Cell Cycle Active, S Phase Specific

ANTIMETABOLITES

Mechanisms

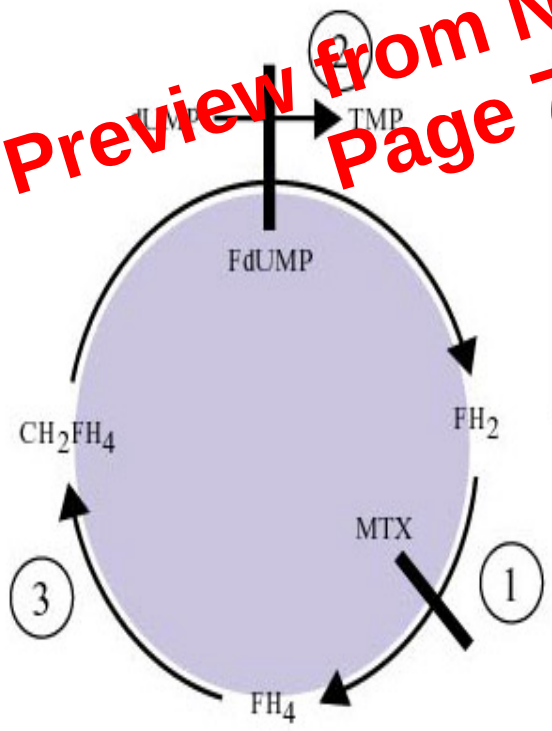
- incorporation of nucleotide analog in DNA or RNA, resulting in abnormal nucleic acids
- inhibition of certain enzymes involved in nucleotide biosynthesis

Examples:

- Pyrimidines
  - Uracil: 5-fluorouracil (5-fluoro-2'-deoxyuridine)
  - Thymine: 3'-azido-3'-deoxythymidine
  - Cytosine: Cytosine arabinoside; 5-azacytidine
- Purines
  - Adenine: 6-mercaptopurine
  - Guanine: 6-thioguanine

ANTIFOLS (METHOTREXATE)

Mechanism: competitive inhibition of dihydrofolate reductase, necessary for generation of methyl donors required for thymidine synthesis.



Sites of action of methotrexate (MTX) and the fluoropyrimidine antimetabolite, fluorodeoxyuridylate (FdUMP): (1) DHFR, dihydrofolate reductase; (2) TS, thymidylate synthase; (3) SHM, serine hydroxymethylate; FH_2, dihydrofolate; FH_4, tetrahydrofolate; CH_2FH_4, N^5, N^{10} -methylene- tetrahydrofolate.

Non Cell Cycle Active

CORTICOSTEROIDS

Mechanisms

- unclear –induce apoptosis of lymphoblasts and effective in lymphoid malignancies
- work via nuclear receptors

Examples

- prednisone
- dexamethasone

Toxicity

- typical steroid toxicity –relatively modest in this context

L-ASPARAGINASE (E. COLI, ERWINIA)

Mechanisms

- l-asparaginase converts asparagine to aspartate and NH3. Normal cells can reverse this process to form asparagine.
- Drug has activity in acute lymphocytic leukemia. Lymphoblasts lack asparagine synthetase and die without preformed asparagine in plasma.

Toxicity

- Hypersensitivity (urticaria, anaphylaxis)
- Pancreatitis
- Hepatotoxicity

- *Expression of an altered gene product*

Drug	Alteration
MTX	DHFR
VCR	Tubulin
5-FU	Thymidylate synthase

D. Acquired Methotrexate Resistance

Acquired MTX resistance has been attributed to a variety of mechanisms. For example, the following have been identified in MTX-resistant sublines of a human squamous cell carcinoma (SCC15) established in culture by progressive dose escalation:

1. Altered transport
2. Defective polyglutamylation
    - Polyglutamate derivatives (MTX-PGs) with 2 to 5 γ-linked glutamyl moieties ($MTX\text{-}Glu_2$ to $MTX\text{-}Glu_5$) are selectively retained by cells.
    - MTX-PGs have a higher affinity for DHFR, cause prolonged inhibition of DNA synthesis and increase cytotoxicity.
3. Increased production of DHFR (gene amplification)
    - Abnormal homogeneously staining regions (HSRs): sites identified in MTX resistant cells which represent amplified DHFR genes on chromosome 2 (mouse) and 5 (human). HSRs are associated with stable resistance.

    - Double minute chromosomes (DMs): small chromosomes of varying size without centromeres, usually occurring in pairs. These chromosomes do not segregate and therefore are lost during the process of cell division. Gene amplification on the double minute chromosome is thus unstable in the absence of selecting agents.
4. Altered DHFR
    - DHFRs in some resistant cells have a low affinity for MTX.
    - An altered DHFR gene has a mutation in the codon for amino acid 22. This mutation (arginine for leucine) decreases both binding of MTX and function of the enzyme.

E. Multidrug or Pleotropic Resistance

1. Tumor cells exposed to a single drug develop cross-resistance to structurally unrelated compounds with different mechanisms of action. The affected drugs include a wide spectrum: anthracyclines, vinca alkaloids, actinomycin, podophyllotoxins.