Molecular Chemistry

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“Central dogma” Of Molecular Biology

- Each cell is specialized, expressing only those functions that are required for it to perform.
- DNA replicate and express only precise information.
STRUCTURE OF NUCLEOTIDES

PO₄ – PO₄ – PO₄ – CH₂

N – glycosidic bond

Nucleoside

Nucleoside monophosphate

Nucleoside diphosphate

Nucleoside Triphosphate

Nucleotides
Purines

Adenine (A)
DNA
RNA

Guanine (G)
DNA
RNA

Modified Purine

Hypoxanthine

Xanthine
Pyrimidines

Cytosine (C)
DNA
RNA

Thymine (T)
DNA

Uracil (U)
RNA

Modified Pyrimidine

3-methylcytidine

pseudouridine

dihydouridine
To which molecule is it similar?

THEOPHYLLINE

CAFFEINE

Allopurinol
- Which organ or cell has more concentration of Adenosine deaminase?
- What is diagnostic important of ADA?
What can be effect of Adenosine deaminase deficiency

- What get accumulate & deficient?
  - Substrate or Product?

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → Deoxyinosine → Hypoxanthine → Uric acid

Dr Piyush Tailor
Ribonucleoside diphosphate → dATP → Deoxyribonucleoside diphosphate

Ribonucleotide reductase

Thioredoxin (2 SH) (reduced) → H₂O → Thioredoxin (S-S) (oxidized)

Thioredoxin reductase

NADP⁺ → NADPH + H⁺
What can happen to reaction if two structurally similar substrate come to enzyme?
What can happen to reaction if two structurally similar substrate come to enzyme?
Gar (Hostel)-Kam

- Name a condition which can happen due to increase serum uric acid level *(Hyperuricemia)*.
- What is difference between uric acid and urate crystal?
- Which part of body especially get affected due to hyperuricemia?
- What type of food ingestion can cause hyperuricemia?
- Which type of condition can increase purine degradation and increase serum uric acid level?
- Which type of condition can decrease excretion of uric acid, which makes increase serum uric acid level?
- What is role of Allopurinol to correct hyperuricemia?
What can theophylline do with following reaction?
NUCLEIC ACID

5' End

PO₄

CH₂

N- Glycosidic bond

Phosphodiester bond

3' End

A

C

G
What can theophylline do with following reaction?
Caffeine

Adenosine
Digestion of Nucleic acid

- Pancreatic & Intestinal Juice contain
  - Ribonuclease, Deoxyribonuclease
  - Nucleotidase liberate phosphate from nucleotides.
- Resulting nucleoside are hydrolysed by nucleosidase forming free nitrogen base & pentose sugar.
- Dietary nitrogen base are never utilized for nucleic acid synthesis.
- They directly catabolised.
NUCLEIC ACID

Phosphodiester bond

5' End

3' End
Phosphodiester bonds

- Phosphodiester bonds join the 3′-OH group of the deoxypentose of one nucleotide to the 5′-OH group of the deoxypentose of an adjacent nucleotide through a phosphate group.
- The resulting unbranched chain with two ends.
- 5′-end (the end with the free phosphate) and 3′-end (the end with the free hydroxyl).
- Ends are not attached to other nucleotides.
Nucleotide sequence of DNA read in 5′ → 3′ direction.
DNA

5' End

3' End

Phosphorus (PO₄)

Hydroxyl (OH)

Chlorine (Cl)

Oxygen (O)

Nitrogen (N)

Carbon (C)

5' End

3' End
DNA double helix

- Look like “twisted ladder”.
- Outside = Hydrophilic = Deoxyribose–phosphate .
- Inside = Hydrophobic = Nitrogen Bases .
- Between the two strands in the helix major (wide) and minor (narrow) groove.
- These grooves provide
  - access for the binding of regulatory proteins to their specific recognition sequences along the DNA chain.
  - Anticancer drugs = Dactinomycin (Actinomycin D)
  - interact into the narrow groove of the DNA double helix
  - Thus inhibit with DNA replication and RNA synthesis.
Double-stranded DNA

“B” DNA

Major groove

Minor groove
What can be effect this protein binding to replicating DNA?
DNA = Watson-Crick Model

- Right handed Double – helix
  - Hydrogen bonding between nitrogenous bases
  - Base pairs (A with T & C with G)
  - Complementary strands
  - Antiparallel
- Composed of a sugar- phosphate backbone
- Sugar is deoxyribose
- Each Spiral = 3.4 nm & 10 Base pairs
- Diameter of helix = 1.9 – 2.0 nm
- Two type of groow = Major & Minor
- Chargaff Rule
  - No. of Adenine is equal to No. of Thymine
  - No. of Guanine is equal to No. of Cytosine
## Type of DNA

<table>
<thead>
<tr>
<th>Type</th>
<th>Shape</th>
<th>Helix</th>
<th>Base pairs per Turn</th>
<th>Width</th>
<th>Base angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Broad</td>
<td>Right Handed</td>
<td>11</td>
<td>2.3 nm</td>
<td>20 Degree tilt from perpendicular line</td>
</tr>
<tr>
<td>B</td>
<td>Intermediate</td>
<td>Right Handed</td>
<td>10</td>
<td>1.9 nm</td>
<td>Perpendicular</td>
</tr>
<tr>
<td>Z</td>
<td>Elongated</td>
<td>Left Handed</td>
<td>12</td>
<td>1.8 nm</td>
<td></td>
</tr>
</tbody>
</table>
Nuclear DNA

- Present in almost every cell
- Nuclear DNA is larger in size

Mitochondrial DNA

- Each cell contains thousands of mt DNA
- Mt DNA is in larger quantities in a cell
Mt DNA = 16,569 bases in length

- It's Code for
  - 13 proteins of respiratory chain
  - 22 tRNAs,
  - 2 rRNAs needed for cell respiration
  - This region has very little variability
  - So everyone’s DNA in this region will be nearly the same sequence of TGCAs
  - 5 – 10 times high mutation rate than nuclear
Mt DNA is inherited from mom

- Every sibling will get their mt DNA from their mother
- Why?
- During fertilization, when egg and sperm join, only female mitochondria survive. So mother mitochondrial DNA are passed onto to new baby.
Why Mother?

- Egg contains
  - 23 chromosomes
  - cell cytoplasm which contains thousands of maternal mitochondria.
- Sperm contains
  - 23 chromosomes
  - very little cytoplasm
Mutations occur in the control region of mt DNA at a regular rate and are passed onto children by the mom.
Mitochondrial Disease

- Mitochondrial myopathy
- Leber's hereditary optic neuropathy
- Leigh syndrome,
- Neuropathy
- Ataxia
- Retinitis pigmentosa
- Myoneurogenic gastrointestinal encephalopathy
- Myoclonic Epilepsy with Ragged Red Fibers Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS)
- mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Denaturation of DNA

Double-stranded DNA

Strand separation and formation of single-stranded random coils

Extremes in pH or high temperature
A-T rich regions denature first

Cooperative unwinding of the DNA strands
Tm for DNA Denaturation

At temperatures above the Tm, DNA is present as a single strand.

Graph showing the relationship between temperature (°C) and relative absorbance at 260 nm. The graph indicates two Tm values for high AT-content and high GC-content DNA.
Intron, Exon & Cistron

- Only 10% of the human DNA contain gene
- **Exon**
  - Segments of gene coding for protein. (Expressed region)
- **Intron**
  - Nonfunctional (Not Expressed for Protein)
  - Interspaced in the DNA with silent areas.
  - Serve as basis for future genes.
  - For evolution of new genes
- **Cistron**
  - The unit of genetic expression
  - One Cistron will code for one polypeptide chain.
The (exon-intron-exon)$_n$ structure of various genes

**histone**
- total = 400 bp; exon = 400 bp

**β-globin**
- total = 1,660 bp; exons = 990 bp

**HGPRT (HPRT)**
- total = 42,830 bp; exons = 1263 bp

**factor VIII**
- total = ~186,000 bp; exons = ~9,000 bp
Human genome
- ~3 X $10^9$ bp of DNA
- 30,000 to 40,000 genes
- Any Genes can have 1 to >75 exons
- Genes can be = in length from <100 to >2,300,000 bp

Mitochondrial genome
- Circular genome of ~17,000 bp
- Contains <40 genes
Condesation of DNA
Nucleosome core
1400 nm
Chromatid
(700-nm diameter)
(c) Chromatin fiber
(300-nm diameter)
Looped domains
Splice DNA plus H1 histone
Histones
DNA
(2-nm diameter)
(a) Nucleosomes
(6-nm x 11-nm flat disc)
(b) Solenoid
(30-nm diameter)
H1 Histone
(d) Metaphase chromosome
Histone octamer plus 147 base pairs of DNA
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Mathematic behind Condensation

- Human genome (in diploid cells) = $6 \times 10^9$ bp
- $6 \times 10^9$ bp $\times 0.34$ nm/bp = $2.04 \times 10^9$ nm = 2 m/cell
- Very thin (2.0 nm), Extremely fragile
- Diameter of nucleus = 5-10 mm
- DNA must be packaged to protect it,
- But it must still be accessible to allow gene expression and cellular responsiveness
HISTONES

- Main packaging proteins
- Rich in Lysine and Arginine
- DNA wraps around it 1 3/4 times for a 7-fold condensation factor.
Nucleosome

- octamer of core histones: H2A, H2B, H3, H4 (each one ×2)
- core DNA
- histone H1
- linker DNA
Nucleosome “bead”
(8 histone molecules + 146 base pairs of DNA)
Chromatin fibril

Beads-on-a-string form of chromatin

11 nm
Beads on a String—10 nm Fiber
A string of nucleosomes is seen under EM as a 10 nm fiber
30 nm Chromatin Fibril

- 30 nm fiber is coil of nucleosomes with 6/turn
The 30 nm Fiber
(Compacts DNA 7X more)

a solenoid

nucleosome  histone core  DNA  linker DNA

b zigzag

linker DNA
Different forms of chromatin show differential gene activity

Heterochromatin

Euchromatin
Euchromatin (E) vs Heterochromatin (H)

Heterochromatin = More condensed
=(tightly packed)
= Resistant to DNase digestion.
Transcriptionally active DNA (an active gene) is in euchromatin.
Histones (H1, H2A, H2B, H3, H4)

- Small nucleio-proteins
- Arginine or Lysine rich: positively charged
- Interact with negatively (due to phosphate) charged DNA
- Following modification decrease positive charge of DNA
  - Phosphorylation
  - Poly(ADP) ribosylation
  - Methylation
  - Acetylation
    - **Hypoacetylation**
      - associate with transcriptional repression
    - **Hyperacetylation**
      - associate with transcriptional activation
- Modified Nucleotide & it’s significant.
- DNA replication is semi-conservative.
Name a condition which can happen due to increase serum uric acid level (Hyperuricemia).

What is difference between uric acid and urate crystal?

Which part of body especially get affected due to hyperuricemia?

What type of food ingestion can cause hyperuricemia?

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What is role of Allopurinol to correct hyperuricemia?
If a section of DNA has 13% thymine and 37% guanine, then there is _____ adenine.

- 13%
- 26%
- 37%
- 74%
The percentage of A + G equals _____.

- 26 %
- 50 %
- 80 %
- 100 %
The sequence of one strand of DNA is 5’ TCGATC 3’. The sequence of the complementary strand would be

- 5’ AGCTAG 3’
- 5’ CTAGCT 3’
- 5’ GCTAGC 3’
- 5’ GATCGA 3’
DNA has antiparallel two nucleotide chain, which is held together by
- phosphodiester bond.
- hydrogen bond.
- N-glycosidic bond
- O-glycosidic bond
All of Following, which has similar structure like purine and use drug for treatment of gouty arthiritis,

- Hypoxanthine
- Xanthine
- Uric acid
- Allopurinol
Adenosine deaminase deficiency cause, except
- increase uric acid level
- increase of adenosine
- increase of d-ATP
- All of above
Uric acid is breakdown product of purine base.

So Which of following condition can increase uric acid level

- chemotherapy
- radiotherapy
- leukemia
- All of above
Mitochondrial DNA is circular, except for maternal inheritance.
- Very lengthy
- Very large in amount
What is incorrect about Histone?

- Positive charged & base in nature
- Contain abundant arginine & lysine
- Help in condensation of DNA
- All are cylindrical in shape
Euchromatine part of chromosome is
- highly condense with nucleosome
- active transcription gene
- seen darkly stained in electron-microscopy
- All of Above