Biochemistry of Carcinogenesis

Lecture # 35

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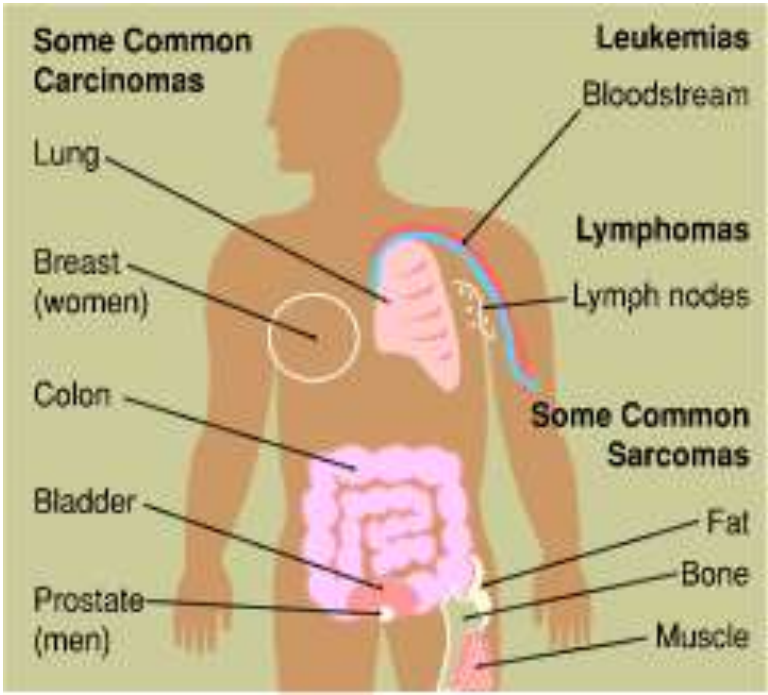
What is Cancer?

- The term "cancer" refers to a group of diseases in which cells grow and spread unrestrained throughout the body.
  - It is difficult to imagine anyone who has not heard about this disease. Most people have been affected because either a loved one, a friend, or even they themselves are cancer survivors.
  - It is therefore important for everyone to have a basic understanding about the nature, diagnosis, causes, prevention, and treatment of cancer.
- Learn about the following topics:
  · What is cancer?
  · How is cancer detected and diagnosed?
  · What causes cancer?
  · What is the link between genes and cancer?
  · What is cancer prevention?

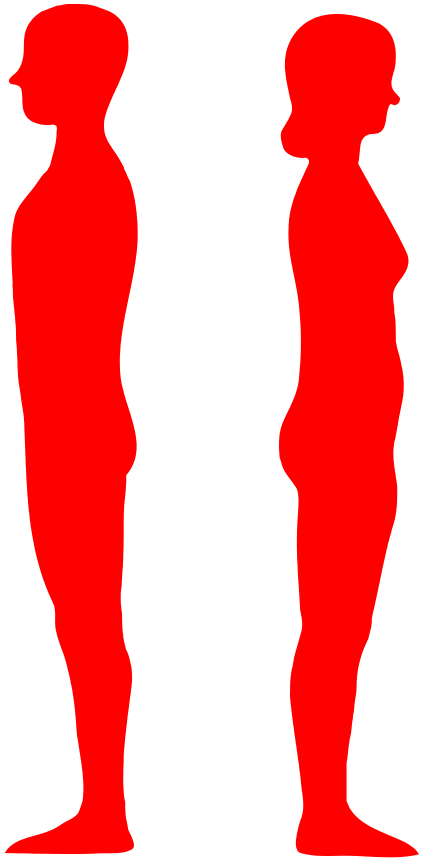
Different Kinds of Cancer

- Cancer can originate almost anywhere in the body.
- **Carcinomas**, the most common types of cancer, arise from the cells that cover external and internal body surfaces.
  - Lung, breast, and colon are the most frequent cancers of this type.
- **Sarcomas** are cancers arising from cells found in the supporting tissues of the body such as bone, cartilage, fat, connective tissue, and muscle.
- **Lymphomas** are cancers that arise in the lymph nodes and tissues of the body's immune system.
- **Leukemias** are cancers of the immature blood cells that grow in the bone marrow and tend to accumulate in large numbers in the bloodstream.



2006 Estimated US Cancer Cases*

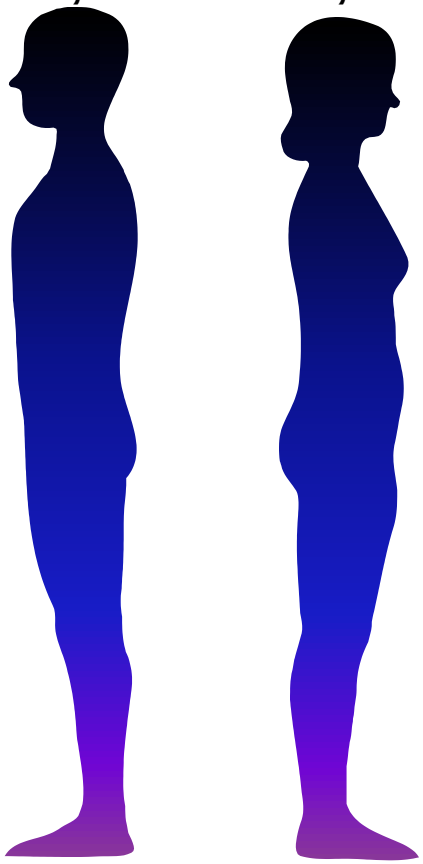
Men 720,280		Women 679,510	
Prostate	33%	31%	Breast
Lung & bronchus	13%	12%	Lung & bronchus
Colon & rectum	10%	11%	Colon & rectum
Urinary bladder	6%	6%	Uterine corpus
Melanoma of skin	5%	4%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	4%	Melanoma of skin
Kidney	3%	3%	Thyroid
Oral cavity	3%	3%	Ovary
Leukemia	3%	2%	Urinary bladder
Pancreas	2%	2%	Pancreas
All Other Sites	18%	22%	All Other Sites



***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2006.

2006 Estimated US Cancer Deaths*

Men 291,270	
Lung & bronchus	31%
Colon & rectum	10%
Prostate	9%
Pancreas	6%
Leukemia	4%
Liver & intrahepatic bile duct	4%
Esophagus	4%
Non-Hodgkin lymphoma	3%
Urinary bladder	3%
Kidney	3%
All other sites	23%

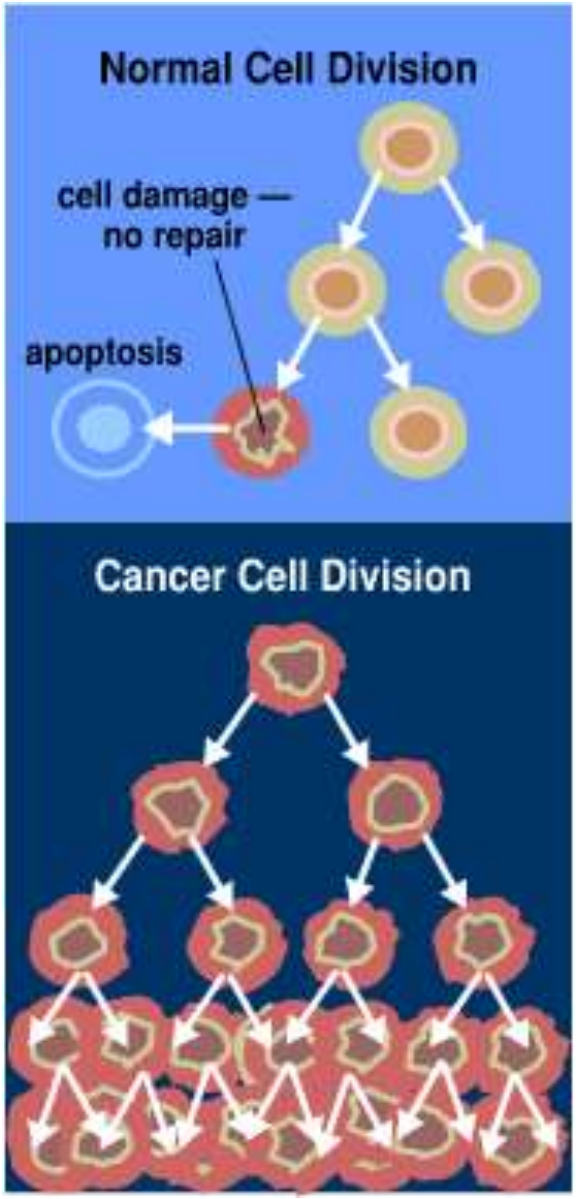


Women 273,560	
26%	Lung & bronchus
15%	Breast
10%	Colon & rectum
6%	Pancreas
6%	Ovary
4%	Leukemia
3%	Non-Hodgkin lymphoma
3%	Uterine corpus
2%	Multiple myeloma
2%	Brain/ONS
23%	All other sites

ONS=Other nervous system.
Source: American Cancer Society, 2006.

Loss of Normal Growth Control

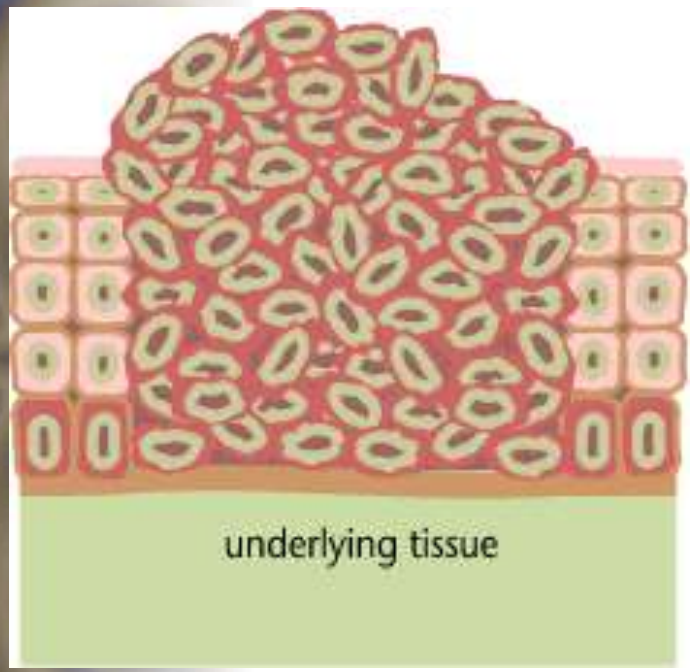
- Cancer arises from a loss of normal growth control.
- In normal tissues, the rates of new cell growth and old cell death are kept in balance.
- In cancer, this balance is disrupted.
  - This disruption can result from uncontrolled cell growth or loss of a cell's ability to undergo "apoptosis." Apoptosis, or "cell suicide," is the mechanism by which old or damaged cells normally self-destruct.



The Beginning of Cancerous Growth

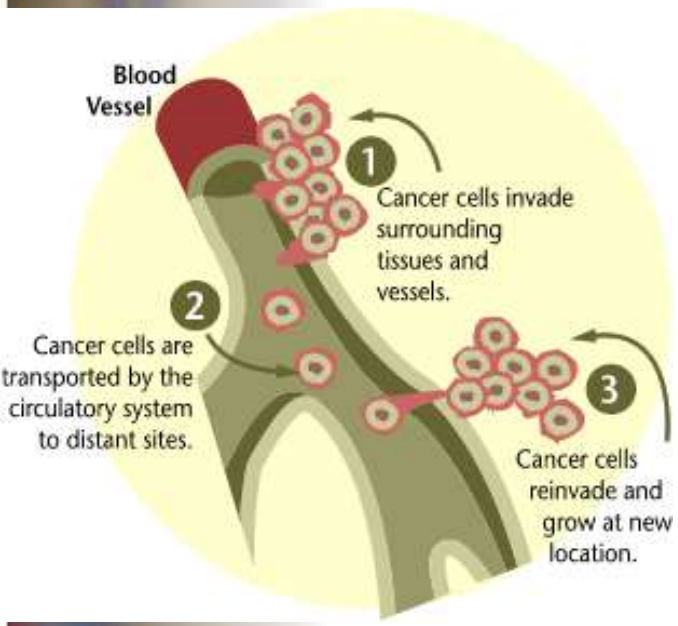
- During the development of skin cancer, the normal balance between cell division and cell loss is disrupted.
- The basal cells now divide faster than is needed to replenish the cells being shed from the surface of the skin.
- Each time one of these basal cells divides, the two newly formed cells will often retain the capacity to divide, thereby leading to an increase in the total number of dividing cells.

Tumors (Neoplasms)



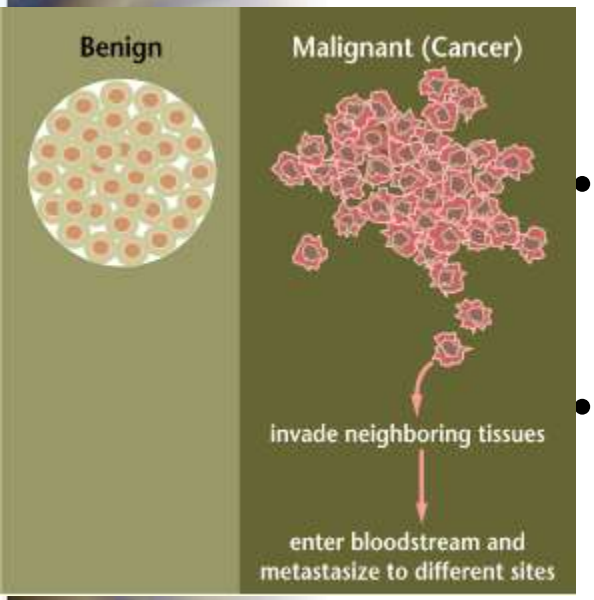
- This gradual increase in the number of dividing cells creates a growing mass of tissue called a "tumor" or "neoplasm."
- If the rate of cell division is relatively rapid, and no "suicide" signals are in place to trigger cell death, the tumor will grow quickly in size; if the cells divide more slowly, tumor growth will be slower.
- But regardless of the growth rate, tumors ultimately increase in size because new cells are being produced in greater numbers than needed.
- As more and more of these dividing cells accumulate, the normal organization of the tissue gradually becomes disrupted.

Invasion and Metastasis



- Cancers are capable of spreading through the body by two mechanisms: invasion and metastasis.
- Invasion refers to the direct migration and penetration by cancer cells into neighboring tissues.
- Metastasis refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade normal tissues elsewhere in the body.

Malignant versus Benign Tumors



- Depending on whether or not they can spread by invasion and metastasis, tumors are classified as being either benign or malignant.
- Benign tumors are tumors that cannot spread by invasion or metastasis; hence they only grow locally.
- Malignant tumors are tumors that are capable of spreading by invasion and metastasis.
- By definition, the term "cancer" applies only to malignant tumors.

Cell Cycle

M phase

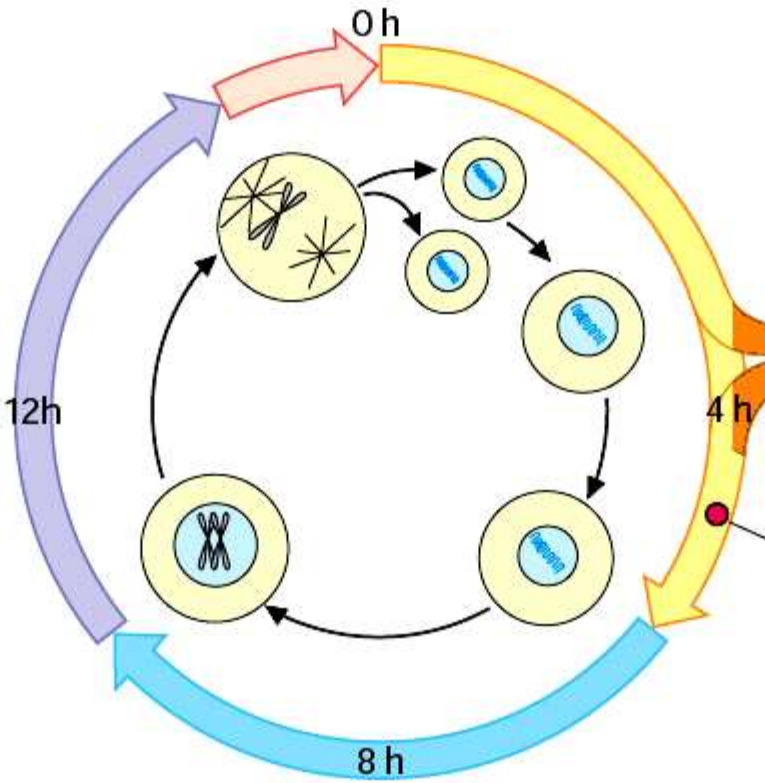
Mitosis
Chromosome separation
Cell division

G_2 phase

Preparation for mitosis

S phase

DNA replication
Histone synthesis
Centrosome formed
Chromosome duplication



G_1 phase

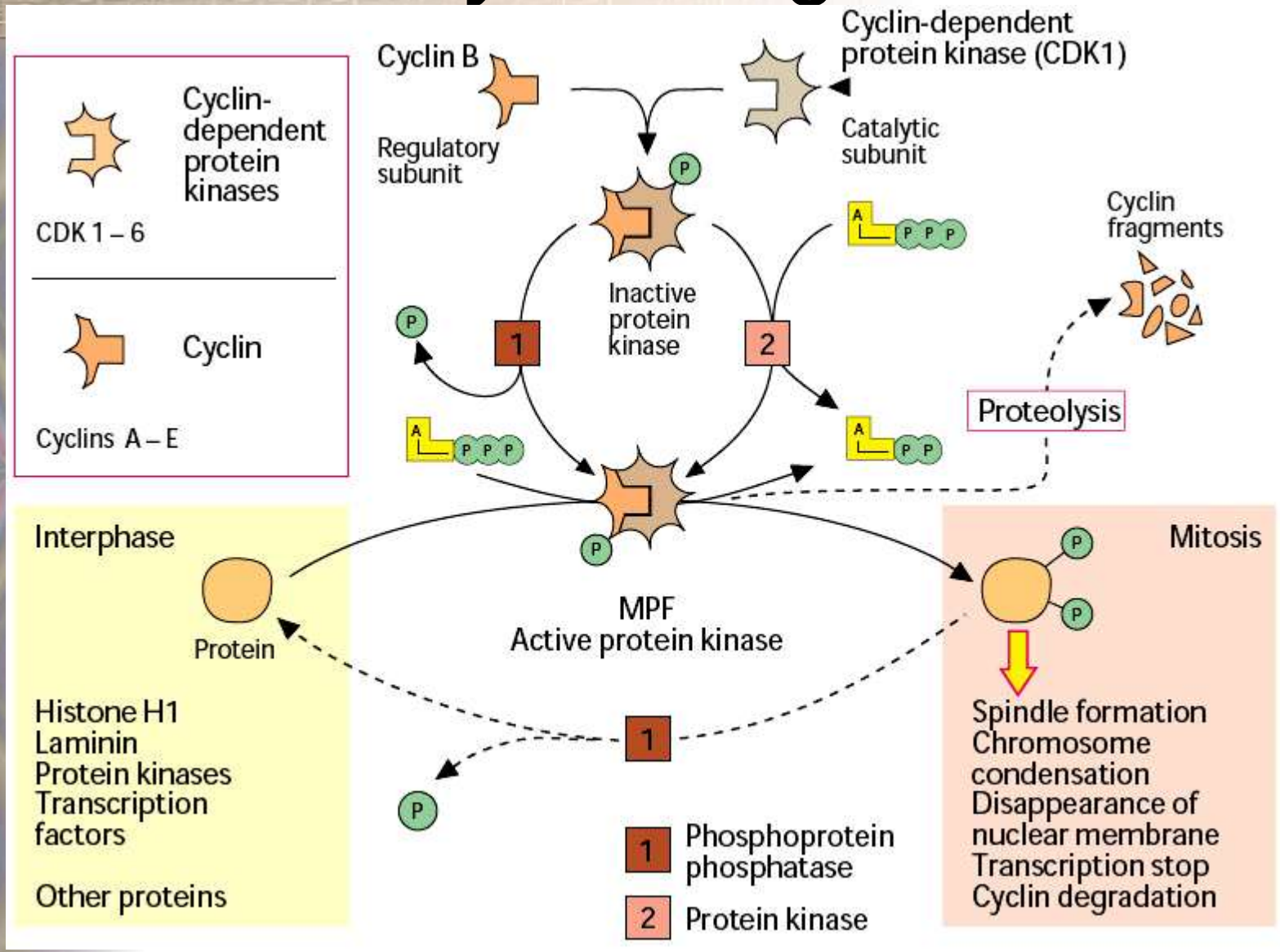
RNA and protein synthesis
Cell growth

G_0 phase

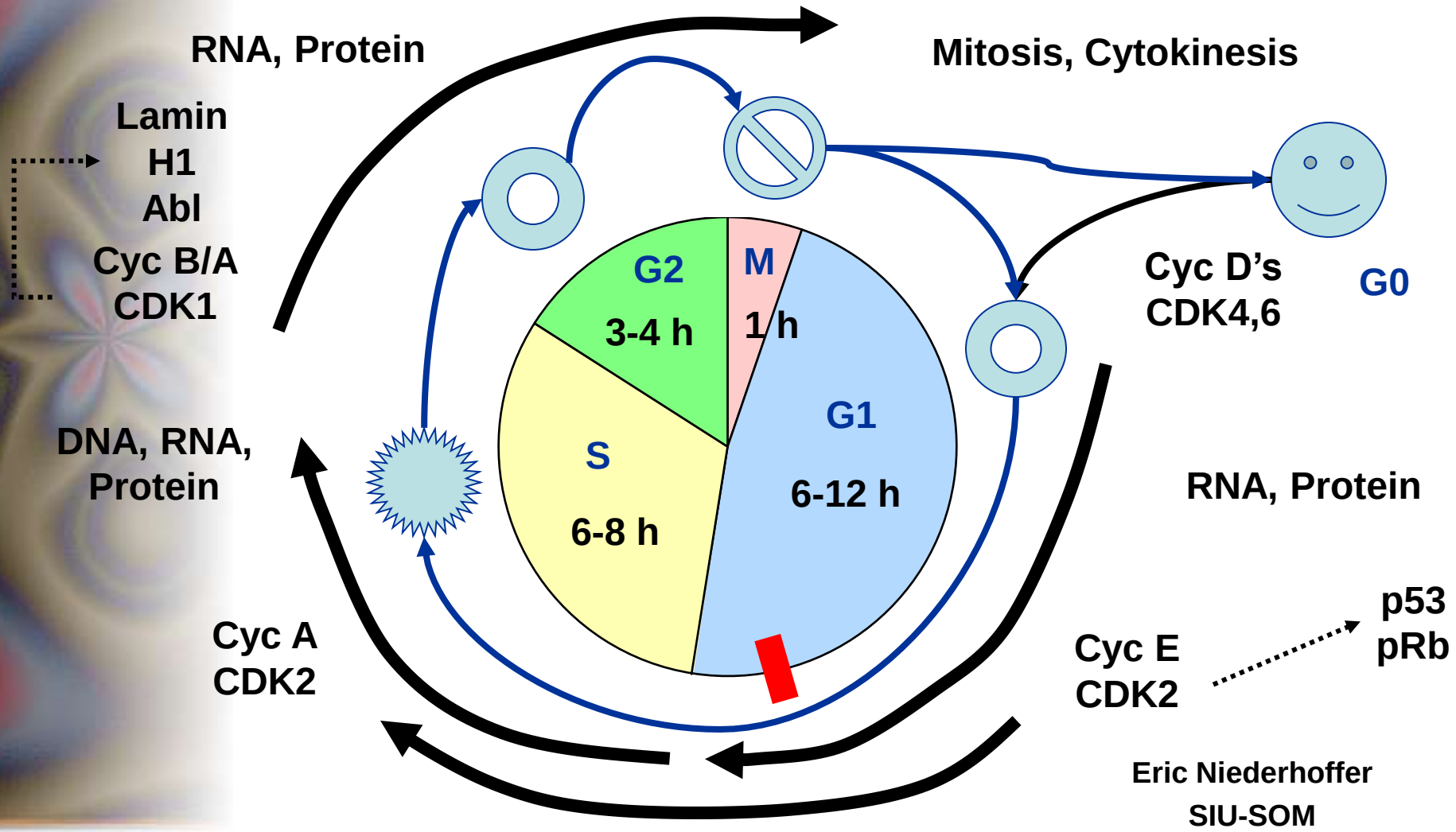
No cell division

Restriction point

Cell Cycle Regulation



Cell Cycle



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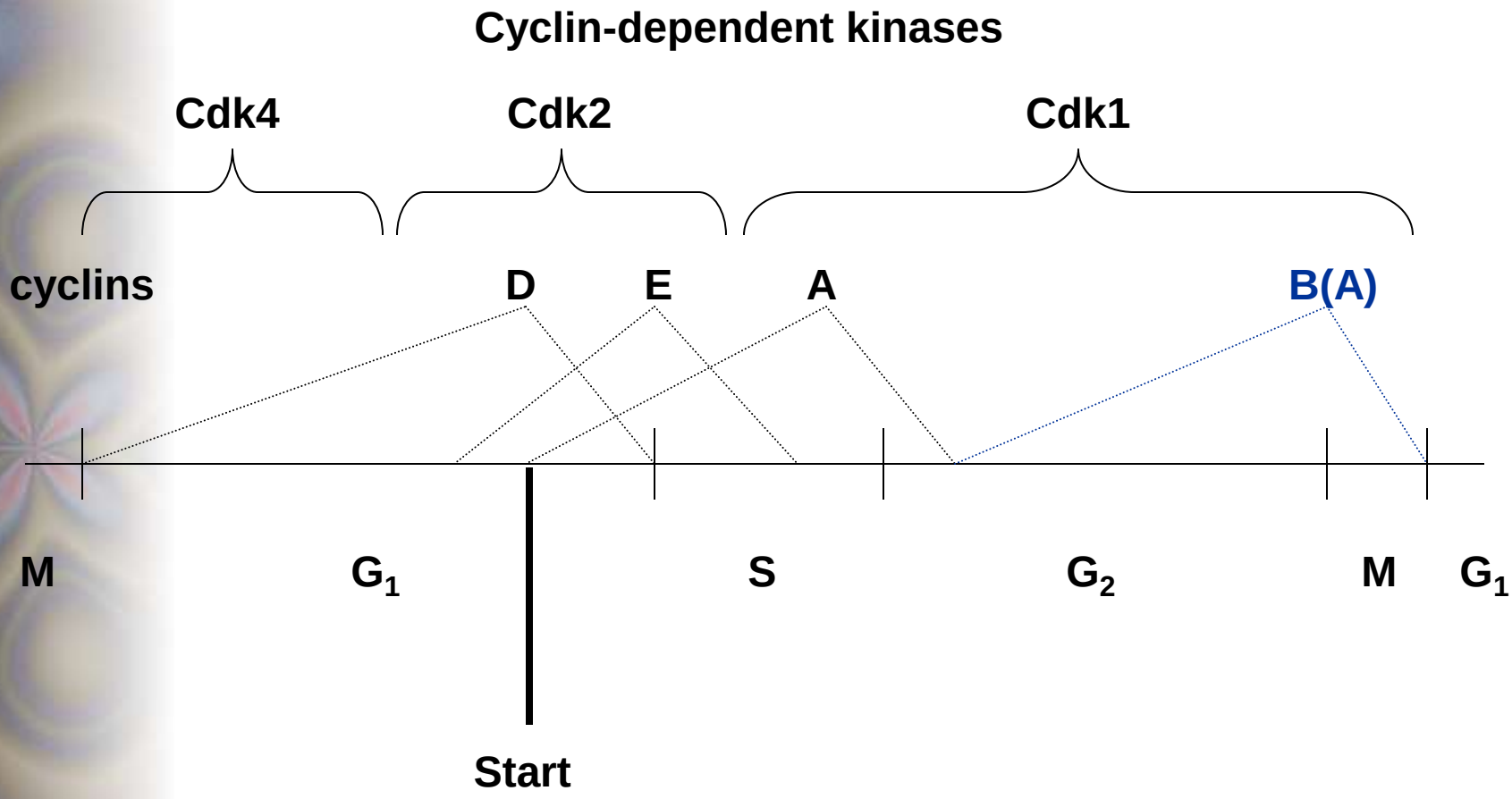
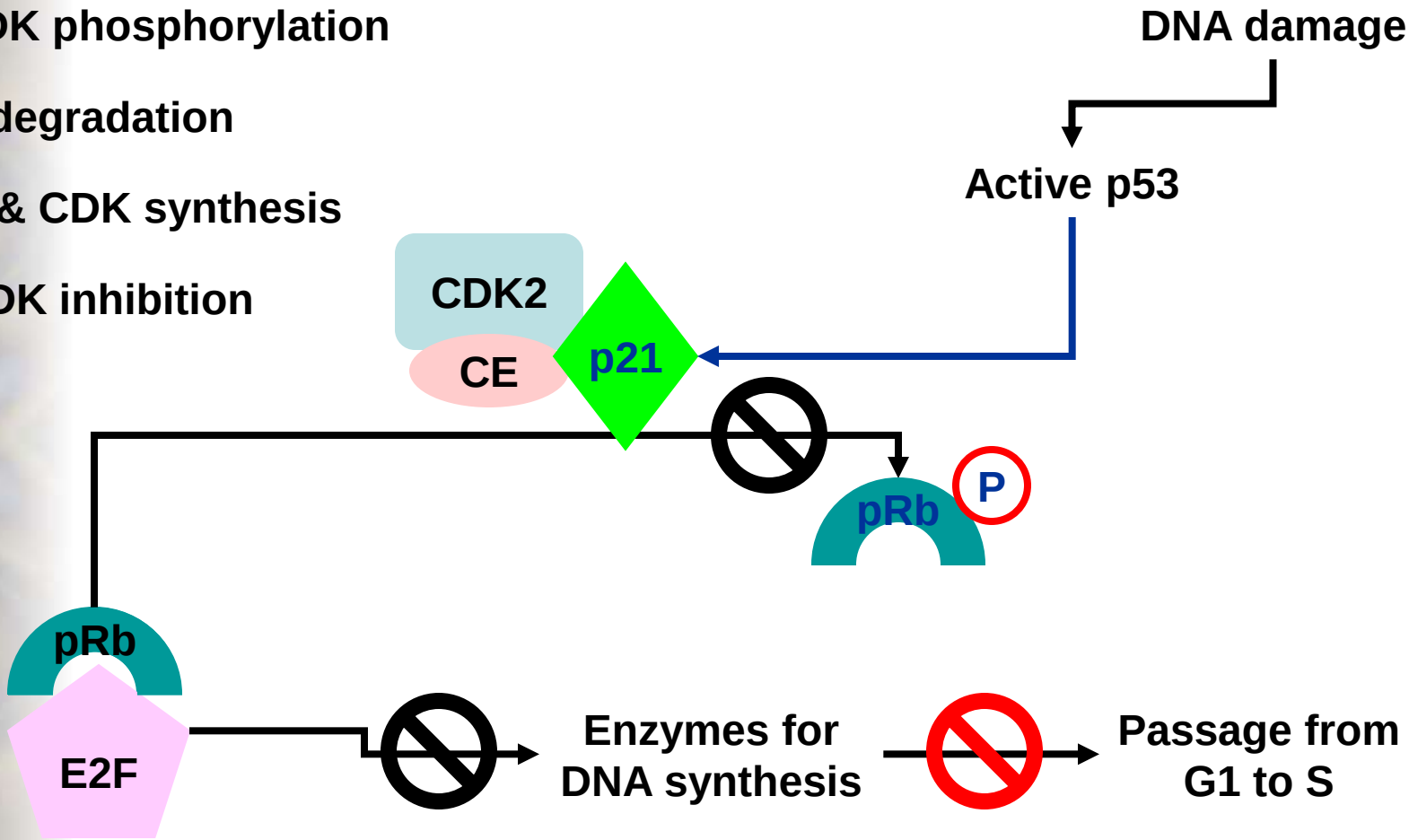
Variation in Cell Cycle Cyclins

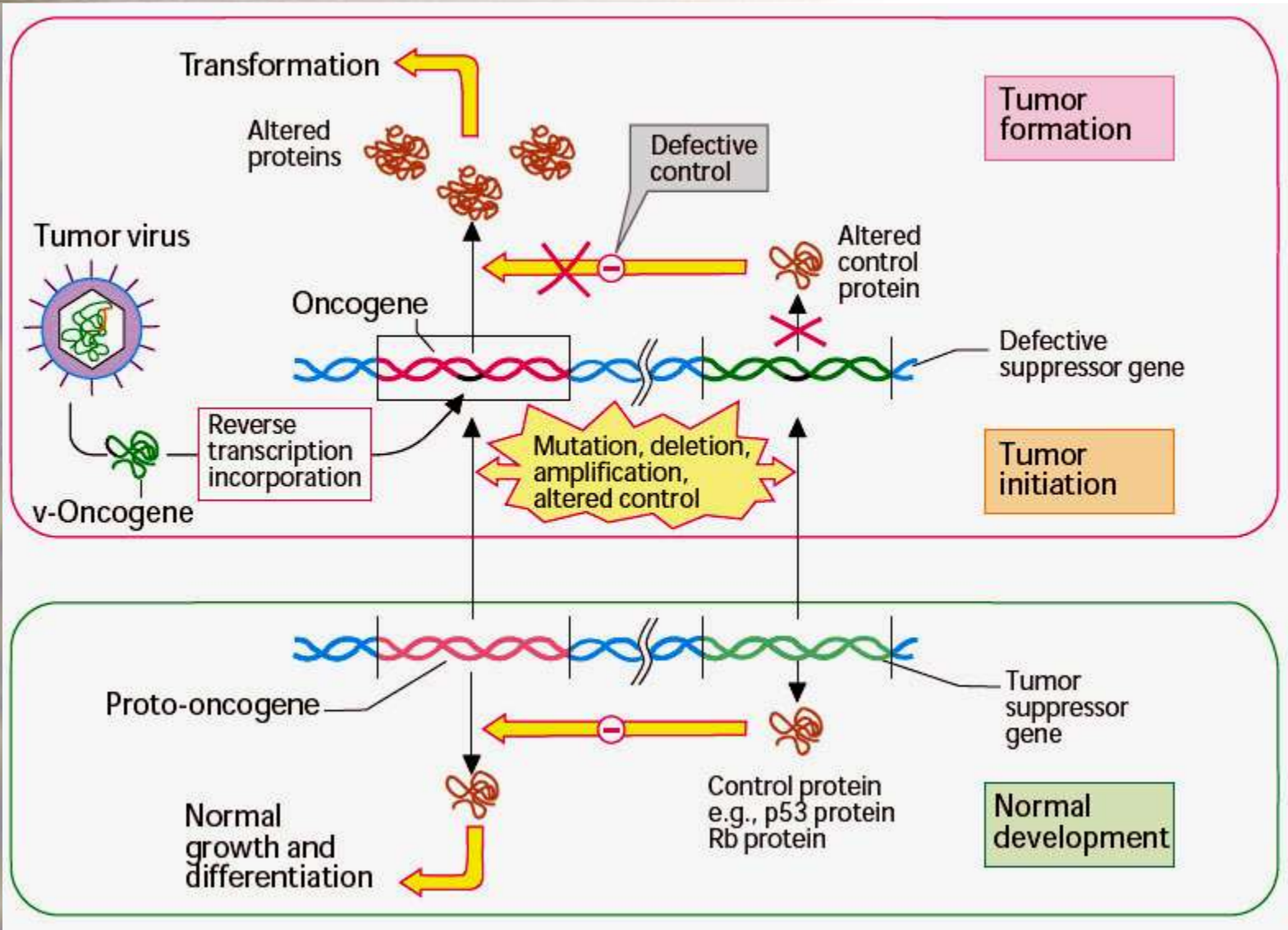


Cell Cycle Regulation

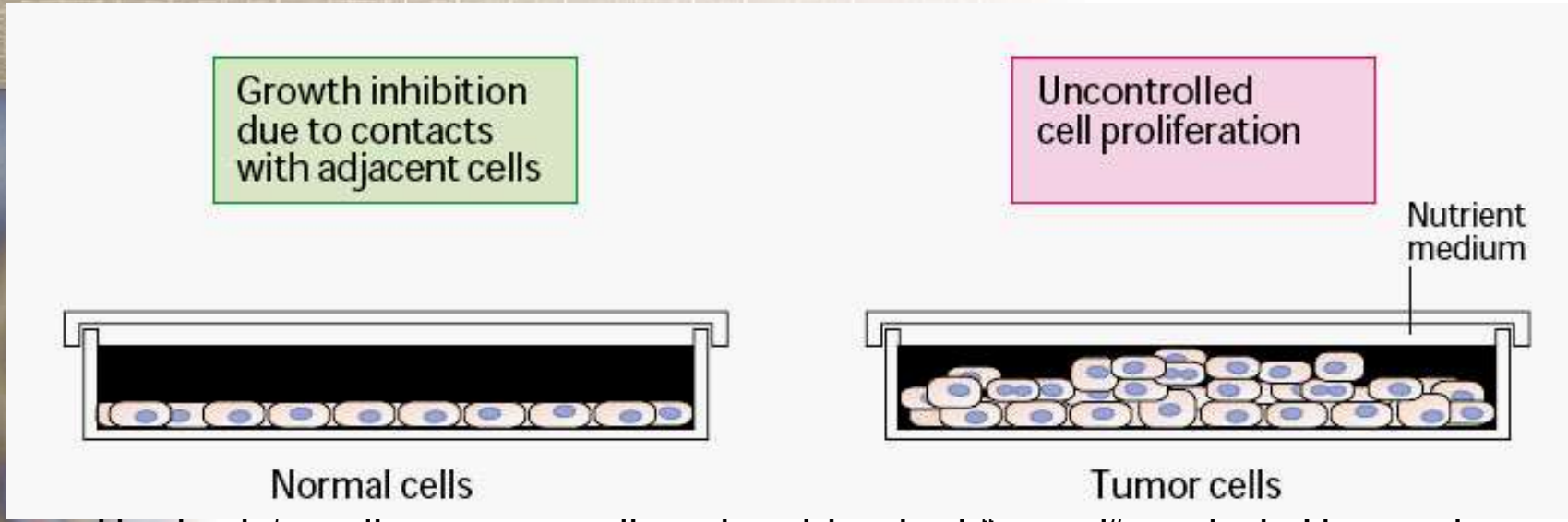
1. CDK phosphorylation
2. C degradation
3. C & CDK synthesis
4. CDK inhibition



Oncogene products - biochemical functions

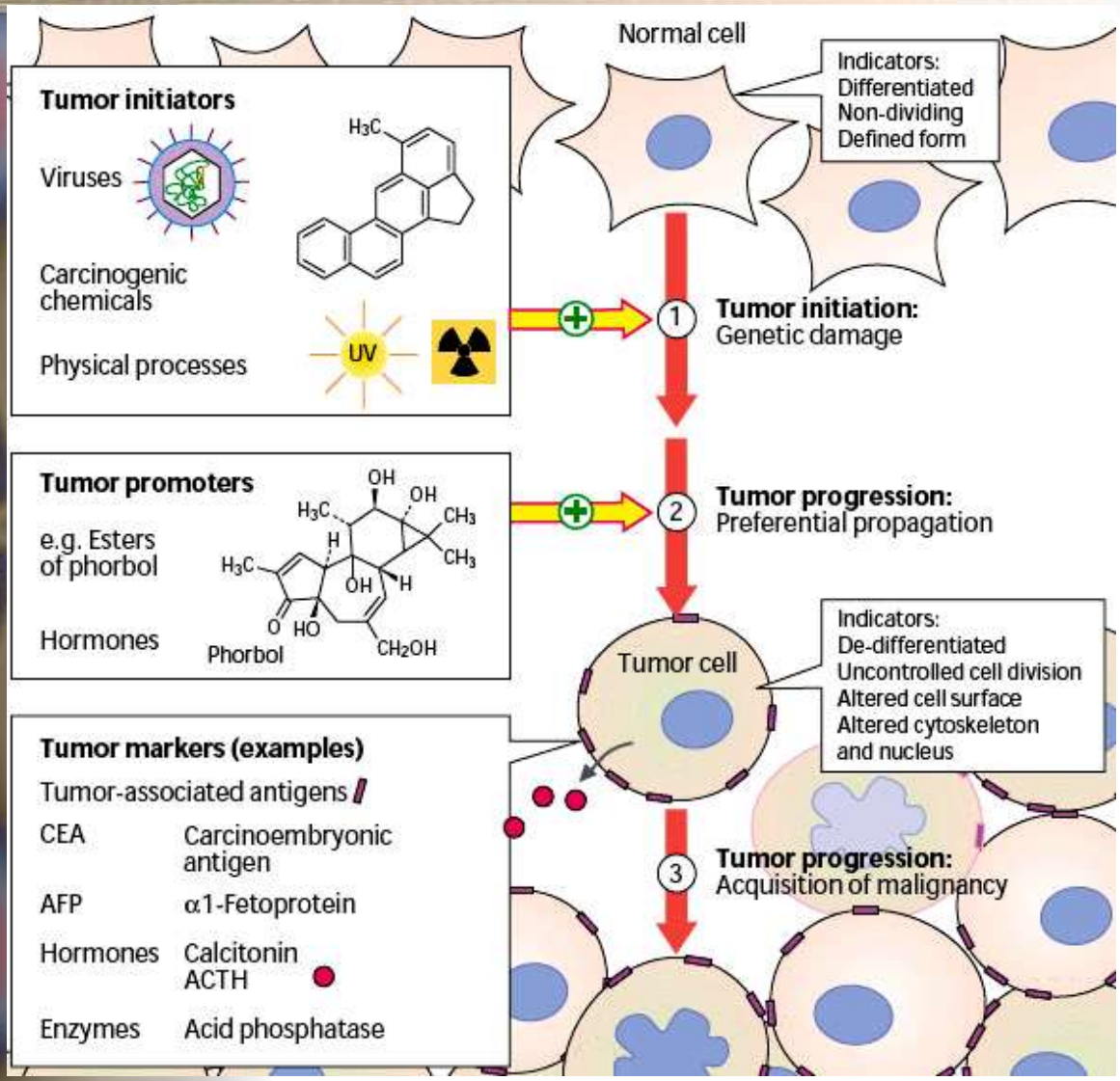


Division Behavior of Cells

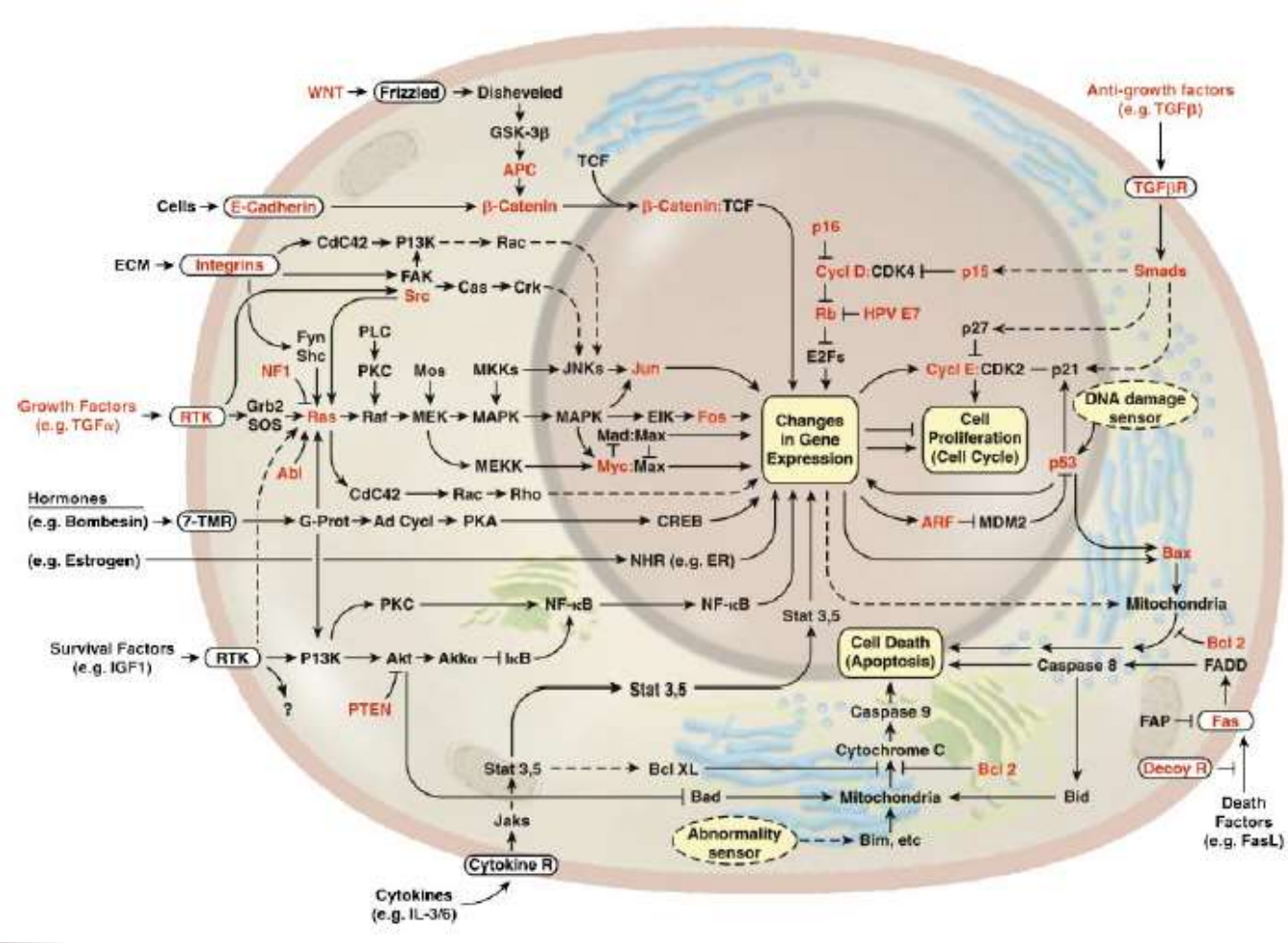


- The body's cells are normally subject to strict "social" control. They only divide until they come into contact with neighboring cells; cell division then ceases due to *contact inhibition.*
- Exceptions to this rule include embryonic cells, cells of the intestinal epithelium (where the cells are constantly being replaced), cells in the bone marrow (where formation of blood cells takes place), and **tumor cells.**
- *Uncontrolled cell proliferation* is an important indicator of the presence of a tumor.
- While normal cells in cell culture only divide 20–60 times, tumor cells are potentially immortal and are not subject to contact inhibition. In medicine, a distinction is made between.

Transformation



Molecular Biology of Cancer



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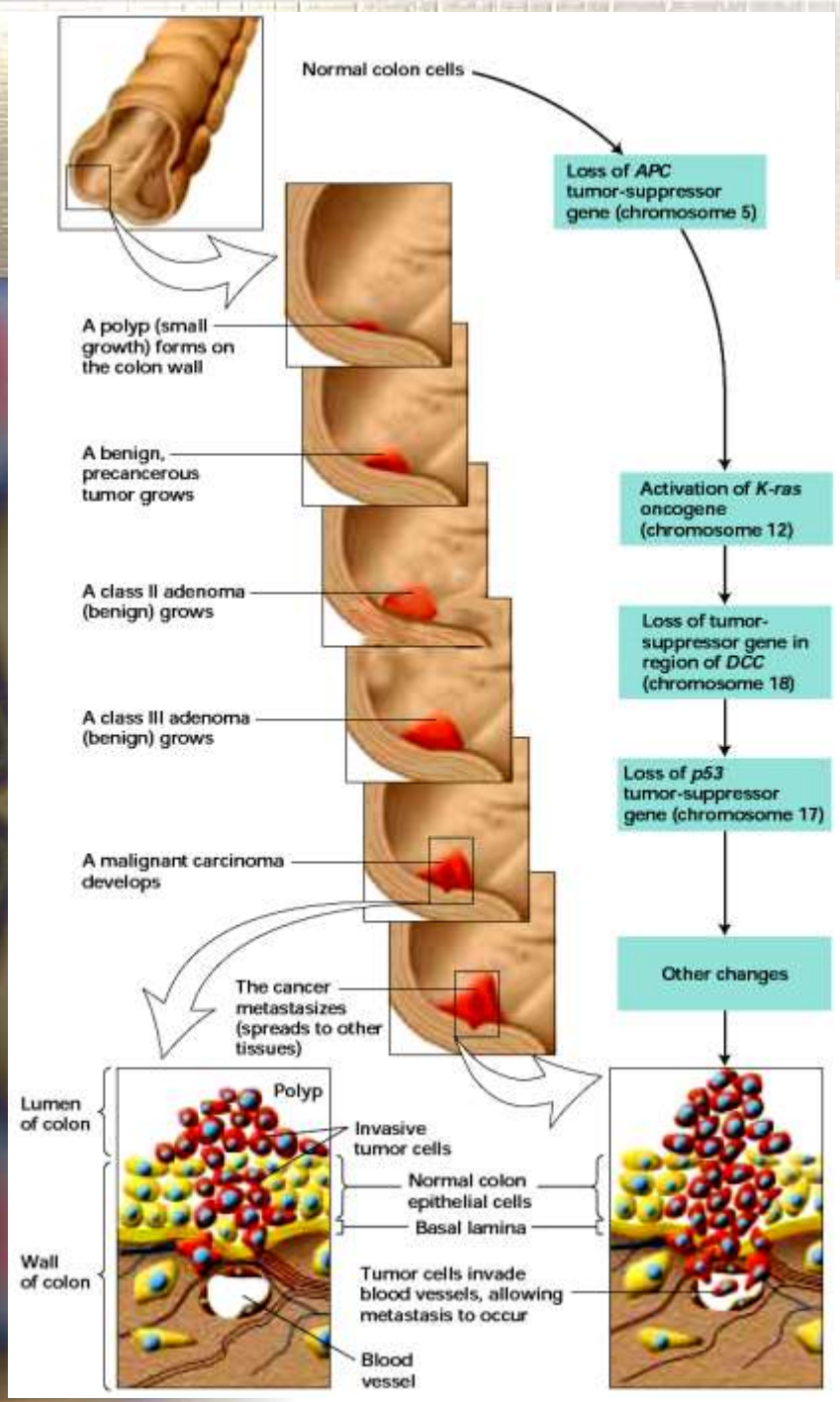
The development and metastasis of human colorectal cancer



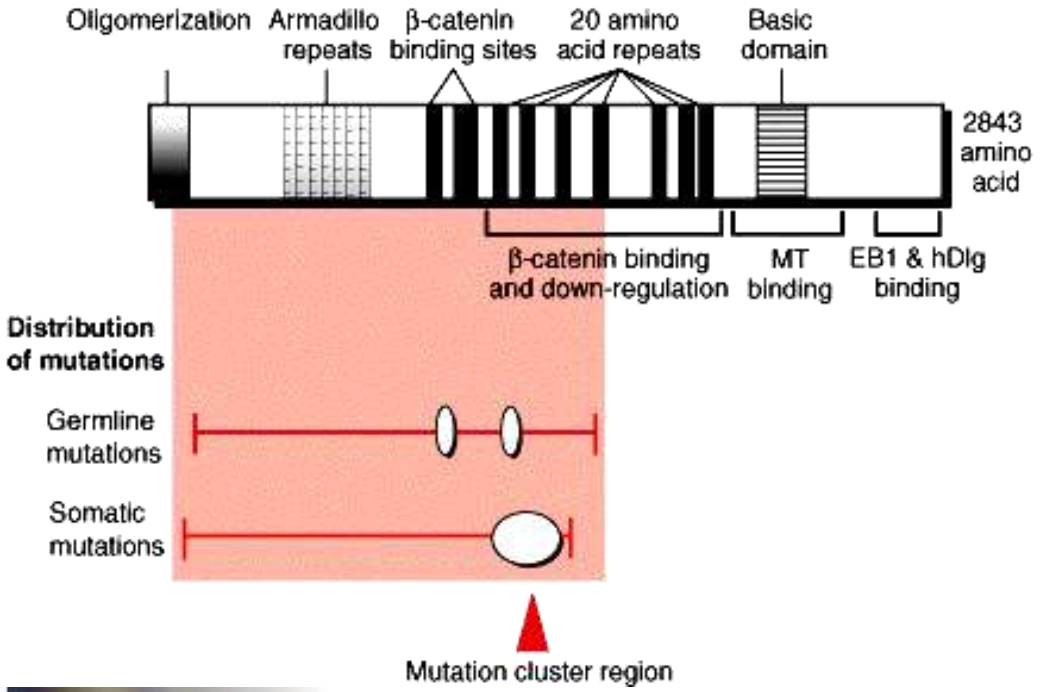
and its genetic basis.

- A mutation in the APC tumor-suppressor gene in a single epithelial cell causes the cell to divide, although surrounding cells do not, forming a mass of localized benign tumor cells, or polyp.
- Subsequent mutations leading to expression of a constitutively active Ras protein and loss of two tumor-suppressor genes – an unidentified gene in the vicinity of *DCC* and *p53*—generate a malignant cell carrying all four mutations. This cell continues to divide, and the progeny invade the basal lamina that surrounds the tissue.
- Some tumor cells spread into blood vessels that will distribute them to other sites in the body.
- Additional mutations permit the tumor cells to exit from the blood vessels and proliferate at distant sites; a patient with such a tumor is said to have cancer.

- [Adapted from B. Vogelstein and K. Kinzler, 1993, *Trends Genet.* **9**:101.]

The APC Gene:

Representation of APC protein domains with respect to mutational analysis results

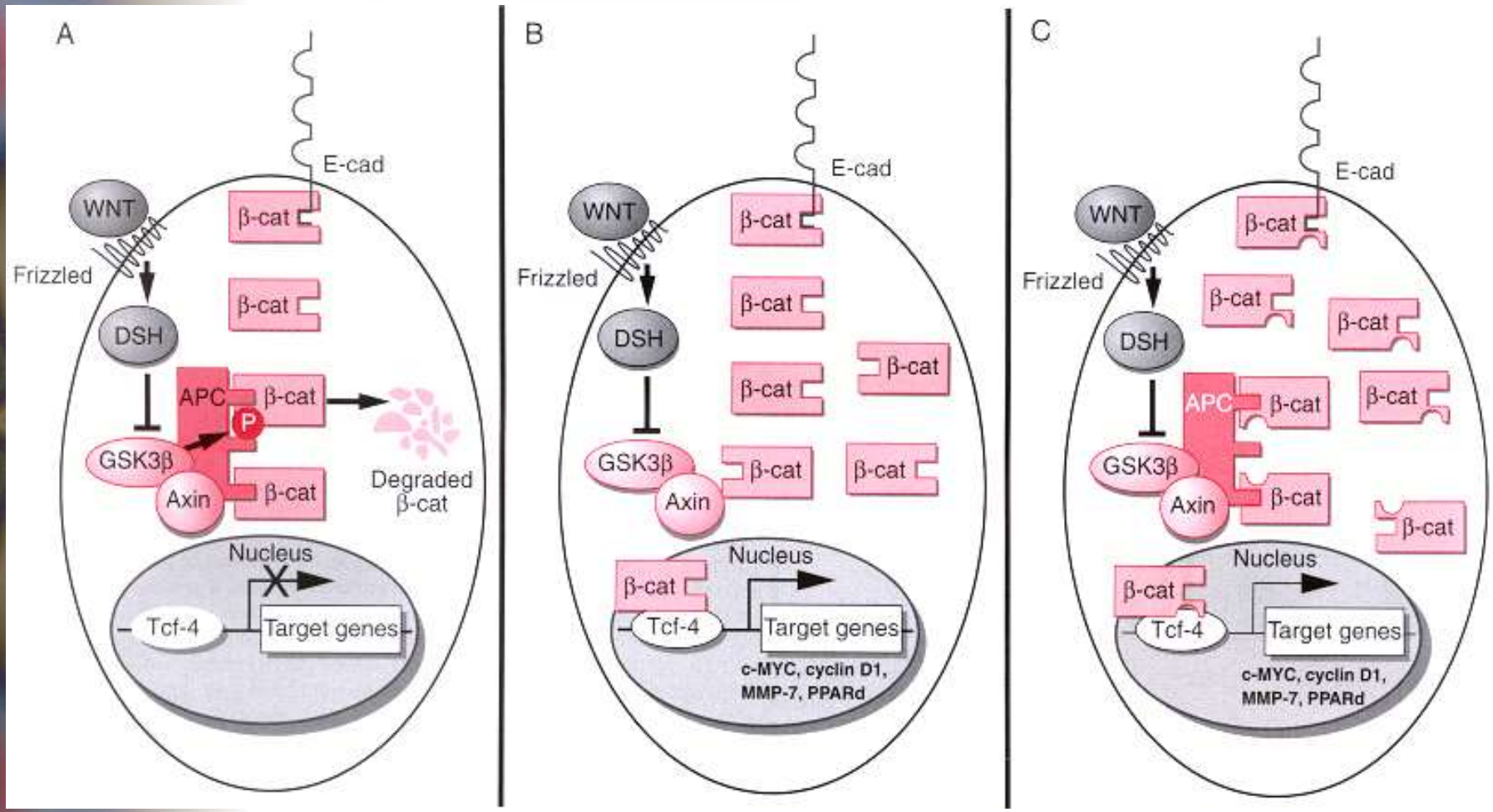


(Modified and reproduced with permission from Fearon ER. Oncogenes and tumor-suppressor genes. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, editors. Clinical oncology, 2nd ed. New York: Churchill Livingstone; 1999. p. 77118.)

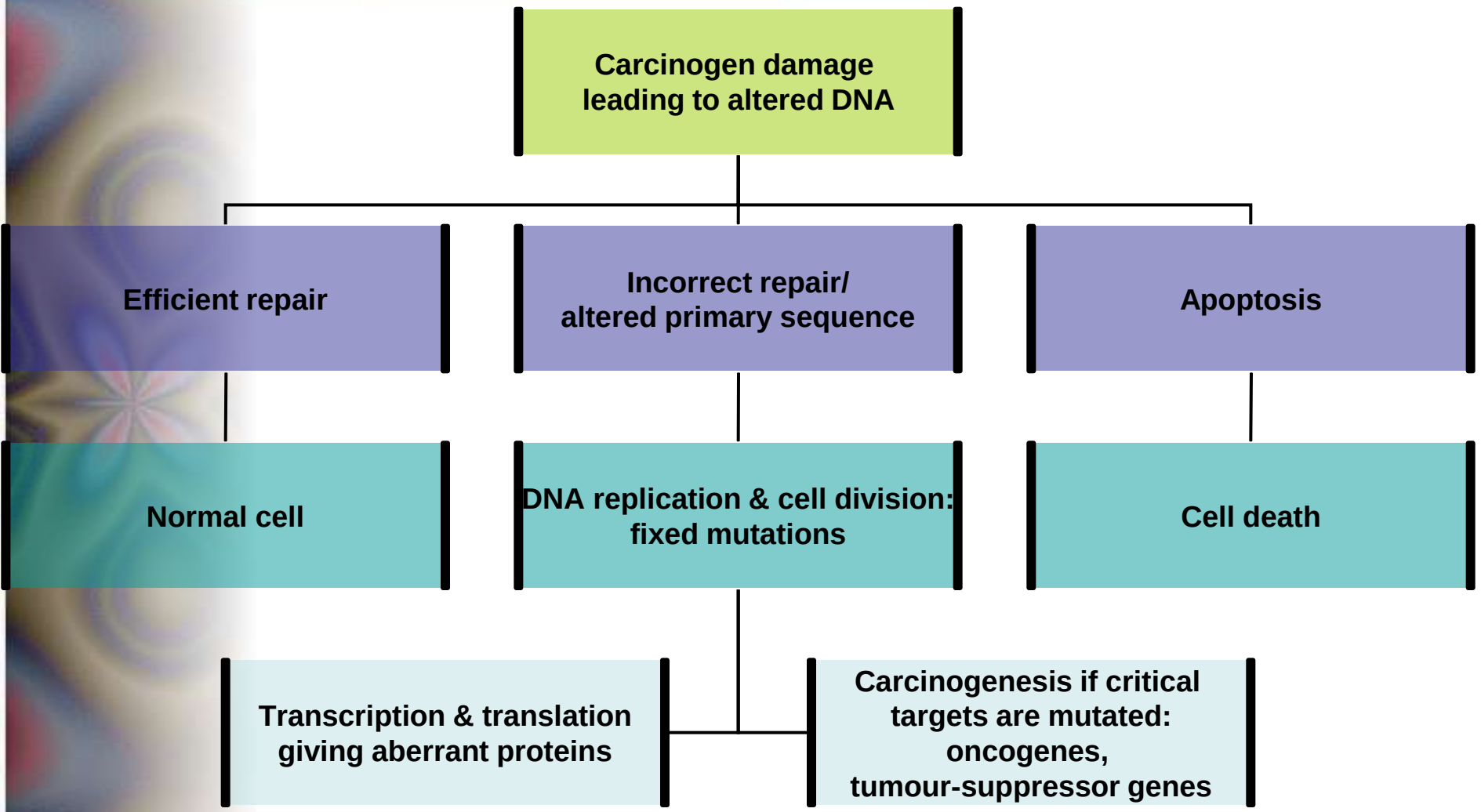
- **The relative positions of various APC domains:**
  - involved in homo-oligomerization of APC (N-terminus).
  - series of repeats of unknown function (similarity to the Drosophila *armadillo* protein),
  - mediate binding to β-catenin and its downregulation,
  - basic domain in the C-terminal third of the protein – facilitate complexing with microtubules (MT),
  - sequences near the C-terminus of APC – interact with the EB1 and human homolog of the Drosophila disc large (hDlg) protein.

Somatic mutations in the APC gene in colorectal cancer appear to cluster in a region termed the **"mutation cluster region,"** and mutations at codons 1309 and 1450 are most common.

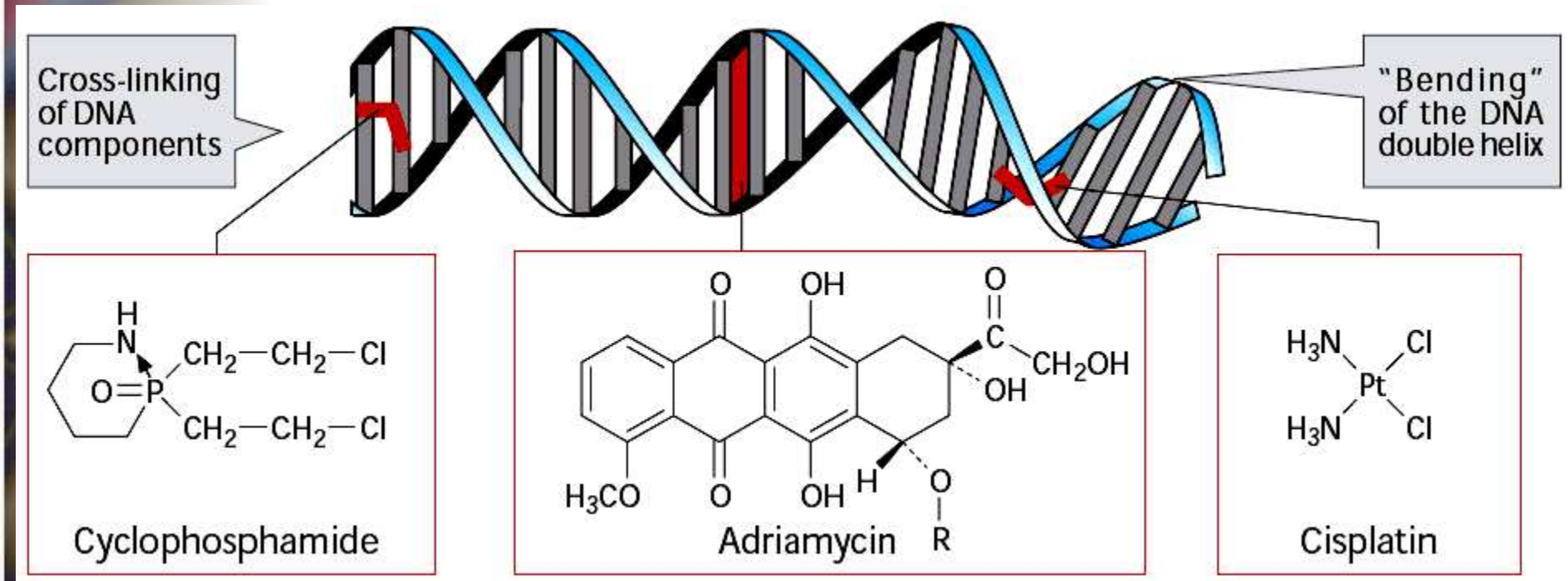
The Function of the APC, Axin, and GSK3β Proteins in the Regulation of β-catenin



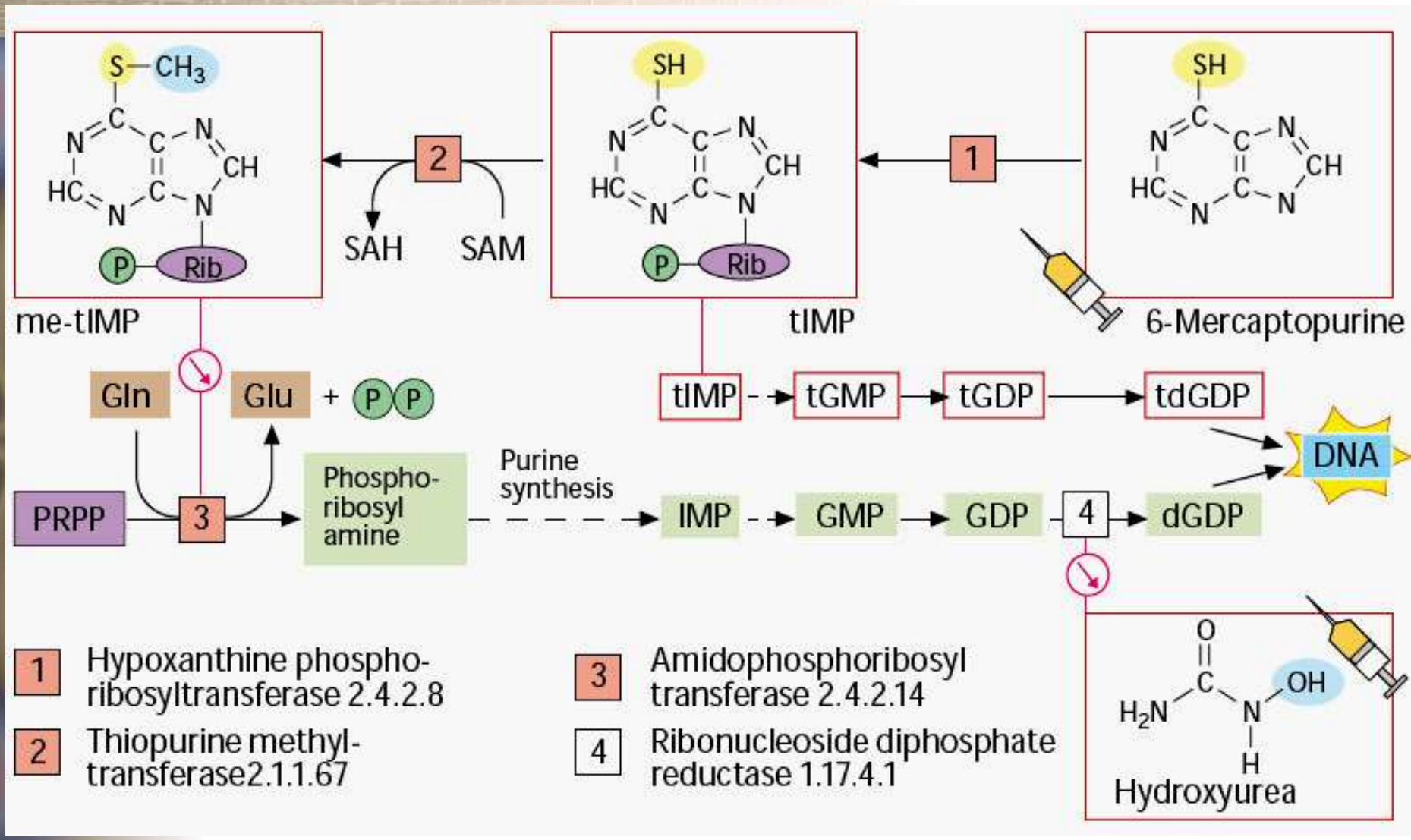
Possible fates for carcinogen-damaged DNA



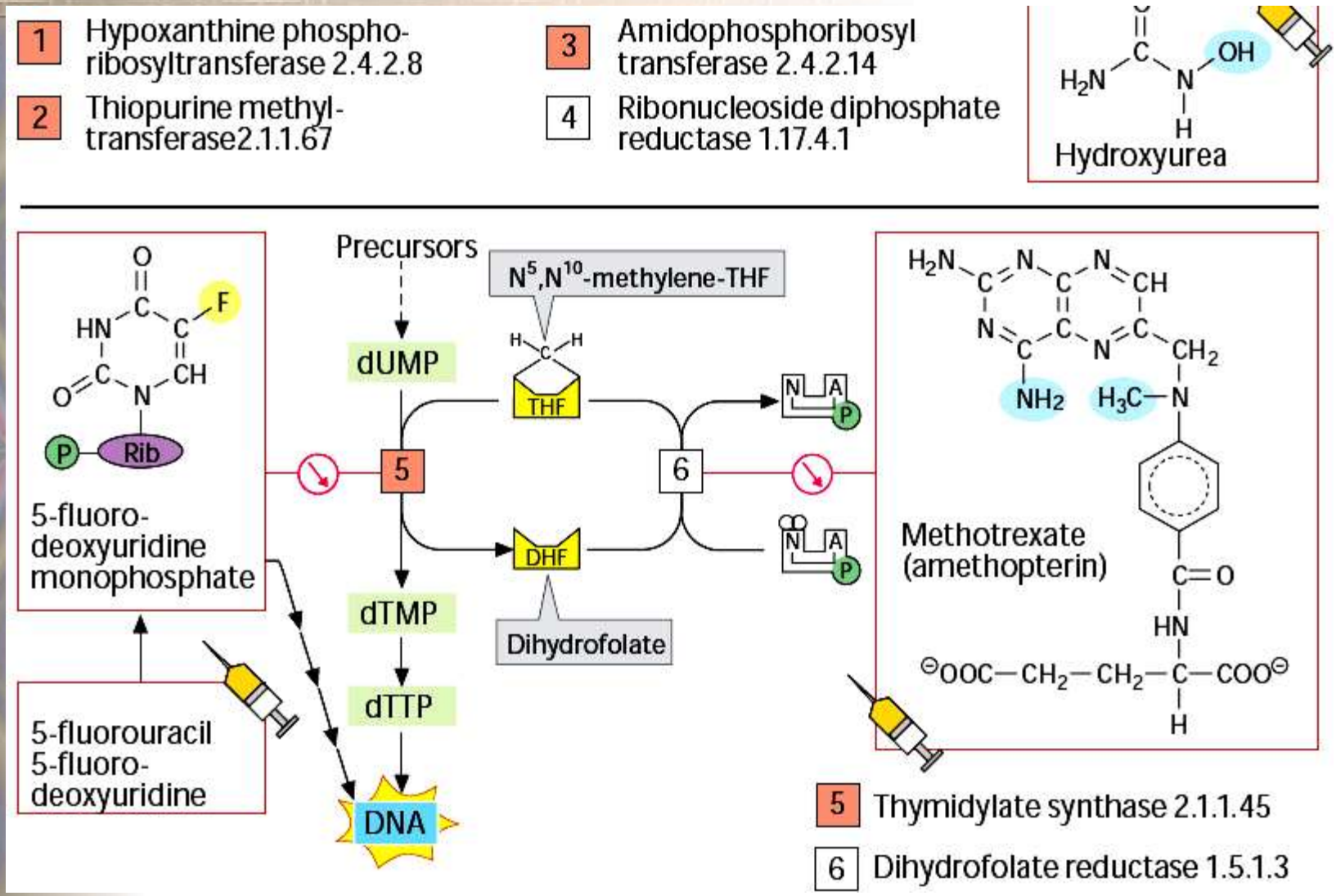
Alkylating agents, anthracyclines



Antimetabolites



Antimetabolites-2



Some Links for Cancerogene Researches

- www.pubmed.org
- http://atlasgeneticsoncology.org/index.html
- http://www.expasy.org/
- http://www.genecards.org/index.shtml
- http://www.ebi.ac.uk/msd


Thank you
for your attention!