

vi. Structure, function and metabolisms of nucleic acids, DNA and RNA

Introduction to Nucleic Acids

1. Definition and Importance

- **Nucleic acids** (DNA and RNA) are polymers of nucleotides, serving as the repositories of genetic information (DNA) and mediators of gene expression (RNA).
- Underpin virtually all aspects of cell function—inheritance, protein synthesis, gene regulation.

2. Nucleotide Composition

- Each nucleotide consists of a **nitrogenous base** (purine or pyrimidine), a **five-carbon sugar** (ribose or deoxyribose), and one or more **phosphate groups**.
- **Purines:** Adenine (A), Guanine (G).
- **Pyrimidines:** Cytosine (C), Thymine (T; in DNA), Uracil (U; in RNA).

3. Types of Nucleic Acids

- **Deoxyribonucleic Acid (DNA):** Typically double-stranded, long-term information storage.
- **Ribonucleic Acid (RNA):** Usually single-stranded, diverse roles in protein synthesis (mRNA, rRNA, tRNA) and regulation (miRNA, lncRNA, etc.).

DNA: Structure and Function

1. Double Helix Model

- **Watson-Crick Structure** (B-form DNA): Two antiparallel polynucleotide strands twisted into a right-handed helix.
- Bases pair via hydrogen bonds (A-T with 2 H-bonds, G-C with 3 H-bonds).
- **Major and Minor Grooves:** Binding sites for proteins (transcription factors, enzymes).

2. Forms of DNA

- **B-DNA:** Most common physiological form.
- **A-DNA:** More compact, right-handed, often in dehydrated samples or RNA-DNA hybrids.
- **Z-DNA:** Left-handed helix, occurs in certain GC-rich regions; implicated in regulatory roles.

3. DNA Packaging

- **Prokaryotes:** Single circular chromosome supercoiled by **DNA gyrase**, packaged in the nucleoid.
- **Eukaryotes:** Multiple linear chromosomes wound around histones, forming **nucleosomes**; further coiling yields higher-order chromatin structures.

4. DNA Functions

- **Genetic Information Storage:** Encodes genes, regulatory sequences.
- **Transmission and Replication:** Ensures faithful inheritance.
- **Long-Term Stability:** Double-stranded structure and repair mechanisms protect genetic content over generations.

DNA Metabolism

DNA Replication

1. Semi-Conservative Mechanism

- Each daughter molecule contains one parental strand and one newly synthesized strand (Meselson-Stahl experiment).
- **Bidirectional** from **origins of replication; forks** proceed in opposite directions.

2. Key Enzymes and Proteins

- **Helicase:** Unwinds the double helix.
- **Single-Strand Binding Proteins (SSBs):** Stabilize unwound template strands.
- **DNA Polymerase:** Catalyzes nucleotide addition in the 5'→3' direction. Different polymerases in prokaryotes (Pol I, III) vs. eukaryotes (Pol α , δ , ϵ).
- **Primase:** Synthesizes short RNA primers.
- **Ligase:** Joins Okazaki fragments on the lagging strand.

3. Leading vs. Lagging Strands

- **Leading Strand:** Synthesized continuously.
- **Lagging Strand:** Discontinuous synthesis forms **Okazaki fragments**, later joined by DNA ligase.

4. High Fidelity and Proofreading

- DNA polymerases often have **3'→5' exonuclease** activity to correct misincorporated nucleotides.
- The **Mismatch Repair** system further enhances accuracy.

DNA Repair

1. Types of Damage

- **Spontaneous** (depurination, deamination), **UV-induced** (thymine dimers), **chemical mutagens**, **ionizing radiation** (strand breaks).

2. Major Repair Pathways

- **Base Excision Repair (BER):** Removes damaged bases (e.g., uracil in DNA) via DNA glycosylases, followed by endonuclease and polymerase fill-in.
- **Nucleotide Excision Repair (NER):** Fixes bulky lesions (thymine dimers).
- **Mismatch Repair (MMR):** Corrects replication errors (mismatched bases).
- **Double-Strand Break Repair:** Non-homologous end joining (NHEJ) or homologous recombination (HR).

RNA: Structure and Types

1. RNA Structure

- Generally single-stranded with **ribose** sugar (2'-OH) and **uracil** instead of thymine.
- Can form **secondary structures** (hairpins, stem-loops) and **tertiary structures** (tRNA cloverleaf, ribozymes).

2. Classes of RNA

3. Messenger RNA (mRNA)

- Encodes protein sequences. In eukaryotes, typically **monocistronic**; in prokaryotes, often **polycistronic**.
- Eukaryotic mRNAs have a **5' cap** and **3' poly(A) tail**.

4. Ribosomal RNA (rRNA)

- Major structural and catalytic component of **ribosomes**.
- In eukaryotes, 28S, 18S, 5.8S, 5S rRNAs. In prokaryotes, 23S, 16S, 5S rRNAs.

5. Transfer RNA (tRNA)

- Adaptor molecules, each carrying a specific amino acid to the ribosome.
- Anticodon loop pairs with mRNA codon, ensuring correct amino acid incorporation.

6. Non-Coding Regulatory RNAs

- **MicroRNAs (miRNAs), small interfering RNAs (siRNAs):** Gene silencing via mRNA cleavage or translational repression.
- **Long noncoding RNAs (lncRNAs):** Chromatin remodeling, transcriptional regulation.
- **snRNA, snoRNA:** Involved in splicing (snRNPs) and rRNA modification (snoRNPs).

RNA Metabolism

Transcription

1. Prokaryotic Transcription

- Single **RNA polymerase** (σ factor confers promoter specificity).
- **Promoters:** -35 and -10 (Pribnow box) regions.
- **Termination:** Rho-dependent or Rho-independent (hairpin loop + U-tract).

2. Eukaryotic Transcription

- **Three RNA Polymerases:**
 - **Pol I:** rRNA.
 - **Pol II:** mRNA, some snRNA.
 - **Pol III:** tRNA, 5S rRNA, small RNAs.
- **Promoters and Enhancers:** TATA box, GC box, etc.
- **General Transcription Factors (TFIIX)** assemble into a preinitiation complex.

- **Termination:** Pol II transcripts cleaved past poly(A) signal; coupled with polyadenylation.

Post-Transcriptional Modifications

1. 5' Capping

- Addition of 7-methylguanosine cap to 5' end of nascent mRNA.
- Protects mRNA from degradation, aids ribosome binding.

2. 3' Polyadenylation

- Poly(A) polymerase adds ~50–250 adenines to 3' end.
- Stabilizes mRNA, facilitates nuclear export.

3. Splicing

- Removes **introns**, ligates, exons. Mediated by the **spliceosome** (snRNPs U1, U2, U4, U5, U6).
- **Alternative Splicing:** Creates multiple protein isoforms from a single gene.

RNA Degradation and Turnover

- **Exoribonucleases** degrade RNA from 5'→3' or 3'→5' directions.
- **RNA interference** pathways (RISC, Dicer) can target specific mRNAs for degradation.

Nucleotide Biosynthesis and Degradation

Purine and Pyrimidine Synthesis

1. De Novo Pathways

- **Purine Synthesis:** Built on a ribose phosphate scaffold (PRPP → IMP → AMP/GMP). Key regulatory enzyme is **glutamine-PRPP amidotransferase**.
- **Pyrimidine Synthesis:** Carbamoyl phosphate + aspartate → orotate → UMP → UTP → CTP. The first enzyme is **carbamoyl phosphate synthetase II** (cytosolic).

2. Salvage Pathways

- Recycling free bases (hypoxanthine, guanine, adenine) via **HGPRT** or adenine phosphoribosyltransferase.
- Lesch-Nyhan syndrome (HGPRT deficiency) exemplifies salvage pathway failure.

Nucleotide Degradation

1. Purine Degradation

- Ultimately forms **uric acid**. Excess → gout (hyperuricemia, crystal deposition in joints).

2. Pyrimidine Degradation

- Broken down to simpler molecules (β -alanine, β -aminoisobutyrate), less clinically problematic.

3. Regulation

- Feedback inhibition of key enzymes ensures balanced purine/pyrimidine pools.

Overall Biological Significance

1. Genetic Information Flow

- **Central Dogma:** DNA → RNA → Protein. Nucleic acids coordinate heredity and phenotype expression.
- **Transcriptional and Post-Transcriptional Regulation:** Vital for cell differentiation, adaptation, disease states (e.g., cancer).

2. Clinical Applications

- **Nucleic Acid Therapies:** Antisense oligonucleotides, RNAi-based drugs, mRNA vaccines.
- **Diagnostic Tools:** PCR, qRT-PCR, sequencing, microarrays.
- **Inherited Disorders:** E.g., **Splice site mutations** causing β -thalassemia, or defects in DNA repair leading to cancer predisposition.

3. Pharmacological Targets

- Many antibiotics (e.g., rifampin, fluoroquinolones) target bacterial DNA/RNA metabolism.
- Anticancer drugs (e.g., 5-FU, methotrexate) inhibit nucleotide biosynthesis.



Concluding Remarks

Nucleic acids—DNA as the stable genetic blueprint and RNA in its myriad functional forms—are central to life's molecular processes. Their **structures** (helices, base pairing, secondary/tertiary folds) govern how genetic information is stored, replicated, transcribed, and translated. The cell's **metabolic** pathways for nucleotides (de novo and salvage synthesis, catabolism) enable dynamic regulation of nucleotide pools, ensuring fidelity and adaptability under changing conditions.

The sophisticated regulation of **DNA replication, repair, transcription, and RNA processing** reflects evolution's solutions to preserve genomic integrity while facilitating complexity in gene expression. Understanding these core biochemistry and molecular biology concepts is paramount for fields as diverse as **genetics, medicine, pharmacology, and biotechnology**, all harnessing nucleic acids for diagnostics, therapeutics, and the quest to unravel life's molecular foundations.

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