BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024,
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Programme: M.Sc., Biomedical science

Course Title : Cancer Biology

Course Code : 18BMS59C16

Unit-I

TOPIC: Introduction to Cancer Biology

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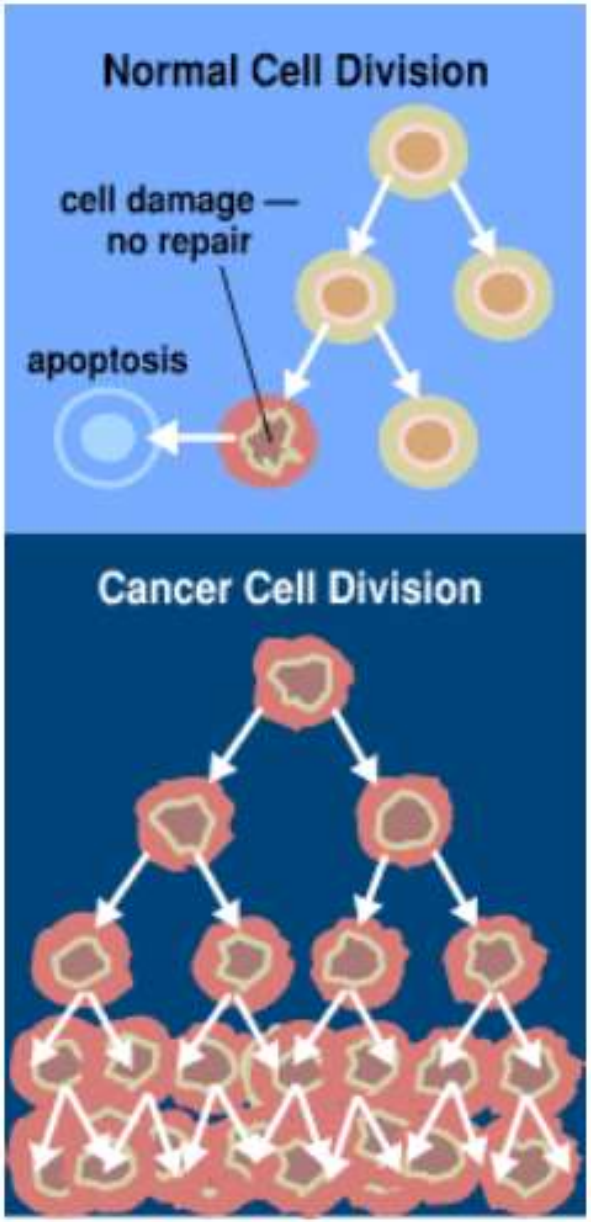
Cancer Overview

1. **Cancer**

   A large group of diseases characterized by uncontrolled growth and spread of abnormal cells.

2. **Neoplasm or Tumor**

   A mass of new tissue growth independent of its surrounding structures; it has no function.



Cancer: Loss of Cell 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.

Tumor Cell Formation

Loss of Cell Cycle Regulation at Checkpoints

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Increased growth rate, escape from apoptosis

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Accumulation of DNA damage, errors in replication, introduction of mutations, chromosomal translocations, aneuploidies

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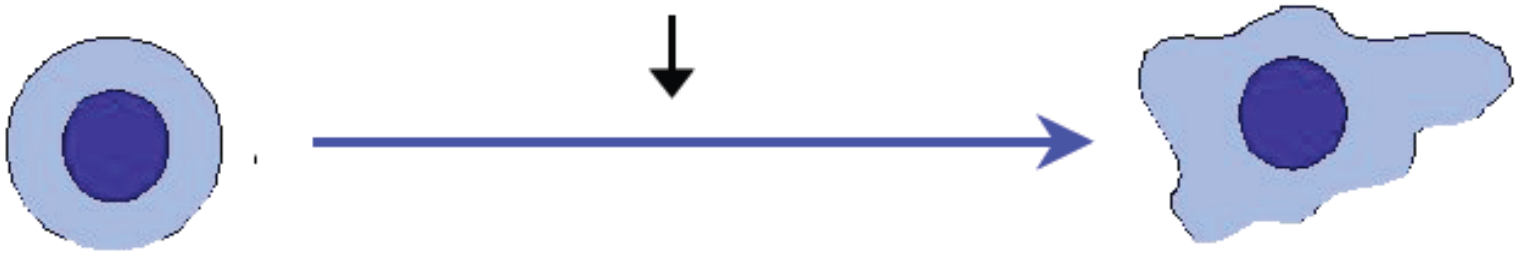
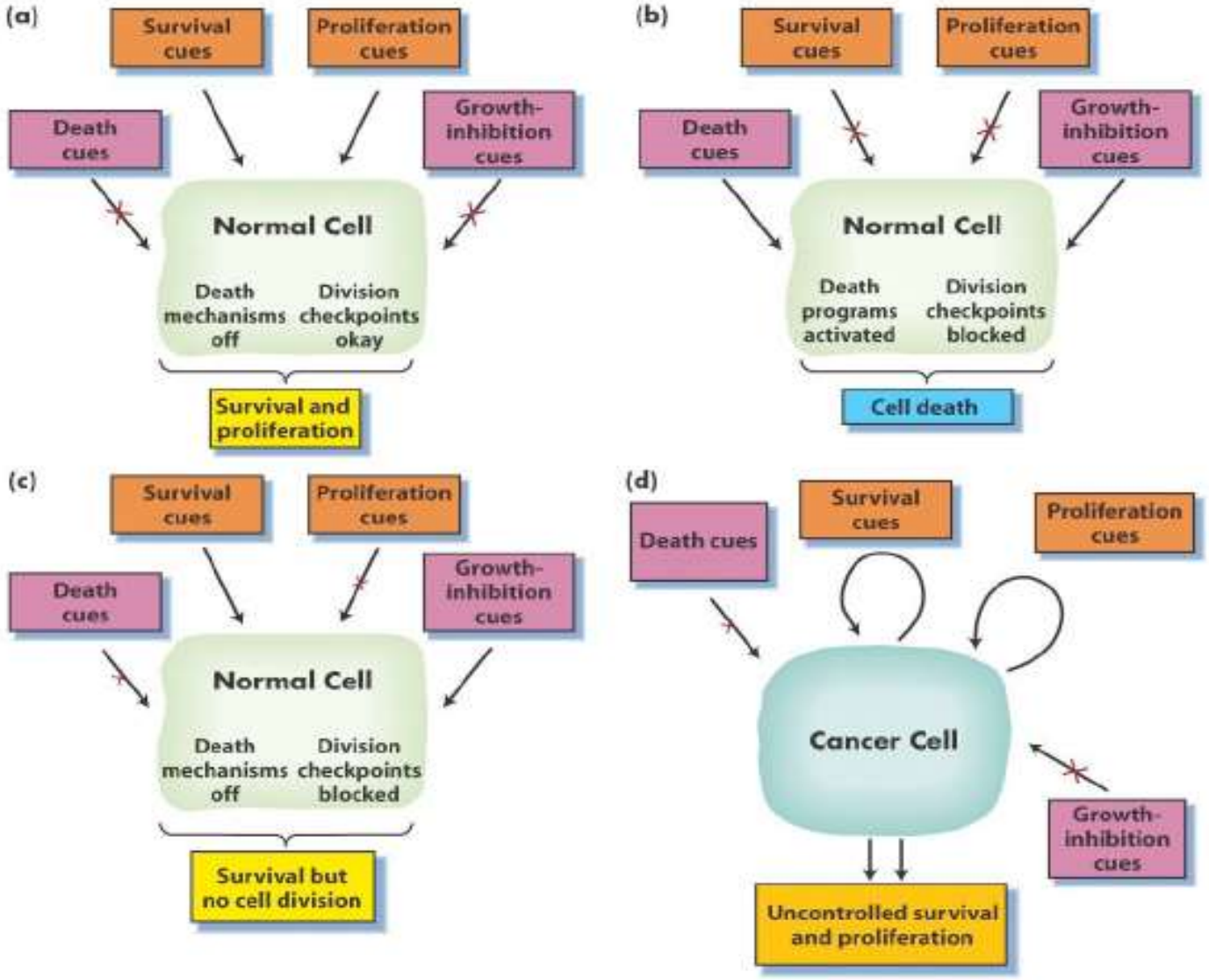
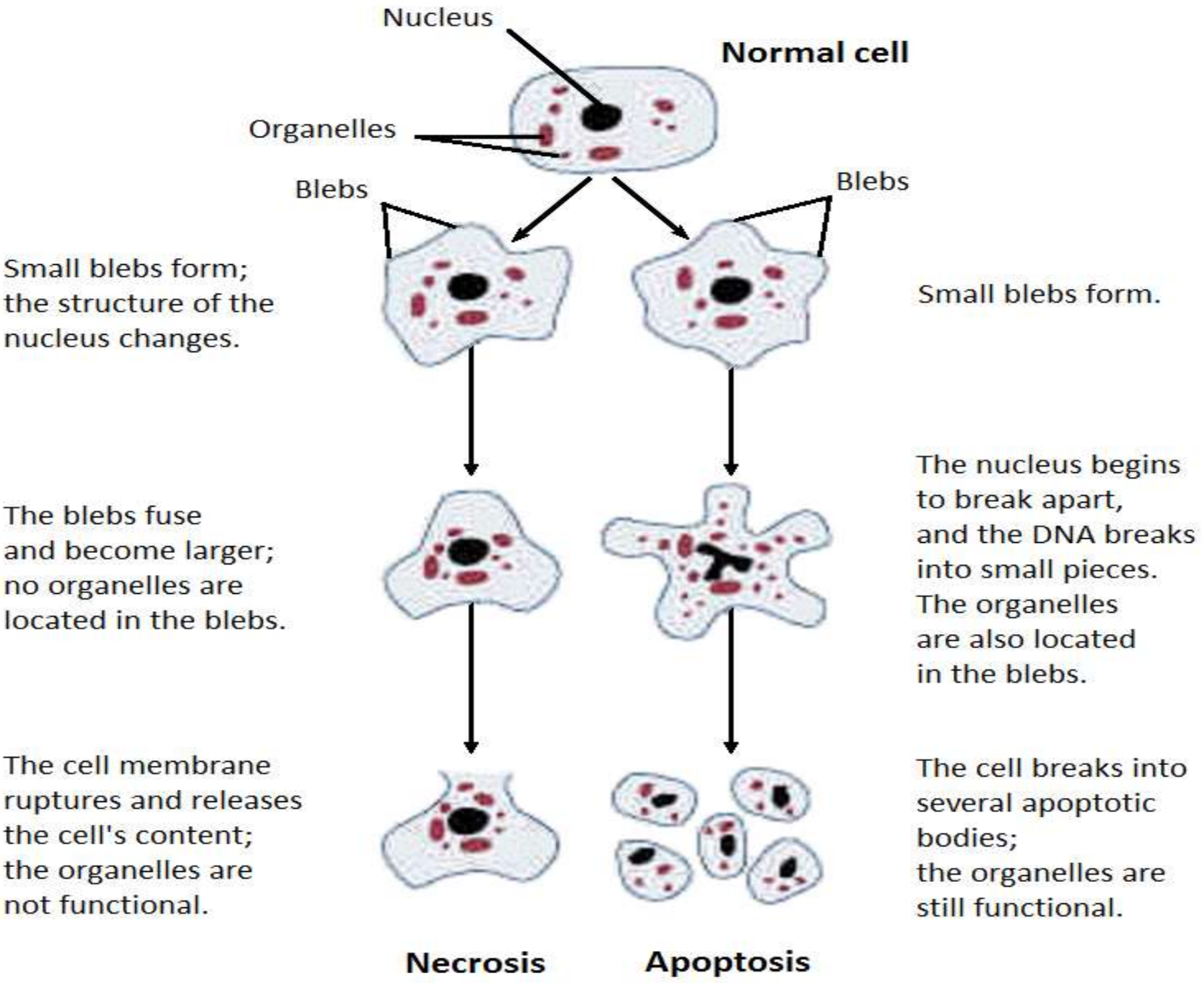


Normal Cell **Tumor Cell**

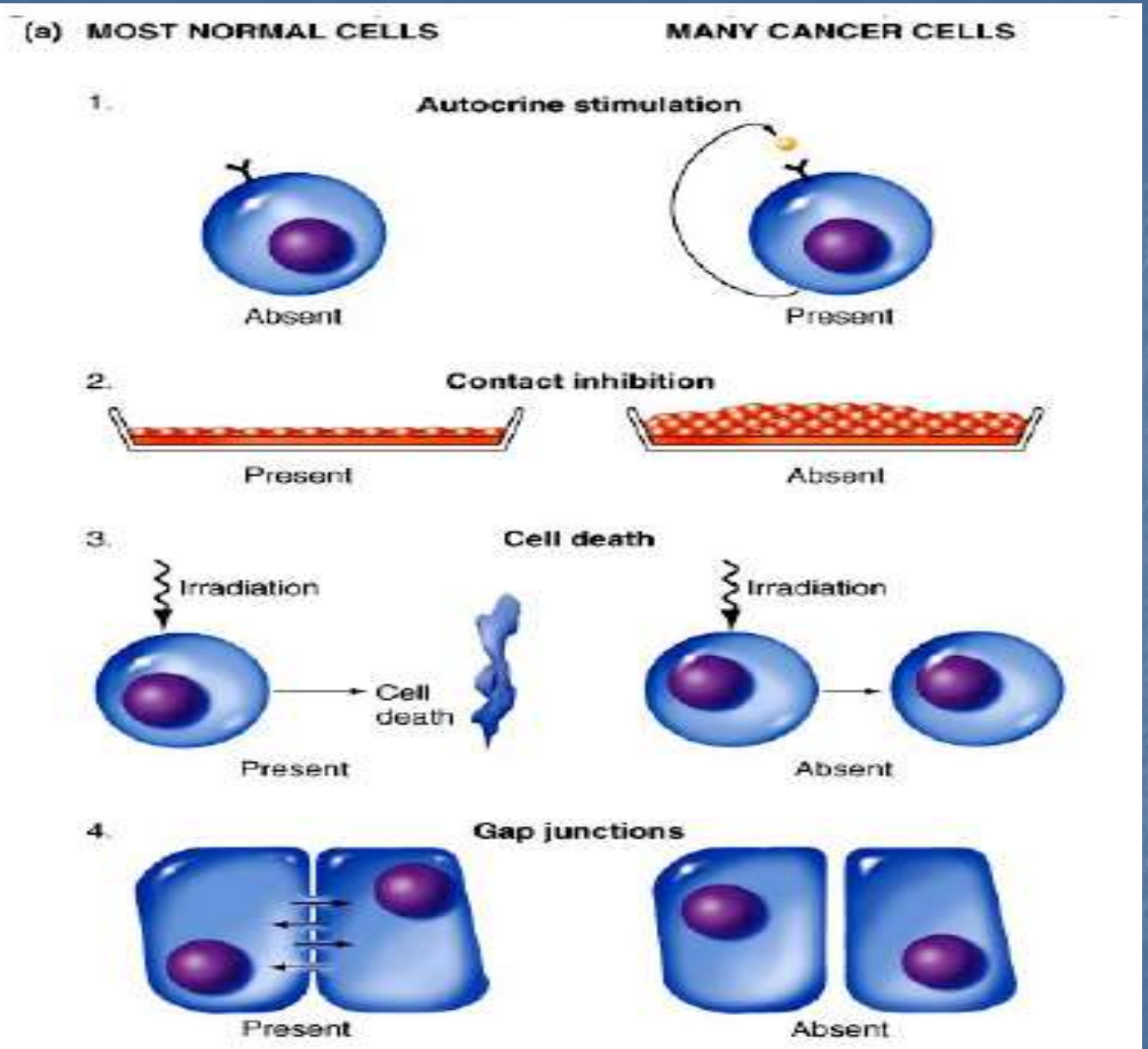
What is Cancer?




Nucleus
Normal cell
Organelles
Blebs
Blebs
Small blebs form;
the structure of the
nucleus changes.
Small blebs form.
The blebs fuse
and become larger;
no organelles are
located in the blebs.
The nucleus begins
to break apart,
and the DNA breaks
into small pieces.
The organelles
are also located
in the blebs.
The cell membrane
ruptures and releases
the cell's content;
the organelles are
not functional.
The cell breaks into
several apoptotic
bodies;
the organelles are
still functional.
Necrosis
Apoptosis

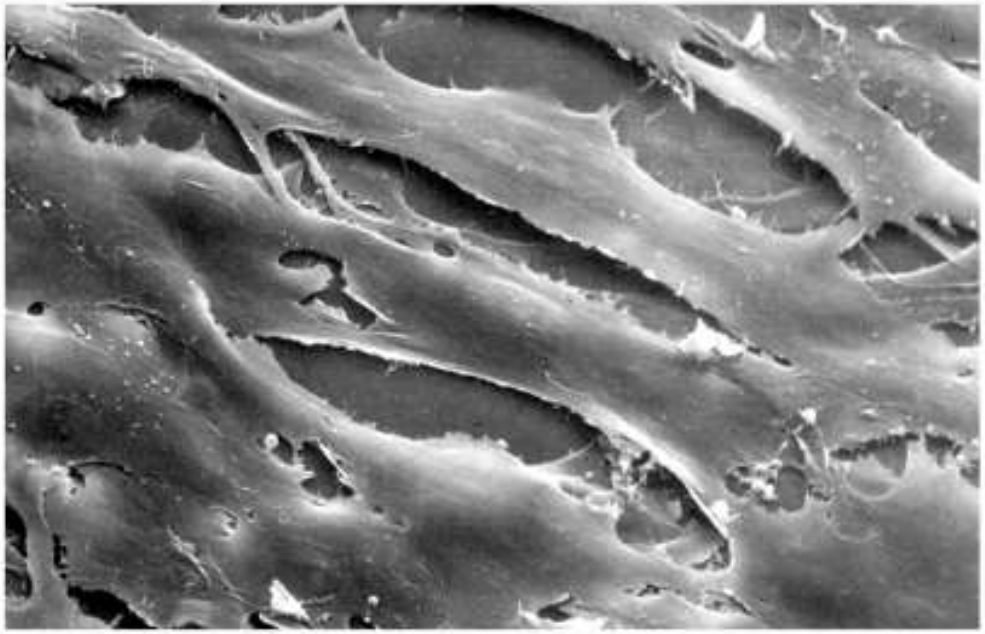
Properties of Cancer Cells

- Cancer cells exhibit several characteristics that are distinct from normal cells.
- Multiple changes are involved in the conversion of a normal cell to a cancer cell:
  - Autocrine stimulation; grow in the absence of growth factors
  - Lack of gap junctions;
  - lack of contact inhibition
  - Resistance to cell death; persistent telomerase activity
  - Rapid growth; overtake population, invade other tissues.
  - Angiogenesis
  - Clonal nature of cancer
  - Genomic Instability: Accumulation of successive mutations
- A germline mutation causes a hereditary cancer.
- A somatic mutation causes a sporadic cancer.

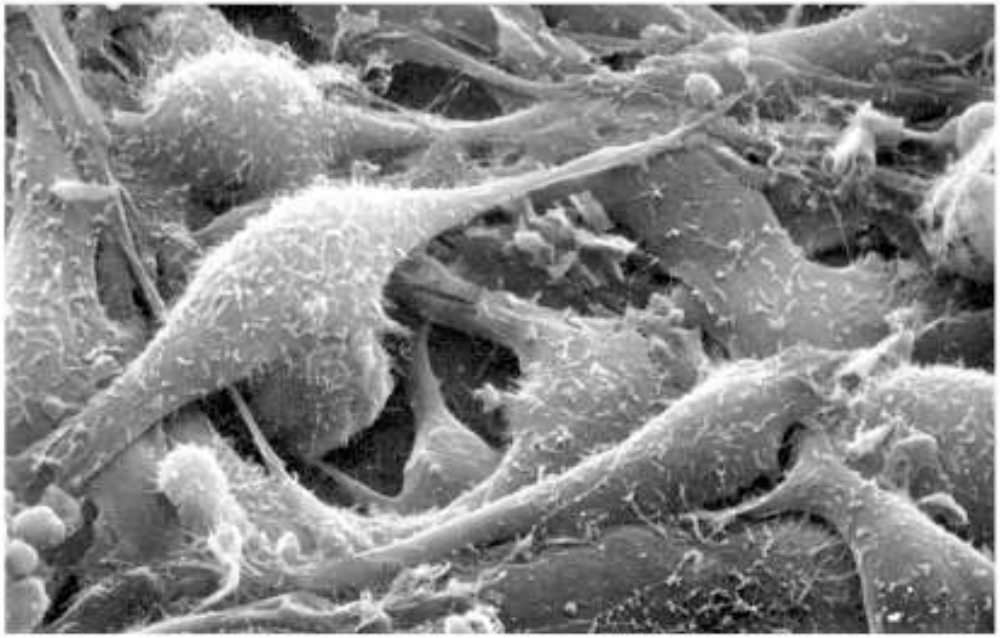


Gap junction channels are composed of a family of transmembrane proteins called connexin

Properties of Cancer Cells: Lack of contact inhibition

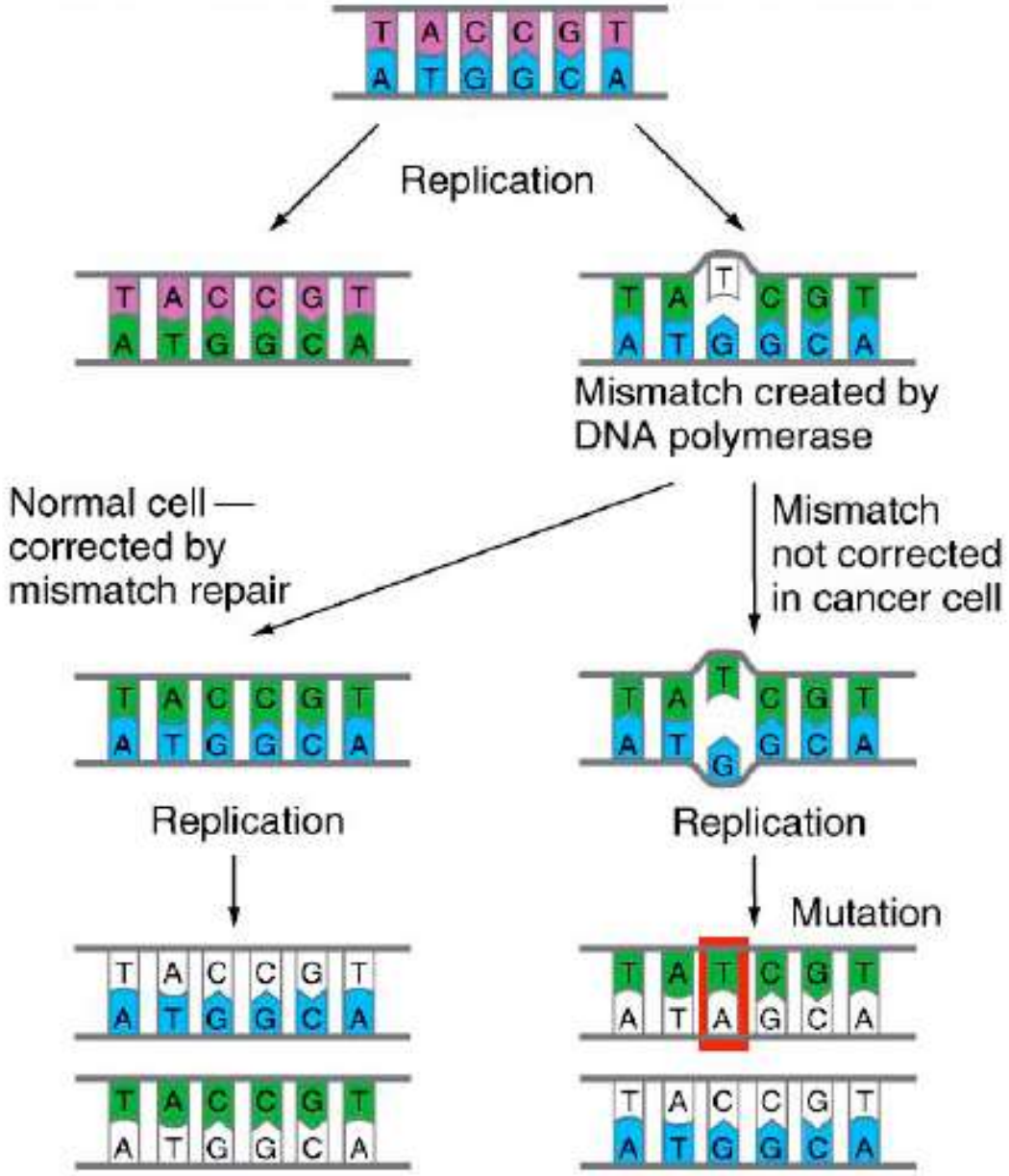


Normal skin cells
Grow in monolayer



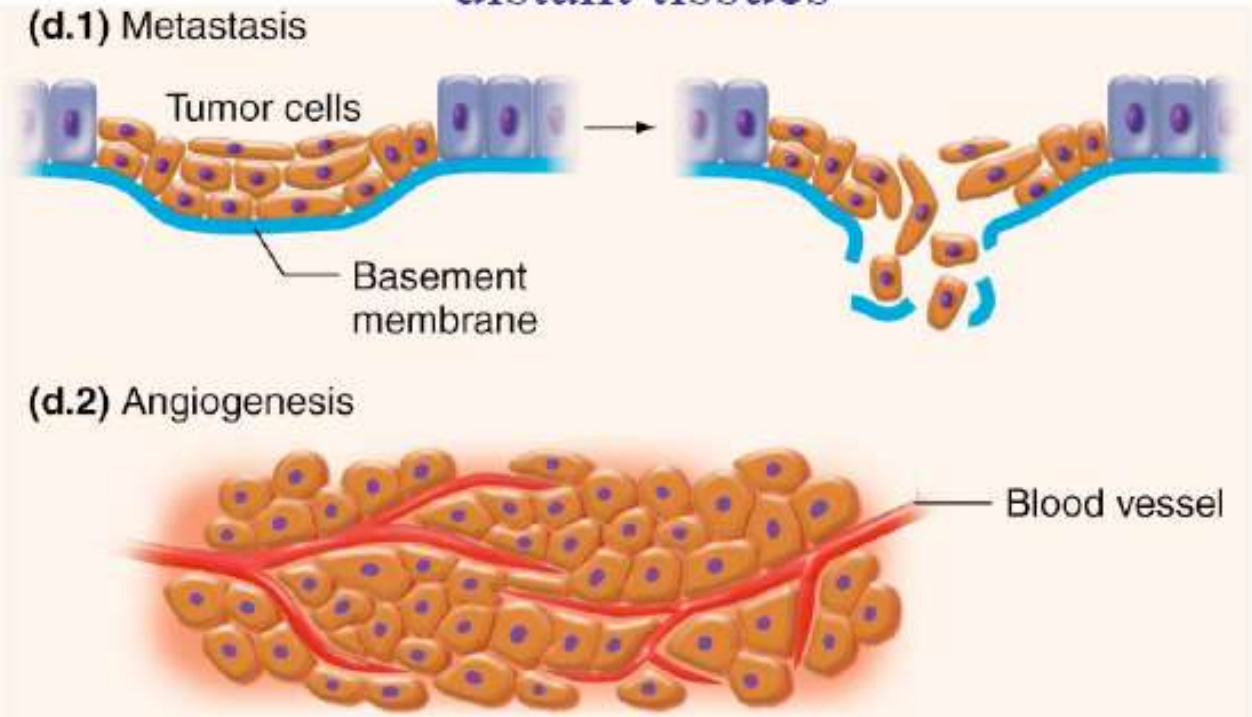
Skin cancer cells
Do not grow in monolayer
Pile up on each other

Properties of Cancer Cells: Genomic Instability



Properties of Cancer Cells:

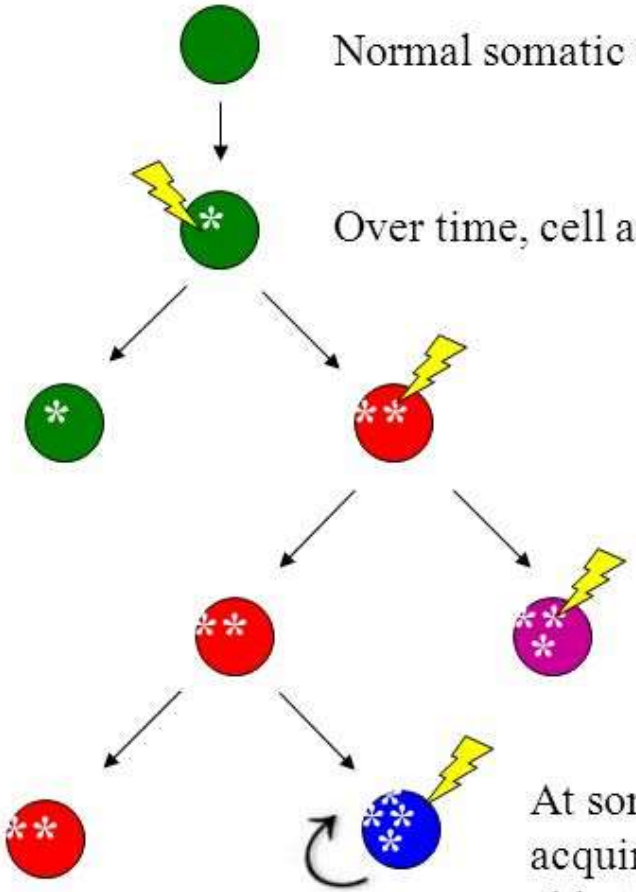
Changes that enable tumor to disrupt local tissue and invade distant tissues



Feature Figure 18.16 d

- Ability to metastasize
- Angiogenesis – secrete substances that cause blood vessels to grow toward tumor
- Evasion of immune surveillance

Clonal Evolution Model



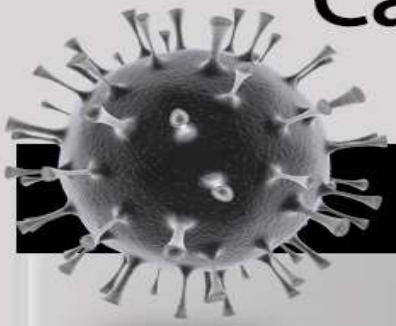
Normal somatic cell within a tissue

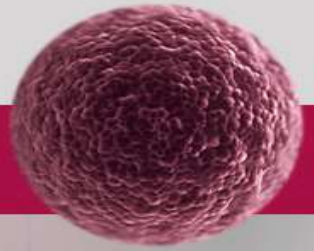
Over time, cell accumulates enough mutations to become cancerous

Increased proliferation of tumor leads to the clonal expansion of cancer cells that harbor unique mutations – which confer unique phenotypes onto the cells that carry them. This accounts for the heterogeneity that is characteristic of many cancers.

At some point, a certain population within the tumor could acquire the ability for self-renewal – these cells would be able to form a new tumor if transplanted into a new host.

Cancer Cell & Normal Cell Characteristics





Cancer Cell	Normal Cell
Shape: Irregular	**Shape:** Regular
Nucleus: Larger, darker	**Nucleus:** Proportionate size
Growth: Out of control	**Growth:** In control, systematic
Maturation: Immature - Doesn't mature	**Death:** Mortal (Apoptosis)
Communication: Doesn't communicate	**Maturation:** Mature (Cell differentiation)
Visibility: Invisible to immune cells	**Communication:** Communicates
Blood Supply: Tumor angiogenesis	**Visibility:** Visible to immune cells,
Oxygen: Doesn't like or require oxygen	**Blood Supply:** Angiogenesis during repair
Glucose: Loves, craves glucose	**Oxygen:** Requires oxygen
Energy Efficiency: Very low (5%)	**Glucose:** Requires some glucose
Amount of ATP: 2 units of ATP	**Energy Efficiency:** Very high (95%)
Cell Environment: Acidic	**Amount of ATP:** 38 units of ATP
Nutrient Preference: Glucose	**Cell Environment:** Alkaline
	Nutrient Preference: Fat, Ketone, Glucose

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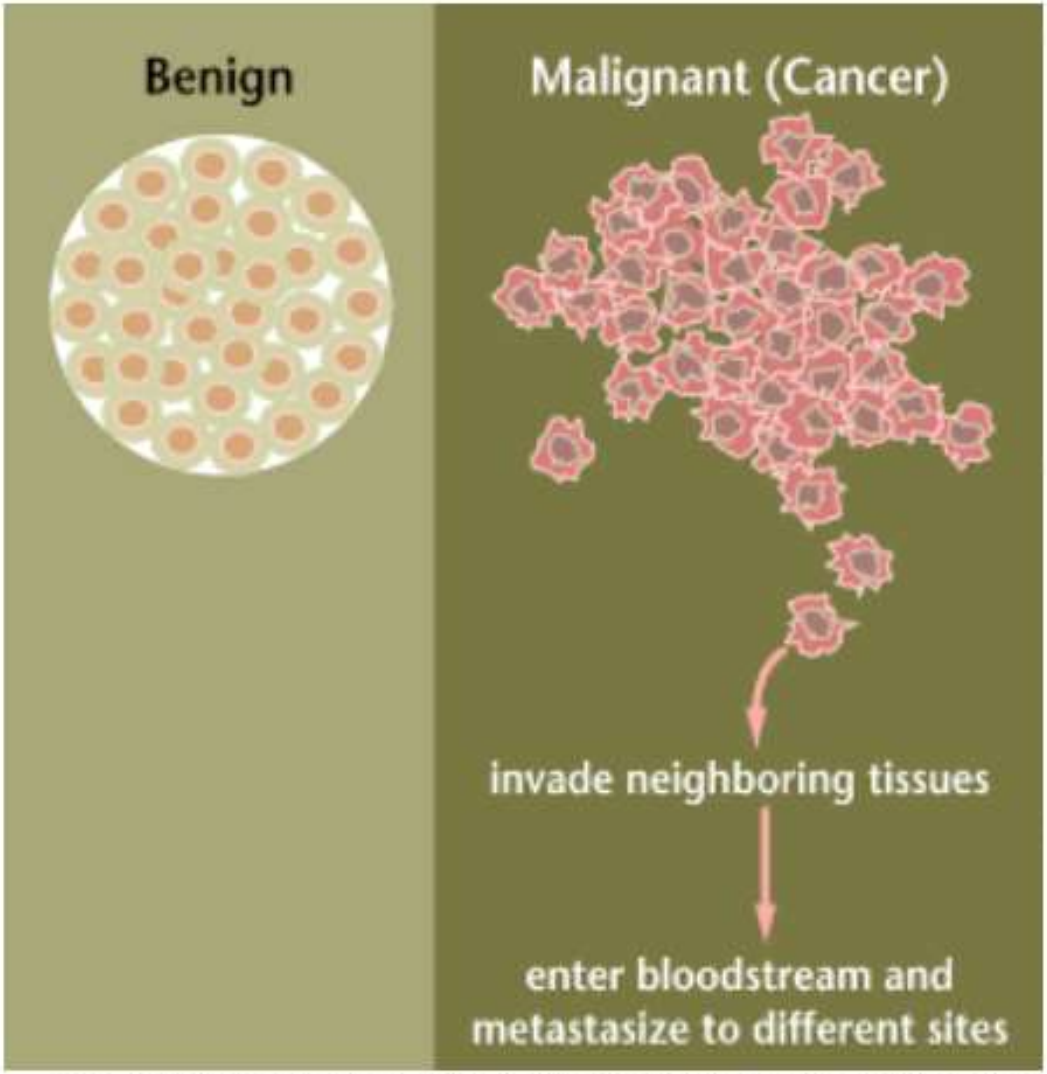
Benign Vs. Malignant Tumors



- 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.

From: National Cancer Institute : http://press2.nci.nih.gov/sciencebehind/cancer/cancer00.htm

General Characteristics

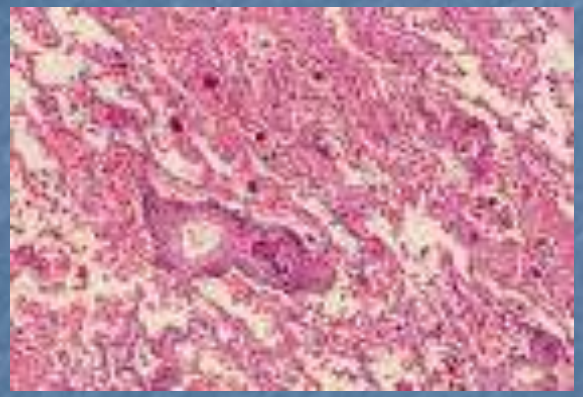
	Benign	Malignant
Local Spread	Expanding, Pushing	Infiltrative and invasive
Distant Spread	Rare	Metastasize
Differentiation	Well Differentiated	Well Differentiated to undifferentiated
Mitotic Activity	Normal	Normal to increased mitotic rate
Morphology	Normal	Normal to pleopmorphic
Effect on Host	Little	Life threatening
Doubling Time	Normal	Normal to accelerated

Pleomorphic:- In various distinct forms

Types of Differentiation

- 1. **Well differentiated**
  - closely resemble the cell of origin
  - easily classified by histology

- 2. **Undifferentiated**
  - do not resemble normal cells
  - more difficult to classify
  - also called "anaplastic"



The environment:

Some environmental agents associated with cancer are:

- Viruses
- Tobacco smoke
- Food
- Radiation
- Chemicals
- Pollution

Causes of Cancer

- Chemicals in the environment
  - Tobacco smoking is associated with lung cancer and bladder cancer.
  - Prolonged exposure to asbestos fibers is associated with mesothelioma
  - malignant (cancerous) cells are found in the mesothelium, a protective sac that covers most of the body's internal organs. Most people who develop mesothelioma have worked on jobs where they inhaled asbestos particles.
  - Hundreds of chemicals have been identified as carcinogens.

Causes of Cancer

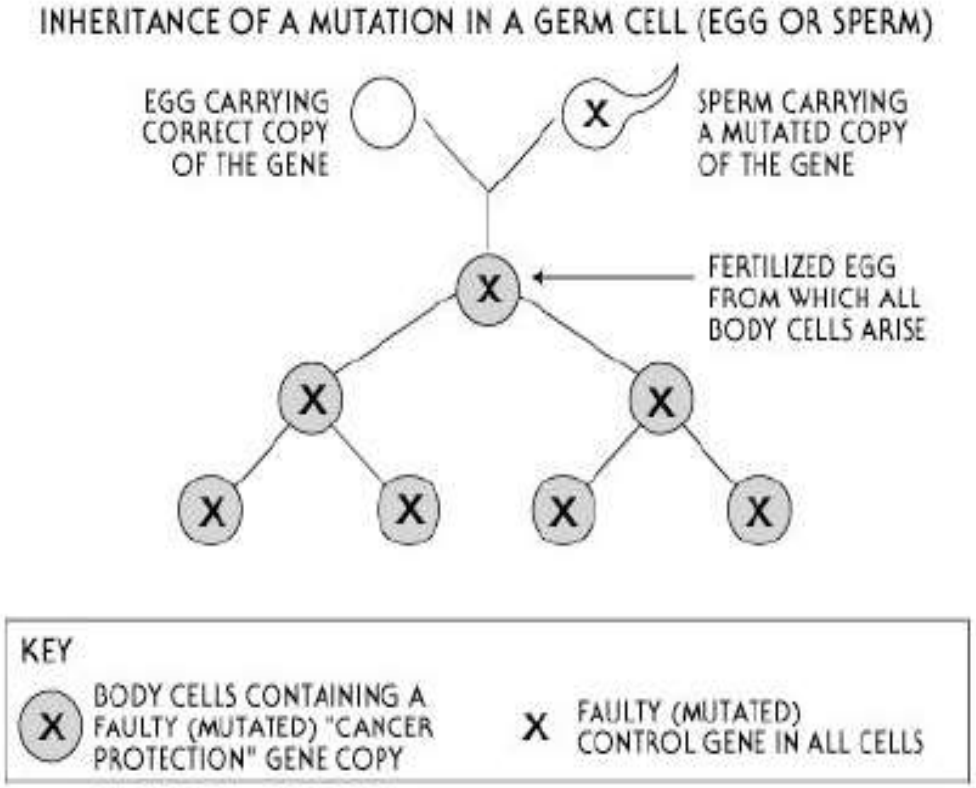
- Ionizing Radiation
  - Sources of ionizing radiation, such as radon gas, can cause cancer. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies.
- Infectious Diseases
  - Virus - The main viruses associated with human cancers are human papillomavirus, hepatitis B and hepatitis C virus, Epstein-Barr virus, and human T-lymphotropic virus.

Sporadic Vs. Familial Cancer

- **Familial:**
- inherited form. The family has a predisposition through a germline mutation.
  - Increases the probability that further mutations will occur.
  - Sometimes the initial germline mutation may be responsible for different cancers:
    - e.g. same family may have individuals with breast, bone, lung, ovarian cancer because of a single inherited germline mutation:
    - e.g.: *p53*.

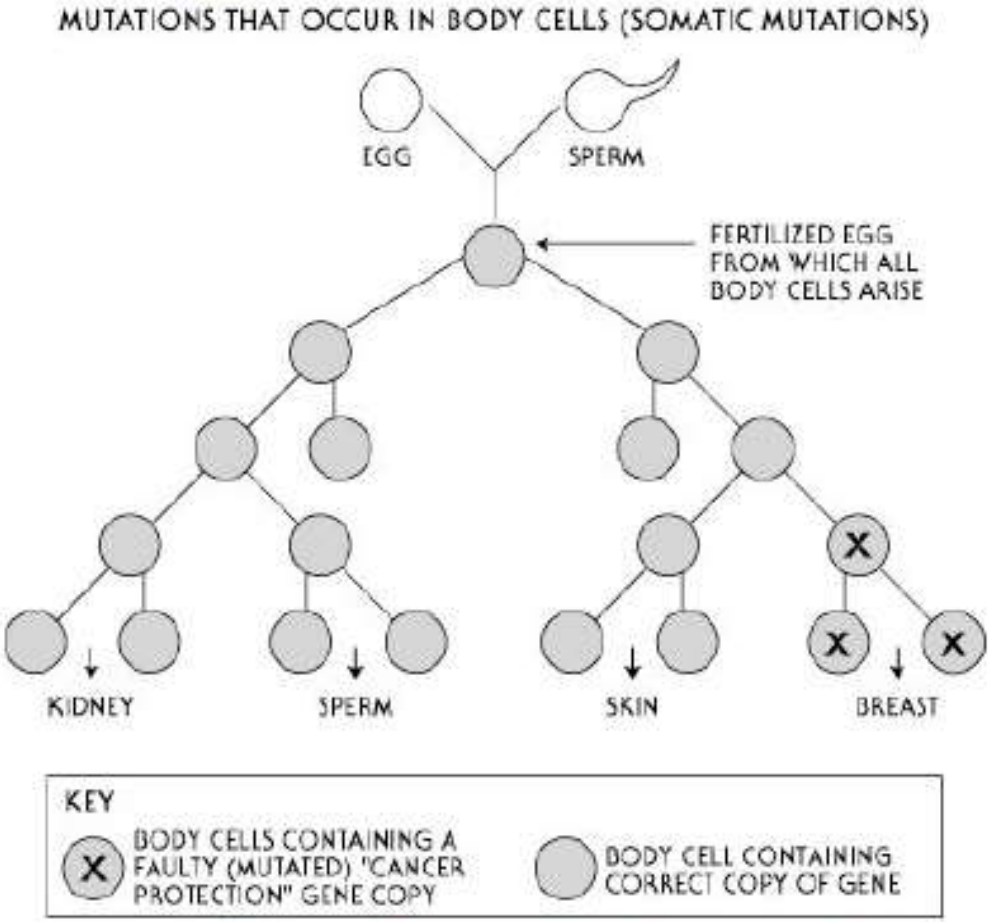
- **Sporadic cancers**:
- new mutations arising in somatic cells of the body.
  - Could result in any type of cancer, depending on the where the mutation occurs.

Familial Cancer



Inheritance of a mutation in a "cancer protection" gene in a germ cell (egg or sperm). The offspring will have both a faulty copy and a correct copy of the "cancer protection" gene in all the cells of their body, and will be predisposed to develop cancer.

Sporadic Cancer



Mutations that occur during life in the body cells (somatic mutations) such as the cells of the breast are confined to the breast tissue. These mutations will not be passed on to the next generation.

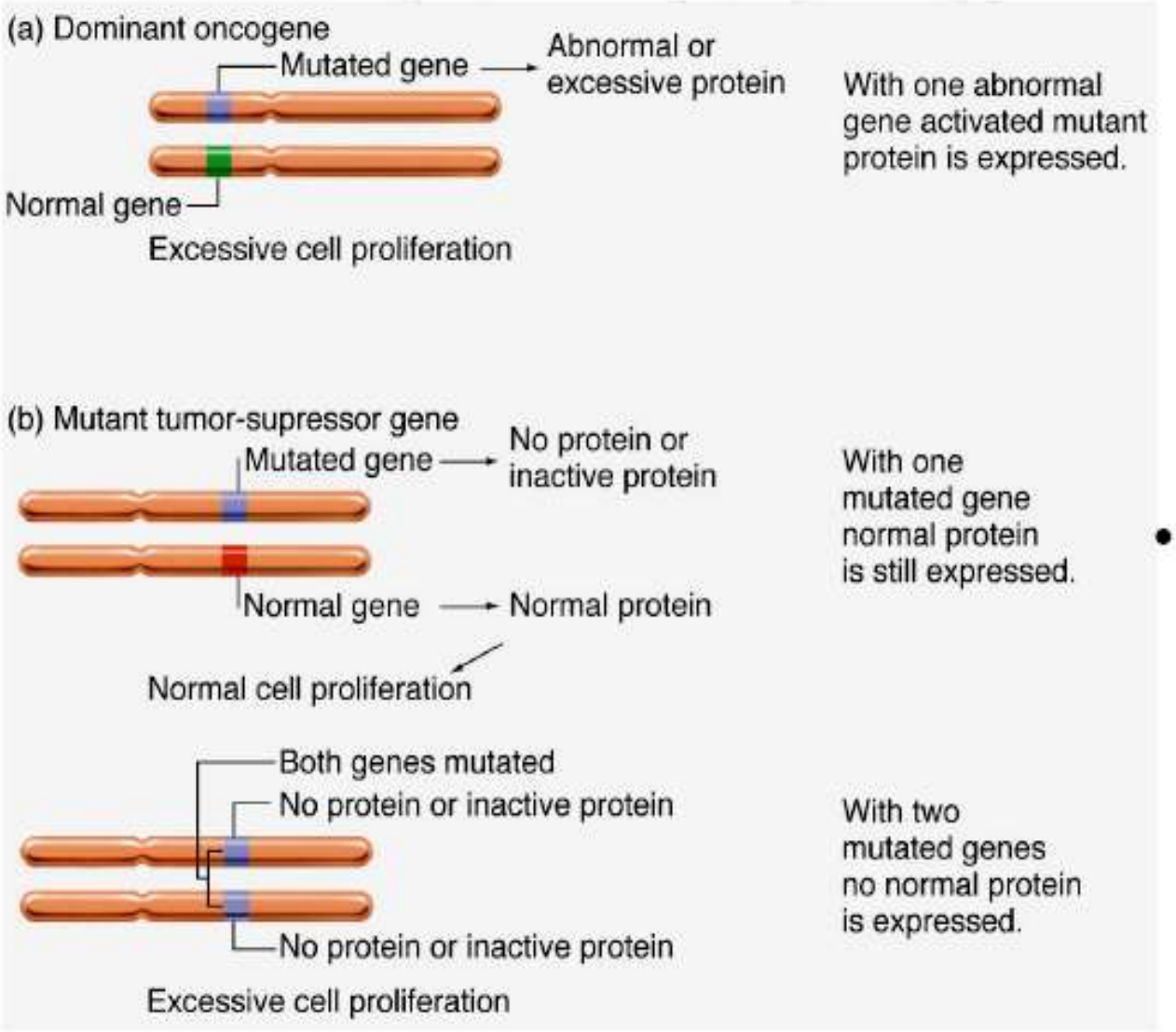
Genes and Cancer

- Two classes of genes are mutated frequently in cancer:
  - **Tumor suppressor genes**: loss of function mutations.
    - Normal function is to prevent cell proliferation.
    - So-called "cancer protection" genes
  - **Protooncogenes**: gain of function mutations.
    - quantitative change in expression of these genes common in cancer
    - Normal function is to promote cell proliferation.

Tumour suppressor genes

- The gene's normal function is to regulate cell division. Both alleles need to be mutated or removed in order to lose the gene activity.
- The first mutation may be inherited or somatic.
- The second mutation will often be a gross event leading to loss of heterozygosity in the surrounding area.

Tumor Suppressors vs. Oncogenes

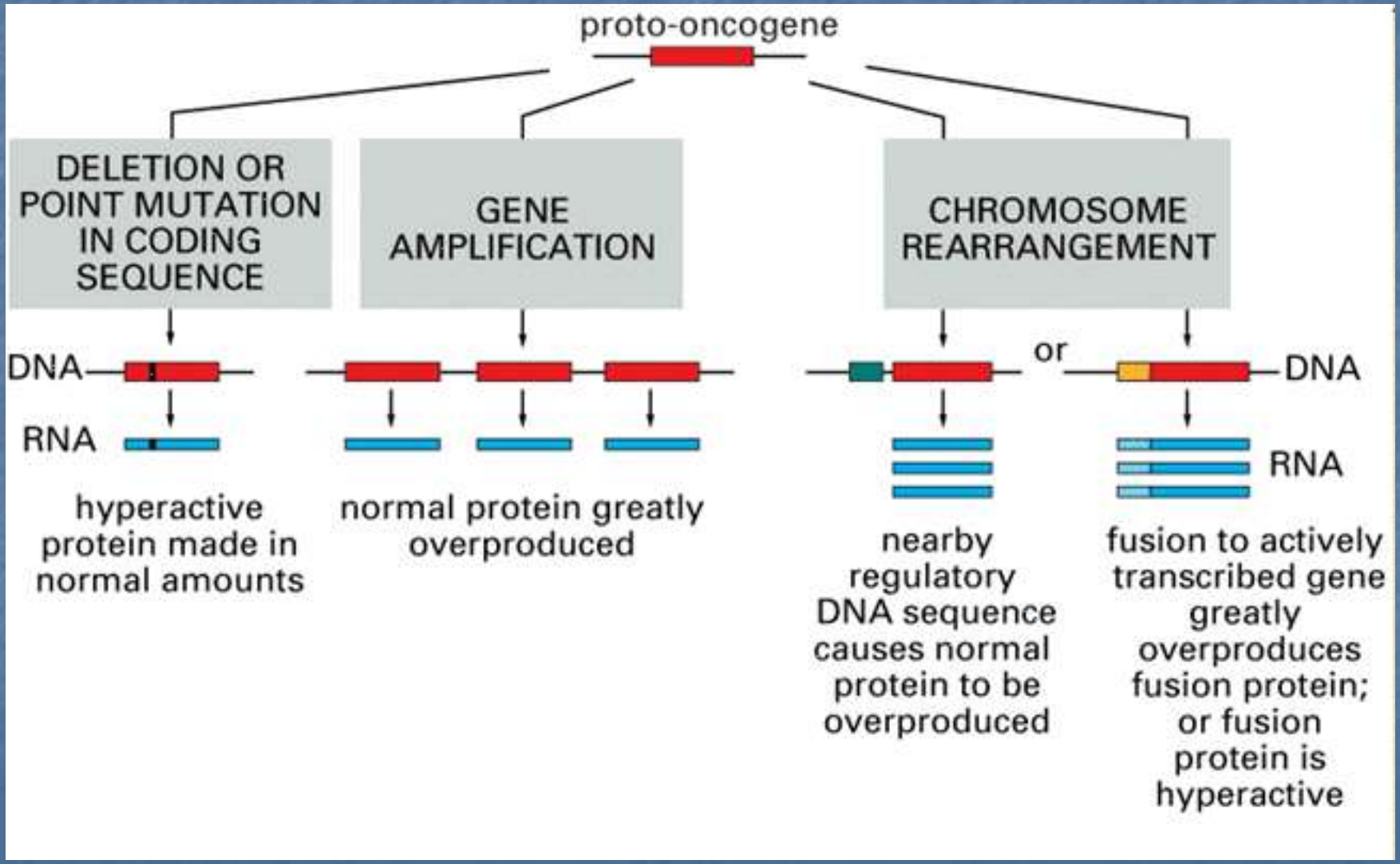


- Oncogenes
  - dominant mutations
- Mutant tumor-suppressor genes
  - recessive mutations

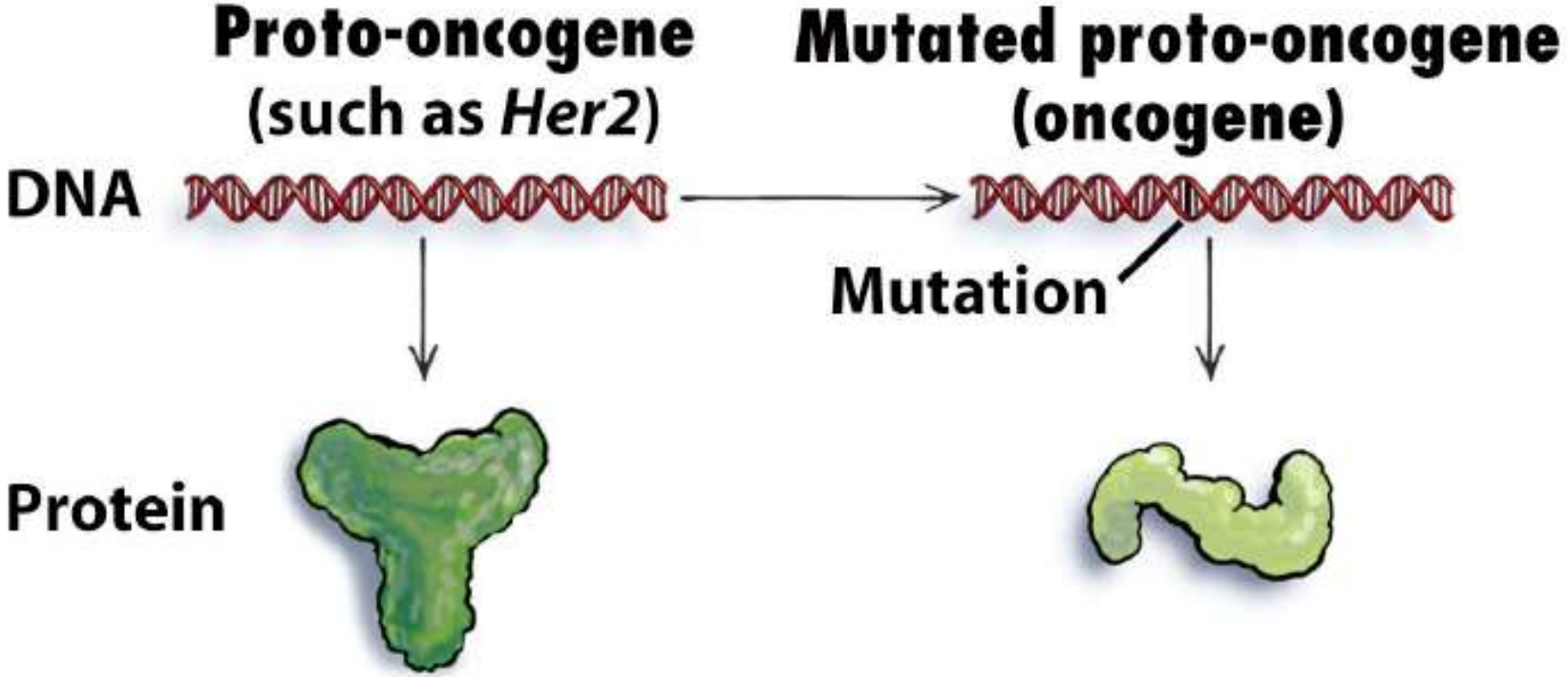
oncogenes

- Cellular oncogene c-onc
- Viral oncogene v-onc
- Proto-oncogene, activated by mutation to c-onc

Proto-oncogene activation



Mutations to proto-oncogenes

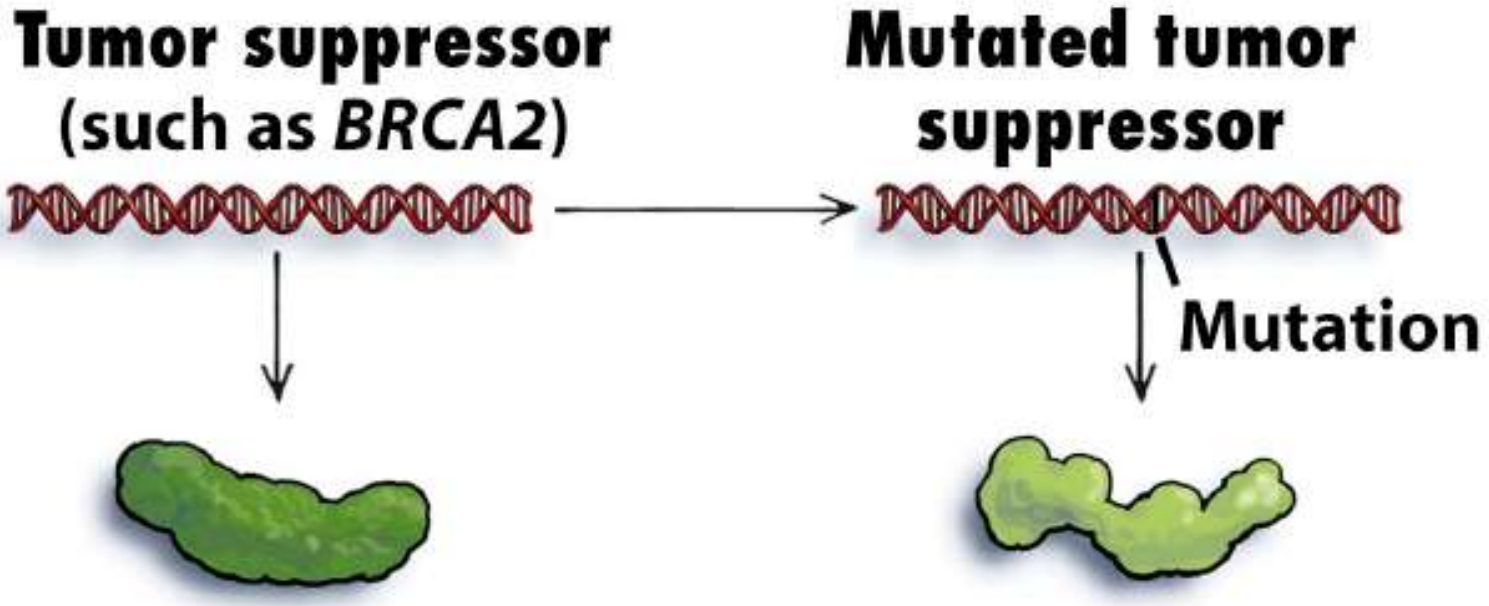


Functional protein only stimulates cell division when conditions are right.

Mutated protein can lead to overstimulation of cell division by overriding checkpoint control.

Figure 5.14a Biology Science for Life 2/e

Mutations to tumor supressor genes

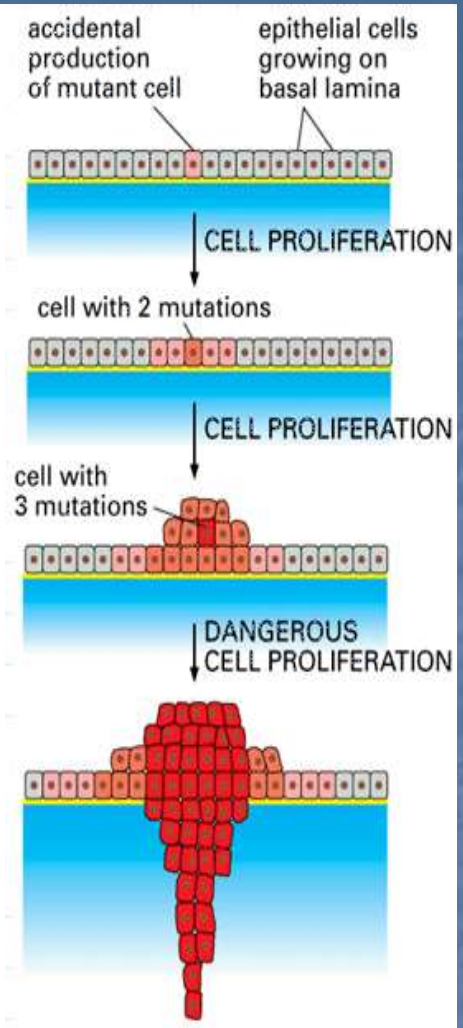


Tumor-suppressor protein stops tumor formation by suppressing cell division.

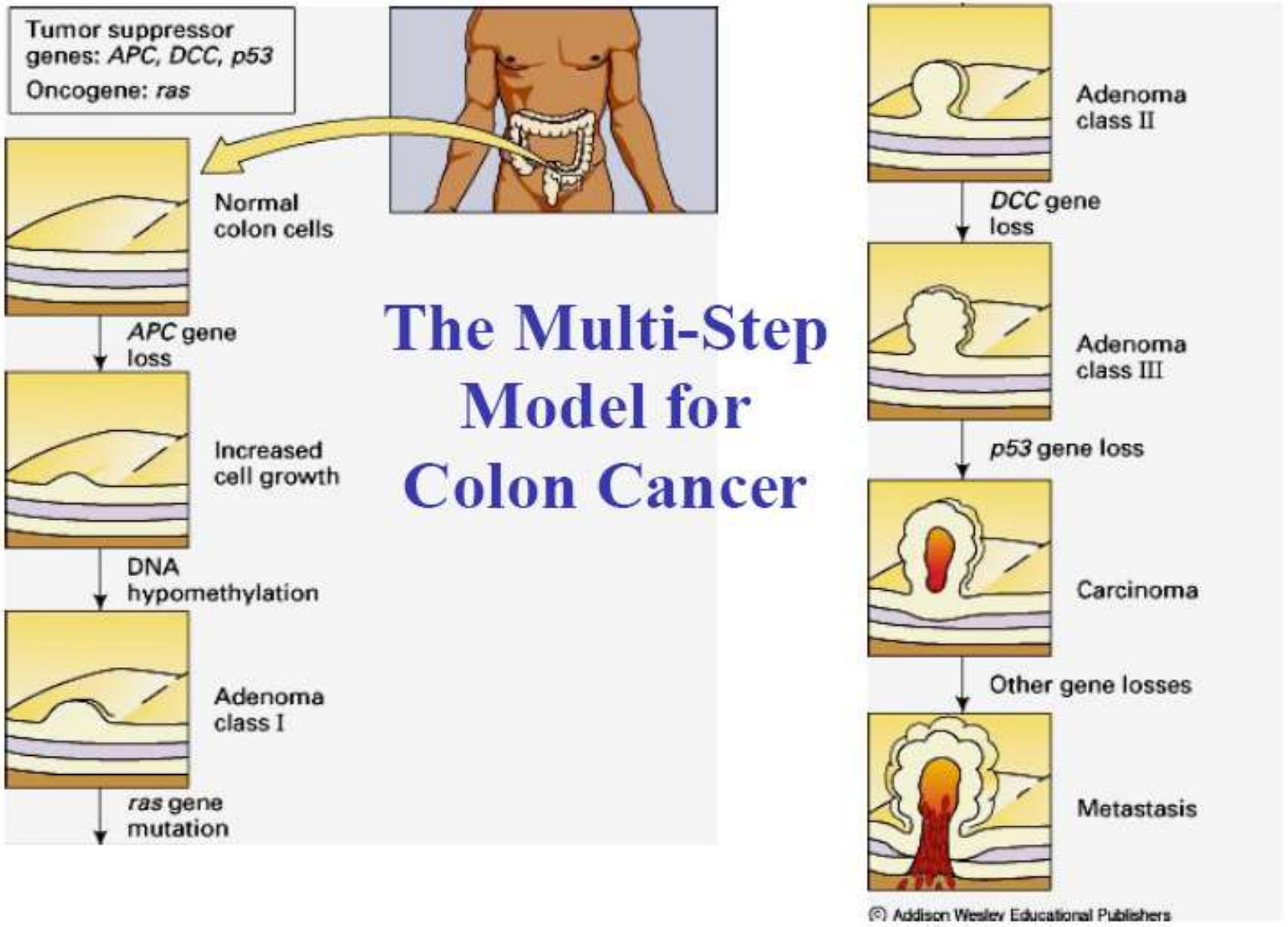
Mutated tumor-suppressor protein fails to stop tumor growth.

Multistep Nature of Cancer

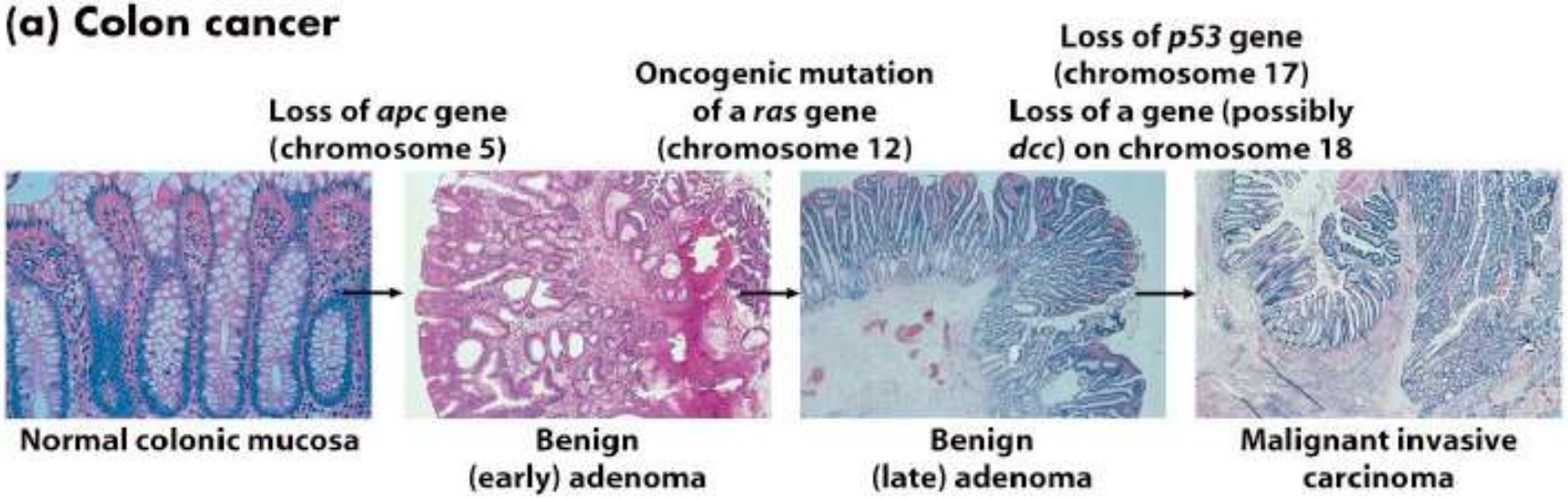
- Cancer develops progressively as mutations accumulate.
- Experimental evidence in mice with either the ***ras*** **OR** the ***myc*** protooncogenes mutated: fewer tumors develop than when **BOTH** genes are mutated.
- Mice with only one allele of the tumor suppressor ***p53*** mutated are not as cancer prone as when both alleles are mutated.
- Hereditary adenomatous polyposis or Familial adenomatous polyposis (FAP):
  - a typical example of the multi-step pathway for cancer.



The Multi-Step Model for Colon Cancer



The Multi-Step Model



- 11% of cancer-related deaths
- Tumor progression may take 10-35 years
- Adenomatous polyp develops into carcinoma

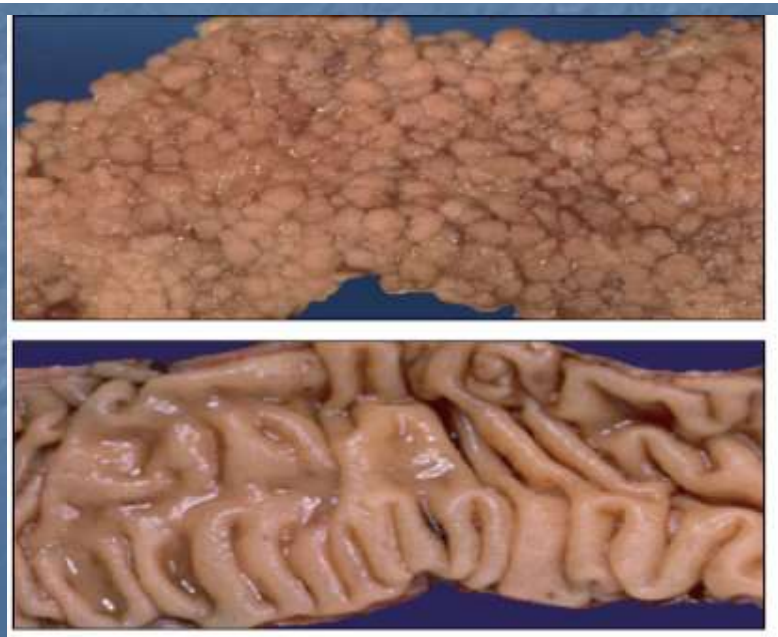


Figure 23–39. Molecular Biology of the Cell, 4th Edition.

Cancer terminology

Classification by tissue type:

- carcinoma
  epithelial cell
  90% of all tumours
  derived from ectoderm (mostly) or endoderm (some)
- sarcoma
  connective tissue
  2% of all tumours
  derived from mesoderm
- leukaemia
  circulatory or lymphatic
  8% of all tumours
  derived from mesoderm

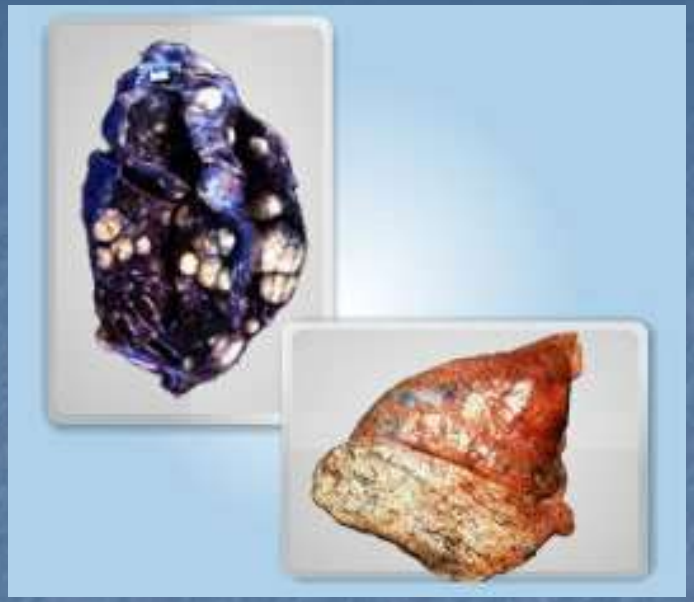
Classification by the type of cells:

- Adenomatous cells
  ductal or glandular cells
- Squamous cells
  flat cells
- Myeloid
  blood cell
- Lymphoid
  lymphocytes or macrophages

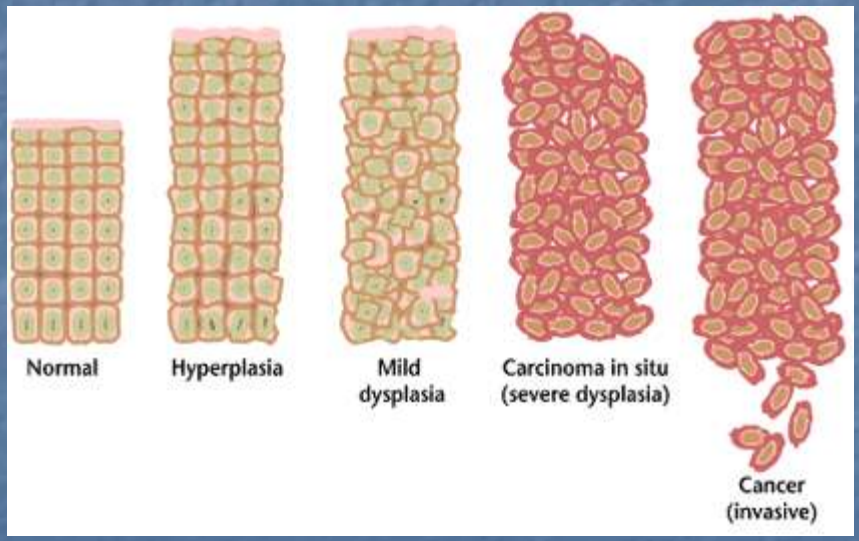
Classifications of Neoplasms

Tissue of Origin	**Benign**	**Malignant**
Glandular epithelium	Adenoma	Adenocarcinoma
Squamous epithelium	Papilloma	Squamous cell carcinoma
Connective tissue smooth muscle	Leiomyoma	Leiomyosarcoma
Hematopoietic		Leukemia
Lymphoreticular		Lymphoma
Neural	Neuroma	Blastoma

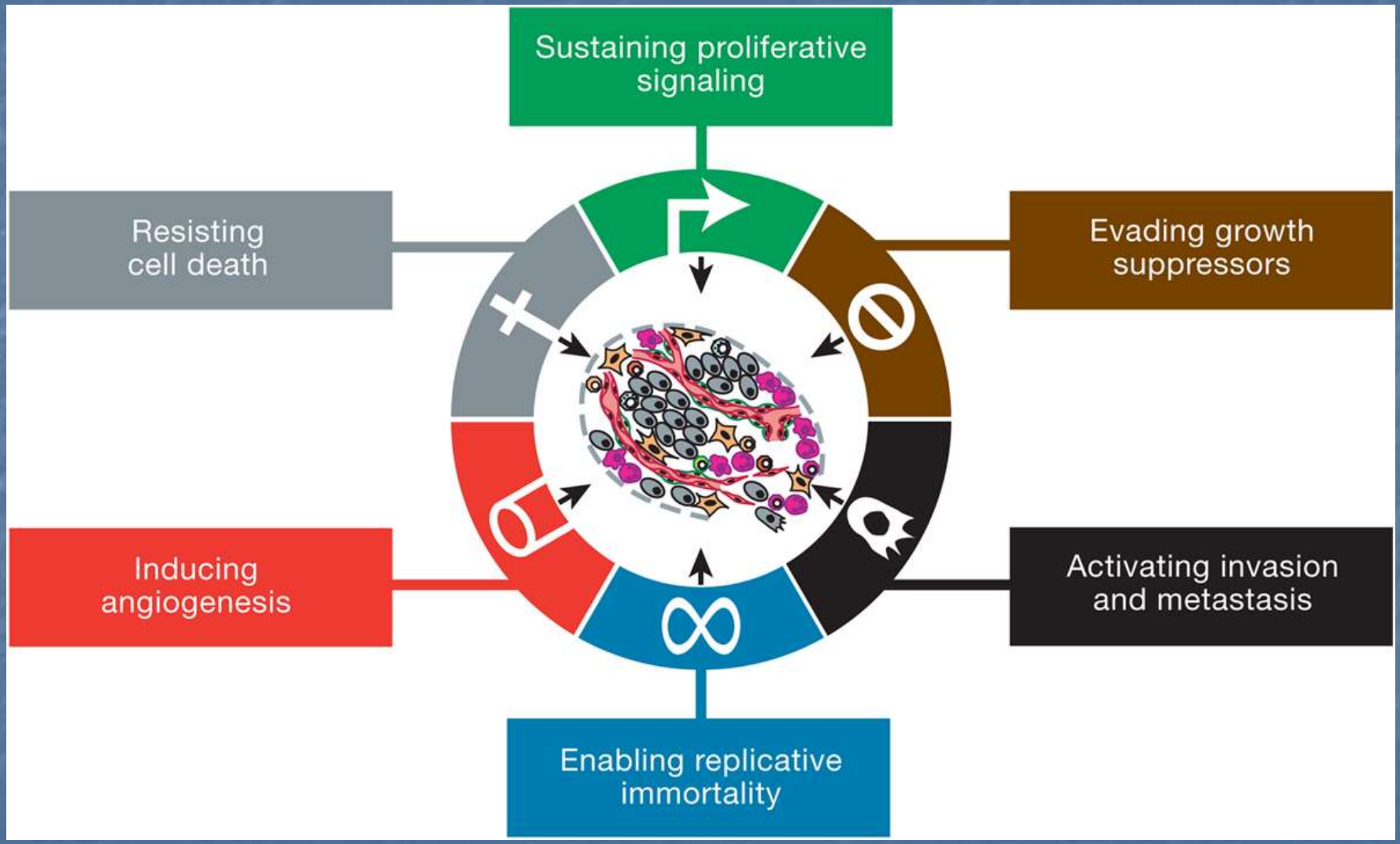
Types of Cancer



- Cancer can affect almost any tissue type in the body.
  - Lung cancer
  - Skin Cancer
  - Liver Cancer
  - Breast Cancer
  - Cervical Cancer
  - Prostate Cancer

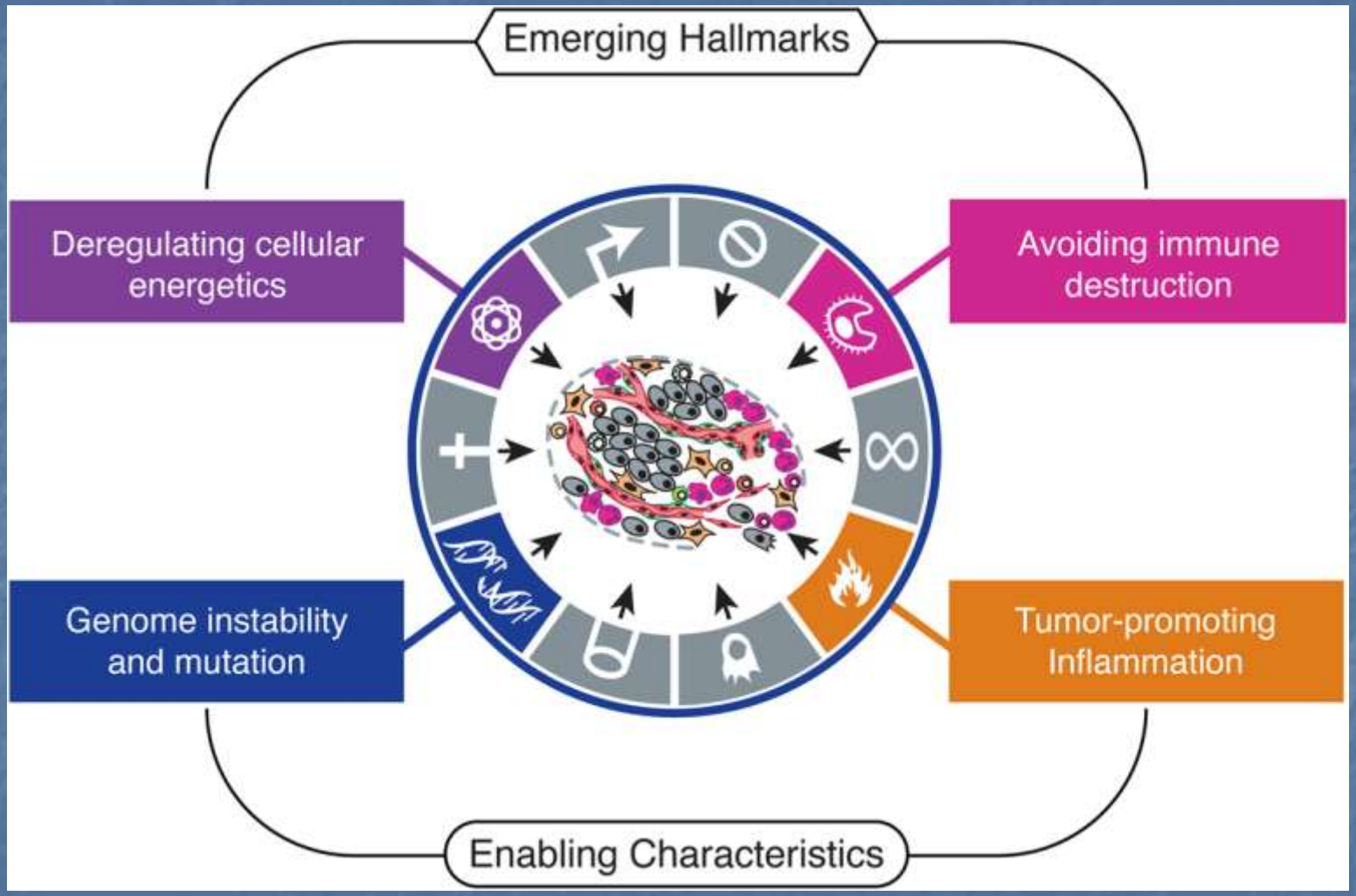


The Hallmarks of Cancer



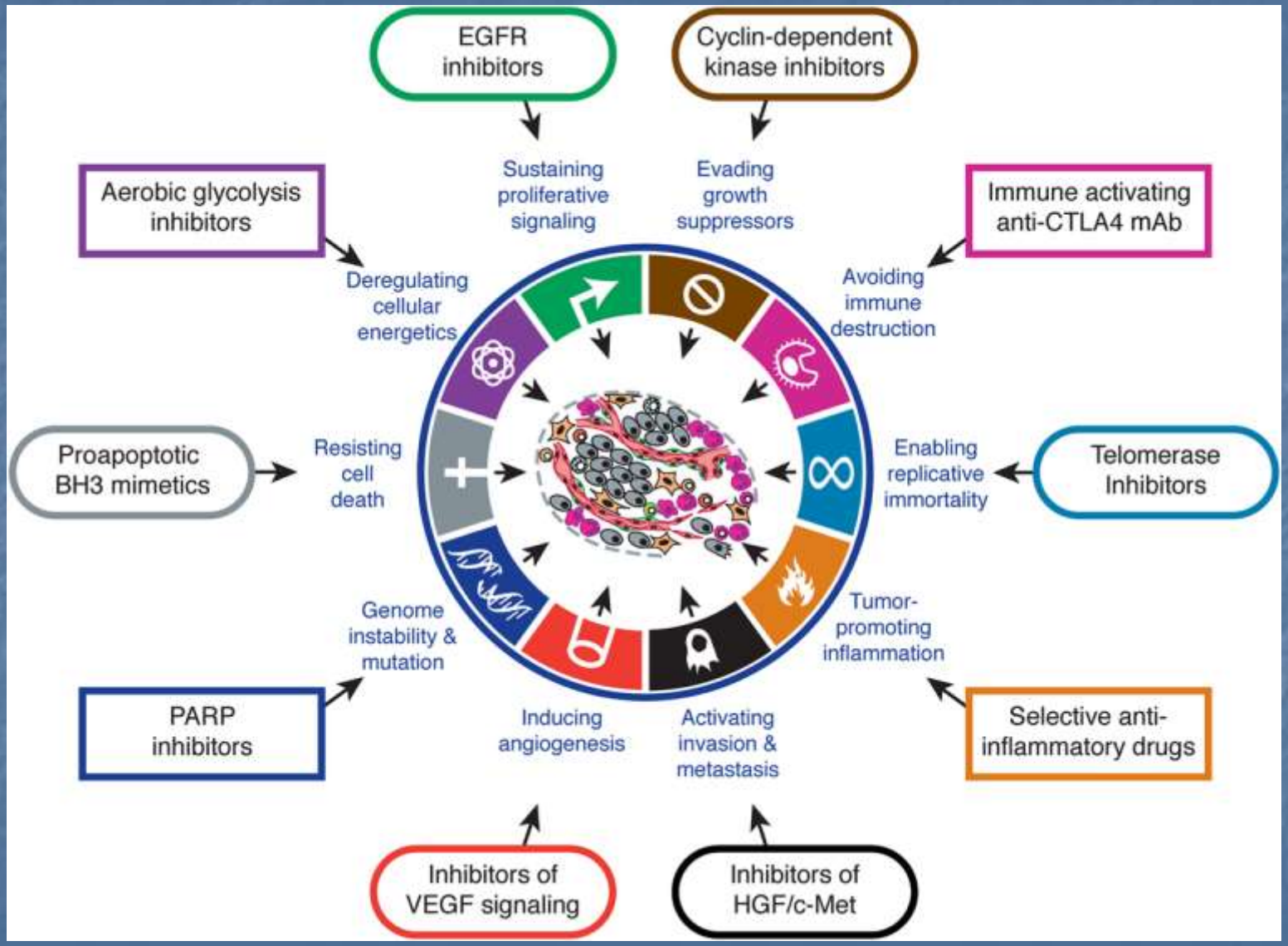
Hanahan and Weinberg, *Cell* 144:646 (2011)

Newer Hallmarks of Cancer



Hanahan and Weinberg, *Cell* 144:646 (2011)

Therapeutic Targeting of the Hallmarks of Cancer



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