ANTI - NEOPLATIC DRUGS I
Introduction & Key concepts

Dr.Nashwa Abo-Rayah

Assistant prof. (clinical &experimental pharmacology)

Mu'tah University- Faculty of Medicine

Objectives

- 1- What is malignant transformation?
- 2- Properties of cancer cells
- 3- Explain doubling time of cancer cells
- 4- Grade and differentiation of cancer cells
- 5- Cell cycle
- 6- Cell cycle regulators
- 7- Cancer genetics
- 8- Telomere and telomerase

Overview

Introduction

- Malignant disease accounts for a high proportion of deaths in industrialized countries.
- The PURPOSE of antineoplastic (anticancer) drug is to give palliation, induce remission and, if possible, cure.

Overview

Introduction

- Malignant transformation:
- Cancer occurs after normal cells have been transformed into neoplastic cells through alteration of their genetic material and the abnormal expression of certain genes.
- Neoplastic cells usually exhibit chromosomal abnormalities and the loss of their differentiated properties.

Properties of neoplastic cells

- Previous changes lead to:
- 1- Uncontrolled proliferation (cell division)
- 2- Resistance to apoptosis (programmed cell death)
- 3- Angiogenesis: production of vascular endothelial growth factor: formation of new blood vessels
- 4- Invasion, metastasis, secondaries
- 5- Avoidance of immune destruction
- 6- Loss of normal function

Doubling time of neoplastic cells

- The time it takes for one cell to divide or for a group of cells (such as a tumor) to double in size.
- The doubling time is different for different kinds of cancer cells or tumors.
- Example: Burkitt lymphoma: 24 hrs, cancer breast: 3 months

Grade and differentiation of cancer cells

- **Low-grade** cancers have cells that are abnormal but look a lot like normal cells. They are also arranged much like normal cells. Low-grade cancers tend to grow slowly and are less likely to spread. Cancers that are well-differentiated are low grade.
- **High-grade** cancers have cells that look very different from normal cells and are arranged differently. They tend to grow more quickly and are more likely to spread (**Undifferentiated** or **poorly differentiated)**.

CELL CYCLE

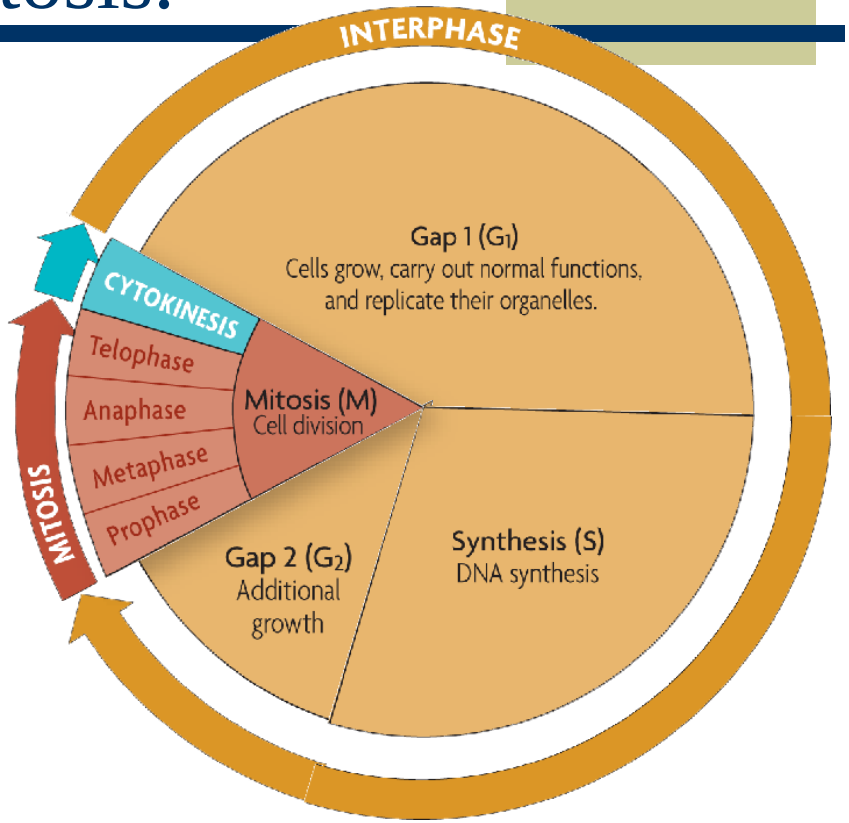
The cell cycle is a repeated pattern of growth and division that occurs in eukaryotic cells.

This cycle consists **of three phases: G1, S, G2**

CELL CYCLE-INTERPHASE

- Interphase: period of growth and DNA replication between cell divisions

- The main stages of the cell cycle are gap 1, synthesis, gap 2, and mitosis.
  - Gap 1 (G_1): cell growth and normal functions
  - DNA synthesis (S): copies DNA
  - Gap 2 (G_2): additional growth (chromatids become replicated chromosomes)
  - Mitosis (M): includes division of the cell nucleus (mitosis) and division of the cell cytoplasm (cytokinesis)



- Mitosis occurs only if the cell is large enough and the DNA undamaged.

Cells divide at different rates.

- The rate of cell division varies with the need for those types of cells.

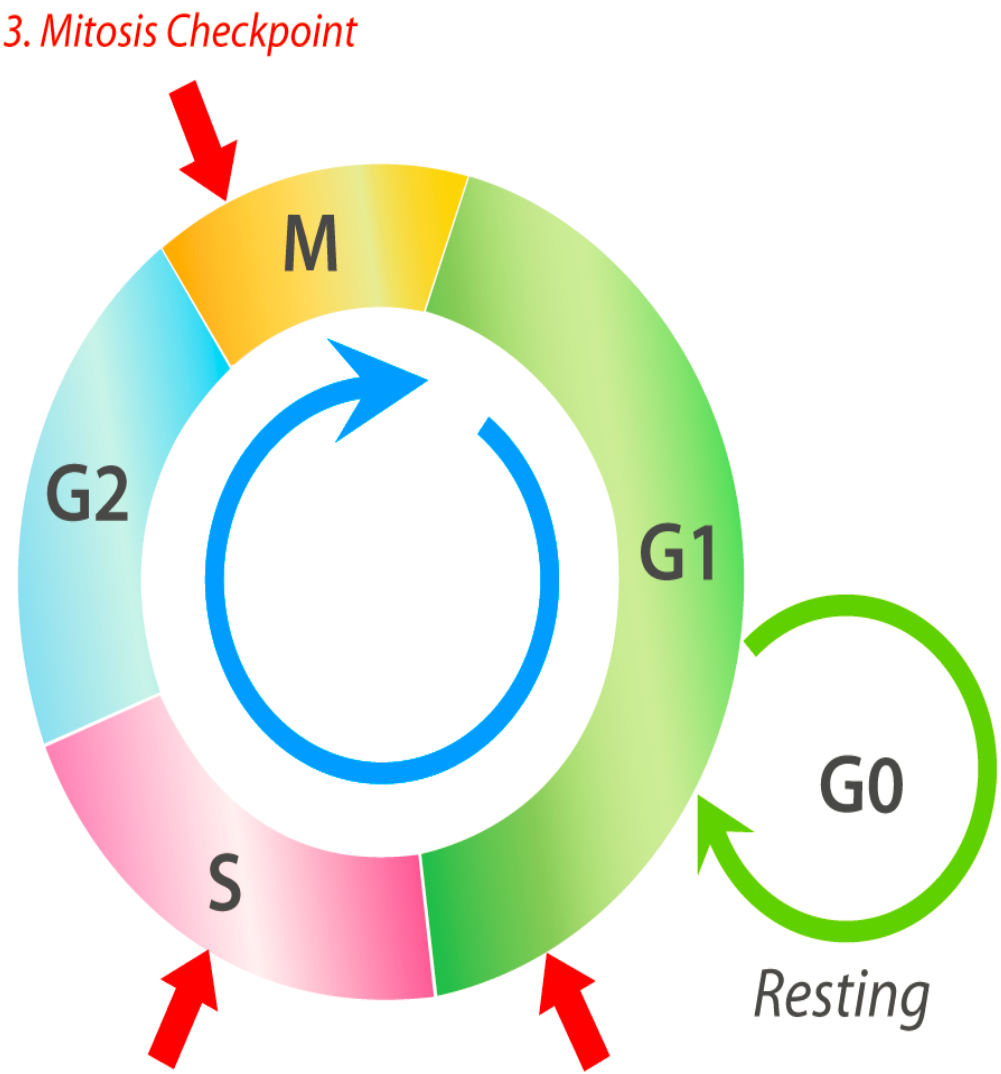
FIGURE 5.2 CELL DIVISION	
CELL TYPE	APPROXIMATE LIFE SPAN
Skin cell	2 weeks
Red blood cell	4 months
Liver cell	300–500 days
Intestine—internal lining	4–5 days
Intestine—muscle and other tissues	16 years

- Some cells are unlikely to divide (G_0).

Control of the Cell Cycle

- Regulatory proteins control the cell cycle at checkpoints:
- G1 Checkpoint
- S Checkpoint
- Mitotic Spindle Checkpoint

The Cell Cycle and the Checkpoints



1. Cell Growth Checkpoint

- Occurs toward the end of growth phase 1 (G1).
- Checks whether the cell is big enough and has made the proper proteins for the synthesis phase.
- If not, the cell goes through a resting period (G0) until it is ready to divide.

2. DNA Synthesis Checkpoint

- Occurs during the synthesis phase (S).
- Checks whether DNA has been replicated correctly.
- If so, the cell continues on to mitosis (M).

3. Mitosis Checkpoint

- Occurs during the mitosis phase (M).
- Checks whether mitosis is complete.
- If so, the cell divides, and the cycle repeats.

Regulatory proteins of cell cycle

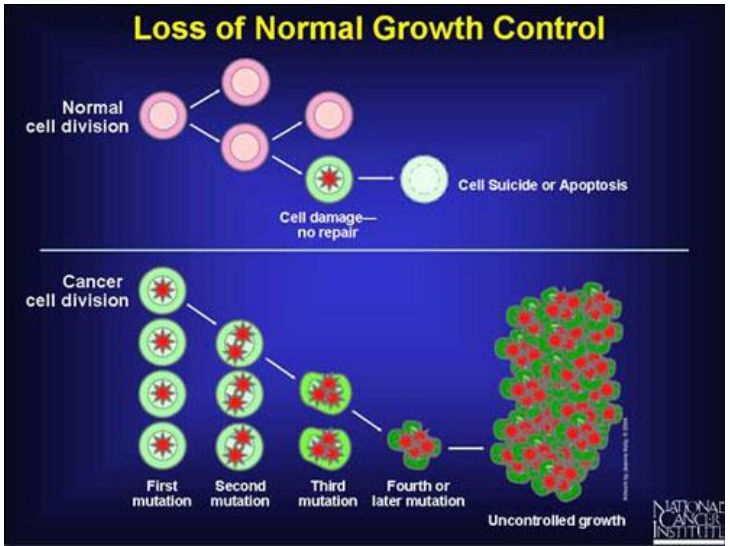
- **Positive proteins**:
- Cyclins
- Cyclin-dependent kinases
- Growth factors
- Signaling proteins
- **Negative proteins**: P53, BRCA1, BRCA2

The *p53* Gene: The Master Tumor-Suppressor Gene

- About 50% of all human cancers are associated with defects in the *p53* gene
- A primary role for the p53 protein is to determine if a cell has incurred DNA damage
  - If so, p53 will promote three types of cellular pathways to prevent the division of cells with damaged DNA

CANCER CELLS

- Result of uncontrolled cell division of cells that have lost ability to regulate cell cycle
- Reproduce more rapidly than normal cells
- Masses formed called ‘tumors’



Cancer genetics

Two major classes of cancer causing genes

Oncogenes - Proto-oncogenes are genes that normally help cells grow. When a proto-oncogene mutates (changes) or there are too many copies of it, it becomes a "bad" gene that can become permanently turned on or activated when it is not supposed to be. When this happens, the cell grows out of control, which can lead to cancer. This bad gene is called an oncogene.

Tumor Suppressor genes - Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as *apoptosis* or *programmed cell death*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.

What is Telomere ?

What are telomeres?

- Telomeres are…
  - Repetitive DNA sequences at the ends of all human chromosomes
  - They contain thousands of repeats of the six-nucleotide sequence, TTAGGG
  - In humans there are 46 chromosomes and thus 92 telomeres (one at each end)

telomeres function

- They protect the chromosomes.
- They separate one chromosome from another in the DNA sequence
- Genes at the periphery of chromosome must covered by telomere to be encoded.
- Telomeres are also thought to be the "clock" that regulates how many times an individual cell can divide. Telomeric sequences shorten each time the DNA replicates

Telomere and aging

- Once the telomere shrinks to a certain level, the cell can no longer divide. Its metabolism slows down, it ages, and dies

Telomerase and cancer

- telomerase activity is present in almost all human tumors but not in tissues adjacent to the tumors.

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Thanks!