Anti Neoplastic Agents

- Anti Cancer Agents
- Anti Neoplastic Agents
- Anti Tumor Agents

Definition of Cancer

- **Cancer, Tumor [*Tumor* – latin for swelling], Neoplasia**
- Abnormal cell proliferation leading to uncontrolled growth.
- Cancers derive from a single aberrant cell and are therefore clonal.
- Acquisition of new traits through mutation and adaptation:
  - Drug resistance
  - Invasiveness
  - Maintenance

Characteristics of Cancer Cells

- The problem:
  - Cancer cells divide rapidly (cell cycle is accelerated)
  - They are "immortal"
  - Cell-cell communication is altered
    - Uncontrolled proliferation
    - Invasiveness
  - Ability to metastasise

Cellular Modifications

- Normal Cells differentiate, grow, mature, divide
  - Regulated, balanced; cell birth=cell death
    - Regulation: intracell signaling
  - **Hyperplasia**: new cells produced with growth stimulus via hormones, endogenous signals
  - **Metaplasia**: replacement of one cell type by another
    - Thicker cell layer better accommodates irritation
    - Replacement cells normal, just different
    - Reversible

Cellular Modifications

- **Dysplasia**: replacement cells disordered in size, shape
  - Increased mitosis rate
  - Somewhat reversible, often precancerous
- **Neoplasia**: abnormal growth/invasion of cells
  - "New growth"
  - Neoplasm = tumor
  - Irreversible
  - Cells replicate, grow without control

Cancer (Neoplastic) Cells

- May be:
  - Well-differentiated
    - Retain normal cell function
      - Mimic normal tissue
      - Often benign
  - Poorly differentiated
    - Disorganized
      - Can't tell tissue of origin
      - Anaplastic

Neoplasms

- Tumors = groups of neoplastic cells
  - Two major types: benign, malignant
- **Benign – "noncancerous"**
  - Local; cells cohesive, well-defined borders
  - Push adjacent tissue away
  - Doesn't spread beyond original site
  - Often has capsule of fibrous connective tissue
- **Malignant** – grow more rapidly; often called "**cancer**"
  - Not cohesive; seldom have capsule
  - Irregular shape; disrupted architecture
  - Invade surrounding cells
  - Can break away to form second tumor
    - "Metastasis" from 1º to 2º site

Classifications of Tumors

- **Solid tumors**
  - May originate in any body organ
  - Carcinomas (originate in epithelial cells)
  - Sarcomas (originate in the mesenchyma)
- **Hematological malignancies**
  - Leukemias and lymphomas; occur in the blood-forming organs

Possible Causes of Cancer

- Genetic predisposition
- Viral infection
- Constant irritation and cell turnover
- Stress
- Lifestyle factors
- Environmental factors

Steps to Cancer

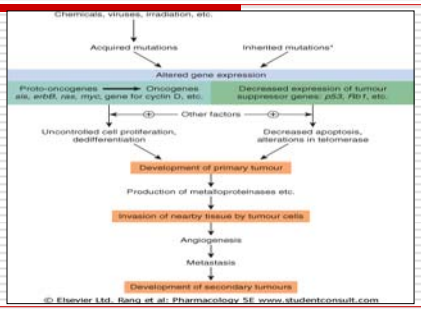
- **Oncogenesis = Process of Tumor Development**
  - Probably multi-step process
  - Decreased ability to differentiate and control replication and growth
- **Initiation** = important change introduced into cell
  - Probably through DNA alteration
  - >1 event probably needed for tumor production
  - Reversible unless and until:
- **Promotion** = biochemical event encourages tumor formation
- **Generally need both initiation and promotion**
  - Initiators, promoters may be toxins OR radiation OR viruses)

Mechanisms of Growth

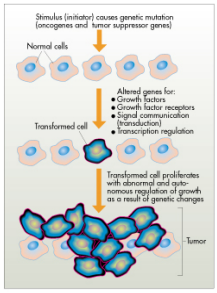
Neoplasm

- **Anaplasia**
  - Cancerous cells lose cellular differentiation and organization; are unable to function normally
- **Autonomy**
  - Cancerous cells grow without the usual homeostatic restrictions that regulate cell growth and control
  - This allows the cells to form a tumor
- **Metastasis**
  - Cancer cells travel from the place of origin to develop new tumors in other areas of the body
- **Angiogenesis**
  - Abnormal cells release enzymes to generate blood vessels and supply oxygen and nutrients to the cells, generating growth
  - Cancerous cells rob the host cells of energy and nutrients and block normal lymph

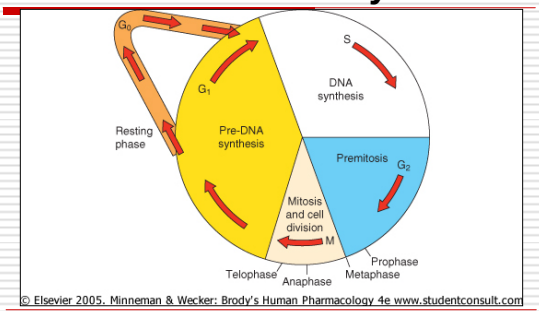
Mechanisms of Growth



Steps to Cancer

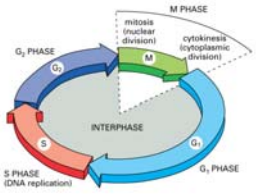


Phases of the Cell Cycle

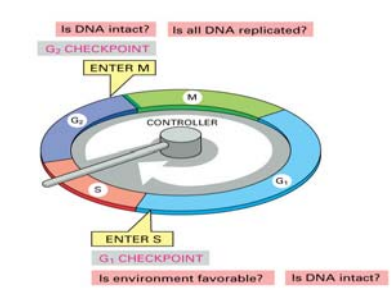


Phases of the Cell Cycle

- **G_0 phase:** Resting phase
- **G_1 phase:** Gathering phase
- **S phase:** Synthesizing phase
- **G_2 phase:** Last substances needed for division are collected and produced
- **M phase:** Actual cell division occurs, producing two identical daughter cells



Cycle Checkpoints



Effect on cell proliferation

- **Tumor cell phase**
  - G_0 phase
  - Cell cycle: $G_1 \rightarrow S \rightarrow G_2 \rightarrow M$
- **Anticancer drugs**
  - Cell cycle nonspecific drugs(CCNS)
  - Cell cycle specific drugs(CCS)
- **Affect cell division**
  - Active on rapidly dividing cells
- **Most effective during S phase of cell cycle**
  - Many cause DNA damage

Mechanisms of Action

- Affecting cell survival
- Boosting the immune system in its efforts to combat the abnormal cells

Mechanisms of Action

- Altering cellular function or disrupting cellular integrity, causing cell death
- Preventing cellular reproduction, eventually leading to cell death

Therapeutic and Toxic Effects

- May alter the cell membrane, causing the cell to rupture and die
- May deprive the cell of certain nutrients, altering the proteins that the cell produces and interfering with normal cell functioning and cell division
- **May affect the normal cells of patients to some extent**

Cancer Therapy

- Six Established Modalities

1. Surgery
2. Radiotherapy
3. Chemotherapy
4. Endocrine therapy
5. Immunotherapy
6. Biological therapy

Aim of Cancer Treatment

- Destroying cancer cells through several methods:
  - Surgery to remove them
  - Stimulation of the immune system to destroy them
  - Radiation therapy to destroy them
  - Drug therapy to kill them during various phases of the cell cycle

Antineoplastic Therapy

- Chemotherapy
  - Alkylation Agents
  - Antimetabolites / Nucleoside Analogs
  - Antibiotics
  - Antimitotic Agents
  - Miscellaneous Antineoplastic Agents
  - Hormonal Therapy

Antineoplastic Therapy

- Combinations of agents with differing toxicities & mechanisms of action are often employed to overcome the limited cell kill of individual anti cancer agents. Each drug selected should be effective alone

Antineoplastic Therapy

Three advantages of combination therapy:

- Suppression of drug resistance - less chance of a cell developing resistance to 2 drugs than to 1 drug.
- Increased cancer cell kill - administration of drugs with different mechanisms of action.
- Reduced injury to normal cells - by using a combination of drugs that do not have overlapping toxicities, we can achieve a greater anticancer effect than we could by using any one agent alone.

Antineoplastic Therapy

General problems with anticancer drugs

- Most of them are antiproliferative, i.e. they damage DNA and so initiate apoptosis.
- They also affect rapidly dividing *normal* cells.
- This leads to toxicity which are usually severe.
- To greater or lesser extent the following toxicities are exhibits by all anticancer drugs.

Antineoplastic Therapy

- **Side effects of antineoplastic chemotherapy**
  - **Severe nausea and vomiting**
  - **Hair loss [alopecia]**
  - **Damage to GI tract epithelium**
  - **Growth depression**
  - **Impaired wound healing**
  - **Severe tissue toxicity [kidneys, liver, bone marrow]**
  - **Sterility**
  - **Teratogenicity**
  - **Cancer**

Classification of Antineoplastic Agents

Classification according to structure

- **Alkylating agents**
  - React chemically with portions of the RNA, DNA, or other cellular proteins
- **Antimetabolites**
  - Have chemical structures similar to those of natural metabolites
- **Antineoplastic antibiotics**
  - Not selective only for bacterial cells; toxic to human cells

Classification of Antineoplastic Agents

Classification according to mechanism of action

- **Drugs affecting biosynthesis of nucleic acid**
- **Drugs destroying DNA structure and function**
- **Drugs interfering with transcription and blocking RNA synthesis**
- **Drugs affecting protein synthesis**
- **Hormonal agents**

Classes of Antineoplastic Agents