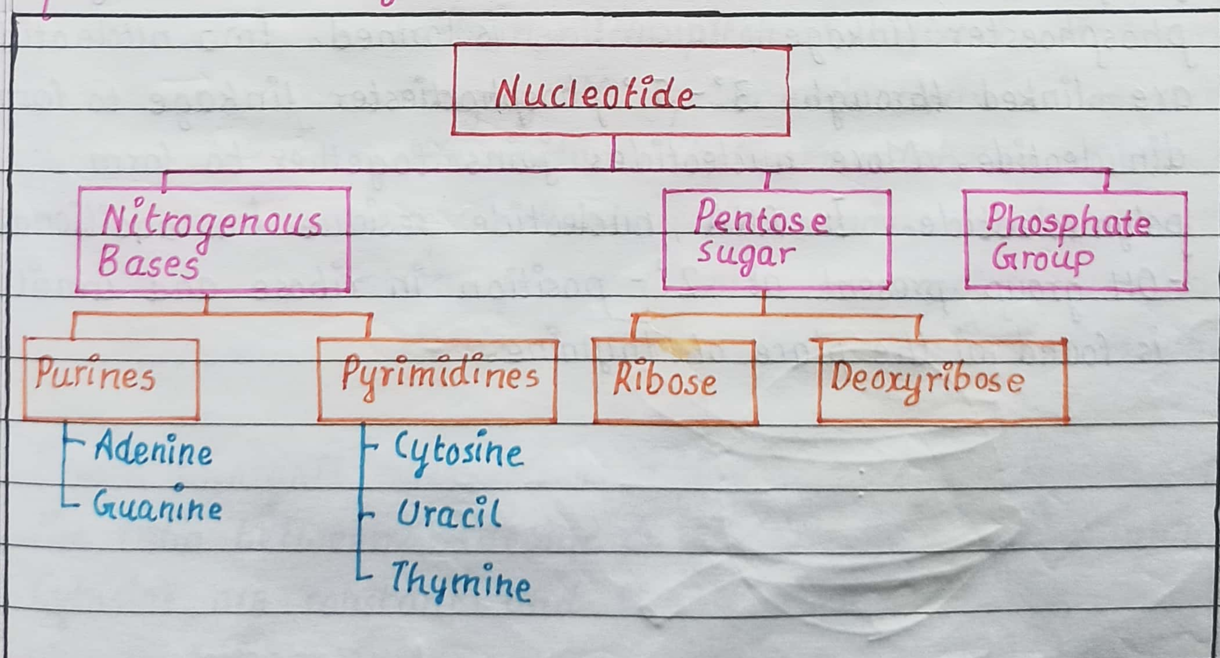
MOLECULAR BASIS OF INHERITANCE

DNA (Deoxyribonucleic Acid) and RNA (Ribonucleic Acid) are two types of nucleic acid found in living organisms. DNA acts as genetic material in most of the organisms. RNA also acts as genetic material in some organisms, as in some viruses and acts as a messenger. It functions as adapter, structural, and in some cases as a catalytic molecule.

The DNA

It is a long polymer of deoxyribonucleotides. A pair of nucleotide is known as base pairs. Length of DNA is usually defined as number of nucleotides present in it. Escherichia coli has 4.6×10^6 bp, and haploid content of human DNA is 3.3×10^9 bp.

Structure of Polynucleotide Chain:



ALPHA NOTES

A nucleotide has three components - a nitrogenous base, a pentose sugar and a phosphate group. There are two types of nitrogenous bases - Purines (Adenine, Guanine) and Pyrimidines (Cytosine, Uracil and Thymine). Thymine is present in DNA, And Uracil is present in RNA in the place of Thymine.

Double stranded polynucleotide chain

→ Phosphate group
→ Pentose sugar
→ Adenine, Guanine
→ cytosine, Thymine

hydrogen bonds

5' 3' OH 3' OH 5'

ALPHA NOTES

A nitrogenous base is linked to pentose sugar with N-glycosidic linkage to form a nucleoside. When phosphate group is linked to OH of 5'C of a nucleoside through phosphoester linkage, nucleotide is formed. Two nucleotides are linked through 3'-5' phosphodiester linkage to form dinucleotide. More nucleotides joins together to form polynucleotide. In RNA, nucleotide residue has additional -OH group present at 2'-position in ribose and uracil is found at the place of thymine.

DNA was first identified as an acidic substance present in nucleus by Friedrich Meischer in 1869. He named it as 'Nuclein'. Double Helix Model for structure of DNA was given by James Watson and Francis crick, based on diffraction data produced by Maurice Wilkins and Rosalind Franklin.

The salient features of Double-helix structure of DNA are as follows:

1. DNA is made of two polynucleotide chains in which backbone is made up of sugar-phosphate and nitrogenous bases projected inside it.
2. Two chains have anti-parallel polarity One 5' ⟶ 3' and with 3' ⟶ 5'.
3. The bases in two strands are paired through H-bonds. Adenine and Thymine forms double hydrogen bond. Guanine and Cytosine forms triple hydrogen bond.
4. Two chains are coiled in right handed Fashion. The pitch of helix is 3.4 nm and roughly 10 bp in each turn. Consequently, the distance between a bp in a helix is approximately 0.34 nm.
5. The plane of one base pair stacks over the other in double helix to confer stability.

Erwin Chargaff observed that for a Double Stranded DNA, the ratio between Adenine & Thymine and Guanine & Cytosine are constant and equals one.

ALPHA NOTES

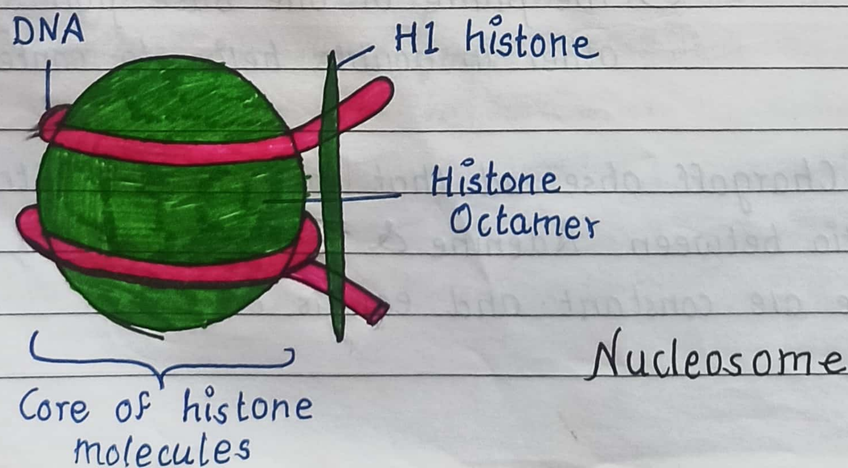
Packing of DNA helix:

In prokaryotes, well defined nucleus is absent and negatively charged DNA is combined with some positively charged proteins called nucleoids.

In eukaryotes, histones, positively charged proteins, organized to form 8 molecules unit called histone octamer. Negatively charged DNA is wrapped around the histone octomer to form nucleosome. Histones are rich in the basic amino acid residues lysines and arginines. Both the amino acid residues carries positive charges in their side chains.

- Single nucleosome contains about 200 base pairs. Chromatin is the repeating unit of nucleosome.
- In nucleus, some region of chromatin are loosely packed and stains light, they are referred as euchromatin. The chromatin that is more densely packed and stains dark are called as heterochromatin. Euchromatin is transcriptionally active chromatin. Heterochromatin is transcriptionally inactive chromatin.

ALPHA NOTES



Nucleosome

The Search for Genetic Material

Transforming Principle

Frederick Griffith in 1928 conducted experiment on bacteria Streptococcus pneumoniae (bacterium responsible for pneumonia). There are two types of strains of this bacteria, some produce smooth shiny colonies (S) and others produce rough colonies (R). Mice infected with the S strain (virulent) die from pneumonia infection but mice infected with the R strain do not develop pneumonia.

S strain ⟶ Inject into mice ⟶ Mice dies
R strain ⟶ Inject into mice ⟶ Mice live
S strain (heat-killed) → Inject into mice ⟶ Mice live
S strain (heat-killed) + R strain (live) → Inject into Mice → Mice die

Griffith concluded that R strain bacteria have somehow transformed by heat-killed S strain bacteria. Some transforming principles transferred from S strain to R strain and enabled the R strain to synthesize a smooth polysaccharide coat and become virulent. This must be due to transfer of genetic material.

Biochemical Characterisation of Transforming Principle

- Oswald Avery, Collin Macleod and Maclyn McCarty worked out to determine the biochemical nature of transforming principle of Griffith. (1933-1944)
- They purified biochemicals i.e., protein, DNA, RNA, etc., from the heat-killed S cells to see which ones could transform live R cells into S cells. They discovered that DNA alone from S bacteria caused R bacteria to become transformed. So, They concluded that DNA is the genetic material.

ALPHA NOTES

The Genetic Material is DNA

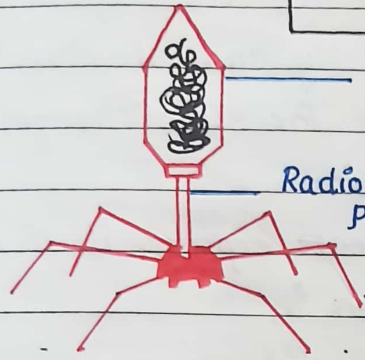
The experimental proof that DNA is the genetic material came from experiments of Alfred Hershey and Martha Chase (1952). They worked with virus that infect bacteria called bacteriophages.

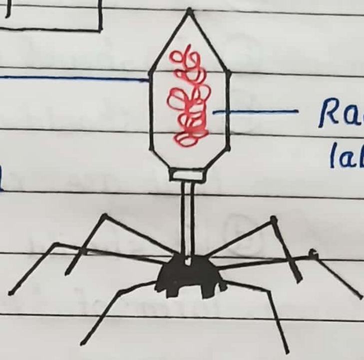
- In one preparation, the protein part was made radioactive and in the other, nucleic acid (DNA) was made radioactive. These two phage preparations were allowed to infect the culture of E. coli. Soon after infection, before lysis of cells, the E. coli cells were gently agitated in a blender, to loosen the adhering phage particles and the culture was centrifuged.
- The heavier infected bacterial cells pelleted to the bottom and the lighter viral particles were present in the supernatant. It was found that when bacteriophage containing radioactive DNA was used to infect E. coli, the pellet contained radioactivity.
- If bacteriophage containing radioactive protein coat was used to infect E. coli, the supernatant contained most of the radioactivity.

THis experiments shows that protein does not enter the bacterial cell and only DNA is the genetic material.

ALPHA NOTES

THE HERSHEY - CHASE EXPERIMENT

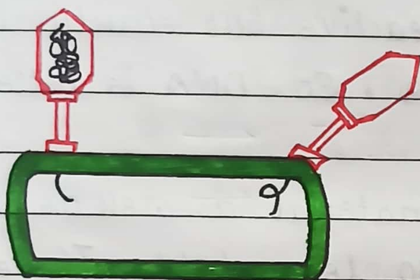


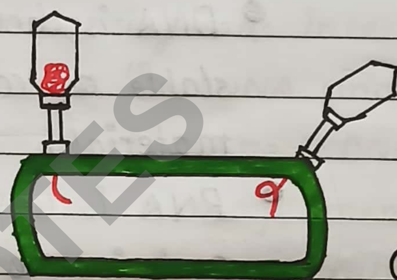


Bacteriophage

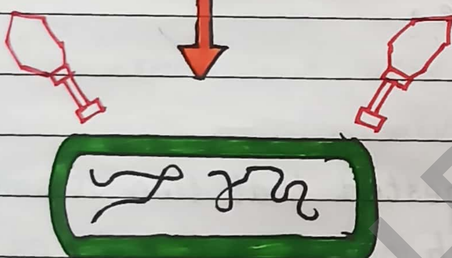
Radioactive (^{35}S) labelled protein capsule

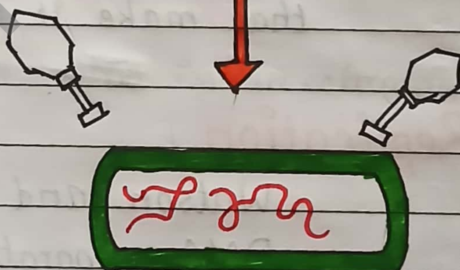
Radioactive (^{32}P) labelled DNA



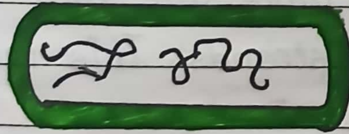


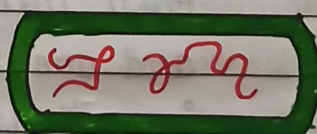
① INFECTION





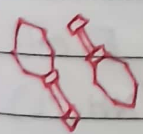
② BLENDING



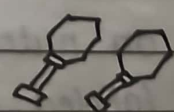


③ CENTRIFUGATION

No Radioactive (^{35}S) detected in cells
+
Radioactive (^{35}S) detected in supernatant



Radioactive (^{32}P) detected in cells
+
No Radioactivity detected in supernatant



ALPHA NOTES

Properties of Genetic Material

ⓐ It should be able to generate its replica (Replication).
ⓑ It should be stable chemically and structurally.
ⓒ It should provide the scope for slow changes (mutation) that are required for evolution
ⓓ It should be able to ~~replicate~~ express itself in the form of 'Mendelian Characters'.

- DNA is chemically less reactive but structurally more stable as compare to RNA. So, DNA is better genetic material.
- RNA is used as genetic material as well as catalyst and is more reactive, so less stable. Therefore, DNA has evolved from RNA with chemical modifications that make it more stable.

Replication

Watson and Crick suggested that two strands of DNA separate from each other and acts as a template for synthesis of new complementary strands. After the completion of replication, each DNA molecule would have one parental and one newly synthesized strands. This method is called semiconservative DNA replication.

The Experimental Proof

Matthew Meselson and Franklin Stahl showed experimental evidence of semiconservative replication by growing E. coli on nutrient medium containing nitrogen salts ($^{15}NH_4Cl$) labeled with radioactive ^{15}N.

ALPHA NOTES

- ^{15}N was incorporated into both the strands of DNA. Such a DNA was heavier than DNA obtained from normal E. coli grown on a medium containing ^{14}N. Then, they transferred the E. coli cells to a medium containing ^{14}N.
- After one generation, when one bacterial cell has multiplied into two, they isolated the DNA and evaluated its density. Its density was intermediate between that of the heavier ^{15}N-DNA and ^{14}N-DNA.
- This is because during replication, new DNA molecule with one ^{15}N old strand and a complementary ^{14}N new strand was formed (semi-conservative replication) and so its density is intermediate between the two.

The experiment proved that the DNA in chromosomes replicate semiconservatively.

The Machinery and The Enzymes

Replication of DNA requires enzyme DNA polymerase, that catalyses the polymerisation in one strand in a direction of 5' ⟶ 3' only after unwinding with the help of Helicase enzyme. So, replication in one strand is continuous and other strand is discontinuous to synthesize okazaki fragments that are joined together by enzyme DNA ligase.

ALPHA NOTES

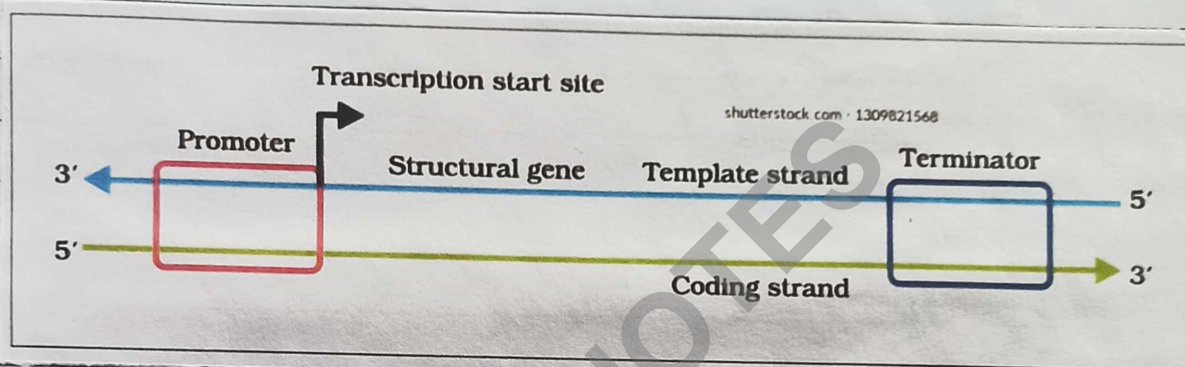
Characters	Leading strand	Lagging strand
① Fragments	It is formed continuously as single fragment.	In the beginning, it is formed in the form of small fragments called okazaki segments.
② RNA primer	It requires only one primer to initiate the growth.	Every fragment requires separate RNA primer to initiate.
③ DNA ligase	Not required	Required to join DNA fragments.
④ Direction of growth	5' → 3'	Of complete strand, it is 3' → 5'. However, for okazaki fragments, it is 5' → 3'.

ALPHA NOTES

Transcription

It is the process of copying genetic information from one strand of DNA into RNA. In transcription, only one segment of DNA and only one strand of DNA is copied in RNA. The Adenine forms base pair with Uracil instead of Thymine.

Transcription of DNA includes a promoter, the structural gene and a terminator. The strand that has polarity 3' → 5' act as template and is called template strand and the other strand which has polarity 5' → 3' is called as coding strand.

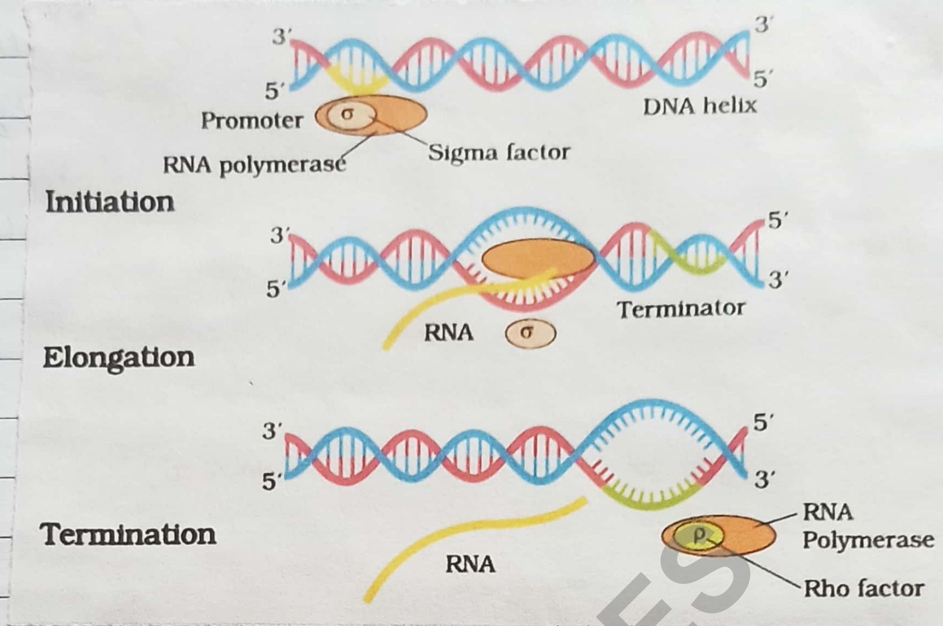


ALPHA NOTES

Template strand → Acts as template for transcription and codes for RNA.

Coding strand → Does not code for any region of RNA during transcription.

Promoter is located at 5' end of the structural gene. It provides binding site for RNA polymerase to start transcription. Sigma factor also helps in initiation of transcription. The terminator is located at 3' end of coding strand and it usually defines the end of transcription where rho factor will bind to terminate transcription.



ALPHA NOTES

A cistron is defined as a segment of DNA that codes for a polypeptide, the structural gene in a transcription unit could be said as monocystronic (mostly in eukaryotes) or polycistronic (mostly in bacteria or prokaryotes). Exons are those sequences that appear in mature and processed RNA. Exons are interrupted by Introns. Introns do not appear in mature and processed RNA.

- In Eukaryotes, there are three different RNA Polymerase Enzymes. They catalyse the synthesis of all types of RNA.
  RNA polymerase I ⟶ rRNA
  RNA polymerase II ⟶ mRNA
  RNA polymerase III ⟶ tRNA

The mRNA provides the template, tRNA brings amino acids and reads the genetic code, and rRNA plays structural and catalytic role during translation.

The primary transcripts contains both exons and introns and are non-functional. It undergoes the process of splicing in which introns are removed and exons are joined in a defined order.

The hnRNA (heterogenous nuclear RNA) undergoes additional processing called as capping and tailing. In capping, an unusual nucleotide (methyl guanosine triphosphate) is added to the 5'-end of hnRNA. In tailing, polyadenylate tail is added at 3'-end in a template independent manner. It is the fully processed hnRNA, now called mRNA, that is transported out of the nucleus for translation.

10 August

Genetic Code

Genetic code is the relationship of amino acids sequence in a polypeptide and nucleotide / base sequence in mRNA. It directs the sequence of amino acids during synthesis of proteins.

George Gamow suggested that genetic code should be combinations of 3 nucleotides to code amino acids.

Har Gobind Khorana developed chemical method for synthesising RNA molecules with defined combination of bases (homopolymers and copolymers).

Marshall Nirenberg's cell-free system for protein synthesis finally helped the code to be deciphered.

Severo Ochoa enzyme (polynucleotide phosphorylase) was also helpful in polymerising RNA with defined sequences in a template independent manner (enzymatic synthesis of RNA).

ALPHA NOTES

First position | Second position | Third position

	U	C	A	G	
U	UUU Phe UUC Phe UUA Leu UUG Leu	UCU Ser UCC Ser UCA Ser UCG Ser	UAU Tyr UAC Tyr UAA Stop UAG Stop	UGU Cys UGC Cys UGA Stop UGG Trp	U C A G
C	CUU Leu CUC Leu CUA Leu CUG Leu	CCU Pro CCC Pro CCA Pro CCG Pro	CAU His CAC His CAA Gln CAG Gln	CGU Arg CGC Arg CGA Arg CGG Arg	U C A G
A	AUU Ile AUC Ile AUA Ile AUG Met	ACU Thr ACC Thr ACA Thr ACG Thr	AAU Asn AAC Asn AAA Lys AAG Lys	AGU Ser AGC Ser AGA Arg AGG Arg	U C A G
G	GUU Val GUC Val GUA Val GUG Val	GCU Ala GCC Ala GCA Ala GCG Ala	GAU Asp GAC Asp GAA Glu GAG Glu	GGU Gly GGC Gly GGA Gly GGG Gly	U C A G

ALPHA NOTES

Salient Features of Genetic Code →

1. The code is triplet. 61 codons code for amino acids and 3 codons do not code for any amino acids, hence they function as stop codon.
2. Some amino acids are coded by more than one codon, hence the code is degenerate.
3. The codon is read in mRNA in a contiguous fashion. There are no punctuations.
4. Codon is unambiguous and specific, code for one amino acid.

5. The code is nearly universal. For example, from bacteria to human UUU would code for Phenylalanine (phe). Some exceptions have been found in mitochondrial codons, and in some protozoans.
6. AUG has dual functions. It codes for Methionine (met), and it also acts as initiator codon.
7. UAA, UAG, UGA are stop terminator codons.

Mutations and Genetic code

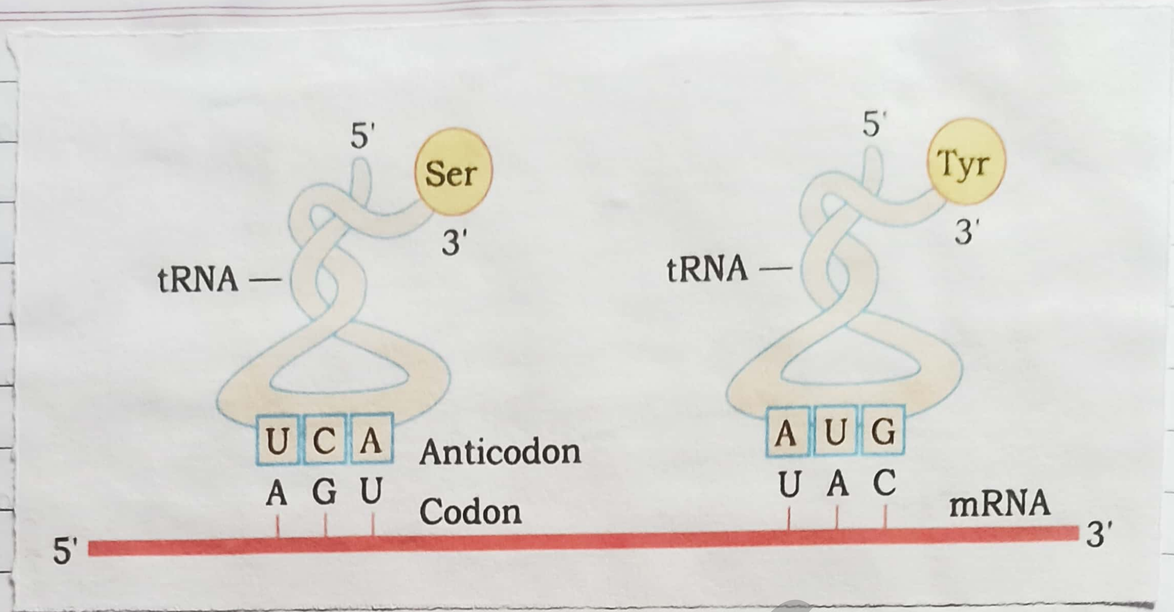
A change of single base pair i.e, point mutation in the sixth position of Beta-globin chain of haemoglobin results due to the change of amino acid residue glutamate to valine. This results in a diseased condition called sickle cell anaemia.

Insertion or deletion of three or its multiple bases insert or delete ~~in~~ one or multiple codon, hence one or multiple amino acids, and reading frame remains unaltered from that point onwards. Such mutations are called non-frameshift insertion or deletion mutations.

ALPHA NOTES

tRNA - the Adapter Molecule

The t-RNA is called as adapter molecule. It has an anticodon loop that has bases complementary to code present on mRNA and also has an amino acid accepter to which the amino acid binds. tRNA is specific for each amino acid. For initiation, there is another specific tRNA that is refferred to as initiator tRNA. The secondary structure of tRNA is depicted as clover-leaf. In actual structure, the t-RNA is a compact molecule which looks like an inverted L.

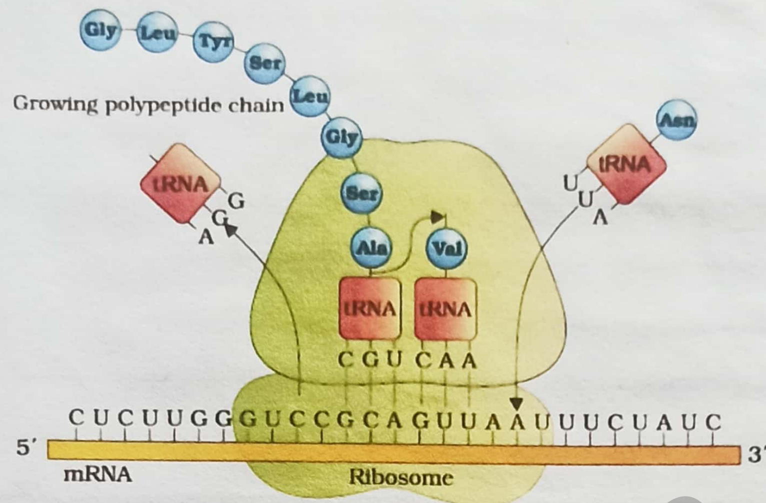


Translation

Translation is the process of polymerisation of amino acids to form a polynucleotide. The order and sequence of amino acids are defined by the sequence of bases in the mRNA. Amino acids are joined by a bond which is known as peptide bond. It involves following steps:
ⓐ Charging of t-RNA or aminoacylation of tRNA.
ⓑ Formation of peptide bond between two charged tRNA.

- The start codon is AUG. An mRNA has some additional sequence that are not translated called untranslated region (UTR).
- For initiation, the ribosome binds to the mRNA at the start codon (AUG). Ribosomes moves from codon to codon along mRNA for elongation of protein chain. At the end, release factor binds to the stop codon, terminating the translation and releasing the complete polypeptide from the ribosome.

ALPHA NOTES



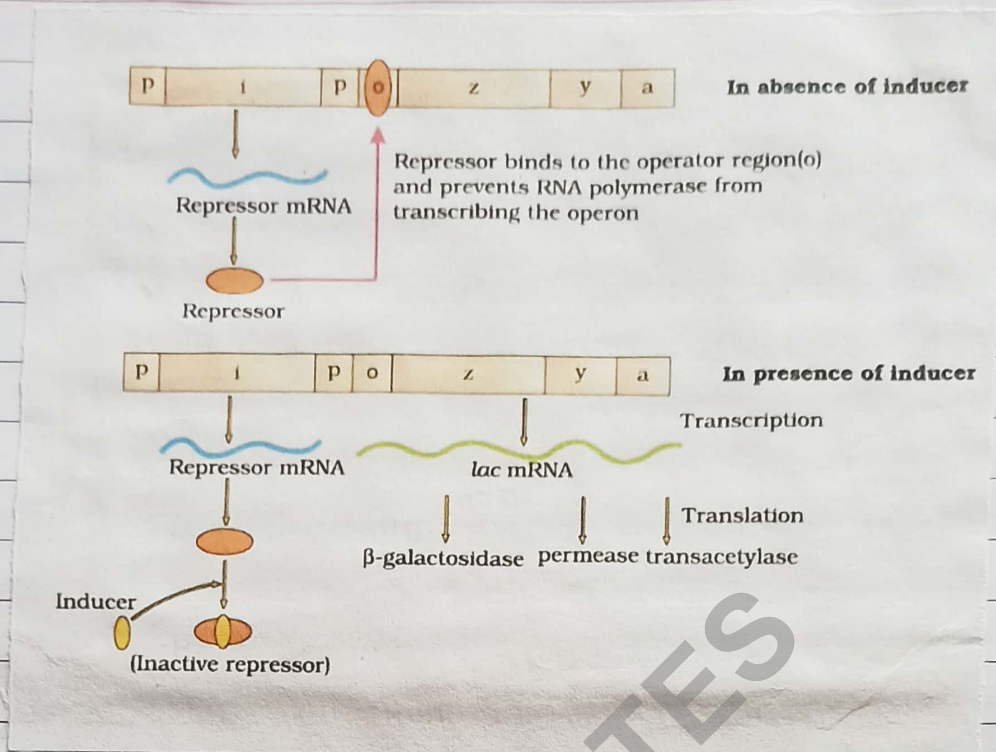
Regulation of Gene Expression

All the genes are not needed constantly. The genes needed only sometimes are called regulatory genes. They are made to function only when required and they remain non-functional at other times. Such regulated genes, therefore required to be switched on or off when a particular function is to begin or stop.

The Lac Operon

Lac operon consists of a regulatory gene (i) and three structural genes (y, z and a). Gene i code for the repressor of the lac operon. The gene z code for beta-galactosidase, which is responsible for hydrolysis of disaccharides, lactose into its monomeric units, galactose and glucose. The gene y code for permease, which increases the permeability of the cell to β-galactosides. The a gene ~~code~~ encodes a transacetylas

ALPHA NOTES



Lactose is the substrate for beta - galactosidase and it regulates switching on ond off of the operon, so it is called inducer.

Regulation of Lac operon by repressor is reffered as negative ~~repressor~~ regulation. Operation of Lac operon is also under the control of positive regulation, but it is beyond the scope of discussion at this level.

ALPHA NOTES

Human Genome Project

The scientific project which deal with the study of base sequences of DNA molecules of complete set of chromosomes is called Human genome project. HGP was closely associated with the rapid development of a new area in biology called as Bioinformatics.

Goals of HGP

a) Identify all the approximately 20,000 - 25,000 genes in human DNA.
b) Determine the sequences of the 3 billion chemical base pairs that make up human DNA.
c) Store this information in databases.
d) Improve tools for data analyses.
e) Transfer related technologies to other sectors, such as, in industry sectors.
f) Address the ethical, legal and social issues (ELSI) that may arise from the project.

ALPHA NOTES

Methodologies

- To identifying all the genes that expressed as RNA reffered to as Expressed Sequence Tags (ESTs).
- Simply sequencing the whole set of genome that contained all the coding and non-coding sequence, and later assigning different regions in the sequence with functions is called as Sequence Annotation.
- The total DNA from a cell is isolated and converted into random fragments of relatively smaller sizes and cloned in suitable host using specialised vectors.

- The commonly used vectors are BAC (bacterial artificial chromosomes), and YAC (yeast artificial chromosomes).
- The fragments were sequenced using automated DNA sequencers.
- Specialized computer based programmes were developed for the alignment of the sequences.
- The sequences were subsequently annotated and were assigned to each chromosome.
- The sequence of chromosome 1 was completed only in May 2006.

Salient Features of Human Genome:

1. The human genome contains 3164.7 million nucleotide bases.
2. The average gene consists of 3000 bases with the largest known human gene being dystrophin at 2.4 million bases.
3. The total number of genes is estimated at 30,000.
4. 99.9 percent nucleotide bases are exactly same in all people.
5. The functions are unknown for over 50 % of discovered genes.
6. Less than 2 % of the genome codes for protein.
7. Repeated sequences make up very large portion of human genome.
8. Repetitive sequences are stretches of DNA sequences that are repeated many times.
9. Chromosome 1 has most genes (2968), and the Y has the fewest (231).

ALPHA NOTES

⑩ Scientists have identified about 1.4 million locations where single base DNA differences (SNPs - single nucleotide polymorphism) occur in humans.

Applications of HGP :

1. All the genes in a genome can be studied together.
2. Helps to understand how tens of thousands of genes and proteins work together in interconnected networks.
3. Helps to diagnose and treat genetic diseases.

DNA Fingerprinting

- The process of comparison of DNA from different sources to establish the identity is called DNA Fingerprinting.
- DNA fingerprinting involves identifying differences in some specific regions in DNA sequence called as repetitive DNA.
- Repetitive DNA are separated from bulk genomic DNA as different peaks during density gradient centrifugation.
- The bulk DNA forms a major peak and the other small peaks are referred to as satellite DNA.
- Satellite DNA is of two types based on base composition, length of segment, and number of repetitive units.
  - micro-satellites
  - mini-satellites

ALPHA NOTES

- Satellite DNA sequences normally do not code for any proteins, but they forms a large portion of human genome.
- Satellite DNA sequence show high degree of polymorphism and form the basis of DNA Fingerprinting.
- An inheritable mutation occuring in a population at high frequency, is referred to as DNA polymorphism.
- Repeated nucleotide sequences in the non-coding DNA of an individual is called Variable Number of Tandem Repeats (VNTR). The size of VNTR varies in size from 0.1 to 20 kb.

DNA Fingerprinting involves the following steps:

1. Isolation of DNA,
2. Digestion of DNA by restriction endonucleases,
3. Separation of DNA fragments by electrophoresis,
4. Transferring (blotting) of separated DNA fragments to synthetic membranes, such as nitrocellulose or nylon,
5. Hybridization using labelled VNTR probe,
6. Detection of hybridized DNA fragments by autoradiography.

Applications of DNA Fingerprinting:

1. In identification of criminals.
2. In determining population and genetic diversities.
3. In solving parental disputes.

ALPHA NOTES

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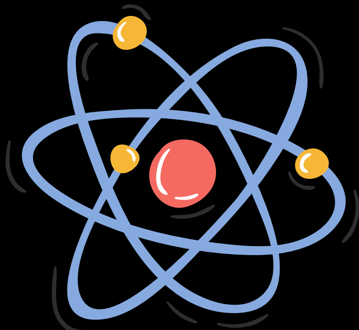
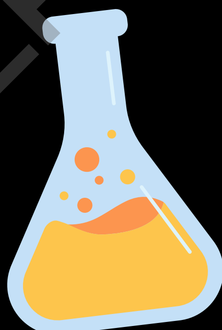


CHEMISTRY



BIOLOGY

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