UNIT – 4 🧬 NUCLEIC ACID METABOLISM AND GENETIC INFORMATION TRANSFER

POINTS TO BE COVERED IN THIS TOPIC

- ➤ BIOSYNTHESIS OF PURINE AND PYRIMIDINE NUCLEOTIDES
- ➤ CATABOLISM OF PURINE NUCLEOTIDES
- ➤ HYPERURICEMIA AND GOUT DISEASE
- ➤ ORGANIZATION OF MAMMALIAN GENOME
- ➤ STRUCTURE OF DNA AND RNA AND THEIR FUNCTIONS
- ➤ DNA REPLICATION (SEMI-CONSERVATIVE MODEL)
- ➤ TRANSCRIPTION OR RNA SYNTHESIS
- ➤ GENETIC CODE
- ➤ TRANSLATION OR PROTEIN SYNTHESIS AND INHIBITORS

🔬 INTRODUCTION

Nucleic acid metabolism encompasses the complex biochemical processes involved in the synthesis, degradation, and regulation of nucleic acids. These processes are fundamental to cellular function, genetic information storage, and protein synthesis. The metabolism of nucleotides and nucleic acids plays a crucial role in maintaining cellular homeostasis and enabling the transfer of genetic information from one generation to the next.

🧪 BIOSYNTHESIS OF PURINE AND PYRIMIDINE NUCLEOTIDES

PURINE NUCLEOTIDE BIOSYNTHESIS

Purine nucleotides are essential components of nucleic acids and serve as energy carriers and signaling molecules. The biosynthesis of purine nucleotides involves a complex multi-step process that occurs primarily in the liver, brain, and other metabolically active tissues.

De Novo Purine Synthesis Pathway:

The de novo synthesis of purine nucleotides begins with the formation of 5-phosphoribosyl-1-pyrophosphate (PRPP) and involves ten enzymatic steps to produce inosine monophosphate (IMP), the first purine nucleotide formed.

Key Steps in Purine Biosynthesis:

- Formation of 5-phosphoribosylamine from PRPP
- Sequential addition of glycine, formyl group, and glutamine
- Ring closure to form the purine ring structure
- Addition of aspartate and subsequent modifications
- Formation of IMP as the branch point nucleotide

Regulation of Purine Synthesis:

- Feedback inhibition by AMP and GMP
- Allosteric regulation of key enzymes
- Control by PRPP synthetase activity
- Coordinate regulation with pyrimidine synthesis

PYRIMIDINE NUCLEOTIDE BIOSYNTHESIS

Pyrimidine nucleotide synthesis follows a different pathway compared to

purine synthesis. The pyrimidine ring is synthesized first and then attached to the ribose phosphate moiety.

De Novo Pyrimidine Synthesis Pathway:

The synthesis begins with the formation of carbamoyl phosphate and involves six enzymatic steps to produce UMP, which serves as the precursor for other pyrimidine nucleotides.

Key Steps in Pyrimidine Biosynthesis:

- Formation of carbamoyl phosphate by carbamoyl phosphate synthetase II
- Condensation with aspartate to form carbamoyl aspartate
- Ring closure and oxidation to form orotic acid
- Attachment to PRPP to form orotidine monophosphate
- Decarboxylation to form UMP

Conversion to Other Pyrimidines:

- UMP → UDP → UTP through phosphorylation
- UDP → CDP through reduction and phosphorylation
- dUMP → dTMP through thymidylate synthase

CATABOLISM OF PURINE NUCLEOTIDES

The catabolism of purine nucleotides involves the breakdown of adenine and guanine nucleotides to their respective bases and ultimately to uric acid in humans. This process is essential for maintaining nucleotide pools and eliminating excess purines.

Purine Catabolism Pathway:

Adenine Nucleotide Catabolism:

- AMP → Adenosine (by 5'-nucleotidase)
- Adenosine → Inosine + NH_3 (by adenosine deaminase)
- Inosine → Hypoxanthine + Ribose (by purine nucleoside phosphorylase)
- Hypoxanthine → Xanthine (by xanthine oxidase)
- Xanthine → Uric acid (by xanthine oxidase)

Guanine Nucleotide Catabolism:

- GMP → Guanosine (by 5'-nucleotidase)
- Guanosine → Guanine + Ribose (by purine nucleoside phosphorylase)
- Guanine → Xanthine + NH_3 (by guanine deaminase)
- Xanthine → Uric acid (by xanthine oxidase)

Key Enzymes in Purine Catabolism:

- 5'-Nucleotidase: removes phosphate groups
- Adenosine deaminase: converts adenosine to inosine
- Purine nucleoside phosphorylase: cleaves nucleosides
- Xanthine oxidase: final steps producing uric acid

🦴 HYPERURICEMIA AND GOUT DISEASE

HYPERURICEMIA

Hyperuricemia is defined as an elevated level of uric acid in the blood, typically above 7.0 mg/dL in men and 6.0 mg/dL in women. This condition results from either overproduction of uric acid or decreased excretion by the kidneys.

Causes of Hyperuricemia:

Overproduction of Uric Acid:

- Increased purine catabolism
- Enhanced PRPP synthetase activity
- Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT)
- Increased cell turnover (malignancy, chemotherapy)
- Dietary factors (high purine intake)

Decreased Excretion of Uric Acid:

- Renal dysfunction
- Genetic defects in uric acid transporters
- Drug-induced interference with renal excretion
- Dehydration and acidosis

GOUT DISEASE

Gout is a metabolic disorder characterized by the deposition of monosodium urate crystals in joints and tissues, resulting from chronic

hyperuricemia.

Pathophysiology of Gout:

- Supersaturation of body fluids with uric acid
- Crystal formation and deposition in joints
- Inflammatory response to urate crystals
- Activation of complement and recruitment of neutrophils
- Release of inflammatory mediators

Clinical Manifestations:

- Acute gouty arthritis (typically affecting the great toe)
- Chronic tophaceous gout with crystal deposits
- Gouty nephropathy and kidney stones
- Joint deformity and disability in advanced cases

Treatment Approaches:

- Acute phase: NSAIDs, colchicine, corticosteroids
- Chronic phase: allopurinol (xanthine oxidase inhibitor)
- Dietary modifications to reduce purine intake
- Adequate hydration and lifestyle changes

🧬 ORGANIZATION OF MAMMALIAN GENOME

The mammalian genome represents a complex organizational structure that contains all the genetic information necessary for cellular function and organism development.

Genome Organization Features:

Nuclear DNA:

- Approximately 3.2 billion base pairs in humans
- Organized into 23 pairs of chromosomes
- Contains both coding and non-coding sequences
- Packaged with histones to form chromatin

Gene Structure:

- Exons: coding sequences that are expressed
- Introns: non-coding sequences removed during processing
- Promoter regions: control transcription initiation
- Enhancers and silencers: regulate gene expression

Non-coding Elements:

- Repetitive DNA sequences (45% of genome)
- Transposable elements and retrotransposons
- Pseudogenes and processed genes
- Regulatory sequences and spacer DNA

Mitochondrial DNA:

- Circular, double-stranded molecule (16,569 bp)
- Contains 37 genes (13 protein-coding, 22 tRNA, 2 rRNA)
- Maternally inherited
- High copy number per cell

Genome Component	Percentage	Function
Protein-coding genes	1-2%	Encode proteins
Introns	25%	Regulate gene expression
Repetitive elements	45%	Structural and regulatory
Intergenic regions	25-30%	Regulatory sequences

🔗 STRUCTURE OF DNA AND RNA AND THEIR FUNCTIONS

DNA STRUCTURE

Primary Structure:

- Composed of deoxyribonucleotides linked by 3'-5' phosphodiester bonds
- Four bases: Adenine (A), Guanine (G), Cytosine (C), Thymine (T)
- Sugar component: 2'-deoxyribose
- Phosphate groups provide negative charge

Secondary Structure (Double Helix):

- Two antiparallel polynucleotide strands
- Complementary base pairing (A-T, G-C)
- Major and minor grooves
- Right-handed helix with 10 base pairs per turn

Tertiary Structure:

- Supercoiling and chromatin organization
- Association with histone proteins
- Formation of nucleosomes and higher-order structures

Functions of DNA:

- Storage of genetic information
- Template for DNA replication
- Template for RNA synthesis (transcription)
- Regulation of gene expression
- Inheritance of traits from parents to offspring

RNA STRUCTURE

Primary Structure:

- Composed of ribonucleotides linked by 3'-5' phosphodiester bonds
- Four bases: Adenine (A), Guanine (G), Cytosine (C), Uracil (U)
- Sugar component: ribose
- Generally single-stranded

Secondary Structure:

- Formation of hairpin loops and stem structures
- Base pairing within the same molecule
- Pseudoknots and bulges
- Complex three-dimensional folding

Types and Functions of RNA:

RNA Type	Function	Location
mRNA	Carries genetic code	Nucleus/Cytoplasm
tRNA	Amino acid transport	Cytoplasm
rRNA	Ribosome structure	Ribosomes
miRNA	Gene regulation	Cytoplasm
snRNA	mRNA processing	Nucleus

Messenger RNA (mRNA):

- Carries genetic information from DNA to ribosomes
- Contains codons that specify amino acids
- Subject to processing (capping, polyadenylation, splicing)
- Relatively short half-life

Transfer RNA (tRNA):

- Cloverleaf secondary structure
- Contains anticodon complementary to mRNA codons
- Carries specific amino acids for protein synthesis
- Modified bases enhance stability and function

Ribosomal RNA (rRNA):

- Structural and catalytic component of ribosomes
- Forms peptide bonds (ribozyme activity)
- Highly conserved across species
- Processed from larger precursor molecules

🔄 DNA REPLICATION (SEMI-CONSERVATIVE MODEL)

DNA replication is the process by which a cell duplicates its DNA prior to cell division, ensuring that each daughter cell receives an identical copy of the genetic material.

SEMI-CONSERVATIVE MODEL

Meselson-Stahl Experiment: The semi-conservative model of DNA replication was established through elegant experiments demonstrating that each new DNA molecule consists of one original (parental) strand and one newly synthesized strand.

Key Principles:

- Each strand of the double helix serves as a template
- New strands are synthesized complementary to templates
- Parental strands remain intact in daughter molecules
- Results in two identical DNA molecules from one original

MECHANISM OF DNA REPLICATION

Initiation:

- Recognition of origin of replication (ori)
- Unwinding of DNA by helicase enzymes
- Formation of replication bubble
- Binding of single-strand binding proteins
- Primer synthesis by primase

Elongation:

Leading Strand Synthesis:

- Continuous synthesis in 5' to 3' direction
- DNA polymerase adds nucleotides to 3'-OH group
- Single primer required for entire strand
- Proceeds toward replication fork

Lagging Strand Synthesis:

- Discontinuous synthesis in short fragments (Okazaki fragments)
- Multiple primers required
- Synthesis away from replication fork
- Fragments later joined by DNA ligase

Key Enzymes in DNA Replication:

- DNA helicase: unwinds double helix
- DNA primase: synthesizes RNA primers
- DNA polymerase: adds nucleotides to growing strand
- DNA ligase: joins Okazaki fragments
- Topoisomerase: relieves tension from unwinding

Termination:

- Meeting of replication forks
- Removal of RNA primers
- Filling of gaps by DNA polymerase

- Final ligation to complete replication

Proofreading and Error Correction:

- 3' to 5' exonuclease activity of DNA polymerase
- Immediate correction of misincorporated nucleotides
- Mismatch repair systems for post-replication correction
- Overall error rate: 1 in 10^{10} nucleotides

📝 TRANSCRIPTION OR RNA SYNTHESIS

Transcription is the process by which RNA is synthesized using DNA as a template. This process is essential for gene expression and occurs in the nucleus of eukaryotic cells.

PROCESS OF TRANSCRIPTION

Initiation:

- Recognition of promoter sequences by RNA polymerase
- Binding of transcription factors
- Formation of transcription initiation complex
- Unwinding of DNA at transcription start site
- Beginning of RNA synthesis

Elongation:

- RNA polymerase moves along DNA template strand
- Addition of ribonucleoside triphosphates to growing RNA chain
- Formation of RNA-DNA hybrid (transcription bubble)

- Continuous unwinding and rewinding of DNA

Termination:

- Recognition of termination signals
- Release of completed RNA transcript
- Dissociation of RNA polymerase from DNA
- Restoration of double-stranded DNA structure

TYPES OF RNA POLYMERASES (EUKARYOTES)

RNA Polymerase I:

- Transcribes most ribosomal RNA genes
- Located in the nucleolus
- Produces large precursor rRNA (45S)

RNA Polymerase II:

- Transcribes all protein-coding genes
- Produces mRNA precursors
- Also transcribes some small RNAs (microRNAs, long non-coding RNAs)

RNA Polymerase III:

- Transcribes transfer RNA genes
- Transcribes 5S ribosomal RNA
- Produces other small RNAs (U6 snRNA)

RNA PROCESSING (EUKARYOTES)

5' Capping:

- Addition of 7-methylguanosine cap
- Protection from 5' exonuclease degradation
- Enhancement of translation initiation
- Nuclear export signal

3' Polyadenylation:

- Addition of poly(A) tail (200-300 adenine residues)
- Stabilization of mRNA
- Enhancement of translation efficiency
- Quality control mechanism

Splicing:

- Removal of introns from pre-mRNA
- Joining of exons to form mature mRNA
- Mediated by spliceosome complex
- Alternative splicing increases protein diversity

🔤 GENETIC CODE

The genetic code represents the relationship between the nucleotide sequence of DNA/RNA and the amino acid sequence of proteins. This universal code enables the translation of genetic information into functional proteins.

CHARACTERISTICS OF GENETIC CODE

Triplet Nature:

- Each codon consists of three nucleotides
- 4^3 = 64 possible codons for 20 amino acids
- Provides redundancy and error tolerance

Degeneracy:

- Most amino acids are specified by more than one codon
- Third position often shows variability (wobble position)
- Reduces impact of mutations on protein function

Universality:

- Same genetic code used by most living organisms
- Minor variations in mitochondrial and some bacterial codes
- Evidence for common evolutionary origin

Non-overlapping:

- Each nucleotide belongs to only one codon
- Reading frame determines amino acid sequence
- Frame-shift mutations alter entire downstream sequence

CODON ASSIGNMENTS

Start Codon:

- AUG: initiates protein synthesis

- Codes for methionine in eukaryotes
- Codes for N-formylmethionine in prokaryotes

Stop Codons:

- UAG (amber), UAA (ochre), UGA (opal)
- Signal termination of protein synthesis
- Recognized by release factors

Standard Genetic Code Table:

1st Base	2nd Base	3rd Base	Amino Acid
UUU, UUC	U	U, C	Phenylalanine
UUA, UUG	U	A, G	Leucine
UCU, UCC, UCA, UCG	C	All	Serine
UAU, UAC	A	U, C	Tyrosine
UGU, UGC	G	U, C	Cysteine

🏭 TRANSLATION OR PROTEIN SYNTHESIS AND INHIBITORS

Translation is the process by which the genetic code in mRNA is decoded to synthesize proteins. This process occurs at ribosomes and involves the coordinated action of multiple RNA and protein factors.

MECHANISM OF TRANSLATION

Initiation:

- Recognition of mRNA by small ribosomal subunit

- Binding of initiator tRNA (Met-tRNA) to start codon
- Assembly of complete ribosome (large and small subunits)
- Formation of initiation complex

Elongation:

- Entry of aminoacyl-tRNA into A site
- Peptide bond formation by peptidyl transferase
- Translocation of tRNA from A to P to E sites
- Movement of ribosome along mRNA (3 nucleotides per step)

Termination:

- Recognition of stop codon by release factors
- Hydrolysis of peptidyl-tRNA bond
- Release of completed polypeptide chain
- Dissociation of ribosomal subunits

RIBOSOME STRUCTURE AND FUNCTION

Prokaryotic Ribosomes (70S):

- Small subunit: 30S (16S rRNA + proteins)
- Large subunit: 50S (23S and 5S rRNA + proteins)
- Three binding sites: A (aminoacyl), P (peptidyl), E (exit)

Eukaryotic Ribosomes (80S):

- Small subunit: 40S (18S rRNA + proteins)

- Large subunit: 60S (28S, 5.8S, and 5S rRNA + proteins)
- More complex than prokaryotic ribosomes

TRANSLATION INHIBITORS

Antibiotics Targeting Prokaryotic Ribosomes:

30S Ribosome Inhibitors:

- Streptomycin: causes misreading of mRNA
- Chloramphenicol: inhibits peptidyl transferase
- Tetracycline: blocks aminoacyl-tRNA binding
- Spectinomycin: inhibits translocation

50S Ribosome Inhibitors:

- Chloramphenicol: inhibits peptide bond formation
- Erythromycin: blocks translocation
- Puromycin: causes premature chain termination
- Lincomycin: inhibits peptidyl transferase

Eukaryotic Translation Inhibitors:

- Cycloheximide: inhibits peptidyl transferase
- Diphtheria toxin: modifies elongation factor
- Ricin: inactivates 60S ribosomal subunit
- Puromycin: affects both prokaryotic and eukaryotic systems

POST-TRANSLATIONAL MODIFICATIONS

Common Modifications:

- Proteolytic cleavage of signal peptides
- Phosphorylation and dephosphorylation
- Glycosylation (N-linked and O-linked)
- Acetylation and methylation
- Ubiquitination for protein degradation

Protein Folding and Quality Control:

- Chaperone-assisted folding
- Disulfide bond formation
- Quality control in endoplasmic reticulum
- Degradation of misfolded proteins

The intricate processes of nucleic acid metabolism and genetic information transfer form the foundation of molecular biology and are essential for understanding cellular function, inheritance, and disease mechanisms. These processes are highly regulated and interconnected, ensuring the faithful transmission and expression of genetic information across generations.