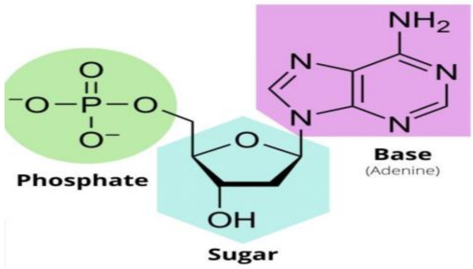
Chemistry of nucleic acid

Introduction :

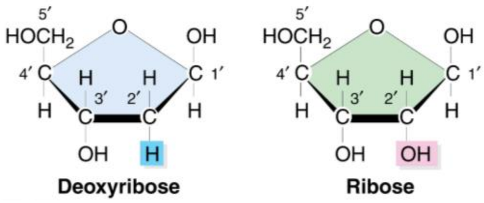
Nucleotides

A compound consisting of a sugar molecule (either ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen containing base.



Pentose Sugars

- Ribose (β-D-Ribofuranose) and deoxyribose (β-D- deoxyribofuranose)



RNA and DNA

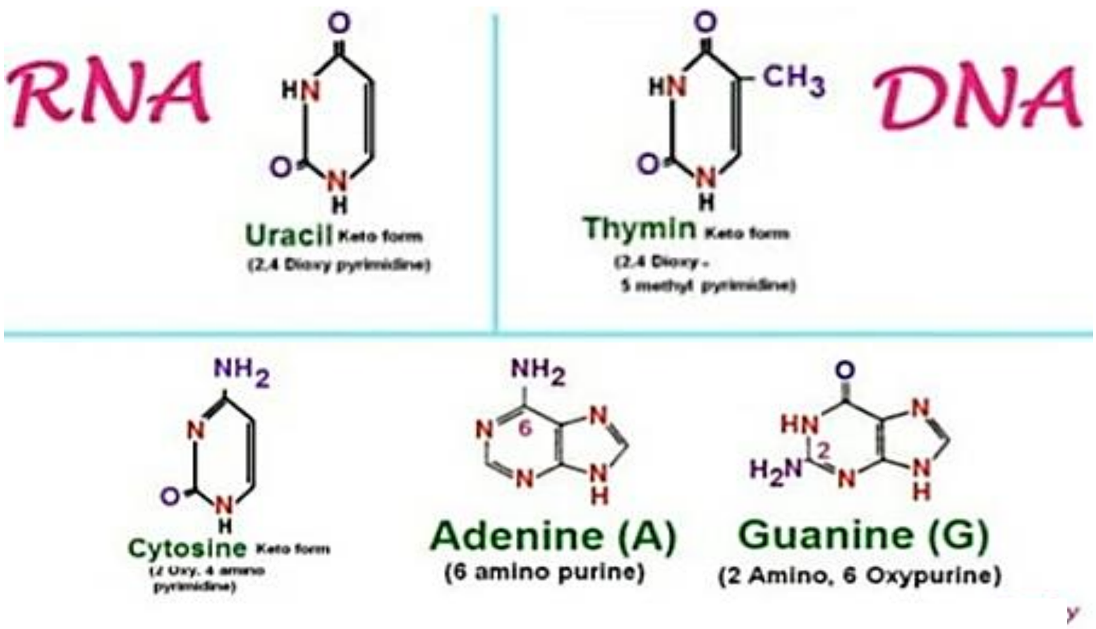
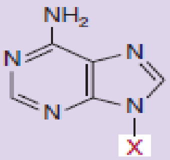
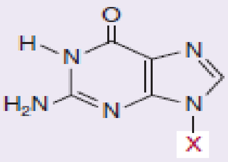
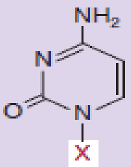
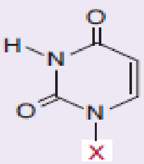
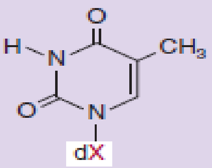


TABLE 32-1 Purine Bases, Ribonucleosides, and Ribonucleotides

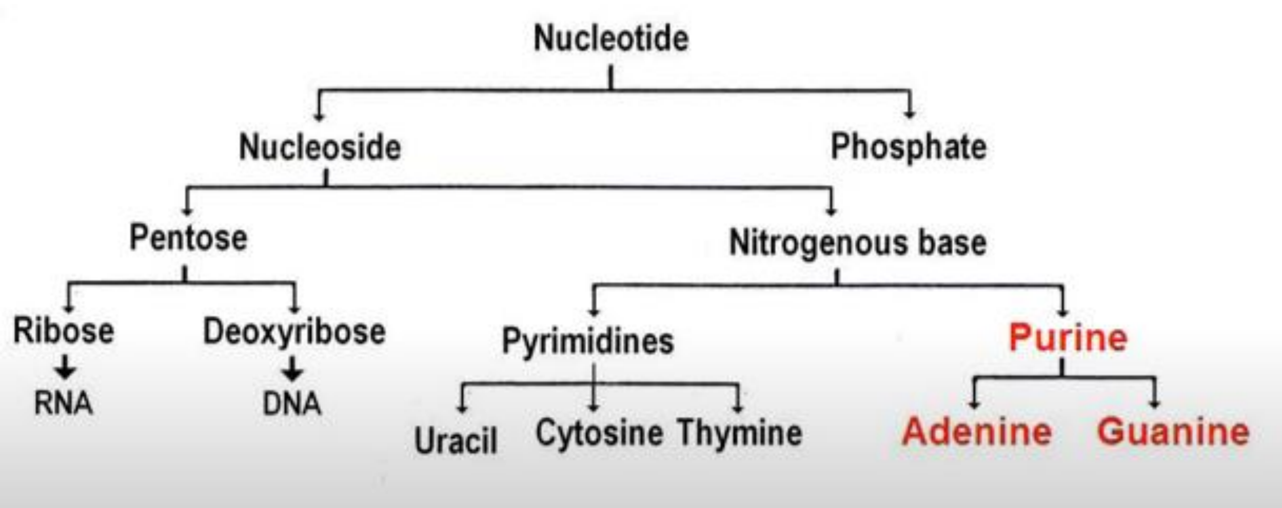
Purine or Pyrimidine	X = H	X = Ribose	X = Ribose Phosphate
	Adenine	Adenosine	Adenosine monophosphate (AMP)
	Guanine	Guanosine	Guanosine monophosphate (GMP)
	Cytosine	Cytidine	Cytidine monophosphate (CMP)
	Uracil	Uridine	Uridine monophosphate (UMP)
	Thymine	Thymidine	Thymidine monophosphate (TMP)

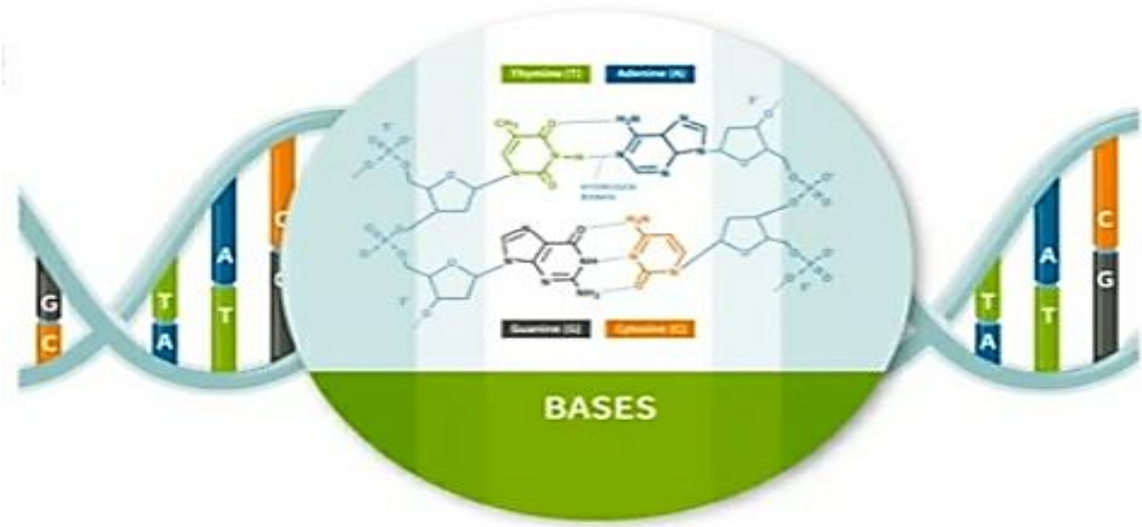
➢ ***Nucleotides functions*** :

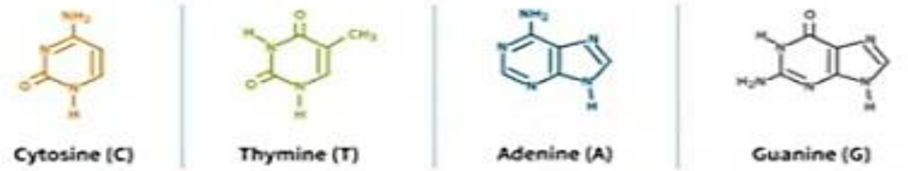
- **They are the building blocks of both DNA and RNA.**
- **Nucleotides also enter in the structure of many free nucleotides and coenzymes**

Thus, they are essential for life and health.

Structure of nucleotides







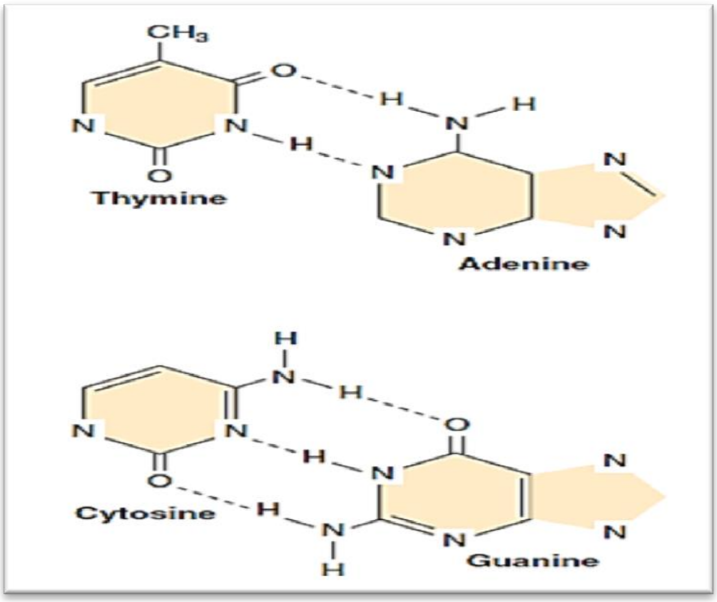


FIGURE 34–3 DNA base pairing between complementary deoxynucleotides involves the formation of hydrogen bonds. Two such H-bonds form between adenine and thymine, and three H-bonds form between cytidine and guanine. The broken lines represent H-bonds

- ***Bases***

The nitrogenous bases are either purines or pyrimidine's.

Purines and pyrimidine's are nitrogen-containing hetero cycles, cyclic structures that contain, in addition to carbon, other (hetero) atoms such as nitrogen. Note that the smaller pyrimidine

molecule has the *longer* name and the larger purine molecule the *shorter* name, and that their six-atom rings are numbered in opposite directions *(Figure 32–1).*

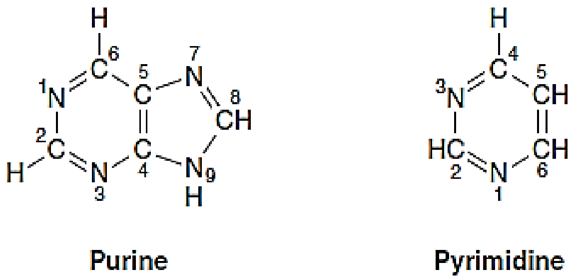
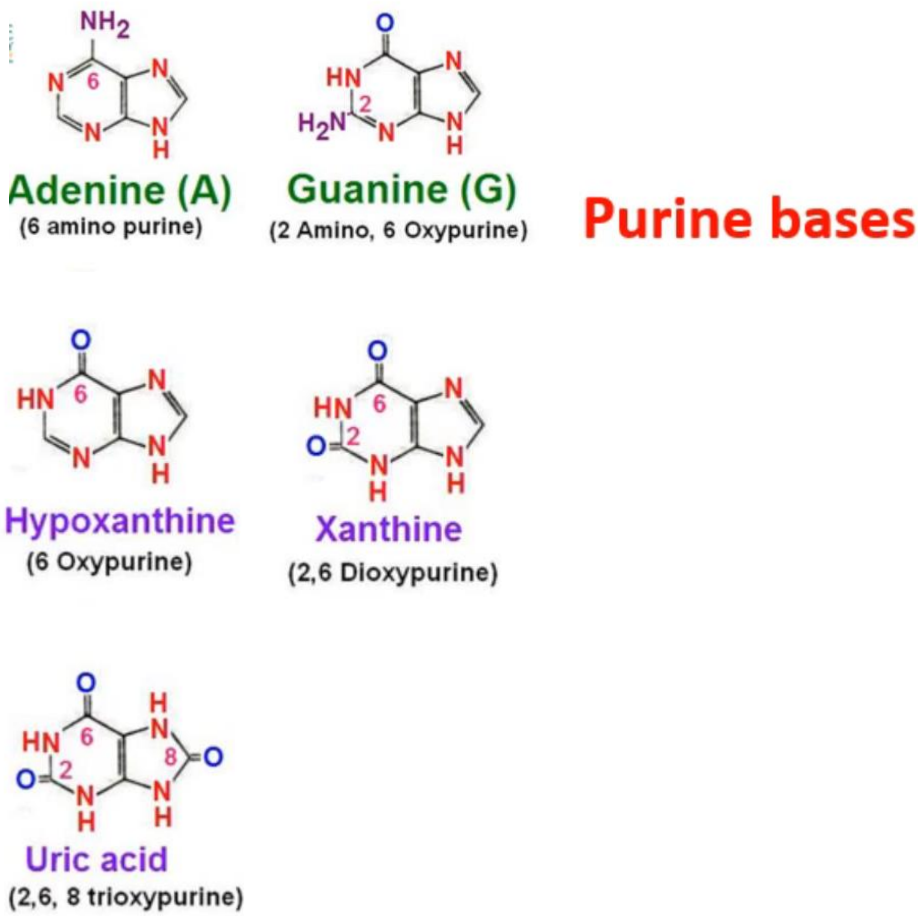


FIGURE 32–1 **Purine and pyrimidine.** The atoms are numbered according to the international system.

Purines or pyrimidine's with a ´NH_2 group are weak bases (pKa values 3-4), although the proton present at low pH is associated, not as one might expect with the exocyclic amino group, but with ring nitrogen, typically N1 of adenine, N7 of guanine, and N3 of cytosine. The planar character of purines and pyrimidine's facilitates their close association, or "stacking," that stabilizes double-stranded DNA.



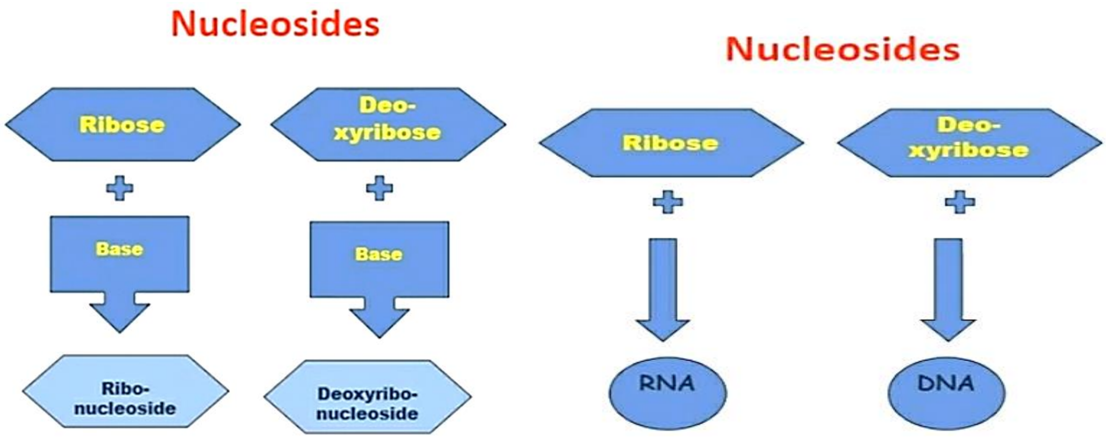
- **End products**
- **Hypoxanthine, xanthine and uric acid are the end products of adenine and guanine catabolism.**
- **Uric acid is excreted in urine**

- **Plasma concentration of uric acid is: 2-7 mg/dl.**

➢ *Nucleoside Are N-Glycosides*

Nucleosides are derivatives of purines and pyrimidine's that have a sugar linked to ring nitrogen of a purine or pyrimidine.

Nucleosides: are formed by the attachment of C_1 of the sugar to the nitrogen 1 of pyrimidine and nitrogen 9 of purine. (Figure 32–3).



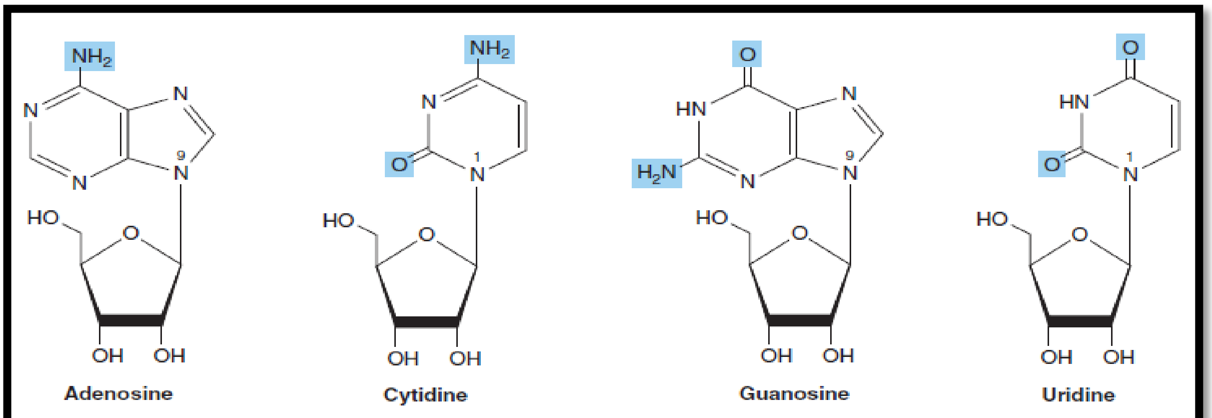
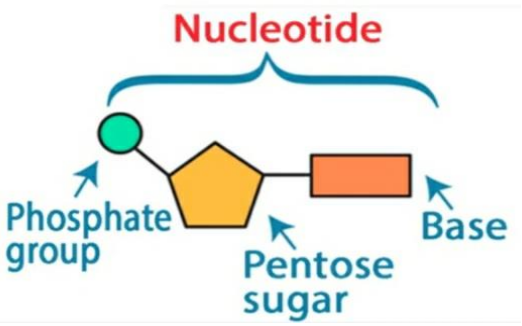
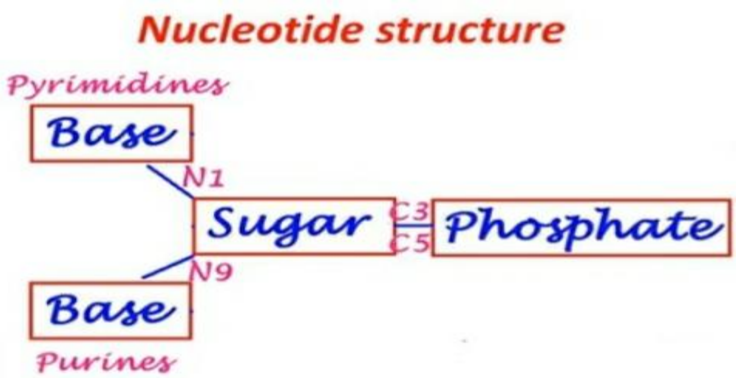


FIGURE 32–3 Ribonucleosides, drawn as the *syn* conformers.

➢ *Nucleotides Are Phosphorylated Nucleosides*

Mononucleotides are nucleosides with a phosphoryl group esterified to a hydroxyl group of the sugar.





Base	Nucleoside (Base + Sugar)	Nucleotide (Base + Sugar + Phosphate)
Adenine (A)	Adenosine	Adenosine monophosphate (AMP)
	Deoxyadenosine	Deoxyadenosine monophosphate (d.AMP)
Guanine (G)	Guanosine Deoxyguanosine	Guanosine monophosphate (GMP) Deoxyguanosine monophosphate (d.GMP)
Xanthine (X)	Xanthosine	Xanthosine monophosphate (XMP)
Hypoxanthine (1)	Inosine	Inosine monophosphate (IMP)
Cytosine (C)	Cytidine Deoxycytidine	Cytidine monophosphate (CMP) Deoxycytidine monophosphate (d.CMP)
Uracil (U)	Uridine	Uridine monophosphate (UMP)
Thymine (T)	Thymidine	Thymidine monophosphate (TMP)

functions of nucleotides

- **Building blocks of both DNA and RNA.**
- **free nucleotides and coenzymes.**

ATP

- **Nitrogenous base (adenine)**
- **Pentose sugar (Deoxyribose)**
- **one, two or three phosphate groups.**

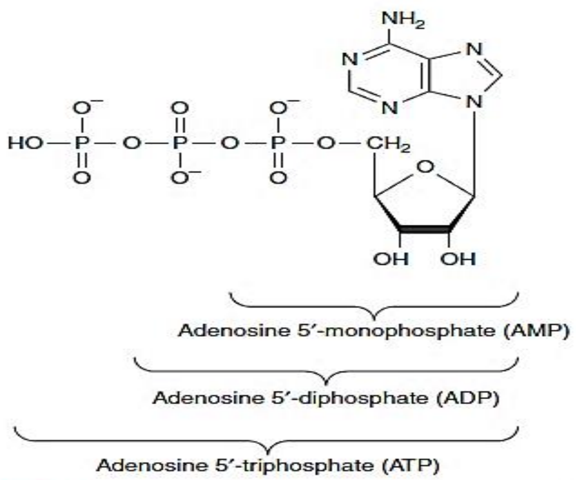
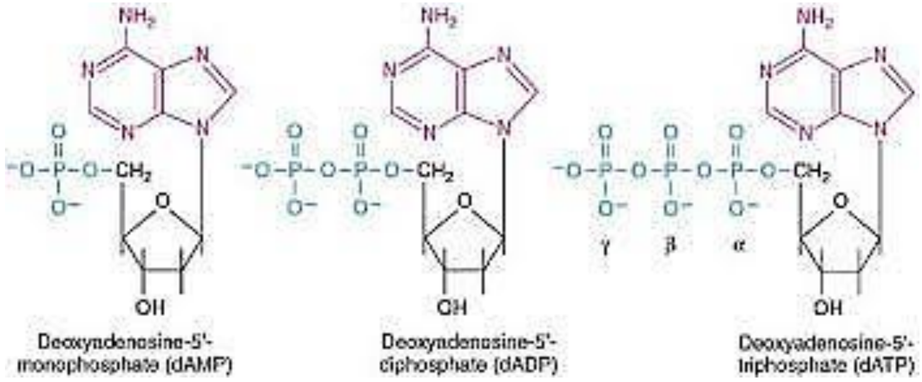


FIGURE 32–4 ATP, its diphosphate, and its monophosphate.

Nucleotides structure



Functions of Purines

ATP	Energy production
NAD and NADP	Hydrogen carriers
cAMP	regulator of carbohydrate and lipid metabolism).
Coenzyme A (CoASH)	Acid carrier
FMN and FAD	Hydrogen carriers
S-adenosyl methionine	methyl donor).

Functions of Pyrimidines

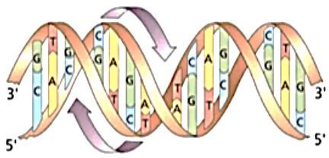
Uridine diphosphate glucose	UDP-Glucose
Uridine diphosphate galactose	Uridine diphosphate galactose
Cytidine diphosphate acylglycerol	CDP-Acylglycerol

Site of DNA

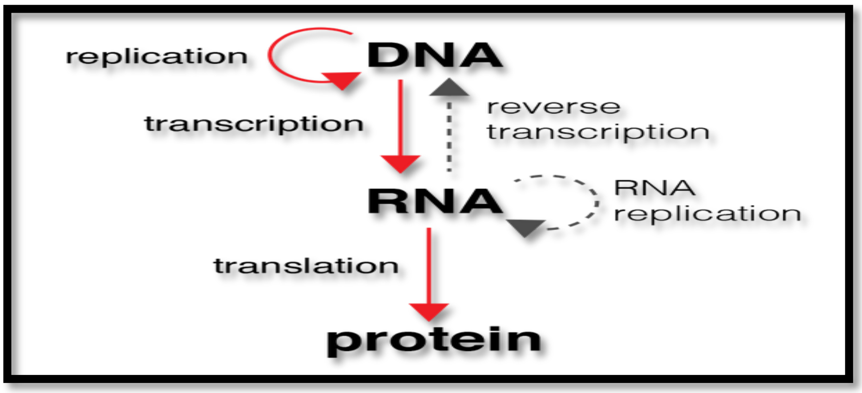
- ***Eukaryotic cells***
  - Nucleus
  - mitochondria
- ***Prokaryotes***
  - Free DNA
  - Plasmids

Functions of DNA

- *Replication (cell division).*
- *Expression of genetic information:*
  = protein synthesis (through RNAs).



Therefore, the Central Dogma of biology is:

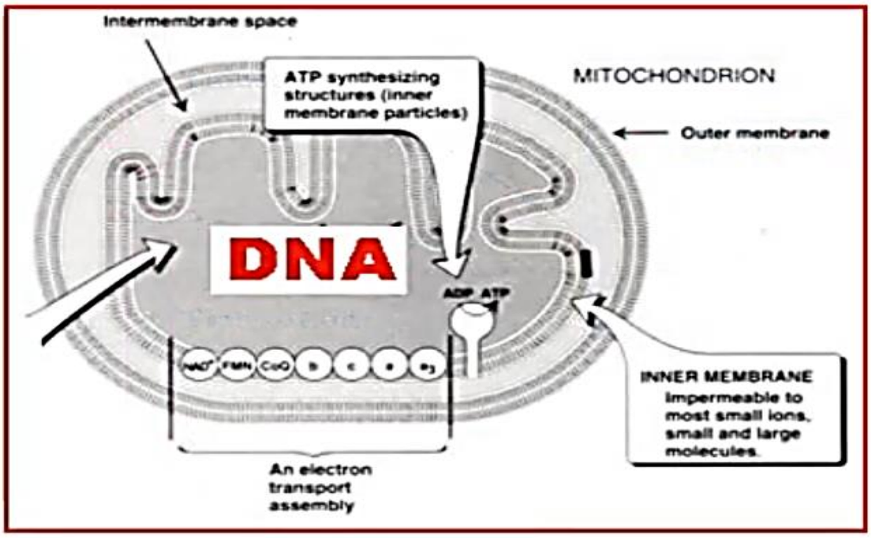


➢ ***Mitochondrial DNA*** There are **2-10 copies of:**

- **small circular**
- **double stranded DNA.**

1. mtDNA replication, transcription and translation of genetic code into proteins occur inside mitochondria.
2. mtDNA is responsible for synthesis of mitochondrial enzymes.
3. Mutation of mitochondrial DNA leads to some diseases e.g. myopathies.

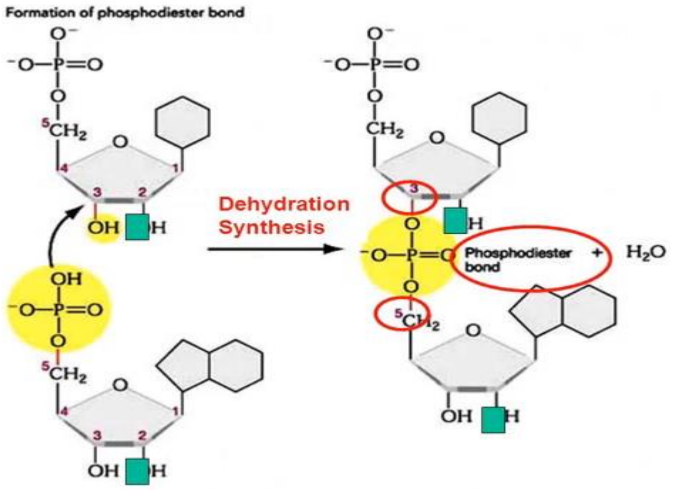
….. How many nucleotides in human DNA? Approximately 3 billion nucleotides



➢ *Phosphodiester bond*

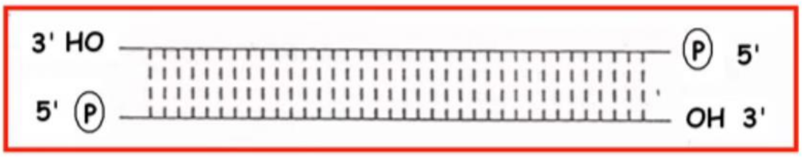
- The nucleotides are arranged in chains covalently linked together by 3', 5' phosphodiester bond between:
- 3-hydroxyl group of the pentose of one nucleotide and 5'- hydroxyl group of the pentose of the next nucleotide...

Note that Phosphodiester bond means one phosphate is linked to 2 sugars → 2 ester bonds.



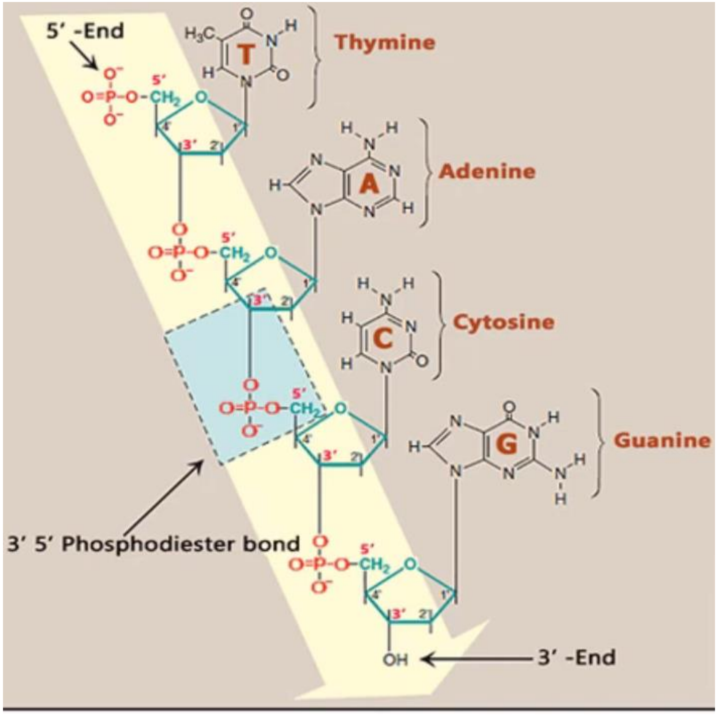
➢ *Structure of Nucleic acids*

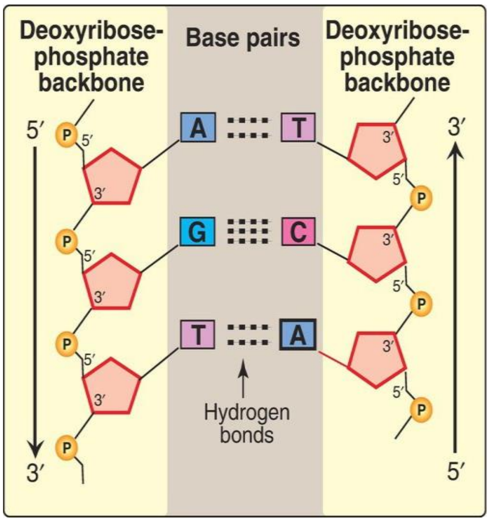
Human DNA consists of 2 strands (chains) of polynucleotides.



- **Phosphodiester bond**

Each polynucleotide chain has 2 terminals. At one terminal, phosphate is only attached to C_5 of first pentose. At the other one, phosphate is only attached to C_3 of last pentose. The nucleotides in the polynucleotide chain are always read in the 5'-3' direction.





Structure of DNA

- **DNA exists as a double stranded molecule in which the two strands form a double helix.**
- **The 2 strands are complementary not identical.**
- **The base pairs are held together by hydrogen bonds:**
  - ✓ **two between A and T,**
  - ✓ **three between G and C.**
- **Thus GC bonding is stronger than AT one.**

Types of RNAs: 3 Main Types & Other many types

All are polynucleotides joined by phosphodiester bonds.

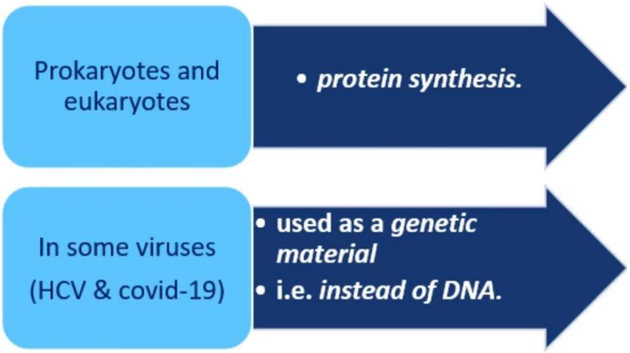
They also differ from each other in size, function and special structural modifications.

1. **mRNA Messenger RNA**
2. **tRNA Transfer RNA**
3. **rRNA Ribosomal RNA**

Structural Differences Between RNA & DNA

1. **They are smaller than DNA.**
2. **They contain ribose instead of deoxyribose.**
3. **They contain uracil instead of thymine.**

General Functions of RNAs

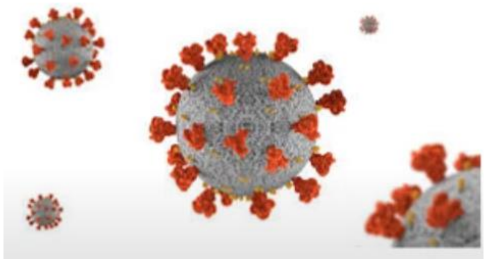


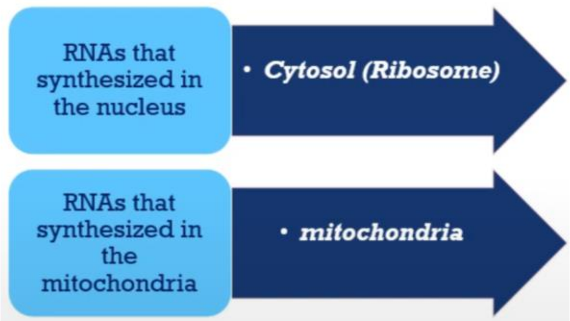
Clinical Correlation

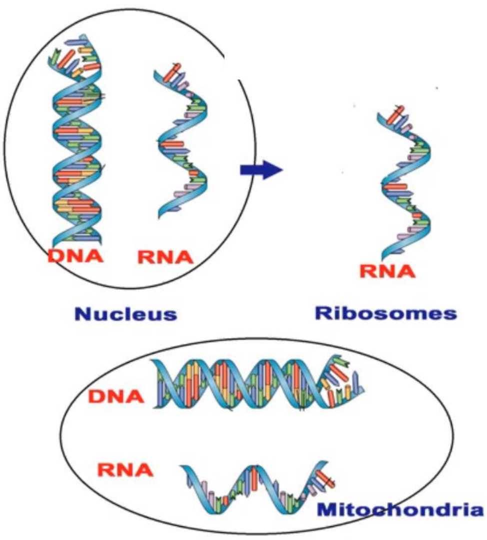
- ✓ **The genetic material of viruses are classified as either DNA or RNA viruses.**
- ✓ **The Corona (Covid 19) and the hepatitis C virus (HCV) are among RNA viruses that cause diseases in mammals and birds.**

Location of RNAs

1. **RNAs are synthesized in the nucleus. They perform their functions in the cytosol (ribosomes).**
2. **RNAs that are synthesized in the mitochondria, remain and perform their functions within this organelle.**



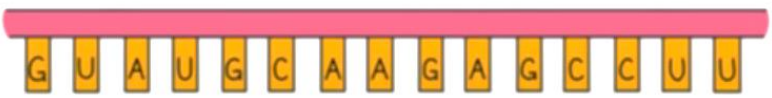




Types of RNA:

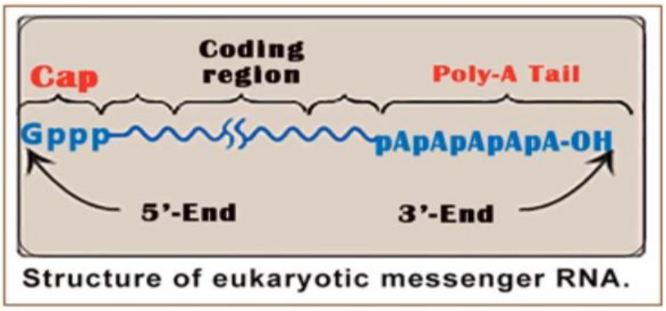
1. **mRNA Messenger RNA**

It is one strand RNA, composed of 400-4000 nucleotides.



Eukaryotic mRNA

Eukaryotic mRNA has special structural characters:

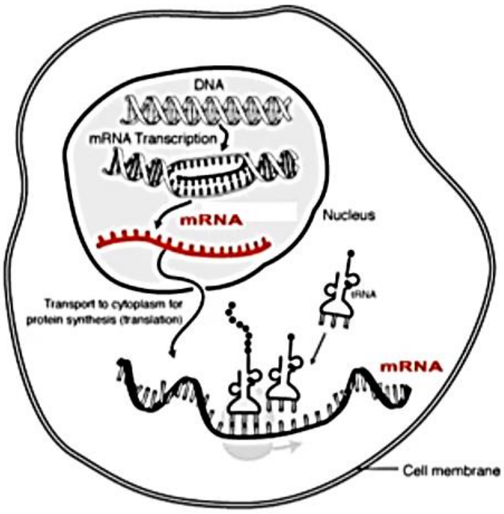


Structure of eukaryotic messenger RNA.

1. Long sequence of adenine on the 3' -end of RNA chain (poly A-tail).
2. Cap on the 5'-end. This cap is consisted of 7-methylguanosine attached through triphosphate linkage.

Function of mRNA

mRNA carries the genetic information from the DNA and is used as a template for protein synthesis.

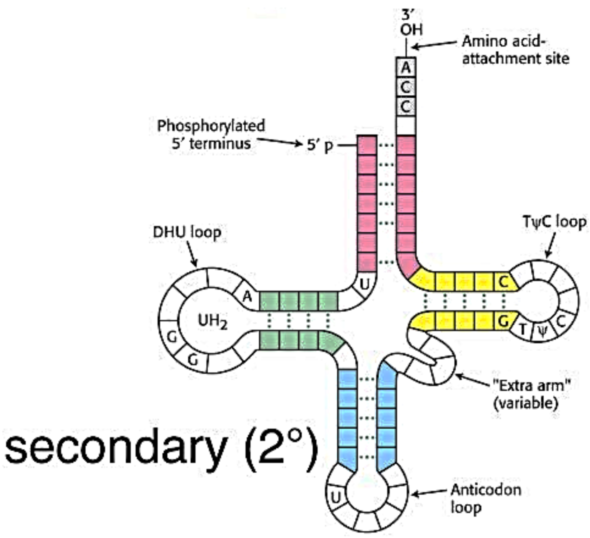


2. tRNA Transfer RNA
   - ✓ It is the smallest of RNA molecules.
   - ✓ t RNAs have between 73 and 93 nucleotides.

tRNA

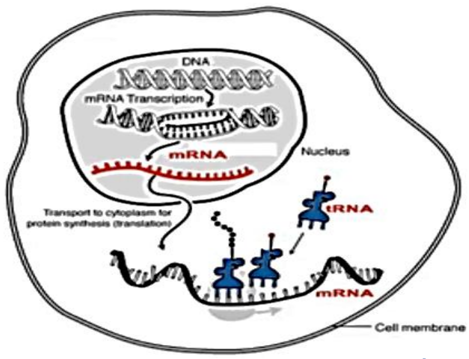
tRNA molecules have extensive interchain base pairing:

1. There is at least one specific type of tRNA molecule for each of 20 amino acids commonly found in proteins.



Function of tRNA

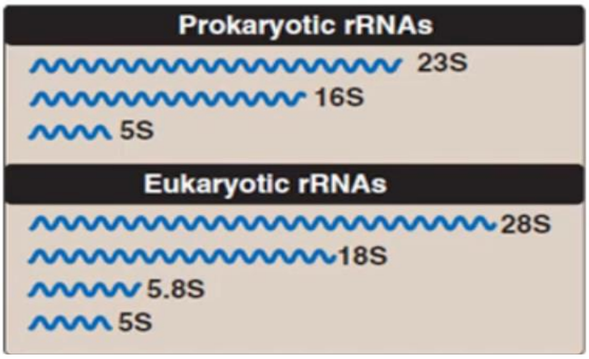
Each tRNA serves as adaptor molecule that carries its specific amino acid to the site of protein synthesis (the mechanism will be mentioned later in protein synthesis).



2. rRNA Ribosomal RNA
   a) In prokaryotes and eukaryotic mitochondria:
      There are three species of rRNA: 23S, 16S and 5S.

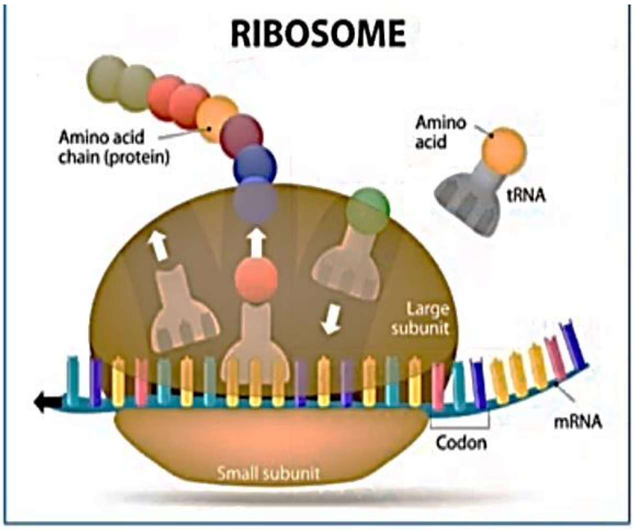
b) **In eukaryotic cytosol:** There are four species of rRNA: 28S, 18S, 5.8S and 5S.

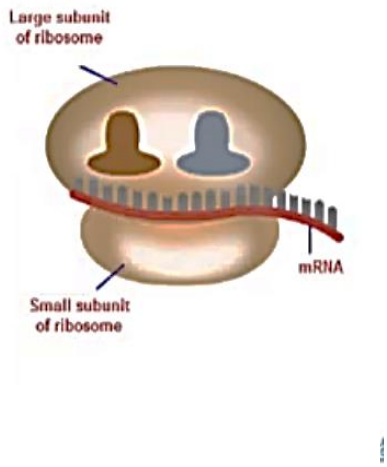
c) rRNAs combine with several different proteins forming the ribosomes.



Function of rRNA

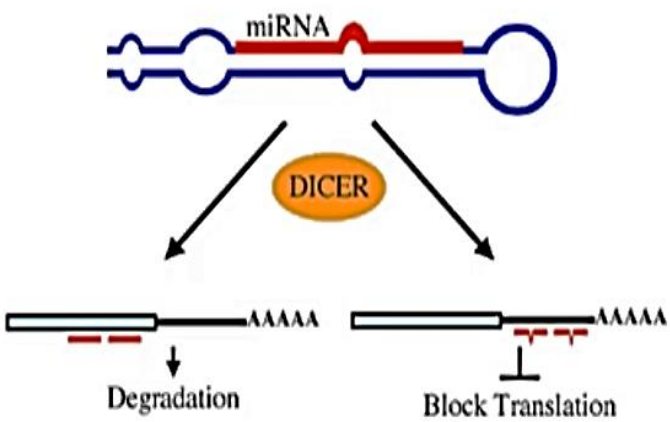
Ribosomes serve as the sites of protein synthesis.





miRNA

1. MicroRNAs (**miRNAs**) are a class of small, endogenous RNAs **of 21-25 nucleotides** in length.
2. They play an **important regulatory role** in **gene expression** post-transcriptionally.
3. They generally **bind to the 3'-UTR** (untranslated region) of their target mRNAs and **repress protein production** by destabilizing the mRNA and translational silencing.



4. There are now over **2000 miRNAs** that have been discovered in humans and it is believed that they collectively regulate one of the genes in the genome.
5. miRNAs have been linked to **many human diseases**.

Differences between DNA and RNA

	DNA	RNA
Site	• Nucleus • Mitochondria	Cytosol
Functions	• Carries genetic information. • (cell division) Replication of DNA • Synthesis of mRNAs (Transcription).	▪ Protein synthesis. ▪ Genetic material in some viruses
Structure	Polynucleotides contain: • Bases: Adenine, guanine, cytosine and **thymine** • Sugar: Deoxyribose.	Polynucleotides contain: • Bases: Adenine, guanine cytosine and **uracil**. • Sugar: Ribose.
Types	One type	3 Main types: • Messenger RNA • Transfer RNA • Ribosomal RNA
No. of strands	2 strands in the form of double helix	One strand

Nucleotides Are Poly functional Acids

The primary and secondary phosphoryl groups of nucleosides have pKa values of about 1.0 and 6.2, respectively. Nucleotides therefore bear significant negative charge at physiologic pH. The pKa values of the secondary phosphoryl groups are such that they can serve either as proton donors or as proton acceptors at pH values approximately two or more units above or below neutrality.

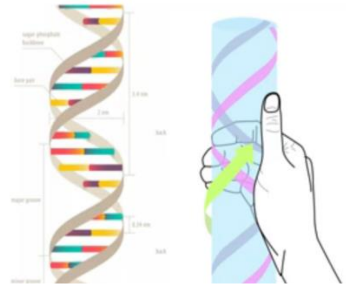
Nucleotides Serve Diverse Physiologic Functions

In addition to their roles as precursors of nucleic acids, ATP, GTP, UTP, CTP, and their derivatives each serve unique physiologic functions discussed in other chapters. Selected examples include the role of ATP as the principal biologic transducer of free energy, and the second messenger cAMP.

The mean intracellular concentration of ATP, the most abundant free nucleotide in mammalian cells, is about 1 mmol/L. Since little cAMP is required, the intracellular cAMP concentration (about 1 nmol/L) is six orders of magnitude below that of ATP. Other examples include adenosine 3′-phosphate-5′- phosphosulfate, the sulfate donor for sulfated proteoglycans and for sulfate conjugates of drugs; and the methyl group donor S adenosylmethionine. GTP serves as an allosteric regulator and as an energy source for protein synthesis, and cGMP serves as a second messenger in response to nitric oxide (NO) during relaxation of smooth muscle.

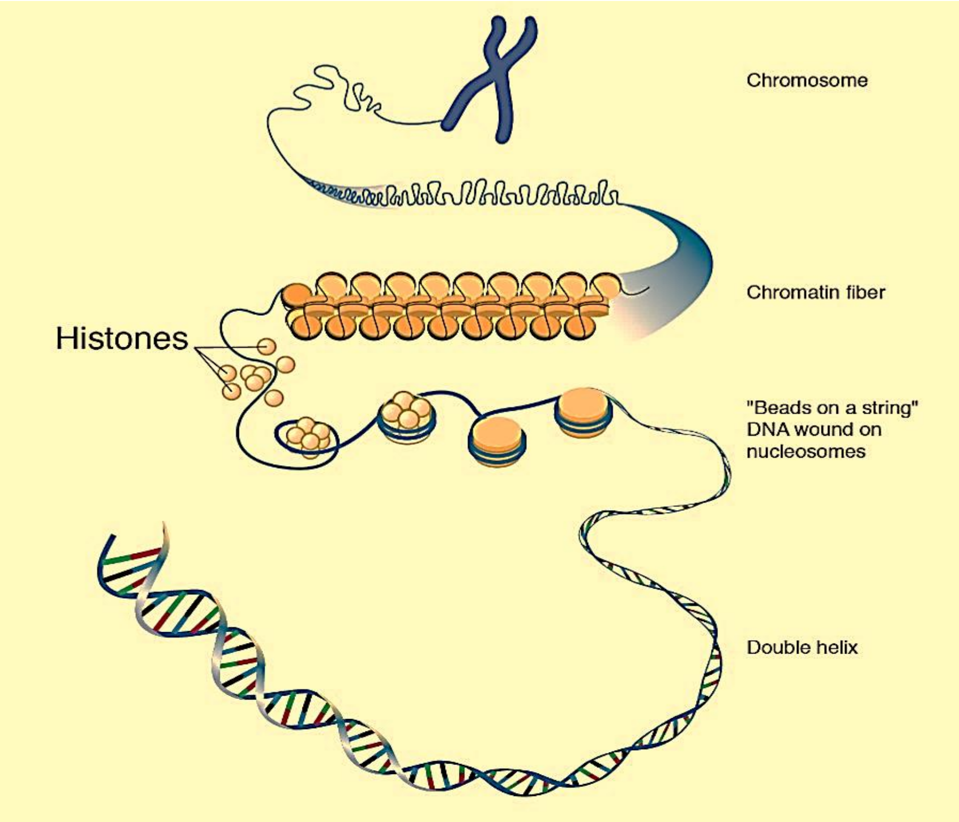
Double Helix

- 2 strands
- Right-Handed twist
- 10 to 10.5 base pairs per turn
- Major and minor grooves
- B-DNA



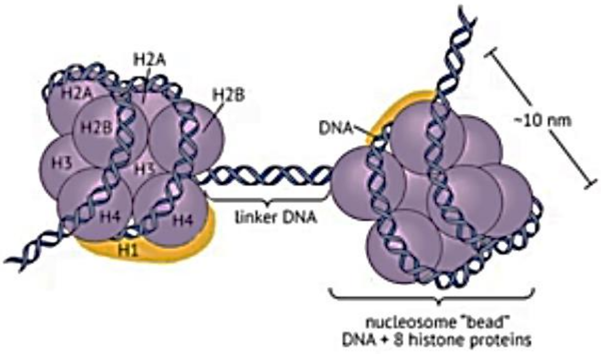
DNA Packaging

- Formation of chromatin
- A complex of DNA and proteins that forms chromosomes within the nucleus of eukaryotic cells
- Components:
  - A very long dsDNA
  - Histones
  - Non-histone proteins
  - Small quantity of RNA



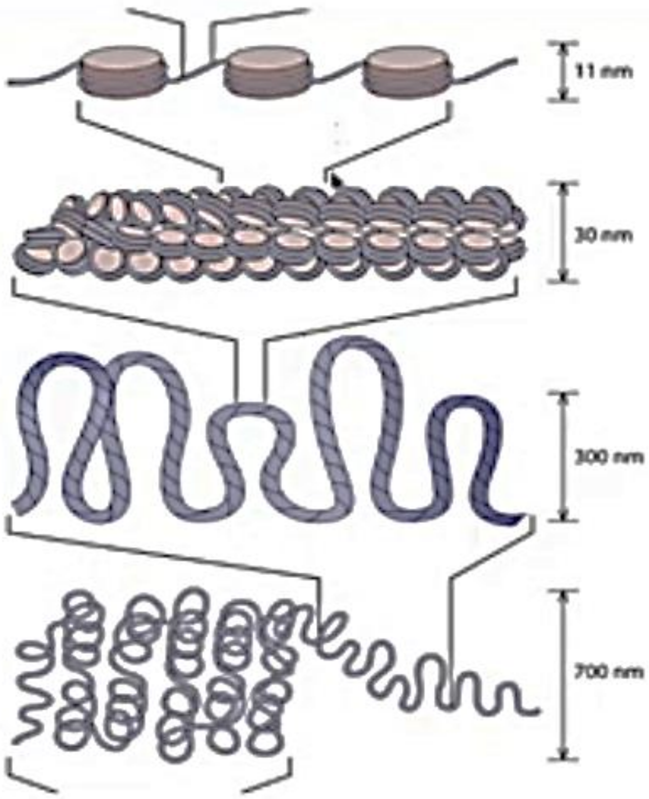
Nucleosomes

- Beads on a string
- 10 nm particle
- DNA wrapped aroud histones
- Histones (8 +ve Proteins):
  - 2 H2A
  - 2 H2B
  - 2 H3
  - 2 H4



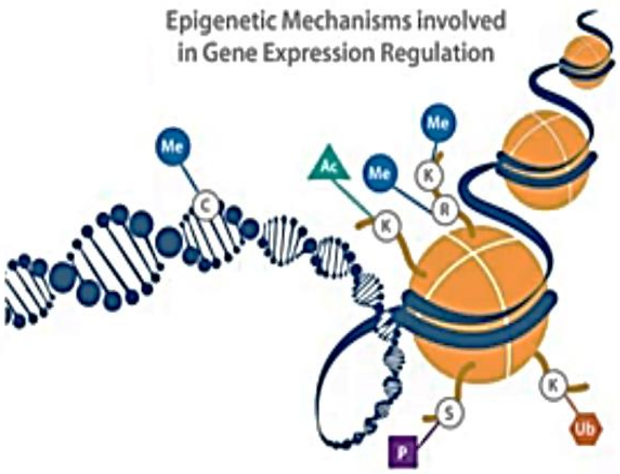
Further Packaging

- Nucleosomes together with H1 form 30 nm fibre
- Association with nuclear matrix (scaffolding proteins) to form looped domains



Histone Modifications

- At least 9 types of covalent modifications (Acetylation, Methylation, Phosphorylation, ubiquitylation, etc.)
- Play an important role in chromatin structure and function
- Acetylation
  - Activates transcription
- Methylation
  - Inactivates transcription



Genetic Code

- The genetic code is the group of codons that constitute the structure of different mRNAs.

- **During the process of protein synthesis each codon is recognized by >>>> a specific anticodon in the specific tRNA**
- **i.e. each base in the codon pairs with its specific complementary Base in the anticodon.**

Number &Types of codon

- **Number: Since, mRNA is formed of 4 nucleotides & each codon is formed of three nucleotides (or 3 nitrogenous bases).**
- **Therefore the number of possible codons = 4^3 =~64 different codon.**
- ***Types of codon:***
- **Three nonsense codons:**
- **Do not code for specific amino acids**
- **Utilized as termination signals (UAA, UA G& UGA)**
- ***61 sense codons:***
- **Code for the 20 amino acids present in proteins.**
- **Some amino acids have more than one codon which usually differs in the third base.**
- **There is one specific initiation codon (AUG) for methionine.**

Characteristics of the genetic code

1. Specificity:

- **That is, a particular codon always codes for the same amino acid.**

2. Degeneracy:

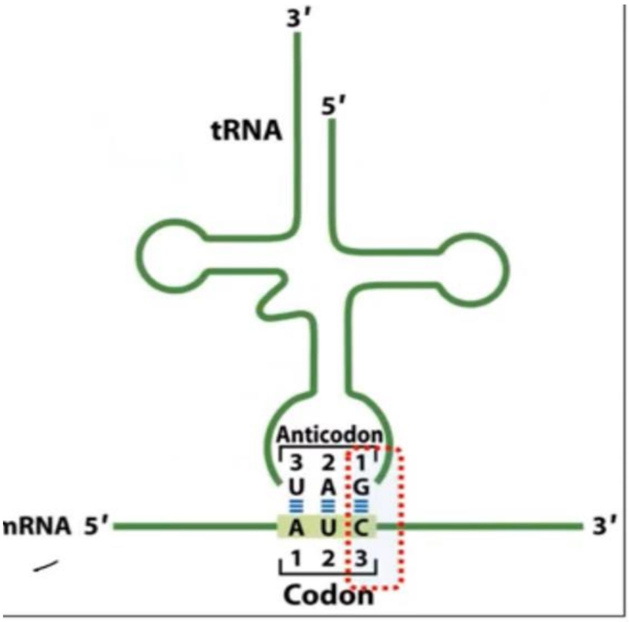
- **Although each codon corresponds to & single amino acid given amino acid may have more than one codon coding for it, e.g , arginine has six different codon**
- **Only Met and trp have just one codon.**

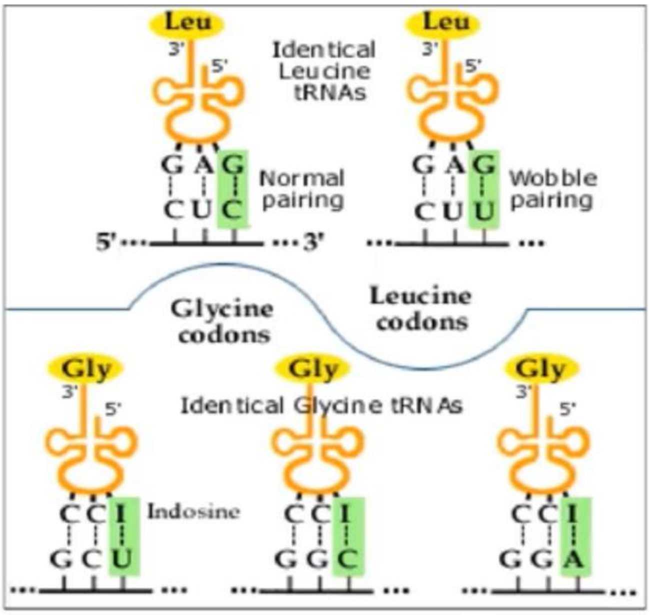
3. Universality:

- **That is its specificity has been conserved from very early stages of evolution with only slight differences in the manner in which the code is translated.**
- **This means that It is the same for all species i.e. plants animal with the exception of mitochondrial genome.**

4. Non over lapping and comma less:

- **That is, the code is read from a fixed starting point(AUG) as a continuous sequence of bases taken three at a time.**
- **For example AGCUGGAUACAU is as >>>>> AGC/UGG/AUA/CAU without any 'punctuation" between the codons.**

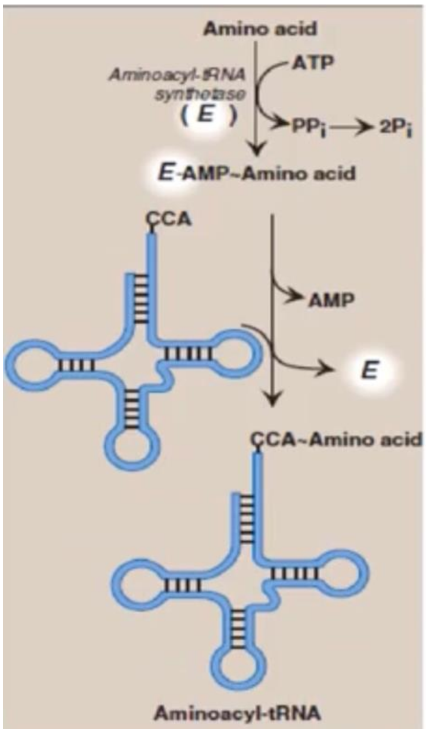




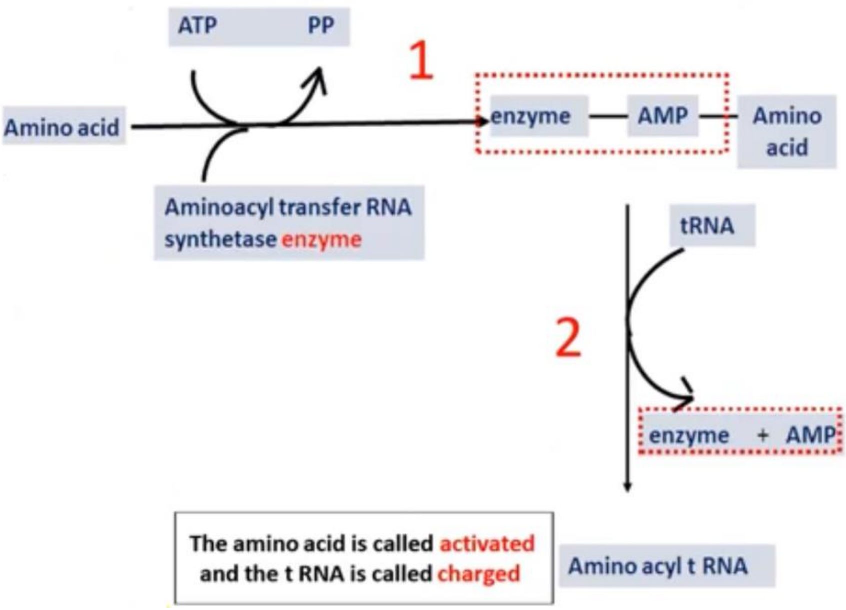
STEPS OF PROTEIN SYNTHESIS

1. **Activation of amino acids (Synthesis of Amino acyl-tRNA)**
2. **Synthesis of Polypeptide Chain (Translation);**

- **The process of translation in eukaryotic is classified into three phases:**
- **Initiation**
    - **Elongation**
        - **Termination**



I- Activation of amino acids & its carriage on tRNA (Synthesis of Aminoacyl-tRNA)



N.B.

- **There is specific tRNA for each of the 20 amino acids that enter in protein structure.**
- **Also, there are 2o different amino acyl-tRNA synthetases each one for can recognize the specific tRNA with its specific amino acid.**
- **The D arm of tRNA:**
  - **Important for Recognition of RNA by amino acyl tRNA synthetase enzyme.**
- **The 3' terminal (CCA) of tRNA :**
  - **For attachment of the amino acid as amino-acyl group.**
- **The thymidine-pseudo Uridine - cytidine (TΨC) arm of tRNA:**
  - **Important for binding of amino acyl-tRNA to ribosomal surface during protein synthesis.**
- **The anticodon loop of tRNA contains the anticodon which is:**
  - **Formed of three nucleotides.**
  - **Complementary and antiparallel to the specific codon in mRNA.**