Topic 5 Nucleic Acids as Drug Targets

Nucleic Acids-Chapter 7 Patrick and Corey 187, 188, 193-194, 198-199
1. DEOXYRIBONUCLEIC ACID (DNA)

1.2 Secondary Structure - Double Helix

Base Pairing

G-C base pairing involves 3 H-bonds
A-T base pairing involves 2 H-bonds
1. DEOXYRIBONUCLEIC ACID (DNA)
1.3 Tertiary Structure

- Double helix coils into a 3D shape - supercoiling
- Double helix has to unravel during replication
- Unravelling leads to strain
- Relieved by enzyme catalysed cutting and repair of DNA chain
- Important to the activity of the quinolone and fluoroquinolone antibacterial agents which act as enzyme inhibitors
2. RIBONUCLEIC ACID (RNA)

2.1 Primary structure

- Similar to DNA with the following exceptions
- Ribose is used instead of deoxyribose
- Uracil is used rather than thymine

[Chemical structures of ribose and uracil are shown.]

Ribose

Uracil
2. RIBONUCLEIC ACID (RNA)

2.2 Secondary structure

- Single stranded

- Some regions of helical secondary structure exist due to base pairing within the same strand (see t-RNA)

- Adenine pairs to uracil; guanine pairs to cytosine
2. RIBONUCLEIC ACID (RNA)

2.3 Tertiary structure

- Three types of RNA are involved in protein synthesis:
  - **Messenger RNA (mRNA)**
    Relays the code for a protein from DNA to the protein production site
  - **Transfer RNA (tRNA)**
    The adapter unit linking the triplet code on mRNA to specific amino acids
  - **Ribosomal RNA (rRNA)**
    Present in ribosomes (the production site for protein synthesis). Important both structurally and catalytically
2. RIBONUCLEIC ACID (RNA)

2.3 Tertiary structure

Base Pairing

mI  Methylinosine
I   Inosine
UH2 Dihydouridine
T   Ribothymidine
Ps  Pseudouridine
mG  Methylguanosine
m2G Dimethylguanosine

Anticodon - the 3 bases are specific for the attached amino acid
- base pair to the complementary triplet code on m-RNA (the codon)
2. RIBONUCLEIC ACID (RNA)

2.5 Translation - protein synthesis

Transfer of growing peptide chain to next amino acid
2. RIBONUCLEIC ACID (RNA)

2.5 Translation - protein synthesis

Overview
Contents

Part 2: Section 7.3 (Drugs acting on DNA)

3. Drugs acting on DNA
   3.1. Intercalating agents
       - Topoisomerase II
       - Example – Proflavine
   3.2. Alkylating agents
   3.3. Chain cutters
3. DRUGS ACTING ON DNA

3.1 Intercalating agents

Mechanism of action

- Contain planar aromatic or heteroaromatic ring systems
- Planar systems slip between the layers of nucleic acid pairs and disrupt the shape of the helix
- Preference is often shown for the minor or major groove
- Intercalation prevents replication and transcription
- Intercalation inhibits topoisomerase II- see Doxorubicin, p.198 Corey.
3. DRUGS ACTING ON DNA

Topoisomerase II

- Relieves the strain in the DNA helix by temporarily cleaving the DNA chain and crossing an intact strand through the broken strand

- Tyrosine residues in the enzyme are involved in the chain breaking process
- The residues form covalent bonds to DNA
3. DRUGS ACTING ON DNA

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3. **DRUGS ACTING ON DNA**

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3. DRUGS ACTING ON DNA

Topoisomerase II

Mechanism of chain cutting
3. DRUGS ACTING ON DNA

3.1 Intercalating agents

Examples

Dactinomycin

Extra binding to sugar phosphate backbone by cyclic peptide

Doxorubicin (Adriamycin)

Extra binding to sugar phosphate backbone by $\text{NH}_3$
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

- Contain highly electrophilic groups
- Form covalent bonds to nucleophilic groups in DNA (e.g. 7-N of guanine)
- Prevent replication and transcription
- Useful anti-tumour agents
- Toxic side effects (e.g. alkylation of proteins)

**Example**
Mechlorethamine (nitrogen mustard)
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

Cross linking

Intrastrand cross linking

Interstrand cross linking
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

**Mechanism of action**

Mechlorethamine $\rightarrow$ Aziridine ion $\rightarrow$ DNA

$G = $ Guanine

Crosslinked DNA
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

Mechlorethamine analogues

Aromatic ring - e withdrawing effect  
N is less nucleophilic  
Less reactive alkylationg agent  
Selective for stronger nucleophiles  
(e.g. guanine)

Uracil mustard  
Used vs leukemia  
Attached to a nucleic acid building block  
Concentrated in fast growing cells  
(tumours)  
Some selectivity
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

Cisplatin

\[
\begin{array}{c}
\text{Cl} \\
\text{Pt} \\
\text{Cl} \\
\end{array}
\quad
\begin{array}{c}
\text{NH}_3 \\
\text{NH}_3 \\
\end{array}
\]

Binds to DNA in regions rich in guanine units
Intrastrand links rather than interstrand
Inhibits transcription

Mitomycin C

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{Me} \\
\text{Me} \\
\text{NH} \\
\end{array}
\quad
\begin{array}{c}
\text{CH}_2\text{OCOCONH}_2 \\
\text{OMe} \\
\end{array}
\]

Converted to alkylating agent in the body
MeOH

O

N

H

2

N

Me

CH2OCONH2

OH

N

H2N

Alkylating agent

H2N-DNA

NH-DNA

Crosslinked DNA
3. DRUGS ACTING ON DNA

3.3 Chain cutters

- Abstracts H from DNA to generate radicals
- Radicals react with oxygen resulting in chain cutting
- Bleomycin also inhibits repair enzymes

Bleomycin
Used vs skin cancer

BLEOMYCIN A2 $R = \text{NHCH}_2\text{CH}_2\text{CH}_2\text{SMe}_2$
BLEOMYCIN B2 $R = \text{NHCH}_2\text{CH}_2\text{CH}_2\text{NHC(NH}_2\text{)=NH}$
Part 3: Section 7.3 (Drugs acting on RNA)

4. Drugs Acting On rRNA
   - Antibiotics

5. Drugs Acting On mRNA
   - Antisense Therapy
   - siRNA

6. Drugs related to nucleic acid building blocks
   - Examples: Antiviral agents
   - Examples
4. DRUGS ACTING ON rRNA

Antibiotics

Chloramphenicol (vs typhoid)

Rifamycins

Chlortetracycline (Aureomycin)

Erythromycin
5. DRUGS ACTING ON mRNA

Antisense RNA Therapy
5. DRUGS ACTING ON mRNA

Antisense Therapy

Advantages

• Same effect as an enzyme inhibitor or receptor antagonist
• Highly specific where the oligonucleotide is 17 nucleotides or more
• Smaller dose levels required compared to inhibitors or antagonists
• Potentially less side effects

Disadvantages

• ‘Exposed’ sections of mRNA must be targeted
• Instability and polarity of oligonucleotides (pharmacokinetics)
• Short lifetime of oligonucleotides and poor absorption across cell membranes
5. DRUGS ACTING ON or through RNA

Small Interfering RNA-siRNA

Targets specific RNA sequences for destruction

si RNA-ds, ~21BP, 2 base overhang + phosphate

“Dicer” enzyme
5. DRUGS ACTING ON or through RNA

Small Interfering RNA-siRNA

http://www.rnaiweb.com/RNAi/RNAi_Web_Resources/RNAi_Therapy___Clinical_Trials/
6. Drugs related to nucleic acid building blocks

**Examples:** Antiviral agents

Azidothymidine (AZT)  
(Zidovudine; Retrovir)

- Enzyme inhibitor
- AZT is phosphorylated to a triphosphate in the body
- Triphosphate has two mechanisms of action
  - inhibits a viral enzyme (reverse transcriptase)
  - added to growing DNA chain and acts as chain terminator
6. Drugs related to nucleic acid building blocks

Examples: Antiviral agents

Acyclovir (Zovirax)

Famciclovir (Famvir)

Notes:
Same mechanisms of action as AZT
Used vs herpes simplex and shingles