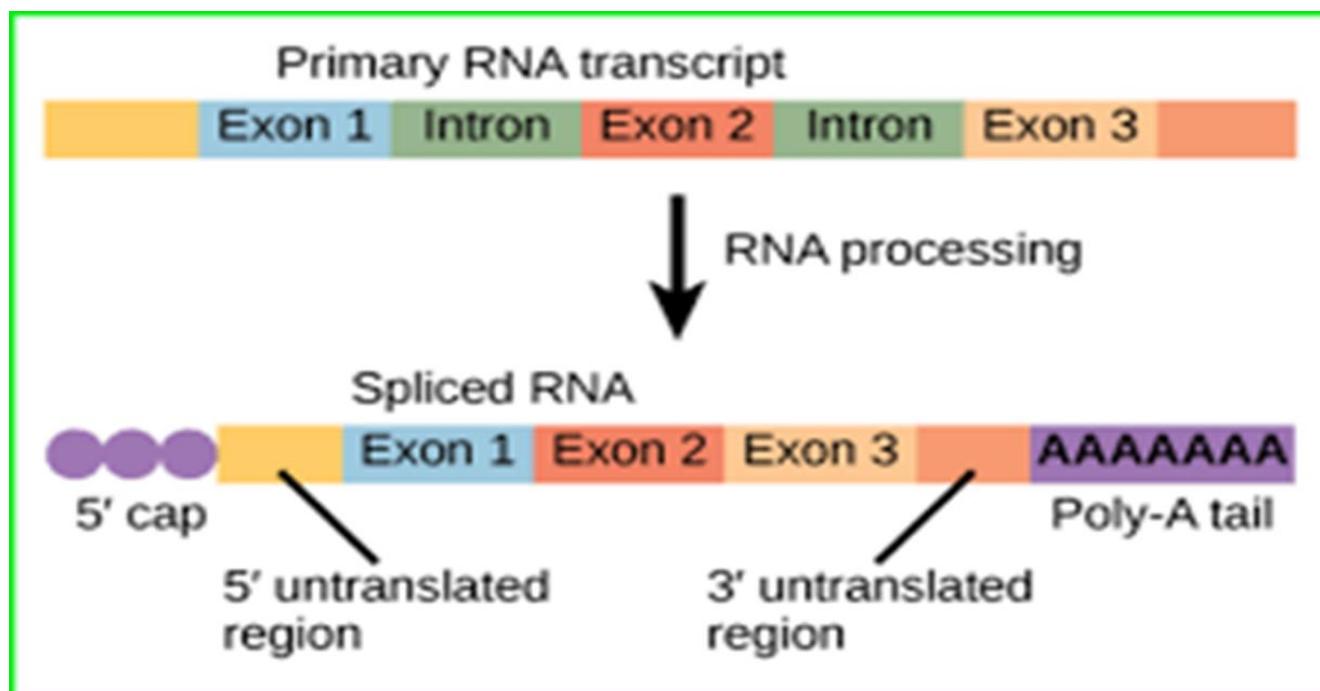
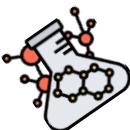
Posttranscriptional modifications:

► Prokaryotic mRNA

Since prokaryotic DNA sequence is mostly coding i.e. most of their genes produce proteins and don't have many intronic sequences, post transcriptional modifications aren't needed.

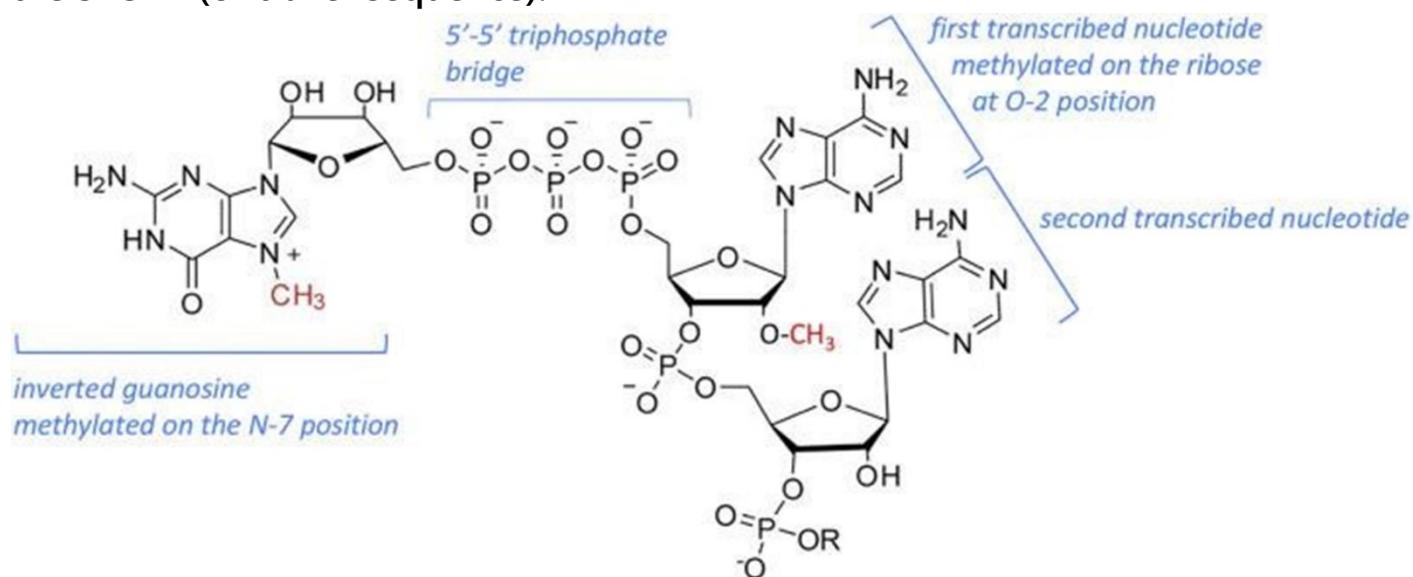
► Eukaryotic mRNA

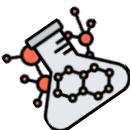
- 5'capping
- Addition of Poly (A) Tail
- Splicing



1. Capping of 5' end by 7-methyl GTP:

The process of 5' capping is vital to creating mature messenger RNA which is then able to undergo translation. Capping ensures the messenger RNA's stability while it undergoes translation in the process of protein synthesis. The untranslated region (or UTR) refers to either of two sections, one on each side of a coding sequence on a strand of mRNA. If it is found on the 5' side, it is called the 5' UTR (or leader sequence), or if it is found on the 3' side, it is called the 3' UTR (or trailer sequence).





2. Addition of Poly (A) Tail:

- What is the tail?
- Enzyme Adds it
- Function

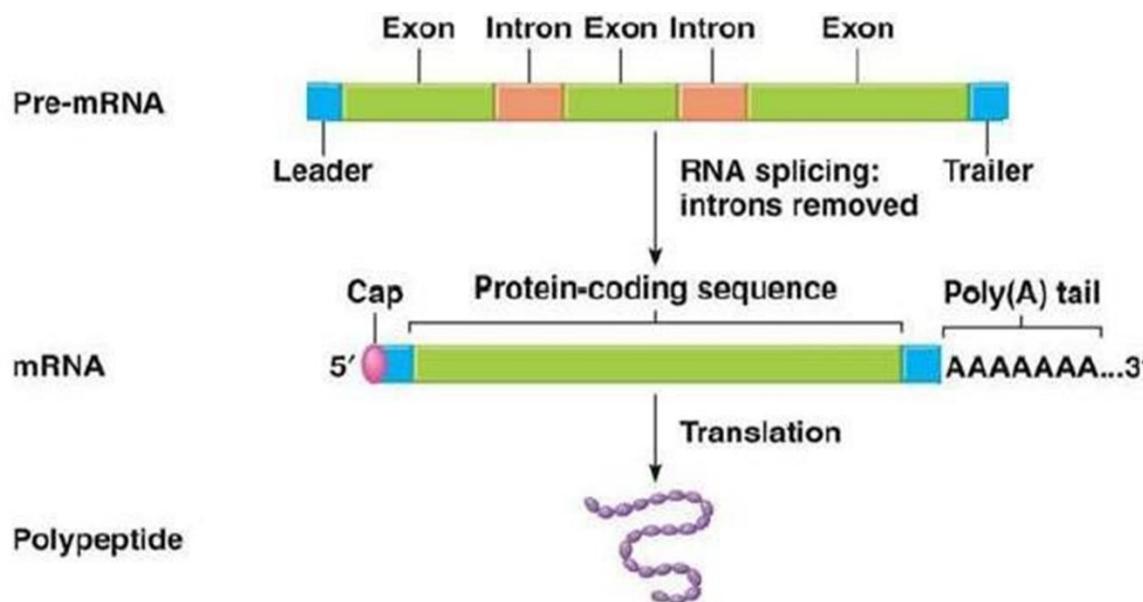
The polyA tail is a long chain of adenine nucleotides that is added to a mRNA molecule during RNA processing. The polyA tail makes the RNA molecule more stable and prevents its degradation and allows the mature mRNA molecule to be exported from the nucleus and translated into a protein by ribosomes in the cytoplasm.

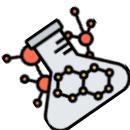
Cleavage and polyadenylation specificity factor (CPSF) is involved in the cleavage of the 3' signaling region from a newly synthesized pre-messenger RNA (pre-mRNA) molecule in the process of gene transcription.

The enzyme that adds poly(A) to mRNAs is a classical poly(A) polymerase.

3. Splicing:

Definition: During splicing, coding-regions of mRNA (exons) are kept and non-coding regions of mRNA (introns) are cut out and removed. mRNA Splicing is an important step in the transcription process, as without removing the introns the correct protein cannot be formed.





3. Spliceosome:

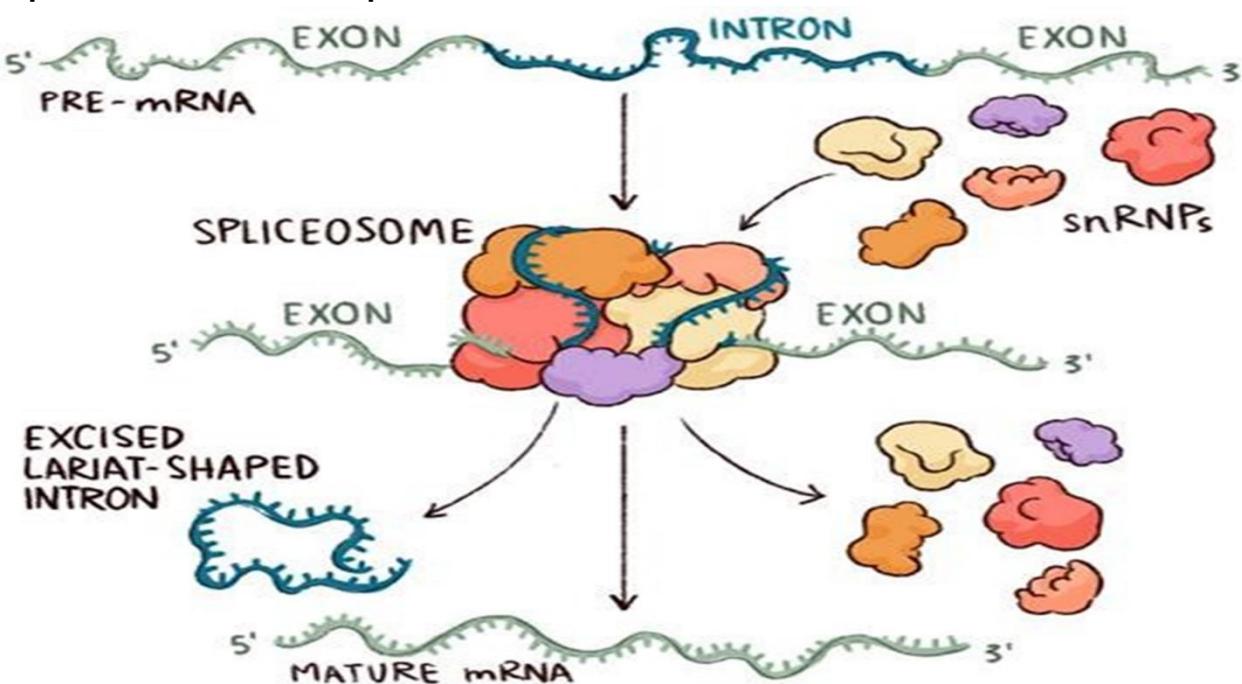
- Definition
- Function

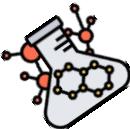
The spliceosome is a large RNA-protein complex that catalyses the removal of introns from nuclear pre-mRNA.

- Advantages:

- Interestingly, introns can carry elements that are important for gene regulation. Furthermore, the cutting of the initial transcript and rejoining of exons allows DNA sequences to be shuffled. This process of mixing and matching exons is known as alternative splicing.
- Alternative splicing is a cellular process in which exons from the same gene are joined in different combinations, leading to different, but related, mRNA transcripts. These mRNAs can be translated to produce different proteins with distinct structures and functions — all from a single gene.

- Mutation of the splice site
- A genetic alteration in the DNA sequence that occurs at the boundary of an exon and an intron (splice site). This change can disrupt RNA splicing resulting in the loss of exons or the inclusion of introns and an altered protein-coding sequence. Also called splice-site variant.





L19 : Translation

Defenition:

mRNA \rightarrow protein

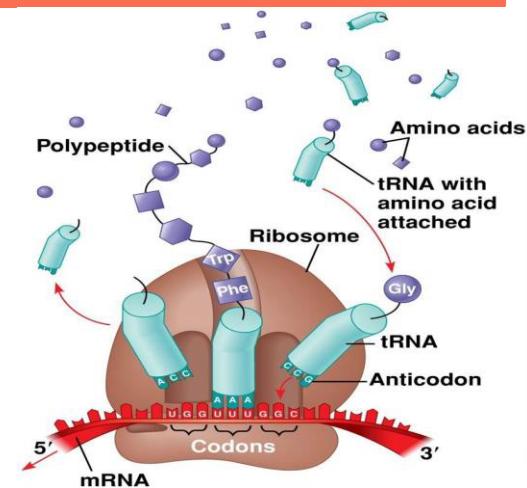
Process of mRNA converting to a protein

Occurs in the cytoplasm – **ribosome**

PROTEIN SYNTHESIS (TRANSLATION):

A protein is synthesized from its N to its C-terminus following the codon in the mRNA from 5' to 3' direction through 3 main steps:

1. Activation of amino acid, in **cytoplasm**.
2. Transcription of RNA in **nucleus**.
3. Translation of mRNA and polypeptide formation, in **ribosomes**



In cytoplasm	In nucleus	In ribosome
Activation of a. a. and their charging by tRNA.	Transcription (Synthesis of RNA).	Translation (Polypeptide formation)

Steps:

1. Activation of amino acids.
2. Translation of mRNA into polypeptide chain
3. Posttranslational modification of the polypeptide chains

1. Activation of amino acid and synthesis of aminoacyl-tRNA:

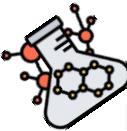
BY: **Aminoacyl-tRNA synthetase**

Steps:

- Activation
- Binding

Activation of amino acid:

Amino acid to be used in the protein, must first activated by an enzyme called **aminoacyl- tRNA synthetase**. It is a very specific enzyme and each amino acid has its specific enzyme.



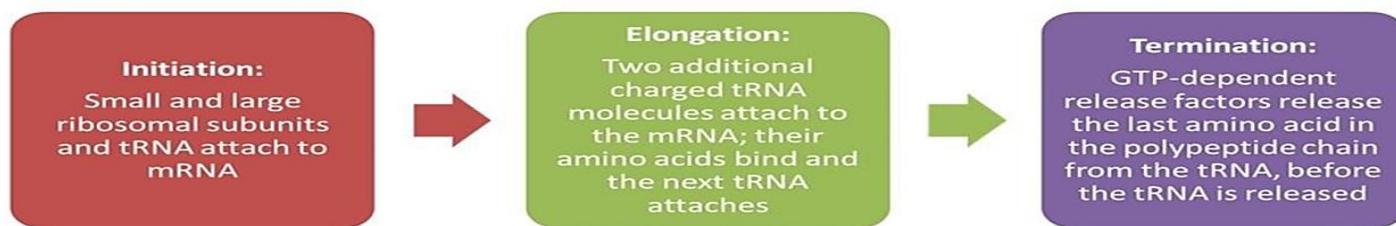
- I. An amino acid first reacts with ATP, forming an enzyme (amino acyl AMP) complex and pyrophosphate. Cleavage of (PPi) drives the reaction.
- II. Aminoacyl-AMP then forms an ester with the 2` or 3` OH group of tRNA specific for that amino acid producing an aminoacyl -tRNA and AMP.

II-Synthesis of polypeptide chain (translation):

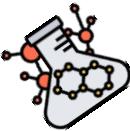
3steps:

Initiation , elongation & termination

Initiation	Small subunit binds to mRNA Start codon AUG – methionine at P site
Elongation	A site recognizes codon and pairs with correct tRNA Peptide bond forms between the carboxyl end of the polypeptide at the P site and amino acid at the A site Amino acid in the A site translocates to the P site
Termination	Stop codon is reached at the A site UAA, UAG, UGA Release factors free the polypeptide from the ribosome



Comparison of Translation in Bacteria Versus Eukaryotes		
Property	Bacteria	Eukaryotes
Ribosomes	70S • 30S (small subunit) • 50S (large subunit)	80S • 40S (small subunit) with 18S • 60S (large subunit)
Amino acid carried by initiator tRNA	fMet	Met
Shine-Dalgarno sequence in mRNA	Present	Absent
Simultaneous transcription and translation	Yes	No



1. Initiation:

Aim: Formation of initiation complex

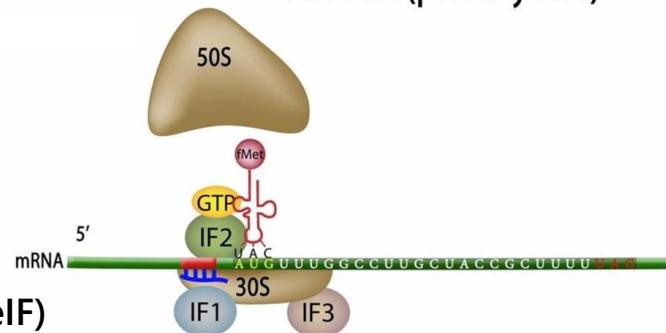
Formation of initiation complex needs:

- a) GTP
- b) Initiation factors

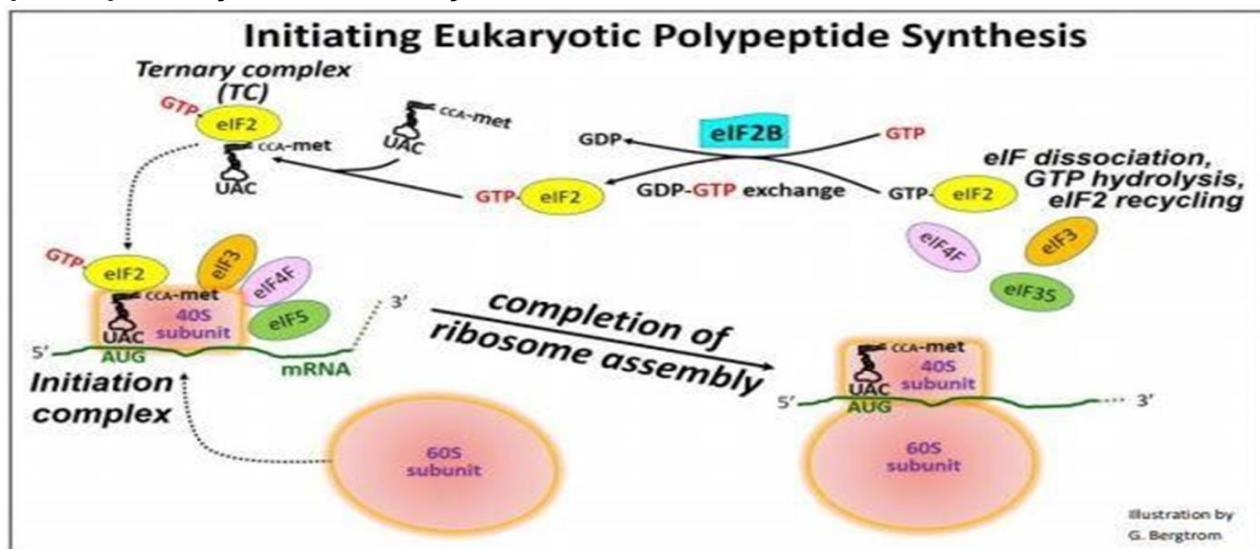
-In eukaryotes : 12 or more initiation factors (eIF)

-In prokaryotes: 3 initiation factors (IF-1, IF-2, and IF-3)

Initiation (prokaryotes)

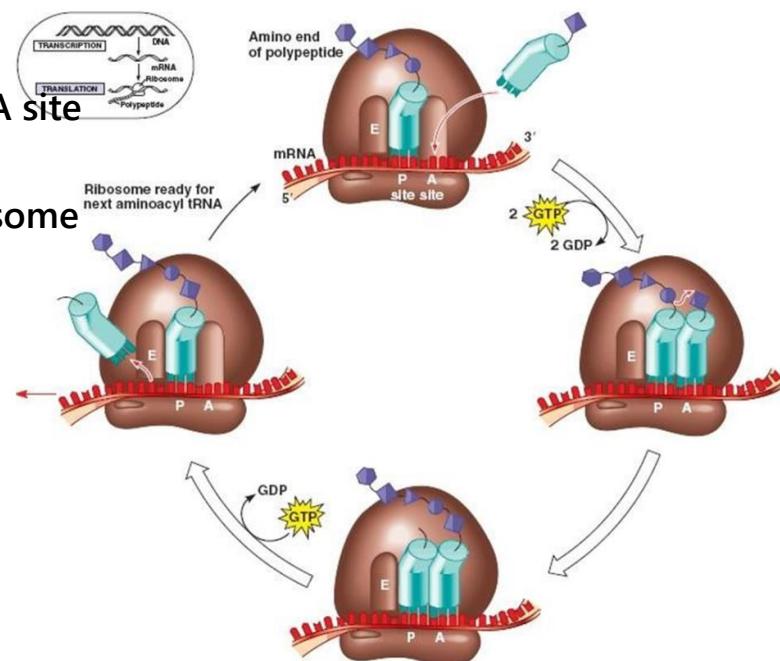


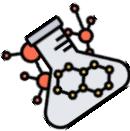
Steps: In prokaryotes & eukaryotes



2. Elongation:

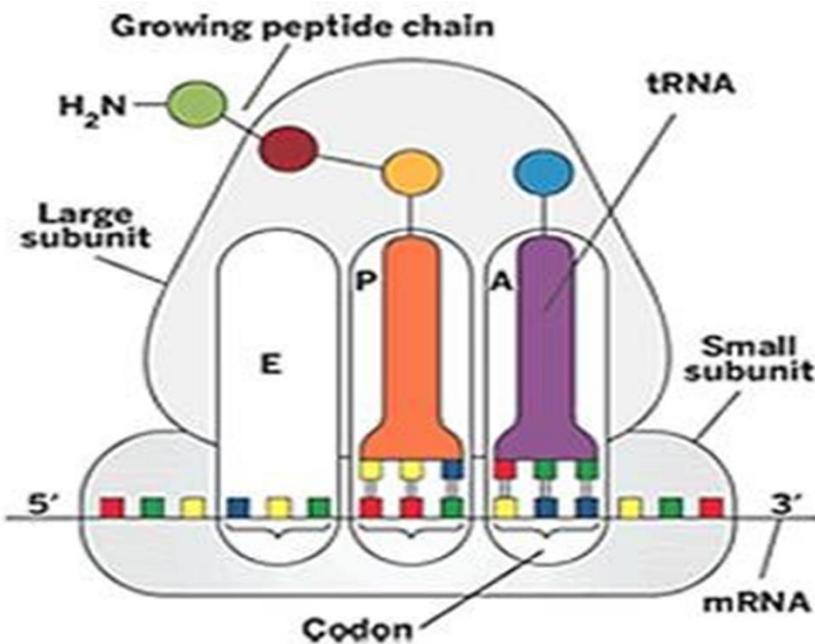
- a) Binding of an aminoacyl-tRNA at the A site
- b) formation of a peptide bond
- c) Translocation (movement) of the ribosome



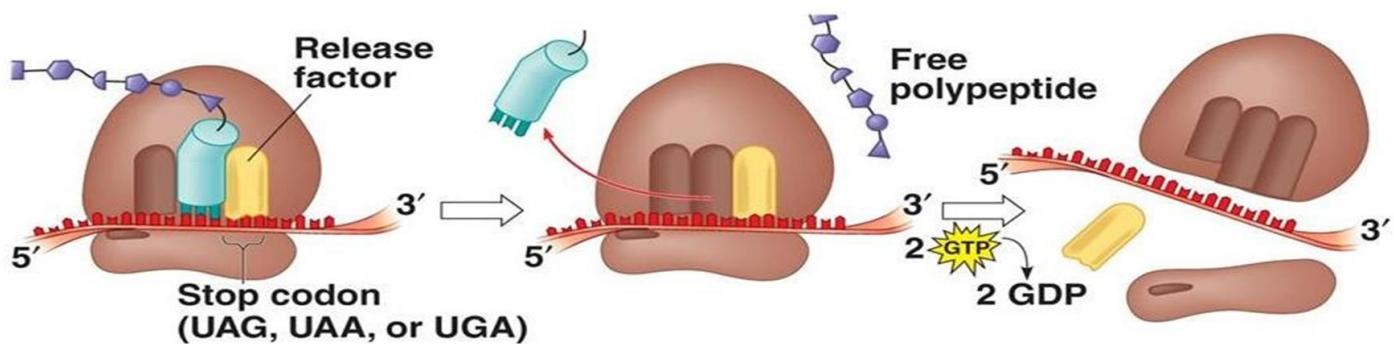


- The ribosome has three binding sites for tRNA molecules: the A, P, and E sites each of which extends over both subunits.

Together, they cover 3 neighboring codons.

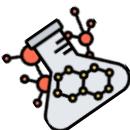


3. Termination



Steps of Termination:

- Ribosome reaches a stop codon on mRNA, the A site of the ribosome accepts a release factor.
- The release factor promotes hydrolysis of the bond between the tRNA and the polypeptide, freeing it from the ribosome
- Components of the ribosomal complex dissociate. Translation is complete.



Bio L 29 : post translational modification

post translational modification include :

- proteolytic cleavage
- covalent modification

Removal of the initiator methionine a.a

AIM

to obtain the functionally active form of the protein with unique sequence in which the 1st a.a is different



Proteolysis of proproteins

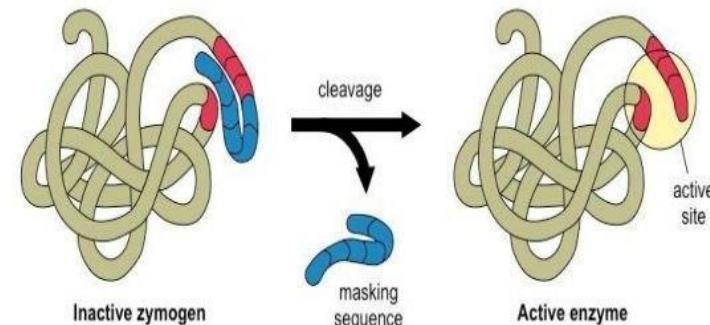
Proproteins are **inactive precursors** of proteins, that are activated by removal of peptides e.g.

- Activation of pancreatic digestive enzymes
as pepsinogen → pepsin, trypsinogen → trypsin.
- Activation of blood clotting factors.

Preproteins are precursor proteins having:

- a. signal peptides (preproteins)
- b. & 'pro' sequence

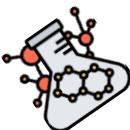
for proteolysis.



A. Signal peptide:

- is present on the N-terminal end of the protein.
- It contains 13-36 a.a. residues (mainly hydrophobic).
- The enzyme signal peptidase removes the signal peptide after passage through the endoplasmic reticulum. → formation of proproteins.

B. Proprotein further undergoes proteolysis to give active protein

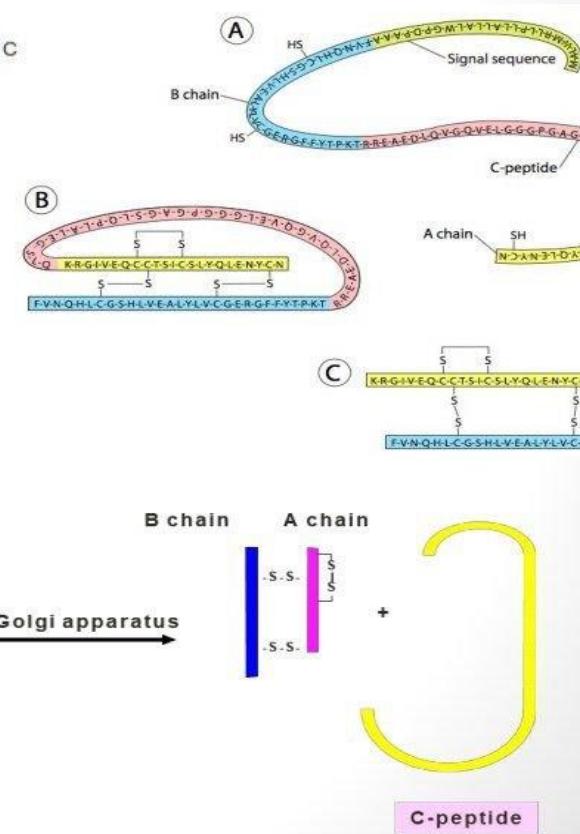
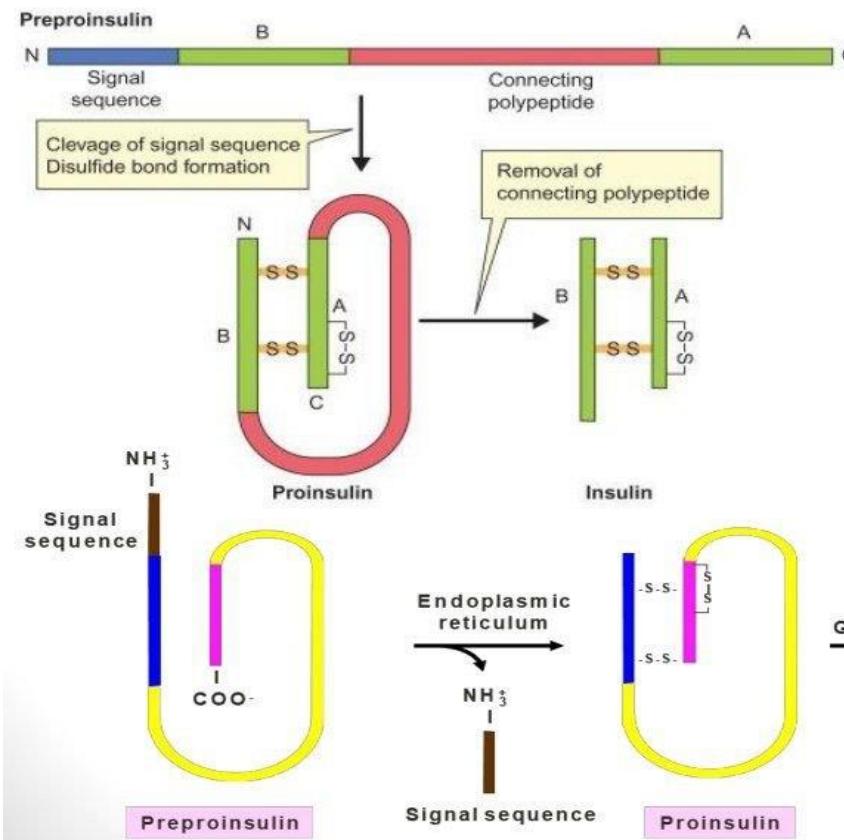
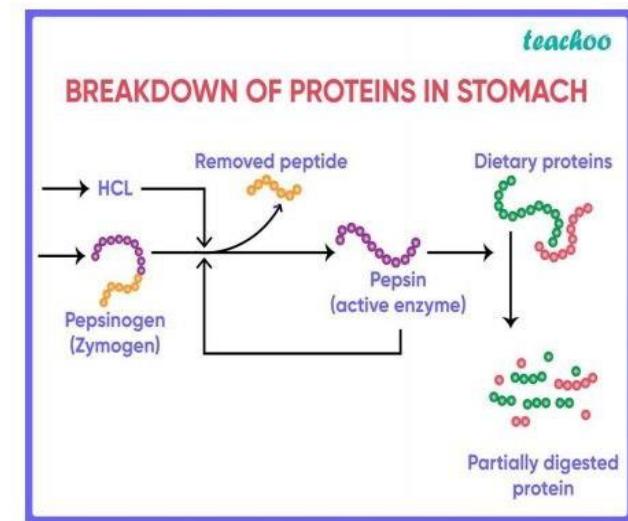


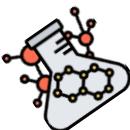
- Signal peptide is essential for protein targeting & limited proteolysis of proprotein is essential for protein secretion & activation

e.g. insulin is secreted from the pancreas as preproinsulin (109 a.as).

Following the cleavage of the 23a.a. signal peptide, the protein folds into proinsulin.

Proinsulin is further cleaved by protease (A further 35 amino acids are removed) to give active insulin (51 a.a.).

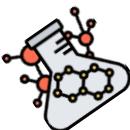




Examples of Covalent modification

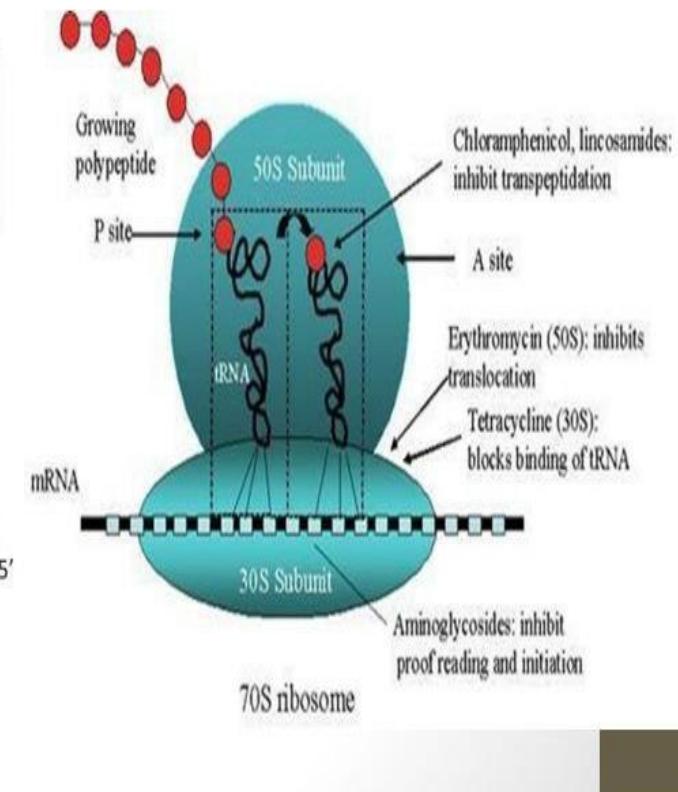
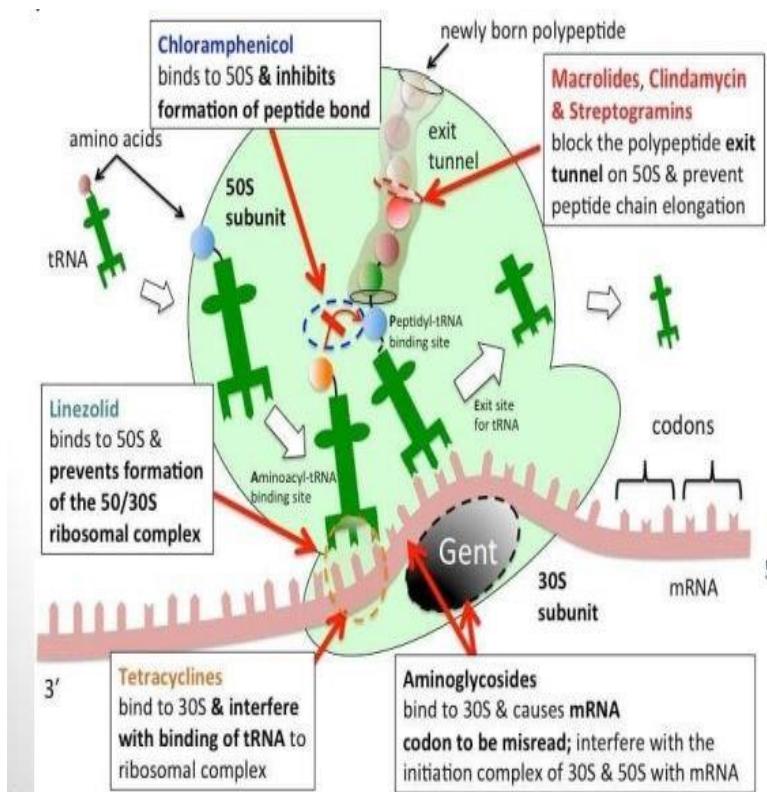
b. Covalent posttranslational modifications: e.

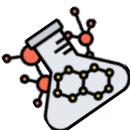
Covalent modification	Meaning or e.g	Importance
1. Glycosylation	<p>Adding CHO residues to specific a.a of proteins</p> <ol style="list-style-type: none"> 1. To asparagine by N-glycosidic bond 2. To serine or threonine by O-glycosidic bond (To form glycoproteins) <p>Usually found in secreted proteins</p>	<ol style="list-style-type: none"> 1. Aid solubility by binding to water.e.g.mucoproteins in membrane secretions. 2. CHOS are essential for protein function as cell-cell recognition & antigenicity
2. Phosphorylation	Adding phosphate gp through covalent bond catalyzed by kinase, dephosphorylation by phosphatase	Important for activation or deactivation Of enzymes e.g. glycogen phosphorylase.
3. Hydroxylation	Of lysine & proline residues in collagen	Important for cross linking of collagen (maturation of collagen)
4. Gamma Carboxylation	Carboxylation of glutamic acid residues in the clotting factors 2,7,9,10	Formation of active form of these clotting factors
5. Acetylation	Adding acetyl gp to proteins as histone proteins	<ol style="list-style-type: none"> 1. Decrease susceptibility of protein for degradation 2. Modulate protein function e.g. acetylation & deacetylation of histone proteins regulate gene expression



Inhibitors of translation

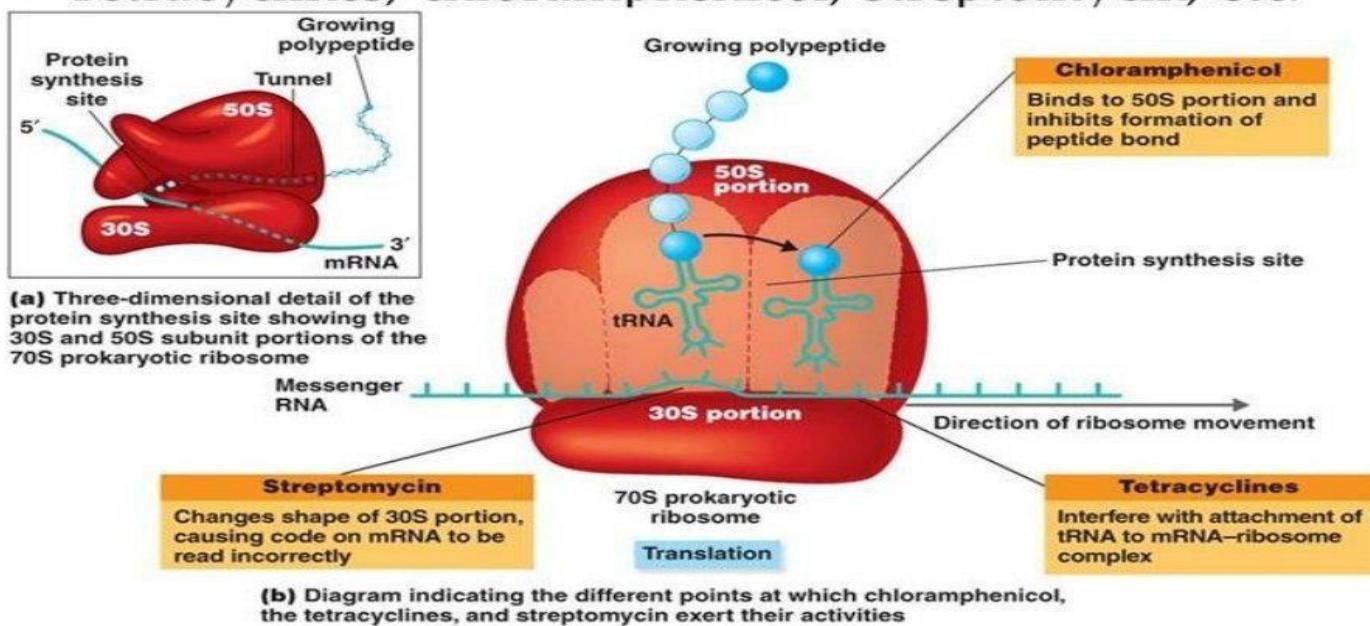
Inhibitor	Action	Uses or nature
In prokaryotes		
Tetracyclines: Tetracycline Doxycycline	Bind to the 30S subunit. They block the A site preventing binding Of aminoacyl tRNA to the ribosomal mRNA com lex at the A site	Antibiotics
Aminoglycosides: Streptomycin Neomycin Gentamicin	Bind to the 30S subunit. They block the formation of initiation complex→ misreading of mRNA They also block the translocation of ribosomes→ --- of elongation.	Antibiotics
Chloramphenicol	Binds to the 50S subunit. It the prokaryotic peptidyl Transferase → --- of elongation	Antibiotics
Erythromycin	Binds to the 50S subunit. It blocks the translocation of peptidyl tRNA to the P site→ --- elongtion	Antibiotics
Linezolid	Binds to 50S subunit & prevent the formation of 50S/ 30 S ribosomal complex	Antibiotics



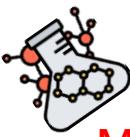


How can they inhibit protein synthesis?

- Tetracyclines, chloramphenicol, streptomycin, etc.



Inhibitor	Action	Nature or uses
In eukaryotes		
Diphtheria toxin	Catalyzes ADP ribosylation of eEF-2 → eEF-2 inactivation → -- translocation	Toxin produced by corynebacterium diphtheriae which is a bacteria
Ricin	It binds to the 60S subunit. It removes one adenine residue from 28S rRNA.	Is a protein obtained from castor bean. Administration of castor oil for a longer period of time to relieve constipation is toxic to the intestinal mucosal cell & may result in diarrhea
Cycloheximide	It binds to the 60S subunit., inhibiting peptidyl transferase → -- elongation	Used for research
In prokaryotes & eukaryotes		
Pauromycin	Structural analogue of aminoacyl-tRNA. It binds to A site& forms peptide bonds with growing polypeptide chain.	Used for research



MCQ :

1) Cleavage of the 24 a.a. signal peptide of preproinsulin leads to the formation of :

- a. Insulin
- b. Proinsulin
- c. Preinsulin
- d. C-peptide

2) The following bind to the 50 S subunit inhibiting the translation of bacterial proteins EXCEPT:

- a. Chloramphenicol
- b. Streptomycin
- c. Erythromycin
- d. Linezolid

3) Cyclophosphamide is inhibitor of protein synthesis. It does so by:

- a. Binds to the 50 S subunit, inhibiting peptidyl transferase
- b. Binds to the 60 S subunit, removing one adenine residue from 28 S rRNA
- c. Binds to the 40 S subunit, inhibiting the formation of initiation complex
- d. Inhibiting the elongation of polypeptide chains in eukaryotes

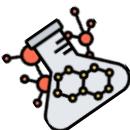
4) Glycosylation of proteins is important for:

- a. Cell-cell recognition
- b. Activation or deactivation of enzymes
- c. Cross linking of collagen
- d. Regulation of gene expression

5) Hydroxylation of amino acids of collagen is important for cross linking of collagen:

- a. Proline and glycine
- b. Glycine and lysine
- c. Proline and lysine
- d. Alanine and proline

”يا طالب العلم لا تركن إلى الكسل
واعجل فقد خلق الإنسان من عجل“



L30: Regulation of gene expression

Regulation of gene expression in prokaryotes and eukaryotes

1) Cis-acting elements (regulatory part)

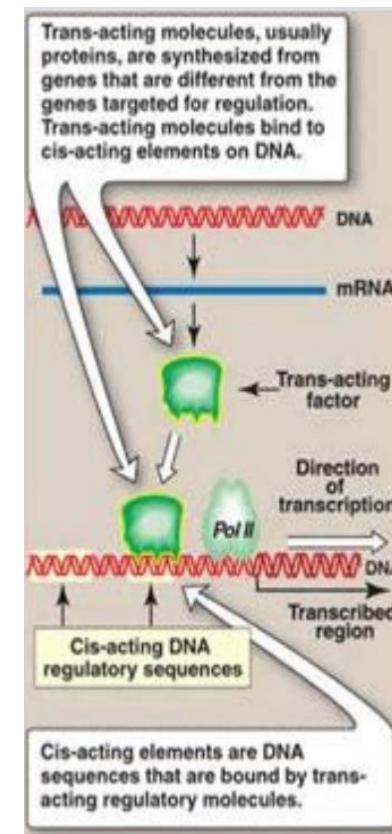
- ❖ It is the special DNA sequence that can affect the expression of the structural gene

2) Regulatory proteins

- ❖ Bind the cis acting elements to regulate gene expression.
- ❖ They are referred to as trans-acting factors as they are produced from another gene.
- ❖ Example Of these regulatory proteins are transcription factors
- ❖ The interaction between these DNA segments and regulatory molecules, such as transcription factors, can increase or repress the transcription.

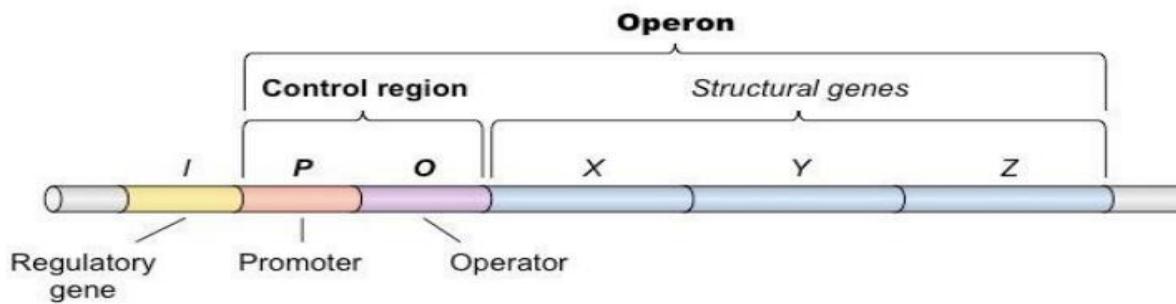
3) The cis acting elements include e.g.

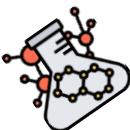
- | | |
|-----------------------------|--------------|
| ❖ Promotor | ❖ Silencers |
| ❖ Enhancers | ❖ Insulators |
| ❖ Operators: in prokaryotes | |



Regulation of prokaryotic gene expression

- 1) In prokaryotes as E.coli regulation of gene expression transcription occurs primarily at level of transcription
 - 2) Bacterial genes are organized into operons
 - 3) An operon is a cluster of genes that are transcribed together to give a Single messenger RNA (mRNA) molecule, which therefore encodes multiple proteins
 - 4) Operon is formed of:
 1. Structural genes
 2. Regulatory genes (promoter, operator, and other regulatory sequences).
- ❖ They are cis acting regulatory sequences





Operator

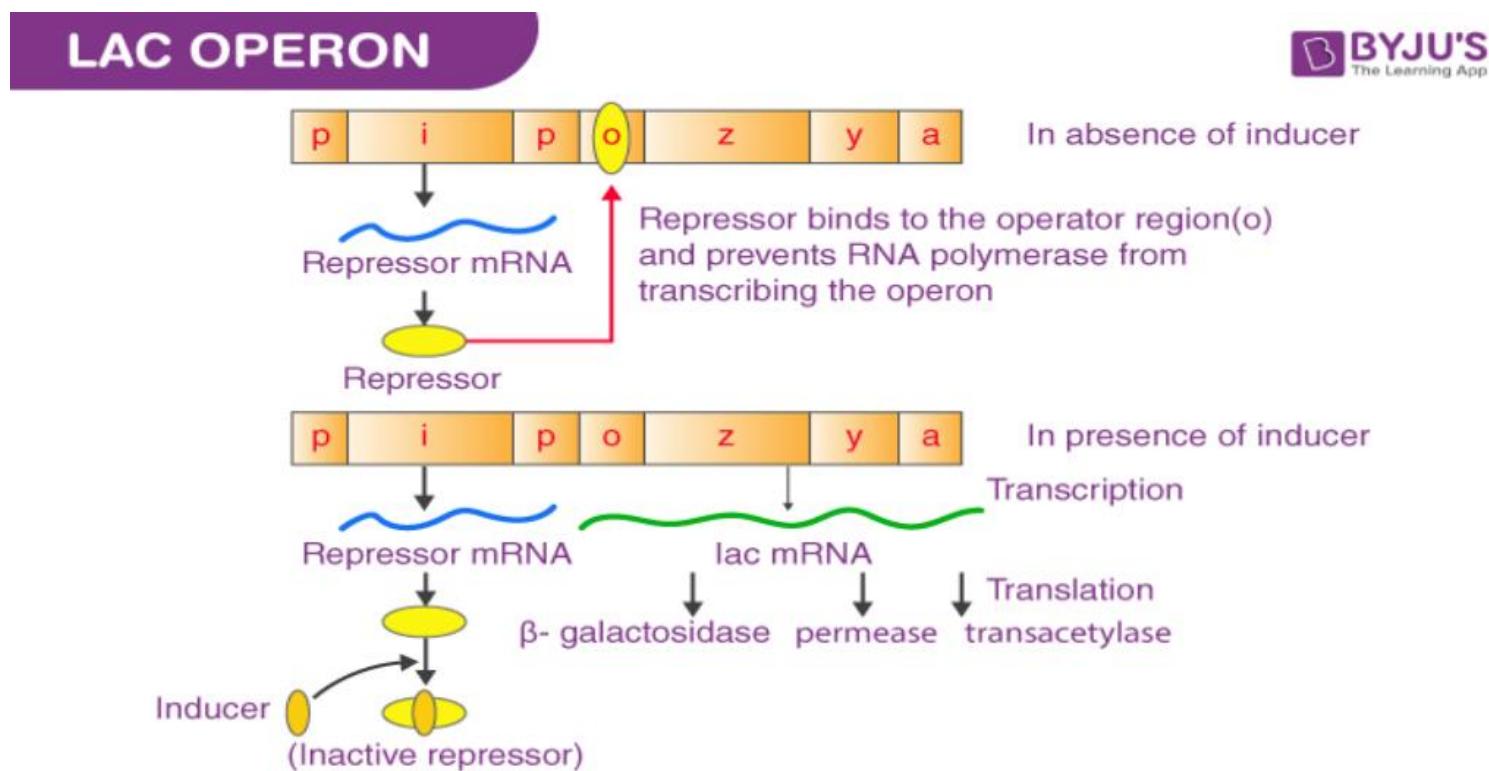
- ❖ It is a DNA sequence adjacent to the structural genes that regulate the transcription of these genes. The **repressor protein** reversibly bind to operator:

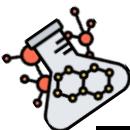
 - 1) If the repressor protein binds the operator, the RNA polymerase cannot bind the promotor to initiate transcription, thus no mRNA is formed
 - 2) If an inducer molecule binds the repressor protein, the repressor shape is changed so no longer binds operator. So, the RNA polymerase binds the promotor to initiate the transcription of the structural genes.

Lactose operon (Lac operon)

It contains the genes that code for the 3 enzymes involved in the catabolism of lactose:

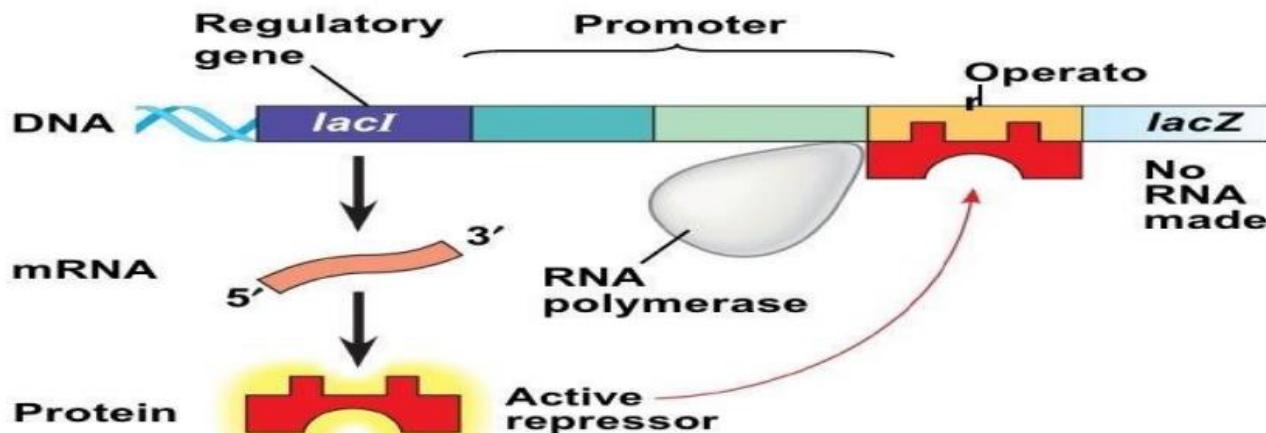
- 1) Lac Z gene
 - ❖ Code for β -galactosidase that hydrolyzes lactose to galactose and glucose
- 2) Lac Y gene
 - ❖ Code for galactoside permease that facilitates the movement of lactose into the cell
- 3) Lac A gene
 - ❖ That codes for thiogalactoside transacetylase Allolactose is the inducer that bind to the repressor protein(as small amount of lactose is converted to the isomer allolactose by β -galactosidase). So β -galactosidase has bifunctional activity



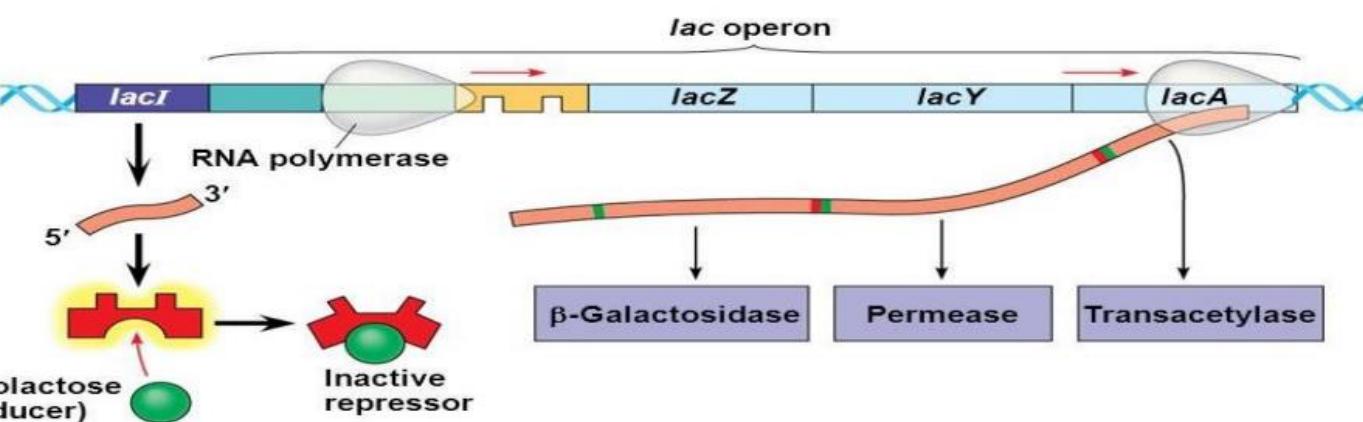


This slide is not for exam

- 1) Galactoside acetyltransferase (also known as Galactoside O-acetyltransferase, thiogalactoside transacetylase, GAT) is an enzyme that transfers an acetyl group from acetyl-CoA to β -galactosides, glucosides and lactosides.
 - ❖ It is coded for by the lacA gene of the lac operon in E. coli.
- 2) The enzyme's role in the classical E.coli lac operon remains unclear.
 - ❖ However, the enzyme's cellular role may be to detoxify non-metabolizable pyranosides by acetylating them and preventing their reentry into the cell
- 3) Galactoside is a glycoside that yields galactose on hydrolysis
- 4) Lactoside is a glycoside that yields lactose on hydrolysis
- 5) Pyranose is cyclic form of monosaccharide six membered ring) (5 carbon atoms & one oxygen atom
 - ❖ There may be other carbons external to ring
 - ❖ Pyranoside is glycoside of pyranose (glycoside that has a pyranose ring)

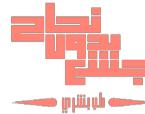


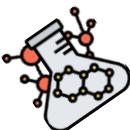
(a) Lactose absent, repressor active, operon off



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(b) Lactose present, repressor inactive, operon on i.e. Genes transcribed to metabolize lactose





Regulation of eukaryotic gene expression

Gene expression can be regulated at 4 levels:

- ❖ Chromatin modification.
- ❖ Transcription.
- ❖ Post-transcriptional modification of mRNA.
- ❖ mRNA translation

1) Chromatin modification

1. Access to DNA

A. Histone acetylation

- ❖ leading to ↓ the positive charge on the basic histones → ↓ bonding of histones to DNA
→ relaxing the nucleosome allowing access of the transcription factors to specific regions on the DNA → gene activation.

B. DNA methylation

- ❖ Cytosine methylation in the CpG islands → gene inactivation.
- ❖ Deacetylation or demethylation reverses the process.

2. Gene amount or arrangement:

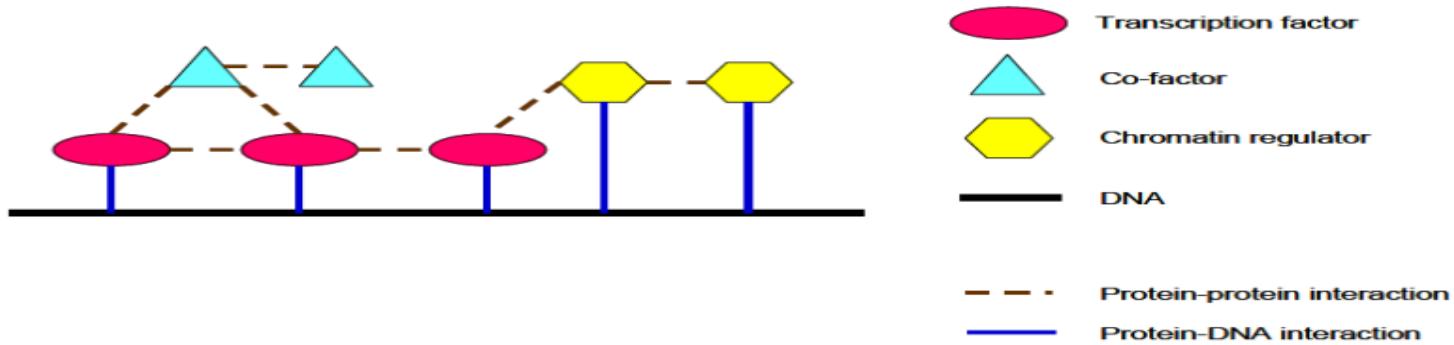
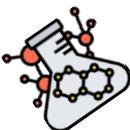
- ❖ Gene amplification → ↑ in the number of copies of a gene → ↑ the number of transcribed genes.
- ❖ Gene diminution → that occurs during RBCs development.
- ❖ Gene rearrangement → allows formation of several millions of immunoglobulins needed for the recognition of the enormous numbers of antigens.

2) Regulation of RNA polymerase II-dependent transcription

- ❖ Transcription at the level of initiation is the primary site of gene expression regulation
- ❖ Like bacteria, transcription in eukaryotic cells is regulated by proteins (**trans-acting elements**) as **transcription factors** that bind to specific regulatory sequences on the DNA (**cis-acting regulatory elements**) and modulate the activity of RNA polymerase to initiate, enhance or suppress transcription .
- ❖ In addition, **cofactors** are proteins which bind **transcription factors** that bind DNA to either induce or repress transcription.

1. N.B. For initiation of transcription

- ❖ The trans-acting protein has 2 domains, one binds DNA and another recruits co-activators and the general transcription factors, that along with RNA polymerase II are needed for the formation of transcription initiation complex at the promoter.



Relationships between the regulators of transcription include protein-protein interactions and protein-DNA interaction.

2. Cis acting regulatory elements are classified into

A. Promotor

B. Enhancers

- ❖ They enhance the transcription of genes on the same molecule of DNA and can be found upstream, downstream, within the introns, or even relatively far away from the gene they regulate.
- ❖ Multiple enhancers can act in a coordinated fashion to regulate transcription of one gene

C. Silencers

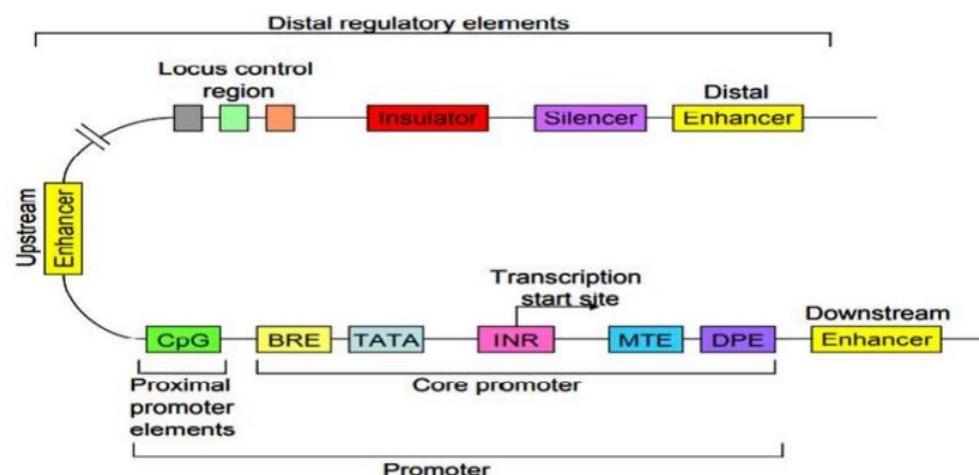
- ❖ Can bind transcription regulation factors (proteins) called repressors, thereby preventing transcription of a gene.

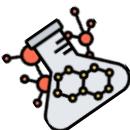
D. Insulators

- ❖ Are thought to act as barriers, preventing enhancers and silencers from regulating neighboring genes.

E. Locus control regions

- ❖ Are cis-regulatory element that enhances expression of linked genes at distal chromatin sites.
- ❖ It functions in a copy number-dependent manner and is tissue-specific, as seen in the selective expression of β -globin genes in red blood cells. β - globin is a component of hemoglobin
- ❖ Expression levels of genes can be modified by the LCR and gene-proximal elements, such as promoters& enhancers.





3) Post-transcriptional processing (modification) of mRNA

1. Alternative splicing

- ❖ Variation in splicing → Tissue specific protein isoforms are made from the same pre-mRNA.

2. Alternative polyadenylation

- ❖ Some pre-mRNA have more than one site for cleavage and polyadenylation.
- ❖ Alternative polyadenylation → generates mRNA with different 3' ends altering the untranslated region or the coding (translated) sequence.
- ❖ 1,2 together with alternative transcription start site explain at least in part how 20,000-25,000 genes in the human genome give > 100,000 protein.

3. mRNA editing

- ❖ Meaning that after full processing of mRNA, a base of mRNA is altered.

4. mRNA stability

- ❖ How long a mRNA remains in the cytosol before degradation affects the number of proteins produced from it e.g. RNA interference is a mechanism by which miRNA decrease expression of mRNA by either repression of translation or by ↑ degradation.

4) mRNA translation

- ❖ One of its mechanisms is the phosphorylation of eIF-2 → inhibits its function → inhibits translation at the initiation step.

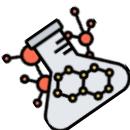
Questions

1) Match the following genes of the Lac operon with their respective products

i gene	Beta-galactosidase
z gene	Permease
a gene	Repressor
y gene	Transacetylase

2) What is an operon?

- protein that binds to an RNA segment and blocks the attachment of RNA polymerase, halting transcription
- Reversibly-bound protein that enhances the transcription of a particular segment of RNA
- A unit of DNA containing a cluster of genes under control of a promoter & a repressor
- A protein around which DNA is coiled until it is transcribed; also the chief protein component of chromatin



3) A drug designed to switch silenced genes back on in cancer cells would result in what?

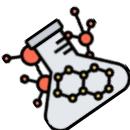
- A. Prevent methylation of DNA and deacetylation of histones
- B. Prevent methylation of DNA and acetylation of histones
- C. Prevent deacetylation of DNA and methylation of histones
- D. Prevent acetylation of DNA and demethylabon of histones

4) Gene A is thought to be associated with color blindness. The protein corresponding to gene A is isolated. Analysis of the protein recovered shows there are actually two different proteins that differ in molecular weight that correspond to gene A. What is one reason why there may be two proteins corresponding to the gene?

- A. One protein had a 5' cap and a poly-A tail in its mRNA, and the other protein did not.
- B. One protein had a 5' UTR and a 3' UTR in its RNA, and the other protein did not.
- C. The gene was alternatively spliced.
- D. The gene produced mRNA molecules with differing stability.

5) What would happen if the operator sequence of the lac operon contained a mutation that prevented the repressor protein from binding the operator?

- A. In the presence of lactose, the lac operon will not be transcribed.
- B. In the absence of lactose, the lac operon will be transcribed.
- C. The cAMP-CAP complex will not increase RNA synthesis.
- D. The RNA polymerase will not bind the promoter.



Bio TUT 6 : DNA Mutation and repair

- Mutation = permanent change(s) in the nucleotide/base sequence of DNA
- may occur due to errors in DNA replication or due to the impacts of chemicals (free radicals & alkylating agents) or physical (X-Ray & UV radiation) injury to the DNA molecule
- Mutation may result in coding sequences for new amino acids in proteins or not !

Types of mutations

I. Point mutations

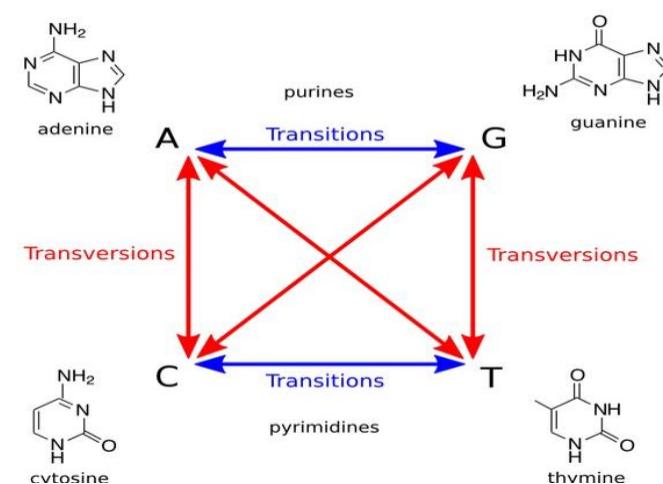
II. Insertion/Deletion of bases

I. Point mutations

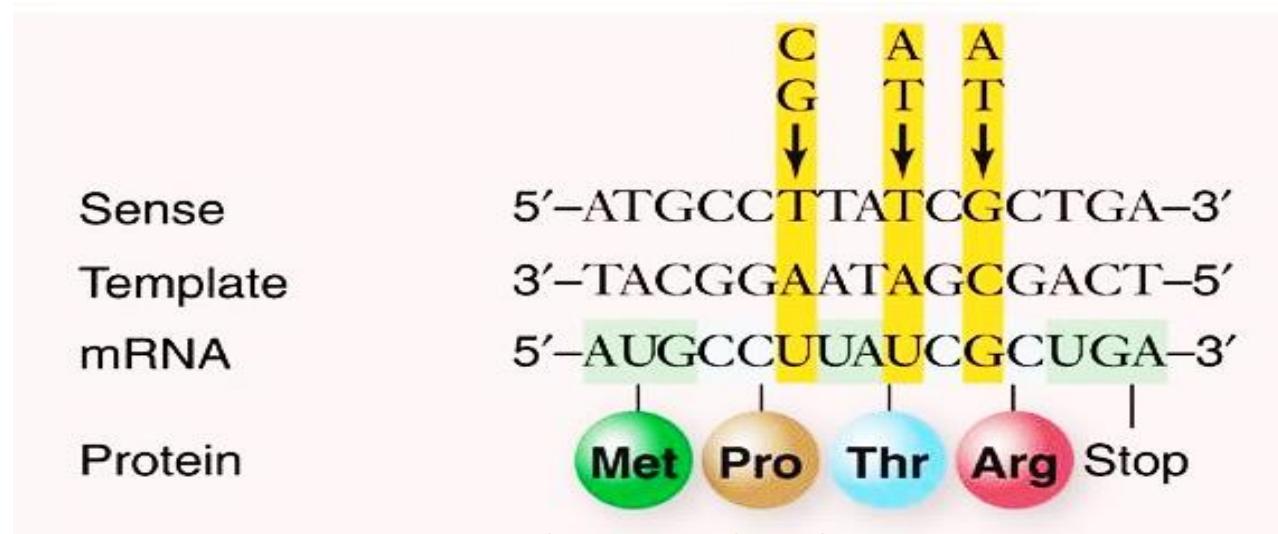
- affect single sites on DNA
- Substitution of 1 base for another

Results of point mutations

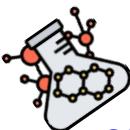
- Silent mutations
- Missense mutations
- Nonsense mutations



Sample outcome of DNA code



Methionine, proline, threonine, arginine, stop



Silent mutation

Due to redundancy of Genetic Code,
no change in amino acid sequence is produced!!

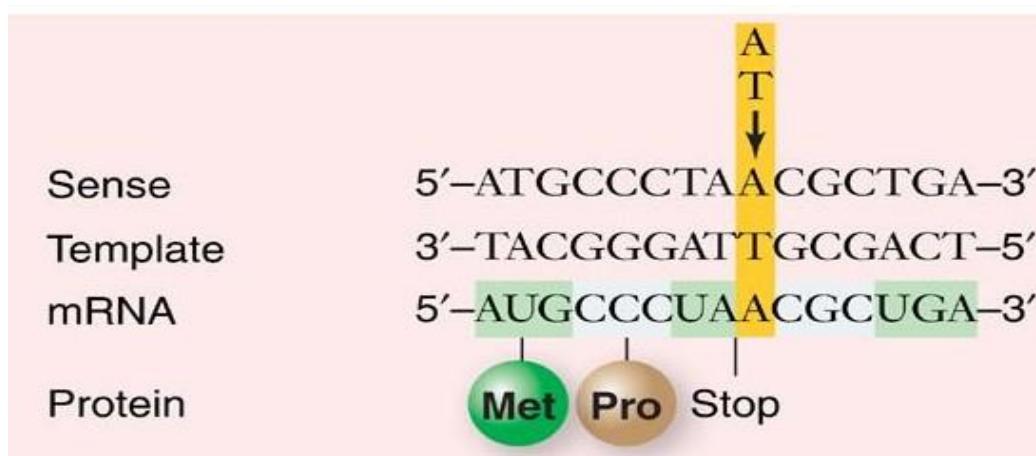
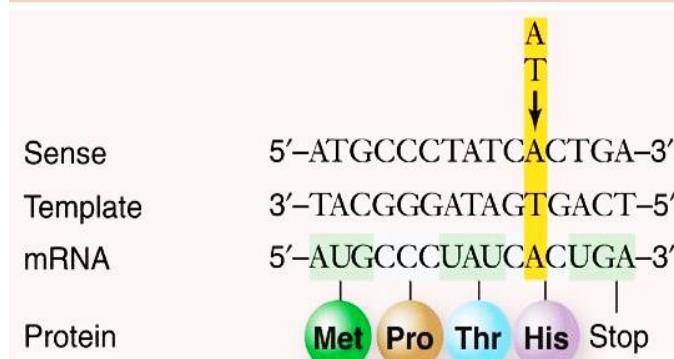
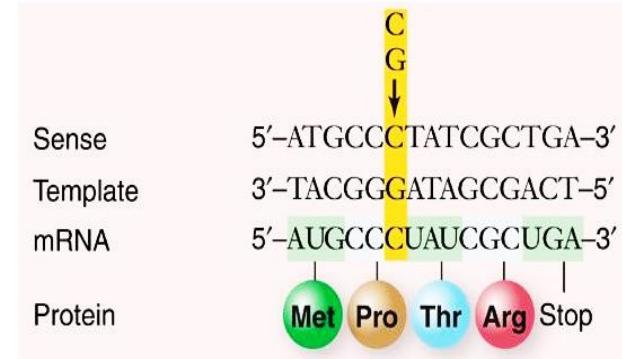
Missense mutation

produces a change (substitution) in amino acid sequence in protein product

(Histidine in for Arginine) may change function of protein or may not!

Nonsense mutation

produces a STOP codon within the mRNA transcript leading to a truncated protein.

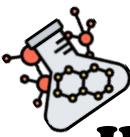


إزيك

بدل ما تستخي وتفضل
خايف من المواجهة
اطلع من جرك وحارب
وخليك أسطر كتکوت



Rana
Ebrahim



II. Insertion/deletion mutations

One or more base

(not multiples of three)

Three or multiples of three

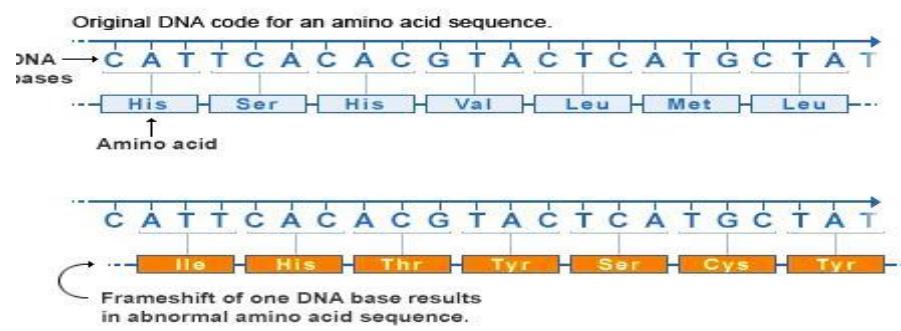
Results of insertion/deletion mutations

1. Frame shift mutation due to addition / deletion of one or more bases (not multiples of three) to a coding DNA region	2. Insertion / deletion of codon or whole gene may result from insertion/deletion of triplet bases (or multiples of three) affecting the coding region
--	---

Frameshift mutation

Frame shift mutation:

- Alteration of reading frame.
- Introduction of a STOP codon.
- New amino acid may be added
- Amino acid is missing



Duplication

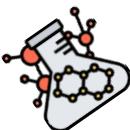
Duplicated



Deletion

Deleted





DNA repair

Definition

- DNA repair: refers to the processes by which the cell identifies and corrects any damage of its DNA .

Importance of DNA repair

- Damaged DNA must be repaired
- If the damage is passed on to subsequent generations, then we use the evolutionary term - **mutation**.

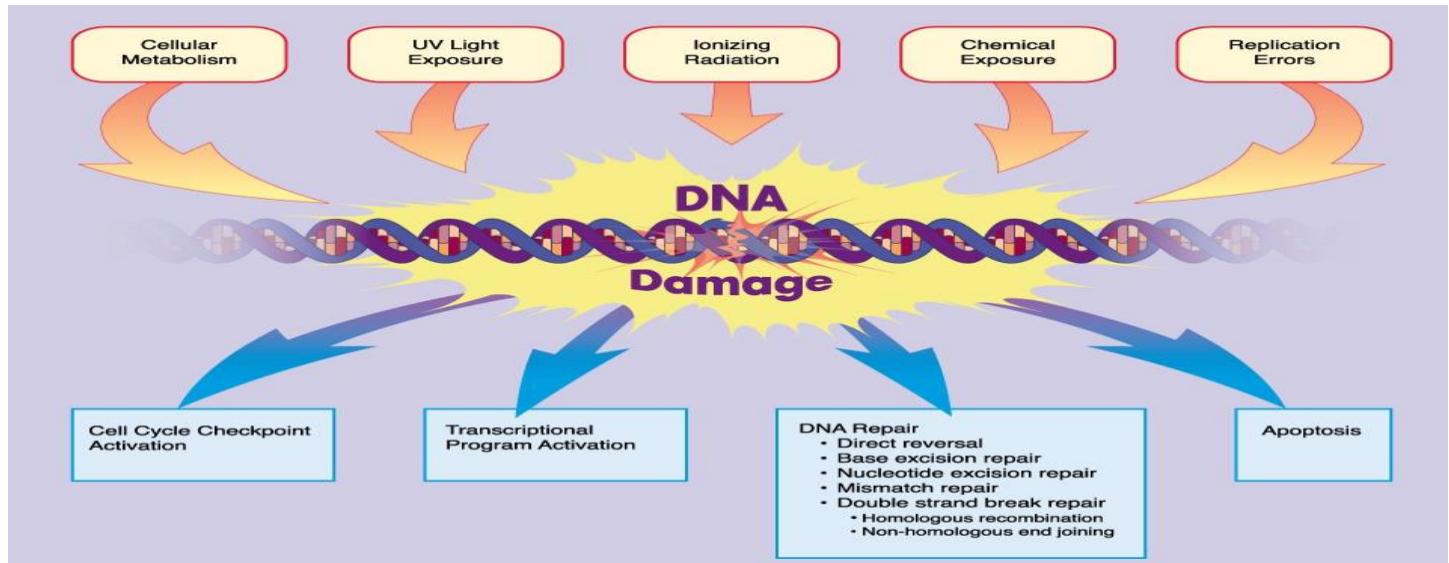
It must take place in the **germ cells** - the gametes - eggs and sperm

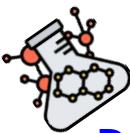
- If damage is to **somatic cells** (all other cells of the body bar germ cells) then just that one individual is affected.

Damage from where?

Causes of DNA damage include

1. DNA replication **errors**
2. **Chemical** agents acting on the DNA e.g Nitrous oxide causes deamination of C to U, alkylating agents and free radicals
3. **Physical** agents: radiation as UV causes pyrimidine dimers and x-rays





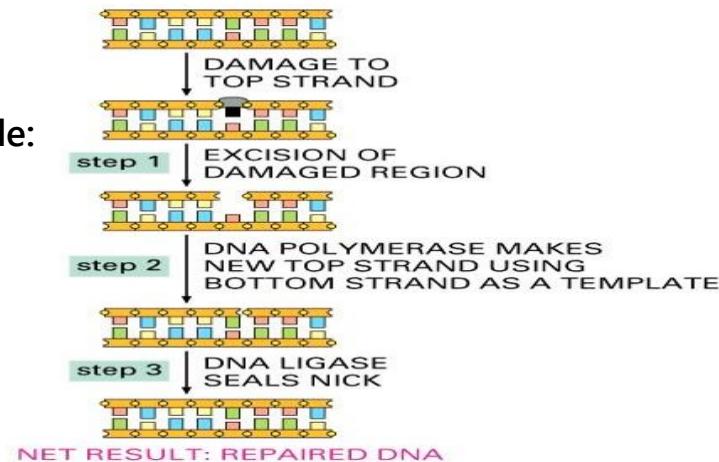
Deamination of DNA

- An amino group of Cytosine is removed and the base becomes Uracil
- An amino group of Adenine is removed and the base becomes Hypoxanthine
- An amino group of Guanine is removed and the base becomes Xanthine

DNA repair mechanisms

The correction (DNA repair mechanisms) include:

- 1) base-excision
- 2) nucleotide-excision
- 3) mismatch repair
- 4) double strand break repair

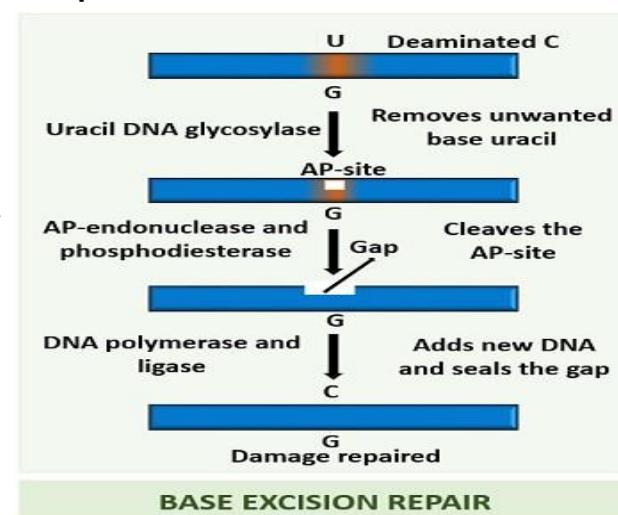
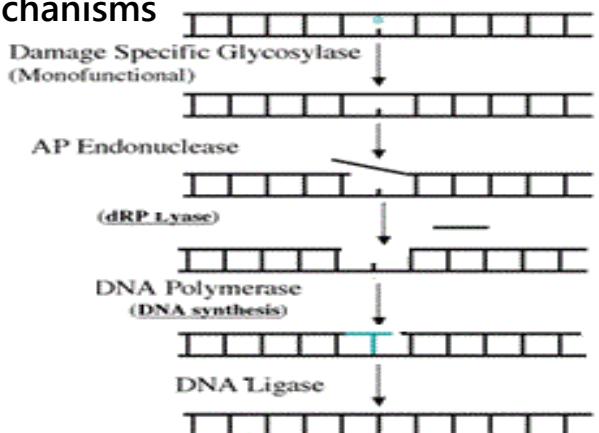


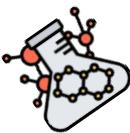
Basic steps are the same for the first three repair mechanisms

- 1) Identify damaged segment
- 2) Remove damaged region
- 3) Resynthesis of DNA
- 4) Ligate

1. Base excision repair

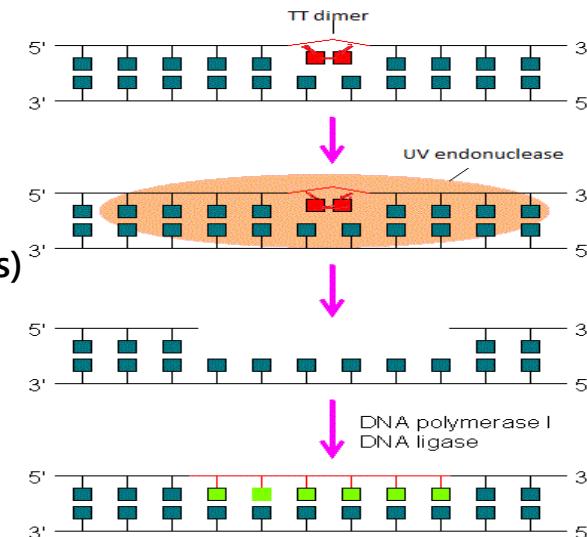
- a. DNA glycosylase **recognizes & Removes** damaged base, leaving deoxyribose sugar thus producing an **Apurinic–Apyrimidinic** site (Ap-site)
- b. AP endonuclease cuts phosphodiester backbone
- c. A deoxyribose phosphate lyase (dRP Lyase) removes the single free sugar-phosphate moiety.
- d. DNA polymerase replaces missing nucleotide
- e. DNA ligase seals nick





2. nucleotide-excision repair

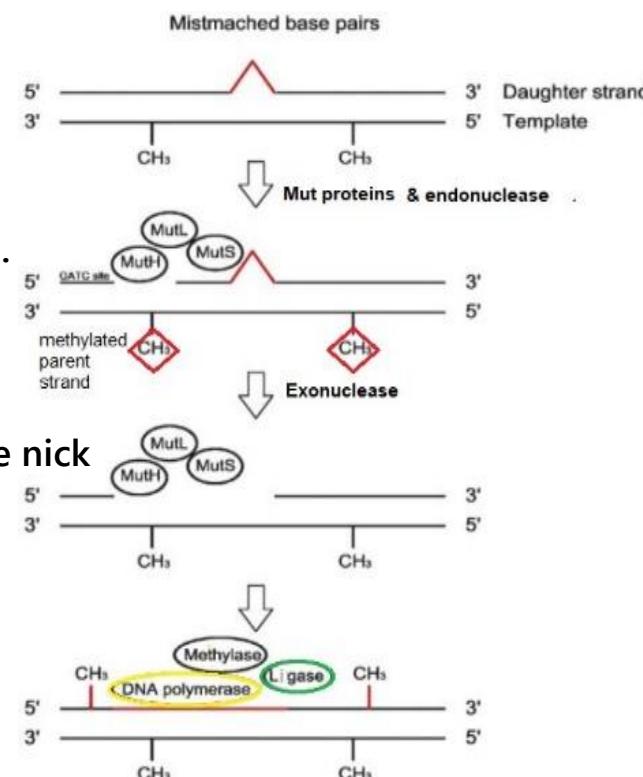
- Same as previous except that
 - It recognizes more varieties of damage
 - Remove larger segments of DNA (10 -100s of bases)
- Usually is used for replacement UV-damaged DNA (covalent joining of two adjacent pyrimidines, usually thymines), producing a dimer
- a large UV-specific endonuclease scans the DNA strand for abnormalities
- upon detection it cuts the strand on both sides (5' &3') of the damage and removes the oligonucleotide
- the gap is repaired by DNA polymerase and DNA ligase enzymes

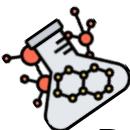


3. Mismatch repair

- Special enzymes scan the DNA for bulky alterations in the DNA double helix
- Sometimes replication errors escape the proofreading function during DNA synthesis, causing a mismatch of one to several bases (AG, AC and CT)
- These are excised and the DNA repaired

1. Mut proteins identify the mismatched strand.
2. Endonuclease nicks the strand with the mismatch.
3. The mismatched nucleotide(s) is/are removed by an exonuclease.
4. DNA polymerase fills the gap, and ligase seals the nick





Defective DNA repair mechanisms

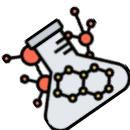
DNA Damage	Repair Mechanism	Disorder due defective mechanism
Alkylated, deaminated and/or depurinated bases	Base excision repair	Point mutation
Pyrimidine (thymine) dimers	Nucleotide excision repair	Xeroderma pigmentosum
Mismatched bases	Mismatch repair	Hereditary non-polyposis colorectal cancer
Double strand breaks	Double strand breaks repair	Immunodeficiency disorders & cancer e.g Ataxia Telangiectasia

Xeroderma Pigmentosum (XP)

Symptoms include:

1. Extreme sensitivity to sunlight
2. dermatitis (skin inflammation) with spots and skin lesions
3. Early onset of skin cancer (8years)





Causes of DNA mutation include the following, except:

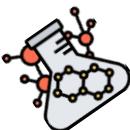
1. UV radiation
2. Alkylating agents
3. Replication error
4. Oxygen

In base –excision repair, the site that is produced by removal of the damaged base is called:

1. Ap site
2. N site
3. Ad site
4. AE site

DNA repair mechanisms include the following, except:

1. Base-excision repair
2. Nucleotide-excision repair
3. Nonsense repair
4. Mismatch repair



Bio TUT 7 : Genetic polymorphism and mutation

Definition

Polymorphism :

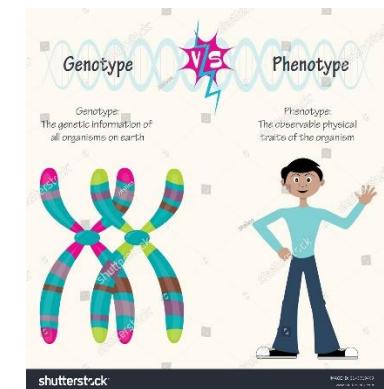
poly = multiple morph = form

polymorphism is a term used in genetics to describe **multiple forms of a single gene** that exists in an individual or among a group of individuals.

Genetic polymorphism

- is a DNA sequence variation that is common in the population = change in genotype
- a sequence variation at a given locus in greater than 1% of a population.

- **Genotype:** The unique sequence of DNA
- **Phenotype:** Observable characteristics or traits of an organism



- ✓ polymorphism can result in:

1. The majority of polymorphisms are **silent**, meaning they do not alter the function or expression of a gene.

however, a polymorphic variant of a gene can lead to:

2. Change in the phenotype that is harmless
3. Change in the phenotype that is rarely cause the disease due to:
 - abnormal expression of normal form of protein

OR

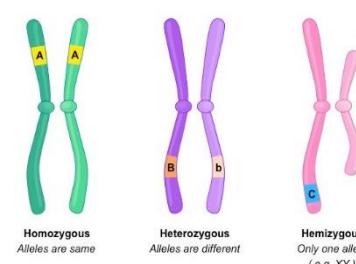
- production of an abnormal form of the protein

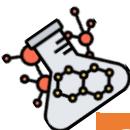
Gene mutation:

is any change in a DNA sequence away from normal (implying that there is a normal allele running through the population and that the mutation changes this normal allele to a rare and abnormal variant.)

N.B. An allele is a variant form of a given gene.

↳ This abnormality may cause or be associated with disease.





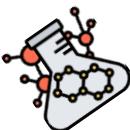
Genetic polymorphism	Gene mutation
DNA sequence variation that is common in the population	change in a DNA sequence away from normal changing the normal allele to a rare and abnormal variant (mutant allele)
the least common allele must have a frequency of at least 1% in the population	the least common allele has a frequency lower than 1% in population That allele is regarded as a mutant allele.
Occur at any part of the genome but more frequent in the non coding DNA sequences	Occur at any part of the genome (coding or non coding)
Most polymorphisms are harmless but some may cause or associated with disease	Potentially harmful causing diseases

Quiz

1. Damage and errors in DNA cause
 - a) Mutation
 - b) DNA repair
 - c) Translation
 - d) Transcription

2. The majority of polymorphisms are:
 - a) harmful
 - b) silent
 - c) causing the disease
 - d) changing the function of a gene





Tut 11 bio : carcinogenic and cancer genetics

❖ Carcinogens:-

- They are substances that can cause cancer.
- All carcinogens are mutagens (cause mutations)
- Carcinogens include:
 1. Physical carcinogens .
 2. Chemical carcinogens.
 3. Biologic carcinogens.
 4. Hormonal carcinogens.

1. Physical carcinogens : as X-ray, gamma-ray and UV-ray

2. Chemical carcinogens: may be introduced into the body by means of:

- a) occupation (as aniline, asbestos)
- b) diet (as aflatoxins, colouring agents, food additives, alcohol)
- c) lifestyle (as tobacco smoking).

❖ Action of Chemical Carcinogens

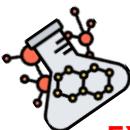
a. Chemical carcinogens are usually ingested as procarcinogens.

They are metabolised in the body, usually in liver to become the active carcinogen.
The enzymes responsible for the activation of procarcinogens are cytochrome P-450 system

b. Direct carcinogens are the ones which interact directly with the target molecules.

❖ Chemical carcinogens may produce the cancer:

- a) At the site of exposure, e.g. buccal cancer in tobacco chewers, skin cancer in tar workers.
- b) At the site of metabolism, e.g. liver cancer produced by aflatoxin.
- c) At the site of elimination, e.g. bladder cancer in persons working with aromatic dyes.



EXAMPLES:

- 1- Aflatoxins are a group of chemically related compounds synthesized by the fungi, *Aspergillus flavus*. The mould grows on rice, wheat and groundnut, when kept in damp conditions. The fungi may grow in cattle fodder, which may enter into human body through the cow's milk. Aflatoxins are powerful carcinogens, which produce hepatomas
- 2- Alcohol intake increases the risk of oral, pharyngeal, esophageal and liver cancers.
- 3- Diet high in total fat and cholesterol, increases the risk of colon, breast and prostate cancers
- 4- Cigarettes contains many carcinogens, the most important group being benzopyrenes. Other important deleterious substances in cigarette smoke are nicotine, carbon monoxide and nitrogen dioxide .
 - Cigarette smoking increases the incidence of lung cancer.
 - Oral cancer is strongly associated with chewing of tobacco

why only some smokers are getting cancer and not all smokers?

Glutathione-S transferase (GST) is involved in the detoxification of various carcinogens, including cigarette smoke.

About 5% of population are lacking in GST. Smokers who are devoid of GST are more prone to develop lung cancer. There are 3 different genes and 3 iso-enzymes for GST.

3. Biologic carcinogens:

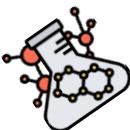
Chiefly viruses, parasites & bacteria. The role of viruses in causing cancer is more significant.

Oncogenic viruses:

- Either DNA or RNA oncogenic viruses

- Mechanism of action:

- DNA viral oncogenesis: DNA virus infects the host cell. Then the viral DNA is integrated into the host DNA (tight binding). This causes alteration of gene



expression of the host cell and forming abnormal proteins leading to cell transformation.

Viral oncoproteins are thought to bind tumor suppressor genes inactivating them

- **RNA viral oncogenesis:** The viral RNA gets copied by reverse transcriptase into single stranded viral DNA, that is copied to form another strand of complementary DNA, resulting in double stranded viral DNA or provirus. The provirus is then integrated into the host DNA & may transform the cell to neoplastic cell.

- Examples of oncogenic viruses:

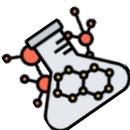
Oncogenic virus	Associated human cancer
Hepatitis B virus	Hepatoma
Human Papilloma virus	Human Papilloma virus
Epstein – Barr virus	- Burkitt's lymphoma – Nasopharyngeal carcinoma

4. Hormonal carcinogens:

o Hormone sensitive tissues developing tumours are the breast, endometrium, myometrium, vagina, thyroid, liver, prostate& testis.

o Examples include:

Hormone	Increase risk of
Estrogen : repeated estrogen therapy or women with ovarian tumours	Endometrial cancer
Contraceptive hormones: certain oral contraceptives	Breast cancer
Anabolic steroids: used by athletes to increase muscle mass	Benign & malignant tumors of the liver



❖ Oncogenes & antioncogenes

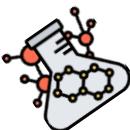
- Oncogenes are genes capable of causing cancer.
- Anti-oncogenes (Oncosuppressor Genes = tumour suppressor genes) are the genes, which normally protect the individual from getting the cancer. When tumor suppressor gene is deleted or mutated, cancer results.
- Oncogenes are of 2 types:
 - a. Viral oncogenes
 - b. Cellular oncogene
- Viral oncogenes: The virus genes become part of the cellular DNA.
→uncontrolled multiplication of the cells. This is called transformation by oncogenic virus as already mentioned above.
- Cellular oncogenes:
 - Within every cell in our body is a class of genes known as proto oncogenes.
 - Proto-oncogene is a normal gene that code for proteins that help to regulate the cell growth and differentiation & stimulate cell division. Cellular Proto-oncogenes code for a number of proteins e.g. growth factors, receptors for growth factors, transcription factors & other proteins involved in cell proliferation

Protooncogenes are activated to oncogenes by mutation or increase expression by:

- Promotor & enhancer insertion
- Chromosomal translocation
- Gene amplification
- Point mutation

When oncogenes are expressed , they produce mutated versions of :

- Growth factors
- Receptors for growth factors
- Proteins involved in signal transduction e.g. protein kinase that phosphorylate tyrosine & serine residues of proteins
- Proteins involved in gene expression in the nucleus leading to increased cell division & proliferation (cancer)



❖ Tumor suppressor genes:

- Are normal genes which inhibit cell division & cellular proliferation.
- Inactivation by mutations increase cellular proliferation can cause cancer
- E.g. retinoblastoma gene & P53 gene

❖ Apoptosis and necrosis

- Apoptosis and necrosis are two mechanisms involved in the cell death in multicellular organisms.
- Apoptosis is a naturally occurring physiological process whereas necrosis is a pathological process, which is caused by external agents like toxins, trauma, and infections.
- Apoptosis is a highly regulated whereas the necrosis is an unregulated, random process.

➤ Apoptosis

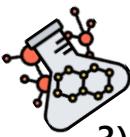
- ✓ Apoptosis, also called programmed cell death. a mechanism that allows cells to self-destruct when stimulated by the appropriate trigger (internal or external).
- ✓ Apoptosis for each cell includes two primary phases:
 - Initiation "death decision,".
 - Execution.
- BCL-2 protein family has at least 25 members. They control the function of pro-apoptotic proteins (Bax and Bak) and anti-apoptotic, proteins as BCL-XL.
- A second family of proteins, the caspase proteolytic enzymes. Caspases function by the activation of other enzymes that dismantle the cellular cytoskeleton and cellular organelles and that degrade the nuclear DNA.

The stimulus for apoptosis:

may be through intrinsic pathway (cancer cells, cells that are infected with bacteria or virus particles, and mutant cells) or extrinsic pathway.

Mechanism of Apoptosis

- 1) The Mitochondrial (Intrinsic) pathway of apoptosis
- 2) The Death Receptor (Extrinsic) pathway of apoptosis



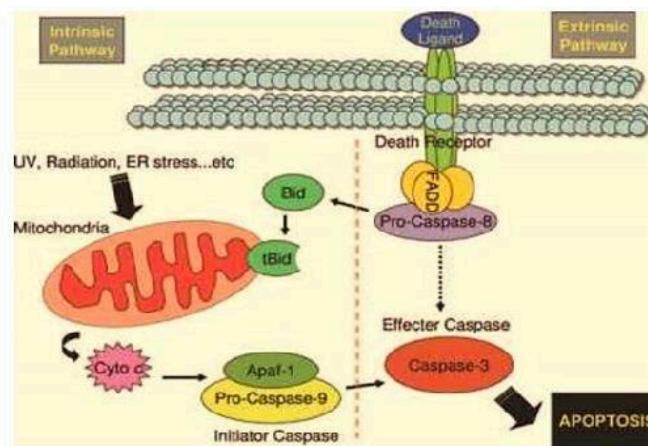
3) Activation and Function of Caspases

4) Clearance of Apoptotic Cells

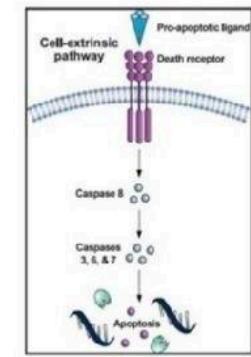
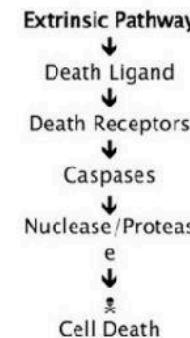
The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of caspases.

In the mitochondrial pathway, proteins of the BCL2 family, which regulate mitochondrial permeability, become imbalanced and leakage of various substances from mitochondria leads to caspase activation.

In death receptor pathway, signals from plasma membrane receptors lead to the assembly of adaptor proteins into a "death-including signaling complex," which activates caspases, and the end result is the same.

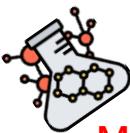


Extrinsic Pathway



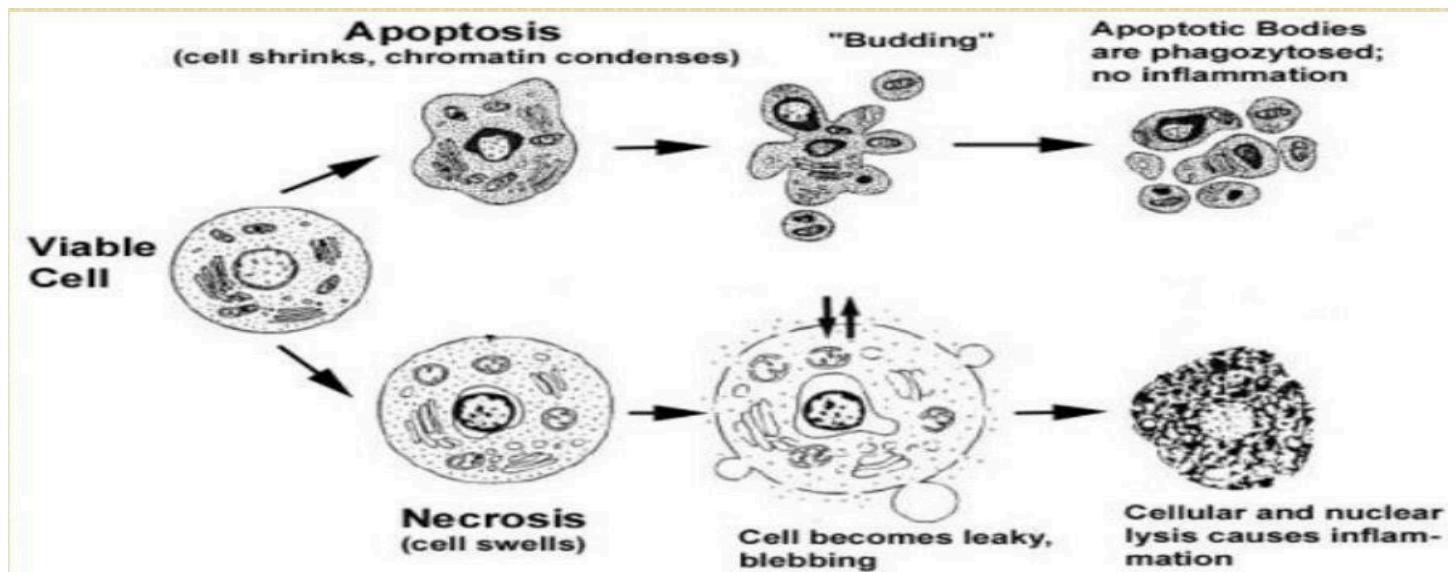
Physiologic Apoptosis

- 1) Programmed destruction of cells during embryogenesis.
- 2) Involution of hormone dependent tissues upon hormone withdrawal Ex:
Endometrial cell breakdown during menstrual cycle, Ovarian follicular atresia in menopause.
- 3) Cell loss in proliferating cell populations to maintain homeostasis Elimination of potentially harmful self-reactive lymphocytes.
- 4) Elimination of cells that have served their useful purpose.



Morphologic Changes

- Cell shrinkage: dense cytoplasm, tightly packed organelles
- Chromatin condensation and DNA fragmentation (most characteristic feature of apoptosis)
- Cytoplasmic blebs and apoptotic bodies
- Phagocytosis of apoptotic cell bodies.

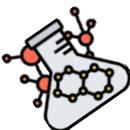


Apoptosis in Pathologic Conditions:

- DNA damage - radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia.
- Accumulation of misfolded proteins.
- Cell injury in certain infections - especially viral.
- Pathologic atrophy in parenchymal organs after duct obstruction

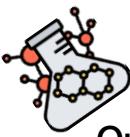
Disorders of Apoptosis:

- Defective apoptosis and increased cell survival (Cancer, Autoimmune disorders)
- Increased apoptosis and excessive cell death (Neurodegenerative diseases)



Difference between Apoptosis & Necrosis

	Apoptosis	Necrosis
Regulation	Genetic programmed	Ischemia, trauma or ATP depletion
Control	Controlled	Uncontrolled
Cell shape	Skrinkage, condensed	Swelling
Plasma membrane integrity	Maintained	Collasped
Cellular process	Budding	Blebbing
Cellular content	Packaged in apoptotic bodies	Leakage to extracellular fluid
DNA	Fragmentation, chromatin condensation	No fragmentation
Energy	ATP required	Not required
Inflammatory response	Absent	Present
Mediator	Caspase	Caspase-independent



Quiz:

1-Which of the following is an active cell death process?

- (a) necrosis
- (b) lysis
- (c) apoptosis
- (d) degeneration

2-Which of the following is Not considered the common risk factor for increasing the chance of mutation in the gene and cancer in humans?

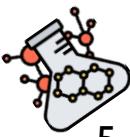
- a) Tobacco use
- b) Ultraviolet sunrays
- c) Frozen foods
- d) High alcohol consumption

3- Name the microorganism associated with an increased risk of uterine cervical carcinoma.

- a) Adenovirus
- b) Epstein –Barr virus
- c) Human Papilloma virus
- d) Hepatitis B virus

4-What is a carcinogen?

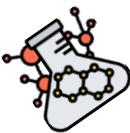
- a) A substance that can cause cancer
- b) A substance that slows down cell division
- c) A substance that causes cell death
- d) A substance that causes infections



5- Proto-oncogenes promote the cell division and _____

genes inhibit the cell division .

- a) recessive
- b) tumor-suppressor
- c) benign
- d) carcinogens



Bio TUT10: principles of heredity

MODE OF INHERITANCE:

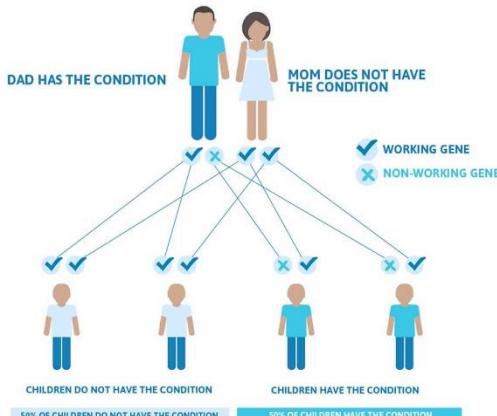
is the manner in which a genetic trait or disorder is passed from one generation to the next.

Each mode of inheritance results in a characteristic pattern of affected and unaffected family members

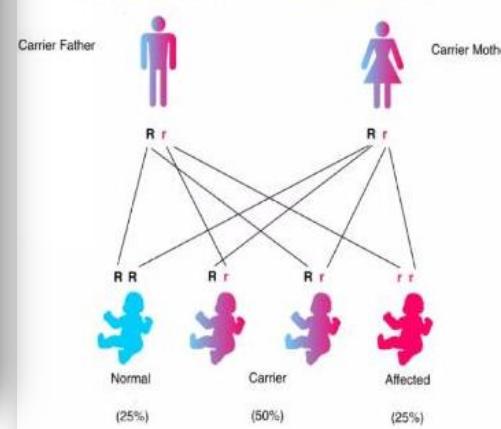
Mode of inheritance

- 1- Autosomal dominant trait
- 2- autosomal recessive trait
- 3- X- linked recessive trait
- 4- X- linked dominant trait
- 5- Y- linked inheritance
- 6- Mitochondrial Inheritance

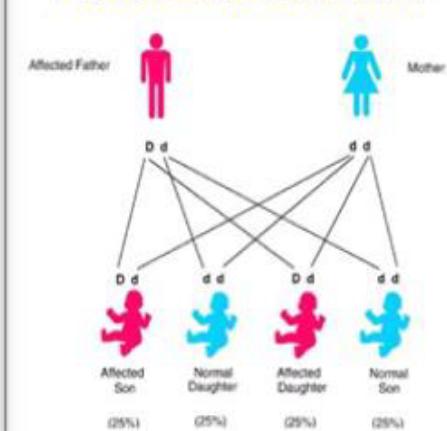
Autosomal Dominant Inheritance Pattern



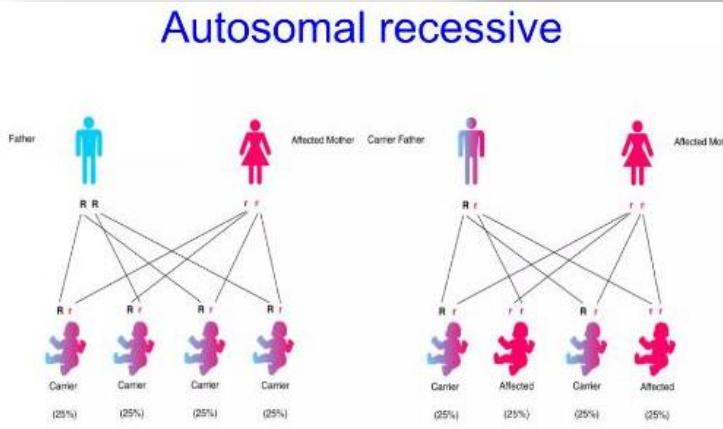
Autosomal recessive



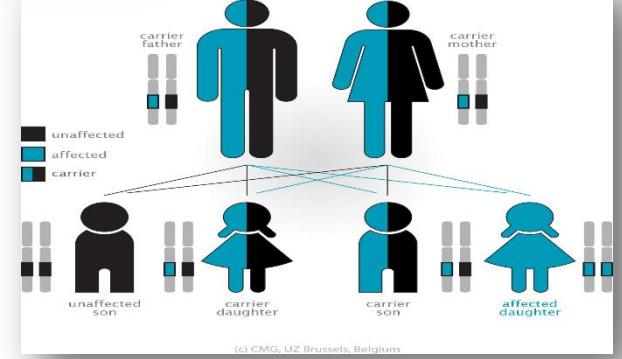
Autosomal dominant

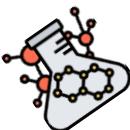


Autosomal recessive

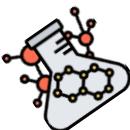


autosomal recessive



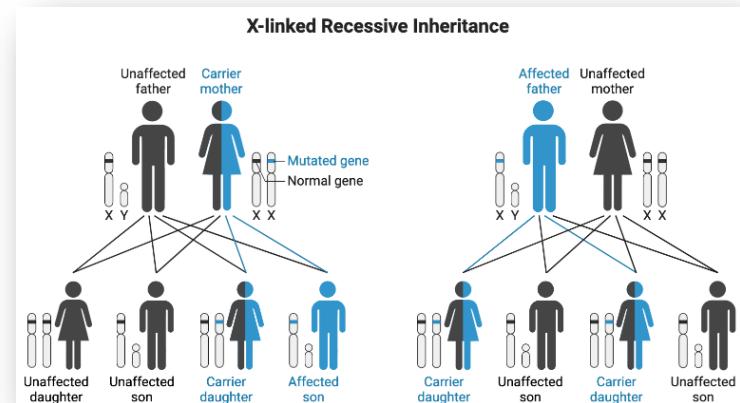


		1- Autosomal dominant	2- Autosomal recessive
Definition		<p>Single gene mutation that is located on the autosomes and express itself whether homozygous or heterozygous.</p>	<p>Single gene mutation that is located on the autosomes and express itself only when homozygous.</p>
Characters		<p>1- Affected person</p> <ul style="list-style-type: none"> -may be homozygous or heterozygous. -Has an affected parent at least. if heterozygous: 50% of his children are affected. if homozygous: 100% are affected. associated usually with structural abnormalities (autosomal recessive disorders are usually due to defective enzyme activity) <p>2- unaffected persons:</p> <ul style="list-style-type: none"> -has no affected gene and do not transmit the trait to his children. <p>3- Transmission:</p> <ul style="list-style-type: none"> -not affected by sex or consanguinity <p>4- Expressivity:</p> <ul style="list-style-type: none"> marked variation in the degree of severity e.g., patients with neurofibromatosis may show only face au lait patches while others are severely affected. 	<p>1- Affected persons:</p> <ul style="list-style-type: none"> must be homozygous. Both parents have at least one affected gene. <p>25% of sibs are affected on the average.</p> <ul style="list-style-type: none"> associated usually with defective enzyme activity <p>2- unaffected persons:</p> <p>May have an affected gene (carrier) and transmit the trait.</p> <p>3- Transmission:</p> <ul style="list-style-type: none"> not affected by sex but parents may be consanguineous (related parents may be more likely to have the same abnormal gene because they have a common ancestor). high incidence in certain group e.g. B thalassemia in mediterranean races (sickle cell disease in Afro-Caribbean)
Examples		<ul style="list-style-type: none"> ✓ Osteogenesis impefecta ✓ Achondroplasia ✓ Marfan syndrome ✓ Neurofibromatosis ✓ Acute intermittent ✓ porphyria 	<ul style="list-style-type: none"> ✓ Cystic fibrosis ✓ Inborn errors of metabolism: (galactosemia, von Gierke's, phenylketonuria, albinism. and mucopolysaccharidoses (except Hunter's)) ✓ Alfa 1 antitrypsin deficiency ✓ Thalassemia ✓ Sickle cell anemia



3- linked recessive Trait

- ❖ Always affect male
- ❖ Female are always carriers
- ❖ Recurrence risk: 50% in male offspring born to carrier mothers (**50% of daughters are carriers**)
- ❖ No father to son transmission



Examples of X-linked recessive disorders:

- ☒ Color blindness (red –green)
- ☒ Duchenne's and Becker's muscular dystrophies
- ☒ Fragile X syndrome
- ☒ Glucose 6 phosphate dehydrogenase deficiency
- ☒ Hemophilia A and B
- ☒ Hunter' s syndrome (mucopolysaccharidosis II)
- ☒ Menke's disease

4- X-linked Dominant Trait

- Affect both males and females it is more common in females (overall ratio 2:1) and more severe in males to the extent that some disorders are lethal in males so all patients will be females
- No male-to-male transmission
- Affected man will have only affected daughters with normal sons
- Half of the offspring of an affected woman will be affected (both sons and daughters)

Examples of X-linked dominant disorders:

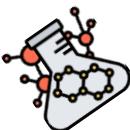
1. Primary hypophosphatemic rickets
2. Rett syndrome
3. OTC (ornithine transcarboxylase) deficiency

5- Y-linked (Holandric) Inheritance

- ✓ Trait expression and transmission is only in males, the individuals with the Y chromosome.
- ✓ If a male has a trait, so should his father and paternal grandfather as well as his sons and their sons.

Example: of 5-Y-linked (Holandric) Inheritance:

- Hairy ear pinna (Hypertrichosis of ear)



6- Mitochondrial Inheritance

- Mitochondria make most of the energy for the cell and have their own genetic material that is different from the genetic material found in the nucleus.
- Mitochondrial DNA is the small circular chromosome found inside mitochondria. There are some human diseases associated with mutations in mitochondria genes.
- These mutations can affect both males and females, but males cannot pass them on as the mitochondria are inherited via the ovum, not the sperm (only passed on by females because all mitochondria come from the mother)

Quiz

1- Mitochondrial DNA is passed down from:

- a) DNA
- b) Mother and Father
- c) Father
- d) Mother

2- If 2 parents who do not show any apparent traits of inherited disease have five sons and two daughters, and three of their sons suffer from a disease while none of the daughters are affected, what would be the mode of inheritance for the disease?

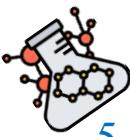
- a) X-linked recessive
- b) X-linked dominant
- c) Autosomal dominant
- d) Y-linked inheritance

3- Why is haemophilia a disease that is more commonly seen in males?

- a) The disease is autosomal dominant
- b) The disease is Y-linked
- c) The disease is X-linked
- d) The disease is autosomal recessive

4- Which of the following statements are true regarding the dominant traits?

1. One dominant allele (heterozygotes) is sufficient to show the dominant trait
2. Both dominant alleles (homozygous) are required to show the dominant trait
3. Heterozygotes (individuals with one allele) are generally carriers
4. None of the Above



5. Which of the following statements are true regarding the recessive traits?

- a) One recessive allele (heterozygotes) is sufficient to show the phenotypic trait
- b) Both recessive alleles (homozygous) are required to show the phenotypic trait
- c) Heterozygotes (individuals with one allele) are generally carriers.
- d) Option a & b
- e) Option a & c