UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES

FUNDAMENTALS OF ONCOLOGY

Proliferation and differentiation

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The course is evaluated with 5 ECTS. There are 4 hours of active teaching per week (2 hours of lectures and 2 hours of work in a small group).

COURSE STRUCTURE:

Module	Name of the module	Week	Lectures weekly	Work in a small group per week	Teacher
1	Molecular basis of oncology	6	2	2	Ivan Jovanović
2	Etiology, progression and tumor immunology	9	2	2	
					∑30+15=45

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EVALUATION:

The student masters the subject in modules. The grade is equivalent to the number of earned points (see tables). Points are earned in two ways:

PRE-EXAM ACTIVITY: In this way, the student can earn up to 30 points by actively participating in small group and answering questions related to this week's lesson. Based on demonstrated knowledge, the student can earn between 0-2 points per week.To pass the module, student needs to acquire more than 50% of the total points for that module (see table).
Students who do not earn more than 50% of the points in pre-exam activity will take the exam by answering 2 questions from each module that they have not passed.

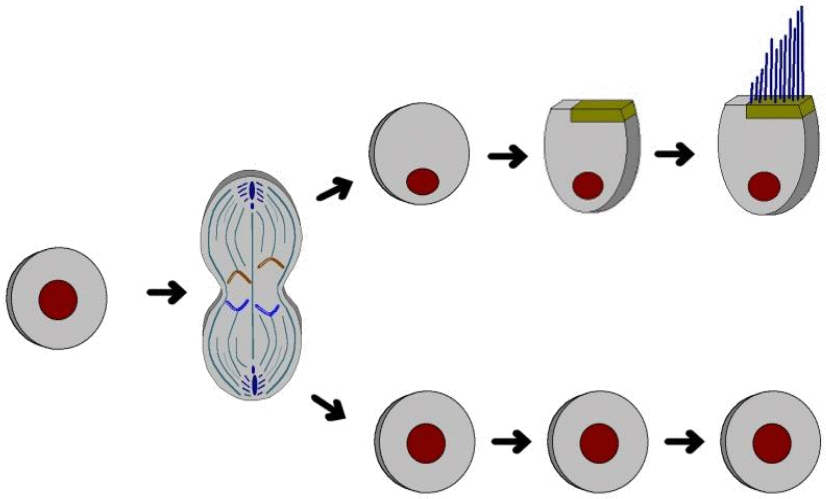
FINAL EXAM: In this way, student can earn up to 70 points. Student takes the test which includes 70 questions that are covering the entire subject material. If the student does not achieve more than 50% correct answers, he/she has not passed the final exam.

Teaching unit 01

Proliferation and differentiation

Cell proliferation

- cell multiplication, cell population growth through cell reproduction - cell division.

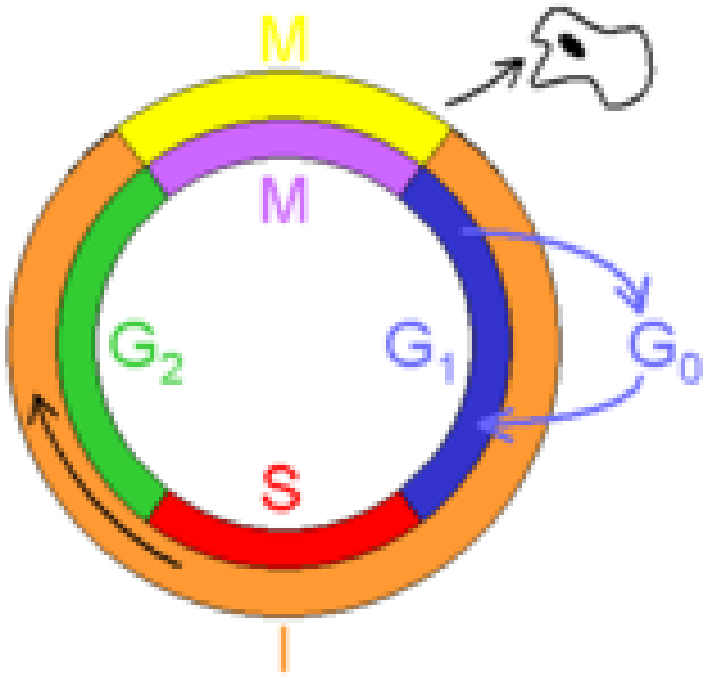


Cell proliferation

- "Path" from zygote to newborn
- Hair growth
- Skin
- Intestinal epithelium
- Immune system
- Tumor cells

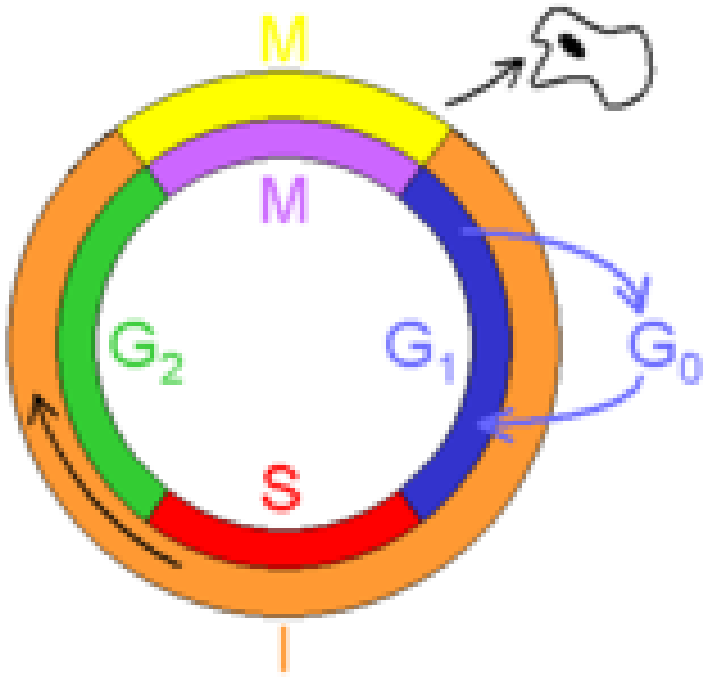
Cell cycle

- 1951. Howard and Pelz:
- GAP1-G1
- Synthetic phase - S
- GAP2 - G2
- mitosis -M



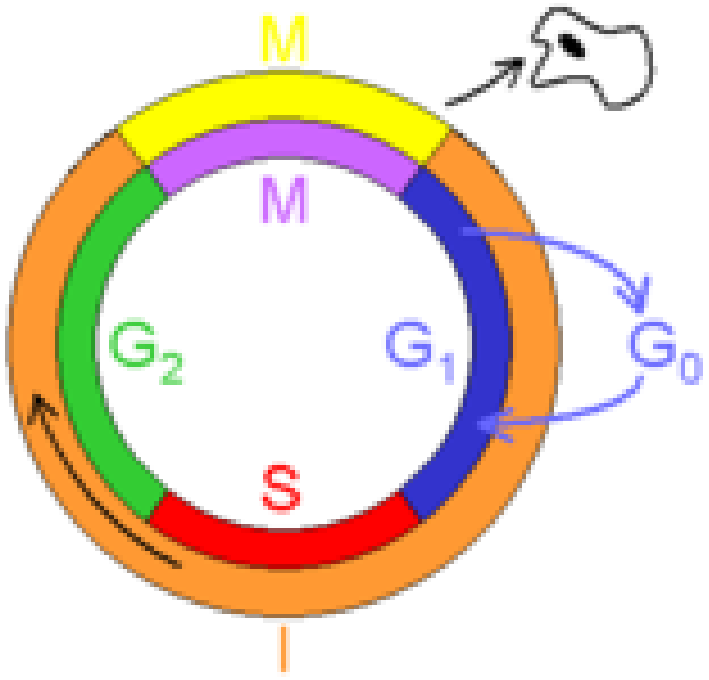
Cell cycle

- G1- preparation for replication
- S- synthesis DNA
- G2- preparation for division
- M- cell division



Cell cycle

G1 and G2 - the so-called silent phases of the cell cycle, during which a large amount of information from the cellular environment as well as from the cell itself is generated and determines whether and when the S and M phases begin, the regulation of the cell cycle.



Cell cycle

Mitosis is divided into five phases:

- Prophase. Chromosomes are condensed. Protein biosynthesis stops. A dividing spindle is formed.
- Prometaphase. Chromosomes attach to the division spindle.
- Metaphase. Paired chromatids are individually attached to spindle microtubules.
- Anaphase. The paired chromatids lose their cohesion and the microtubules pull them towards the poles of the cell.
- Telophase. Reversed prophase. Chromosome decondensation. Protein biosynthesis begins.

Complete physical separation of daughter cells after mitosis- cytokinesis.

- Proliferative fraction

- Resting faction

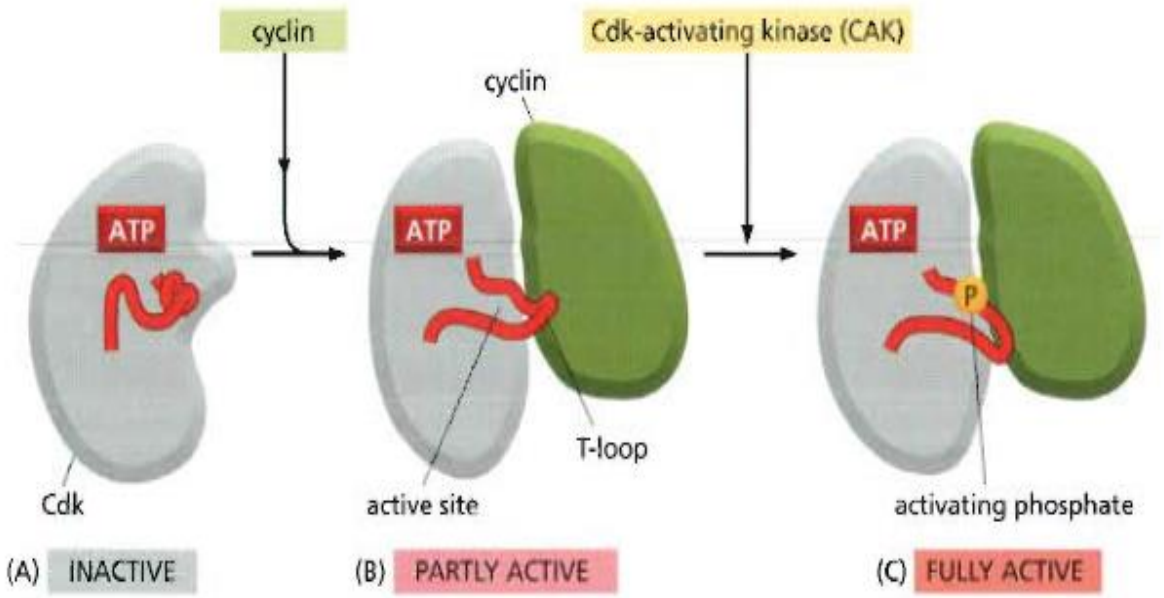
Cell cycle

Today we know that cell cycle is regulated by cyclin-dependent kinases.

- Cyclin-dependent kinases (eng. **CDK**, cyclin dependent kinases) represent enzymes very important for the initiation of replication.
- Cyclins (eng. Cyclin) are activating proteins for CDKs.
- Cyclins are necessary for the activation of CDKs, their expression is transient so that their concentration changes depending on the phase of the cell cycle.

- Inhibitors of cyclin-dependent kinase(**CKI**) when are present in sufficient concentration prevent activity of Cyclin- CDK.

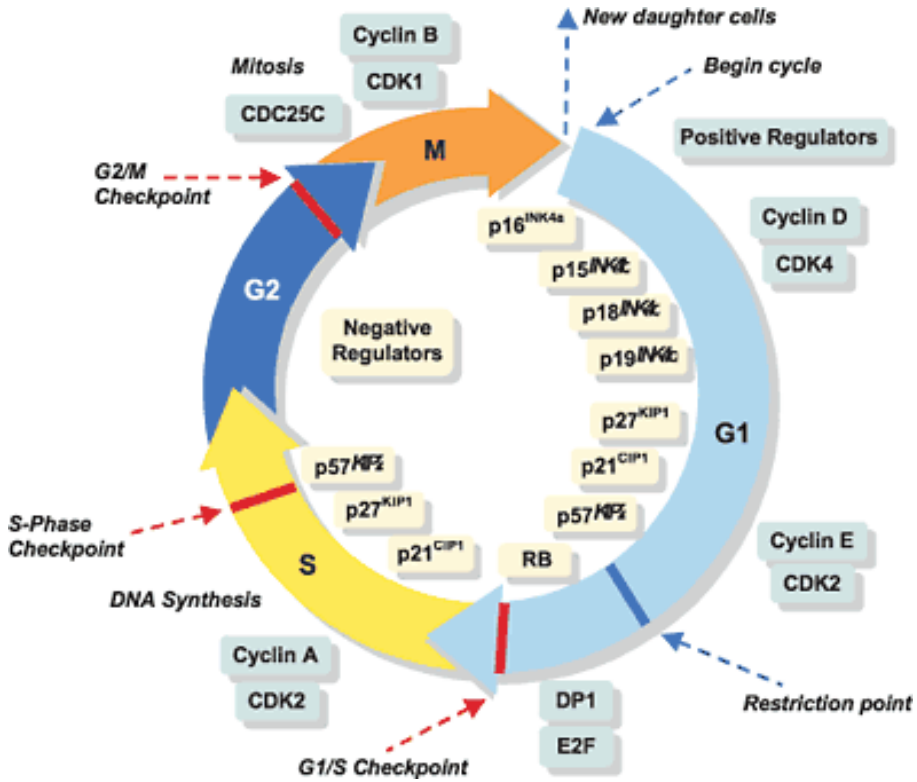
Cell cycle



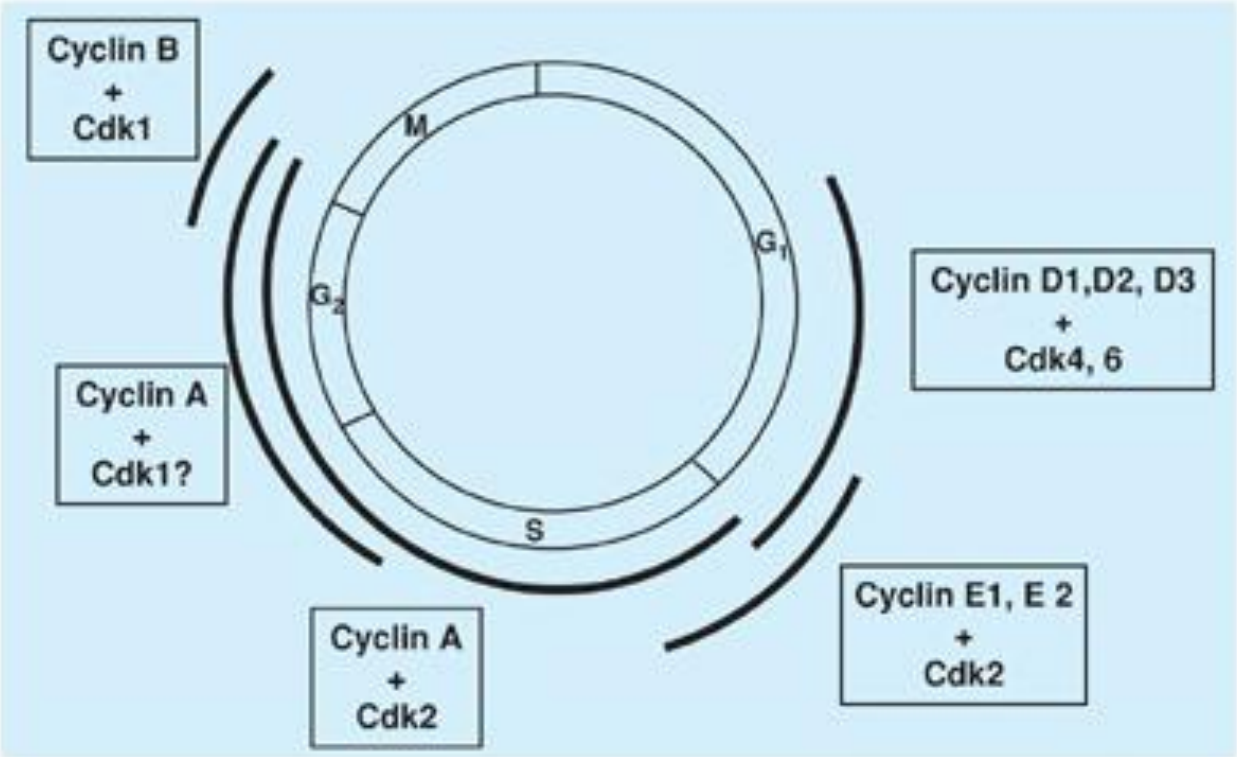
- Phosphorylation of CDK change the shape of T-loop, which enables better binding to cyclin and thus complete activation of CDK

Cell cycle

- Cyclin D1, D2, D3 ⟹ CDK4, CDK6 ⟹ G1/S
- Cyclin E1, E2 ⟹ CDK2 ⟹ G1S,early S phase
- Cyclin A⟹CDK2 ⟹ S/G2
- Cyclin A⟹ CDK1 ⟹ ?, G2
- Cyclin B ⟹ CDK1 ⟹ G2/M



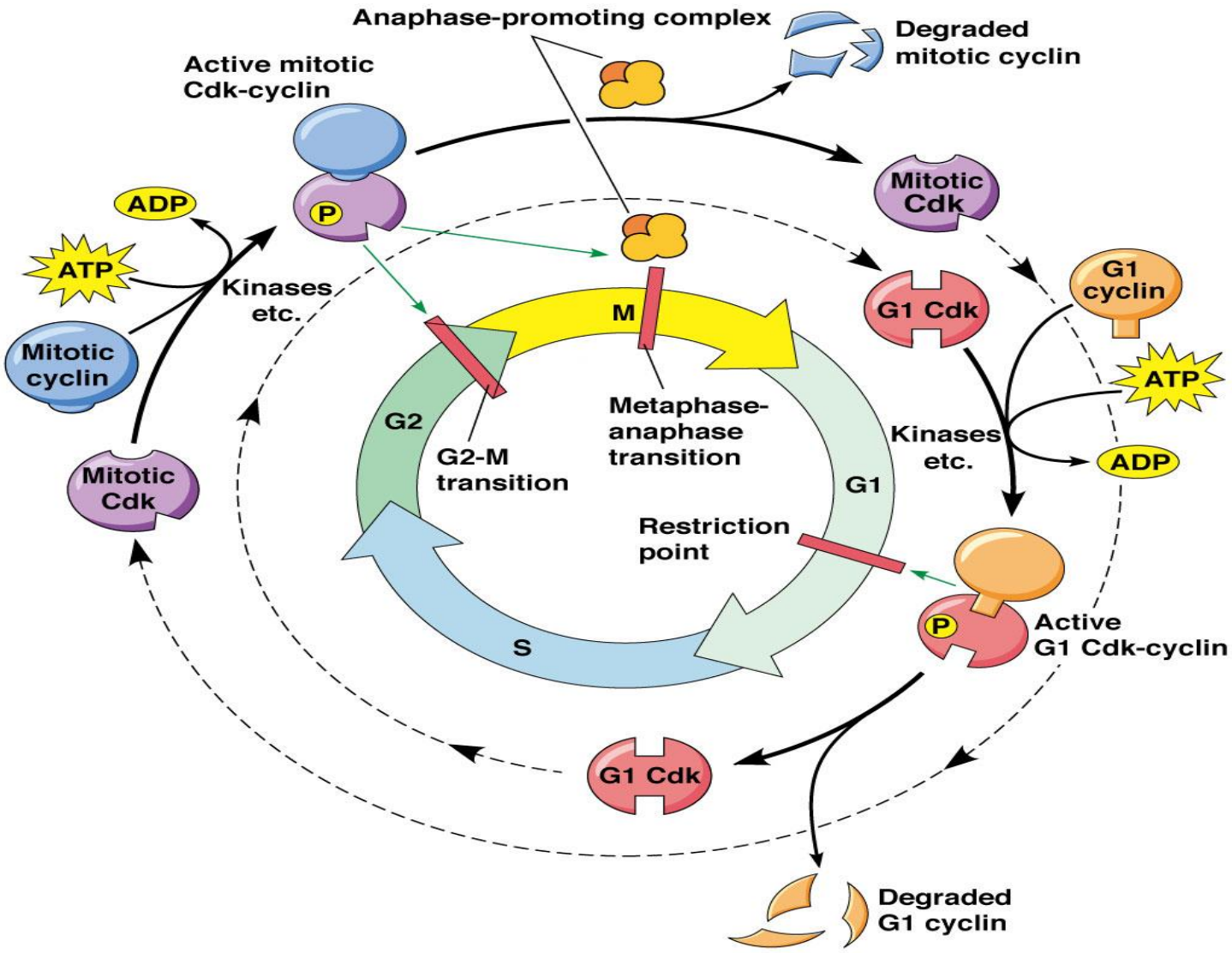
Cell cycle



Cell cycle

- *CDK* is not functional if cyclin is not attached to it. The first level of regulation is the presence of cyclins.
- Only the phosphorylated complex of cyclin- *CDK* is active.
- Additional phosphorylation inactivates the complex - negative regulation.
- Inhibitors of *CDK* can be attached directly to *CDK* and so they inhibit it.

Regulation of the cell cycle



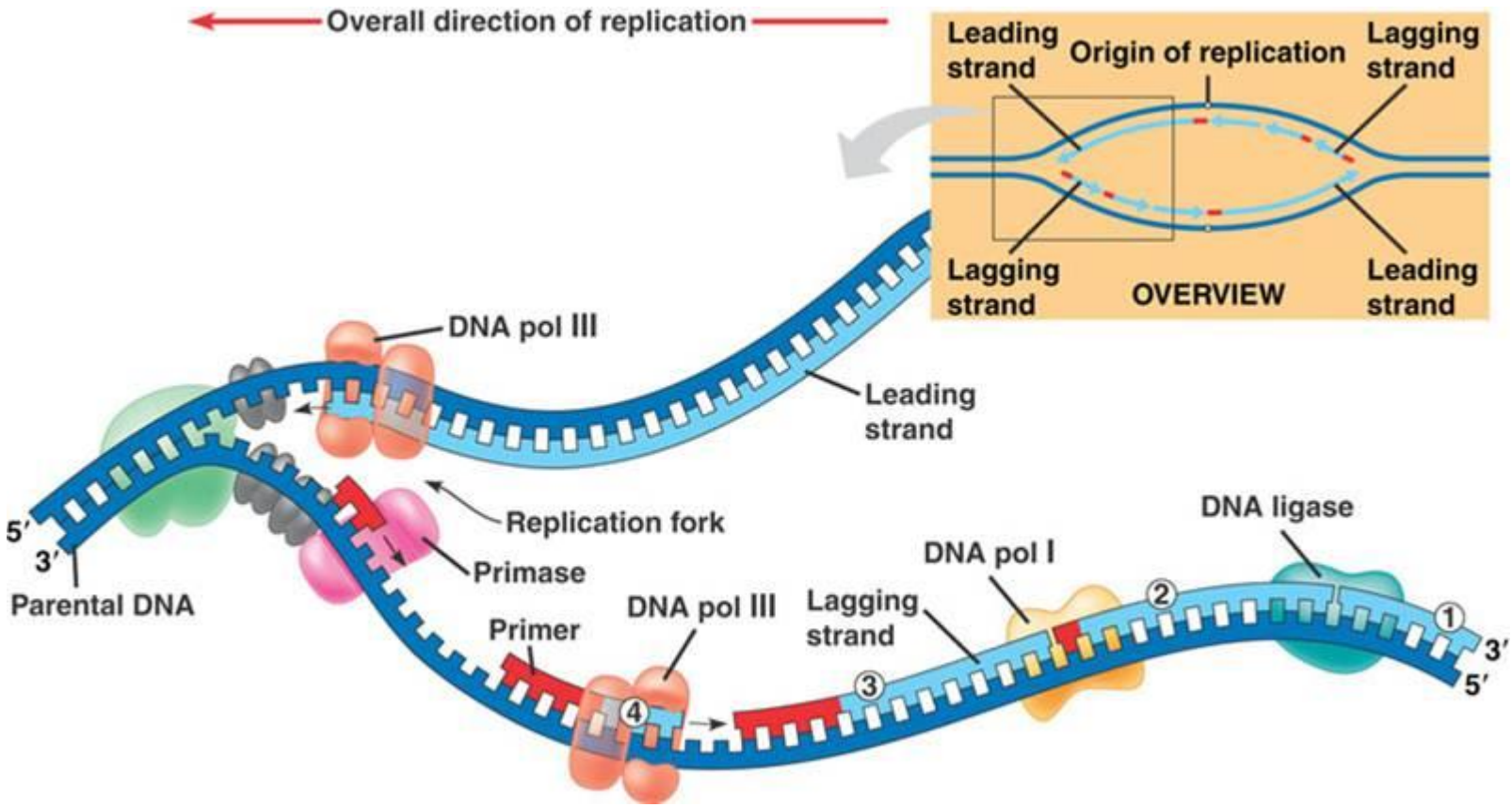
Regulation of the cell cycle

- *Proto-oncogenes*
- *anti-oncogenes (tumor suppressor genes)*
- *DNA repair system genes*

Regulation of the cell cycle

- Cell division is a strictly regulated process.
- The emergence of an adult organism from a fertilized egg cell involves countless cell divisions (duplications), each of which requires a precise division of genetic material and most other cellular components into daughter cells.

- Basis of proliferation:
- Splitting of genetic material-replication



Regulation of the cell cycle

- Organisms have mechanisms that prevent the occurrence of errors in the division and transfer of genetic material or, if errors occur, mechanisms that correct them.
- Even so, mistakes happen with measurable frequency.

Regulation of the cell cycle

- Cells constantly suffer damage, which can originate from the cell itself as by-products of metabolism or from the environment such as chemical agents or radiation.

- Most often, damage to the genetic material occurs during S phases as a result of an error in the synthesis process of DNA.

- Such damage can affect the "survival" of the cell, so a mechanism to remove the damage is developed in response.

Regulation of the cell cycle

Within damage control of DNA the flow of the cell cycle is stopped at three points:

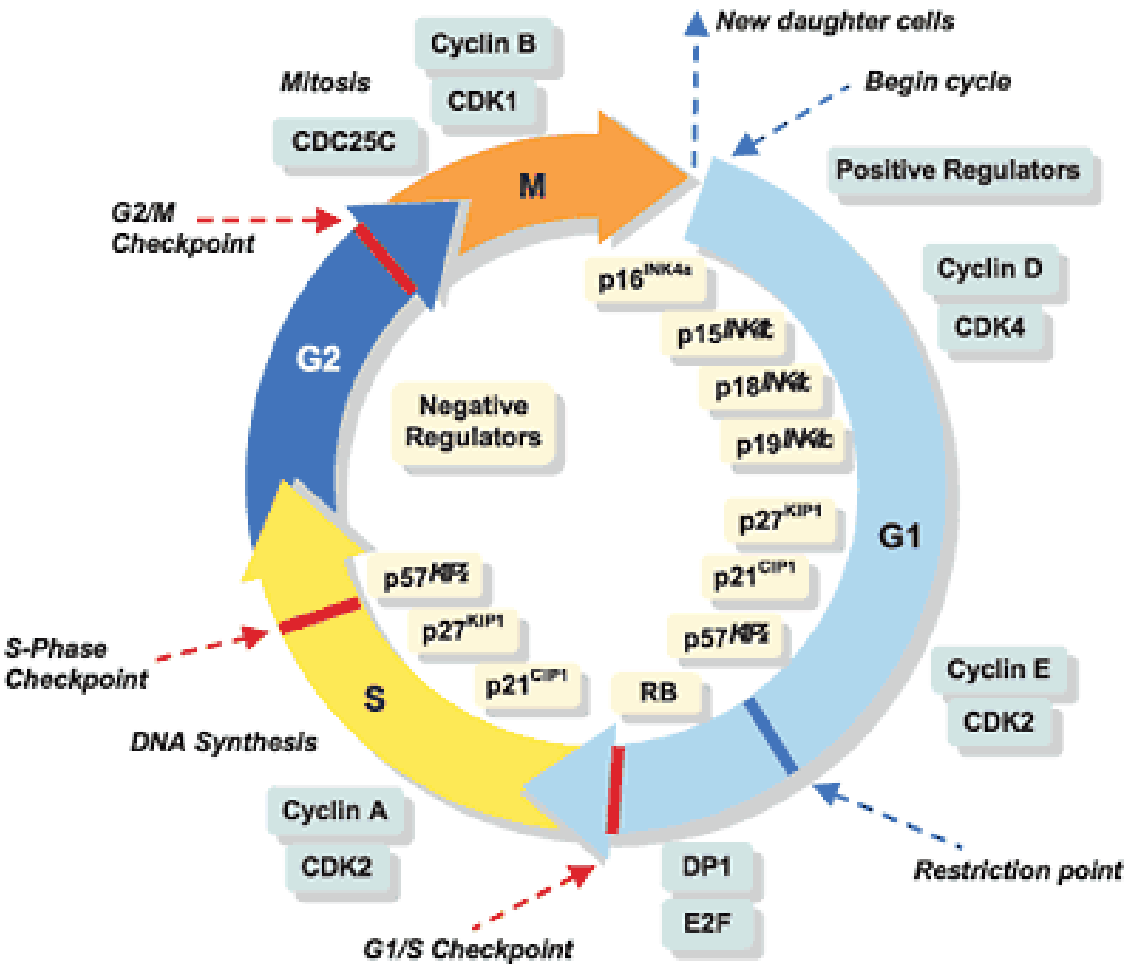
- before entering S phase (damage control DNA in G1 phase)
- During S phases (intra-S damage control of DNA)
- before entering the M phase (damage control of DNA in G2 phase).

Although it responds to different forms of DNAdamage they are not identical, but they are similar enough to generalize the principle of action.

Regulation of the cell cycle

- DNA damage of different forms is initially detected by a protein complex related toDNA. In mammalian cells, two proteinsATM and ATR represent damage-activated primary signal generators of DNA in all stages of the cell cycle.

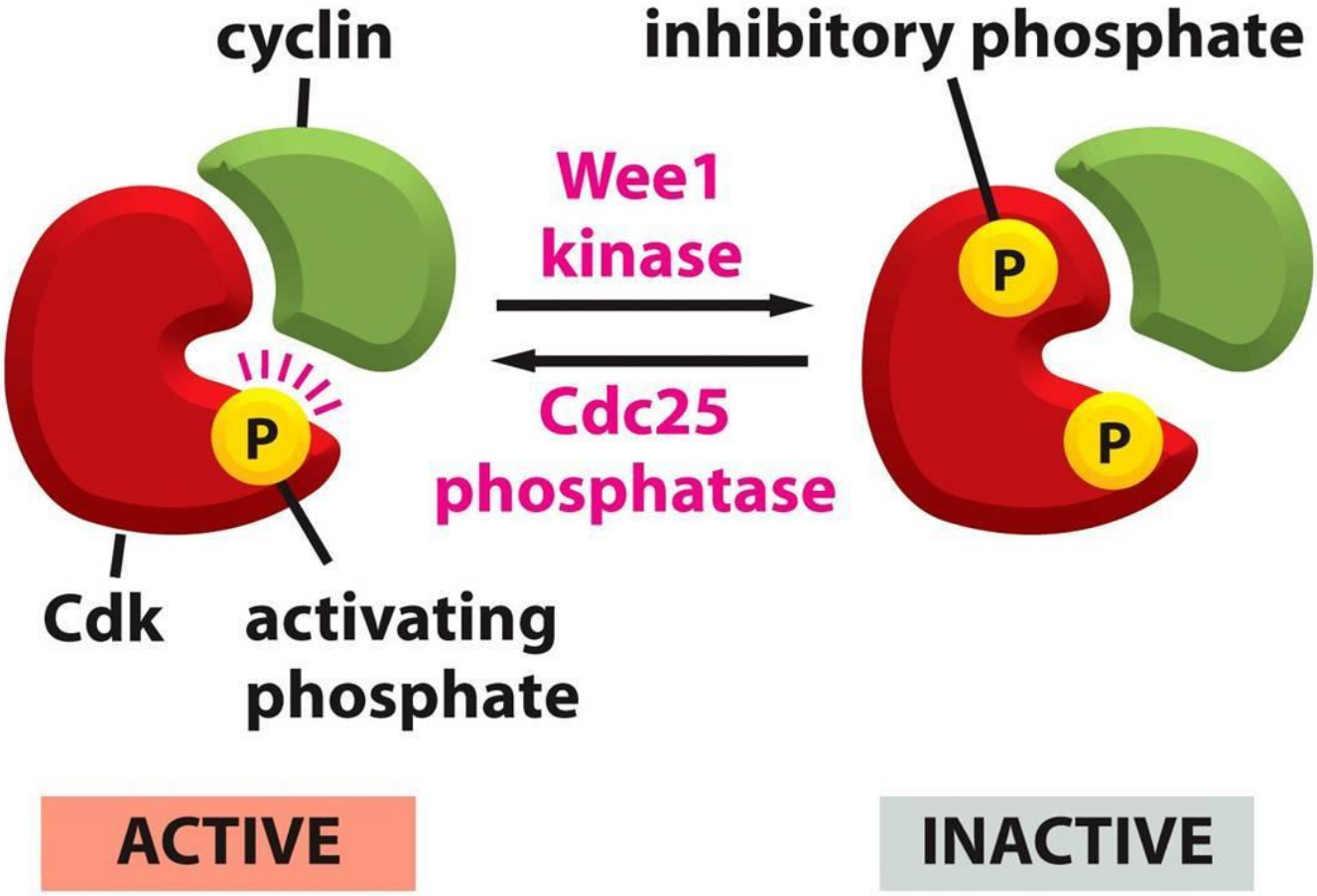
Regulation of the cell cycle



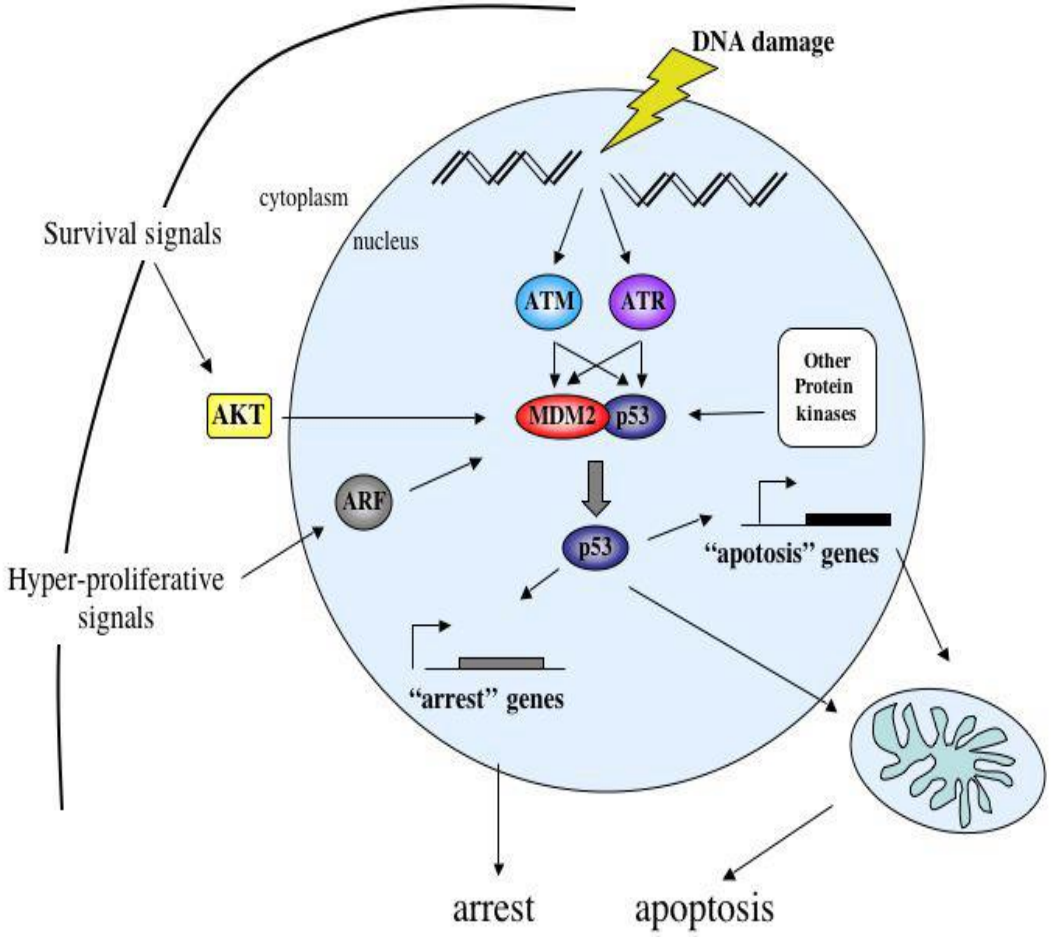
Tumor suppressor genes

- On damage registered in G_1 and G_2 checkpoints the cell responds to via a transcription factor known as p53.
- Signals over ATM and ATR activate p53.
- One of the dominant activation effects of p53 is an p21 expression. A high level of this inhibitor blocks the activity of the cyclin complex E (A) cdk2, and most likely cdk4 and cdk6, which stops the cell cycle in G_1 phase.

Regulation of the cell cycle

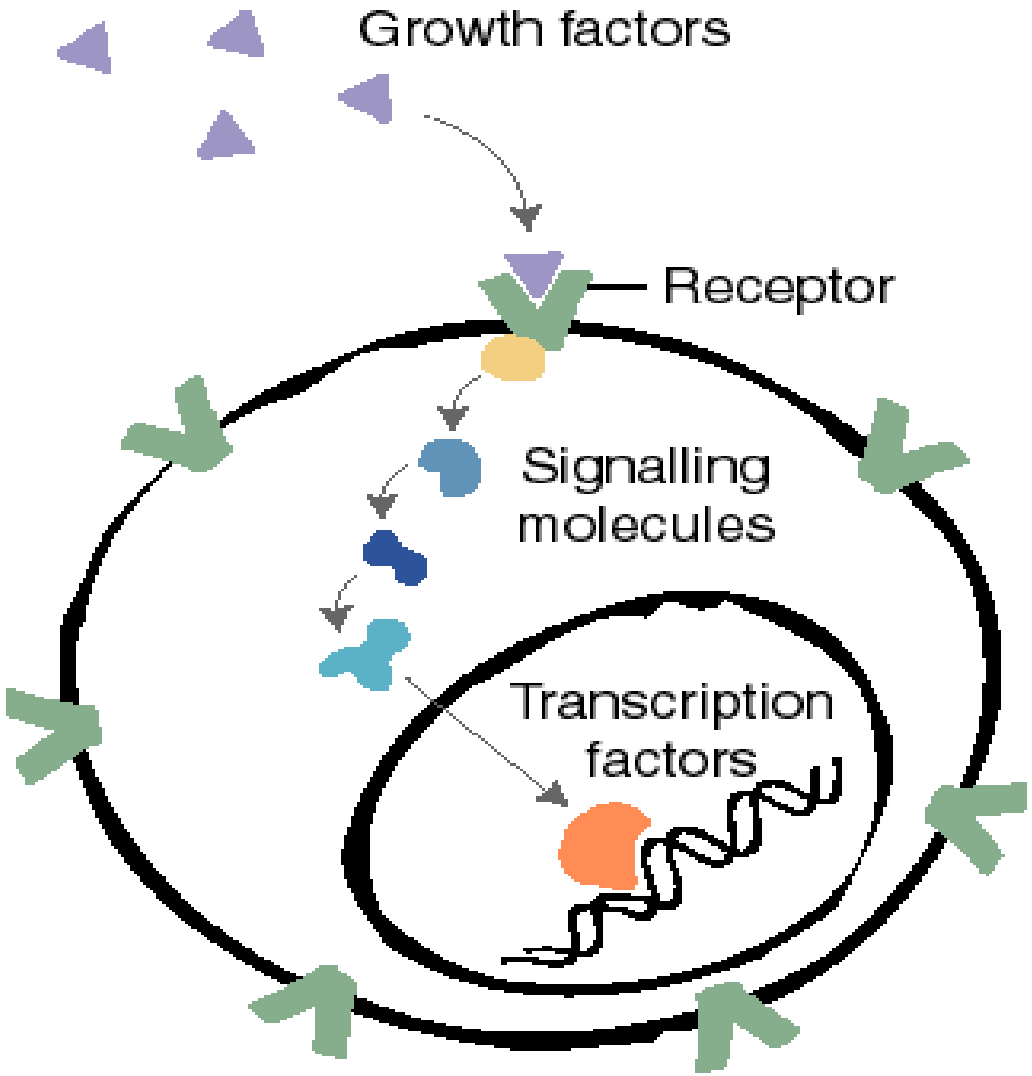


r53



- p53 ↑ Chip/Kip-p21
- Chip/Kip-p21↓cdk2;4,6
- G1 arrest
- p53 ↑ BAX, FAS,☠

Oncogenes


Growth factors
Receptor
Signalling molecules
Transcription factors

Extracellular control of the cell cycle

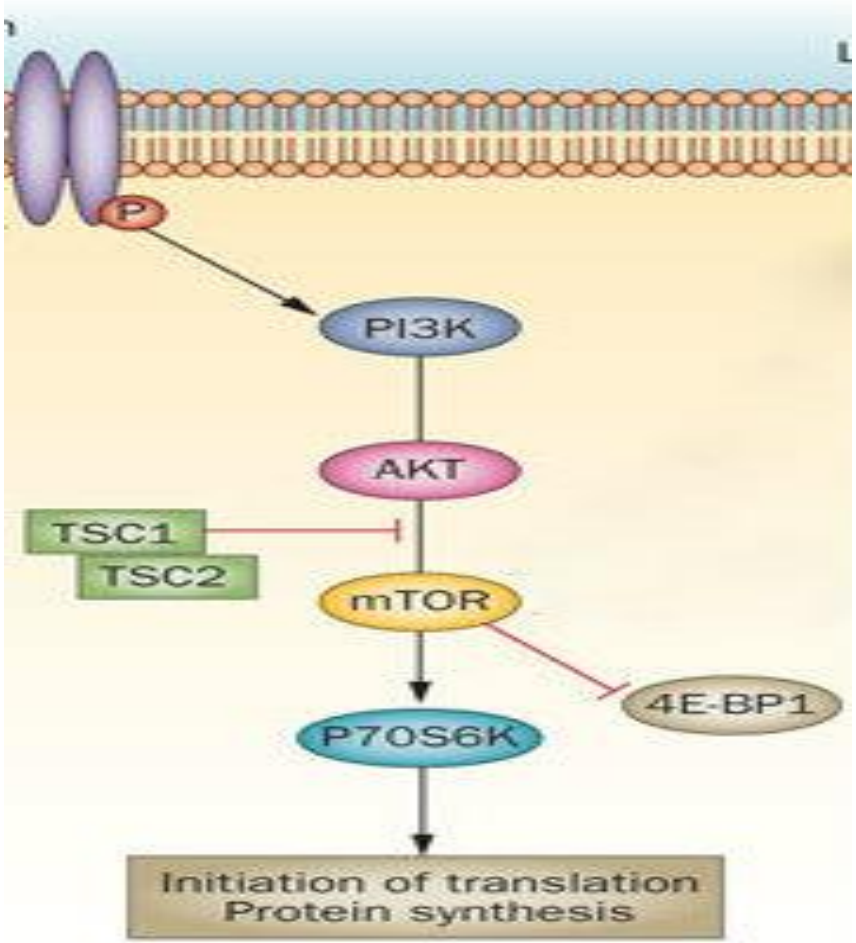
Mitogens

- stimulate cell division by activating G1/S CDK
- Platelet-derived growth factor (PDGF)
- Epidermal growth factor (EGF)
- erythropoietin

Extracellular control of the cell cycle

Growth factors

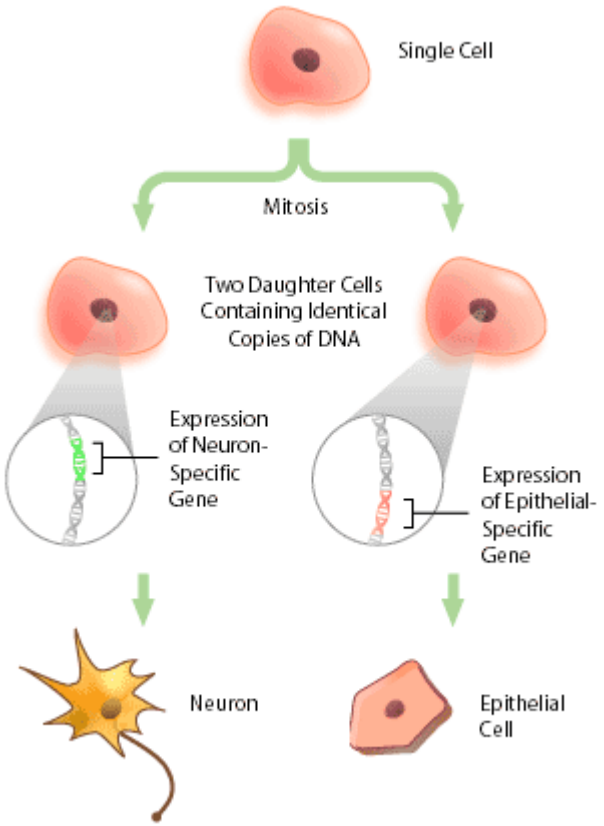
Growth factor and growth factor receptor



Cell differentiation

an adaptive process characterized by the expression of certain genes that dictate the synthesis of a series of proteins forming a specific cellular phenotype.

Cell differentiation

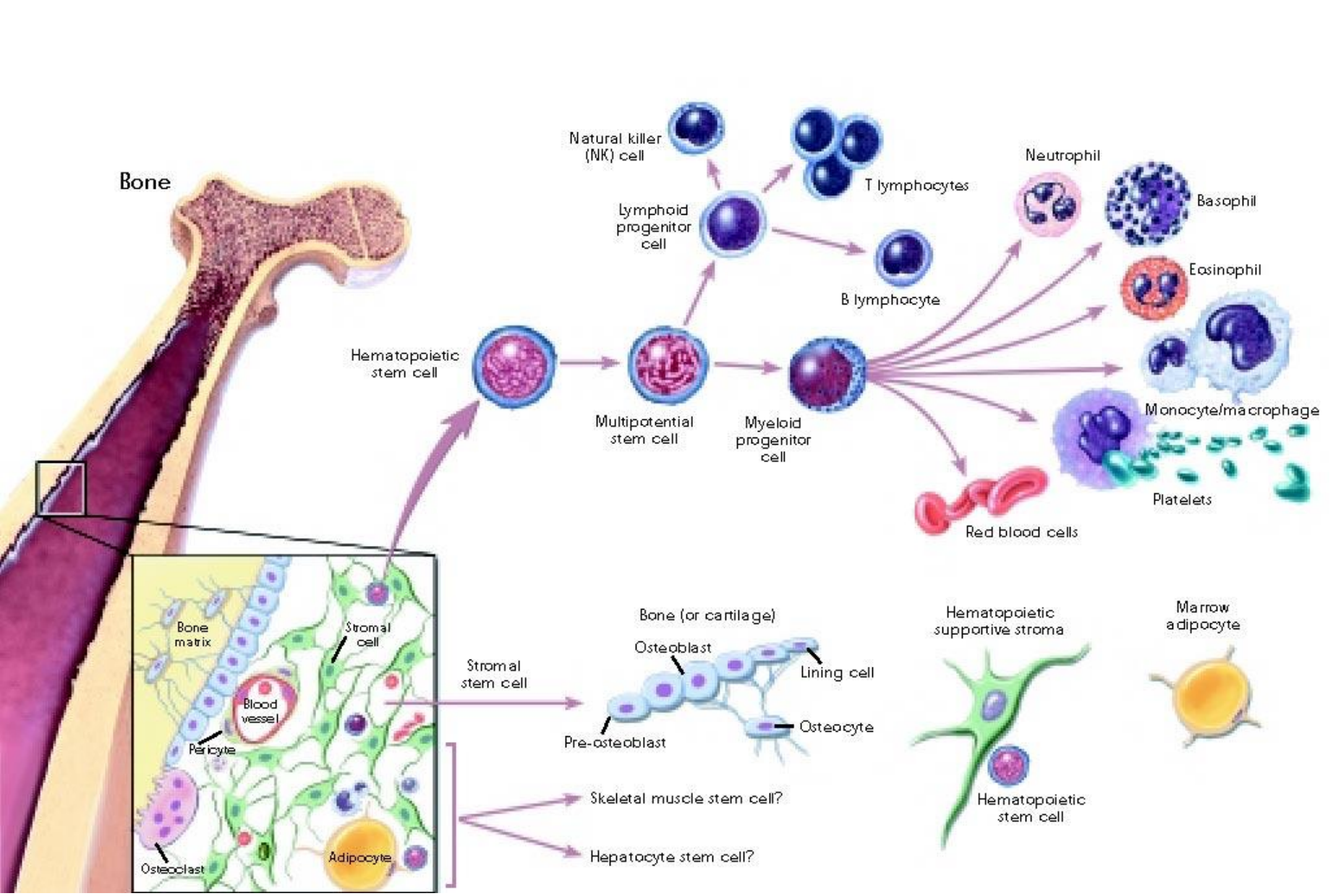


All cells of an organism come from a fertilized egg cell.
Almost all cells of an organism "carry" the same genetic material, originating from the mentioned fertilized egg cell.
Cells are phenotypically very different from each other even though they have the same genetic material.
During the embryonic development of the organism, cells located in different parts of the embryo begin to divide-they adapt, take on different phenotypes-type characteristics and inputs into the process **differentiation**.
Differentiated cells form different tissues and contain the same set of genes.

The stem cell

- an undifferentiated cell that has an unlimited ability to divide, whereby after each division one of the newly formed daughter cells grows and differentiates in a certain direction, while the other remains undifferentiated, the mother cell
- According to development potential:
  - totipotent
  - pluripotent
  - multipotent
  - unipotent.

Cell differentiation



Cell differentiation

Exiting the cell cycle represents a component and the first step of cell differentiation:

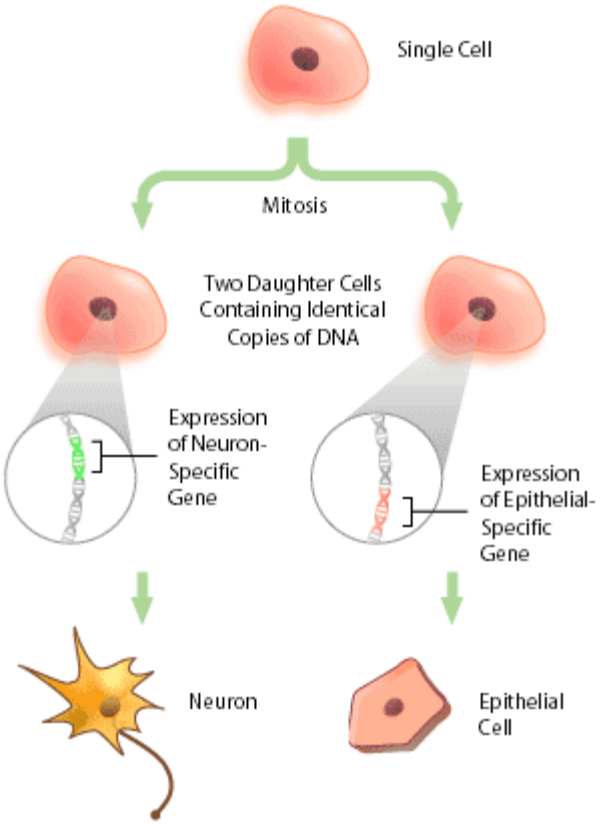
- Accumulation of G1/S CDK inhibitors
- Accumulation of INK4,CDK4 and CDK6
- Accumulation of Cip/Kip,CDK2
- Accumulation of Rb protein- p130, CDK2

"lagging" cells in G1phase

Cell differentiation

- Gene rearrangement.
- Intron splicing.

Cell differentiation



- *housekeeping* genes (15,000)
- tissue-specific genes (1,000)

Differentiation is characterized by the expression of genes characteristic for that type of cells. These genes dictate the synthesis of a series of proteins that form a specific cellular phenotype.

Cell differentiation