

Teaching unit 04

Oncogenes

Tumor suppressor gene

- Every gene, which, by losing its function, contributes to tumor development.
- The inactivation of tumor suppressor genes plays a role in the pathogenesis of tumors as important as the activation of oncogenes, and for many tumors even more important.

(un)controlled proliferation

- <http://www.youtube.com/watch?v=IeUANxFVXKc>
- <http://www.youtube.com/watch?v=LEpTTolebqo>

let us remind ourselves...

10×10^9 cells/24h

Growth and dying

proliferation

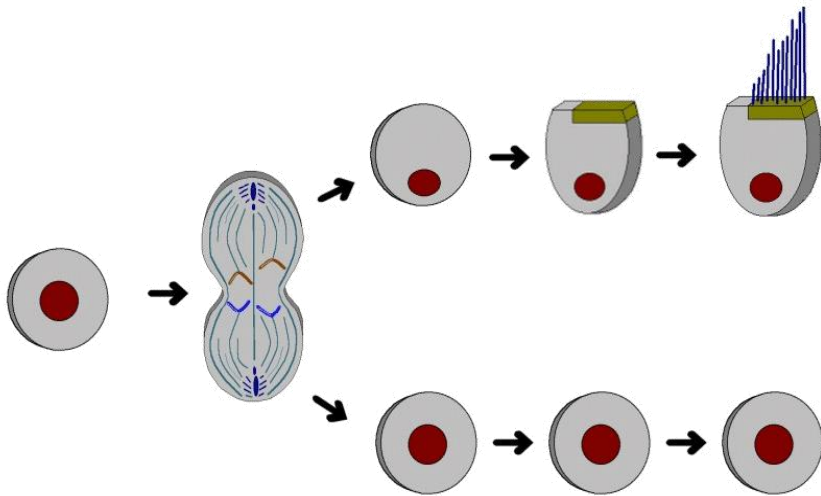
apoptosis



let us remind ourselves...

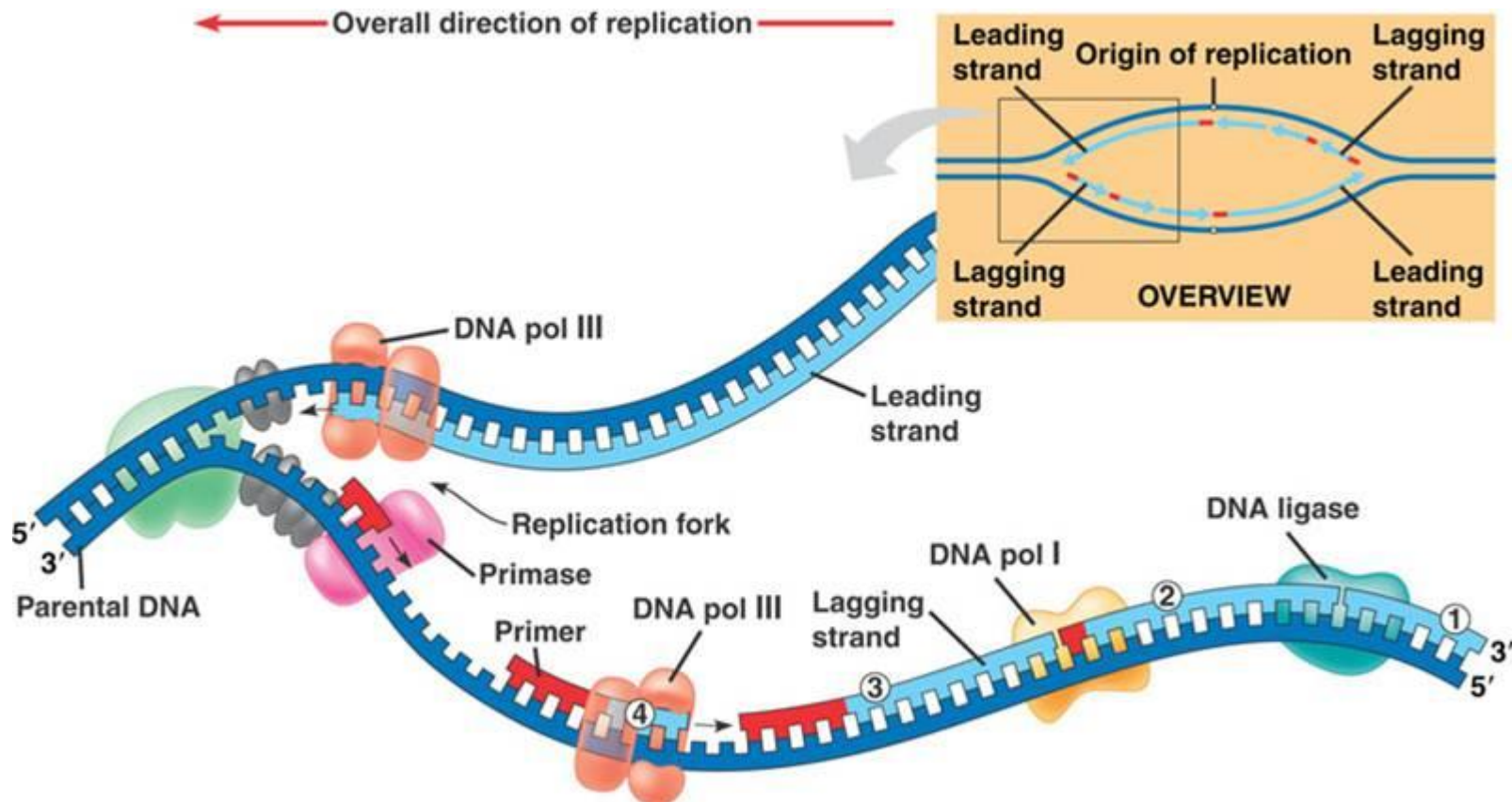
Cell proliferation

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



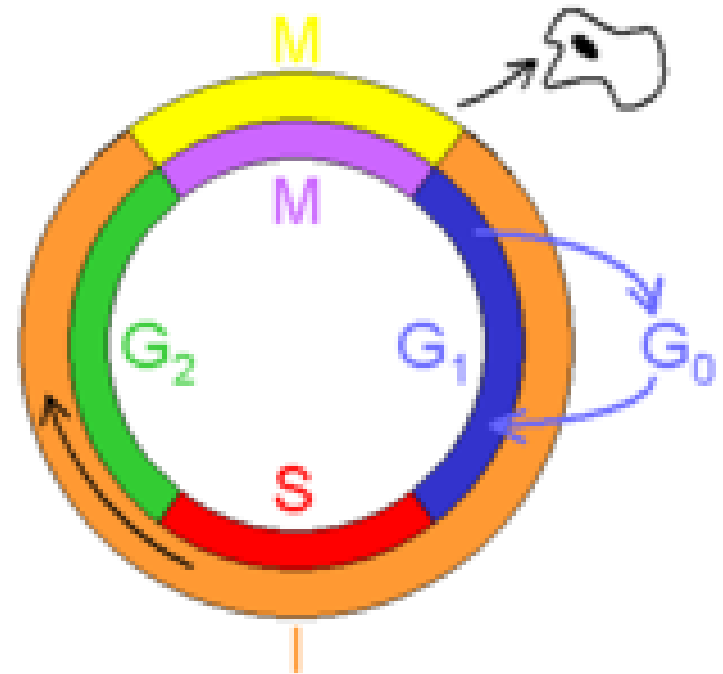
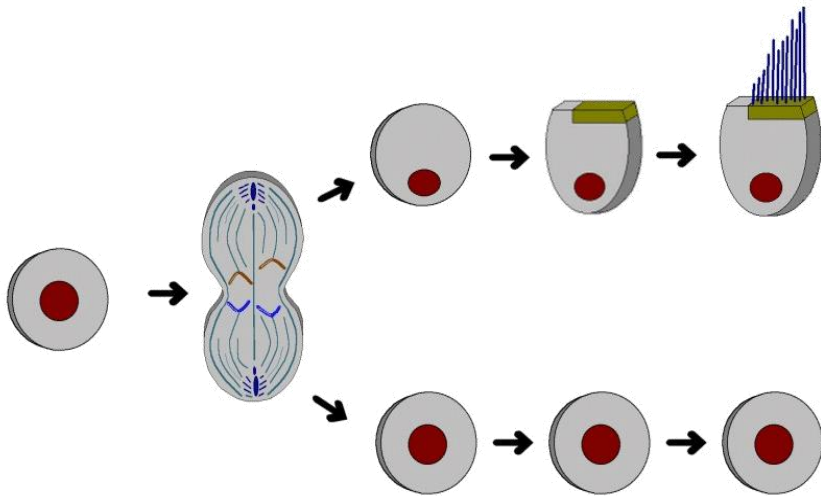
let us remind ourselves...

- At the root of proliferation:
- Splitting of genetic material - replication



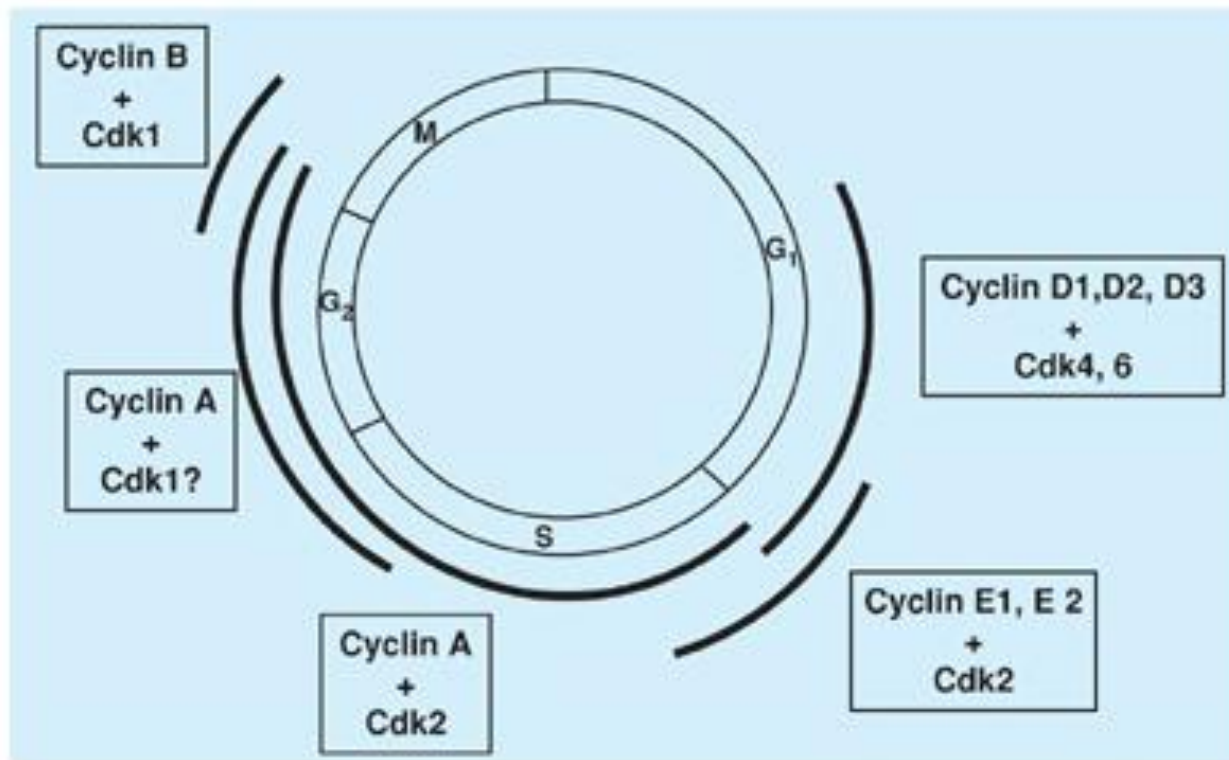
let us remind ourselves...

- 1951. Howard and Pelc:
- GAP1- G1
- *syntetic phase* - S
- GAP2 - G2
- *mitosis* - M



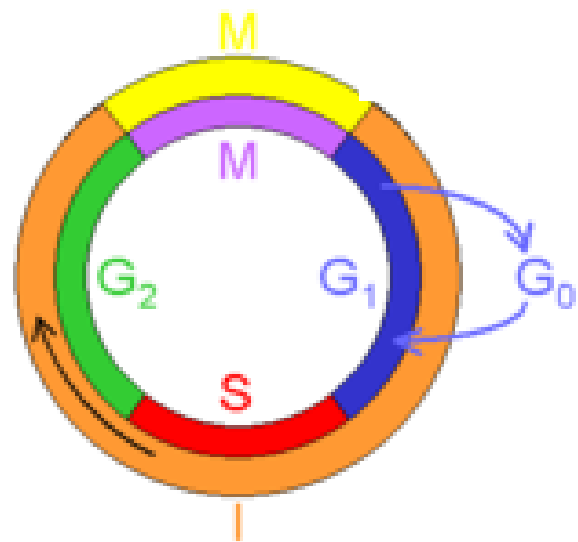
let us remind ourselves...

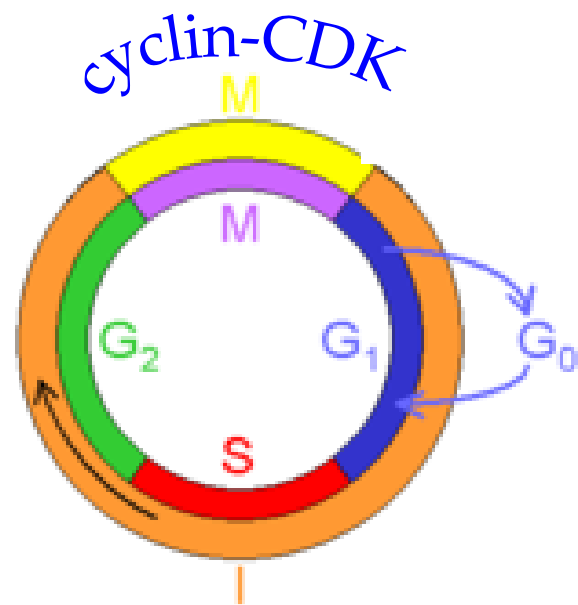
The cell cycle is regulated by cyclin-cyclin-dependent kinases **CDK**



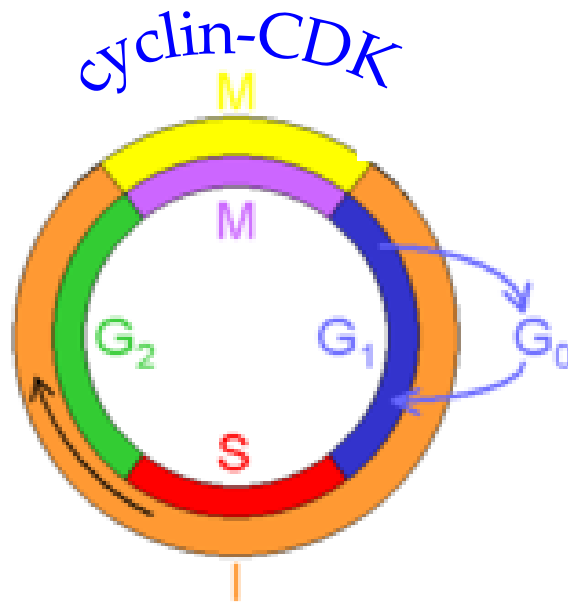
let us remind ourselves...

- ❏ The cell cycle is regulated at several levels.
- ❏ The mechanisms underlying the control and regulation of the cell cycle are extremely conserved.
- ❏ Proto-oncogenes
- ❏ Anti-oncogenes (tumor suppressor genes)
- ❏ DNA repair system genes

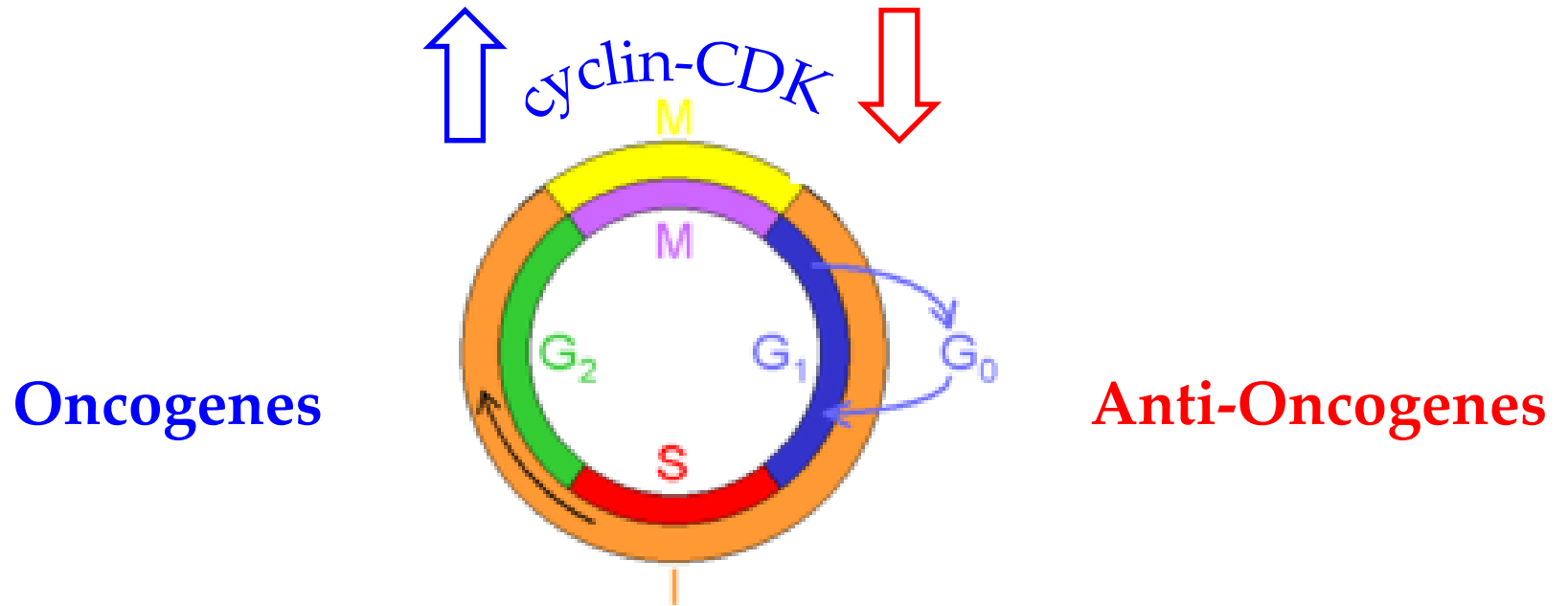


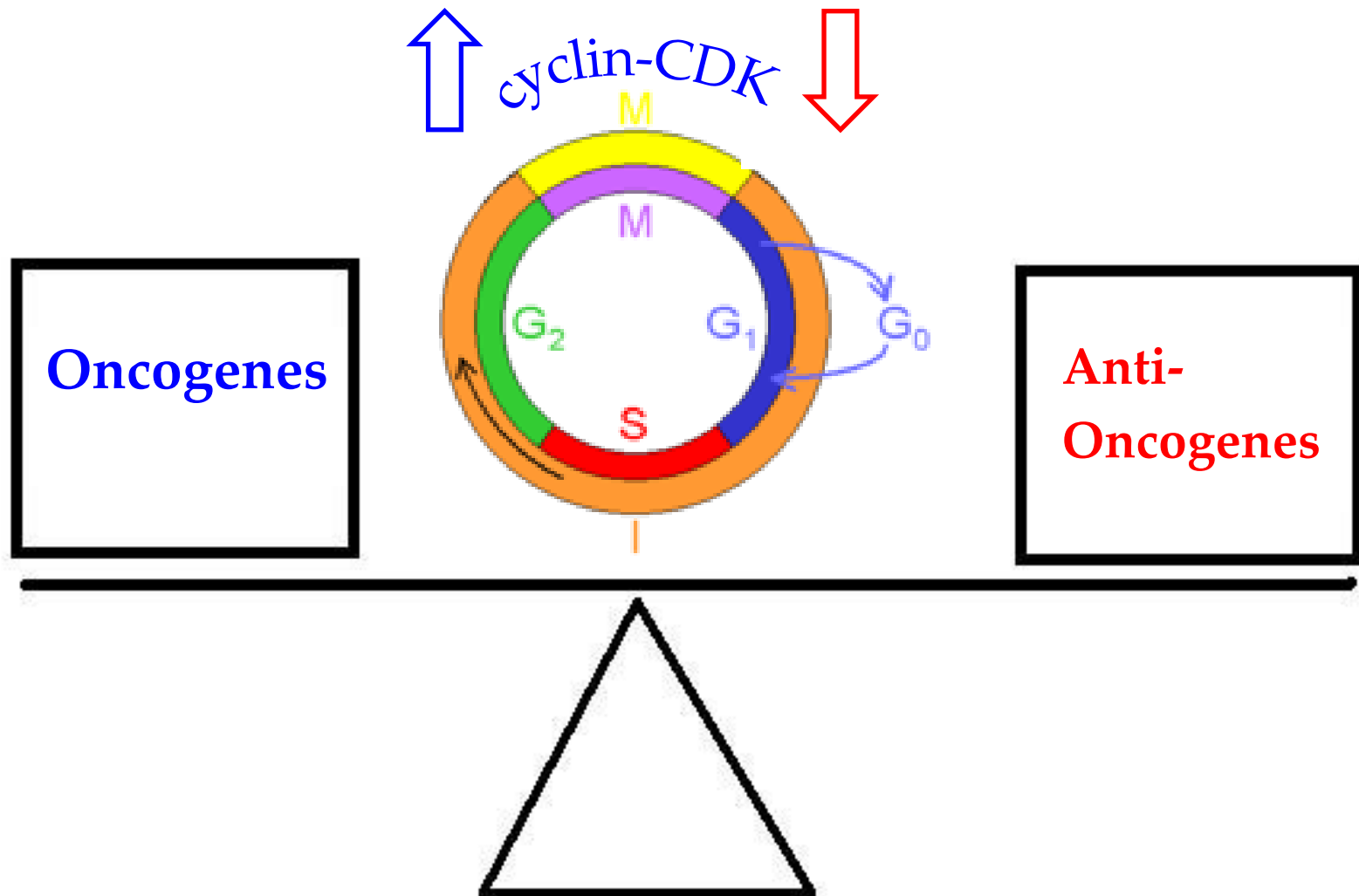


Oncogenes



Anti-Oncogenes





A diagram illustrating the relationship between cell proliferation and apoptosis. At the top is an oval labeled 'Cell'. Below it is an equals sign (=). At the bottom are two ovals: 'PROLIFERATION' on the left and 'APOPTOSIS' on the right, separated by a minus sign (-). Both bottom ovals have a vertical line extending down to a horizontal baseline.

Cell

=

PROLIFERATION

-

APOPTOSIS

CELL

=

PROLIFERATION

—

APOPTOSIS

ONCOGENES

—

**TUMOR
SUPPRESSOR
GENES**

CELL

=

PROLIFERATION

—

APOPTOSIS

ONCOGENES

—

**TUMOR
SUPPRESSOR
GENES**

**PRO-
APOPTOTIC
FACTORS**

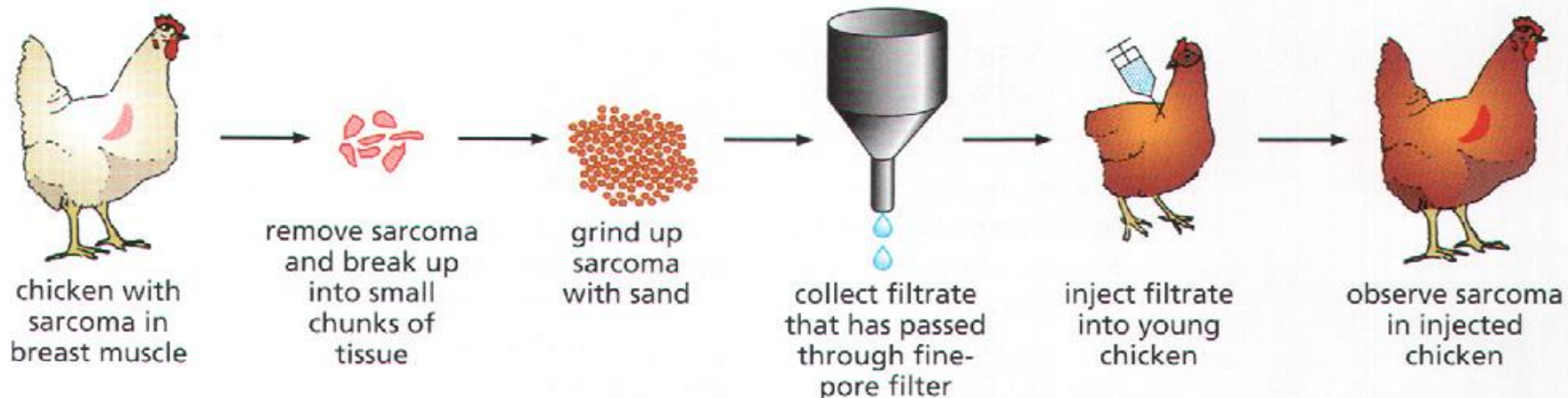
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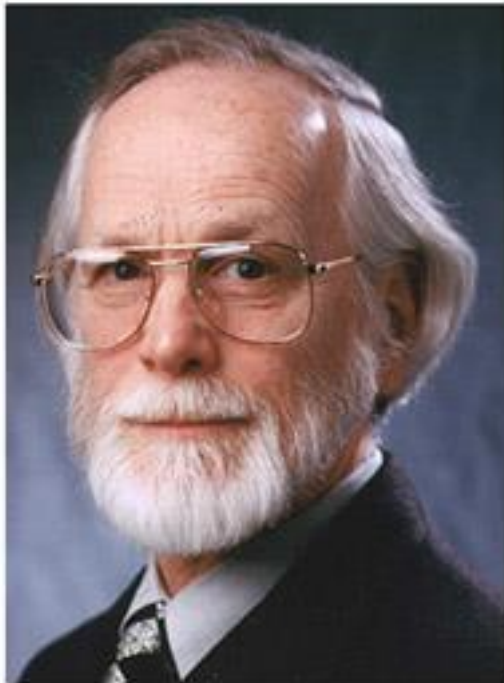
**ANTI-
APOPTOTIC
FACTORS**



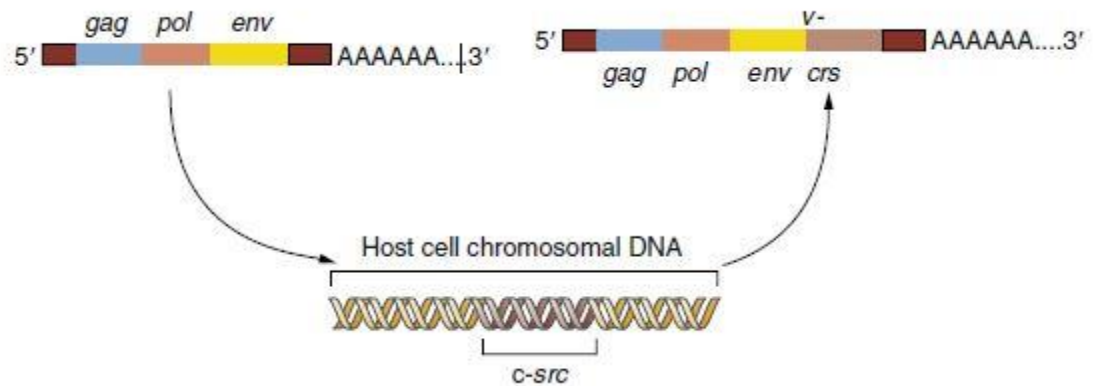
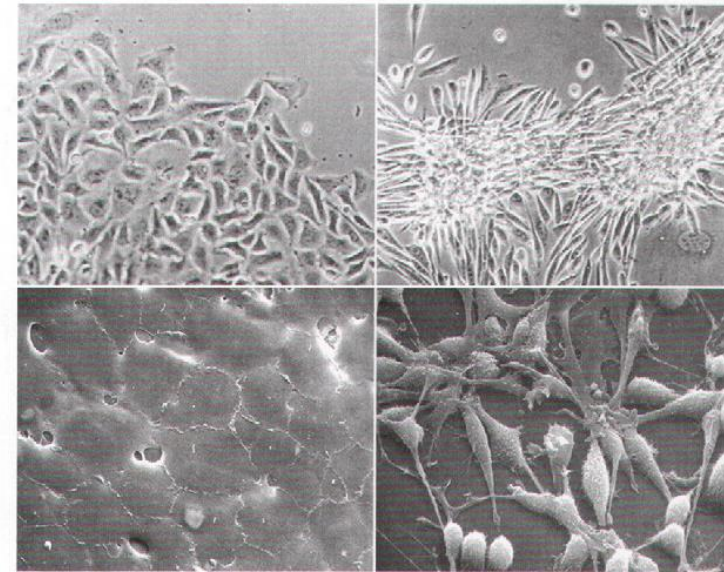
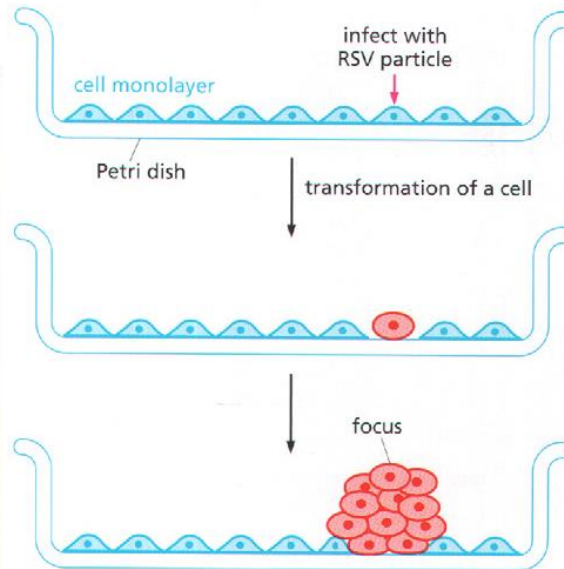
Figure 3.1 Peyton Rous and the hen that launched modern cancer research (A) Francis Peyton Rous began his work in 1910 that led to the discovery of Rous sarcoma virus (RSV) (left). More than 50 years later (1966), he received the Nobel Prize in Medicine and Physiology for this seminal work—a tribute to his persistence and longevity (right). (B) His good fortune began when a Long Island, NY chicken farmer brought Rous, then working at the

Rockefeller Institute in New York, a prized barred Plymouth Rock hen. The farmer wanted Rous to treat the large tumor growing in its chest muscle; Rous saw experimental opportunity and dispatched the hen, extracting the tumor. The arthritic hands are likely those of the chicken farmer. (A, courtesy of the Rockefeller University Archives. B, from P. Rous, *J. Exp. Med.* 12:696–705, 1910.)





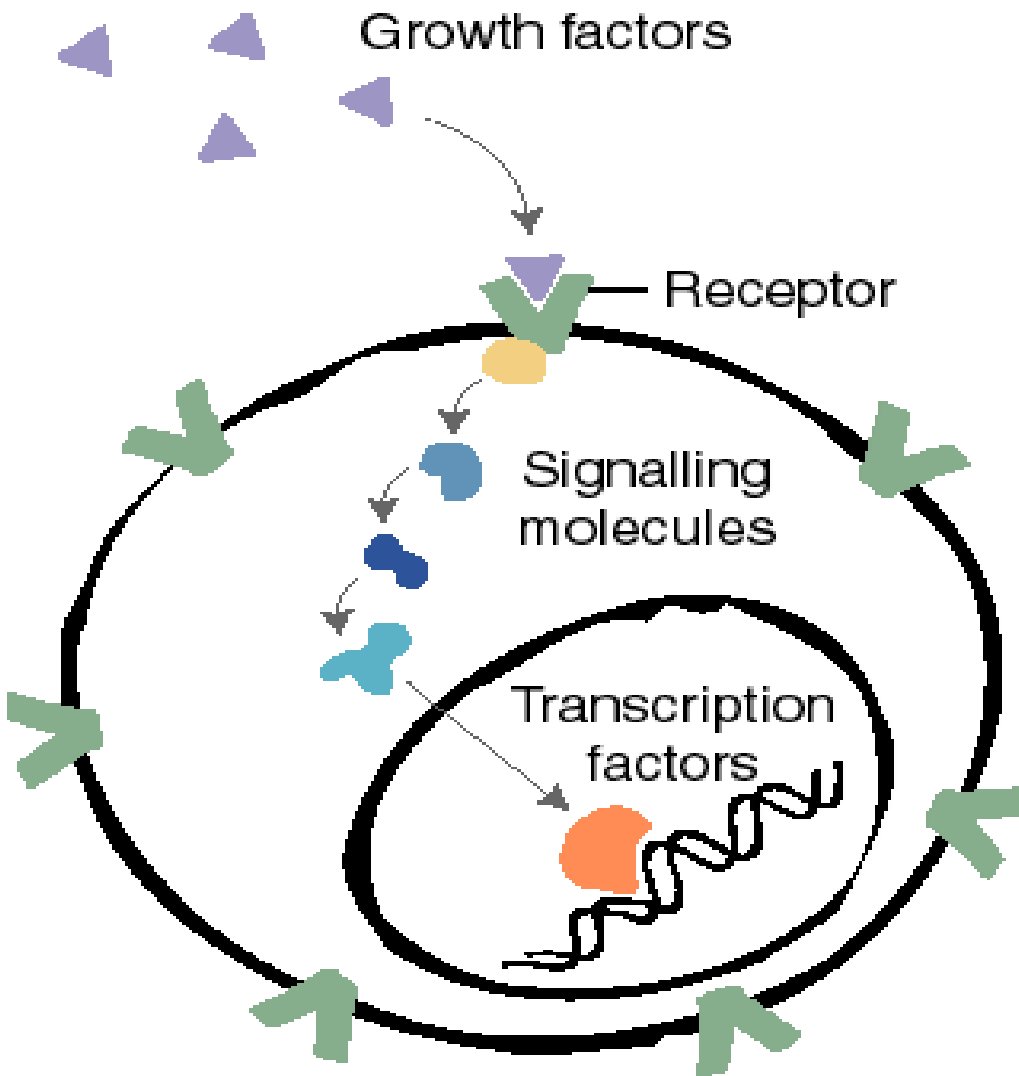
Courtesy of Dr. J. Bishop, University of California, San Francisco.
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Multilevel vs.
single-hit model

(PROTO)ONCOGENES

- Evolutionarily highly conserved genes
- Despite the name, their function is not to induce the formation of tumors
- Over 100 identified
- Necessary for many normal biological processes in the cell:
 - Proliferation
 - Apoptosis
 - differentiation



Oncogenes encode:

Growth factors

Growth factor receptors

Signal transducers

Transcription factors

One of the causes of disturbances in the regulation of cell proliferation is hyperactivity of proto-oncogenes

(hyper)Activation of oncogenes

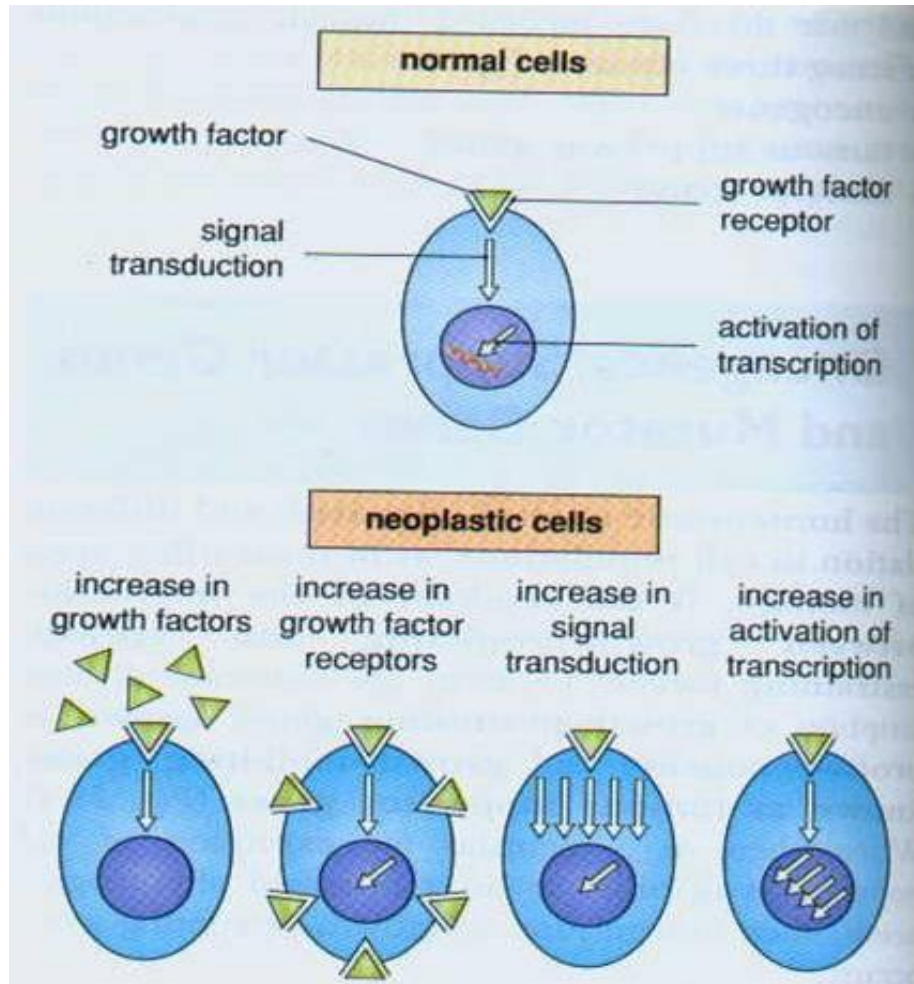
- DNA damage: proto-oncogene activation
- Qualitative and quantitative changes

Mechanisms:

- Point mutations
- Reciprocal translocations (interruption of two chromosomes and reciprocal exchange of genetic material)
- Deletions
- Duplications
- Inversions
- Insertion of viral DNA or RNA into the genome of a cell

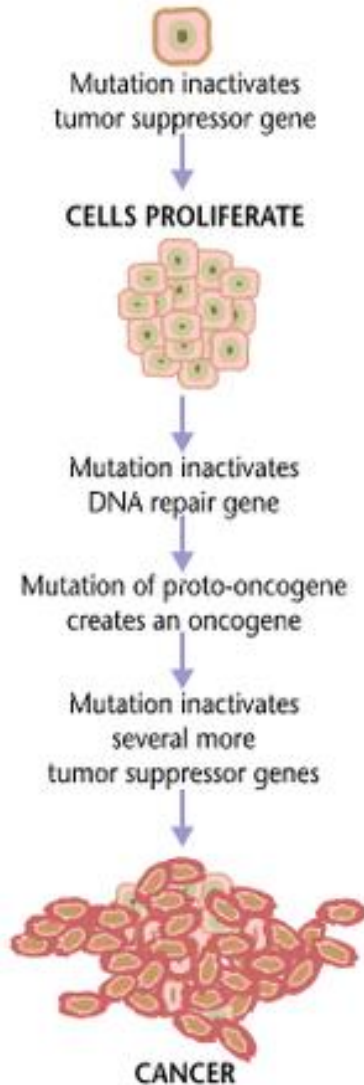
<http://www.youtube.com/watch?v=2wIVwZksIt4>

The consequence of excessive activation of oncogenes...



- Increased amount and activity of growth factors
- Increased number of receptors for growth factors
- Increased number of proteins involved in various signaling pathways
- Increased creation of transcription factors.

Immortalization...



- Tumor cells are normal cells that have lost control of the cell cycle:
- **Immortalization:** independent growth (proliferation)
- Transformation: growth autonomy, independence from growth factors and contact inhibition
- Metastasis

Growth factors

- Granulocyte colony stimulating factor (G-CSF)
- Granulocytic monocytic colony stimulating factor (GM-CSF)
- Nerve growth factor (NGF)
- Neurotrophins
- Platelet-derived growth factor (PDGF)
- Erythropoietin (EPO)
- Thrombopoietin (TPO)
- Myostatin (GDF-8)
- Fibroblast growth factors (FGF)
- Epidermal growth factor (EGF)
- Hepatocyte growth factor (HGF)
- Vascular endothelial growth factor (VEGF)

Platelet-derived growth factor - PDGF (platelet-derived growth factor)

- Mitogen and chemoattractant for mesenchymal cells (fibroblasts and vascular smooth muscle cells)
- Embryonic development, proliferation, cell migration and angiogenesis
- Signaling pathways via Ras, PI3K and phospholipase C
- Receptors for PDGF: colorectal cancer, lung and breast cancer.
- Avoiding the cell cycle checkpoint at the G1 phase checkpoint

VEGF (vascular endothelial growth factor)

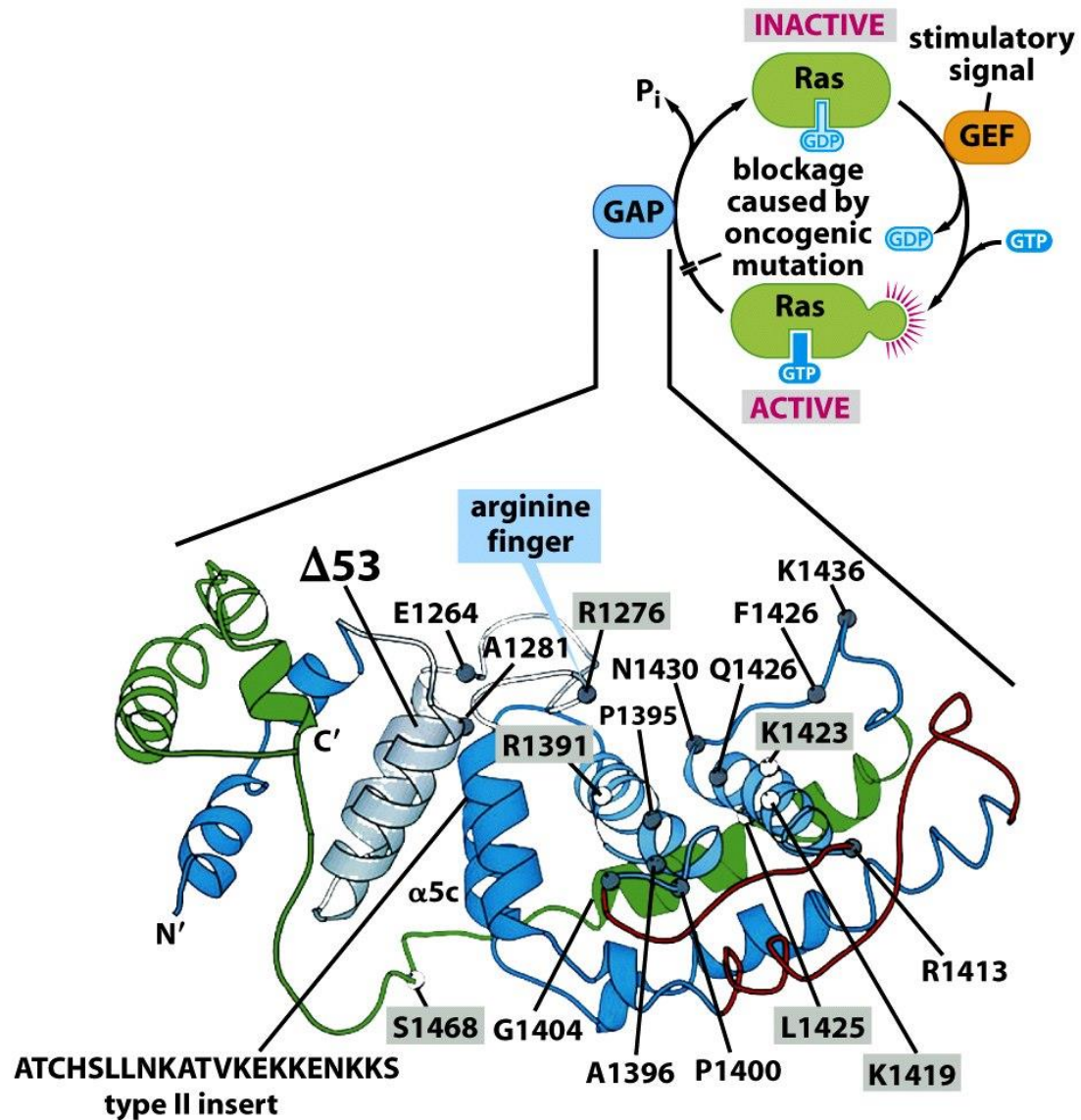
- Family of 6 proteins (VEGF-A)
- 3 VEGF receptors (VEGFR-2)
- VEGF-A + VEGFR-2 → migration and proliferation of endothelial cells and increased permeability of blood vessels
- downstream signaling pathways PI3K/AKT, ERK1/2 and MAPK

http://www.youtube.com/watch?v=K9B_4WIu7KQ

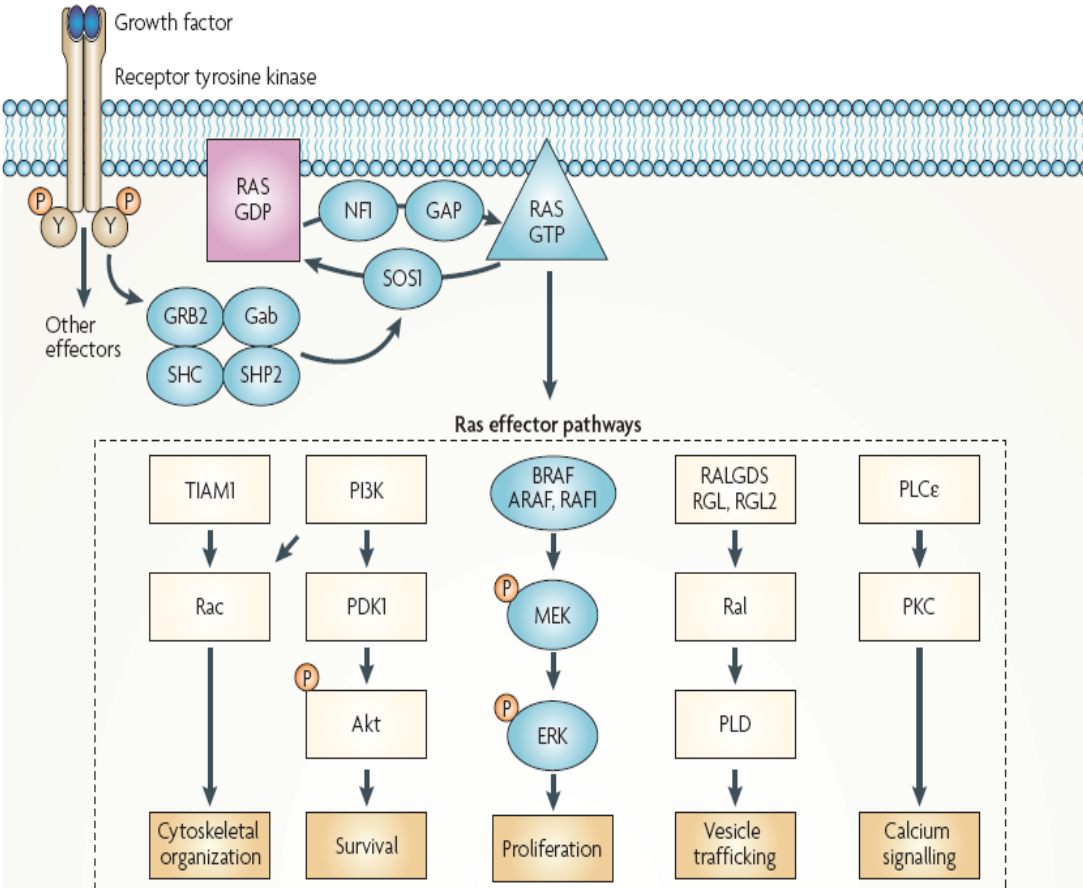
Ras oncogenes

- The products of Ras genes are G-proteins
- They bind guanine nucleotides and activate different sets of signaling cascades
- When bound to GDP (guanosine diphosphate), the Ras protein is in an inactive form
- With the help of SOS proteins (Son-Of-Sevenless), which substitute GDP for GTP (guanosine triphosphate), it undergoes conformational changes and becomes the active form.
- The signal is then transmitted downstream to the nucleus where it activates various transcription factors including c-myc.

Ras signaling pathway



Ras signaling pathway



The growth factor binding to its receptor induces the mobilization of numerous adapter proteins responsible for the conversion of Ras-GDP (inactive form) to Ras-GTP (active form).

Ras activation results: cell proliferation, cytoskeletal reorganization, survival, vesicle transport, and calcium release.

Ras oncogenes

- Mutation of the Ras gene creates oncoproteins that stimulate cell division independently of growth factors-locked Ras-GTP → MAPK
- They are considered to have an important role in angiogenesis and tumor metastasis
- Ras gene mutation induces increased production of pro-angiogenic vascular endothelial growth factor (VEGF)

c-myc oncogene

- Transcription factor, an important component in the control of cell growth.
- It participates in various cellular processes:
 - Proliferation
 - Differentiation
 - Apoptosis
- Expression of the c-myc gene is tightly regulated in normal cells:
 - In cells that are at rest and not dividing, its expression is unmeasurable
 - after mitogenic stimulation the expression increases
 - in proliferating cells it remains expressed at a very low level

Oncogene cooperation

- Important molecular concept of oncogenesis.
- Ras and c-myc oncogenes:
 - c-myc-a is responsible for the increased sensitivity of cells to apoptosis.
 - Ras reduces their sensitivity.

Ras + c-myc →

arrest of terminal differentiation

↑ proliferation

↑ resistance to apoptosis

c-myc oncogene

- It can induce various types of tumors and is necessary for the maintenance of malignant cell transformation.
- Overexpression of c-myc has been detected in various tumors.
- Its ectopic expression can induce disruption of DNA synthesis and genetic instability.
- Favors angiogenesis.
- With the repression of adhesive molecules (LFA-1), malignant cells lose contact inhibition and continuously proliferate.
- It enhances the activity of telomerase, the enzyme that synthesizes telomeres.

c-myc oncogene

- Discovered for the first time in patients with Burkitt's lymphoma showing frequent translocations on chromosome 8.
- Mutated or over-transcribed c-myc oncogene becomes an oncogene that increases cell proliferation.
- c-myc oncogene translocates to the region of the immunoglobulin gene promoter (on chromosomes 2, 14 and 22).
- Promoters activate the c-myc oncogene instead of immunoglobulin genes and induce continuous lymphocyte proliferation.

HER2/neu

- HER2/neu gene encodes a receptor with tyrosine kinase activity.
- This gene is overexpressed in about 25% of breast cancers.
- Breast cancers with hyperexpression of HER2/neu are clinically much more aggressive.
- HER2/neu hyperexpression is due to gene amplification. Multiple copies of genes accumulate in tumor cells. An increased number of HER2/neu receptors on tumor cells results in increased sensitivity of the ras-MAP kinase pathway and intensification of proliferation.
- Discovery of HER2/neu amplification in breast cancer led to the development of the monoclonal antibody Herceptin. Herceptin binds to HER2/neu on the cell surface and thus blocks the receptor. It also induces tumor cell killing by the host's immune system.

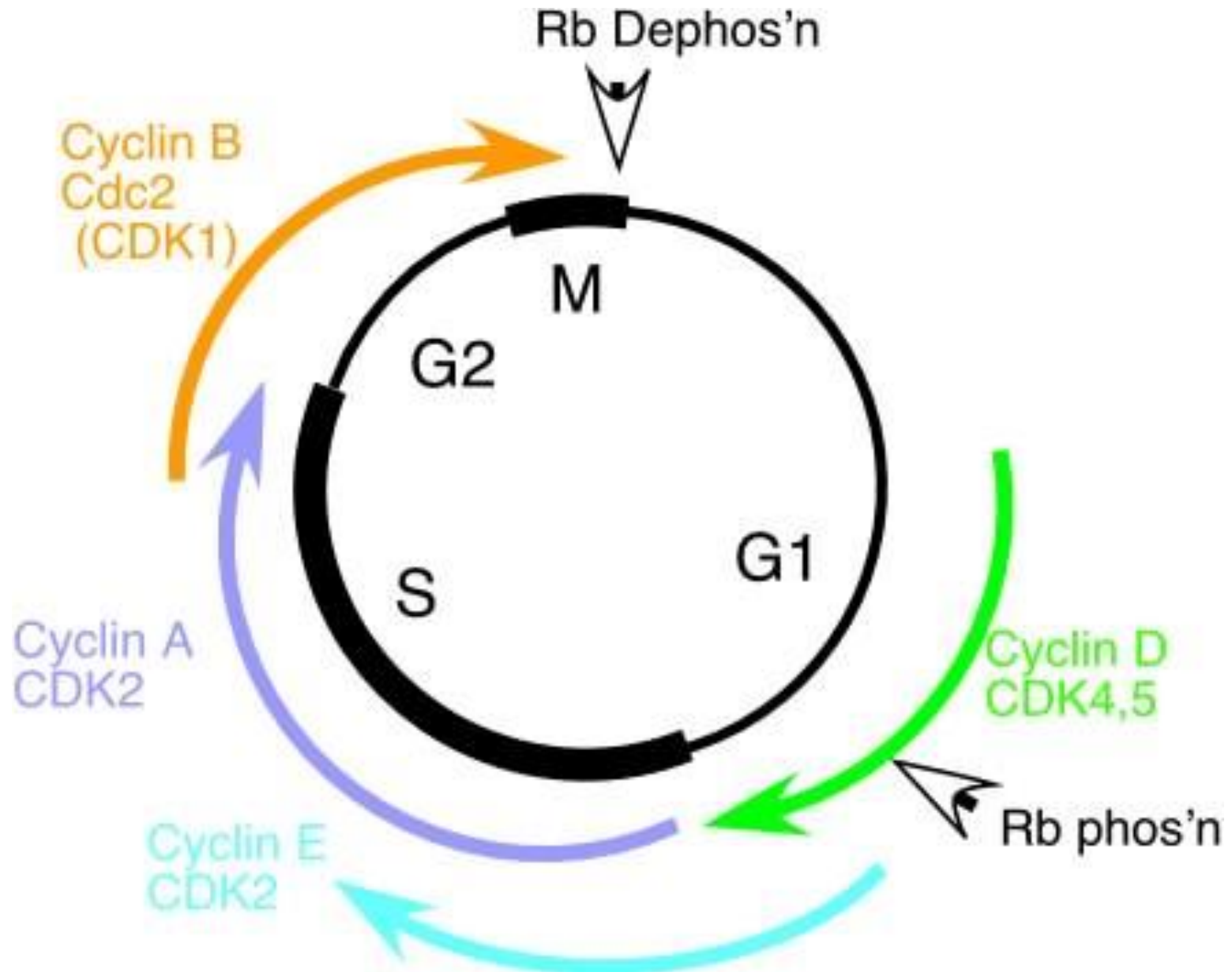
Cyclin D

- Synthesis begins during the G1 phase and enables the G1/S transition.
- Cyclin D interacts with CDK 2, 4, 5 and 6.
- In proliferating cells, accumulation of cyclin D-CDK4/6 allows cell cycle progression.
- This complex phosphorylates and thus inactivates the Rb anti-oncogene protein. Inhibition of Rb induces the expression of some genes (eg cyclin E) important for the transition of the cell cycle to the S phase.
- Activation of the MAP kinase pathway in the cell activates the transcription factors Myc and AP-1, which consequently drive the transcription of the genes for Cdk4, Cdk6 and cyclin D.

Cyclin D

- In a normal cell, increased expression of cyclin D shortens the duration of the G1 phase of the cell cycle.
- Increased concentration of cyclin D and cyclin D-CDK4 complex can induce cell transition from G0 to S phase of the cell cycle even in the absence of growth factors.

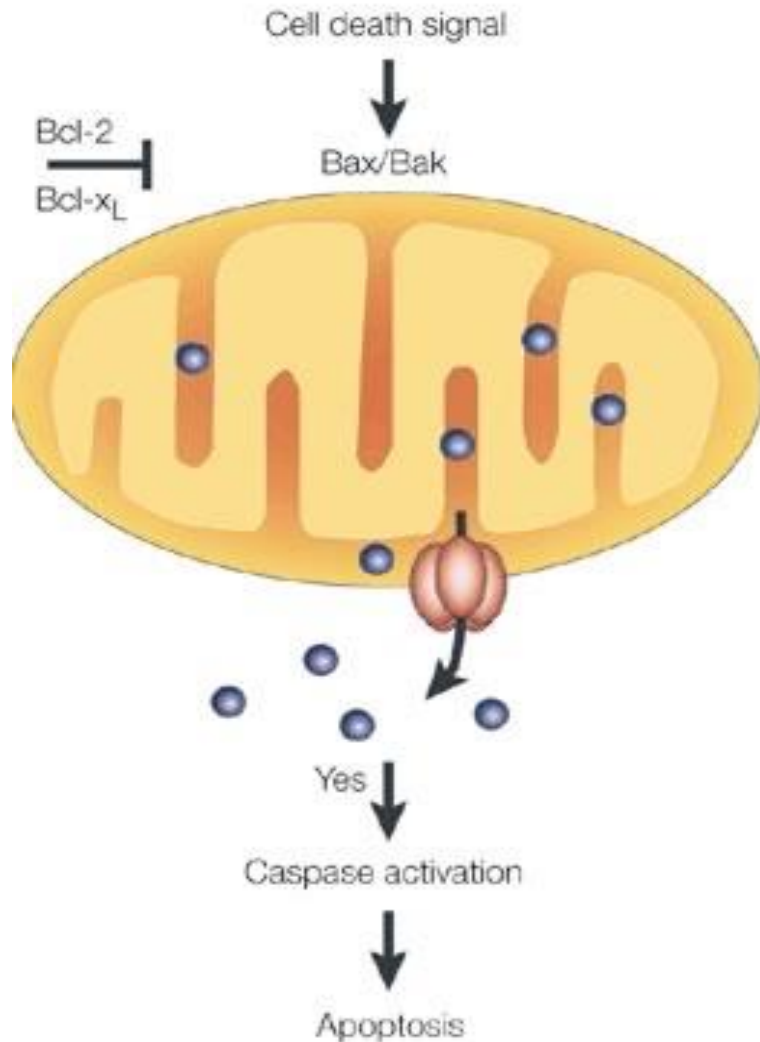
Cyclin D



Cyclin D

- It is part of the cyclin D-Cdk complex that functions by inactivating the Rb anti-oncogene protein by phosphorylating it.
- Cyclin D is often overexpressed in cancer, reducing the activity of Rb.
- In breast carcinoma, this gene is often hyperactive.

Bcl-2



The anti-apoptotic members (Bcl-2, Mcl-1 and Bcl-x_L) contain four BH domains

- The pro-apoptotic effector Bcl-2 proteins (BAH and BAK) contain four BH domains
- BID and BIM pro-apoptotic proteins contain only BH3 domains
- The Bcl-2 gene locus is translocated in several different tumor types, follicular lymphoma and CLL

Oncogenes in colorectal cancer

- K-ras, H-ras, N-ras.
- K-ras gene mutation (40% of colorectal cancers).
- Frequency of K-ras mutations depends on the size of the adenoma:
 - 10% of adenomas < 1 cm have K-ras mutations
 - > 50% of adenomas > 1 cm have K-ras mutations
- Ras → phosphatidyl-inositol-3-phosphate (PIP3) signaling pathway, → B/AKT → antoapoptotic factors and mTOR → cell growth.
- HER2/neu, c-myc, cyclin D, cyclin E.

Oncogenes in breast cancer

- HER2 amplification and increased expression (20-30% of invasive breast cancers) - accelerated growth and more aggressive disease.
- Deregulation of G1/S, increased activity of cyclin D1, E as well as cdk6.
- Beatson: Estrogen plays a significant role in the growth of breast cancer.
- Estrogen → ER- α (70% of breast cancer).
- ER- α → transcription of cyclin D and myc. an important biological target of breast tumor therapy.
- Therapy of all ER- α expressing tumors.
- Tamoxifen is a selective inhibitor of the ER signaling pathway (resistance).

Oncogenes in lung cancer

- c/kit: PDGF/c-kit family of receptors that activate JAK-STAT, PI3K and MAPK signaling pathways in the cell. SCF ligand (stem cell factor).
- Also expressed in many lung cancers (SCLCs).
- HER2 is intensively expressed in one third of NSCLCs, especially adenocarcinomas. Increased expression of HER2 is a poor prognostic factor for lung cancer.
- Activation of the nuclear product of oncogenes, such as those encoded by the myc family of genes (MYC, MYCN...), is often the final link of the signaling cascade. Activated MYC functions as a transcription factor very important for cell proliferation, differentiation and apoptosis. Amplifications and transcriptional disturbances of the myc gene are frequently encountered in SCLC, and much less frequently in NSCLC.

Онкогенеза

