Clinical oncology
Malignant tumors

Introductory lecture. Malignant tumors.

- Basic principles of oncology
- Molecular biology of tumors
- Basics of oncogenesis
- Biology of tumor metastasis

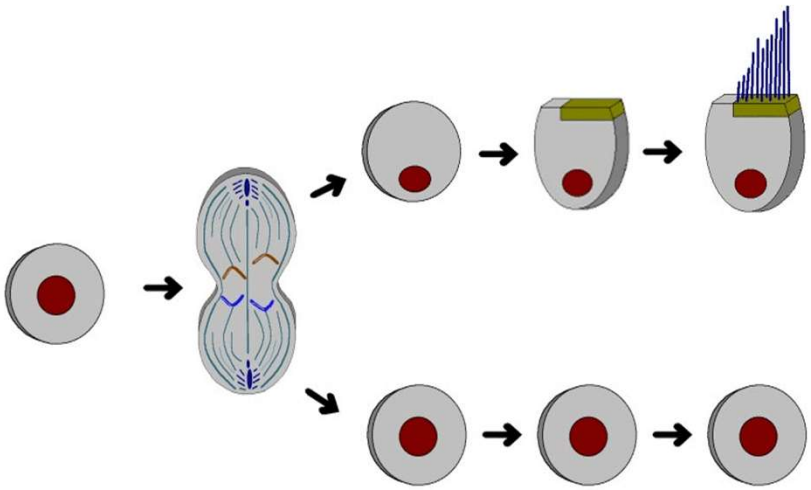
let us remind ourselves...

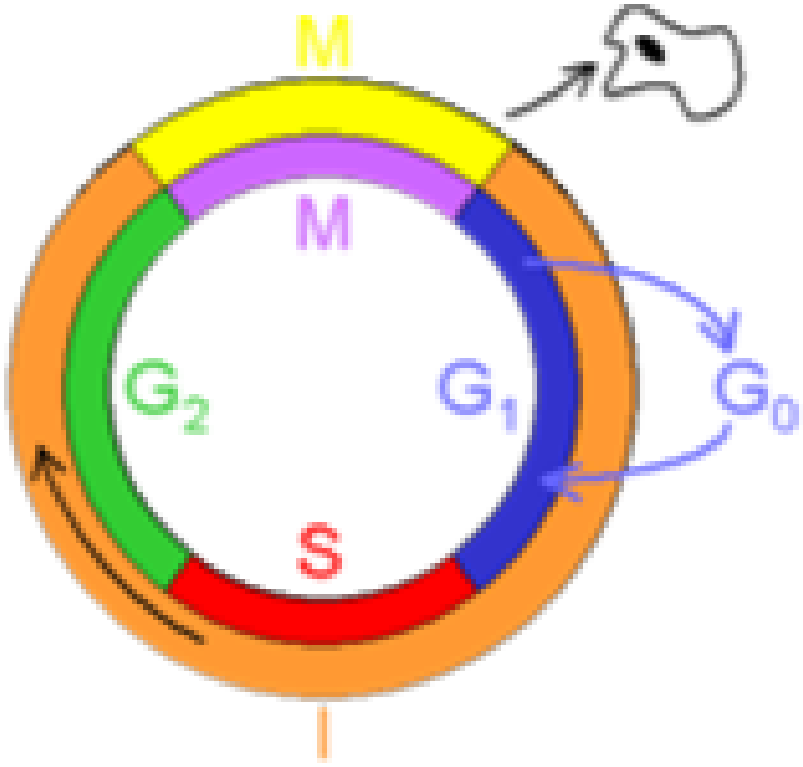
10×10^9 cells/24h

growth and dying

let us remind ourselves...

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



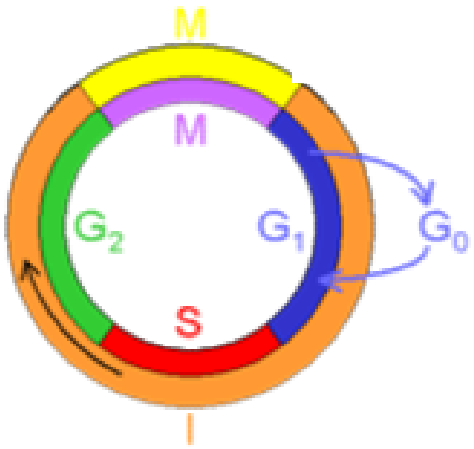


proliferative and resting fraction of cells

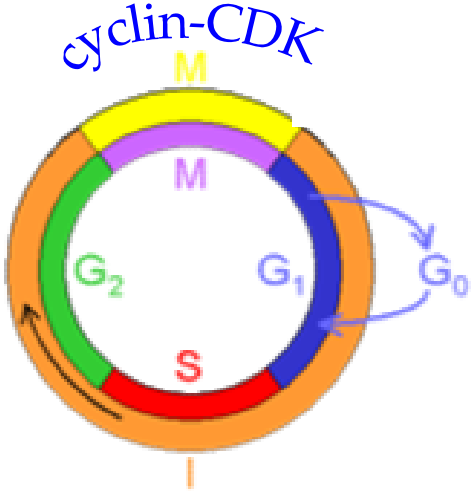
- Entering the G1 phase, the cell divides. Such a cell is in the proliferative phase and is part of the proliferative fraction in the tissue. On average, about 20% of the cells in typical cancers are in the proliferative phase at any given time. Some normal tissues, such as bone marrow and mucosa of the digestive tract, have a higher proliferative fraction than many tumors, even tumors of the same tissues.

- A cell that enters the prolonged G0 phase is in the resting phase (non-proliferative fraction). Some differentiated cells, such as neurons, are permanently non-proliferative.

cell cycle

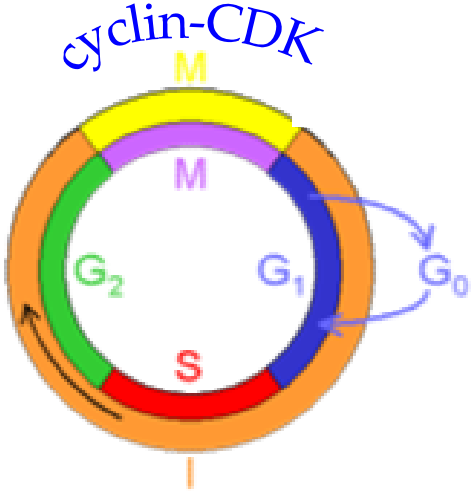


cell cycle - regulation



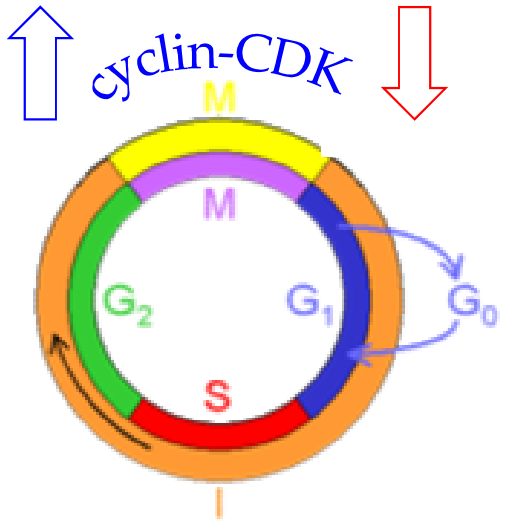
cell cycle - regulation

oncogenes



anti-oncogenes

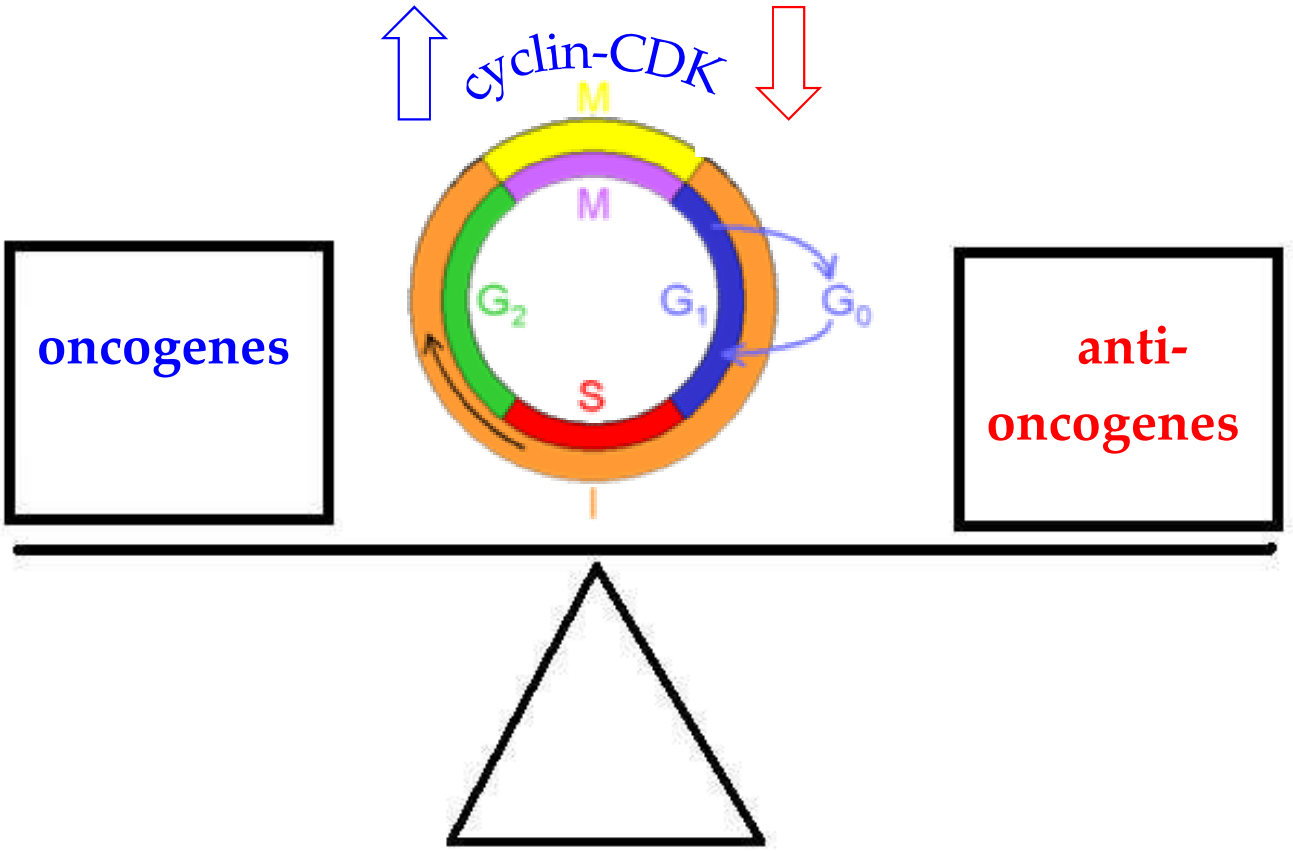
cell cycle - regulation



oncogenes

anti-oncogenes

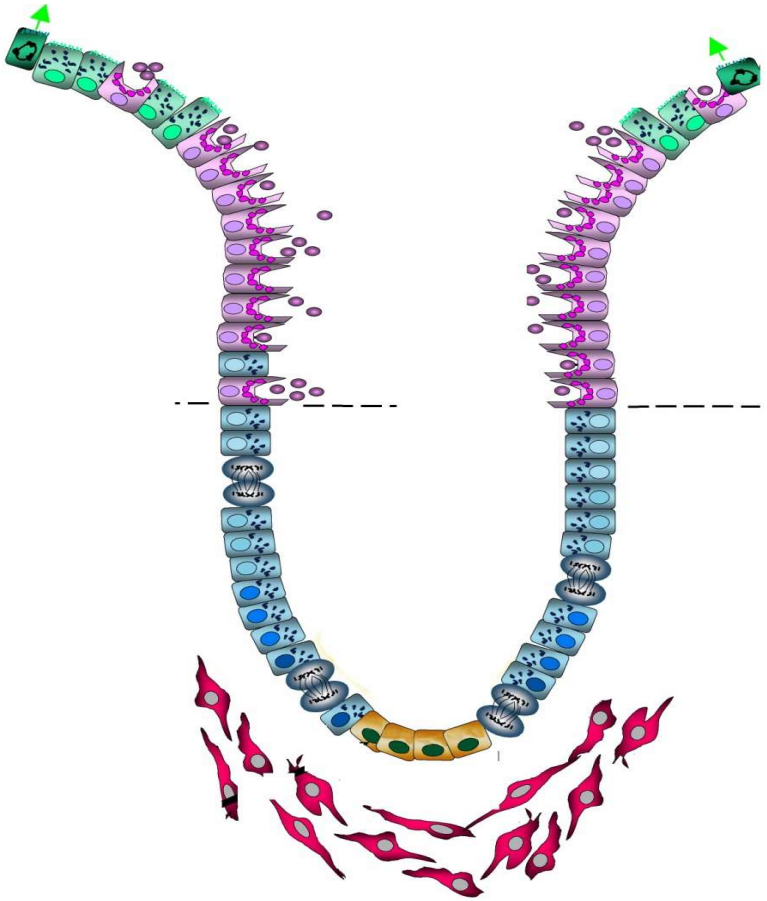
cell cycle - regulation



prevention mechanisms for genetic changes accumulation

- The tissues in the human body are organized in such a way as to prevent the accumulation of cells with damaged genetic material:
  - cells that are in constant contact with factors of the external environment (cells of the skin, GIT and bronchial epithelium) have a short life cycle with rapid elimination of differentiated cells that are directly exposed to potentially harmful noxes.
  - in tissues such as the colon, stem cells are protected in crypts.

localization of stem cells and cells in differentiation



Differentiated cells

villi

Proliferating cells

crypt

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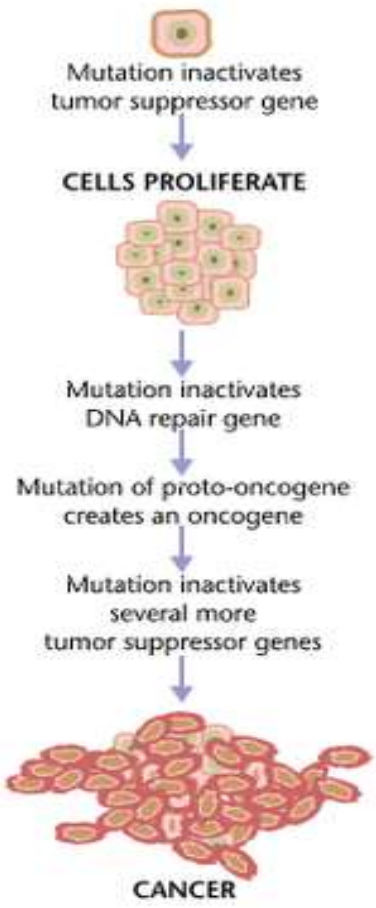
- However, this system is not perfect.
- In addition to numerous protection mechanisms against damage to genetic material, genetic changes occur in cells that escape detection.
- Continuity of cell cycles and unresponsiveness to genetic changes will allow the accumulation of DNA damage that can induce oncogenesis.

oncogenesis



- Oncogenesis is a complex process that, in essence, involves inadequate activation of oncogenes and inactivation (loss of function) of other types of genes, ie tumor-suppressor genes.

- The formation of tumors is the result of the accumulation of genetic mutations that cause "uncontrolled" proliferation of cells that become **immortalized** and consequently able to invade and metastasize to other tissues..

continuous proliferation- cell immortalization

- Some genetic changes → cessation of differentiation → formation of undifferentiated cells with self-renewal capacity.

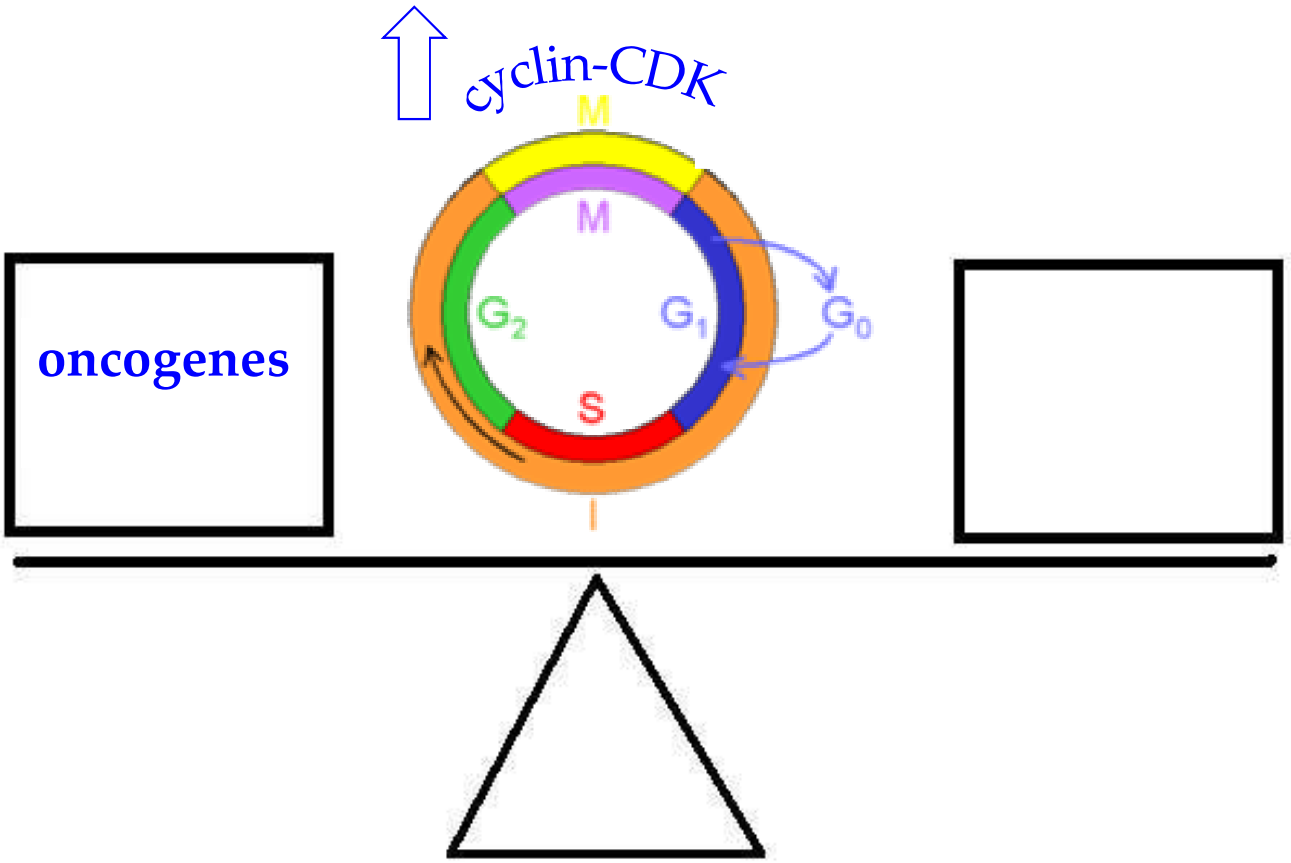
- Others, on the other hand, block apoptosis, enabling a longer cell life.

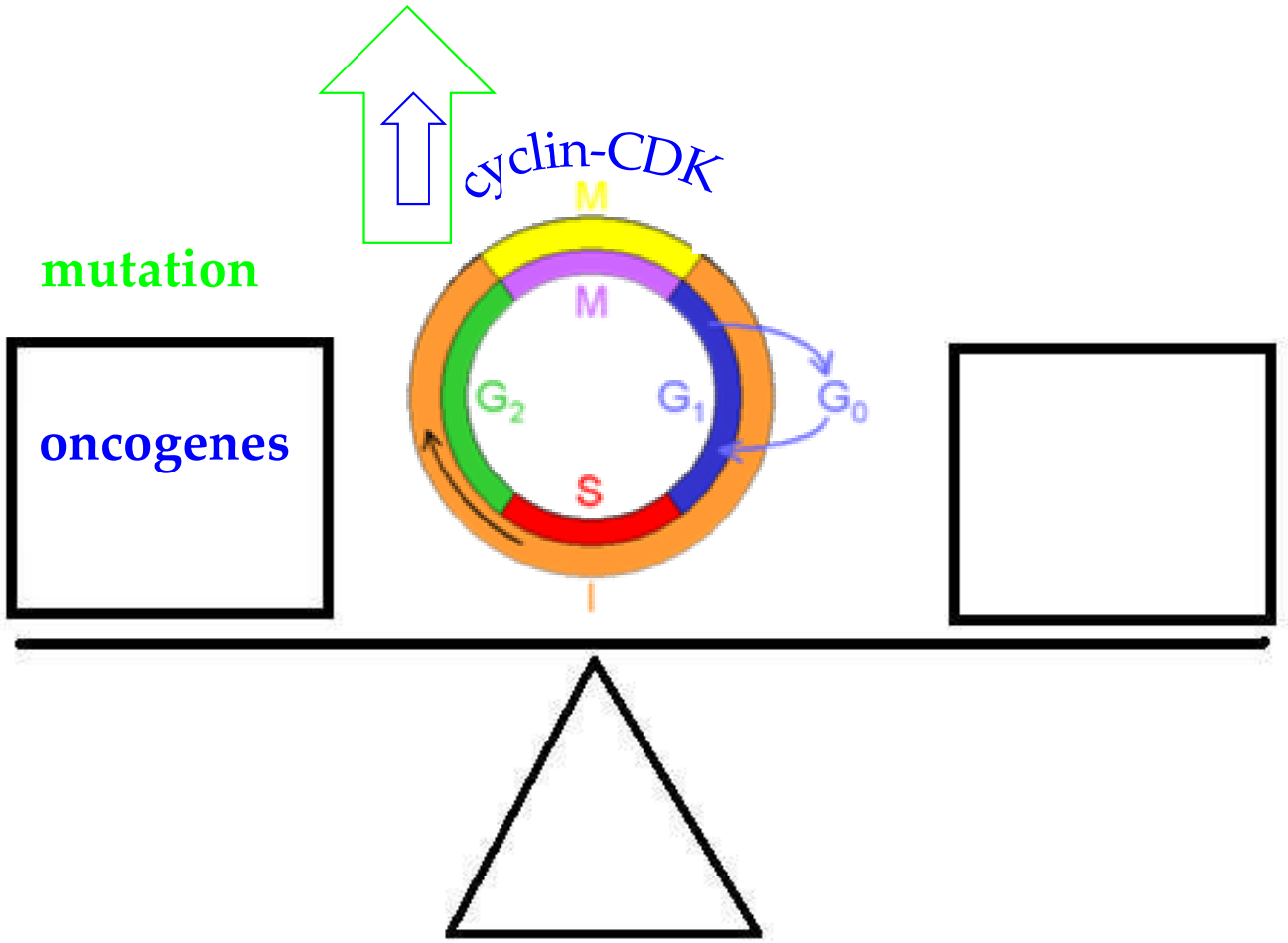
- Such genetic changes induce:
  - permanent activation of signaling pathways for cell growth (proliferation)
  - suppression of cell death (apoptosis)
  - changes in DNA damage control mechanisms

- The aforementioned processes result in "uncontrolled" cell growth and extended cell life → **immortalization**.

continuous proliferation- cell immortalization

- A tumor is partly a disease of "**uncontrolled proliferation**".
- Cell proliferation is a tightly regulated process
- Tumorogenesis is characterized by mutations and changes in the regulation of gene activity for:
  - DNA damage control
  - regulation of the cell cycle
- Genes that after mutation show enhanced function that accelerates cell growth and malignant transformation are called **oncogenes** (proto-oncogenes). Inadequate expression of these genes can trigger tumor formation.


cyclin-CDK
M
M
G2
G1
G0
S
I
oncogenes



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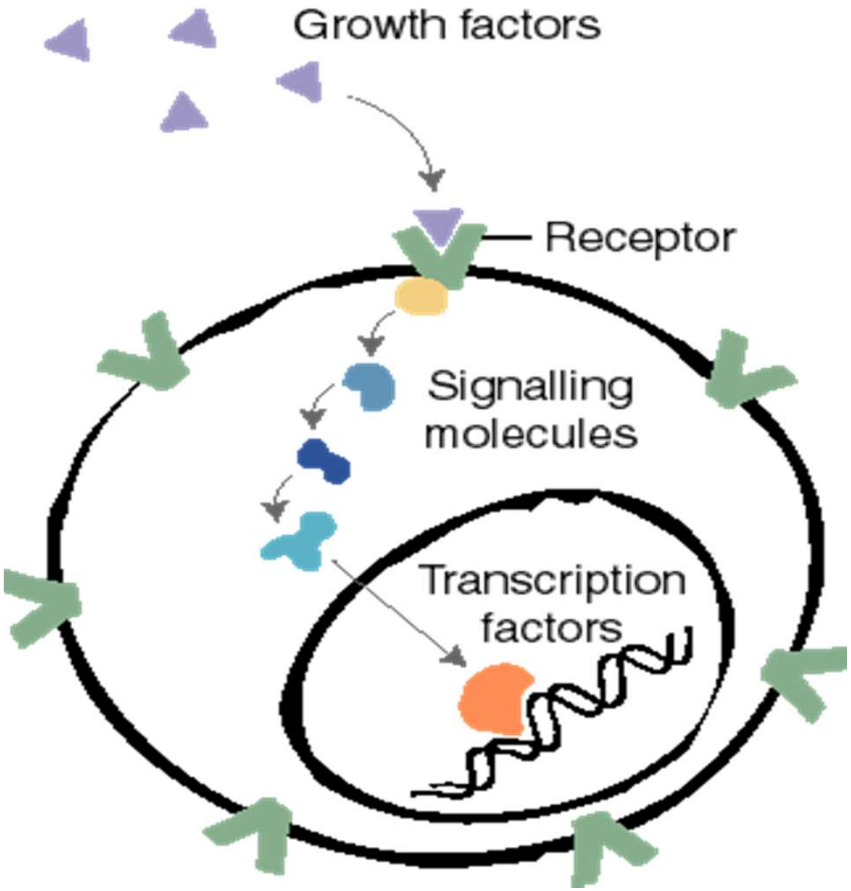
oncogenes



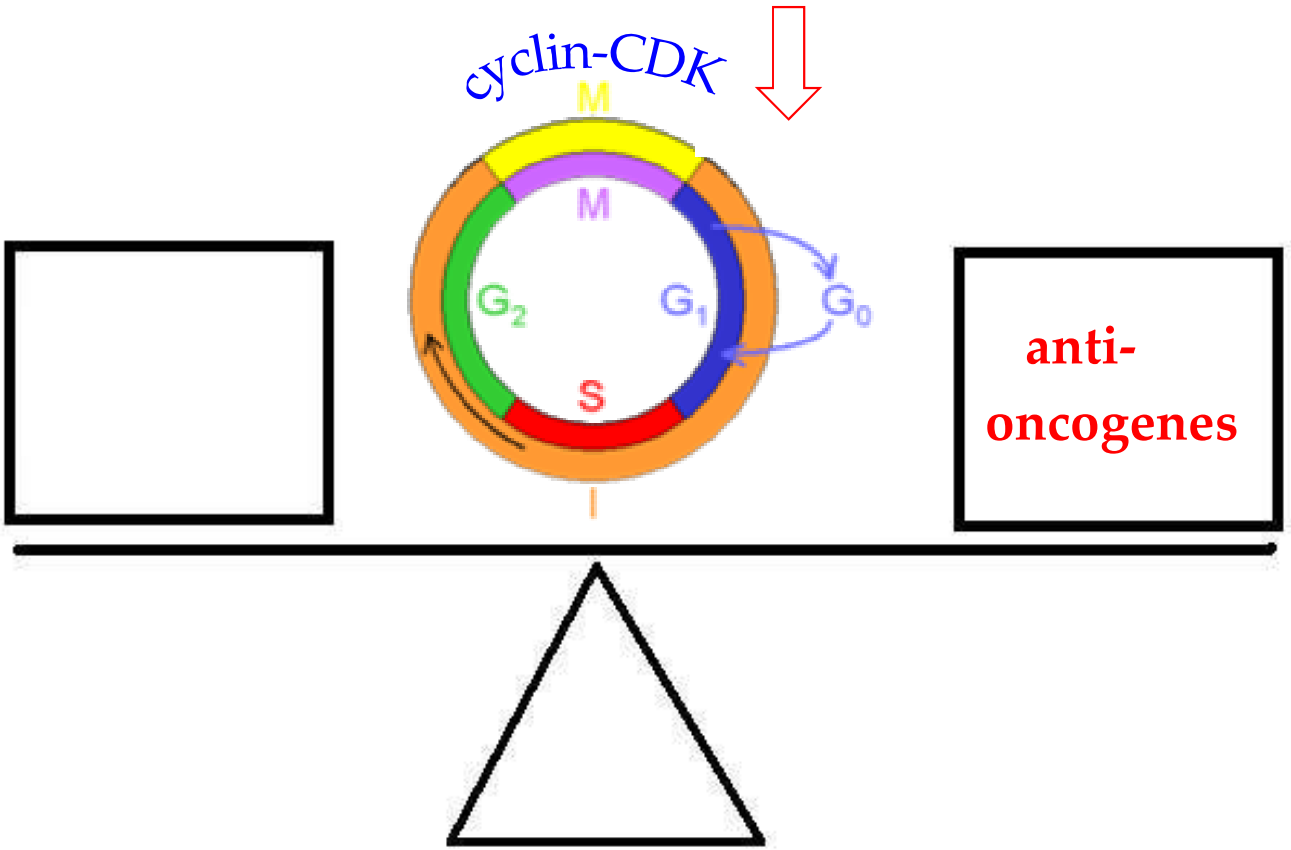
are necessary for many normal biological processes in the cell:

Proliferation
Apoptosis
Differentiation

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

Tumor-suppressor genes - anti-oncogenes

- they are very sensitive to critical DNA damage.
- they represent a significant physiological barrier to clonal expansion or genetic mutations.
- They are capable of preventing the growth and metastasis of cells that are triggered by uncontrolled proliferation mediated by oncogenes.
- They contribute to oncogenesis by losing their function.
- These genes, which include the retinoblastoma gene (Rb-1) and p53, stop cell proliferation.


cyclin-CDK
M
M
G2
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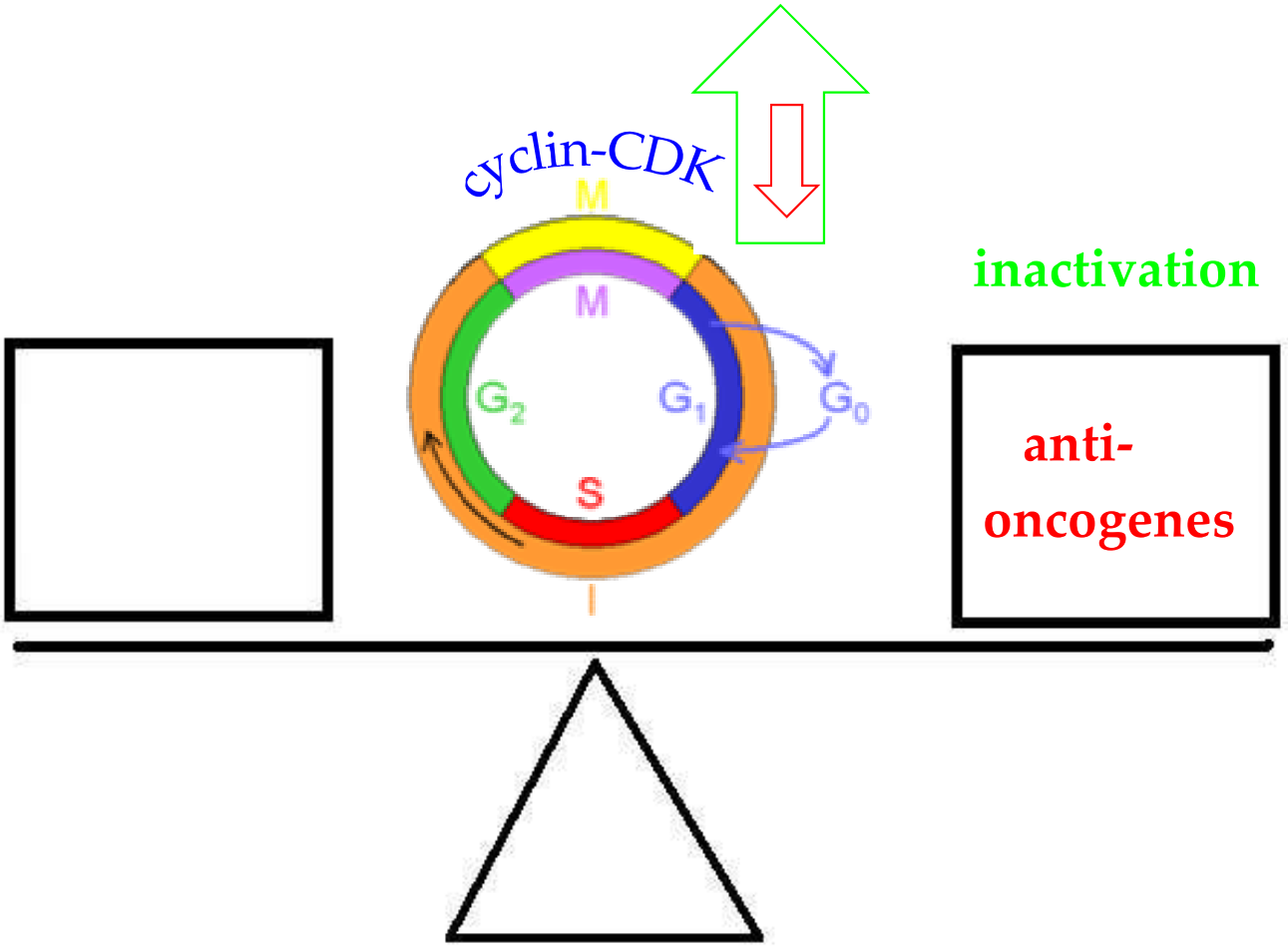
oncogenes


cyclin-CDK
M
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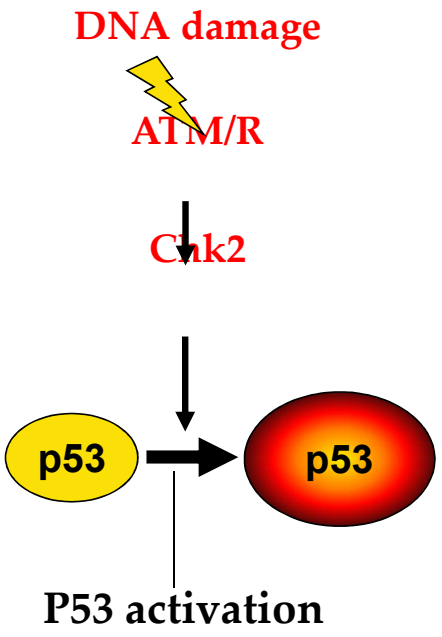
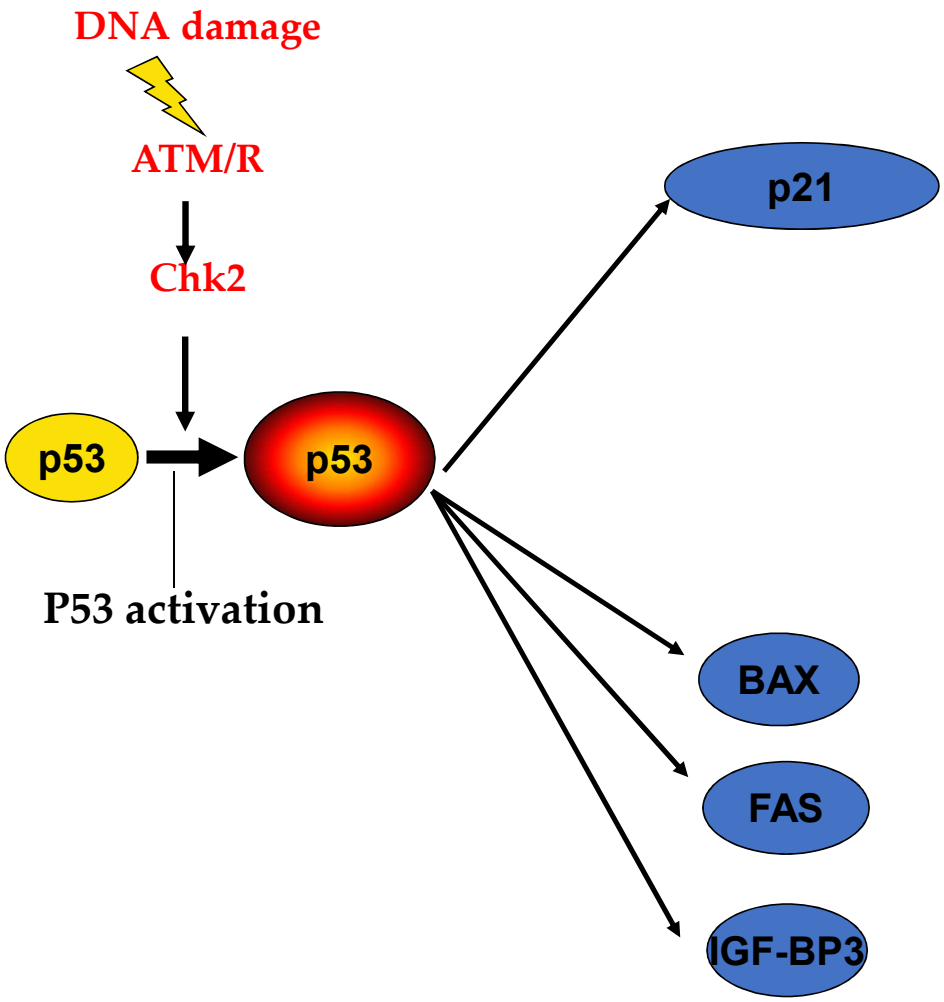
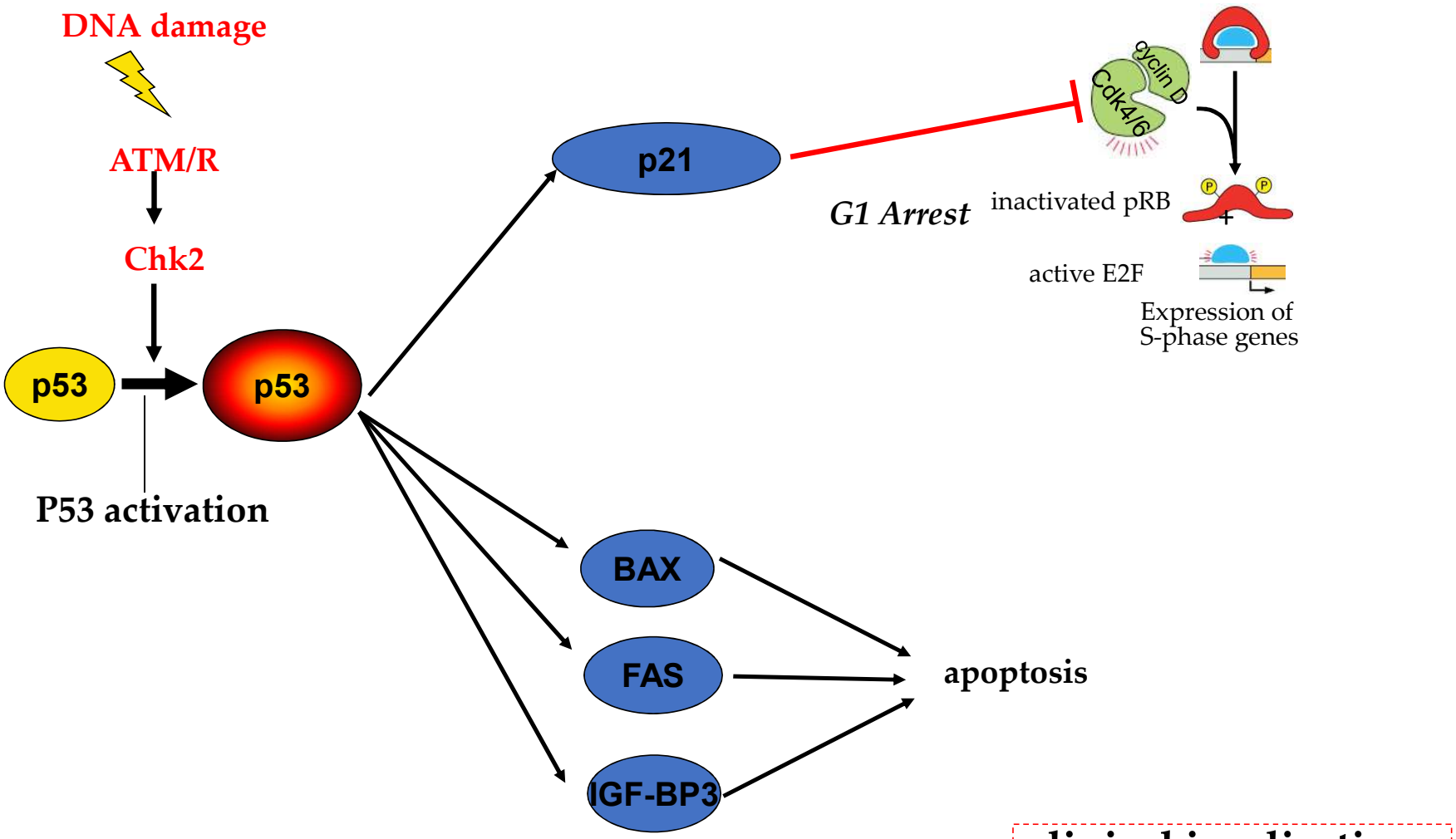
inactivation
anti-
oncogenes

p53- guardian of the genome

- sensitive to DNA damage
- temporarily stopping cell division allowing enzymes of the DNA repair system to correct the error
- In case of severe damage it induces:
  - apoptosis or
  - irreversible stopping of cell division, the so-called "replicative aging" (senescence).
- or eliminates or prevents further division of genetically altered cells
- UV radiation and DNA double-strand breaks induce p53 expression


DNA damage
ATM/R
Chk2
p53
p53
P53 activation


DNA damage
ATM/R
Chk2
p53
p53
P53 activation
p21
BAX
FAS
IGF-BP3



clinical implications

clinical implications

Conventional tumor therapy

DNA damage

p53, *senescence*, apoptosis

tissues with a high proliferative fraction

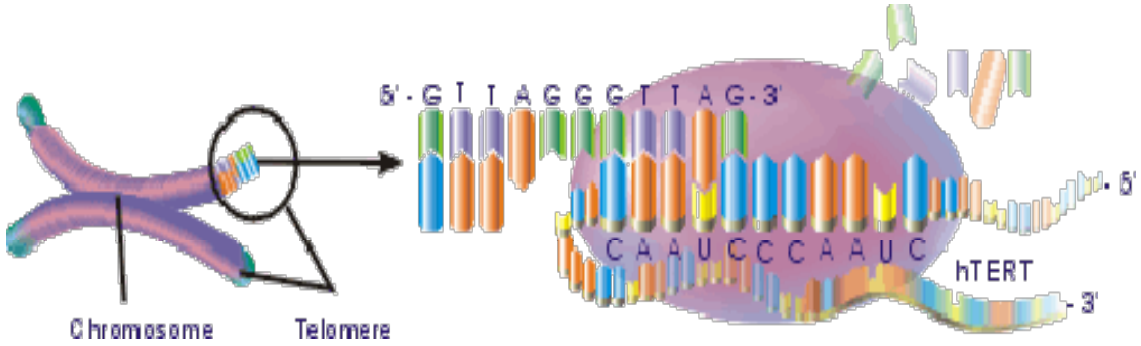
Immortalization and oncogenesis

„ Death occurs because exhausted tissue cannot be endlessly renewed and because the number of cell divisions of an individual cell is finite.“

August Weissmann, biologist 1881.

replicative aging

- 1960. Leonard Hayflick- limited replicative potential (50-100 divisions)
- replicative aging- mechanism of protection against malignancy - shortening of telomeres
- specialized nucleoprotein complexes - RNA primer for the start of replication (25-200bp)
- 1932 Hermann Myollar, Nobel prize winner "Telomere"



replicative aging

- accumulation of cdk inhibitor
- scell cycle arrest

- mitotic clock (number of divisions and cell lifespan)
- increased telomerase activity in most primary tumors
- potential targets in anti-tumor therapy

autophagy

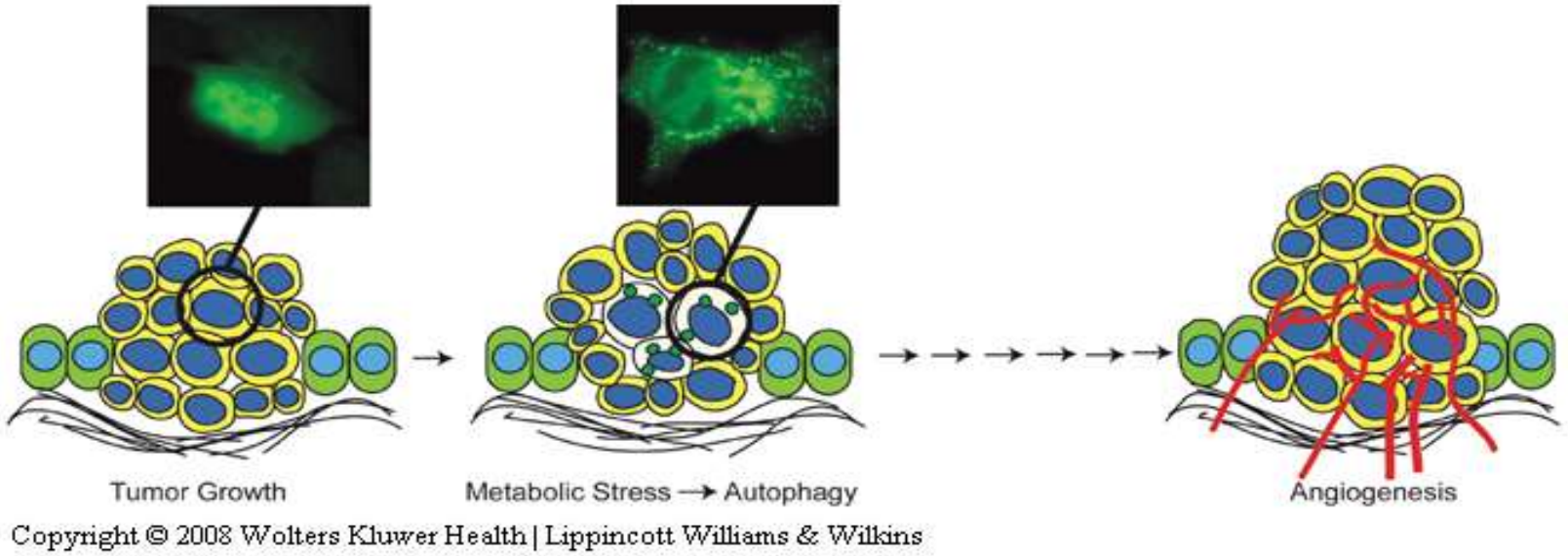
Early stages of oncogenesis, autophagy $\Longrightarrow$ tumor suppressor

Higher level of protein synthesis for tumor growth

Inhibition of autophagy $\Longrightarrow$ sustained tumor growth

Autophagy reduces mutation rates and suppresses oncogenesis by eliminating damaged organelles that produce genotoxic factors such as free radicals

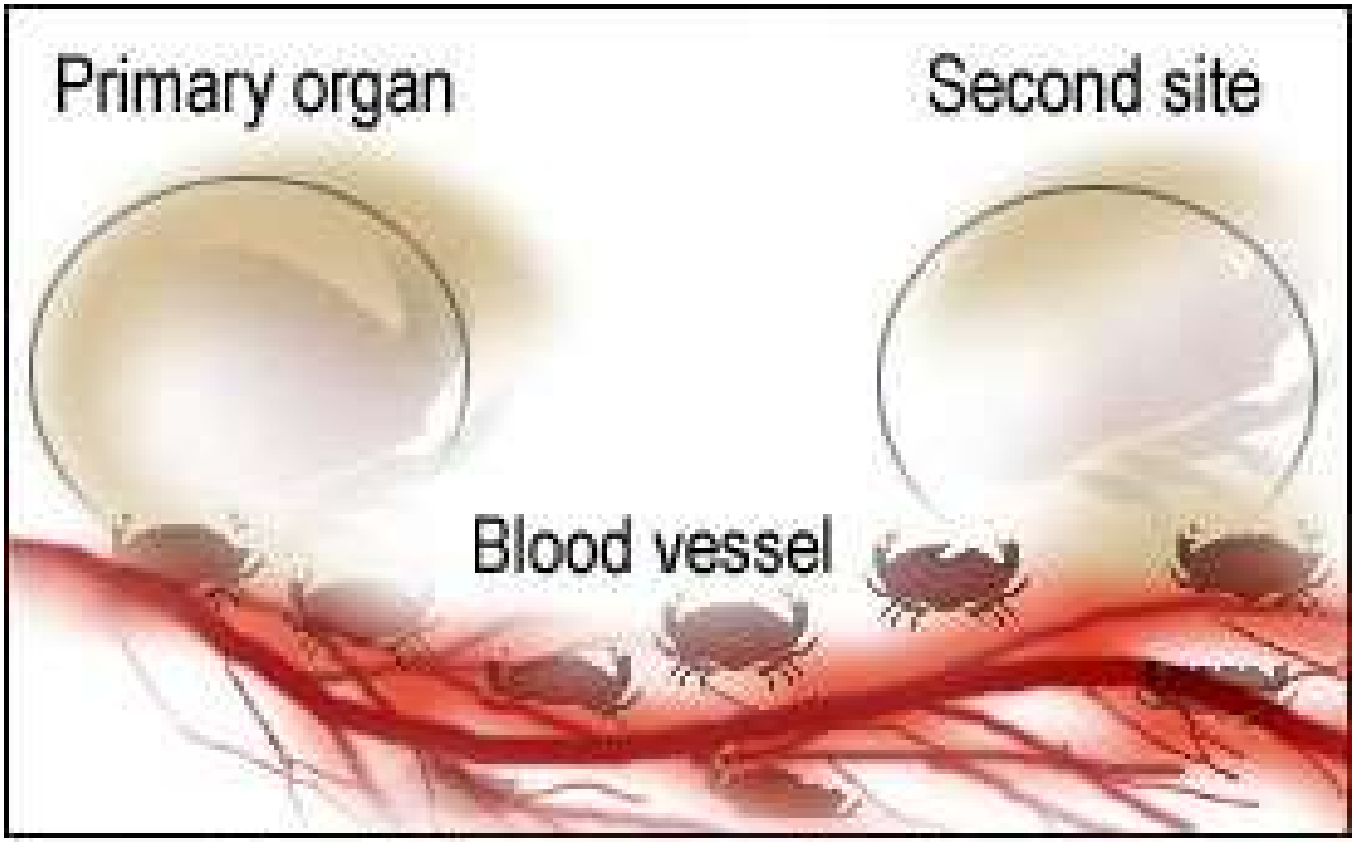
Autophagy of tumor cells



Epithelial tumor cells rapidly proliferate multilayered. Insufficient blood supply induces metabolic stress in the parts of the tumor furthest from nutrients and oxygen, inside the tumor. Tumor cells, in regions of metabolic stress, can survive by autophagy.

Also, autophagy induces **local neoangiogenesis**, through intensifying the proliferation and migration of endothelial cells, which facilitates tumor growth and development.

metastasis



Blood-borne metastases

Final step in tumor development (progression)

metastasis

- Metastasis represents the last step in tumor progression. As with tumorigenesis, tumor cells with metastatic capacity arise through a process analogous to Darwinian natural selection, facilitated by genetic changes. The dominant clone of tumor cells in the primary tumor acquires an "evolutionary advantage" through a series of genetic changes. ability to metastasize.

- Another theory holds that metastases arise from a small number of "metastatic forms" in primary tumors. According to this theory, not all primary tumor cells have the same metastatic capacity. The ability to metastasize does not give these cells an advantage in growth and they form a small population within the primary tumor.

metastatic cascade

- The process of metastasis formation is now commonly called the metastatic cascade. This cascade consists of a series of interdependent events:

1) Invasion and mobility.
2) Intravasation and survival in circulation
3) Extravasation of malignant cells into parenchymatous organs
4) Growth of metastatic colonies in distant organs, sensitivity to paracrine growth factors, proliferation and angiogenesis

site of metastasis

1) 1889. Stephen Paget (seed and soil):
   - some tumors metastasize in specific organs
   - the site of metastasis is not a coincidence
   - target organ microenvironment

2) James Ewing (tissue tropism):
   - mechanical factors and circulation
   - CRC » portal system » liver metastases

These two theories are not completely mutually exclusive and recent research supports both theories. Namely, the drainage of the portal circulation through the liver makes this organ the primary site of metastasis of advanced colorectal cancers. However, it has also been confirmed that the liver microenvironment influences the growth of metastatic tumor cells through as yet unexplored mechanisms.

site of metastasis

- Bones are one of the most common sites of metastasis of many types of malignancies, such as lung, kidney and breast cancer.
- The lungs are one of the predilection sites of metastases of malignant melanoma, breast cancer, colon cancer, bladder cancer.
- In colorectal cancer, the establishment of metastases in the liver is characteristic, where the malignant cells reach this place through the portal circulation. On the other hand, tumor cells of melanoma, lung and breast cancer reach the liver using the systemic circulation. The microenvironment of the liver is particularly favourable for the establishment of metastases in gastrointestinal cancer. In addition to the local microenvironment of the liver, signaling molecules expressed on the metastatic cells themselves are also involved in the process of metastasis.
- The brain is the site of metastases of lung, breast, kidney, colorectal cancer, and melanoma.
- Tumor metastasis to regional lymph nodes is one of the early signs of metastatic potential and/or spread to distant organs.

development of metastases

- It has been experimentally shown that only 0.01% of metastatic tumor cells form metastatic colonies.
- The number of circulating tumor cells correlates with the size of the primary tumor, more tumor cells are separated from a larger tumor. However, the number of circulating tumor cells does not correlate with the clinical outcome of metastases.
- The inability of tumor cells to complete the metastatic cascade is due in part to the fact that only those tumor cells that acquire the necessary genetic changes can successfully form metastatic foci.
- Another reason for the inability of tumor cells to complete the metastatic cascade is that most tumor cells that reach the circulation are in the process of dying. Tumor cells in the circulation are characterized by twice as much spontaneous apoptosis compared to the cells in the primary tumor. Not all circulating tumor cells are metastatic competent, able to colonize distant organs.

development of metastases

- a large number of genetic changes are required for a cell to develop metastatic potential
- genetic changes will accumulate more intensively in a larger population of cells
- larger tumors - higher probability of metastatic competent cellsmetastatic risk: BC 2cm, sarcoma 5cm

- transcriptome of primary tumor cells
- non-metastatic vs. metastatic
- 70 genes
- series of genetic changes

survival in circulation

- mouse model 0.01%
- human ovarian cancer, peritoneal venous shunts, millions of malignant cells from the peritoneum into the venous circulation, for years without metastases

- Anoikis (apoptosis): 72h
- When malignant cells are separated from the primary tumor and enter the circulation, they become the target of mechanical influences in small blood vessels. In the presence of mechanically retained metastatic cells, the hepatic sinusoids become activated and begin to secrete nitric oxide. Nitrogen monoxide can cause apoptosis of tumor cells trapped in this place.
- Immune system cells can also actively attack circulating malignant cells.