Tissue engineering and cancer

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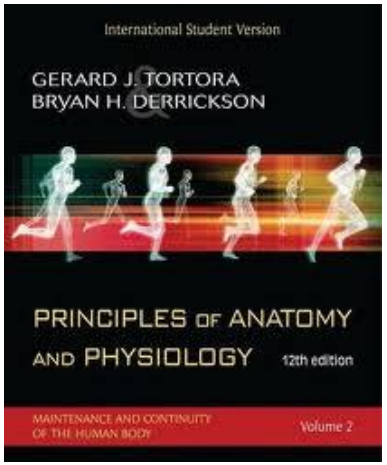
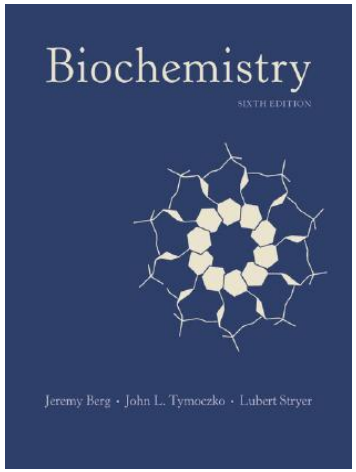
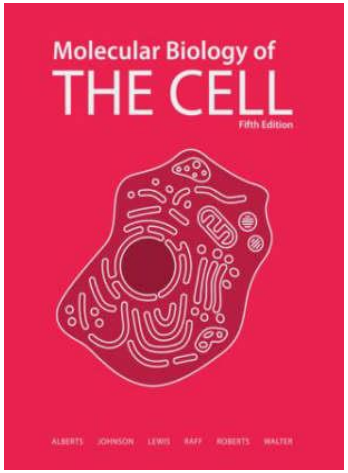
INSPIRING INNOVATION INNOVANTE PAR TRADITION

Bibliography

- **Biochemistry by *Jeremy M. Berg***
  - ISBN 10 1429276355
- **Molecular Biology of the Cell 5^{E} by *Bruce Alberts***
  - ISBN10 0815341067
- **Principles of Anatomy and Physiology by *Gerard J. Tortura***
  - ISBN 10 0470233478

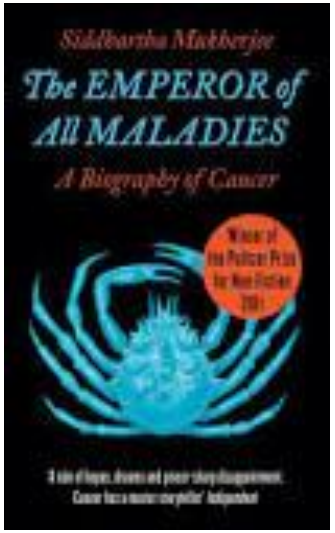


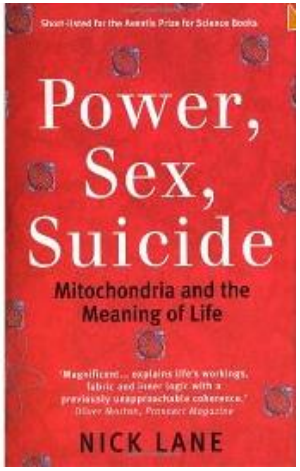


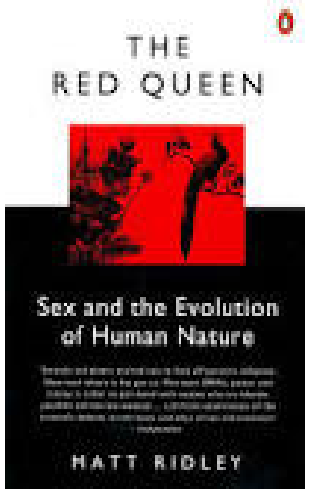


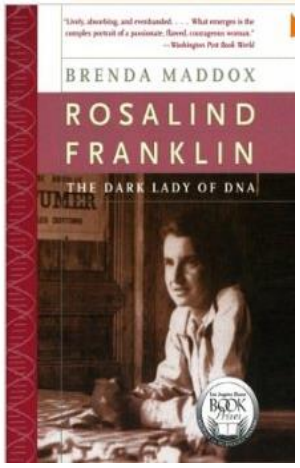
Some light reading

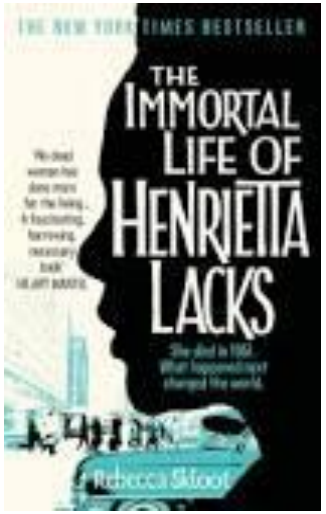
- The emperor of all maladies, *Siddhartha Mukherjee*
- The immortal life of Henrietta Lacks, *Rebecca Skloot*
- The dark lady of DNA, *Brenda Maddox*
- The red queen, *Matt Ridley*
- Power, Sex, Suicide, *Nick Lane*
- The Spark of Life, *Frances Ashcroft*











Questionnaire

- What are the four different tissue types?
- What is the general type of tissue structure
- What are the processes that go awry in cancer?

Cellular Diversity

- The average adult has nearly 100 trillion cells
- There are about 200 different types of cells
- Cells come in a variety of shapes and sizes
- Cellular diversity permits organization of cells into more complex tissues and organs

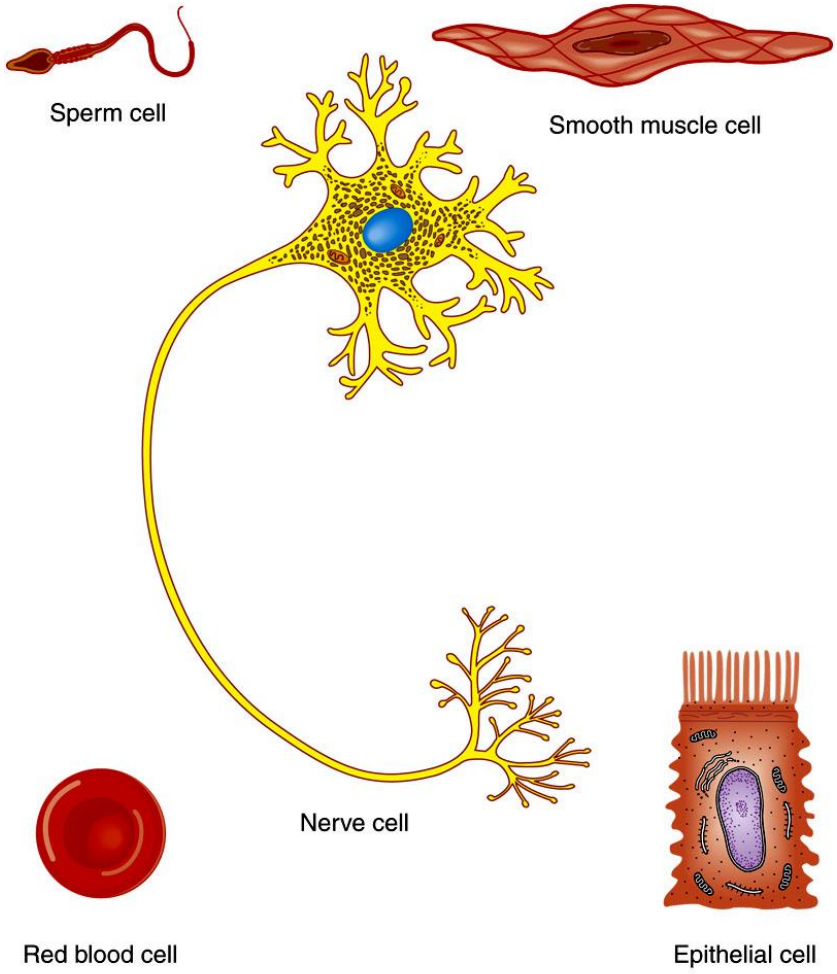


Figure 03.35 Tortora - PAP 12/e

What is a Tissue?

- **A tissue is a group of cells**
  - Common embryonic origin
  - Function together to carry out specialized activities
- **Hard (bone), semisolid (fat), or liquid (blood)**
- **Histology is the science that deals with the study of tissues.**
- **Pathologist specialized in laboratory studies of cells and tissue for diagnoses**

Development of Tissues

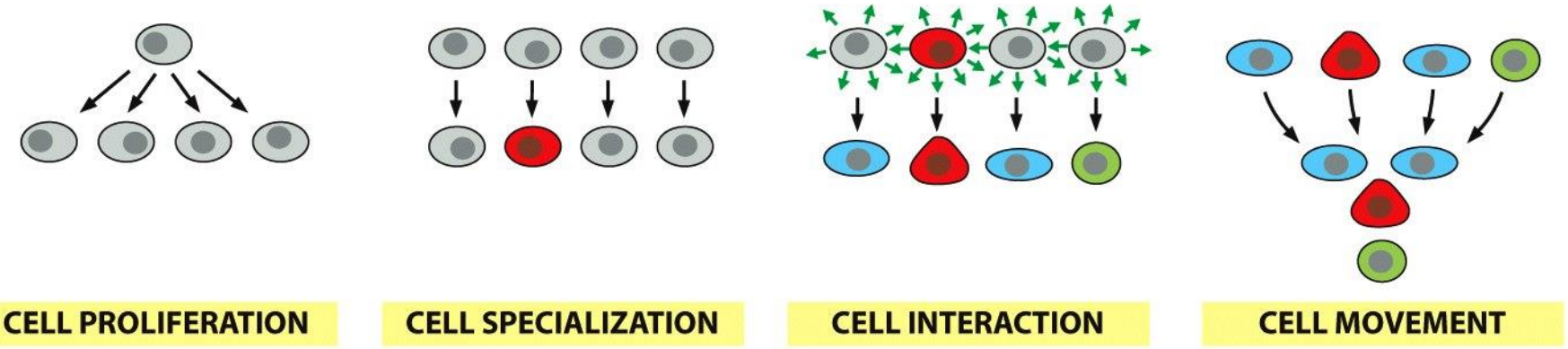


Figure 22-1 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

- **Tissues of the body develop from three primary germ layers:**
  - —Ectoderm, Endoderm, and Mesoderm
  - Epithelial tissues develop from all three germ layers
  - All connective tissue and most muscle tissues drive from **mesoderm**
  - Nervous tissue develops from **ectoderm**

Development of Tissues

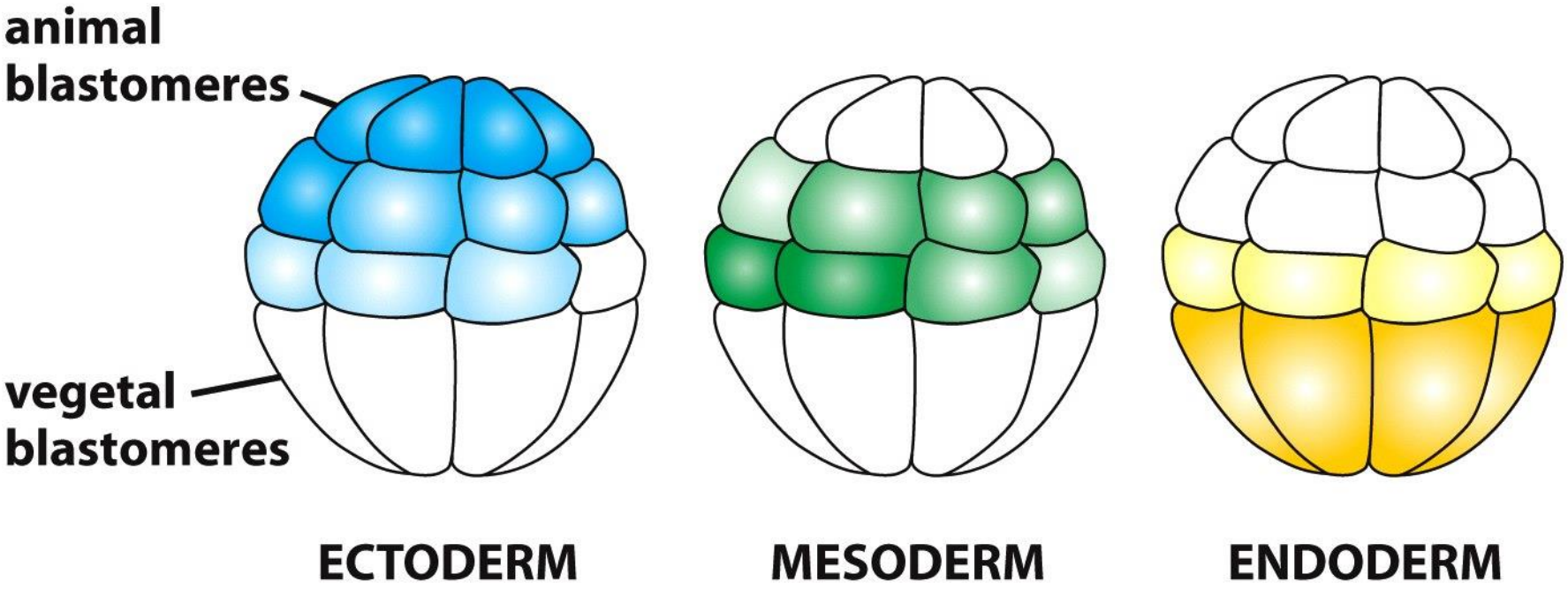


Figure 22-70 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Model for studying development: *C. elegans*

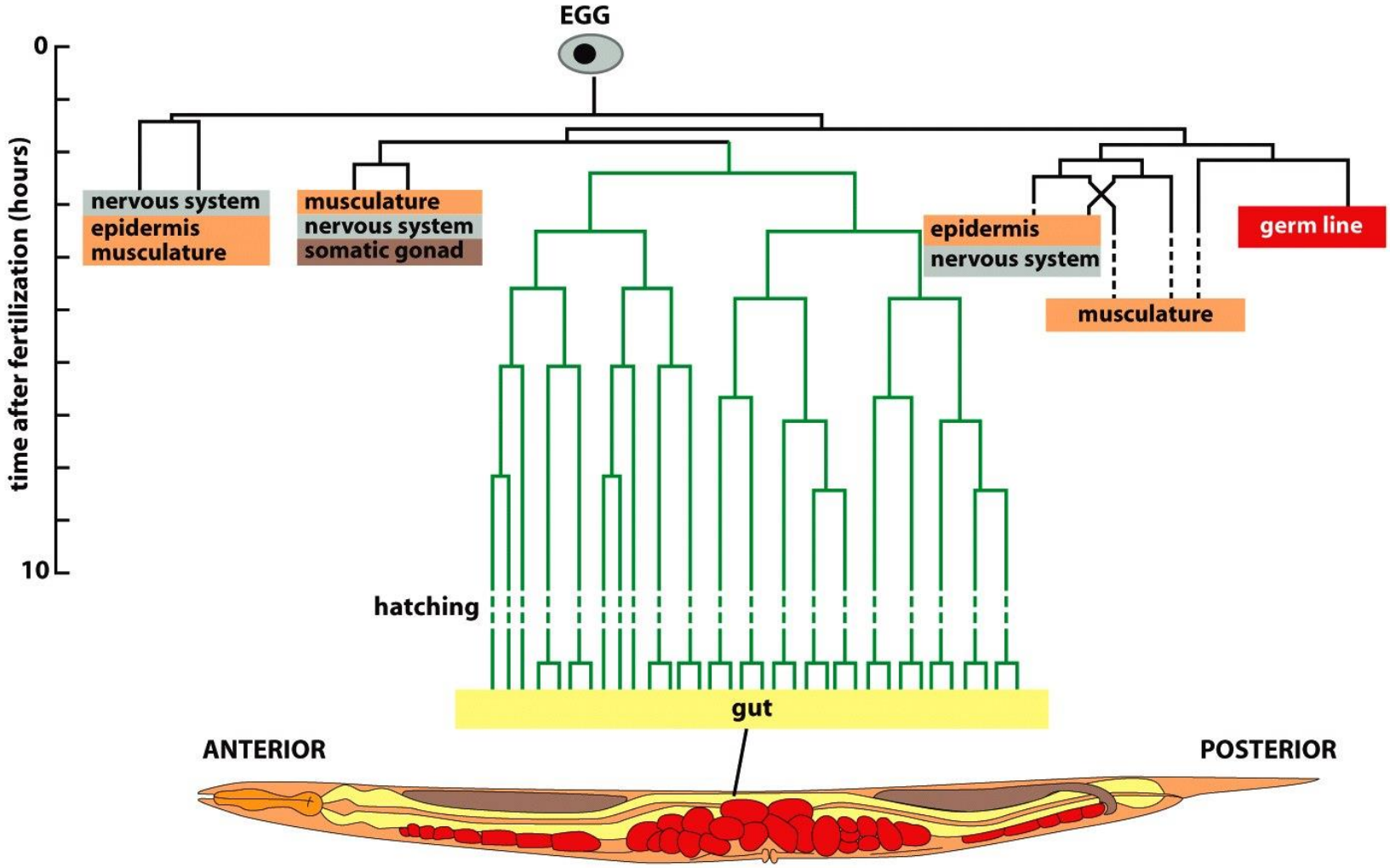
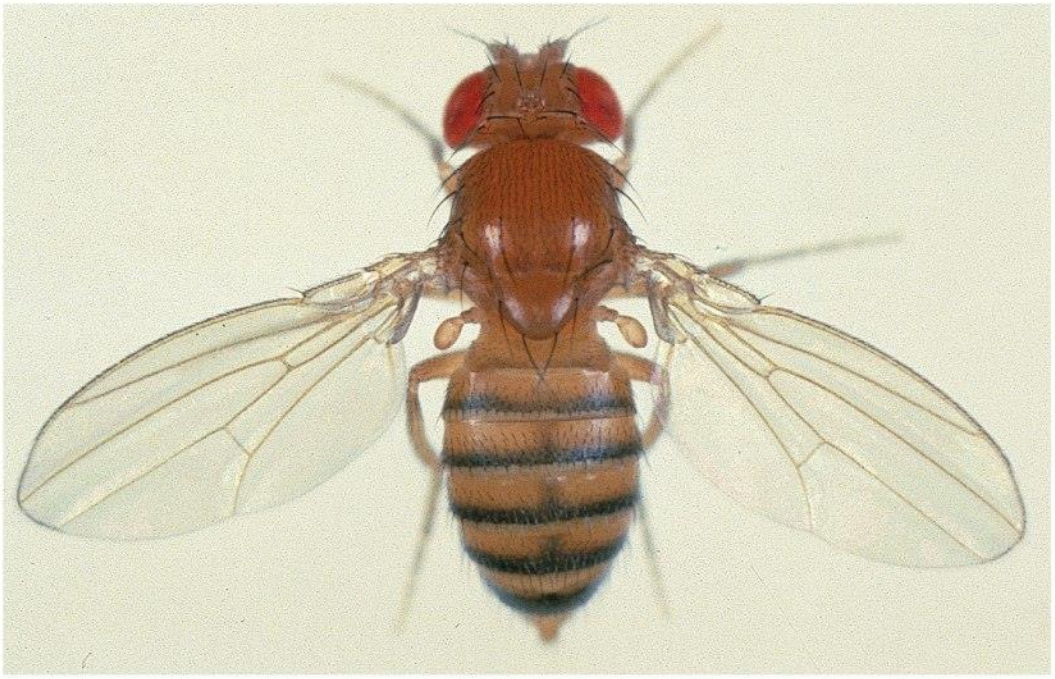


Figure 22-18 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Model for studying development: *D. melanogaster*

Drosophila



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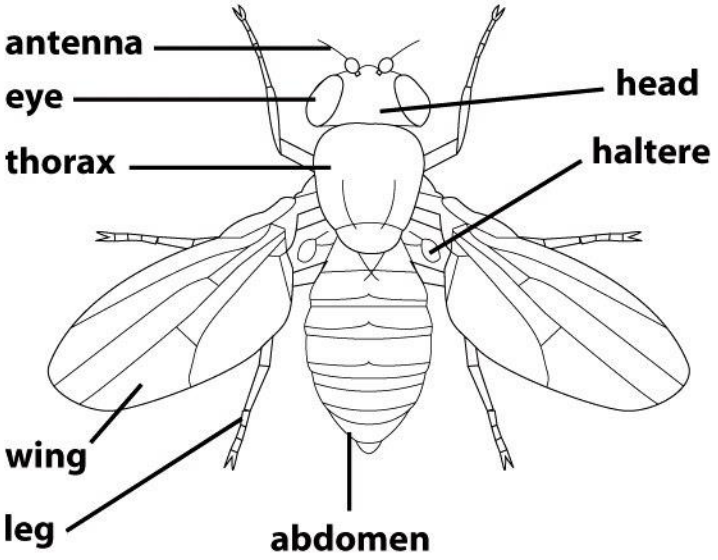


(B)

Figure 22-24 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Model for studying development: *D. melanogaster*

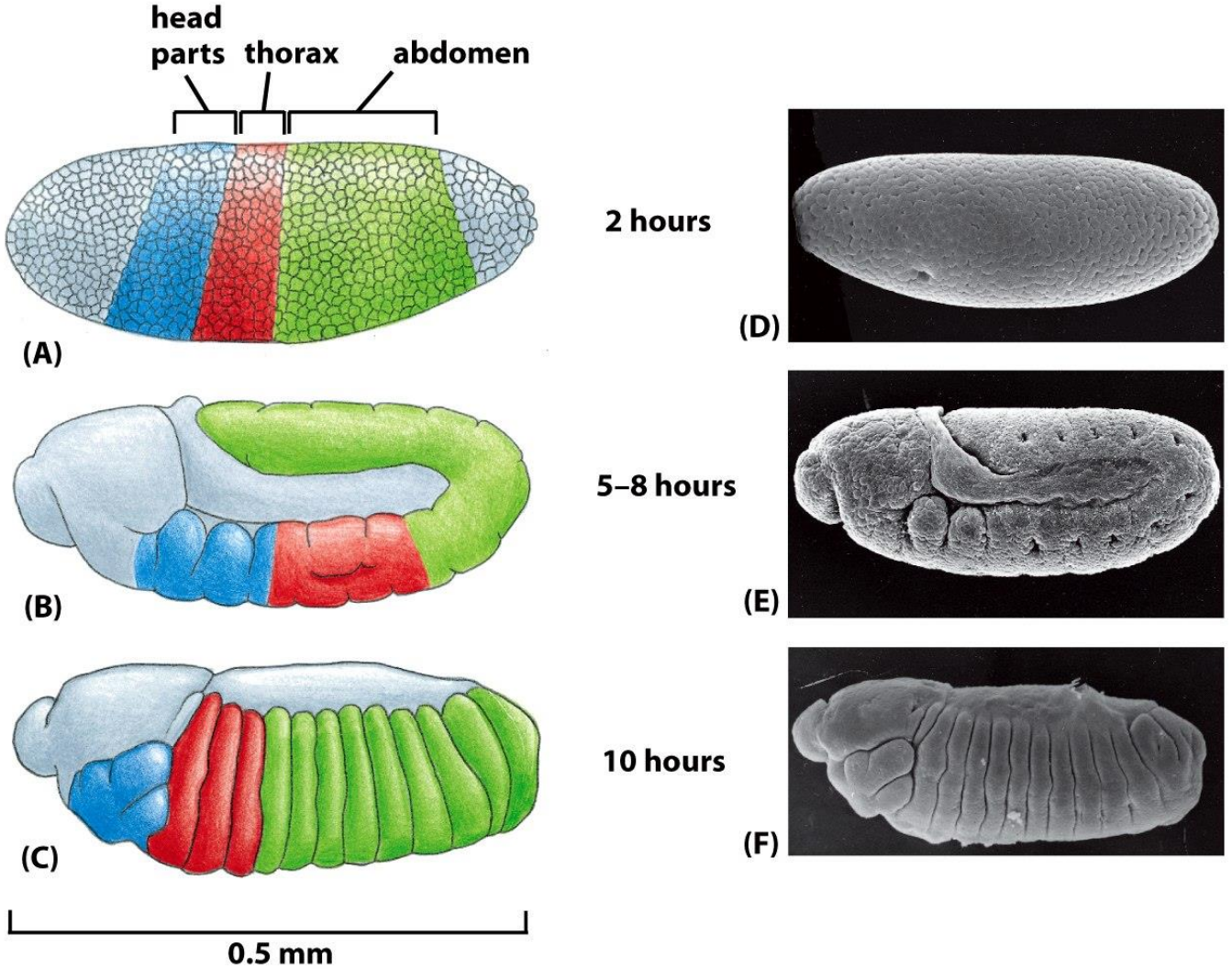


Figure 22-26 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Differentiation

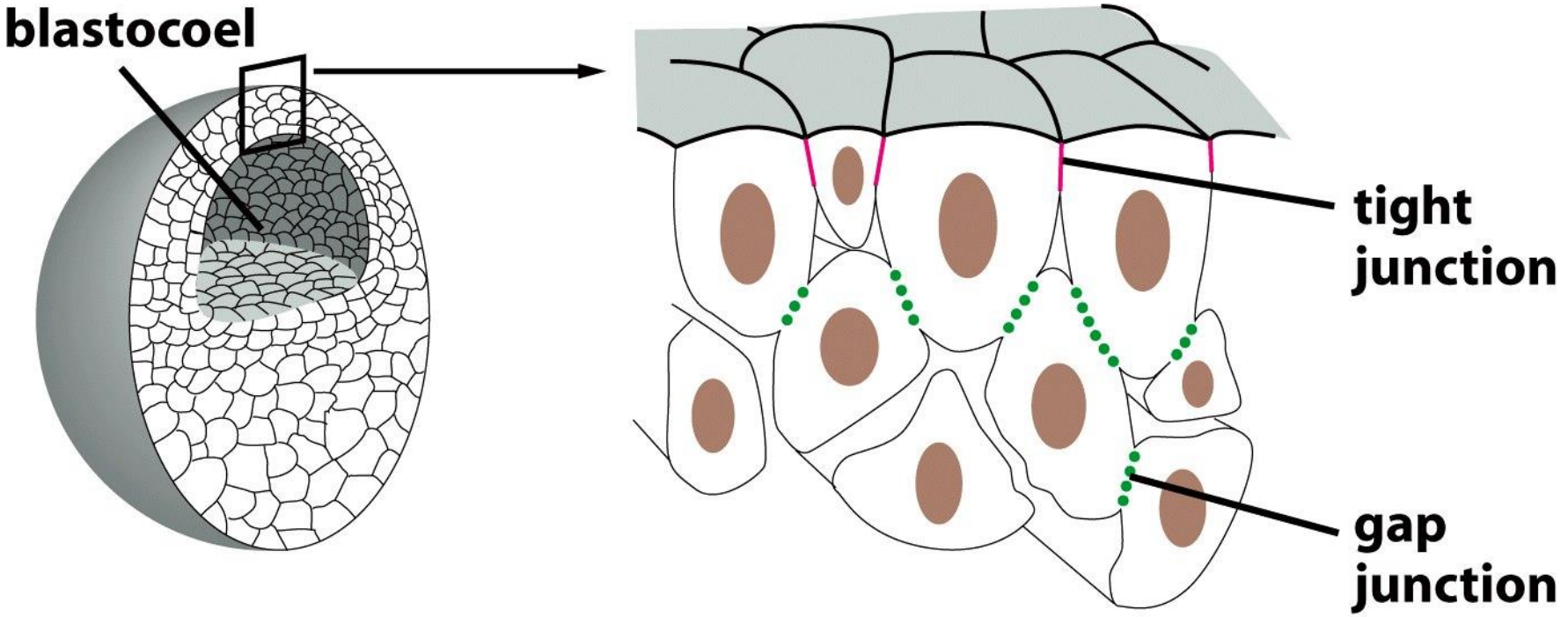


Figure 22-71 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Differentiation

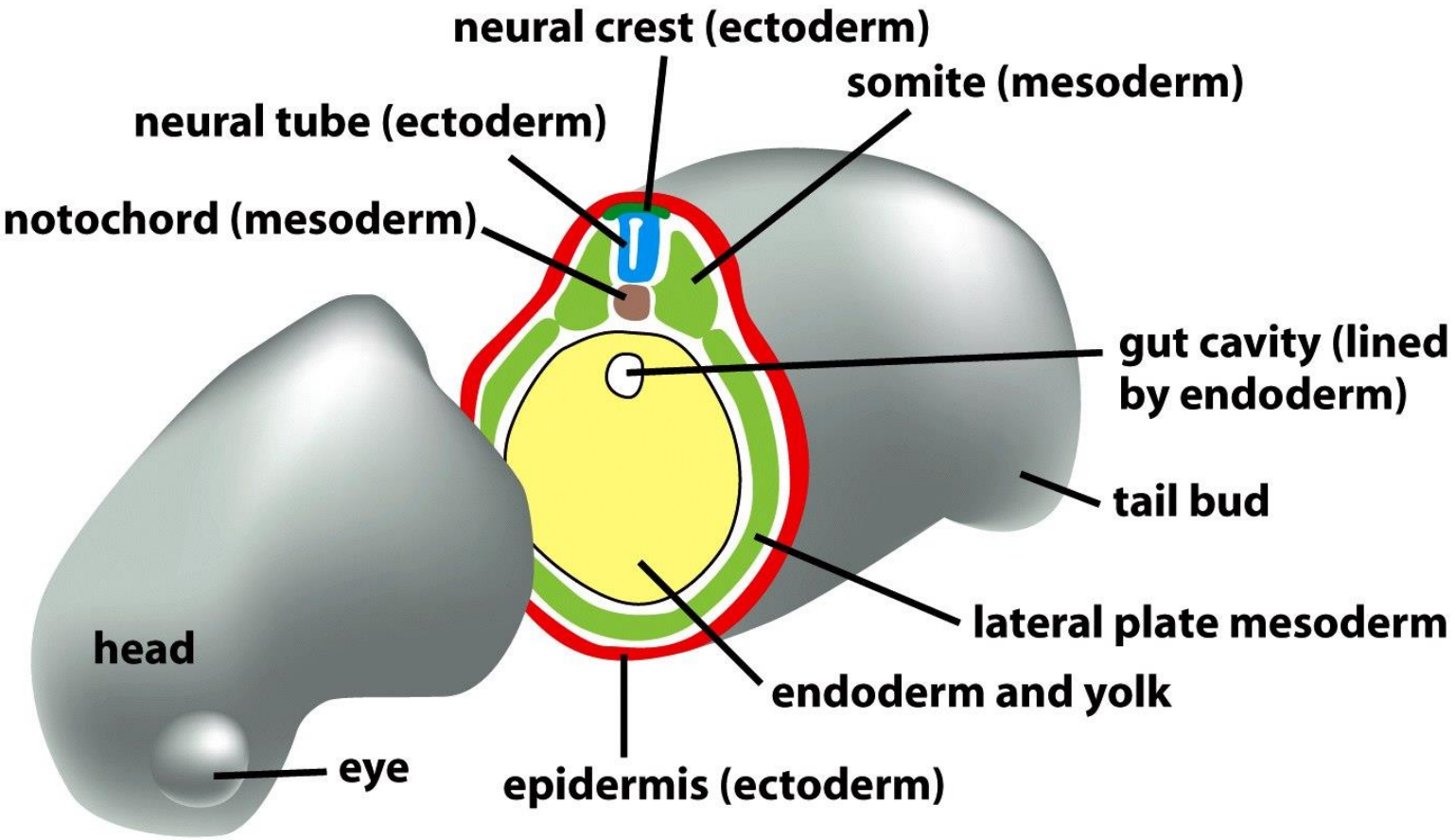


Figure 22-72 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Differentiation

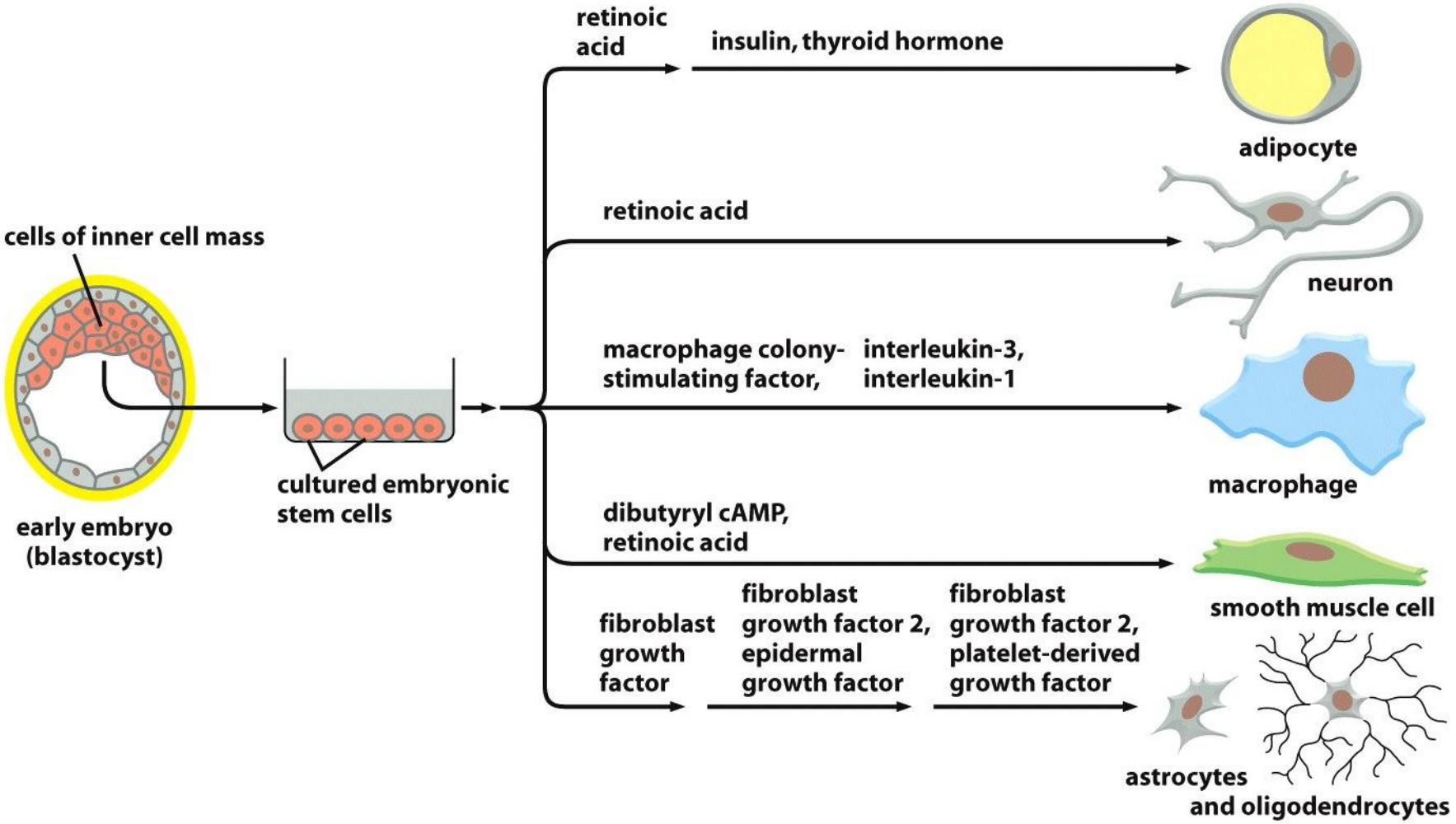


Figure 23-68 *Molecular Biology of the Cell* (© Garland Science 2008)

Development of Tissues

Differentiation

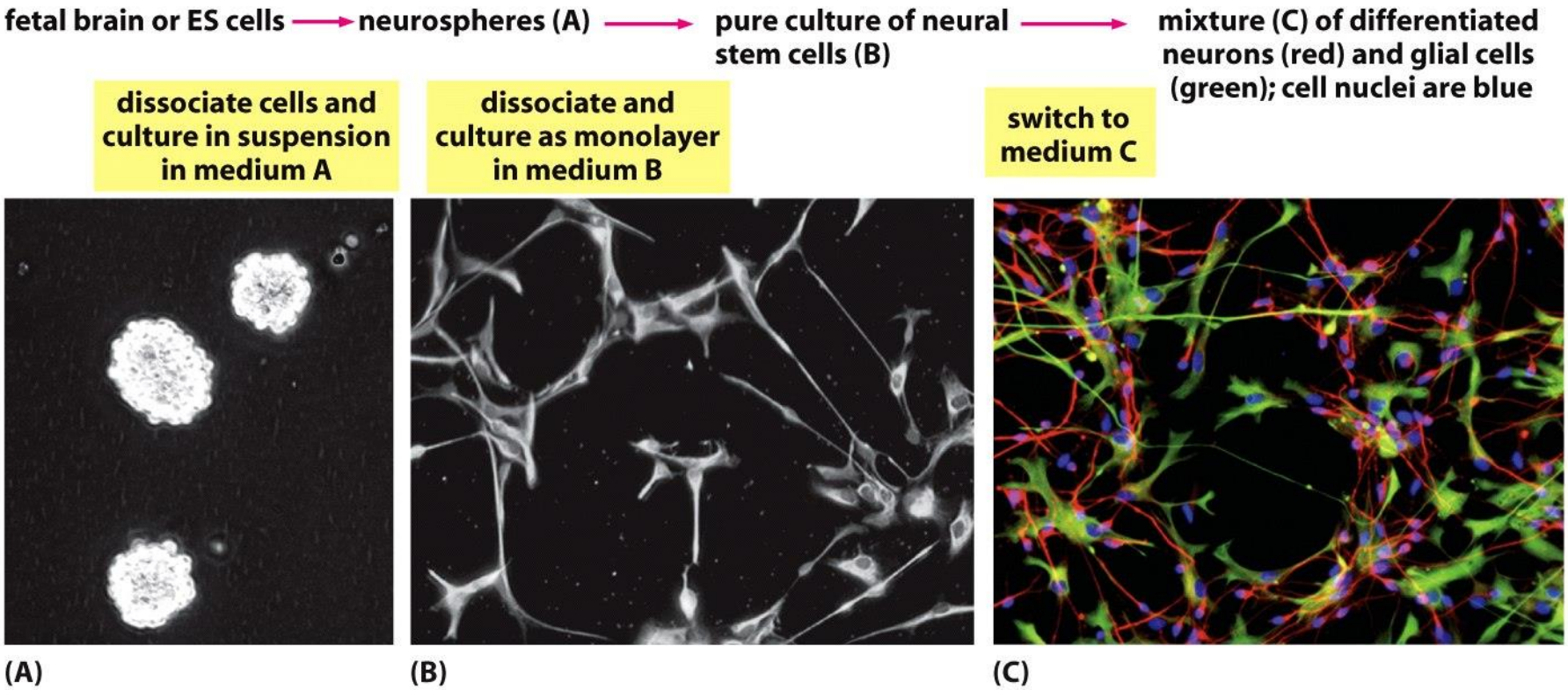
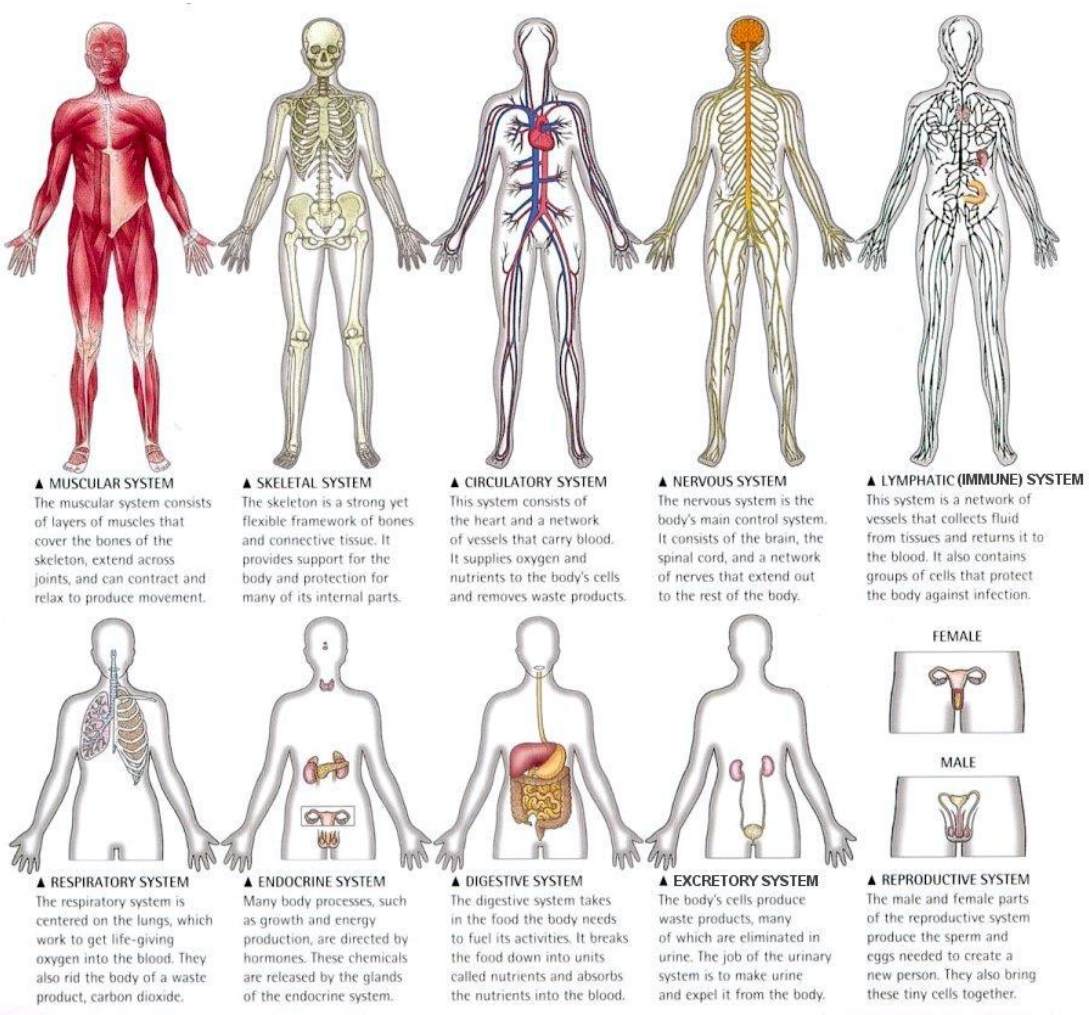


Figure 23-66 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissues as building blocks of organ systems



Human body

↓

10 major organ systems

↓

Each organ (e.g., lung)

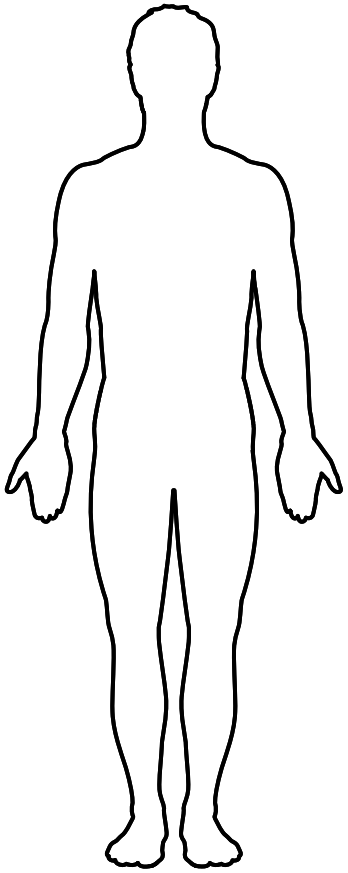
↓

Functional units (e.g., alveoli)

↓

Tissues

Tissue types



Four Types of Animal Tissue:

1. ***Epithelial/Barrier Tissue***
   - ***Covers body surfaces and lines organs, cavities and ducts, glands too***
2. *Connective Tissue*
   - *Protects and supports. Bind organs, stores energy as fat, helps provide immunity*
3. *Muscle Tissue*
   - *Generates physical force to make body move and generates body heat*
4. *Nervous Tissue*
   - *Detects changes in environment inside and out and responds by generating action potentials that activate muscle contractions and secretions*

Tissue types

Epithelial Tissues

- **Epithelial tissue consists of cells arranged in continuous sheets, in either single or multiple layers**
  - Closely packed and held tightly together
  - Covering and lining of the body
  - Free surface
- **3 major functions:**
  - Selective barrier that regulates the movement of materials in and out of the body
  - Secretory surfaces that release products onto the free surface
  - Protective surfaces against the environment

Tissue types

General Features of Epithelial Cells

- **Surfaces of epithelial cells differ in structure and have specialized functions**
  - **Apical (free) surface**
    - Faces the body surface, body cavity, lumen, or duct
  - **Lateral surfaces**
    - Faces adjacent cells
  - **Basal surface**
    - Opposite of apical layer and adhere to extracellular materials

Tissue types

General Features of Epithelial Cells

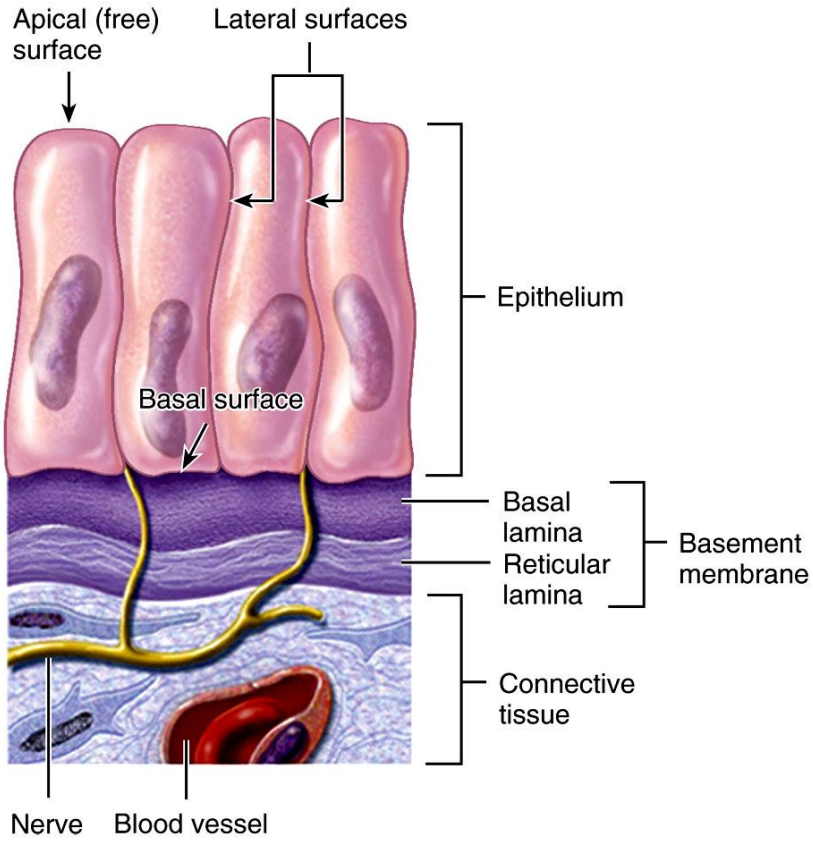


Figure 04.02 Tortora - PAP 12/e

Basement membrane

- Thin double extracellular layer that serves as the point of attachment and support for overlying epithelial tissue

Basal lamina

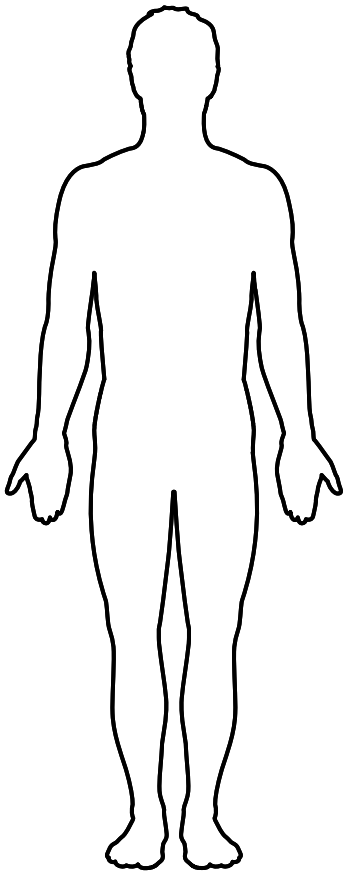
- Closer to and secreted by the epithelial cells
- Contains laminin, collagen, glycoproteins, and proteoglycans

Reticular lamina

- Closer to the underlying connective tissue
- Contains collagen secreted by the connective tissue cells

Tissue types

Connective tissue



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Tissue types

Connective tissue

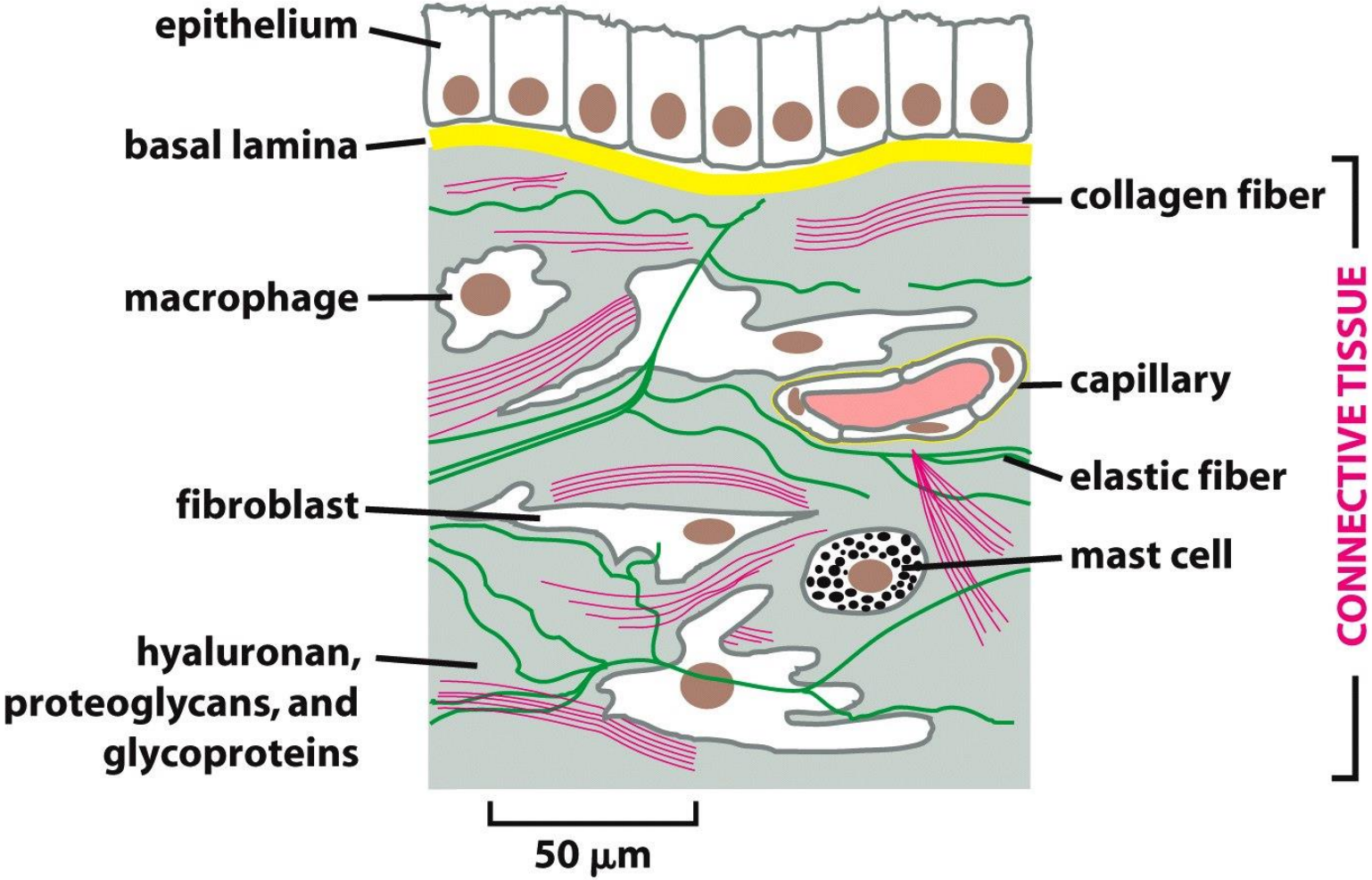


Figure 19-53 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Connective tissue

Most abundant and widely distributed tissues in the body

Numerous functions

- Binds tissues together
- Supports and strengthen tissue
- Protects and insulates internal organs
- Compartmentalize and transport
- Energy reserves and immune responses

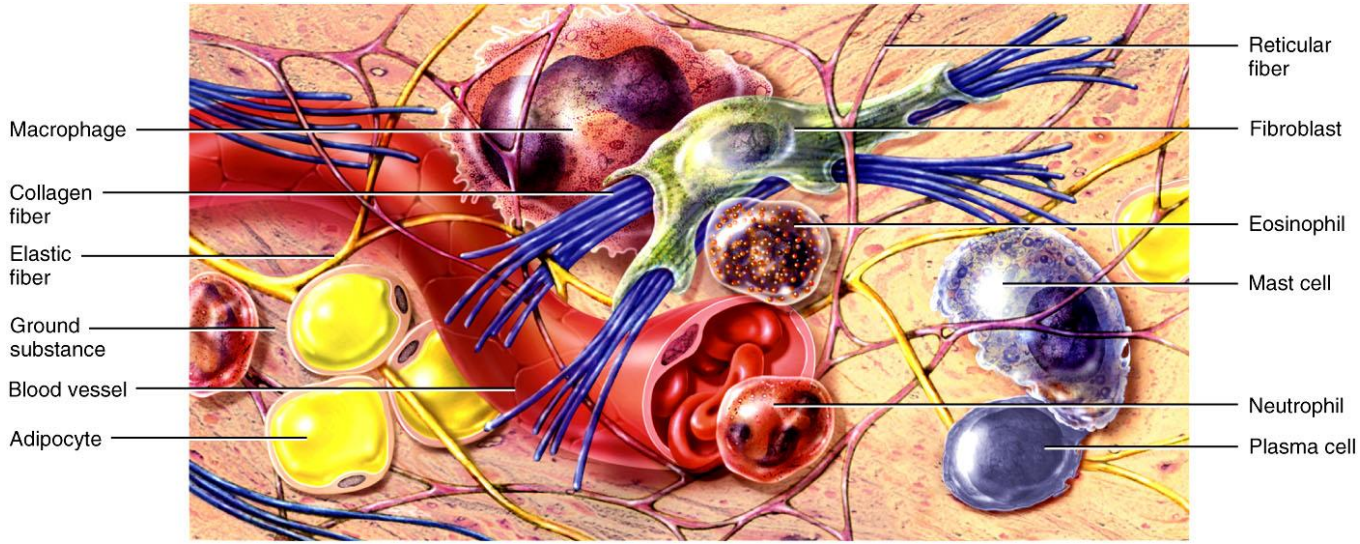


Figure 04.06 Tortora - PAP 12/e

Tissue types

Extracellular matrix of Connective Tissue

Extracellular matrix is the material located between the cells

- Consist of protein fibers and ground substance
- Connective tissue is highly vascular
- Supplied with nerves
- Exception is cartilage and tendon. Both have little or no blood supply, no nerves

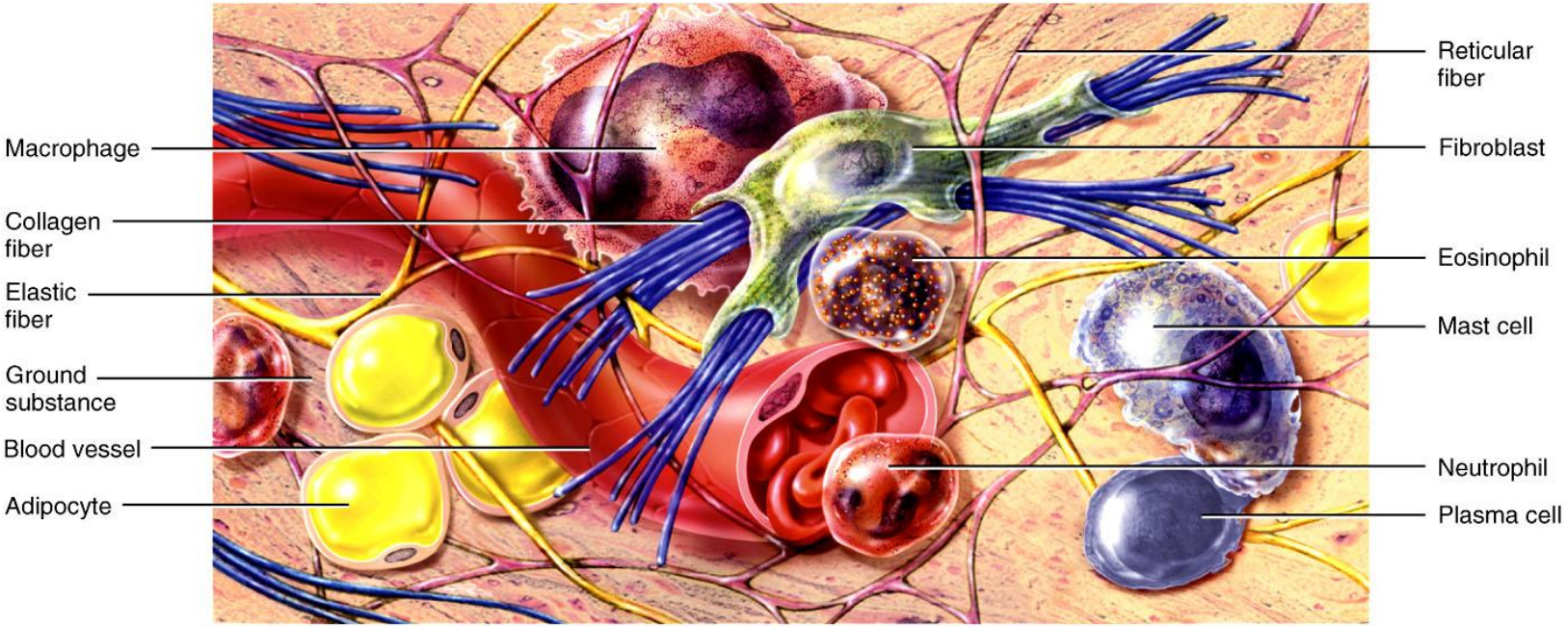


Figure 04.06 Tortora - PAP 12/e

Tissue types

Connective Tissue Cells

Fibroblasts

- Secrete fibers and components of ground substance

Adipocytes (fat cells)

- Store triglycerides (fat)

Mast cells

- Produce histamine

White blood cells

- Immune response
- Neutrophil and Eosinophils

Macrophages

- Engulf bacteria and cellular debris by phagocytosis

Plasma cells

- Secrete antibodies

Tissue types

Connective Tissue Cells

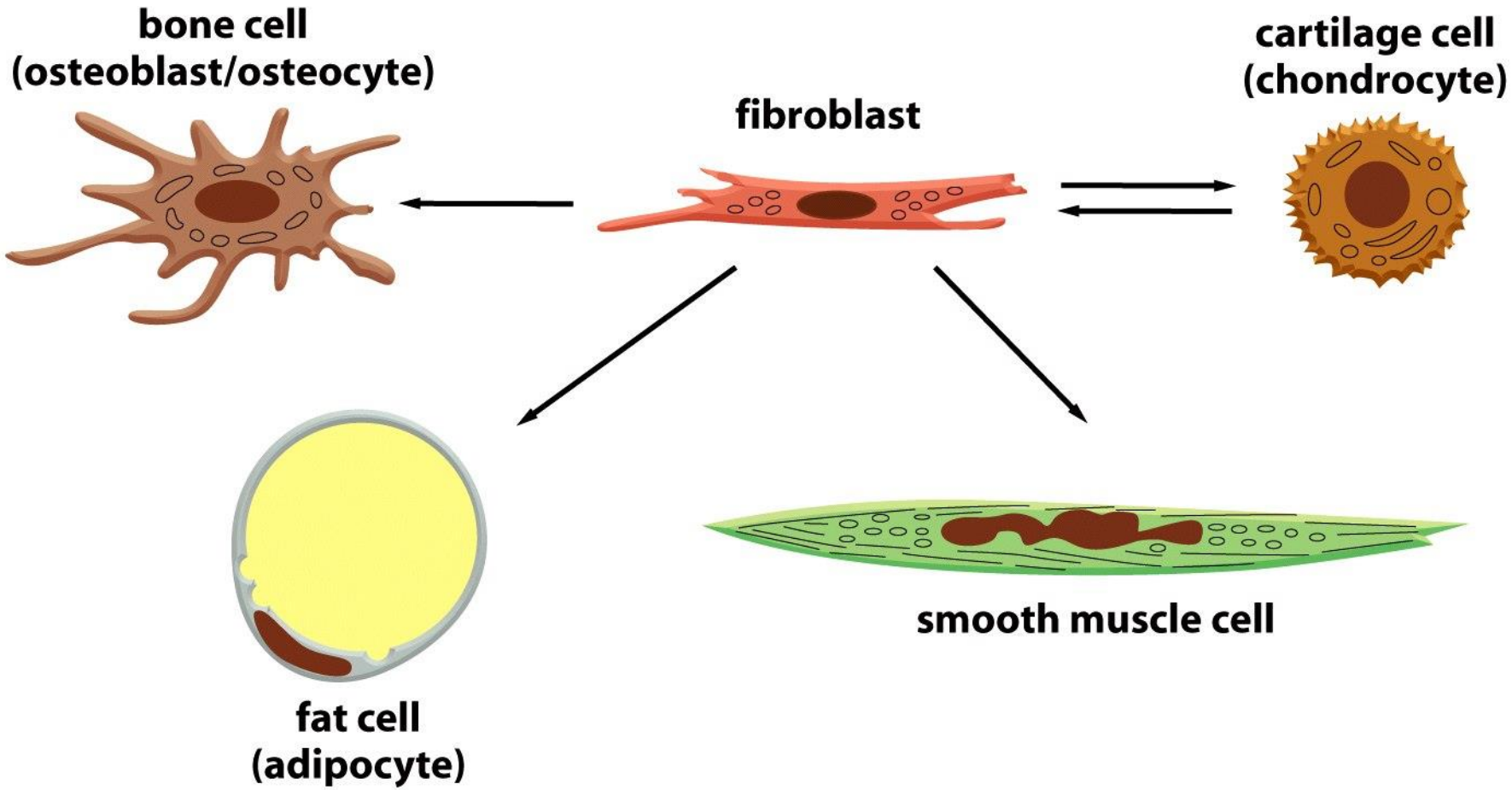


Figure 23-52 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Connective Tissue Cells: Fibroblasts

Figure 23-53a *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Connective Tissue Cells: Adipocytes

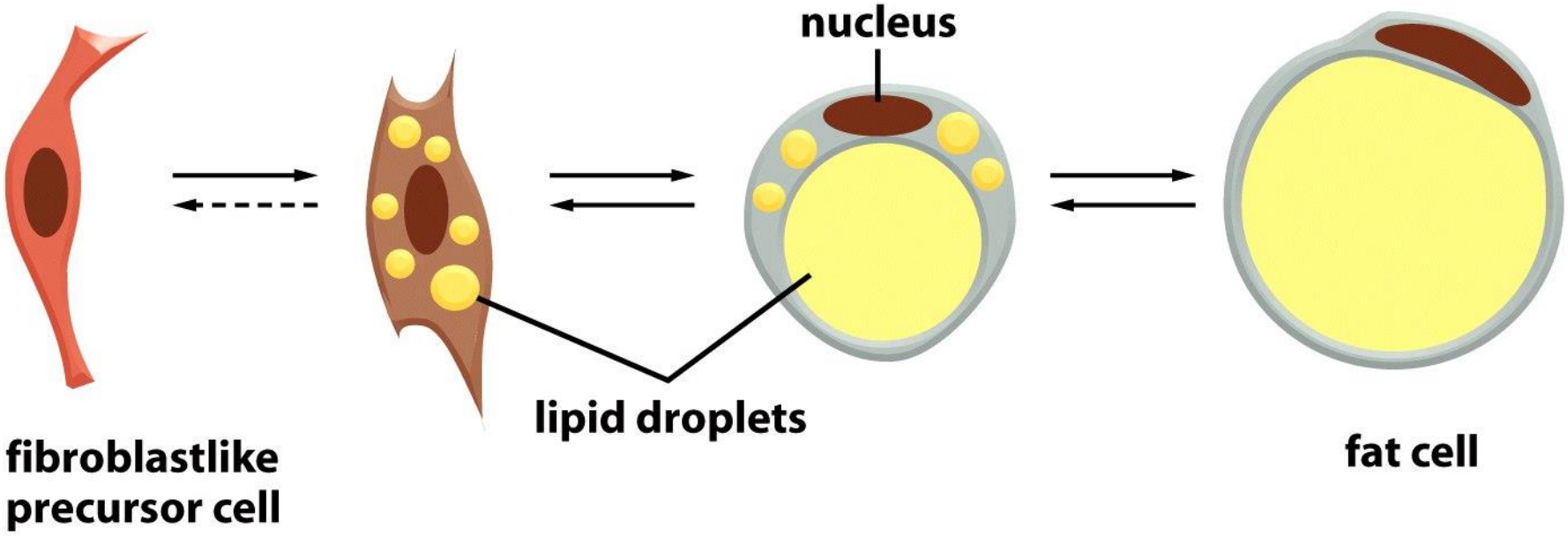


Figure 23-62 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Connective Tissue Cells: Adipocytes

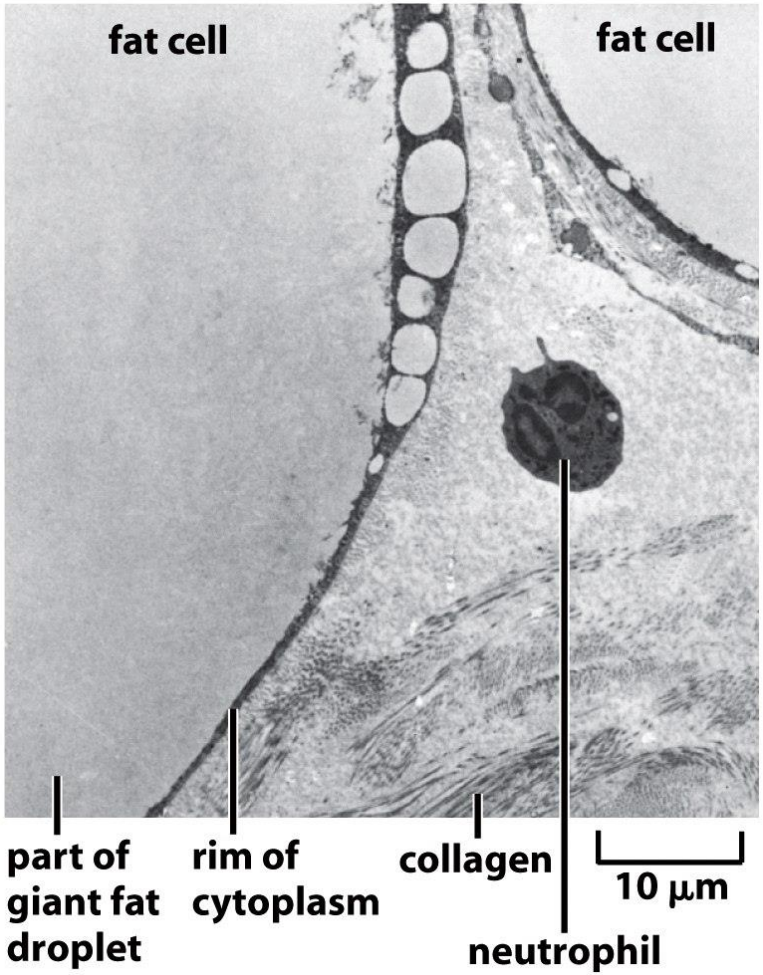
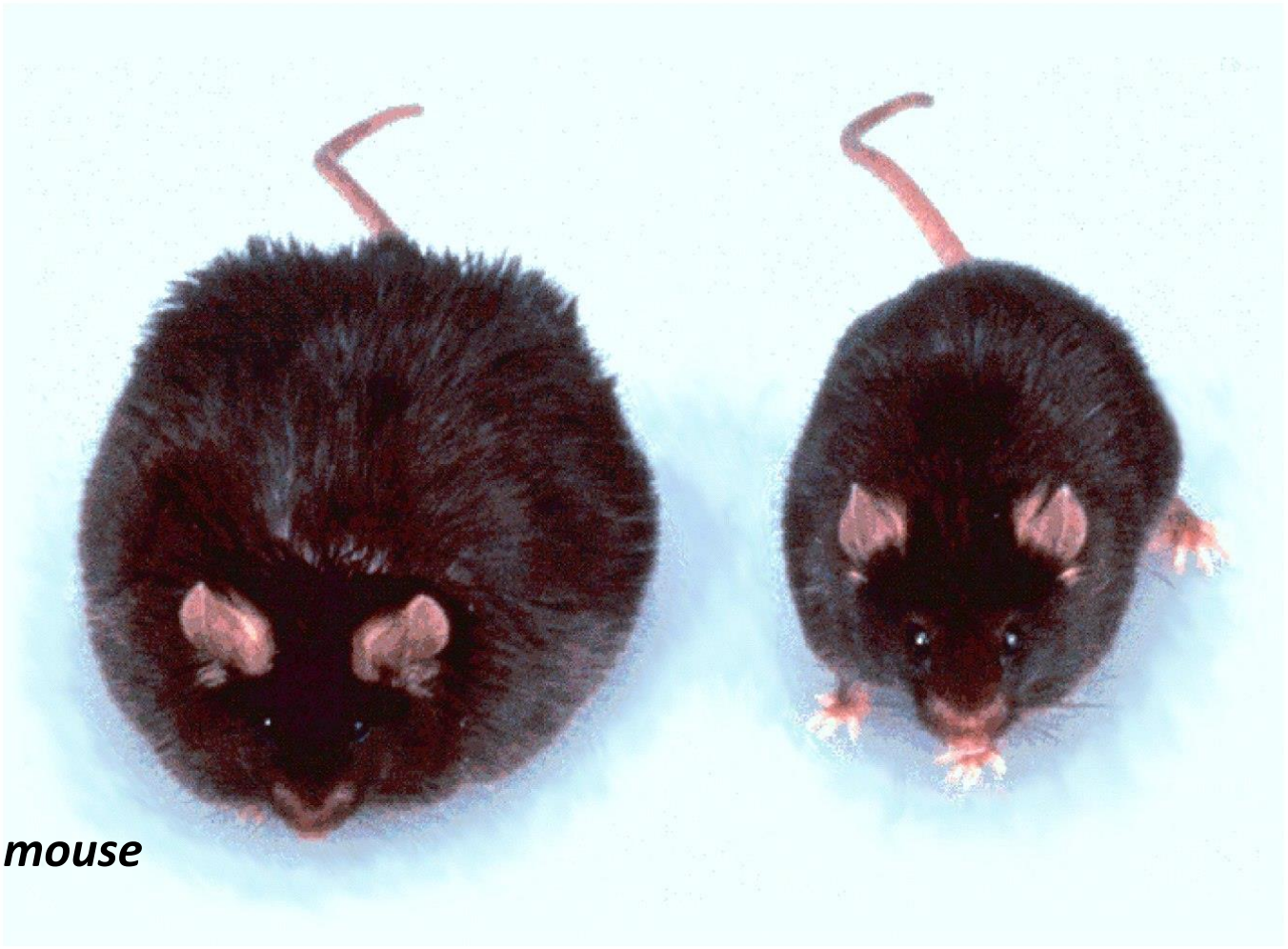


Figure 23-63 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Connective Tissue Cells: Adipocytes



Leptin deficient mouse

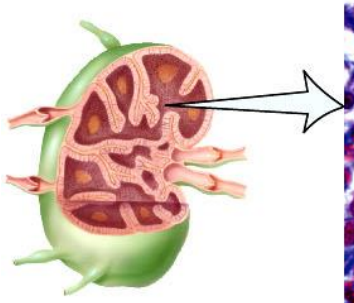
Figure 23-64 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

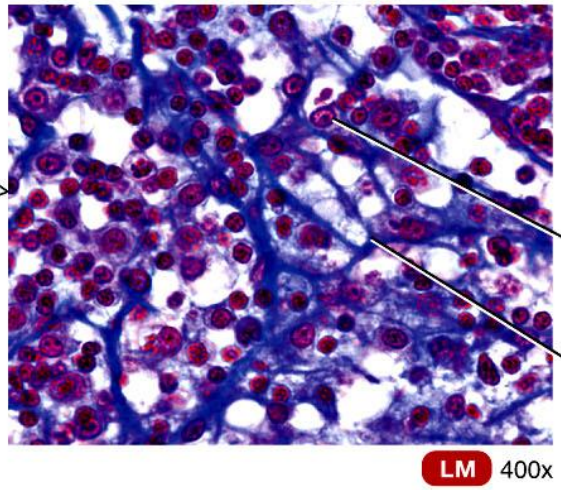
Connective Tissue Cells: Adipocytes

Reticular Connective Tissue

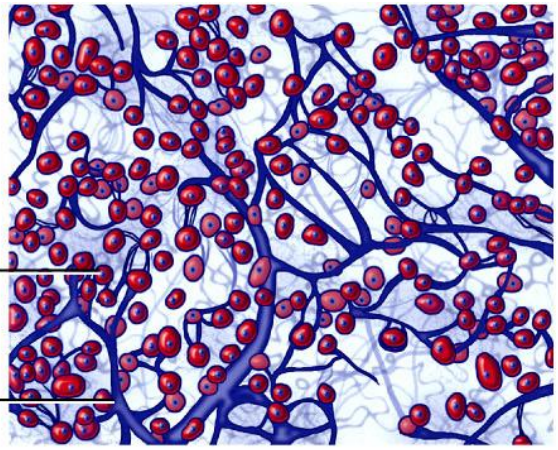
- Fine interlacing reticular fibers and cells
- Forms the stroma of liver, spleen, and lymph nodes



Lymph node



Sectional view of reticular connective tissue of a lymph node



Reticular connective tissue

Table 04.table 04c Tortora - PAP 12/e

Tissue types

Types of Mature Connective Tissue

Cartilage is a dense network of collagen fibers and elastic fibers firmly embedded in chondroitin sulfate

- **Chrondrocytes**
  - Cartilage cells found in the spaces called lucunae
- **Pericondrium**
  - Covering of dense irregular connective tissue that surrounds the cartilage
  - Two layers: outer fibrous layer and inner cellular layer
- **No blood vessels or nerves, except pericondrium**

Tissue types

Connective Tissue Cells: chondrocytes

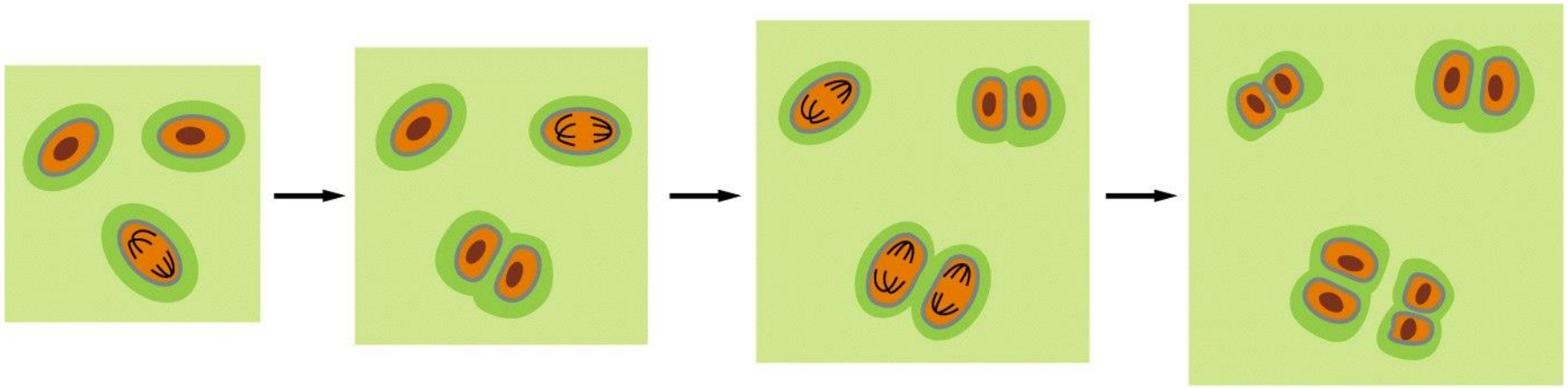


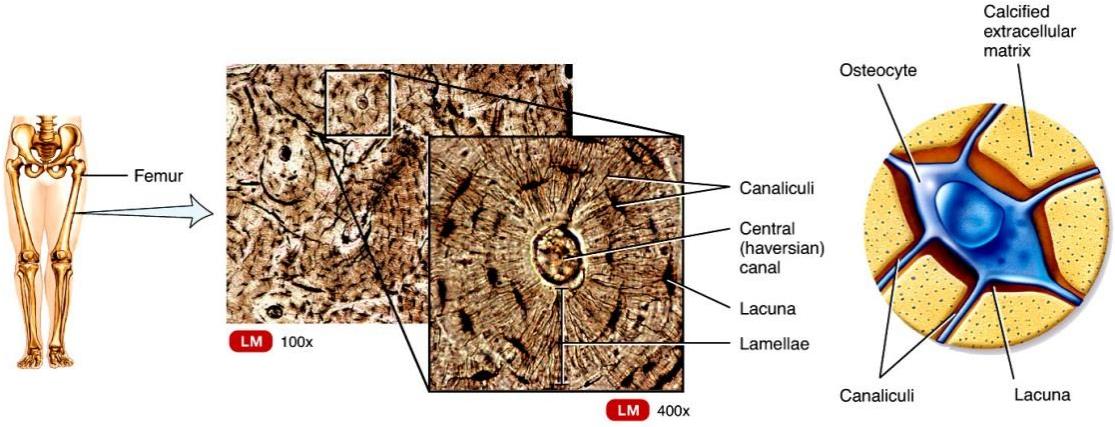
Figure 23-54 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Bone tissue

Bones are organs composed of several different connective tissues: bone (osseous) tissue, periosteum, and endosteum.

- **Compact or spongy**
- **Osteon or haversian system**
  - Spongy bone lacks osteons. They have columns called **trabeculae**



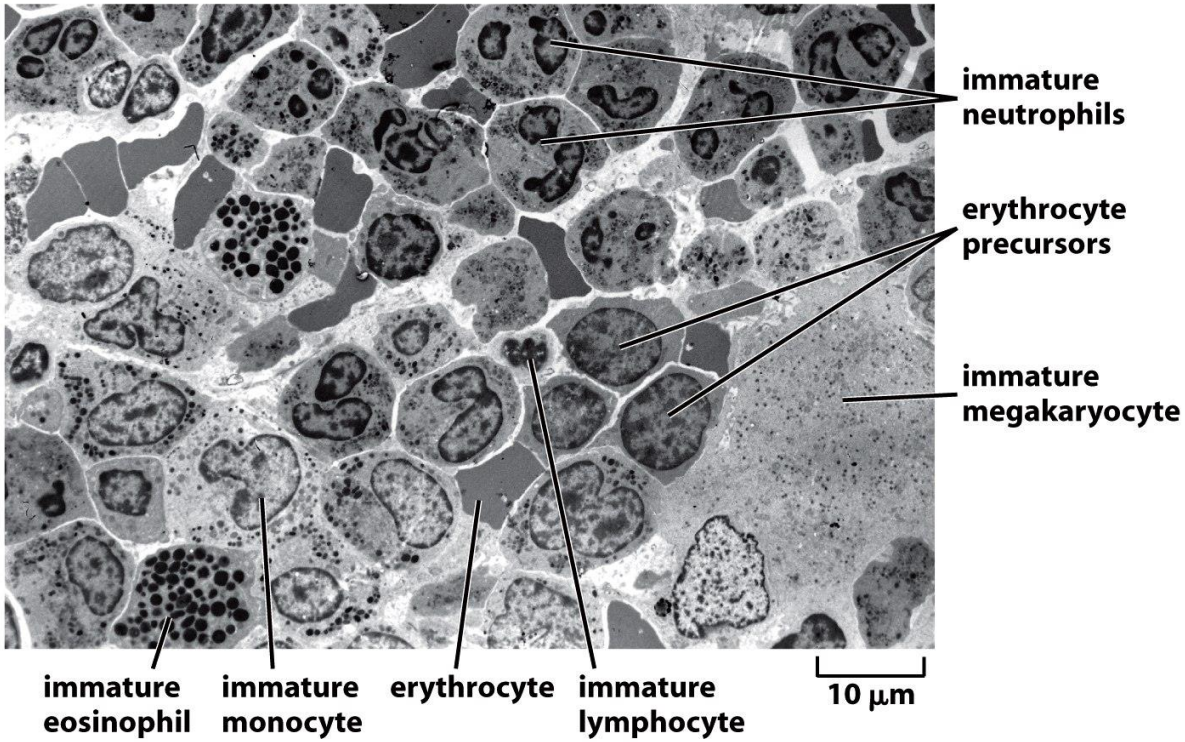
Sectional view of several osteons (haversian systems) of femur (thigh bone) and details of one osteon

Details of an osteocyte

Tissue types

Liquid Connective Tissue

- **Blood tissue**
  - Connective tissue with liquid extracellular matrix called blood plasma
- **Lymph**



Tissue types

Blood cells

Table 23–1 Blood Cells

TYPE OF CELL	MAIN FUNCTIONS	TYPICAL CONCENTRATION IN HUMAN BLOOD (CELLS/LITER)
Red blood cells (erythrocytes)	transport O_2 and CO_2	5×10^{12}
White blood cells (leucocytes)		
Granulocytes		
Neutrophils (polymorphonuclear leucocytes)	phagocytose and destroy invading bacteria	5×10^{9}
Eosinophils	destroy larger parasites and modulate allergic inflammatory responses	2×10^{8}
Basophils	release histamine (and in some species serotonin) in certain immune reactions	4×10^{7}
Monocytes	become tissue macrophages, which phagocytose and digest invading microorganisms and foreign bodies as well as damaged senescent cells	4×10^{8}
Lymphocytes		
B cells	make antibodies	2×10^{9}
T cells	kill virus-infected cells and regulate activities of other leucocytes	1×10^{9}
Natural killer (NK) cells	kill virus-infected cells and some tumor cells	1×10^{8}
Platelets (cell fragments arising from *megakaryocytes* in bone marrow)	initiate blood clotting	3×10^{11}

Humans contain about 5 liters of blood, accounting for 7% of body weight. Red blood cells constitute about 45% of this volume and white blood cells about 1%, the rest being the liquid blood plasma.

Table 23-1 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Blood cells

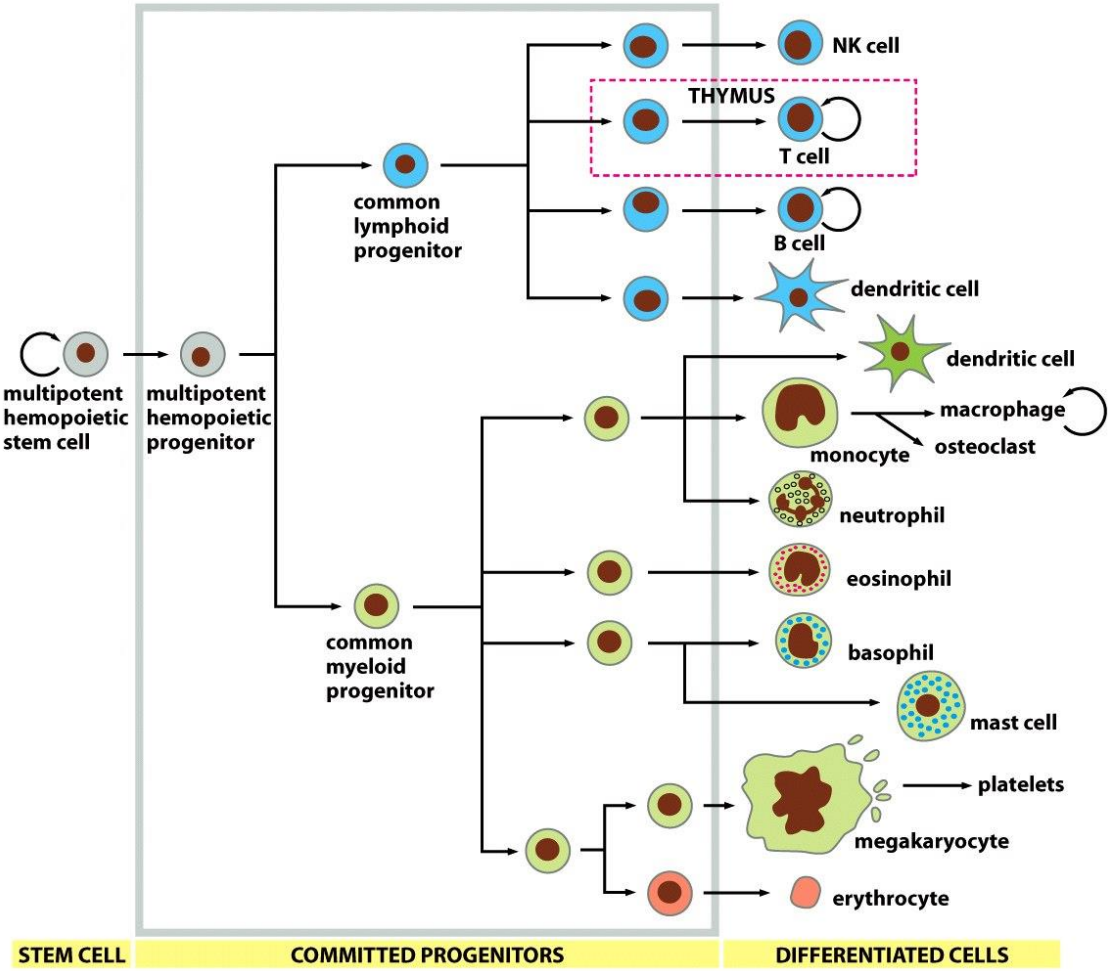
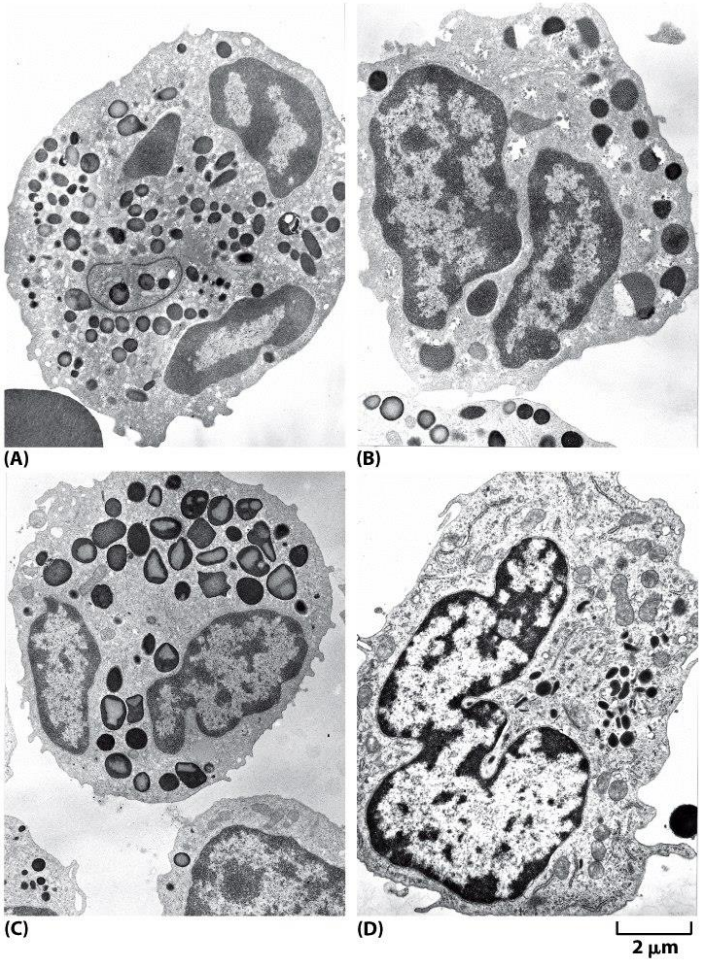


Figure 23-42 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

White blood cells



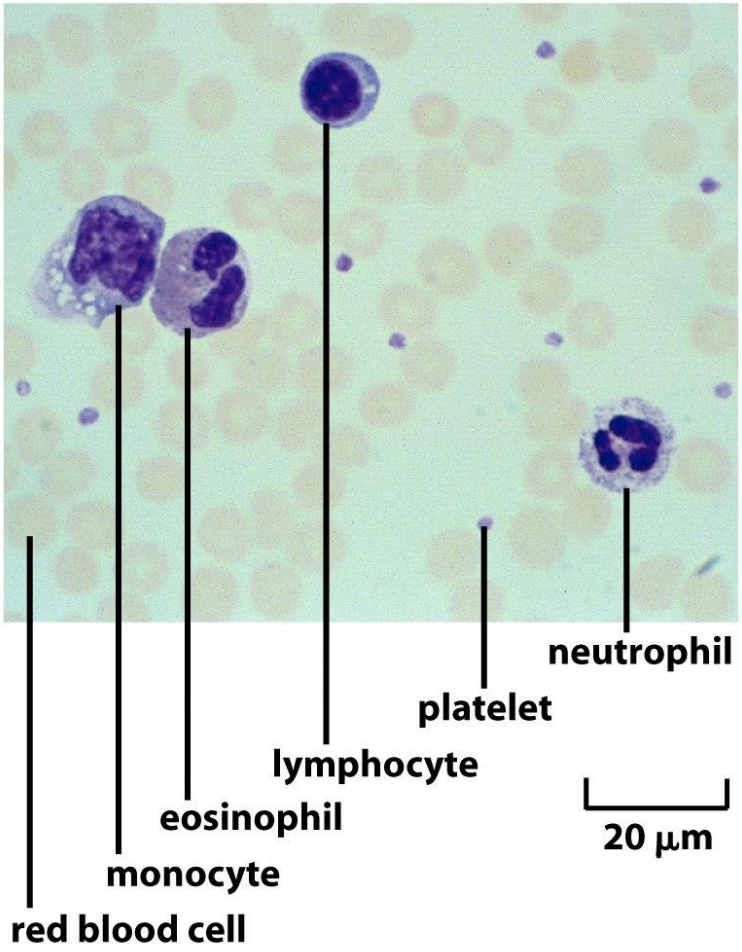


Figure 23-37a-d *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Blood: artery

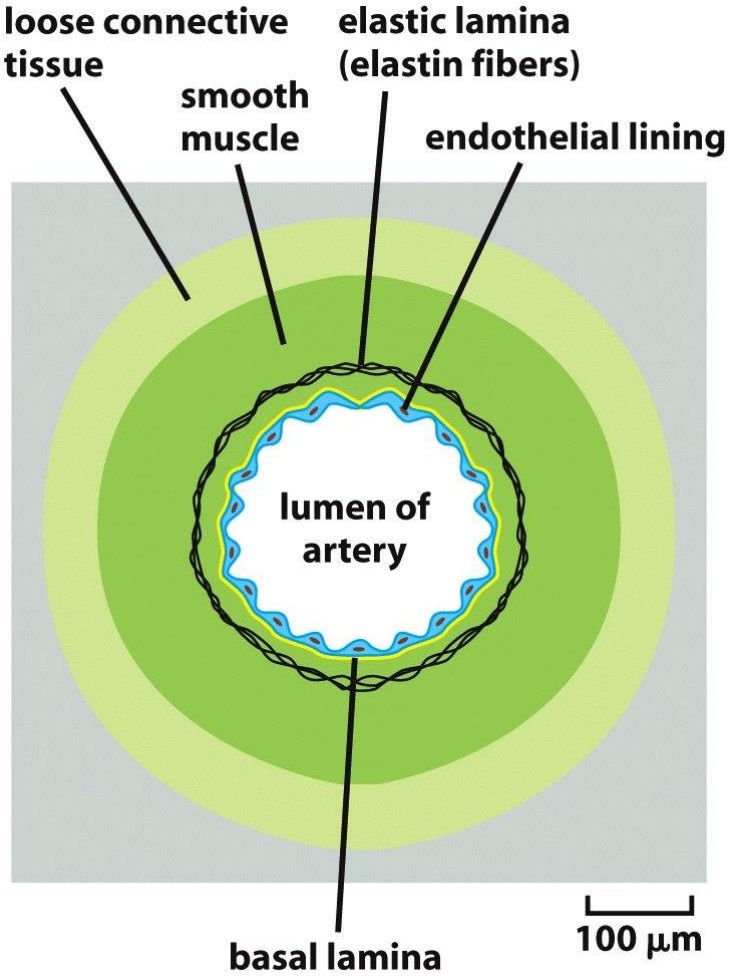


Figure 23-30 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Blood: capillary

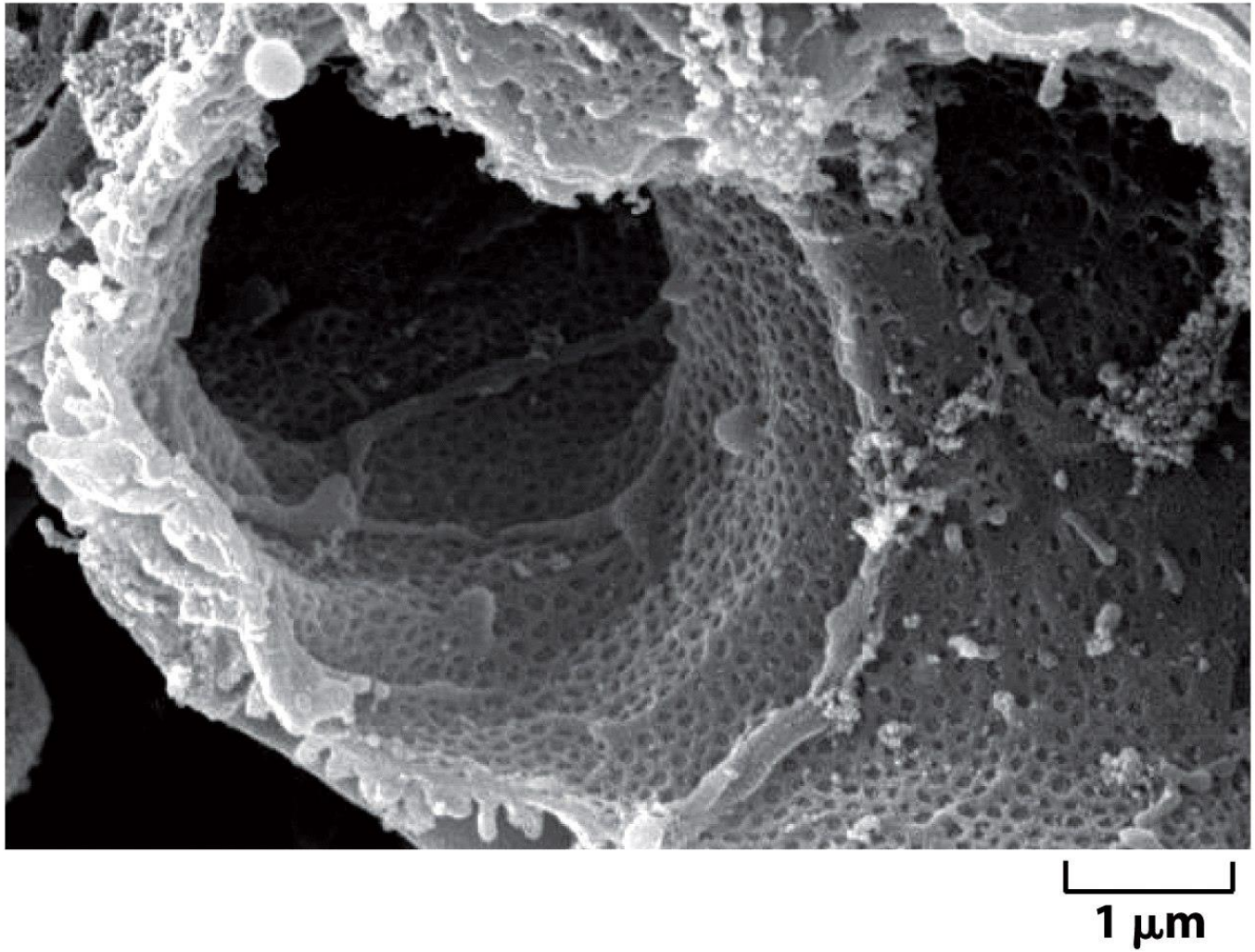


Figure 23-31b *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Blood: new capillaries after wound

Figure 23-34 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Blood: angiogenesis

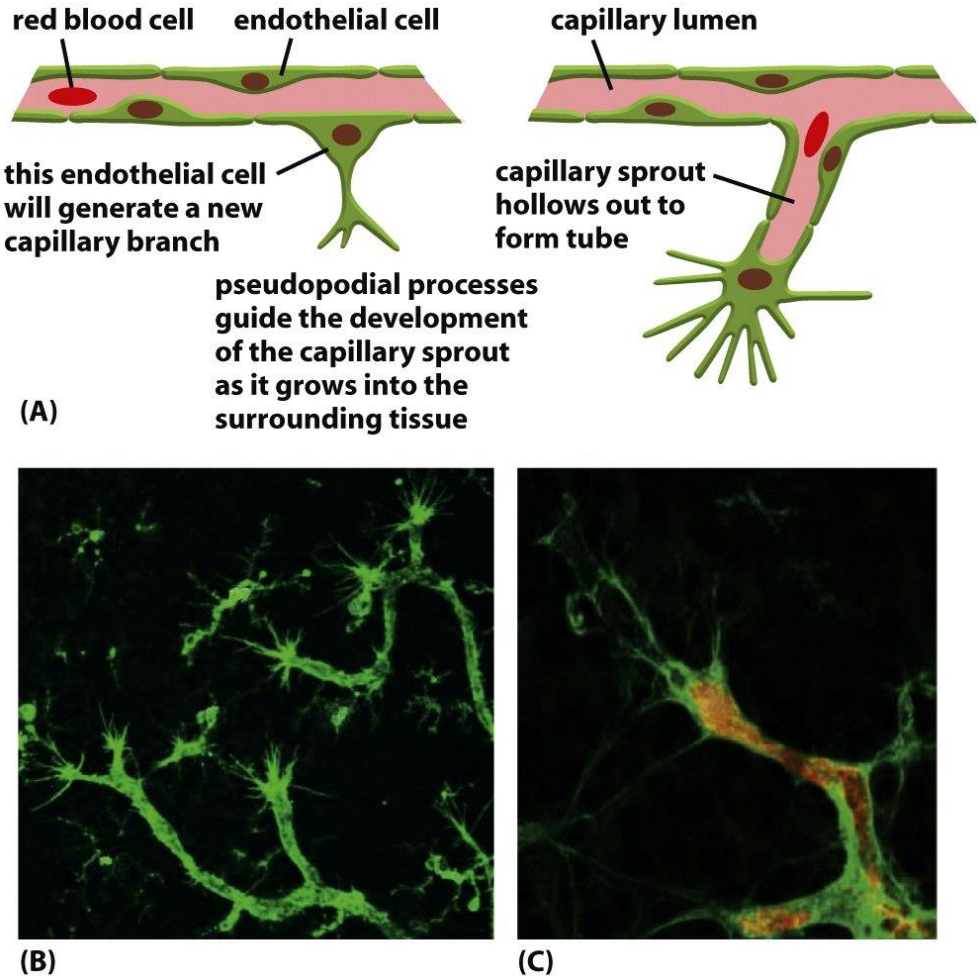


Figure 23-33 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Blood: angiogenesis

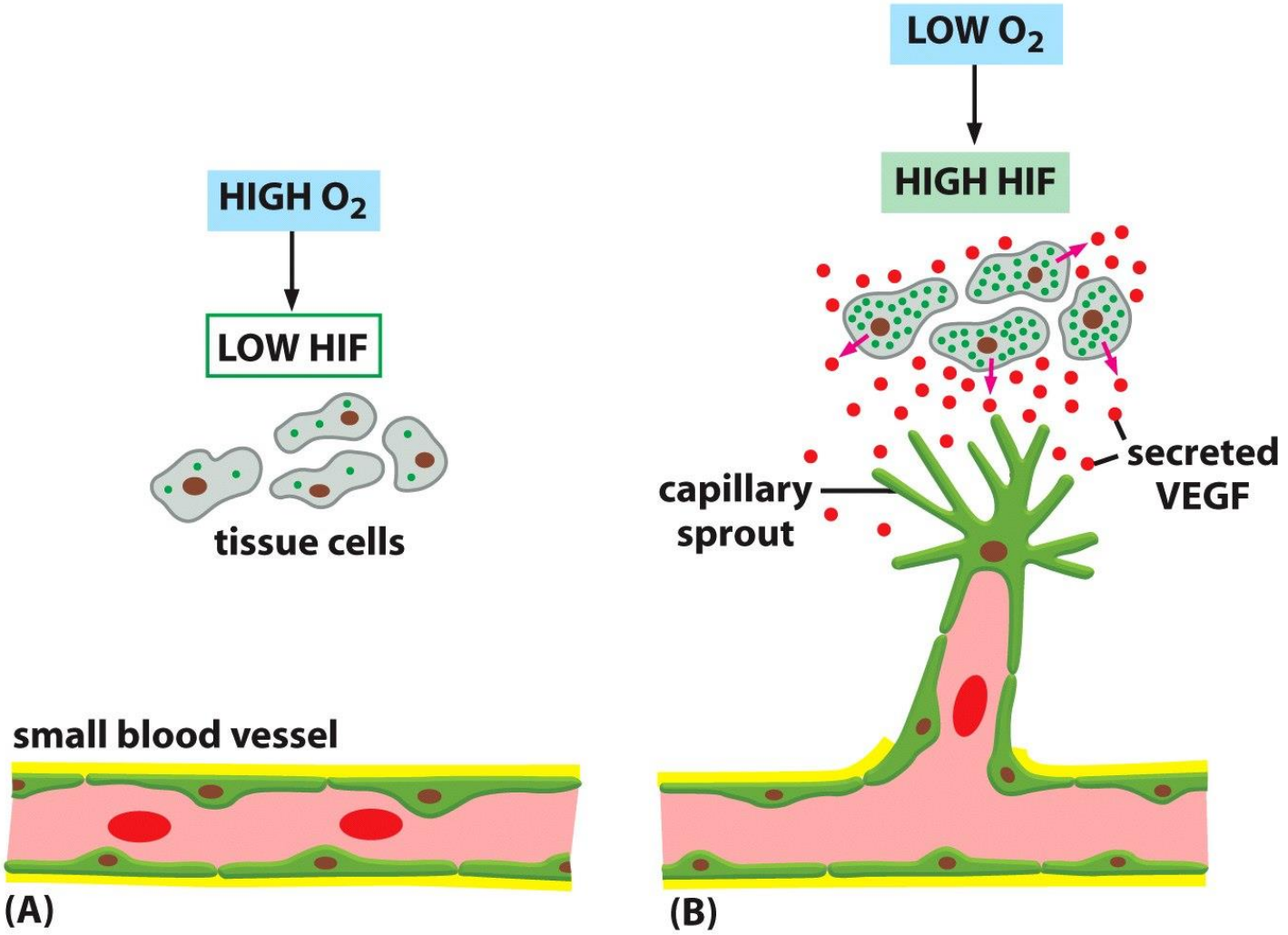


Figure 23-35 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types
Blood cells in clot

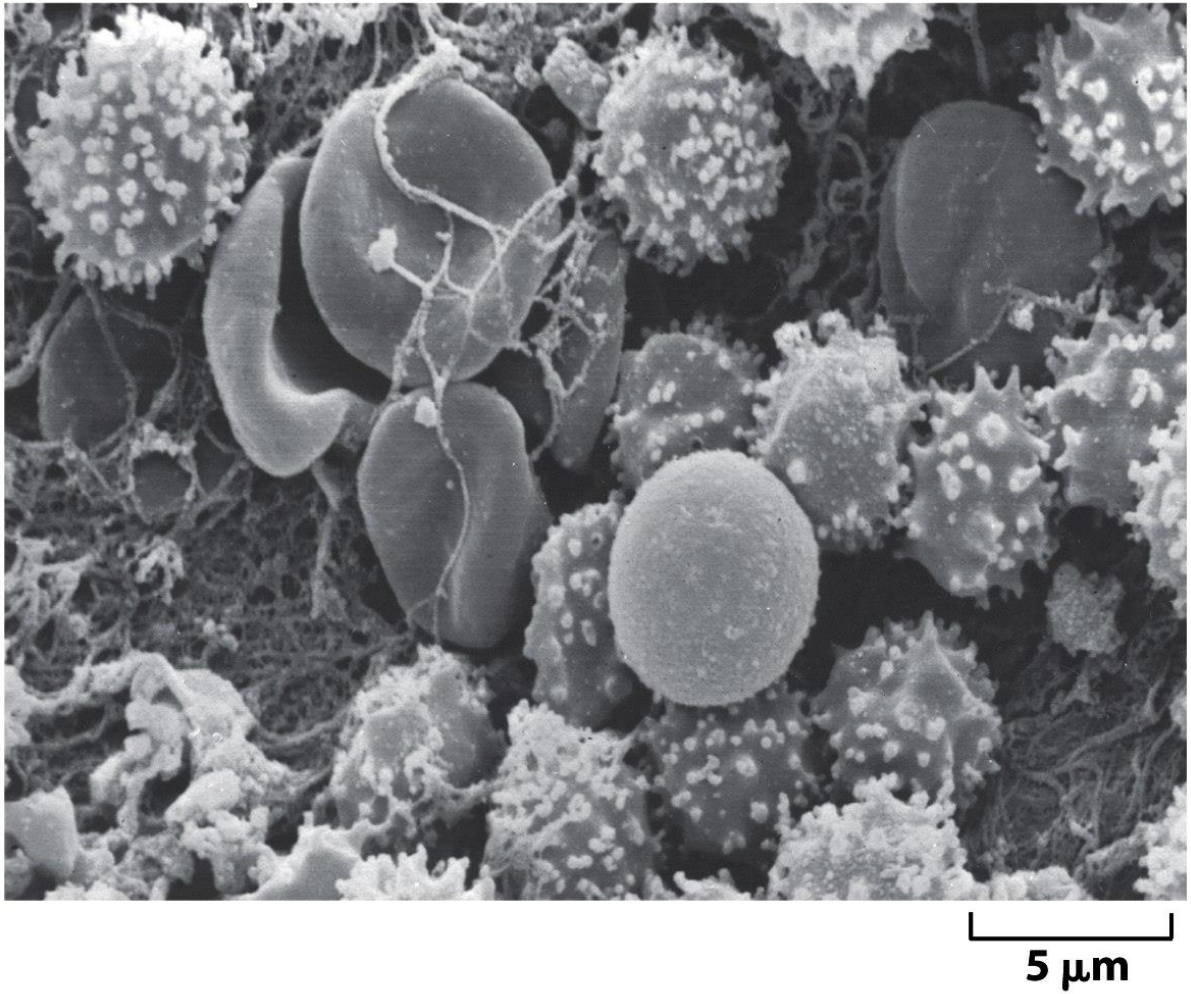


Figure 23-36 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types
Blood cells in inflammation

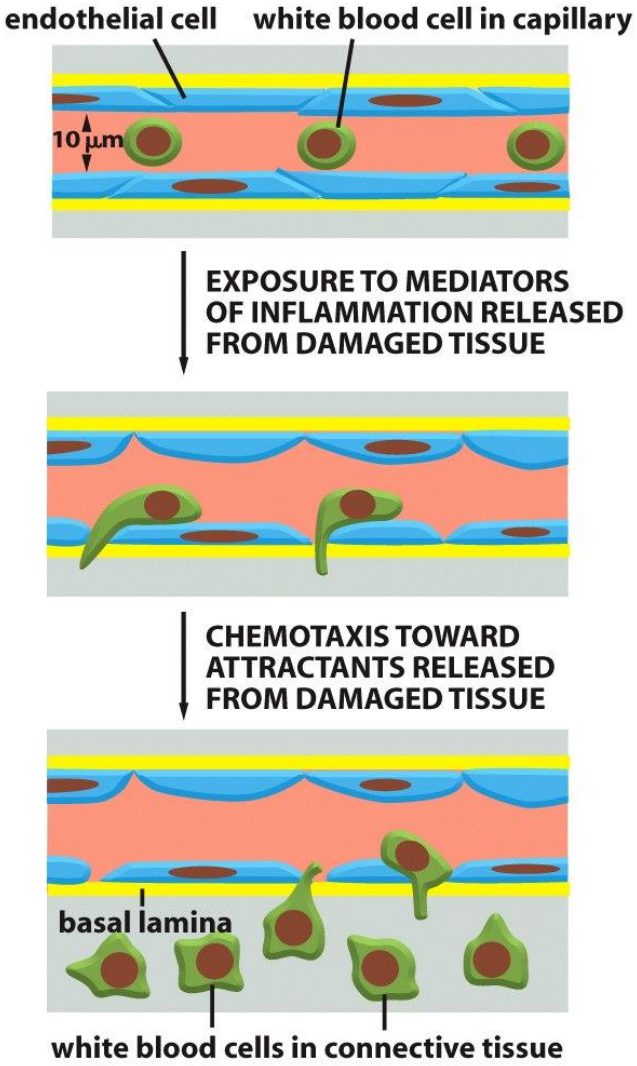


Figure 23-38 *Molecular Biology of the Cell* (© Garland Science 2008)

Movie on leukocyte rolling 19.2

Tissue types

Membranes

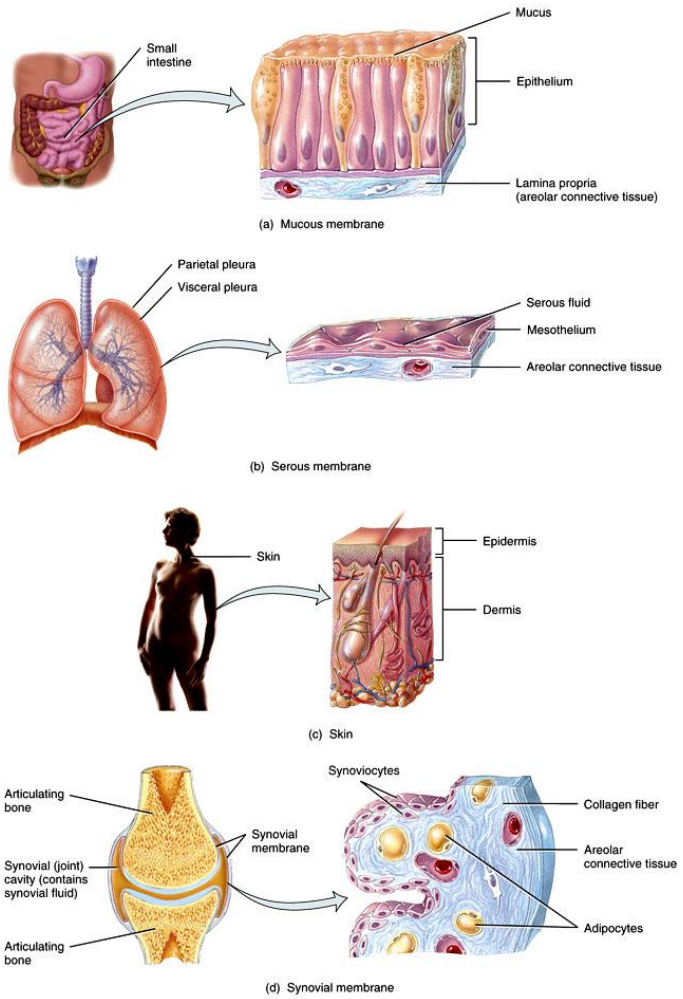


Figure 04.07 Tortora - PAP 12/e

Membranes are flat sheets of pliable tissue that cover or line a part of the body

Epithelial membranes are a combination of an epithelial layer and an underlying connective tissue layer

- Mucous, Serous, and Cutaneous membranes

Synovial membranes

- Lines joints and contains connective tissue but not epithelium

Tissue types

Epithelial Membranes

- **Mucous membranes**
  - Lines a body cavity that opens directly to the exterior
  - Epithelial layer is important for the body's defense against pathogens
  - Connective tissue layer is areolar connective tissue and is called **lamina propria**
- **Serous membranes or serosa**
  - Lines a body cavity that does not open directly to the exterior. Also covers the organs that lie within the cavity
  - Consist of areolar connective tissue covered by mesothelium (simple squamous epithelium) that secrete a serous fluid for lubrication

Skin

- Covers the entire surface of the body
- Consists of epidermis (epithelial layer) and dermis (connective layer)

Tissue types

Epithelial Membranes: skin

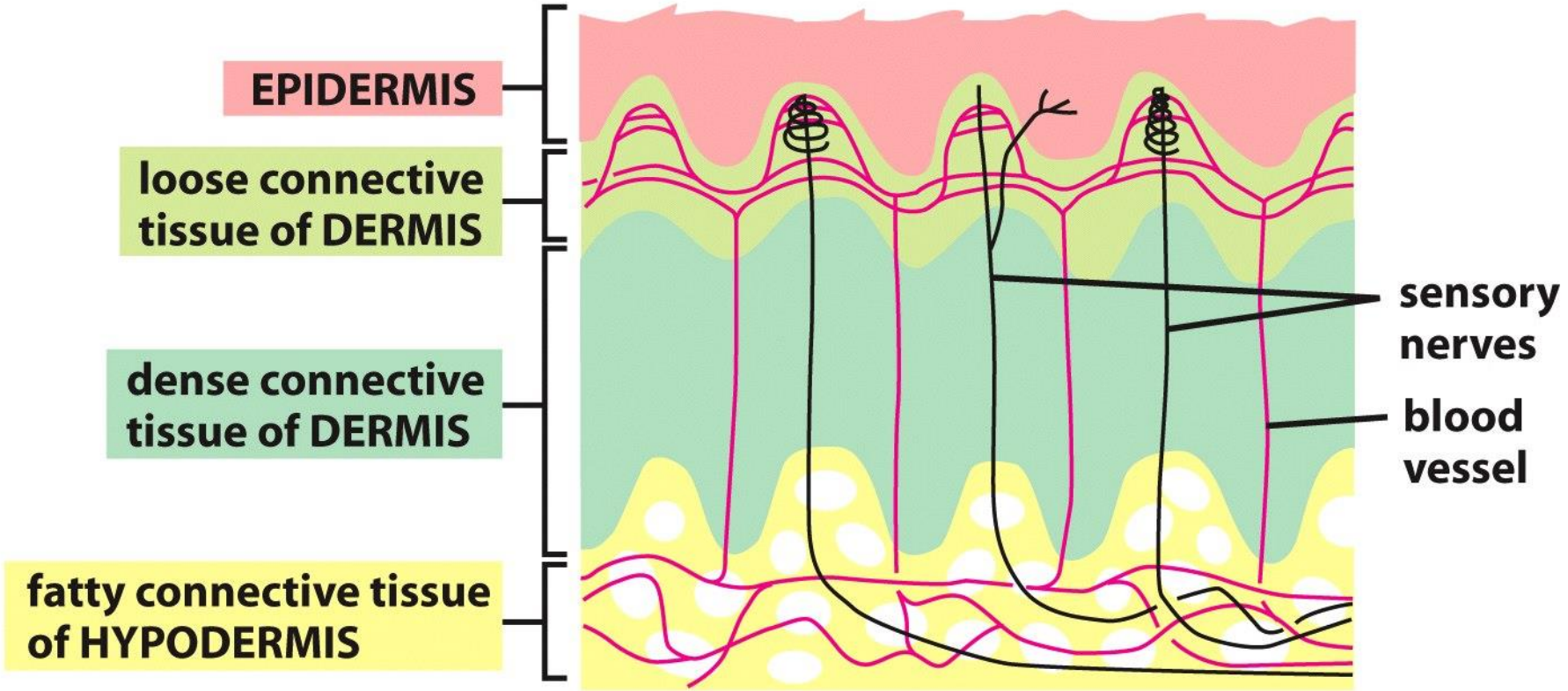


Figure 23-1a (part 1 of 2) *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Epithelial Membranes: skin

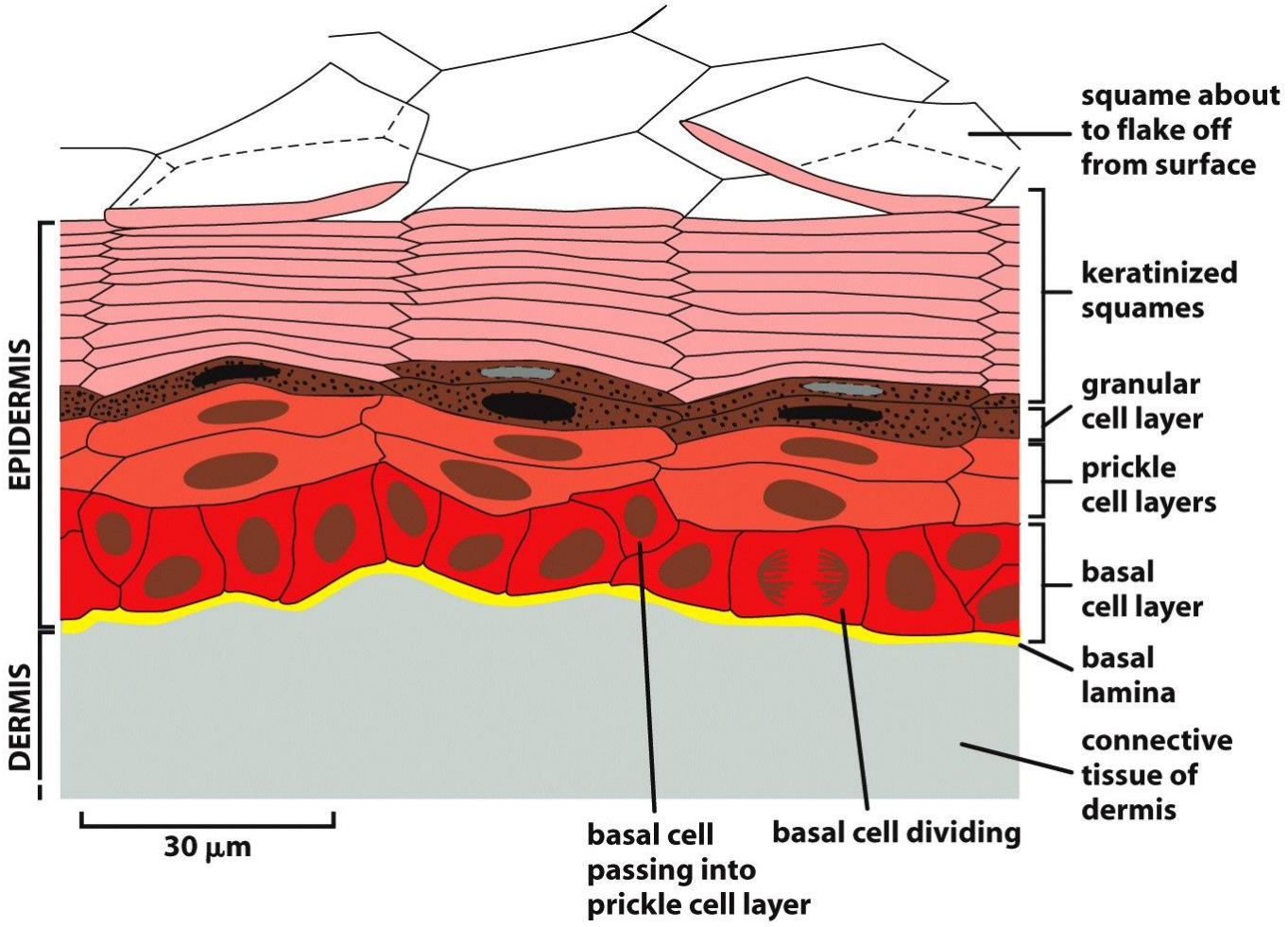
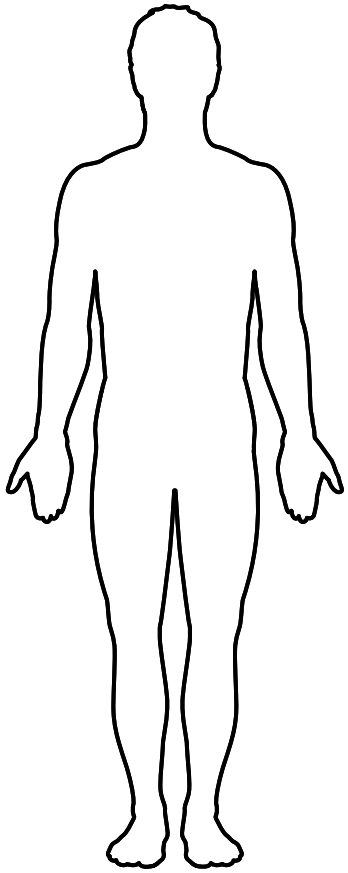


Figure 23-3 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Muscle tissue



Four Types of Animal Tissue:

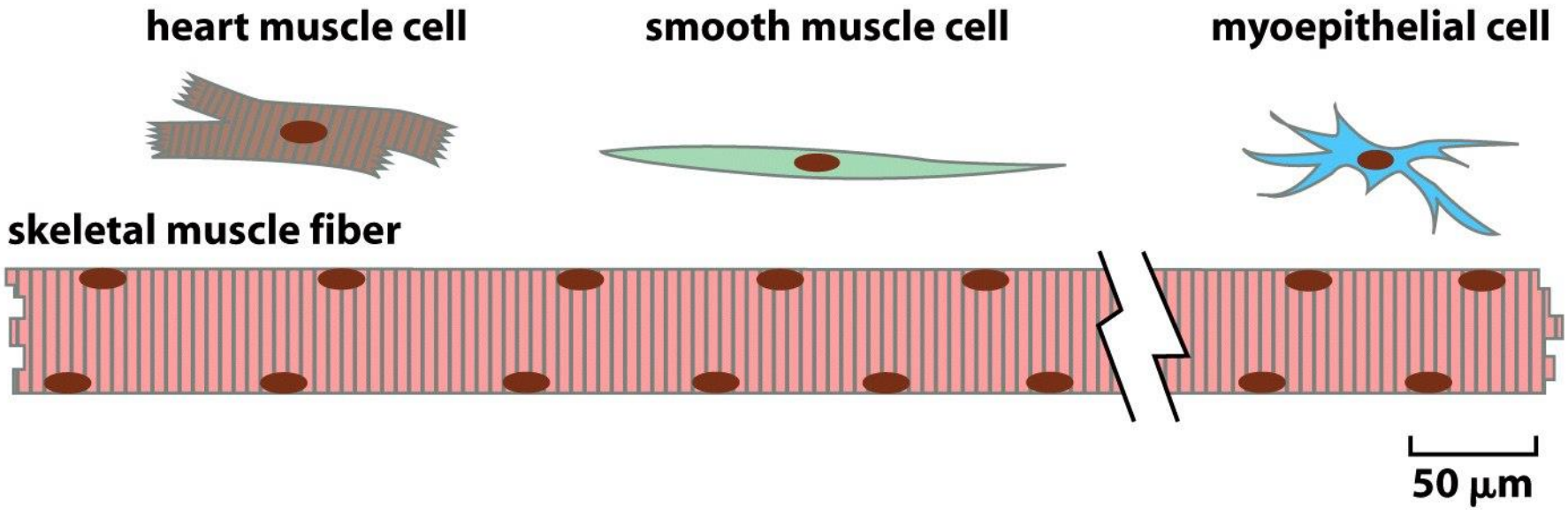
1. *Epithelial/Barrier Tissue*
   - *Covers body surfaces and lines organs, cavities and ducts, glands too*
2. *Connective Tissue*
   - *Protects and supports. Bind organs, stores energy as fat, helps provide immunity*
3. ***Muscle Tissue***
   - ***Generates physical force to make body move and generates body heat***
4. *Nervous Tissue*
   - *Detects changes in environment inside and out and responds by generating action potentials that activate muscle contractions and secretions*

Tissue types

Muscular Tissue

Consists of elongated cells called muscle fibers or myocytes

- Cells use ATP to generate force
- Several functions of muscle tissue
- Classified into 3 types: **skeletal, cardiac,** and **smooth muscular tissue**



Tissue types

Fusion of myocytes

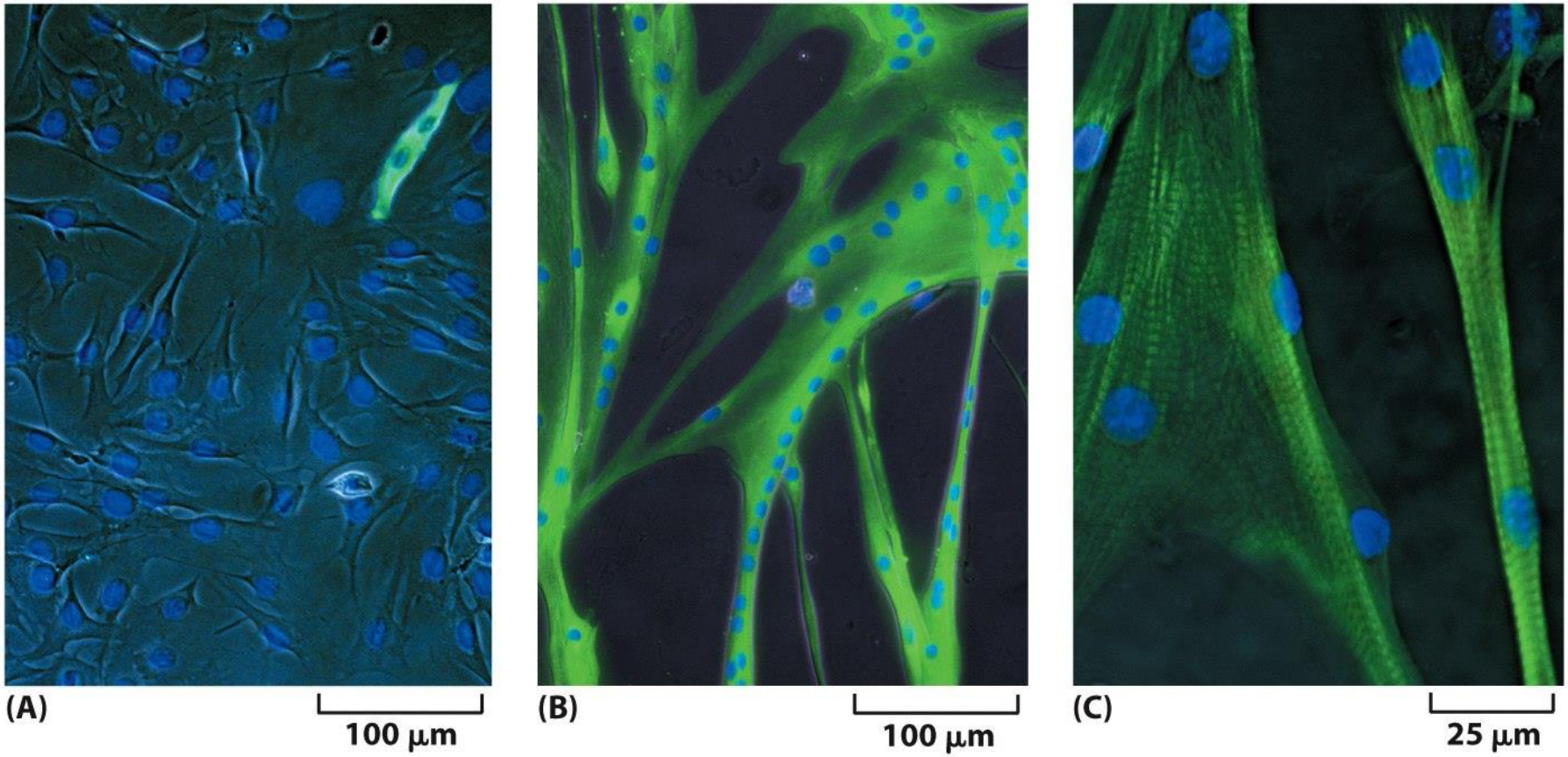


Figure 23-48 *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Skeletal Muscle Tissue

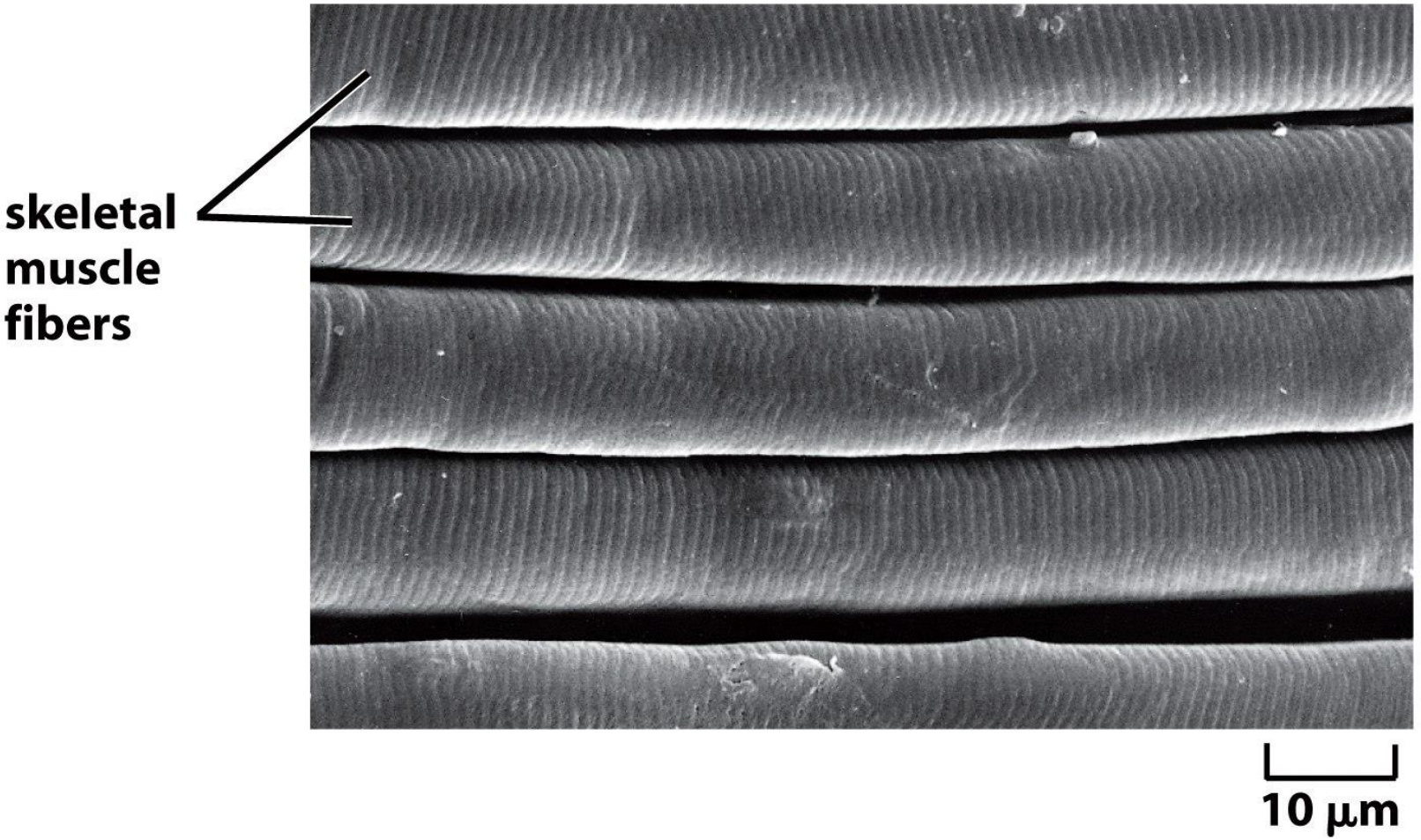


Figure 23-47b *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Cardiac muscle tissue

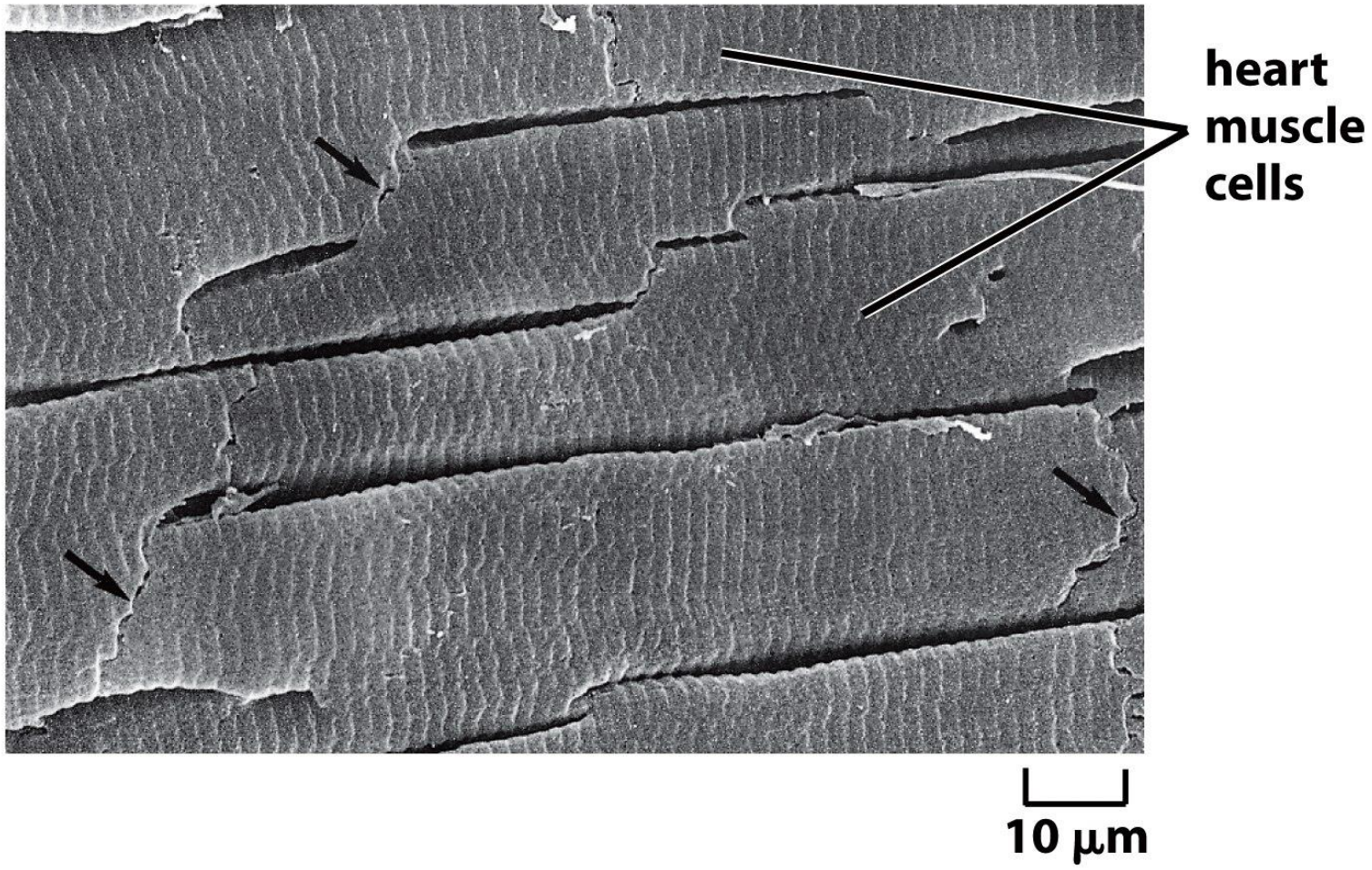


Figure 23-47c *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Smooth Muscle Tissue

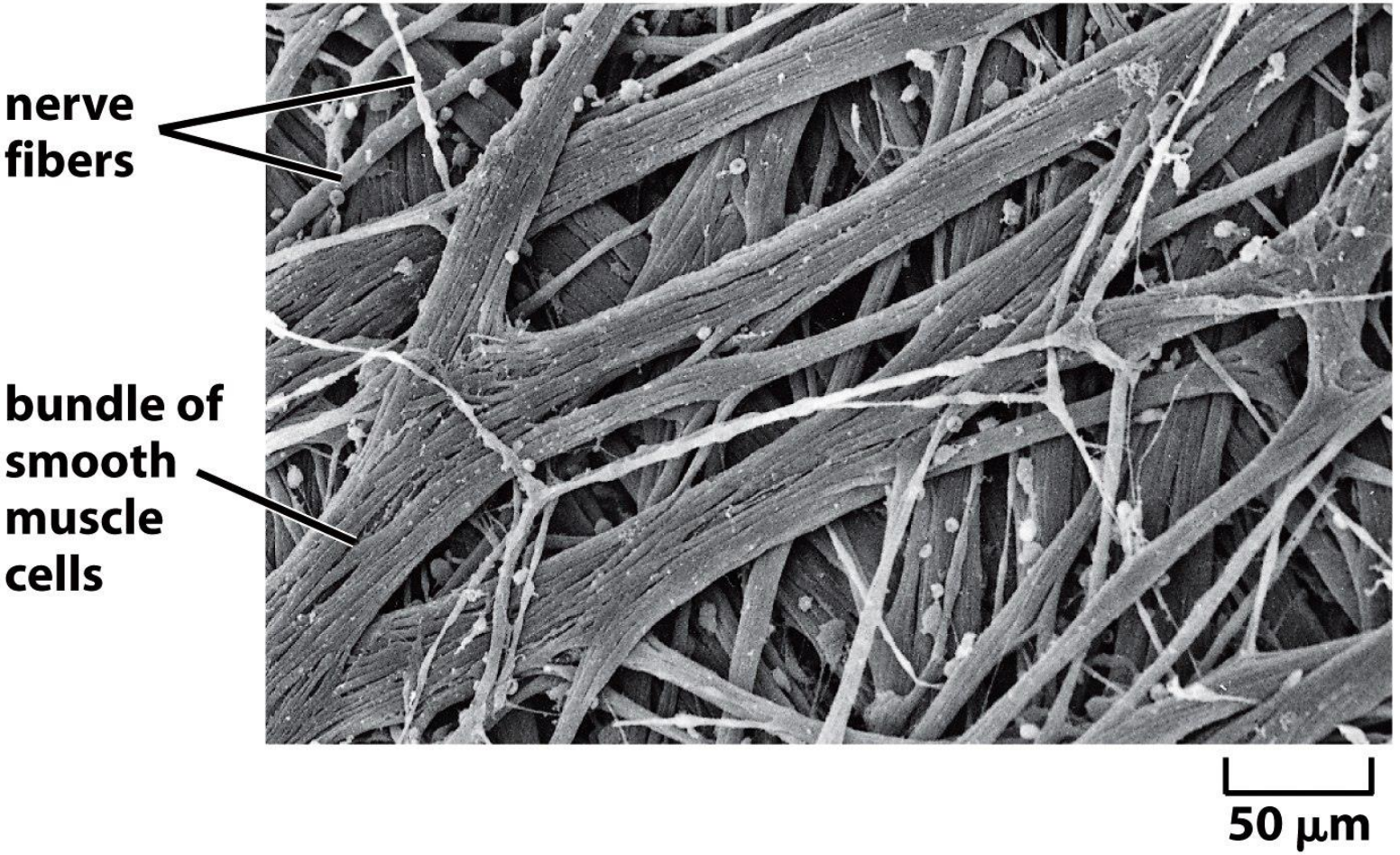
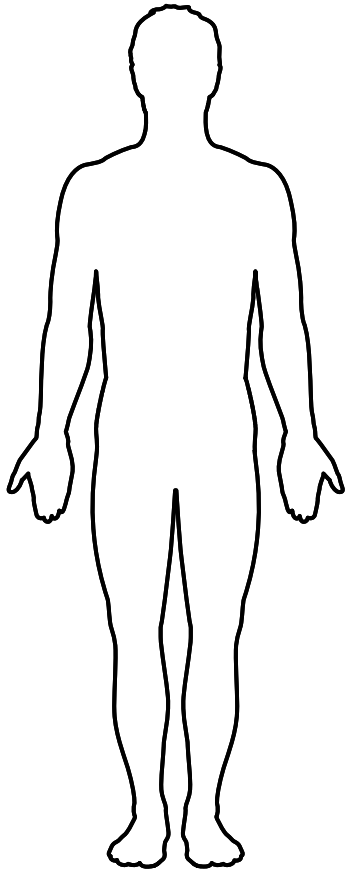


Figure 23-47d *Molecular Biology of the Cell* (© Garland Science 2008)

Tissue types

Nervous tissue



Four Types of Animal Tissue:

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2. *Connective Tissue*
   - *Protects and supports. Bind organs, stores energy as fat, helps provide immunity*
3. *Muscle Tissue*
   - *Generates physical force to make body move and generates body heat*
4. ***Nervous Tissue***
   - ***Detects changes in environment inside and out and responds by generating action potentials that activate muscle contractions and secretions***

Tissue types

Nervous Tissue

- **Consists of two principle types of cells**
  - Neurons or nerve cells
  - Neuroglia

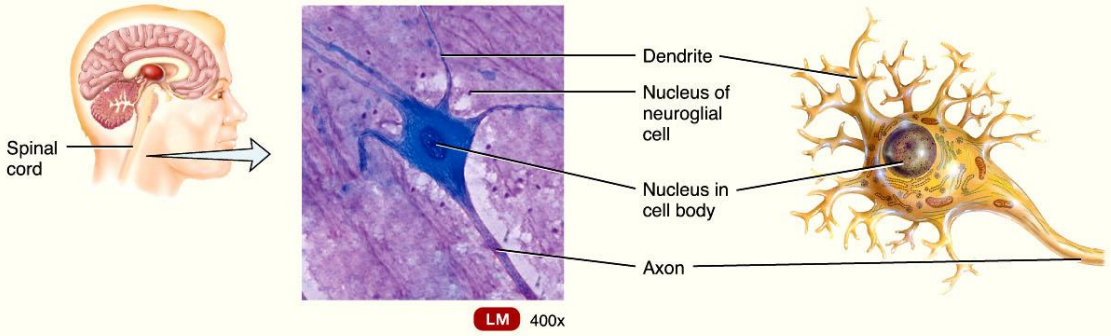
TABLE 4.6

Nervous Tissue

Description: Consists of neurons (nerve cells) and neuroglia. Neurons consist of a cell body and processes extending from the cell body (multiple dendrites and a single axon). Neuroglia do not generate or conduct nerve impulses but have other important supporting functions.

Location: Nervous system.

Function: Exhibits sensitivity to various types of stimuli, converts stimuli into nerve impulses (action potentials), and conducts nerve impulses to other neurons, muscle fibers, or glands.



Neuron of spinal cord

Table 04.06 Tortora - PAP 12/e

Tissue types

Excitable Cells

- **Neurons and muscle fibers**
- **Exhibit electrical excitability**
  - The ability to respond to certain stimuli by producing electrical signals such as action potentials
  - Actions potentials propagate along a nerve or muscle plasma membrane to cause a response
    - Release of neurotransmitters
    - Muscle contraction

Tissue types

Overview of the nervous system

- The nervous system, along with the endocrine system, helps to keep controlled conditions within limits that maintain health and helps to maintain homeostasis.
- The nervous system is responsible for all our behaviors, memories, and movements.
- The branch of medical science that deals with the normal functioning and disorders of the nervous system is called neurology.

Tissue types

Major structures of the nervous system

- Central nervous system (CNS)
  - consists of the brain and spinal cord
- Peripheral nervous system (PNS)
  - consists of cranial and spinal nerves that contain both sensory and motor fibers
  - connects CNS to muscles, glands & all sensory receptors

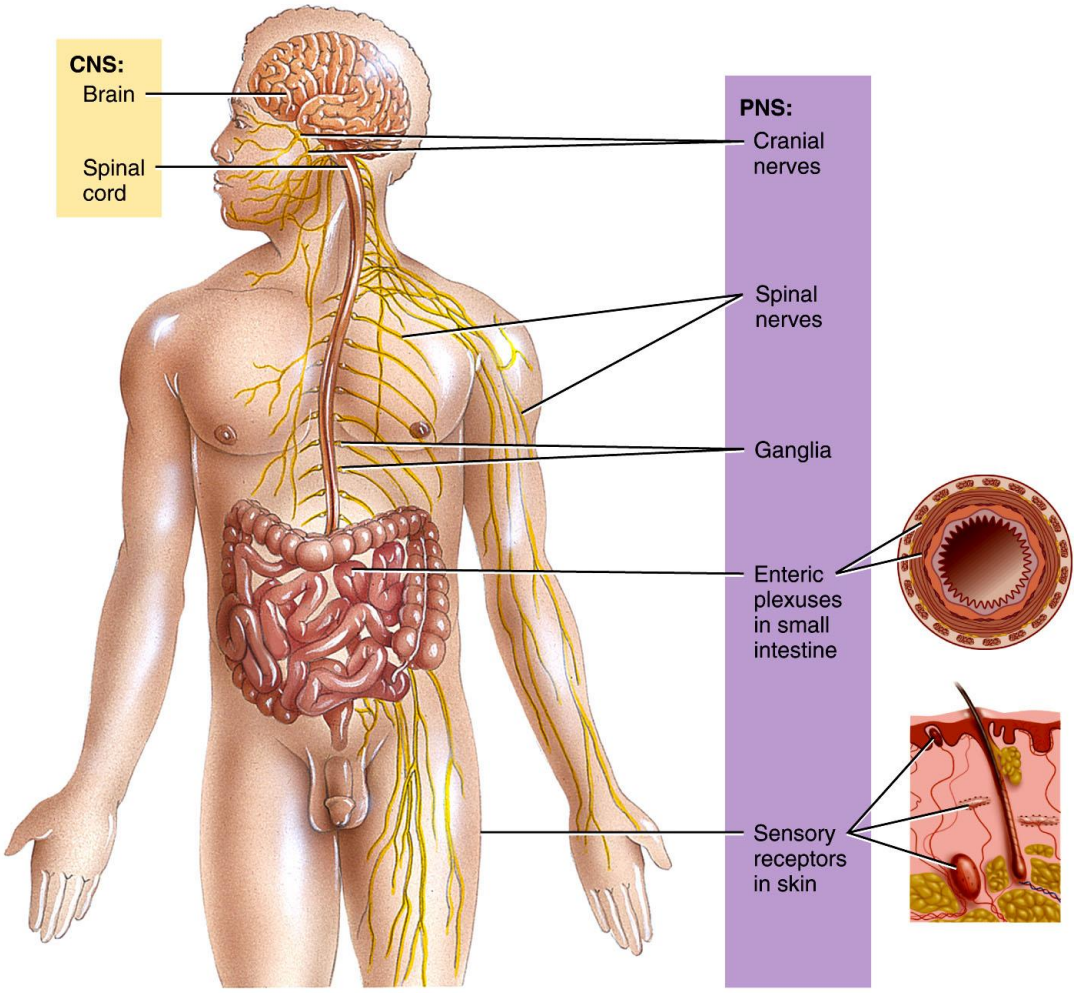


Figure 12.01 Tortora - PAP 12/e

Tissue types
Structure of a multipolar neuron

- Functional unit of nervous system
- Have capacity to produce action potentials
  - electrical excitability
- Cell body
  - single nucleus with prominent nucleolus
  - Nissl bodies (chromatophilic substance)
    - rough ER & free ribosomes for protein synthesis
  - neurofilaments give cell shape and support
  - microtubules move material inside cell
  - lipofuscin pigment clumps (harmless aging)
- Cell processes = dendrites & axons

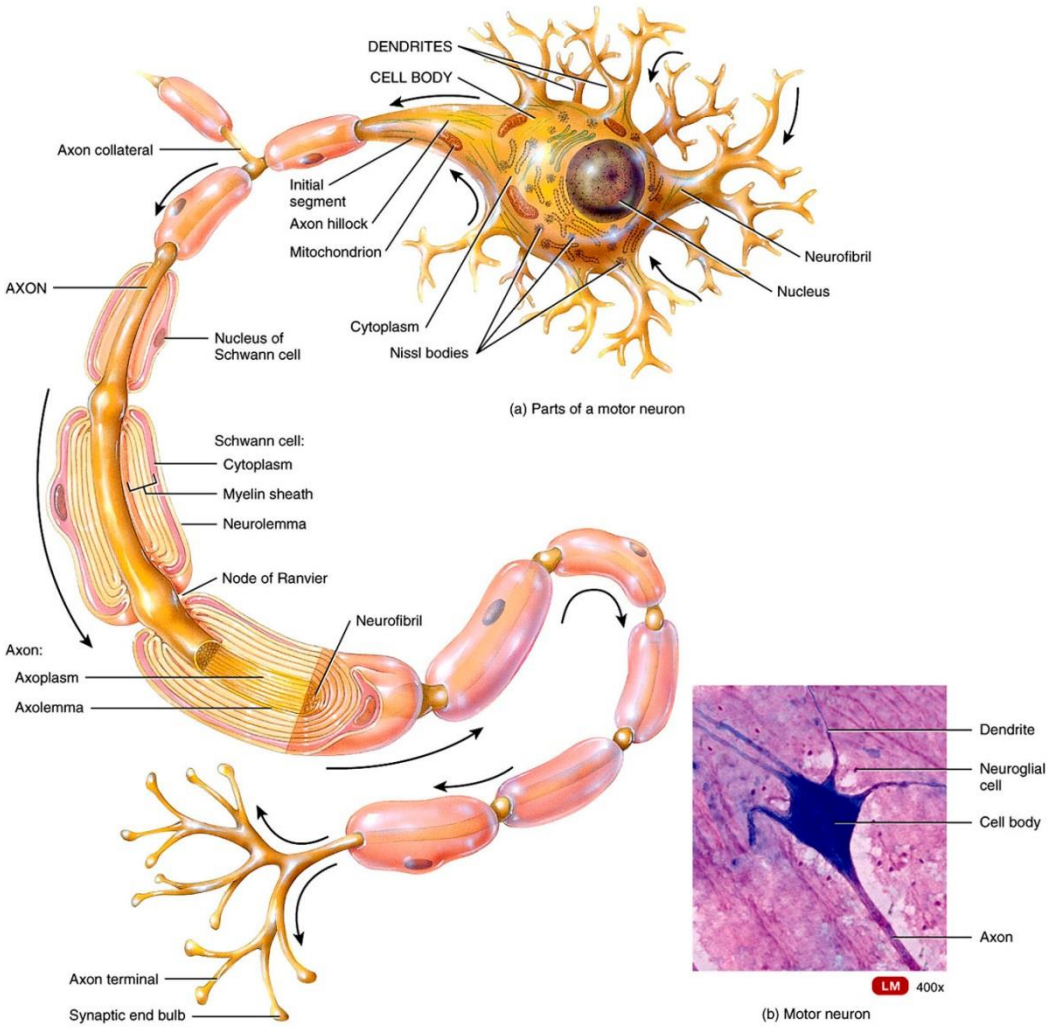


Figure 12.02 Tortora - PAP 12/e

Tissue types

Neuroglia of the CNS

- Most common glial cell type
- Each forms myelin sheath around more than one axons in CNS
- Analogous to Schwann cells of PNS

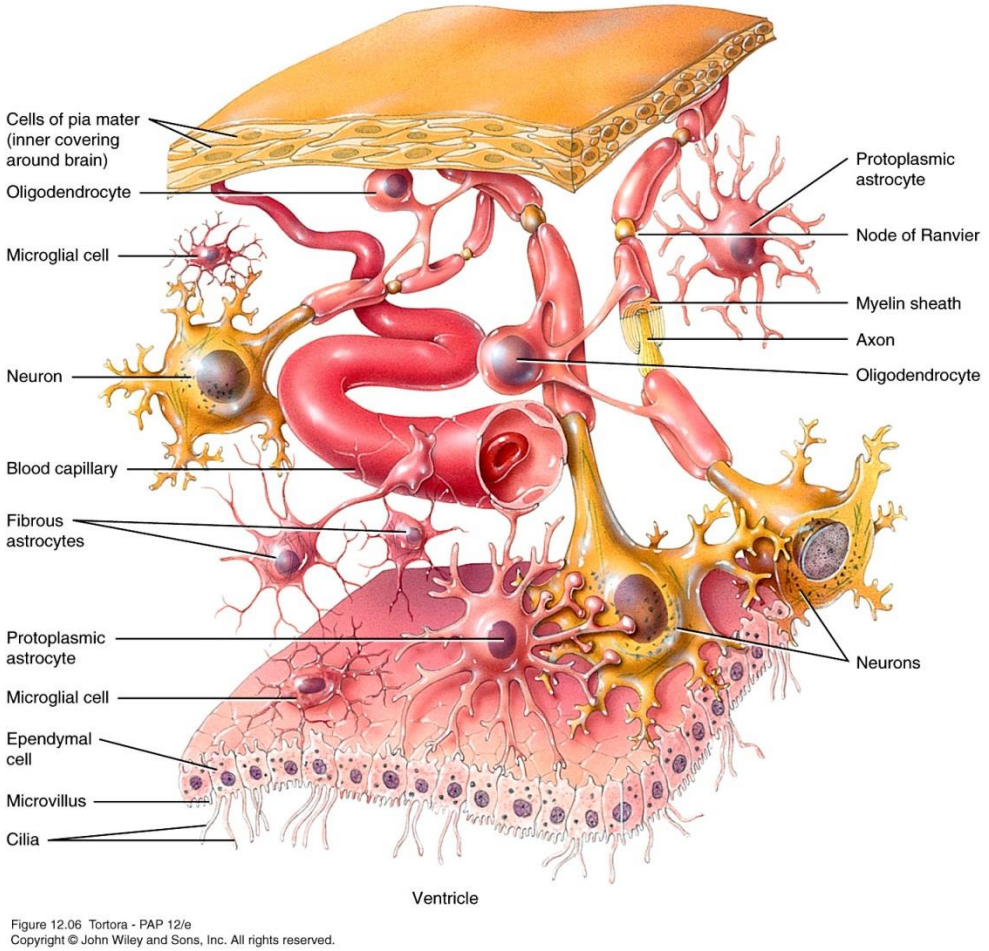


Figure 12.06 Tortora - PAP 12/e

Tissue types

Regeneration & Repair

- **Plasticity maintained throughout life**
  - sprouting of new dendrites
  - synthesis of new proteins
  - changes in synaptic contacts with other neurons
- **Limited ability for regeneration (repair)**
  - PNS can repair damaged dendrites or axons
  - CNS no repairs are possible
- **Formation of new neurons from stem cells was not thought to occur in humans**
- **There is a lack of neurogenesis in other regions of the brain and spinal cord.**
- **Factors preventing neurogenesis in CNS**
  - inhibition by neuroglial cells, absence of growth stimulating factors, lack of neurolemmas, and rapid formation of scar tissue

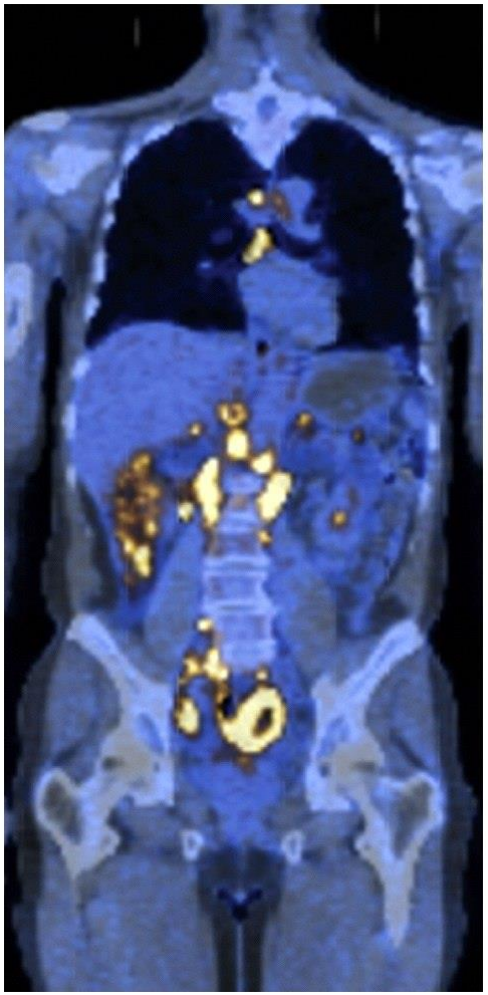
Cancer
Where do we stand?

US Mortality, 2007

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	616,067	25.4
2.	**Cancer**	**562,875**	**23.2**
3.	Cerebrovascular diseases	135,952	5.6
4.	Chronic lower respiratory diseases	127,924	5.3
5.	Accidents (unintentional injuries)	123,706	5.1
6.	Alzheimer disease	74,632	3.1
7.	Diabetes mellitus	71,382	2.9
8.	Influenza & pneumonia	52,717	2.2
9.	Nephritis*	46,448	1.9
10.	Septicemia	34,828	1.4

***Includes nephrotic syndrome and nephrosis.**
Source: US Mortality Data 2007, National Center for Health Statistics, Centers for Disease Control and Prevention, 2010.

Cancer
Where do we stand?



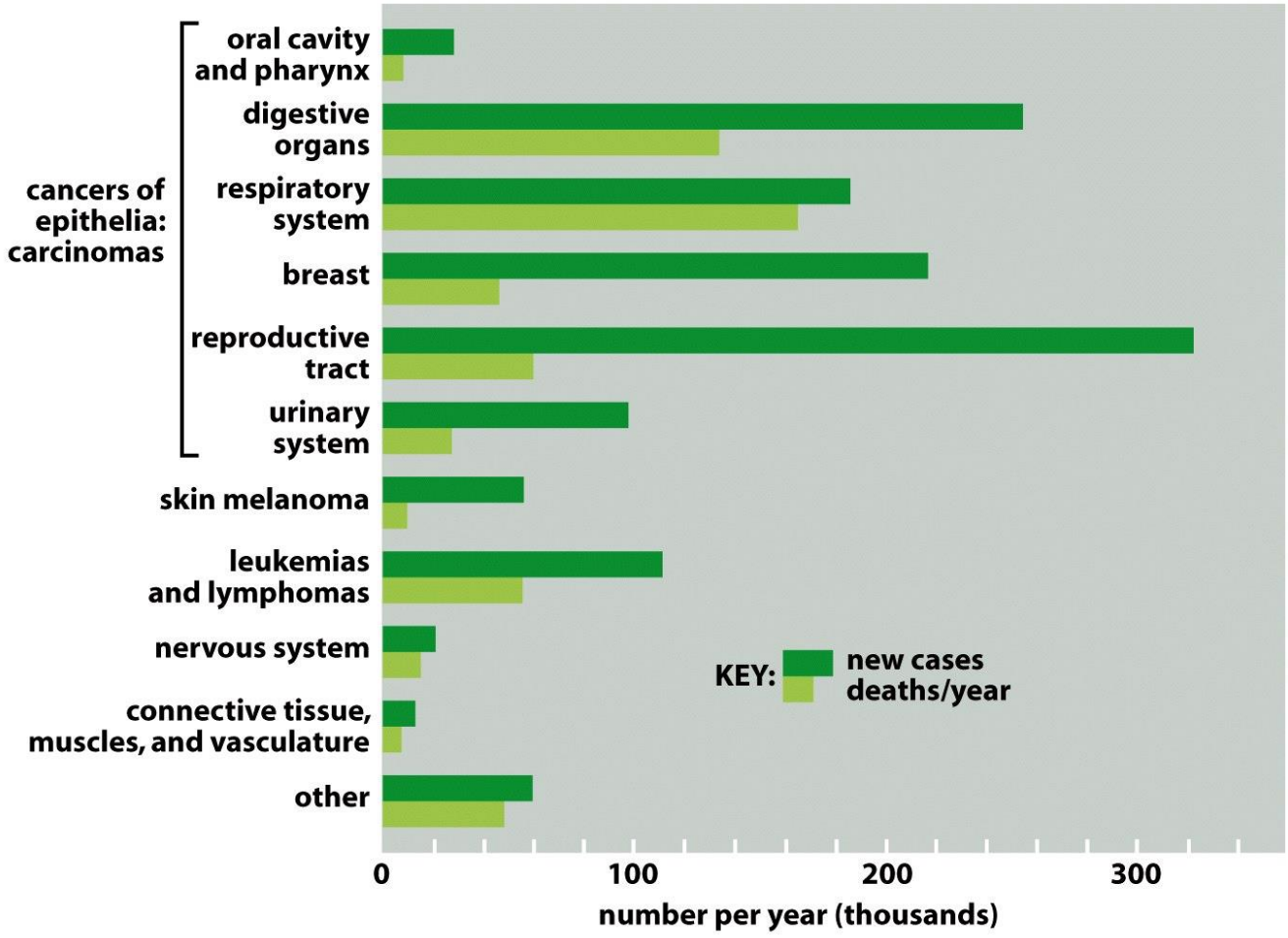
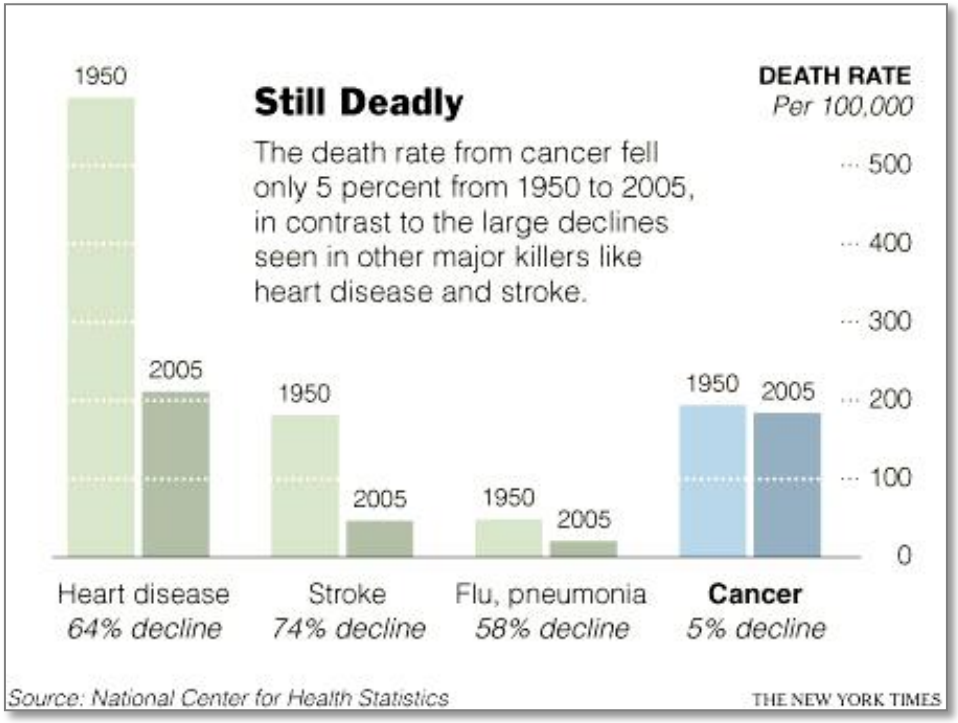


Figure 20-1 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

The War on Cancer

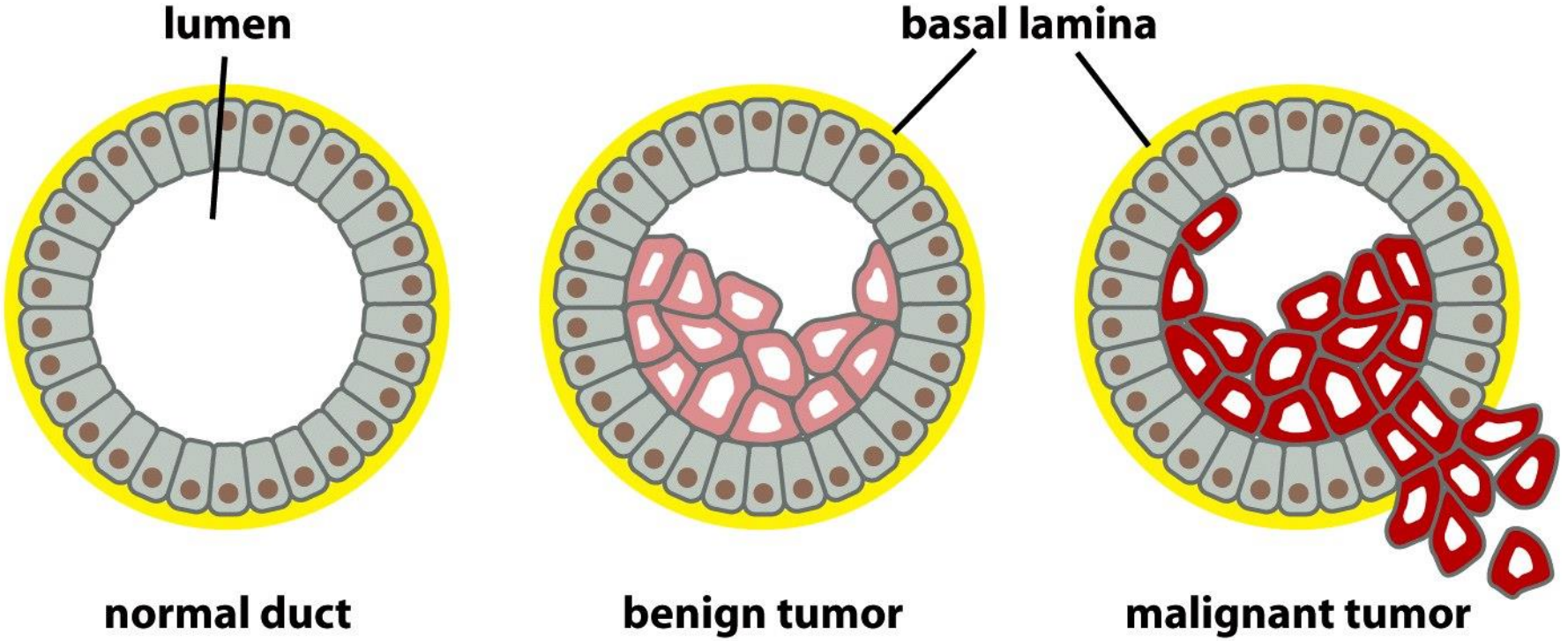
- **Richard N. Nixon:**
  - announced in 1971 that cancer would be cured by 1976
- **Barack Obama:**
  - increased federal money for cancer research by a third as part of stimulus package
- **NCI:**
  - 4,000 employees
  - $105 billion spent since 1971
- **New (costly) therapies:**
  - Up to $10,000 per month



New York Times, 2009 Science Series: Forty Years' War

Cancer

Benign vs malignant tumor



Cancers arise from carcinogenesis: can be due to chemical carcinogen or radiation

Figure 20-3 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Carcinogen exposure

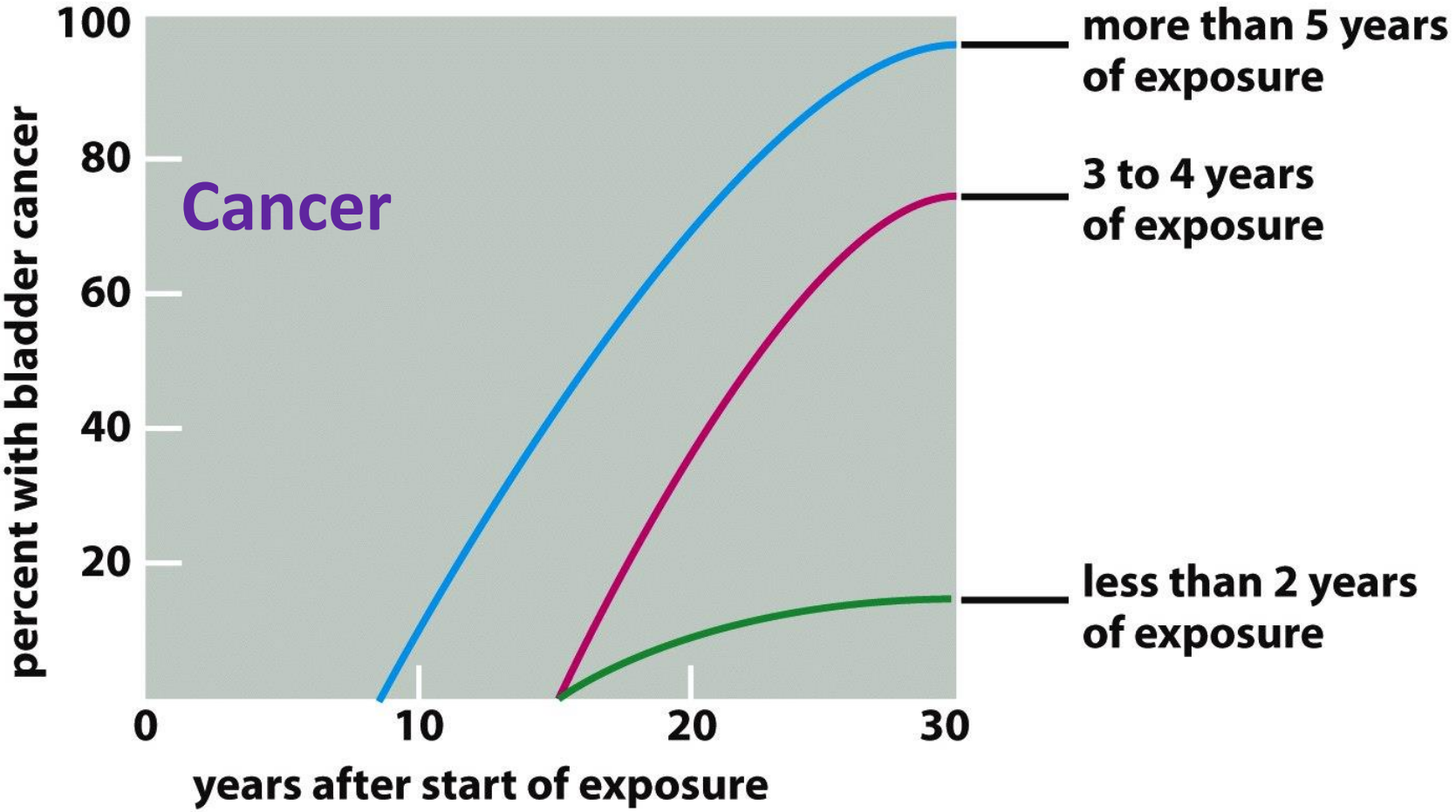
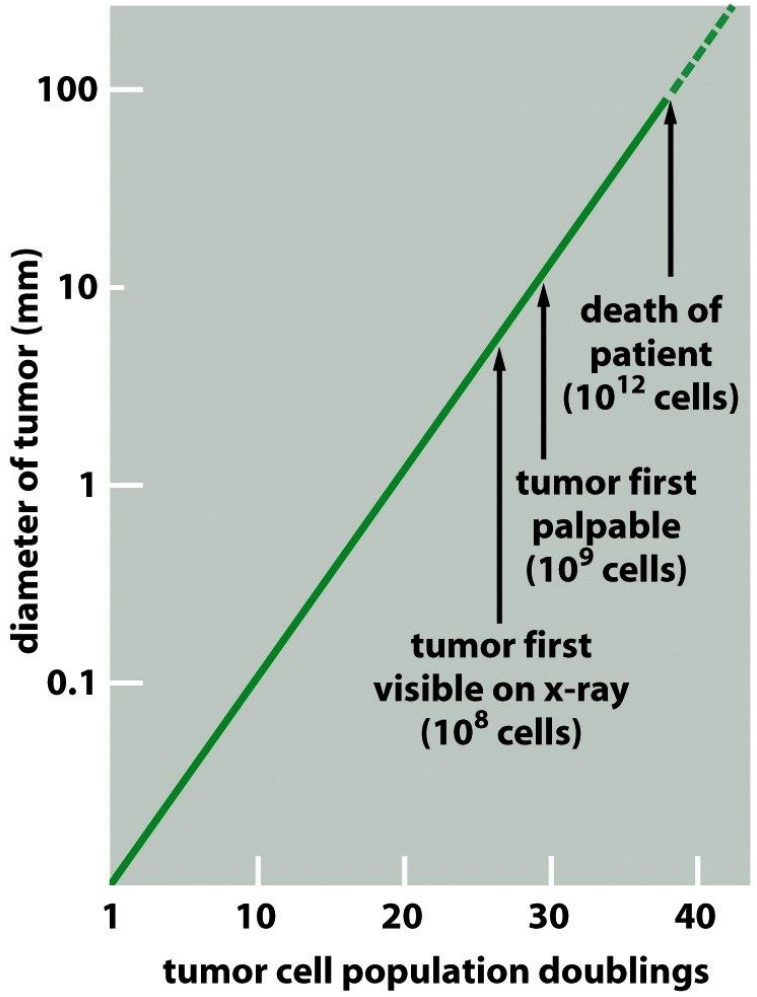


Figure 20-8 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Cancer statistics



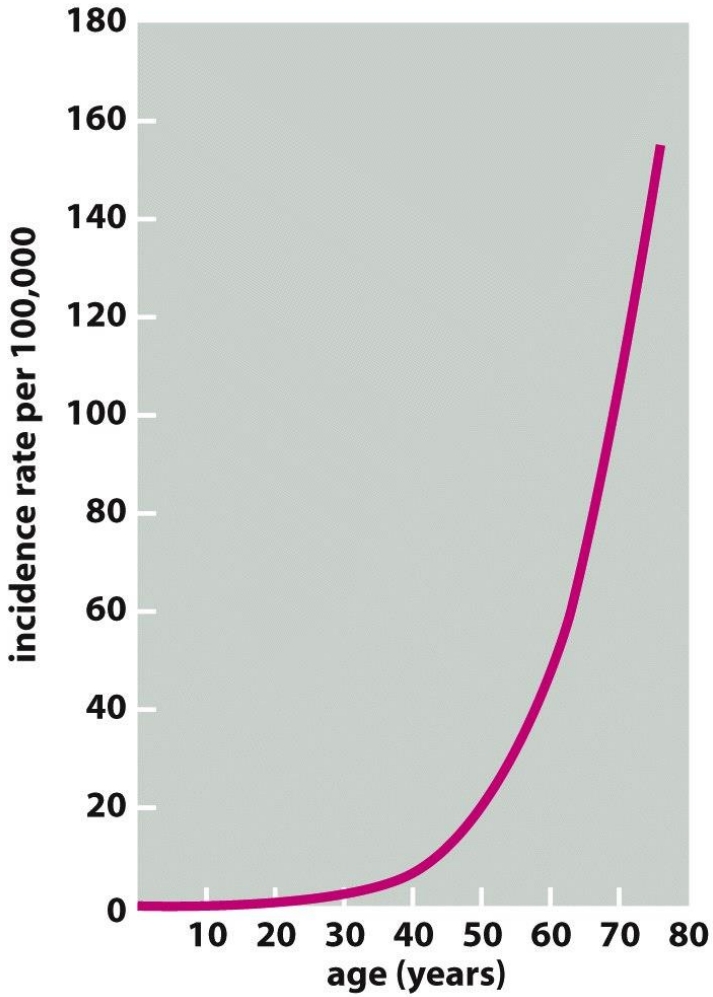


Figure 20-4 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Cancer has monoclonal origin

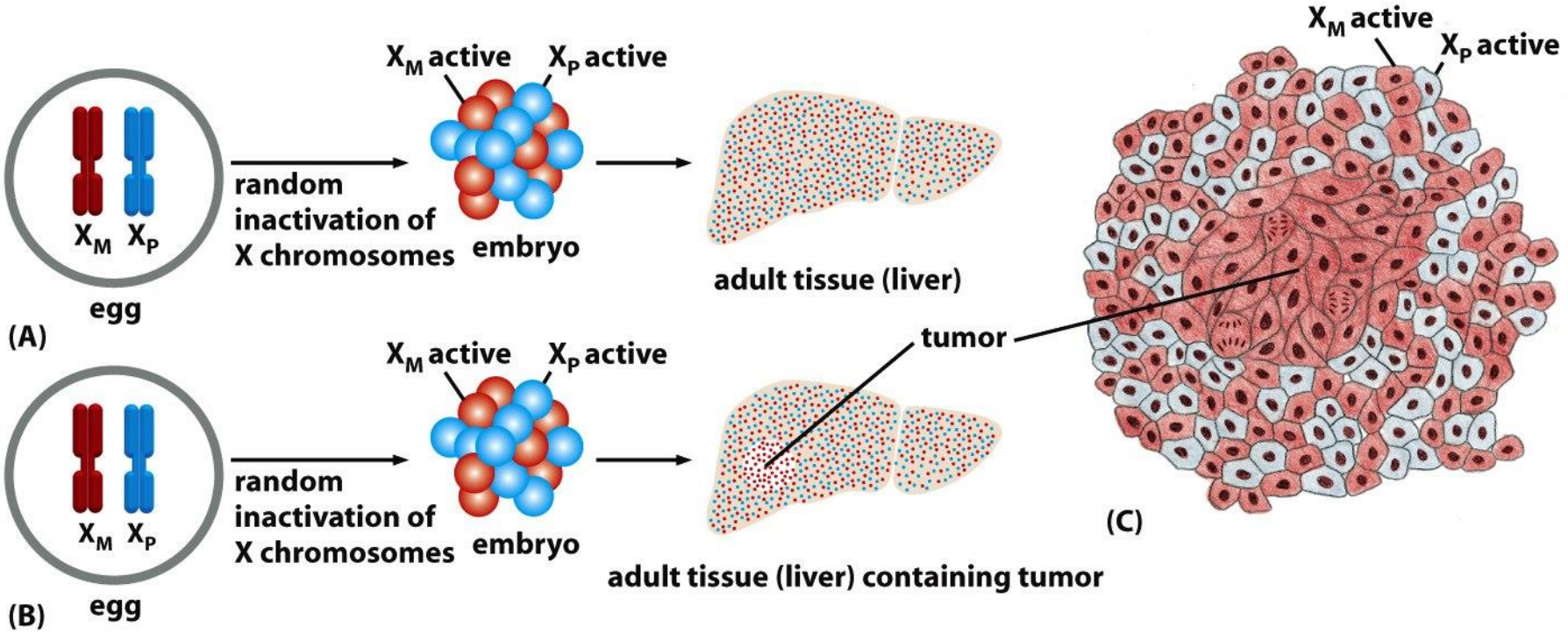


Figure 20-6 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer
Early detection is key!

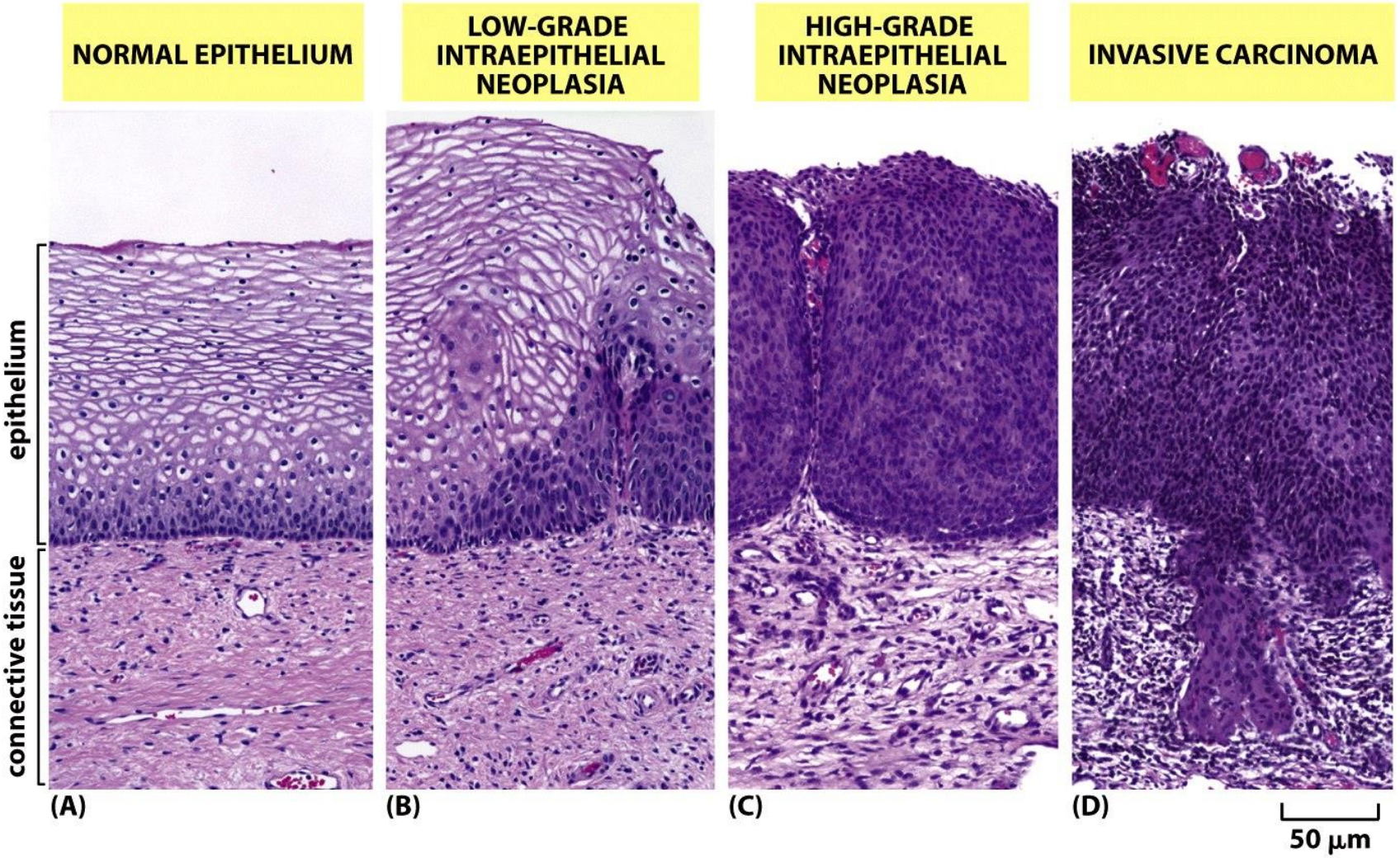


Figure 20-9 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Early detection is key: pap smear

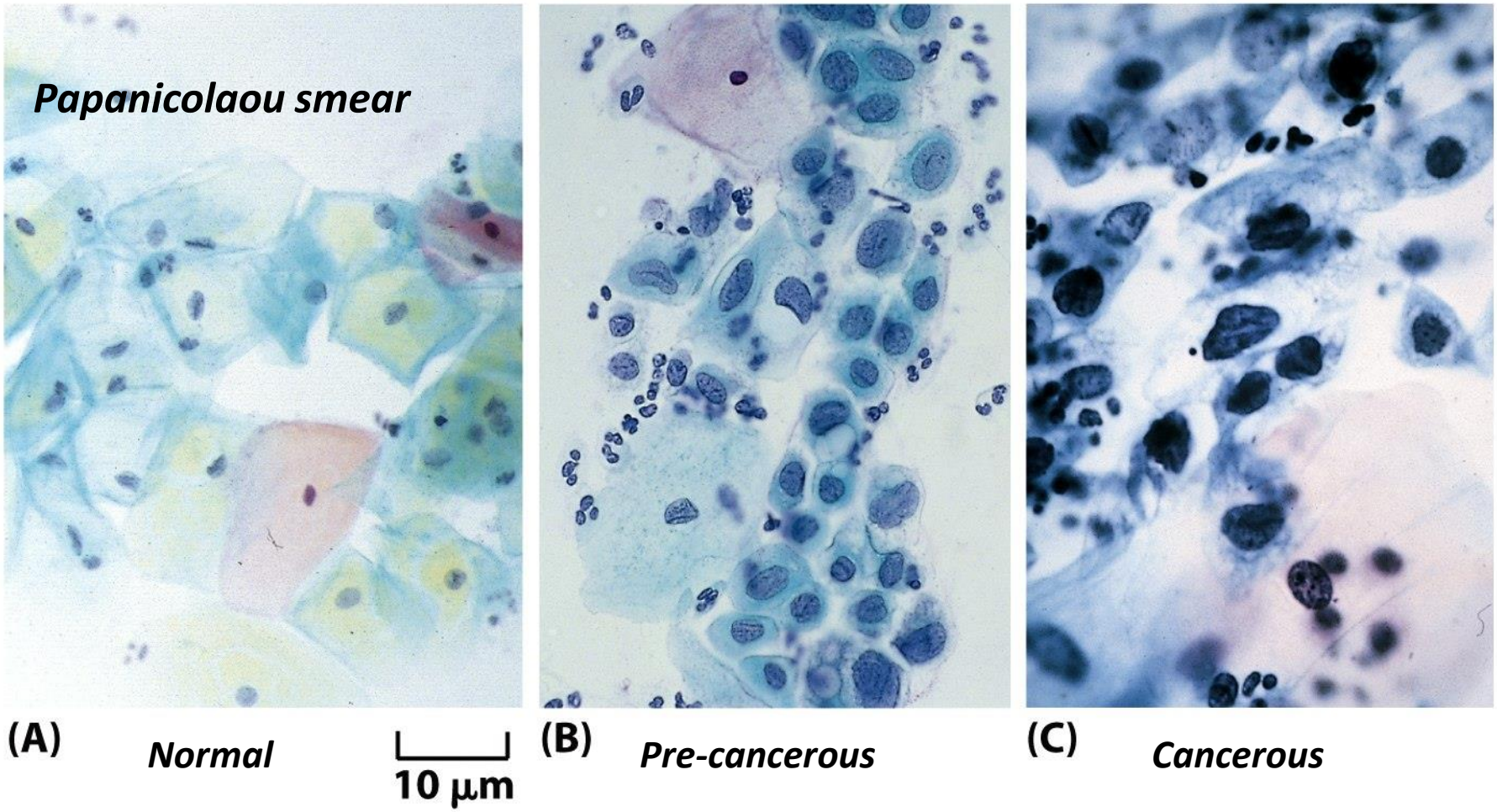


Figure 20-10 *Molecula* 2008)

MINES Saint-Étienne

Cancer

More than one mutation

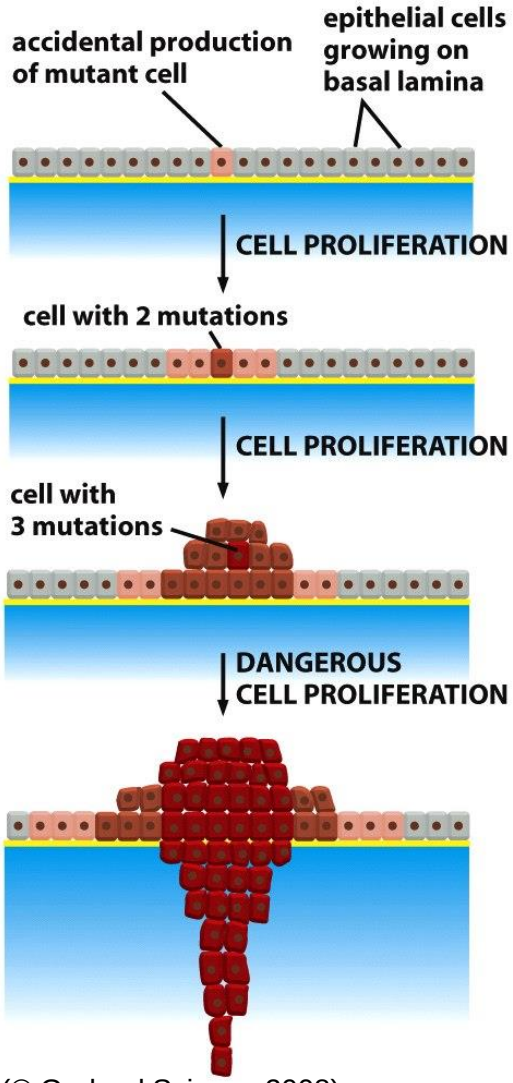


Figure 20-11 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Genetics vs epigenetics

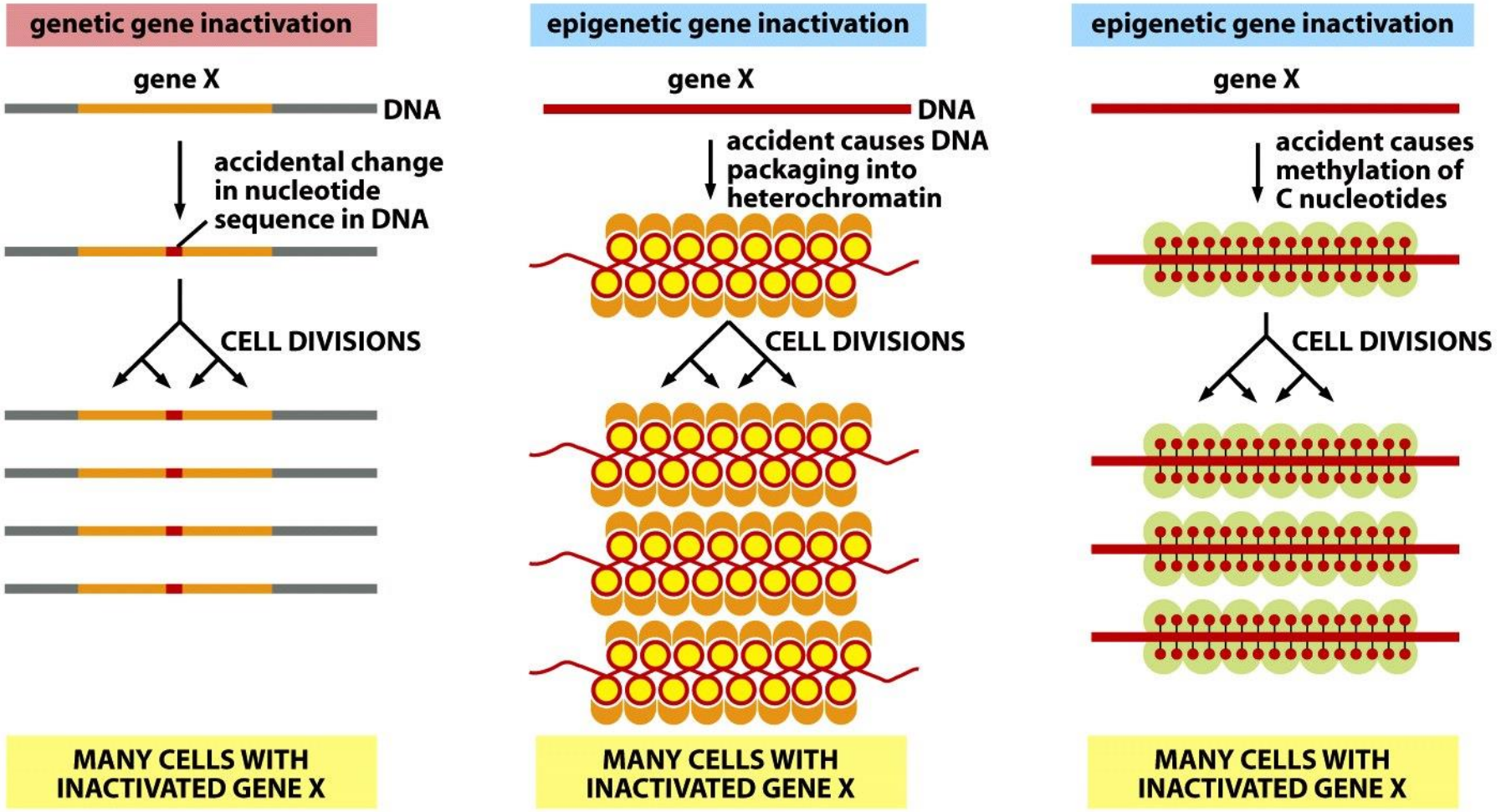


Figure 20-12 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Balance between increased cell division and decreased apoptosis

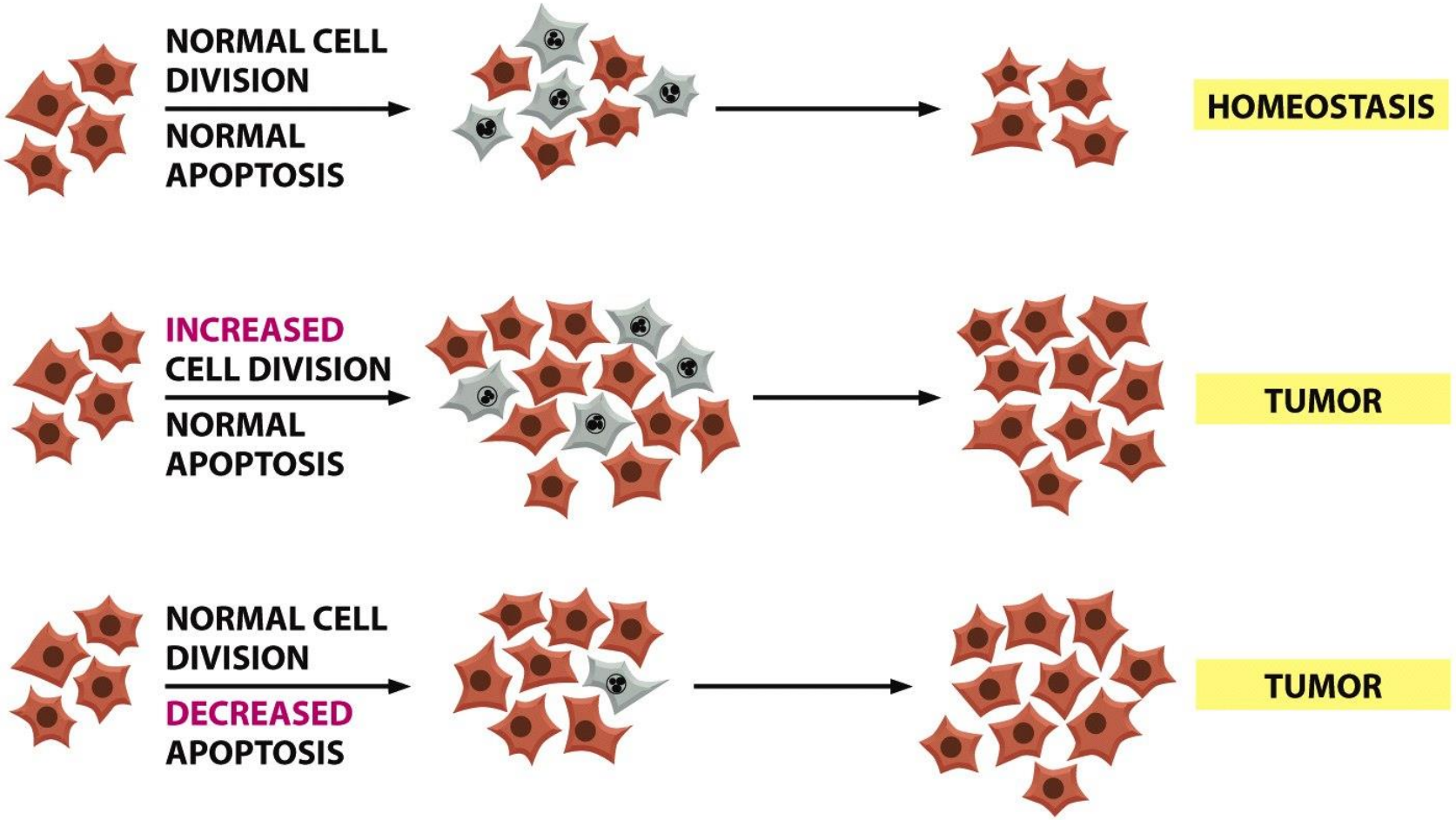


Figure 20-14 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

By analogy with automobiles, defects in cancer-critical genes have been likened to broken brakes and stuck accelerators which are caused in some cases through faulty service by bad mechanics. Using this analogy decide how the cell cycle, programmed cell death and DNA maintenance genes relate to broken brakes, stuck accelerators and bad mechanics. Explain the basis for your choices.

Cancer

Metastasis

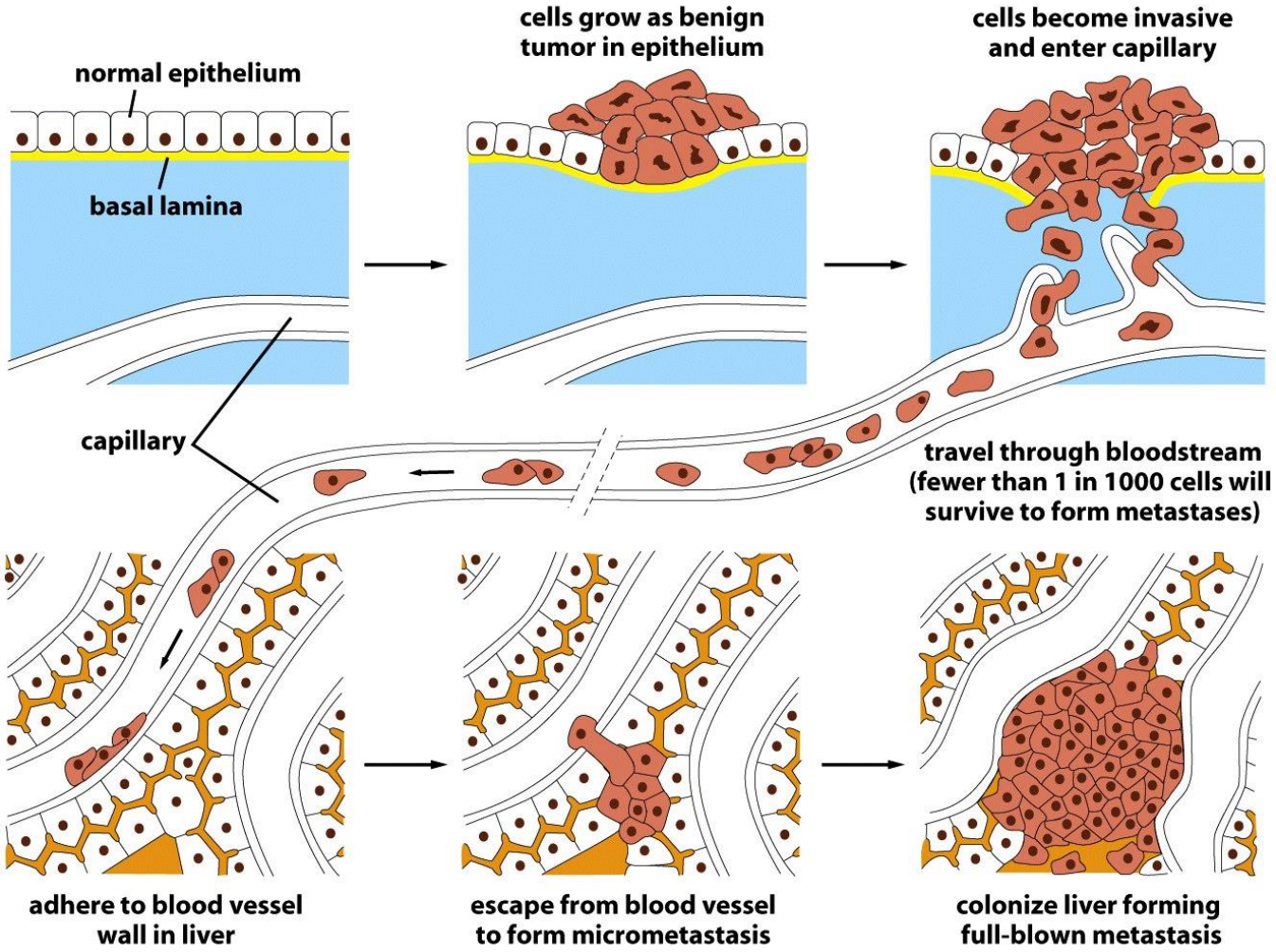


Figure 20-17 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Metastasis

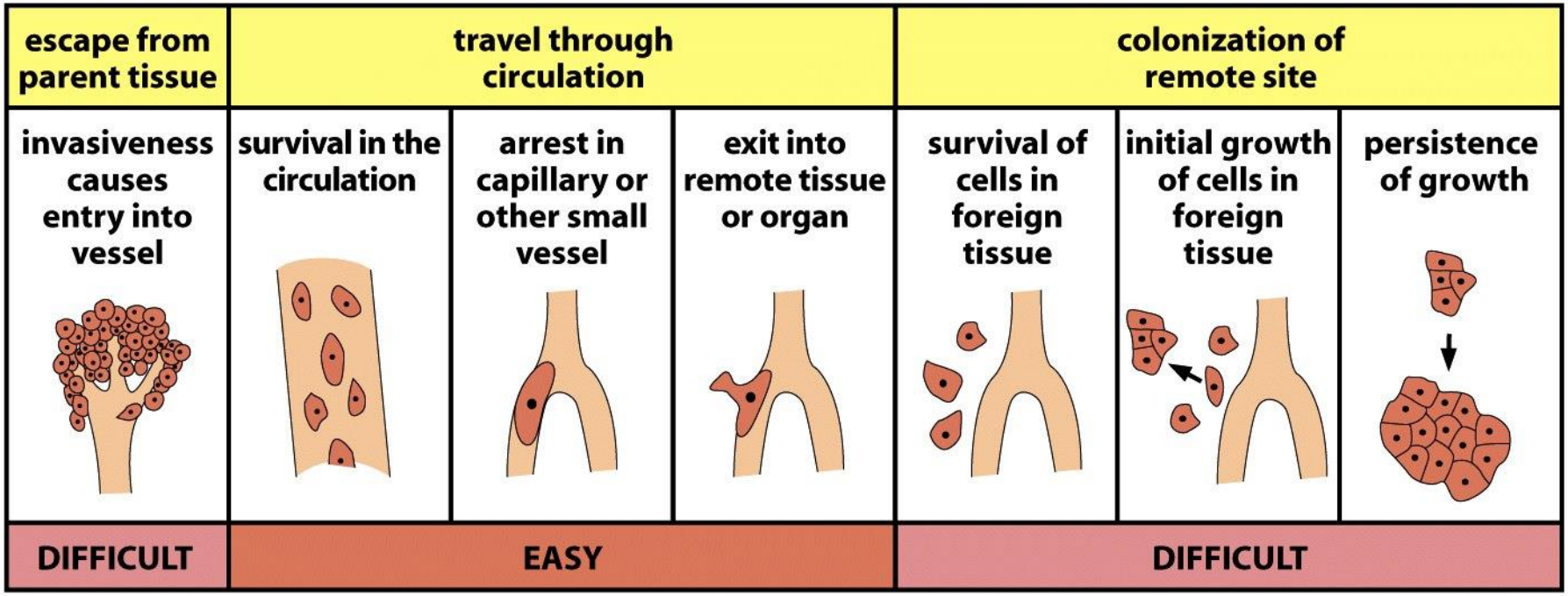


Figure 20-44 *Molecular Biology of the Cell* (© Garland Science 2008)

Colon adenocarcinoma metastasis in lung

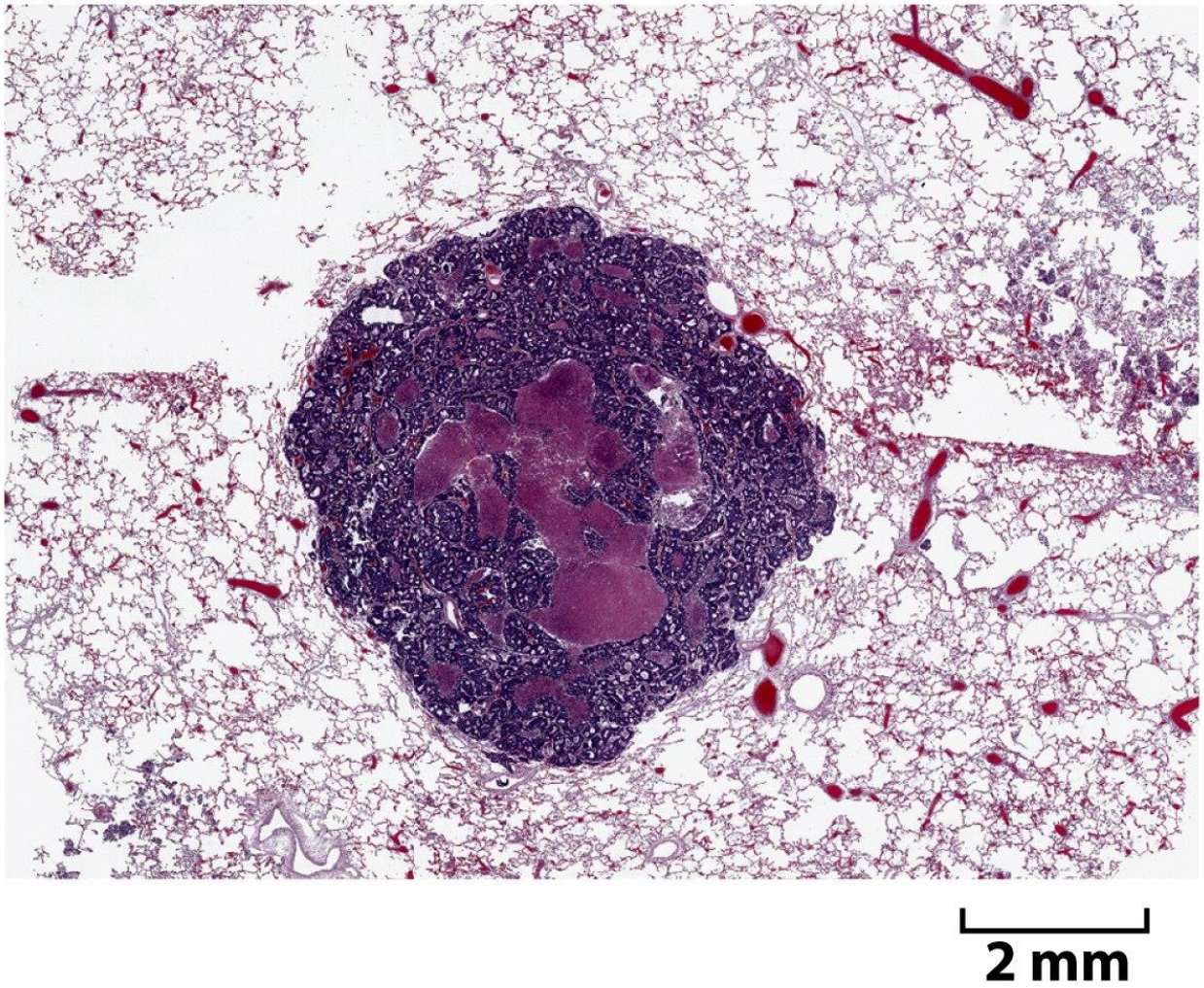
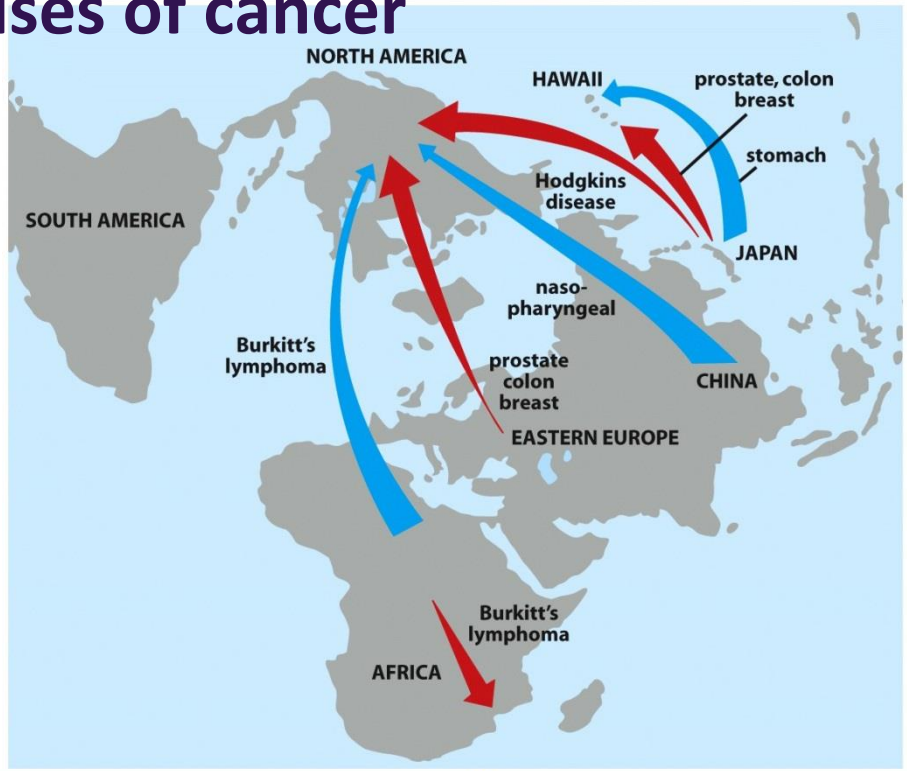


Figure 20-18 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Preventable causes of cancer

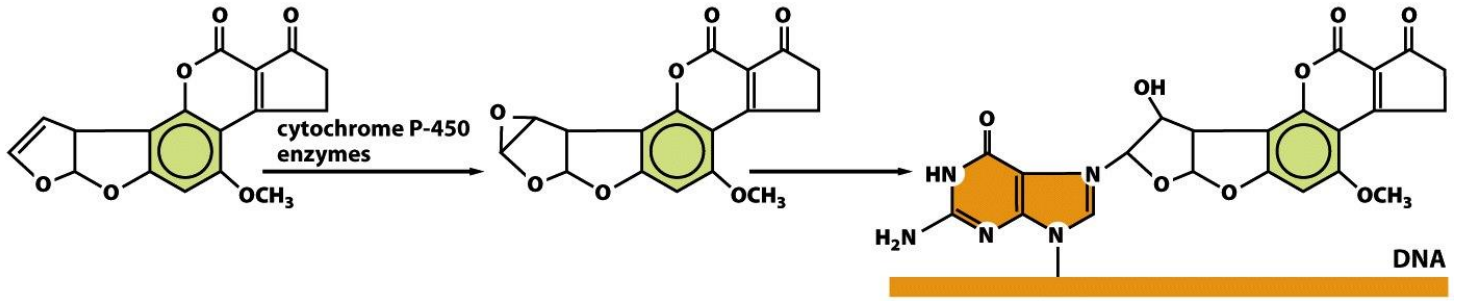


environmental and lifestyle factors	cancer	% total cases
• occupational exposure	various types	1–2
• tobacco related	lung, kidney, bladder	24
• diet: low in vegetables, high salt, high nitrate	stomach, esophagus	5
• diet: high fat, low fiber, fried and broiled foods	bowel, pancreas, prostate, breast	37
• tobacco and alcohol	mouth, throat	2

Figure 20-20a *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Known carcinogens



(A) AFLATOXIN AFLATOXIN-2,3-EPOXIDE CARCINOGEN BOUND TO GUANINE IN DNA

- **VINYL CHLORIDE:**
  liver angiosarcoma
- **BENZENE:**
  acute leukemias
- **ARSENIC:**
  skin carcinomas, bladder cancer
- **ASBESTOS:**
  mesothelioma
- **RADIUM:**
  osteosarcoma

(B)

Figure 20-22 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer
Tumor initiators vs promoters

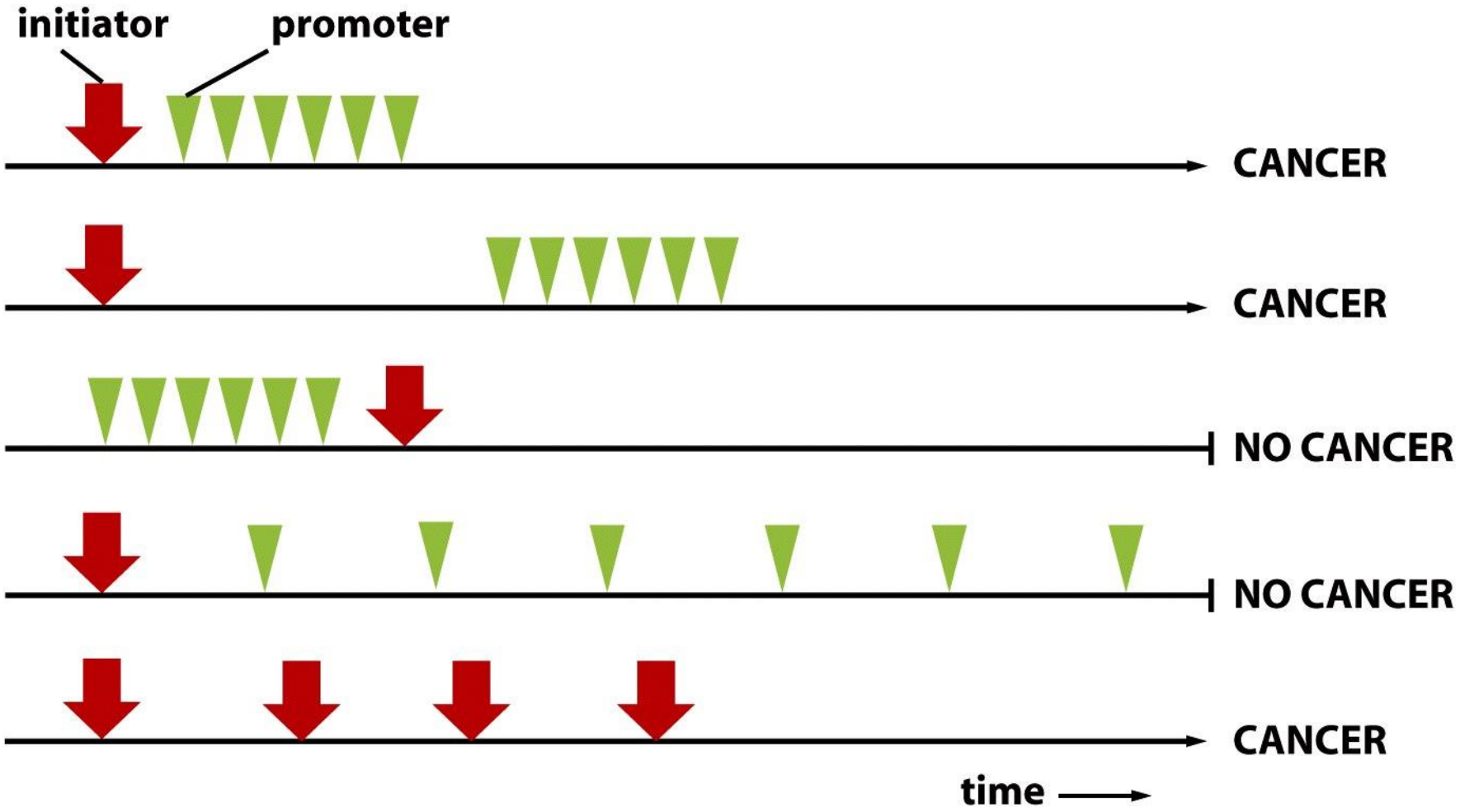


Figure 20-23 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer
Tumor initiators vs promoters

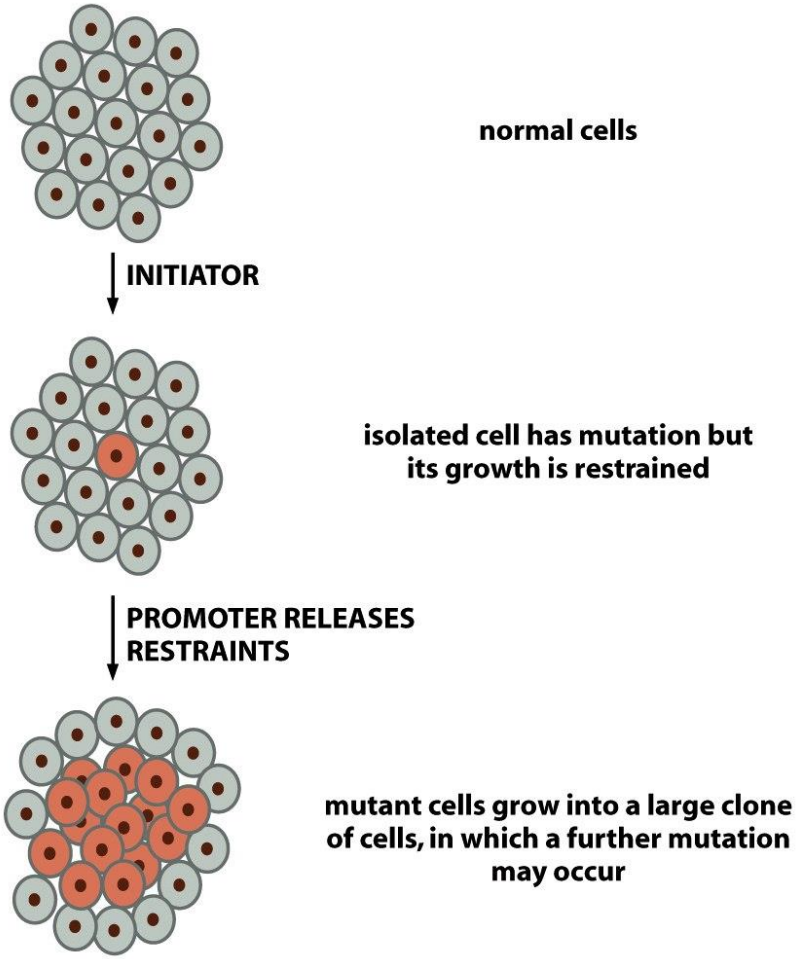


Figure 20-24 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Tumor initiators: viruses

Table 20–1 Viruses Associated with Human Cancers

VIRUS	ASSOCIATED CANCER	AREAS OF HIGH INCIDENCE
DNA viruses		
Papovavirus family		
Papillomavirus (many distinct strains)	warts (benign) carcinoma of the uterine cervix	worldwide worldwide
Hepadnavirus family		
Hepatitis-B virus	liver cancer (hepatocellular carcinoma)	Southeast Asia, tropical Africa
Hepatitis-C virus	liver cancer (hepatocellular carcinoma)	worldwide
Herpesvirus family		
Epstein–Barr virus	Burkitt's lymphoma (cancer of B lymphocytes) nasopharyngeal carcinoma	West Africa, Papua New Guinea Southern China, Greenland
RNA viruses		
Retrovirus family		
Human T-cell leukemia virus type I (HTLV-1)	adult T-cell leukemia/ lymphoma	Japan, West Indies
Human immuno-deficiency virus (HIV, the AIDS virus)	Kaposi's sarcoma	Central and Southern Africa

For all these viruses, the number of people infected is much larger than the numbers who develop cancer: the viruses must act in conjunction with other factors. Moreover, some of the viruses contribute to cancer only indirectly; HIV, for example, destroys helper T lymphocytes, which allows a herpes virus to transform endothelial cells. Similarly, hepatitis-C virus causes chronic hepatitis, which promotes the development of liver cancer.

Table 20-1 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Other tumor initiators

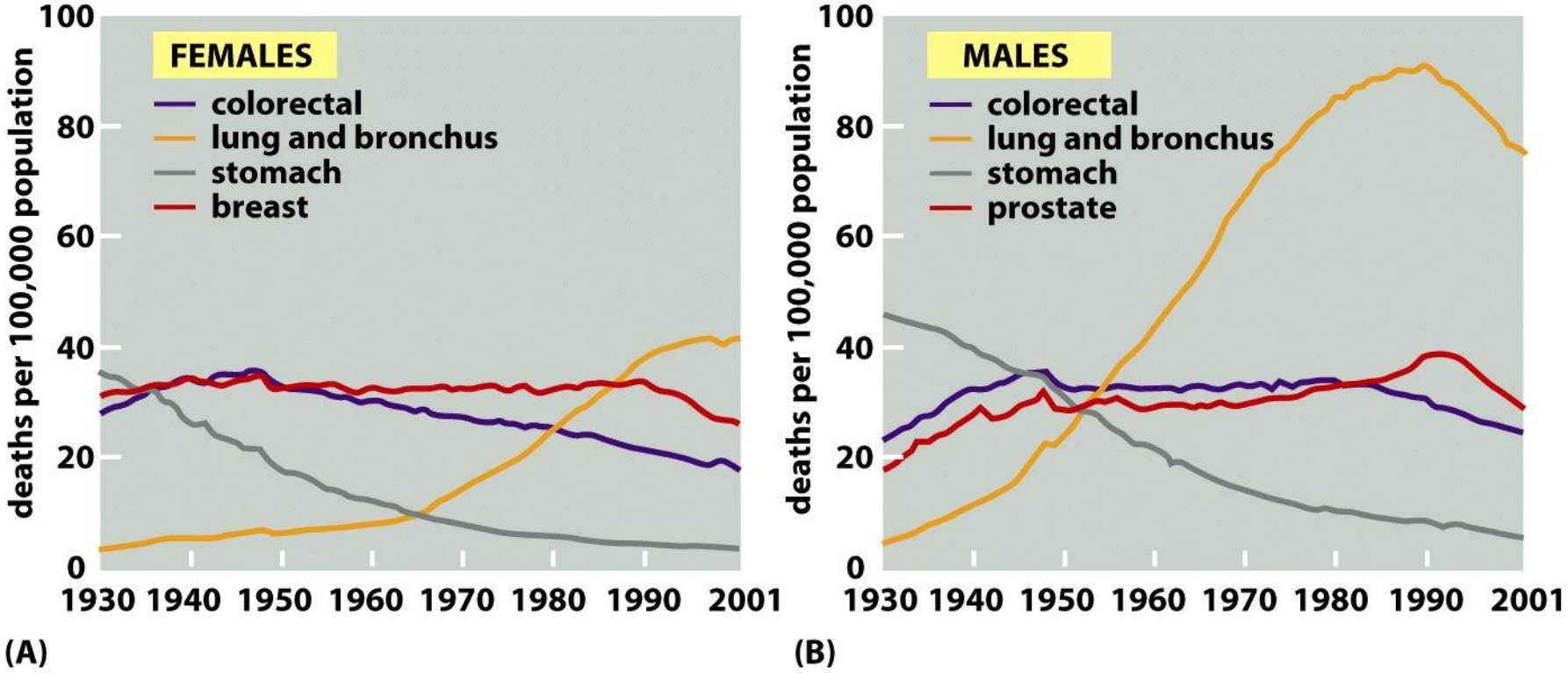


Figure 20-25 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Other tumor initiators

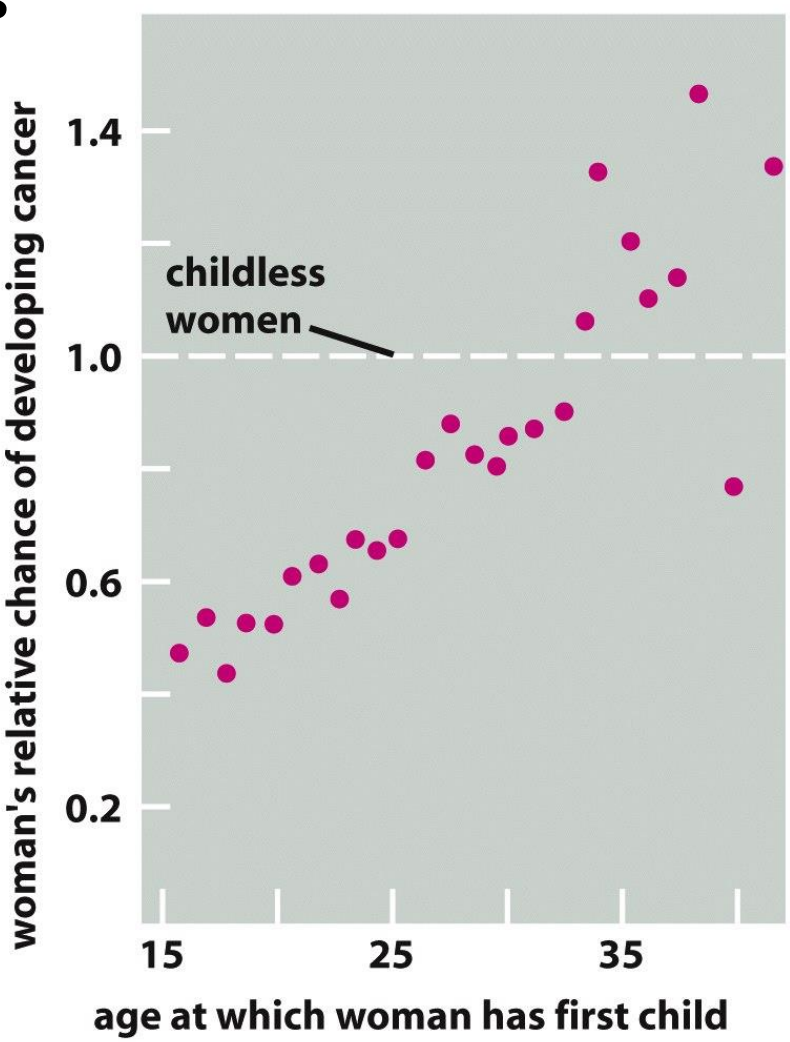


Figure 20-26 *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Other tumor initiators

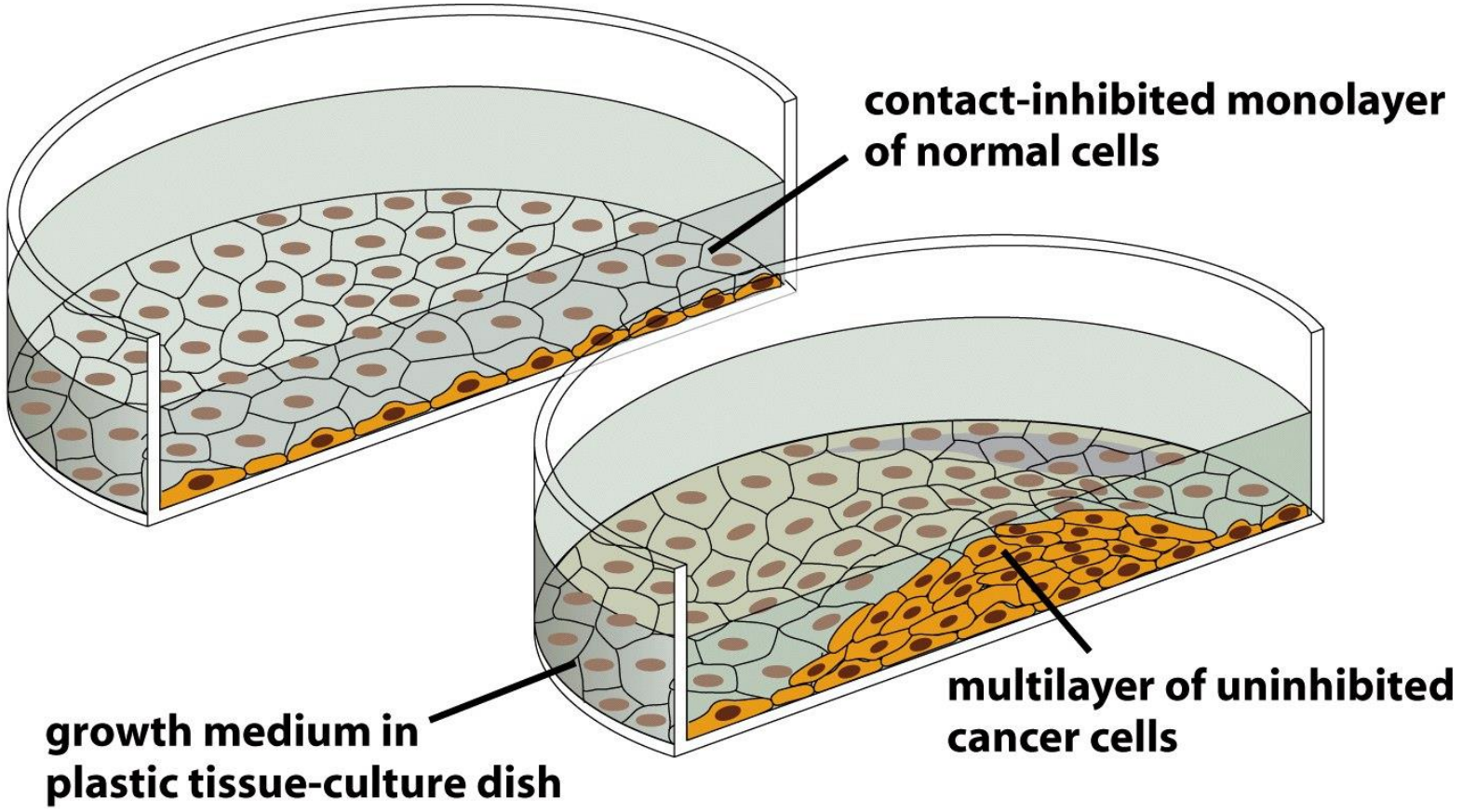


Figure 20-29 *Molecular Biology of the Cell* (© Garland Science 2008)

Movie on wound healing assay 23.9

Cancer

Tumor profiling

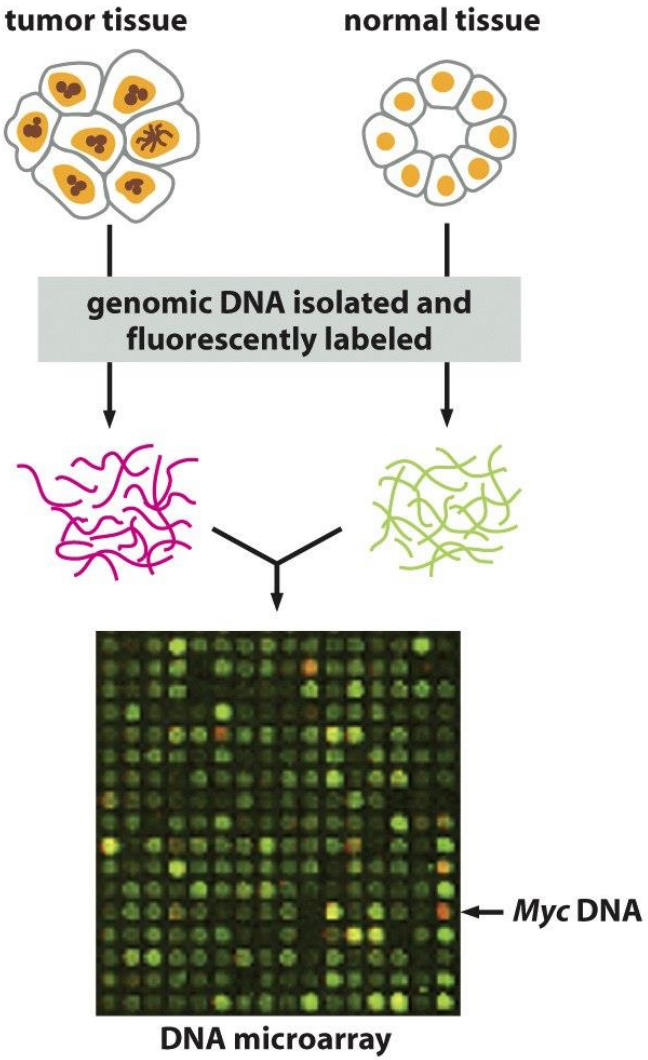


Figure 20-35a *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

Tumor profiling

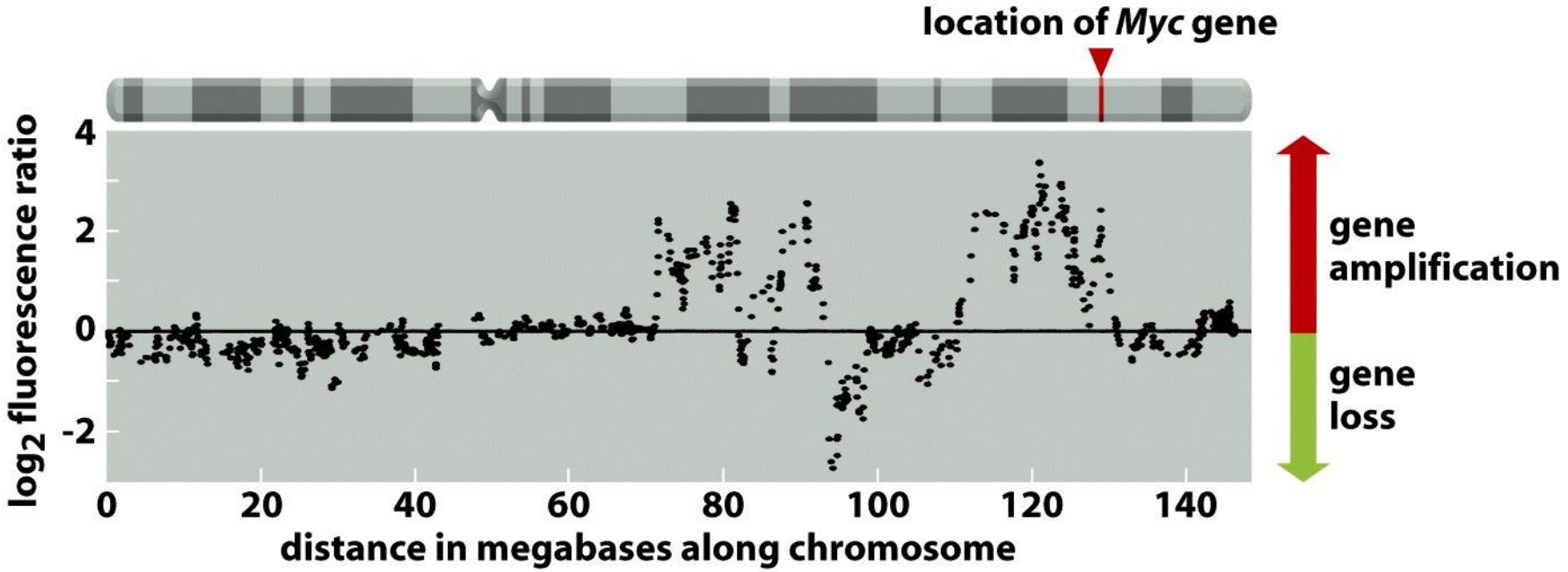


Figure 20-35b *Molecular Biology of the Cell* (© Garland Science 2008)

Cancer

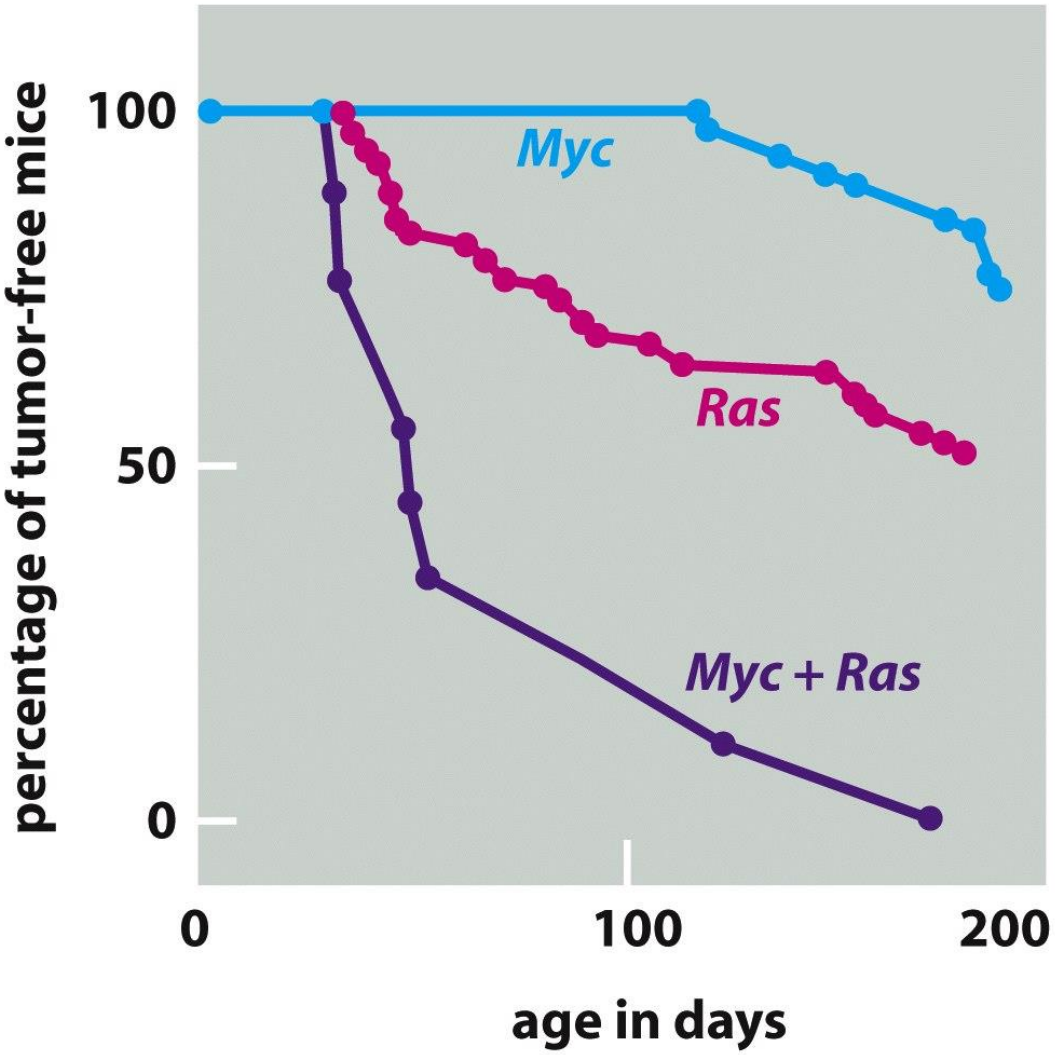


Figure 20-36 *Molecular Biology of the Cell* (© Garland Science 2008)

Major signaling pathways in cancer

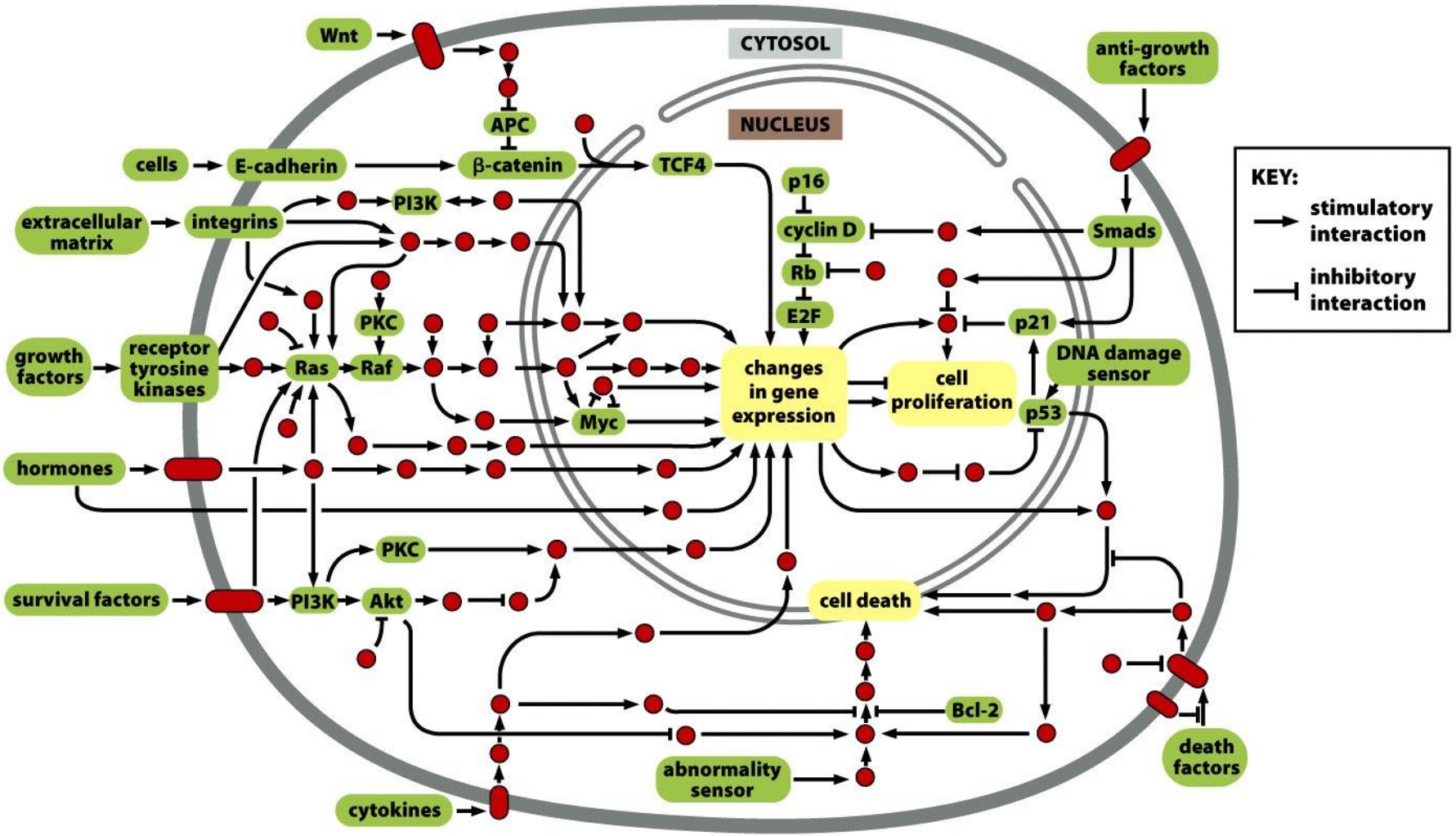


Figure 20-37 *Molecular Biology of the Cell* (© Garland Science 2008)

Multiple cues needed for cell proliferation

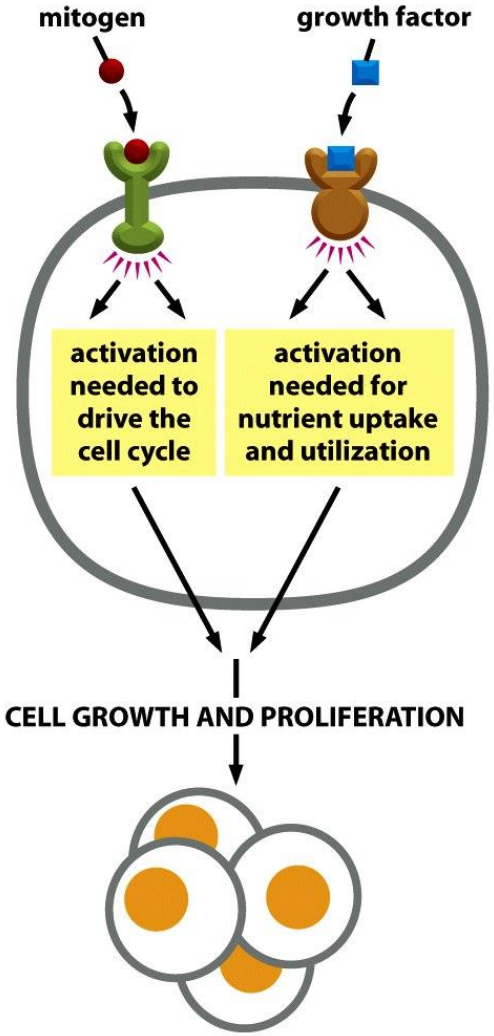


Figure 20-39a *Molecular Biology of the Cell* (© Garland Science 2008)

Multiple cues needed for cell proliferation

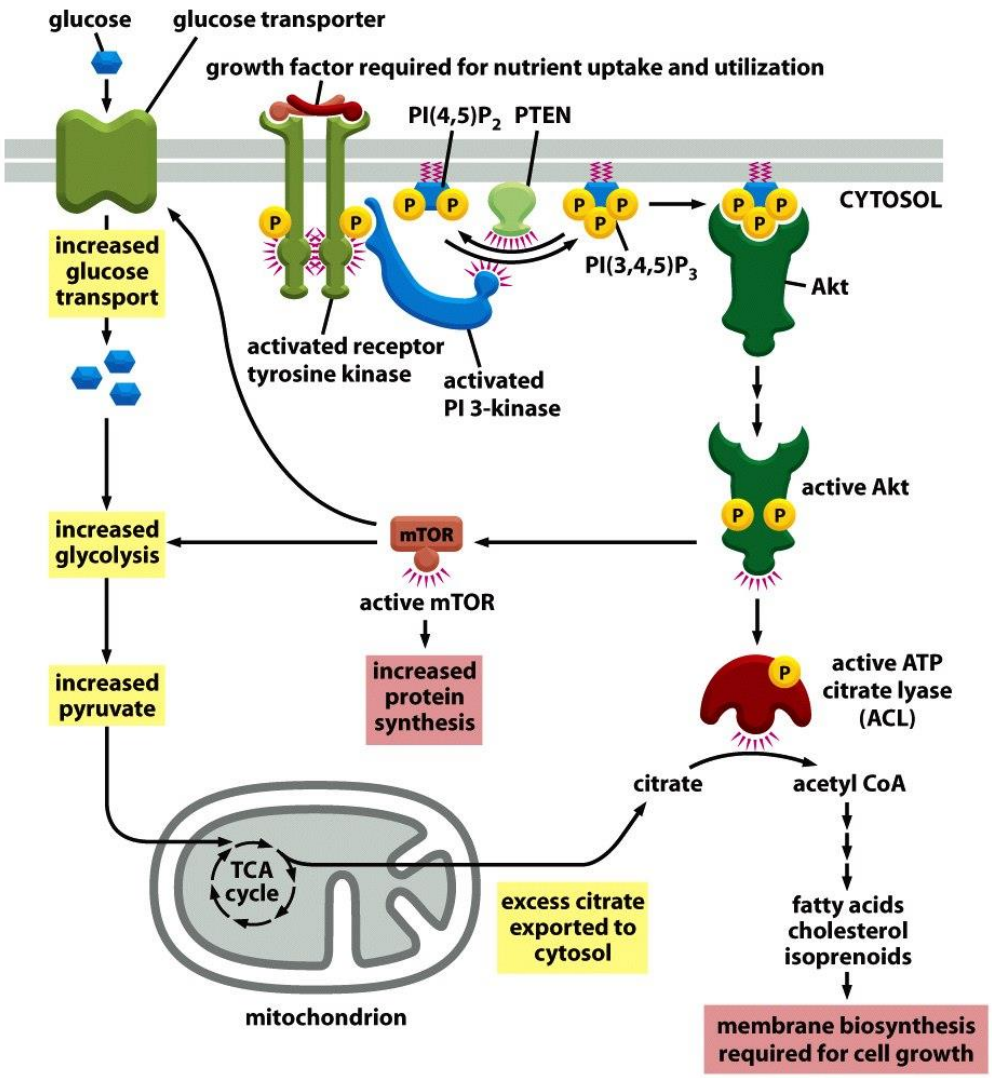


Figure 20-39b *Molecular Biology of the Cell* (© Garland Science 2008)

P53 tumor suppressor

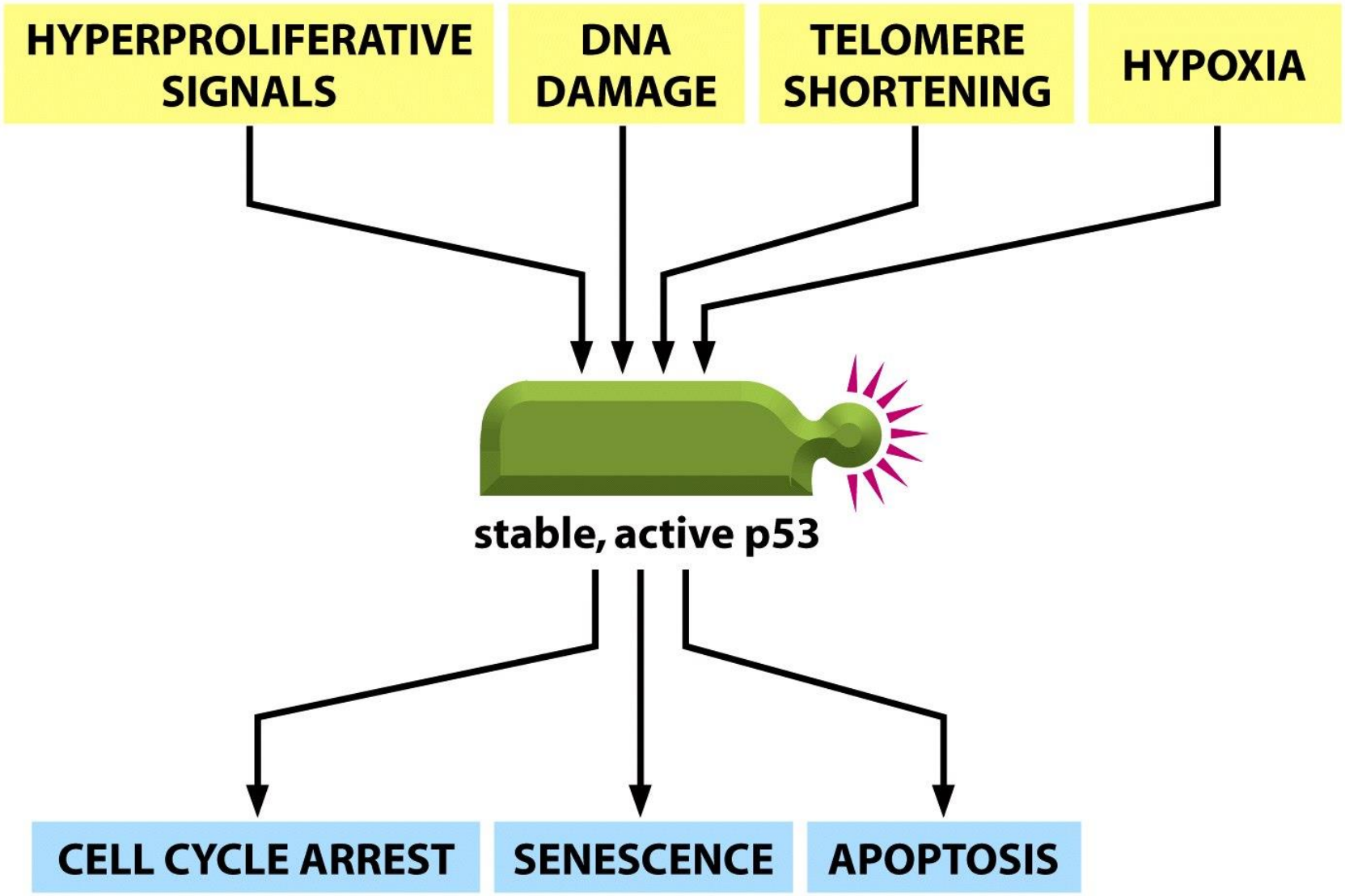


Figure 20-40 *Molecular Biology of the Cell* (© Garland Science 2008)

Virus related tumors

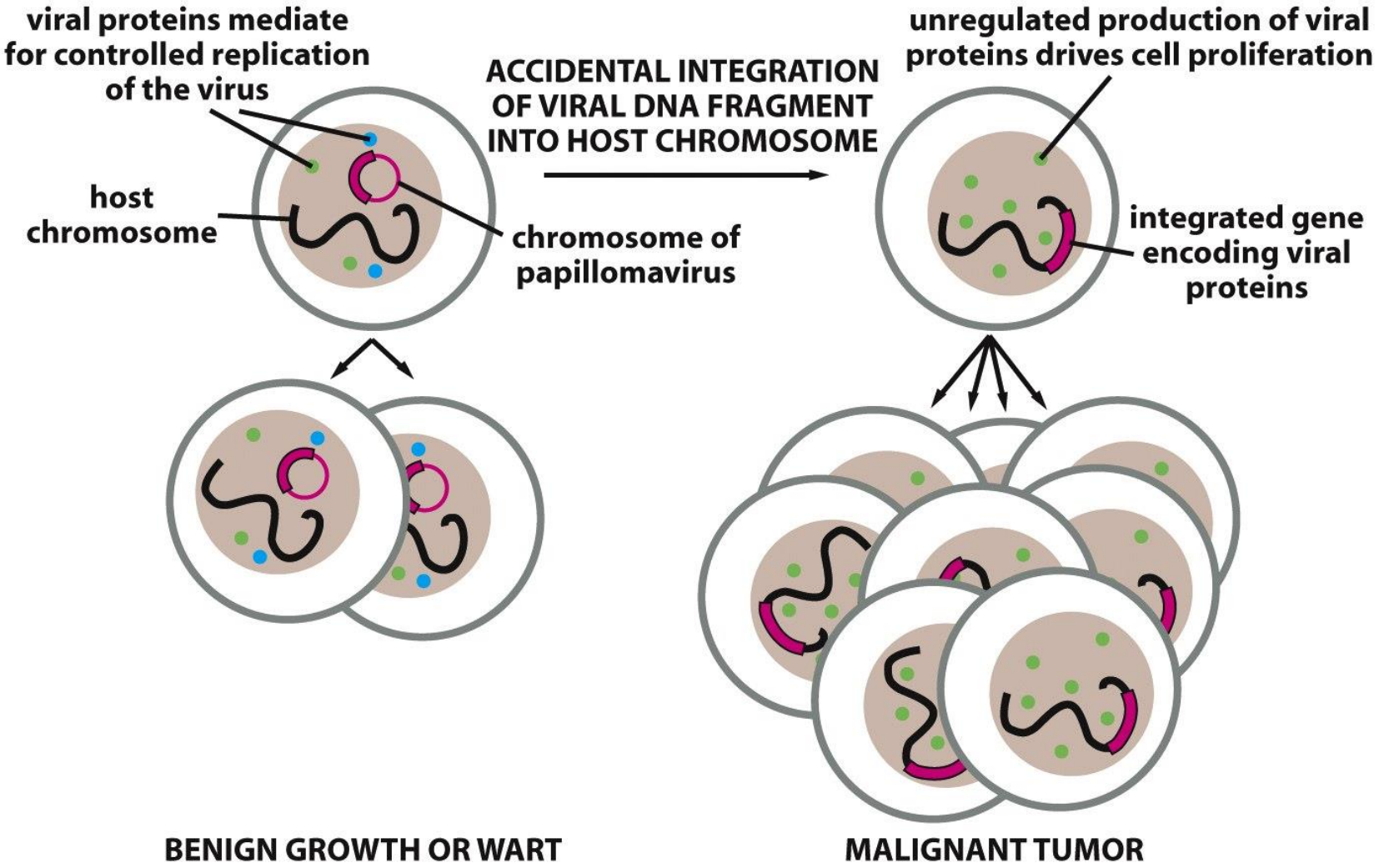


Figure 20-42 *Molecular Biology of the Cell* (© Garland Science 2008)

Colorectal tumor

Table 20–2 Some Genetic Abnormalities Detected in Colorectal Cancer Cells

GENE	CLASS	PATHWAY AFFECTED	HUMAN COLON CANCERS (%)
K-Ras	oncogene	receptor tyrosine-kinase signaling	40
β-catenin [1]	oncogene	Wnt signaling	5–10
Apc [1]	tumor suppressor	Wnt signaling	> 80
p53	tumor suppressor	response to stress and DNA damage	60
TGFβ receptor II [2]	tumor suppressor	TGFβ signaling	10
Smad4 [2]	tumor suppressor	TGFβ signaling	30
MLH1 and other DNA mismatch repair genes	tumor suppressor (genetic stability)	DNA mismatch repair	15 (often silenced by methylation)

The genes with the same superscript act in the same pathway, and therefore only one of the components is mutated in an individual cancer.

Table 20-2 *Molecular Biology of the Cell* (© Garland Science 2008)

Colorectal tumor

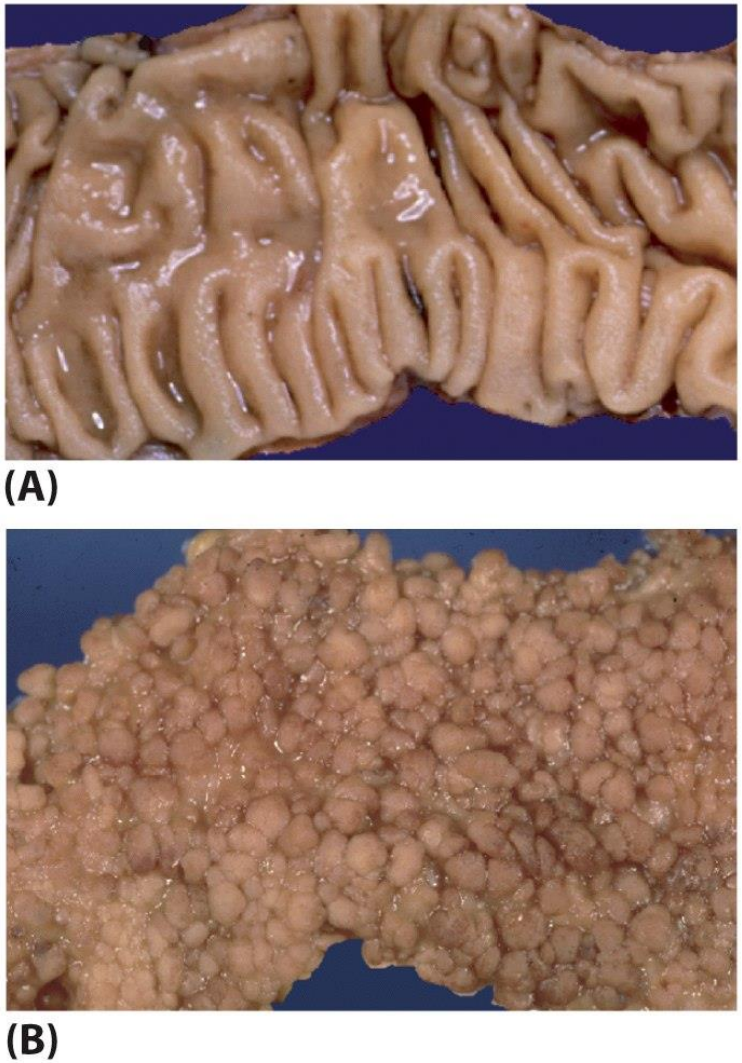


Figure 20-46 *Molecular Biology of the Cell* (© Garland Science 2008)

Progression of colorectal tumor

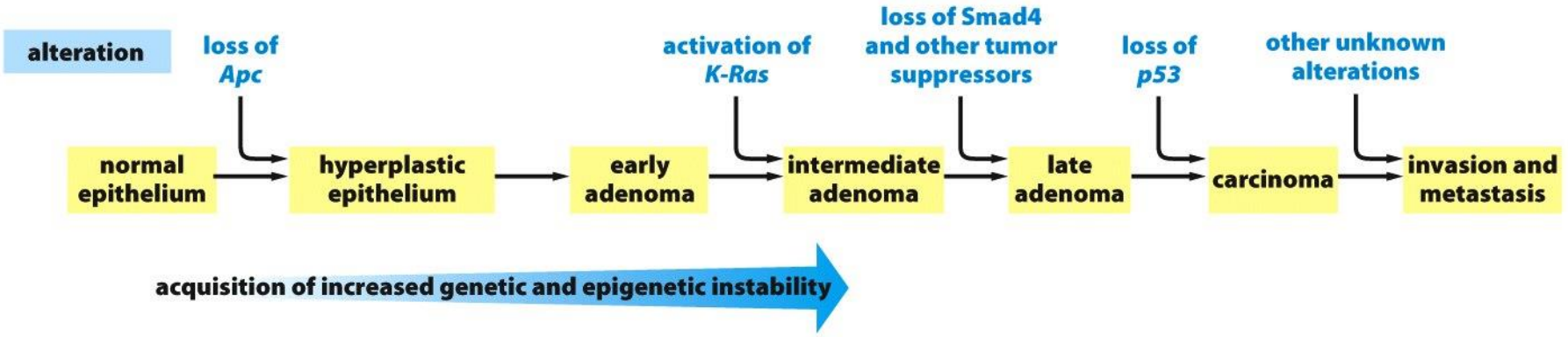
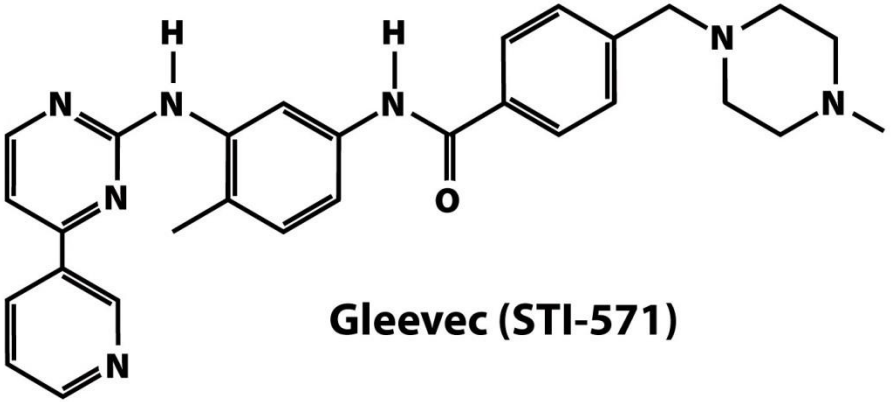


Figure 20-48 *Molecular Biology of the Cell* (© Garland Science 2008)

Anti cancer drugs



Gleevec (STI-571)

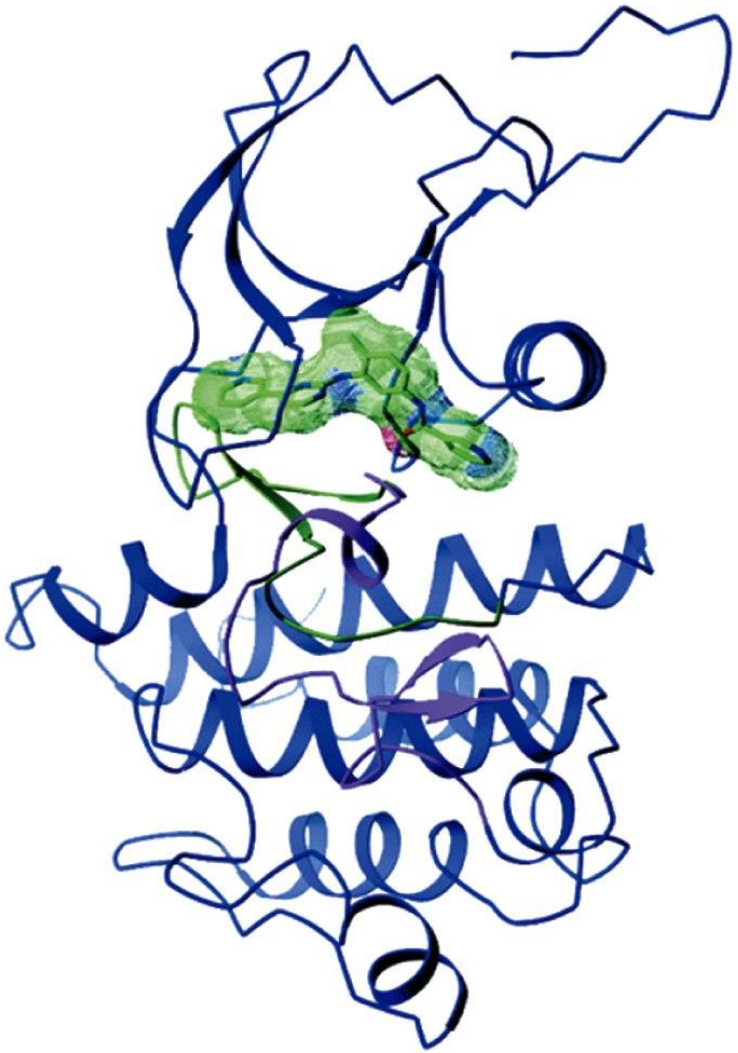


Figure 20-52b *Molecular Biology of the Cell* (© Garland Science 2008)

Anti cancer drugs

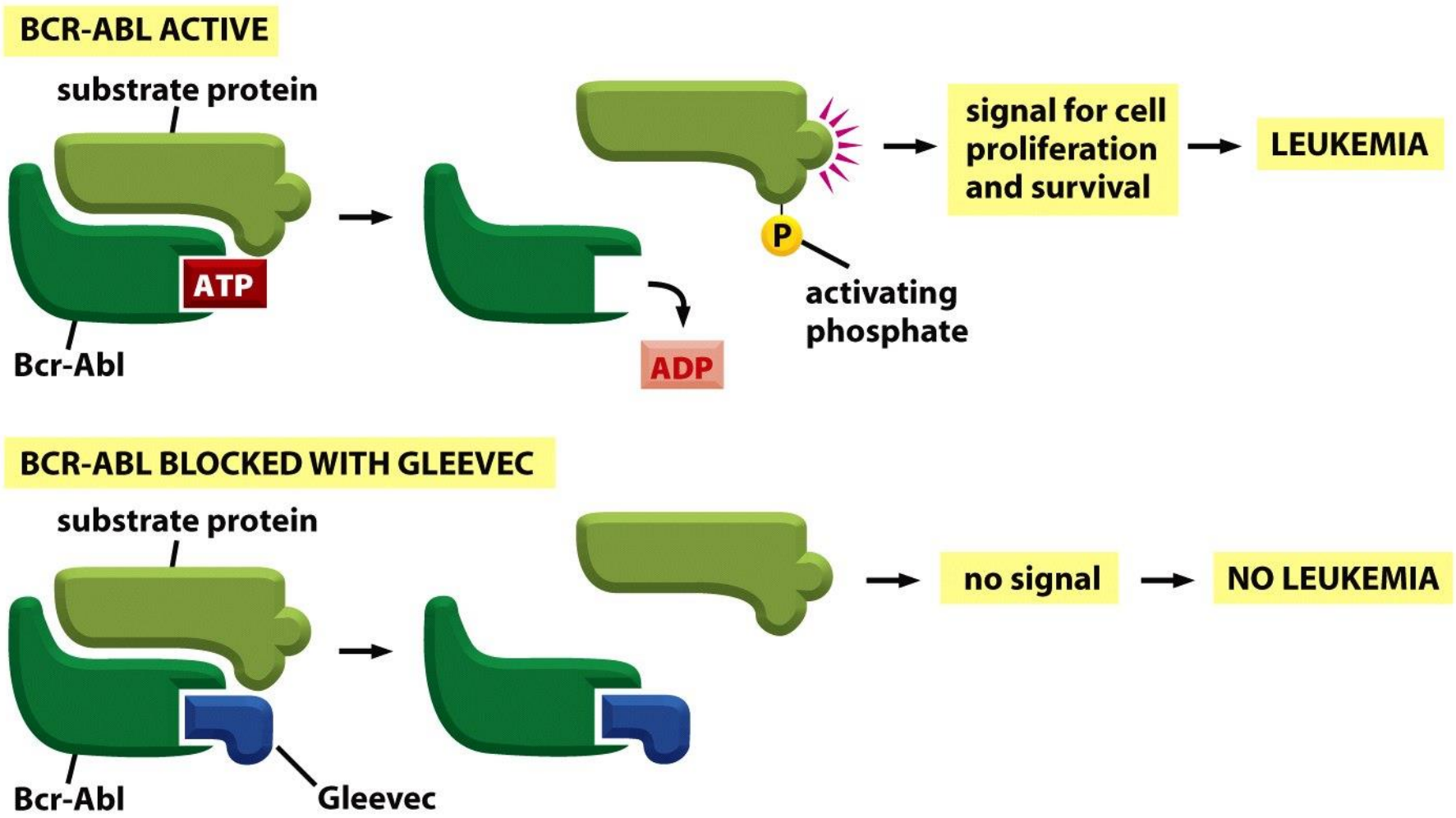


Figure 20-52c *Molecular Biology of the Cell* (© Garland Science 2008)

Multidrug treatment

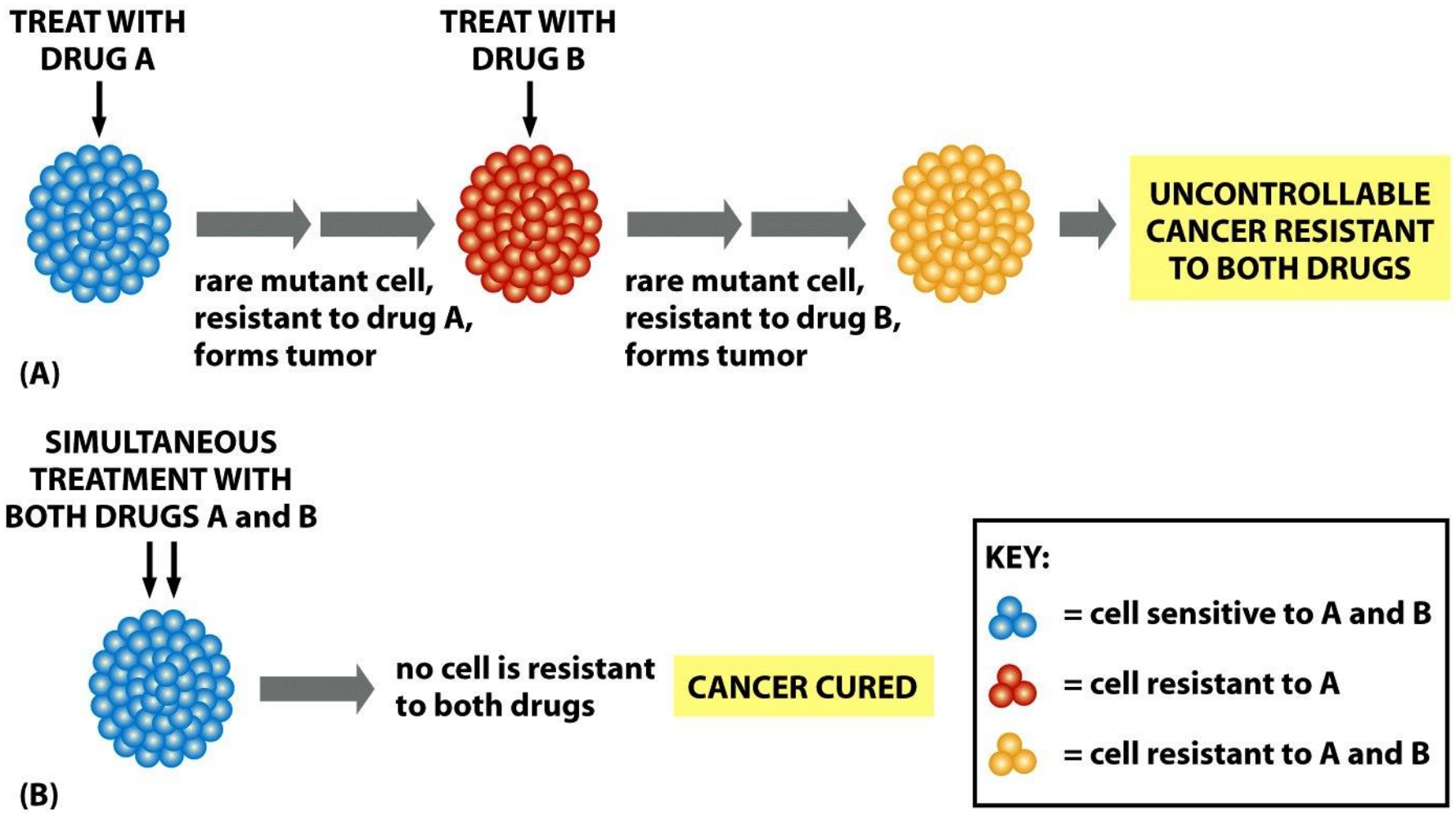
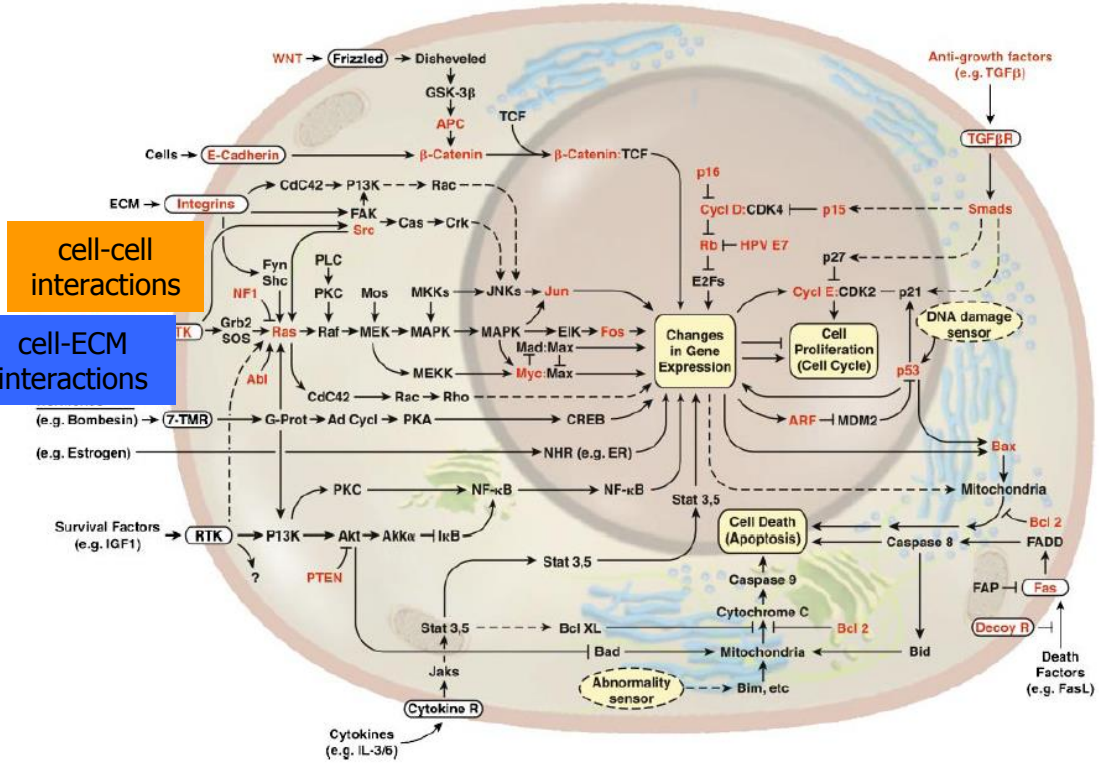


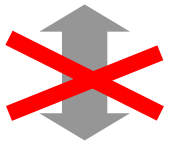
Figure 20-53 *Molecular Biology of the Cell* (© Garland Science 2008)

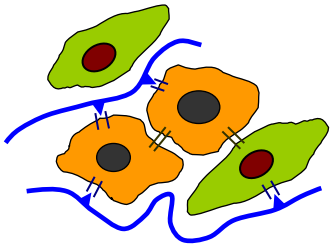
Current approaches to basic research of cancer



Hanahan, *Cell*, 2000

2-D cell culture





3-D microenvironmental signals

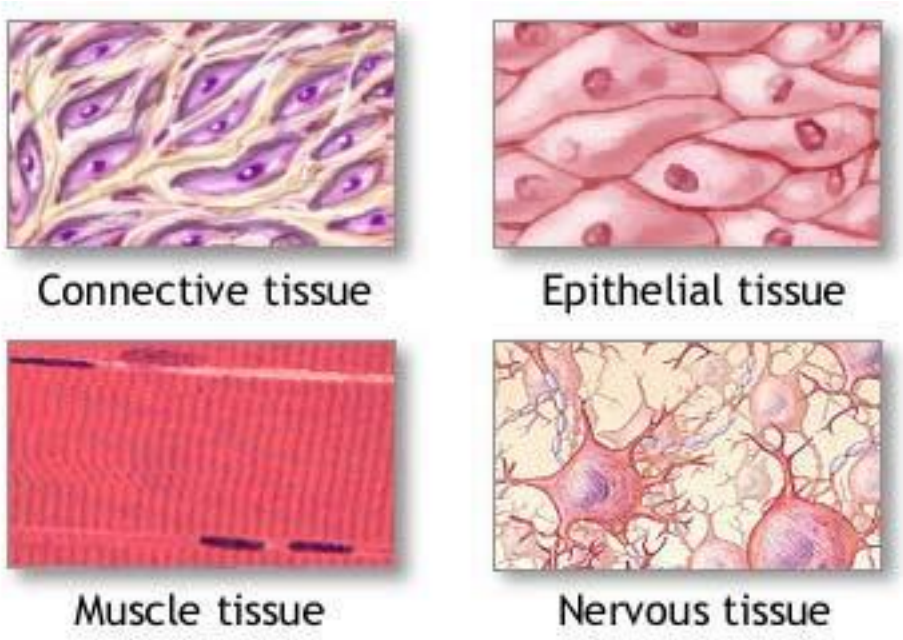
Differential cell signaling?

➔ Analysis of signaling mechanisms in 2-D cell culture lacks tissue mimicry

MINES Saint-Étienne

Tissue Organization

4 major tissue types



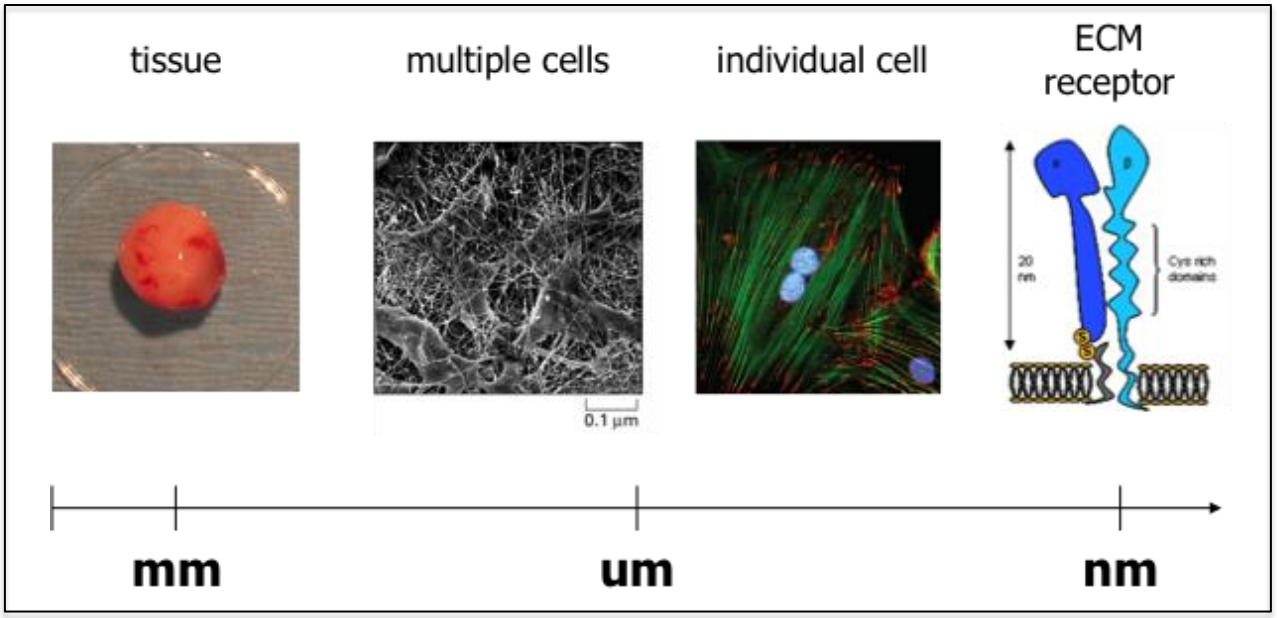
Cells + Extracellular Matrix (ECM)

Classification of tumors

Categories	Origin
Carcinoma	epithelial tissue (>80%)
Sarcoma	Connective (mesenchymal) tissue
Lymphoma and leukemia	hematopoetic (blood-forming) cells

ECM functions across scales

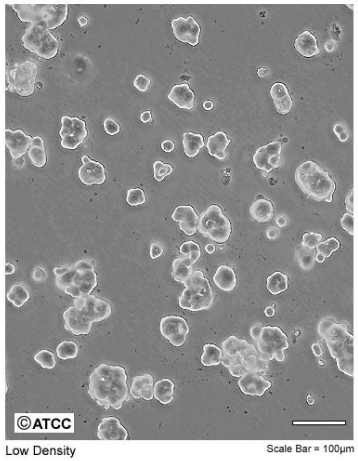
- **Scaffolding for orderly tissue renewal**
- **Mechanical support for cell anchorage**
- **Regulates cell orientation and migration**
- **Control of cellular signaling:**
  - Directly: via ECM receptors (integrins)
  - Indirectly: via modulating growth factor signaling



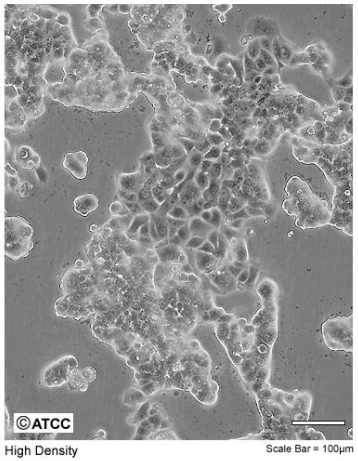
Characteristics of epithelial and mesenchymal cells

Epithelial cells

Low density



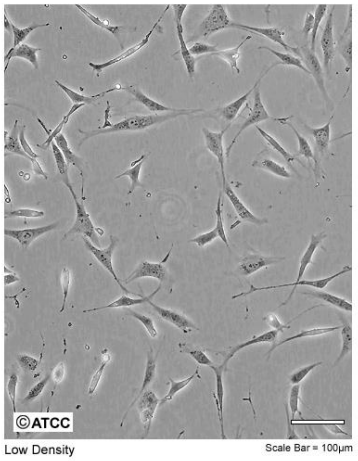
High density



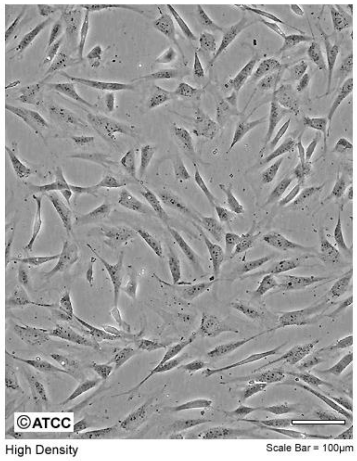
- Cuboidal morphology
- Tight cell-cell interactions
- Polar functionality

Mesenchymal cells

Low density

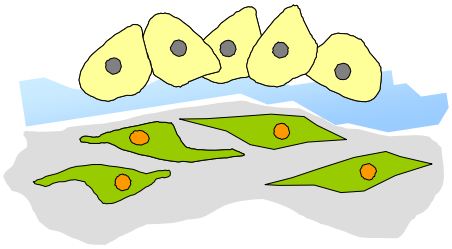


High density



- Bipolar morphology
- Exist alone or losely connected
- Most common mesenchymal cell type: fibroblast

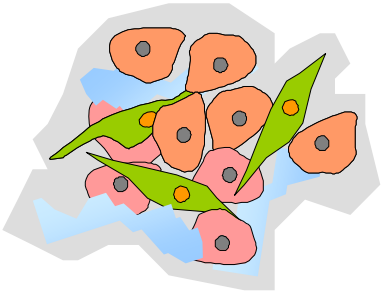
Epithelia and derived carcinoma



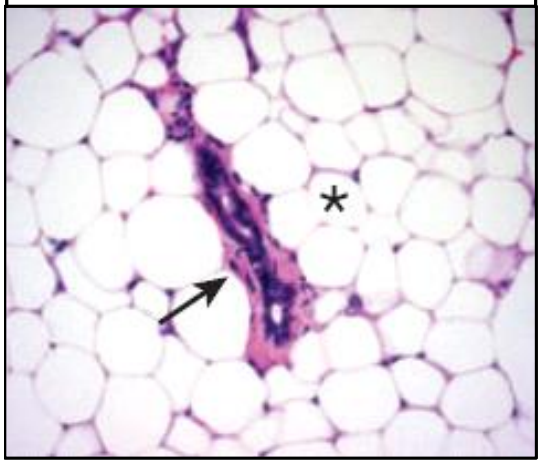
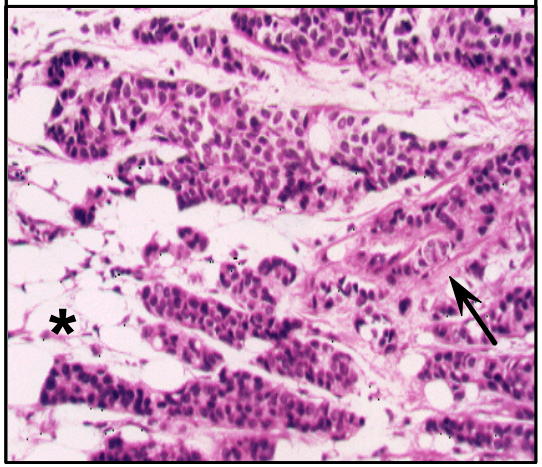
Epithelial tissues
(e.g., breast, skin)

Malignant

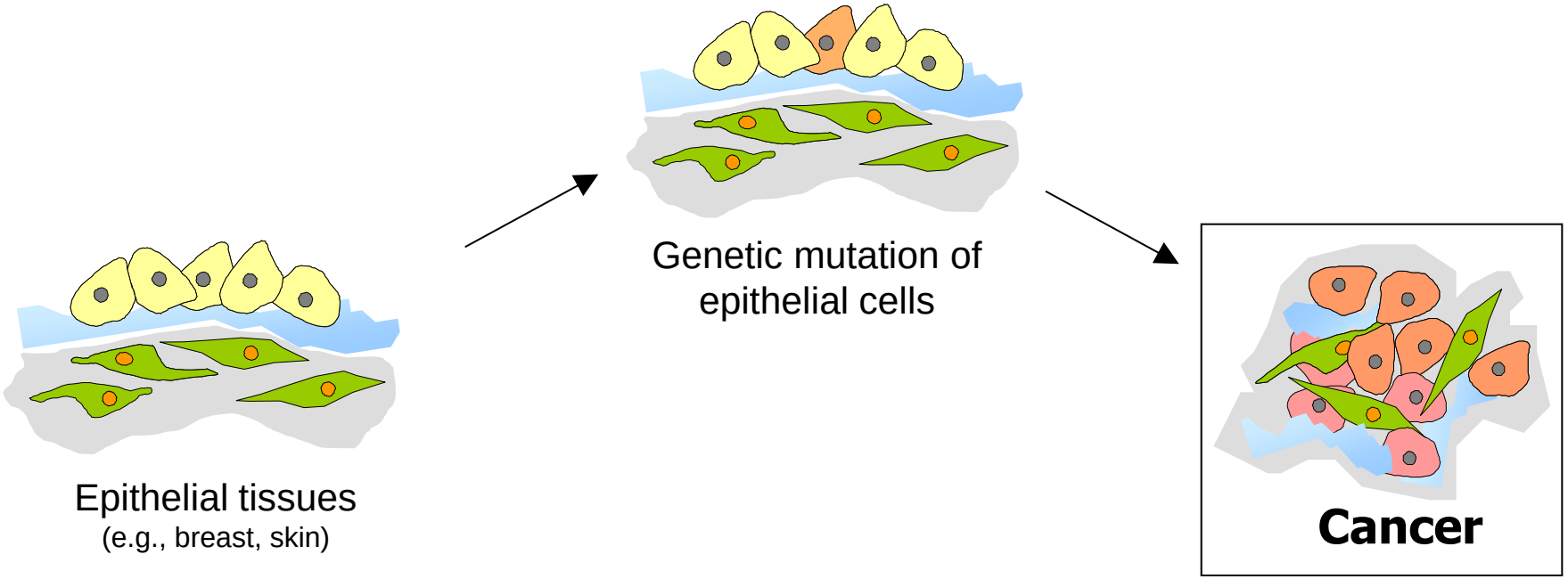
transformation



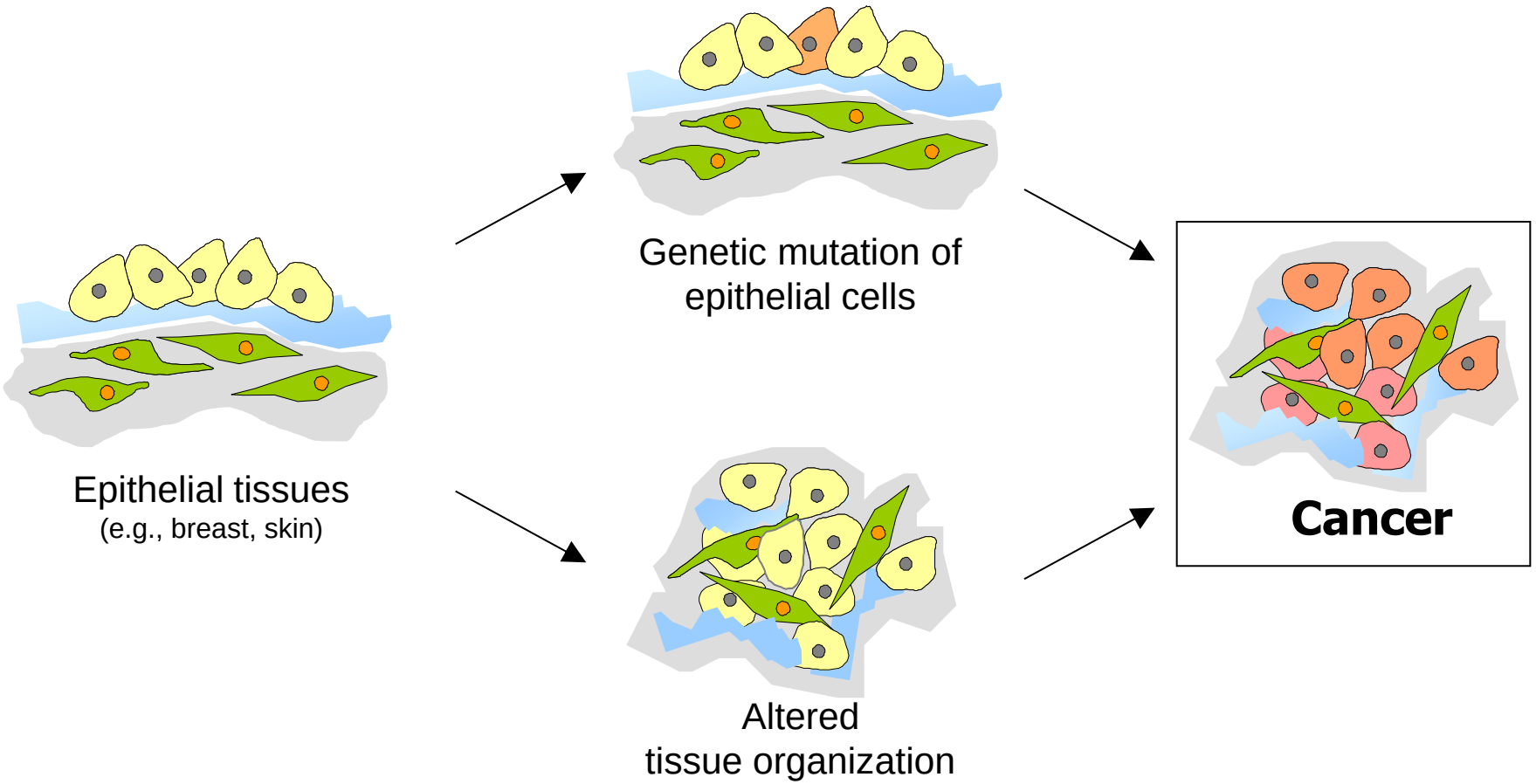
Cancer

normal mammary gland	invasive breast cancer
	

Genetic and/or microenvironmental control of cancer

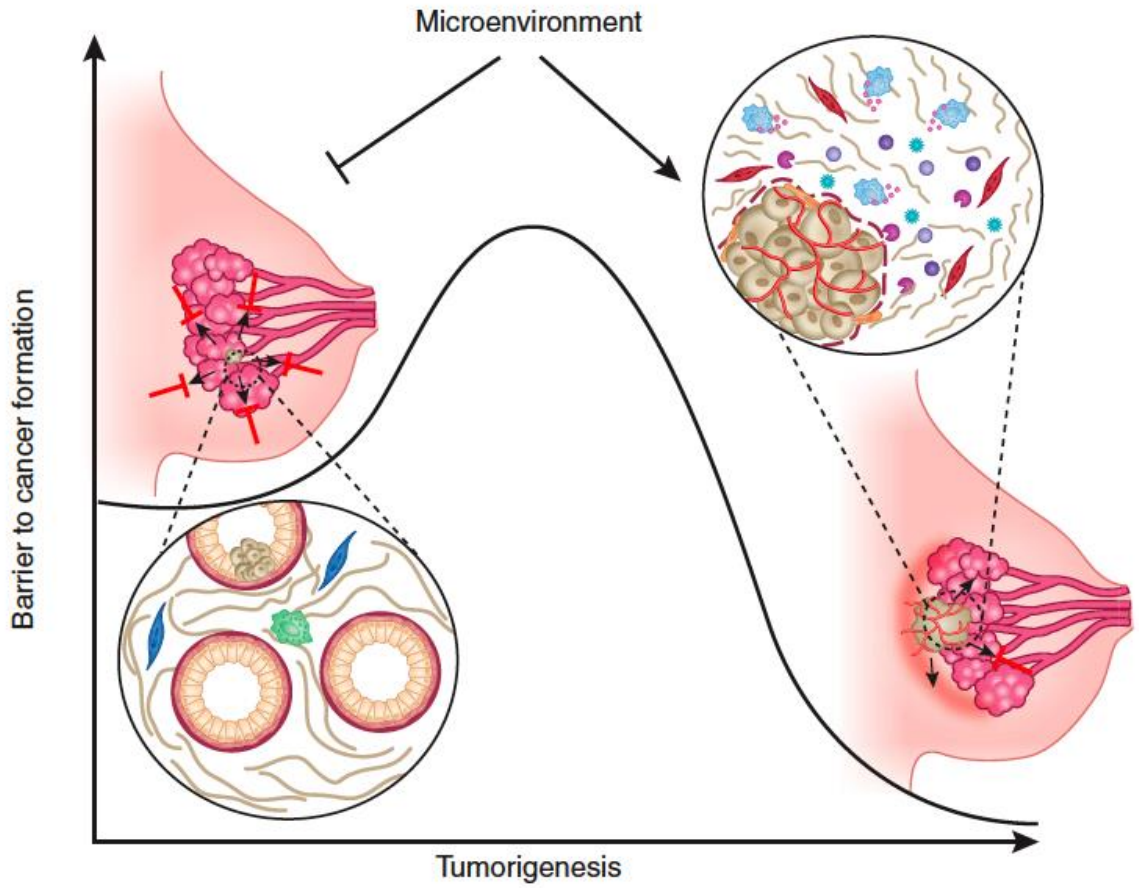


Genetic and/or microenvironmental control of cancer



➔ Genetic mutation of cells leads to compromised tissue architecture and cancer?
➔ Compromised tissue architecture is implicated in genetic mutations and cancer?

Microenvironmental control of cancer



Suppressive forces

- Tissue architecture
- Tissue-specific ECM
- Myoepithelial cells
- Tissue macrophage
- MMP inhibitors
- Normal metabolism
- Antioxidants
- Fibroblast

Promotional forces

- Loss of architecture
- Aberrant ECM (context matters!)
- Aberrant myoepithelial cells
- CAFs
- Inflammation
- Fibrosis
- Tumor associated macrophage
- Angiogenesis
- Cytokines
- MMPs/aberrant proteases
- ROS
- Growth factors
- Hormones
- Mutagens

Bissell, Hines, Nat. Medicine, March 2011

➔ Normal tissue homeostasis and architecture inhibit cancer, but microenvironmental changes activate a cancerous switch

Movie on breast cancer 20.1

Tumor microenvironment

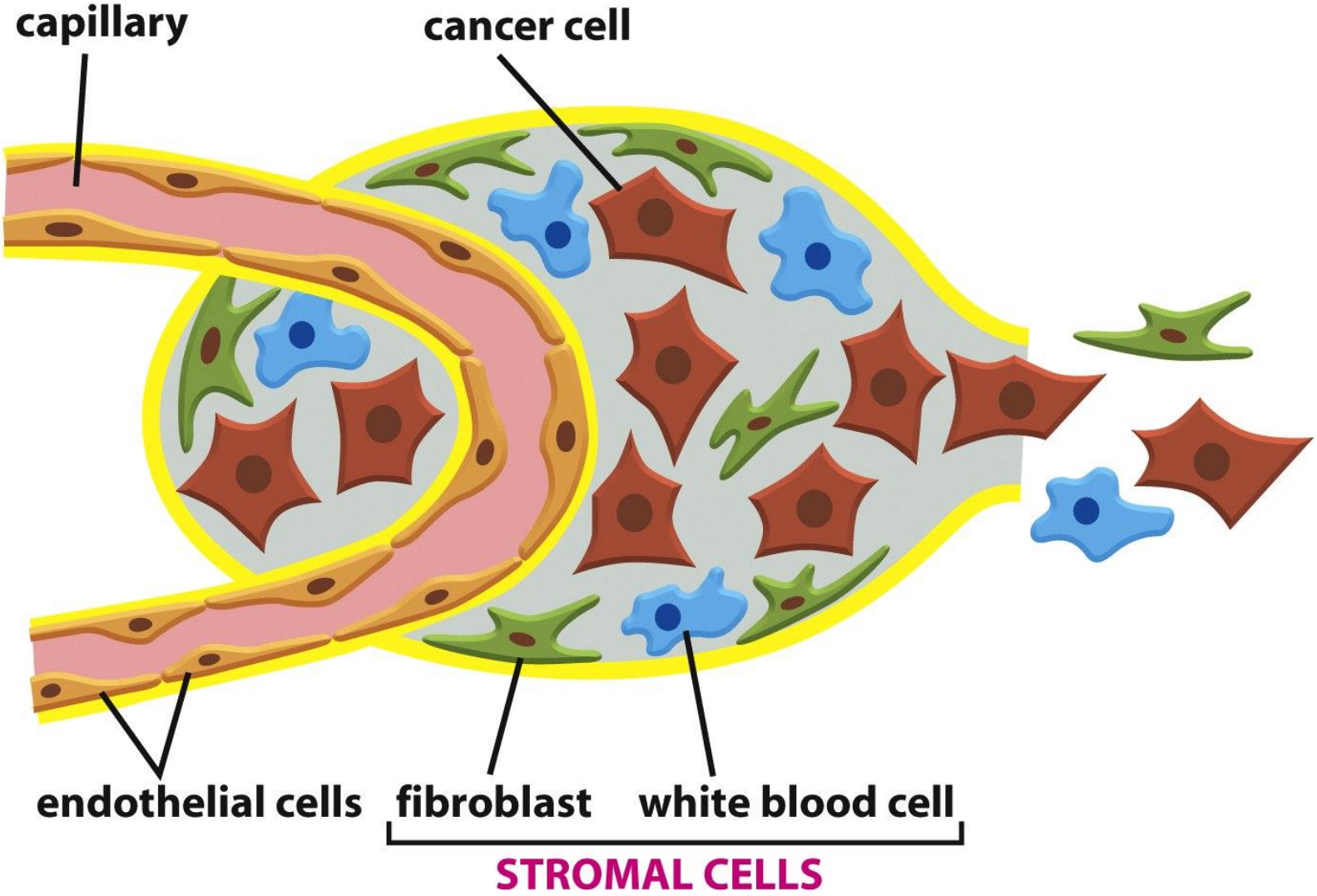
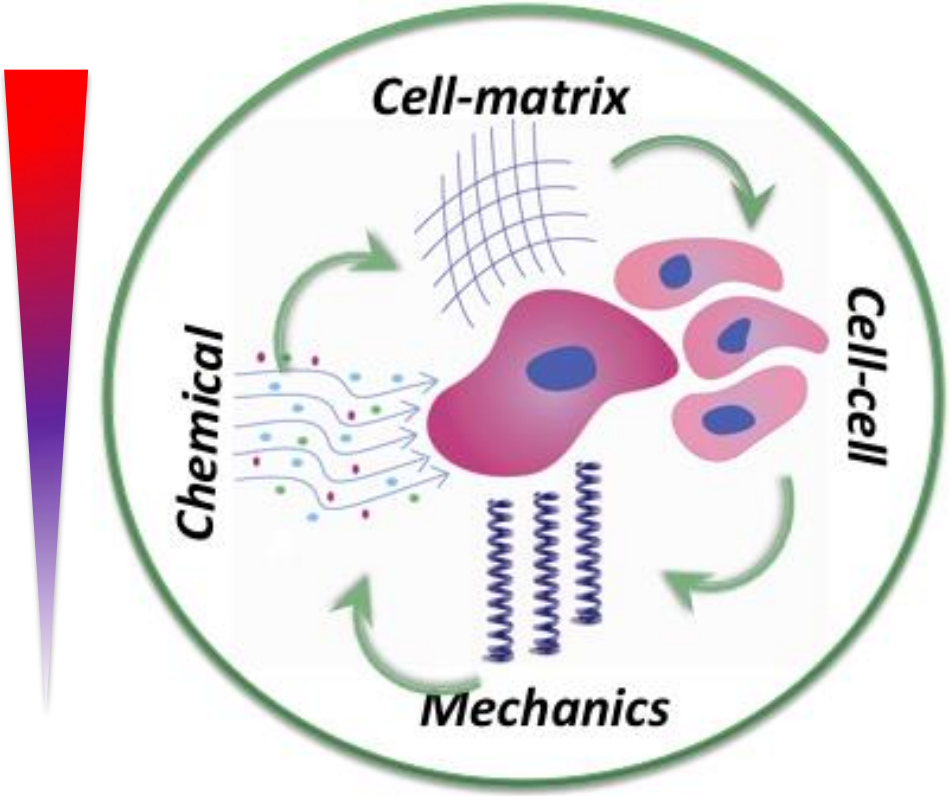


Figure 20-19 *Molecular Biology of the Cell* (© Garland Science 2008)

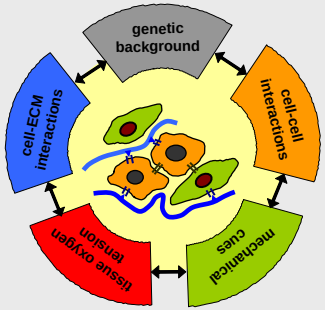
Microenvironmental regulators of cell fate

- Secreted soluble factors
- Cell-extracellular matrix interactions
- Direct cell-cell interactions
- Mechanical forces
- Metabolic gradients



More insights through alternative strategies?

Physiologically more relevant model systems



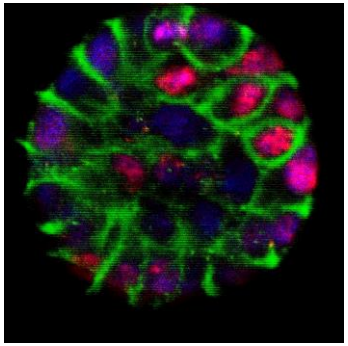
Recreation of microenvironmental conditions

New insights into pathogenesis

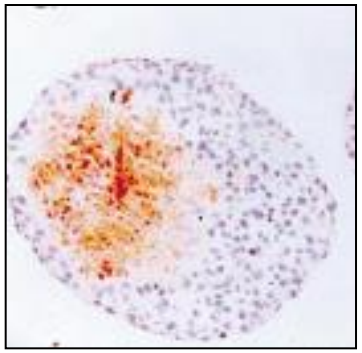
↳Development of therapies

Requirements:

- Mechanical stability
- Applicable both in vitro and in vivo
- **Reproducibility**
- Spatiotemporal Control over cell signaling
- Recreation of homo/heterotypic cell-cell interactions



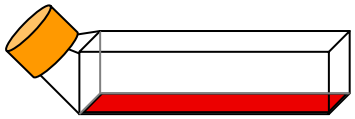
Matrigel



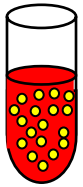
Spheroids

Tissue engineering strategies?

Tissue Engineering



Cell expansion



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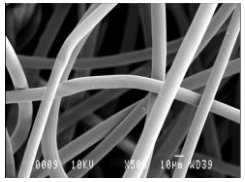
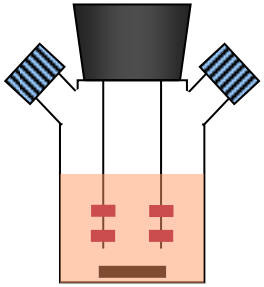
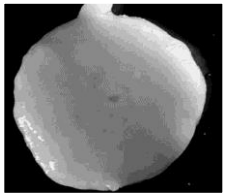


cells

polymer matrix



Cell seeding / culture in bioreactor



new tissue

Transplantation

patient

Cell isolation

Tissue Engineering

Cell expansion

Cell isolation

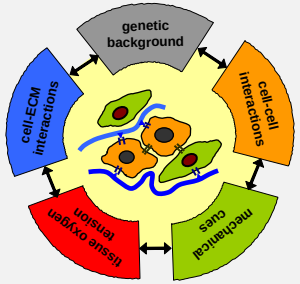
cells + polymer matrix

Cell seeding / culture in bioreactor

new tissue

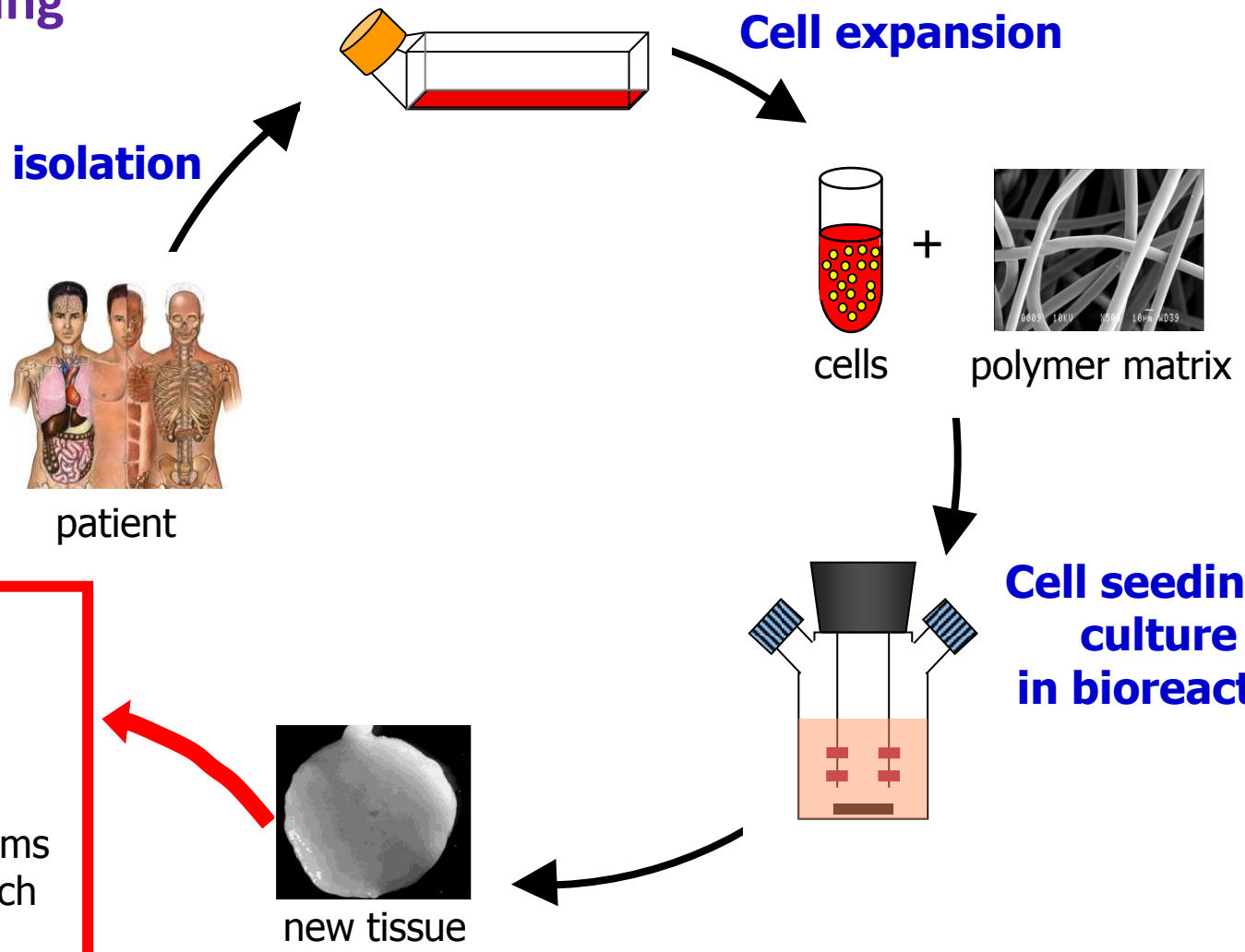
Reorganization into new tissue:

- Recreation of microenvironmental conditions
- Phenotypic changes



Tissue Engineering

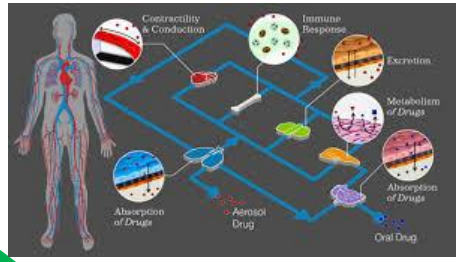
Tissue Engineering



Cell growth *in vitro:* monitoring should adapt

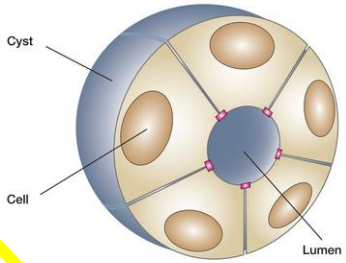
Cell culture systems should be:

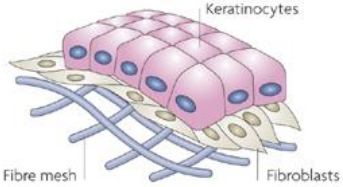
- ***Suitable for long-term measurements***
- ***Preferably multiple (human) cell types***
- ***Recreate physiological niche***
- ***Take into account physical and chemical cues***
- ***Should be multi-parameter!!!***



Organoids
Organ-on-chi
Body-on-chip

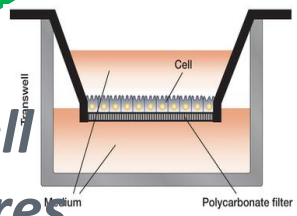
3D cell cultures

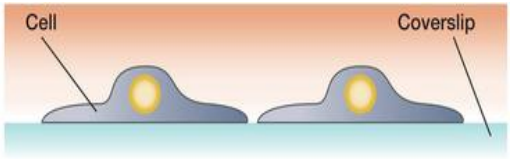




Co-cultures
Layered cultu
Cysts
Spheroids

2D cell cultures





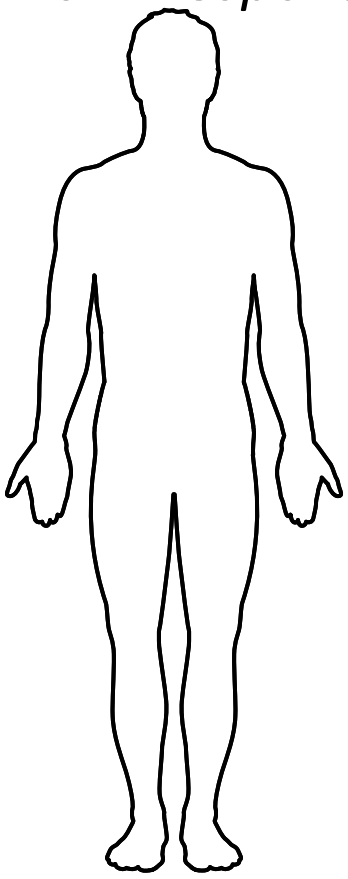
In vivo vs *in vitro* toxicology?

Animal experiments currently gold standard for toxicology

- Only way to get 'whole organism' response

- Size
- Genome
- Susceptibility
- Lifestyle

Mus musculus

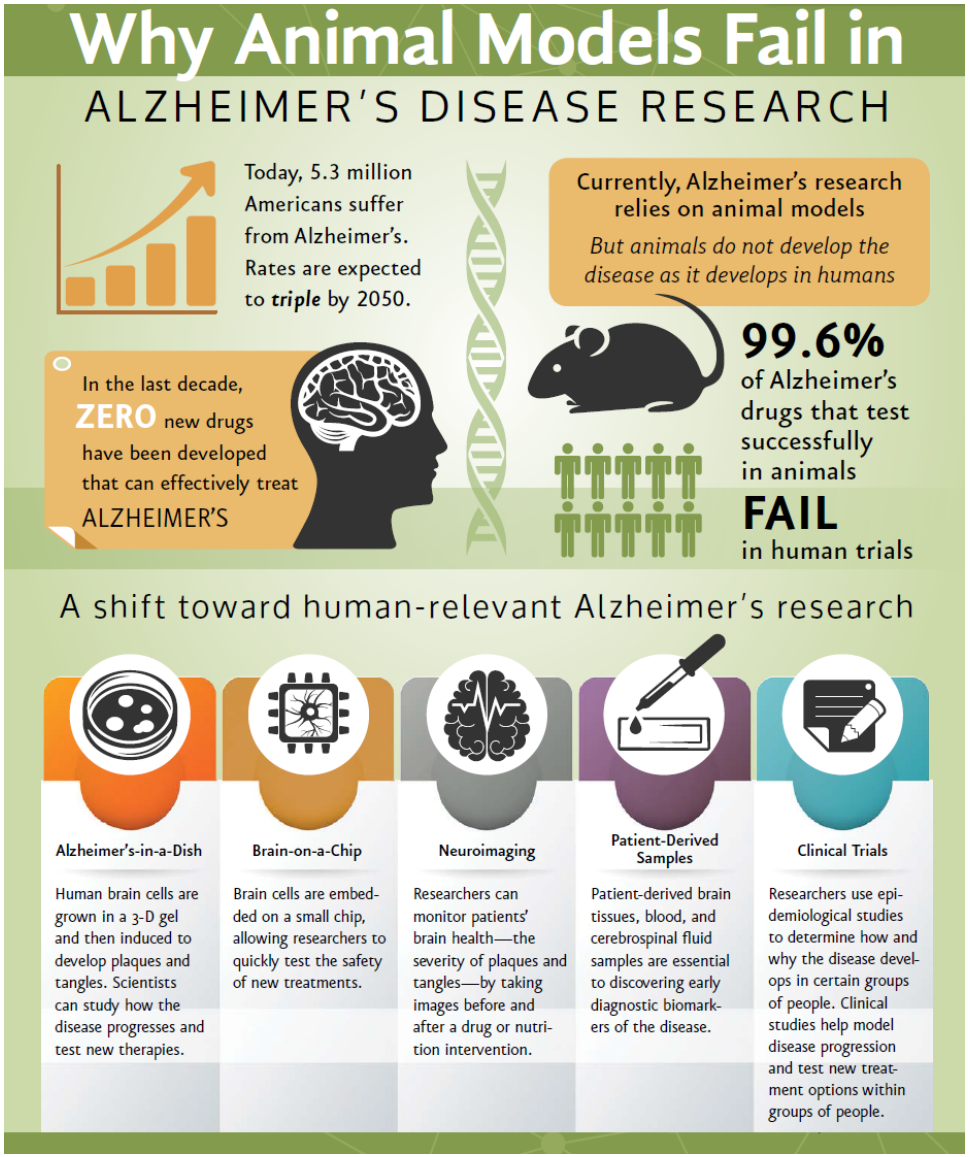


Homo sapiens

Average drug cost = 1.2Bn€
Average time for devel. = 12yrs
Average attrition = 90%

" > 30 % of promising pharmaceuticals have failed in human clinical trials because they are determined to be toxic despite promising pre-clinical studies in animal models" TOX21

Animal models for Alzheimer's research



- **99.6% failures**
- **Zero new drugs in the last decade**