Connective Tissue-1

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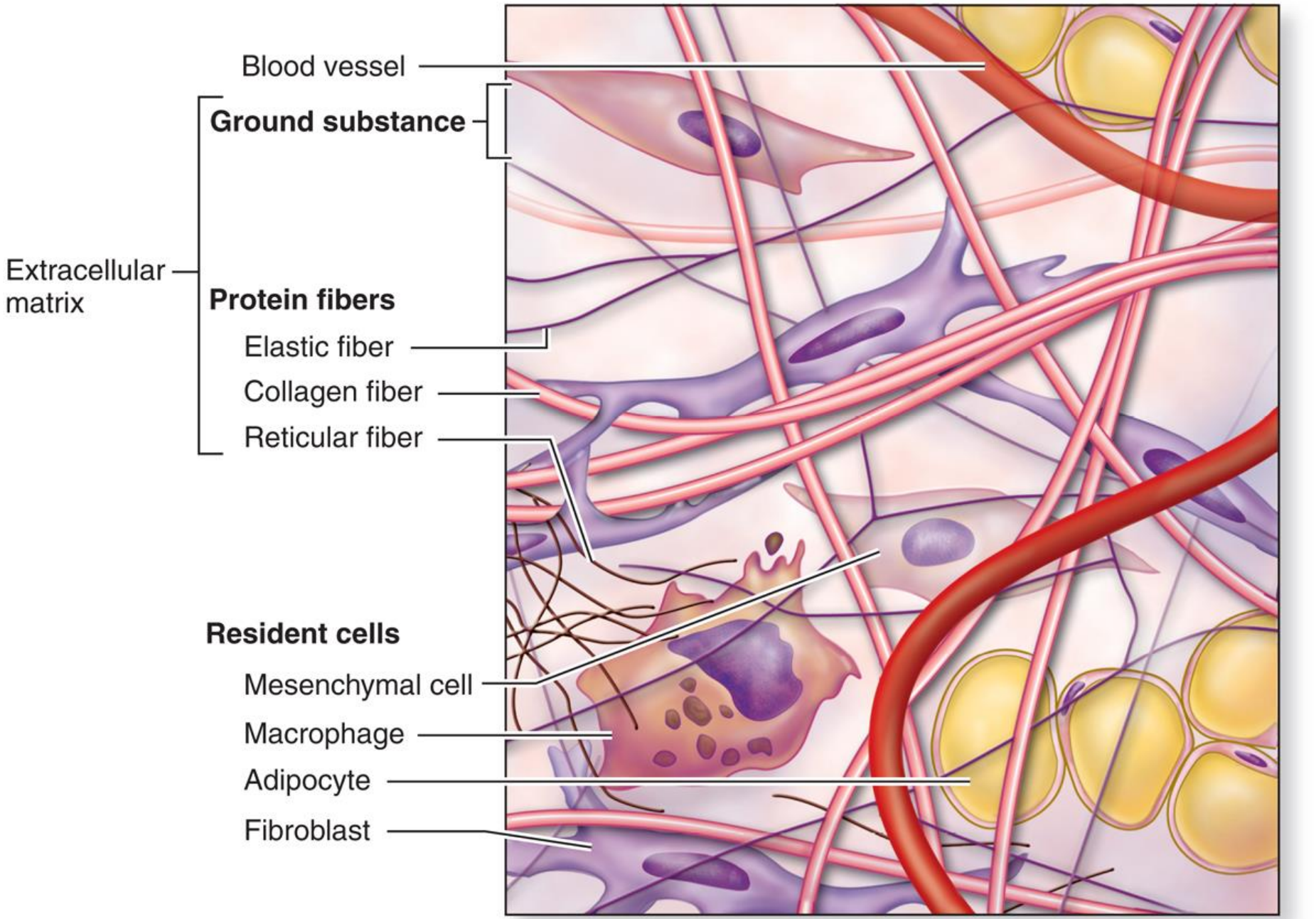
Introduction

- **C**onnective tissue provides a matrix that supports and physically connects other tissues and cells together to form the organs of the body.
- Unlike the other tissue types (epithelium, muscle, and nerve), which consist mainly of cells, the major constituent of connective tissue is the **extracellular matrix (ECM)**.
- Extracellular matrices consist of different combinations of **protein fibers** (collagen and elastic fibers) and **ground substance**
- The variety of connective tissue types in the body reflects differences in composition and amount of the cells, fibers, and ground substance.

Components

- Cells
- Protein Fibers
- Ground Substance

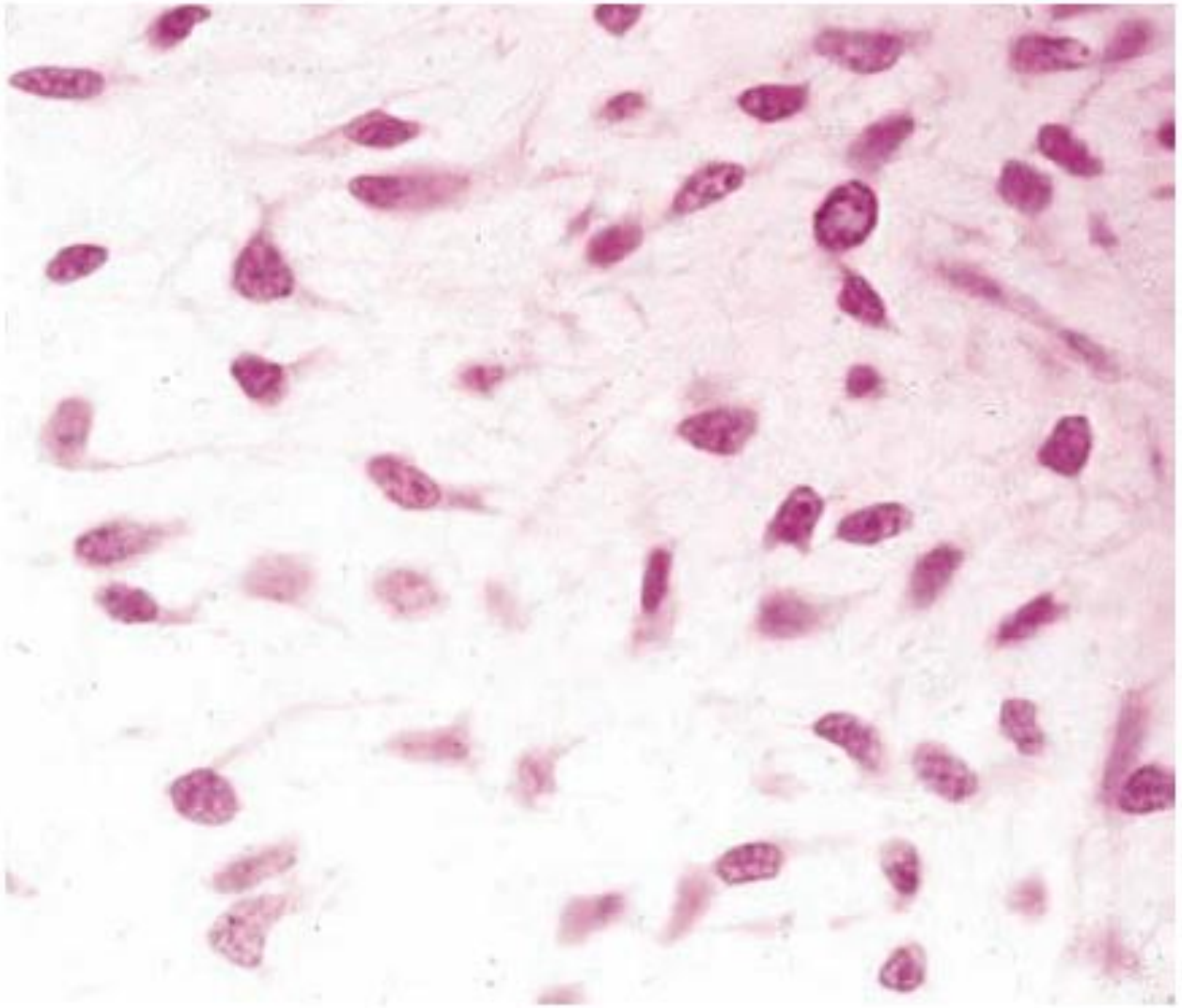
Extracellular matrix


Blood vessel
Ground substance
Extracellular matrix
Protein fibers
Elastic fiber
Collagen fiber
Reticular fiber
Resident cells
Mesenchymal cell
Macrophage
Adipocyte
Fibroblast

Embryonic origin of connective tissue

- All connective tissues originate from embryonic **mesenchyme**, a tissue developing mainly from the middle layer of the embryo, the mesoderm
- Mesenchyme consists largely of viscous ground substance with few collagen fibers
- **Mesenchymal cells** are undifferentiated and have large nuclei, with prominent nucleoli and fine chromatin.

- Mesenchyme consists of a population of undifferentiated cells, generally elongated but with many shapes, having large euchromatic nuclei and prominent nucleoli that indicate high levels of synthetic activity.
- These cells are called **mesenchymal cells**.
- Mesenchymal cells are surrounded by an ECM that they produced and that consists largely of a simple ground substance rich in hyaluronan (hyaluronic acid), but with very little collagen



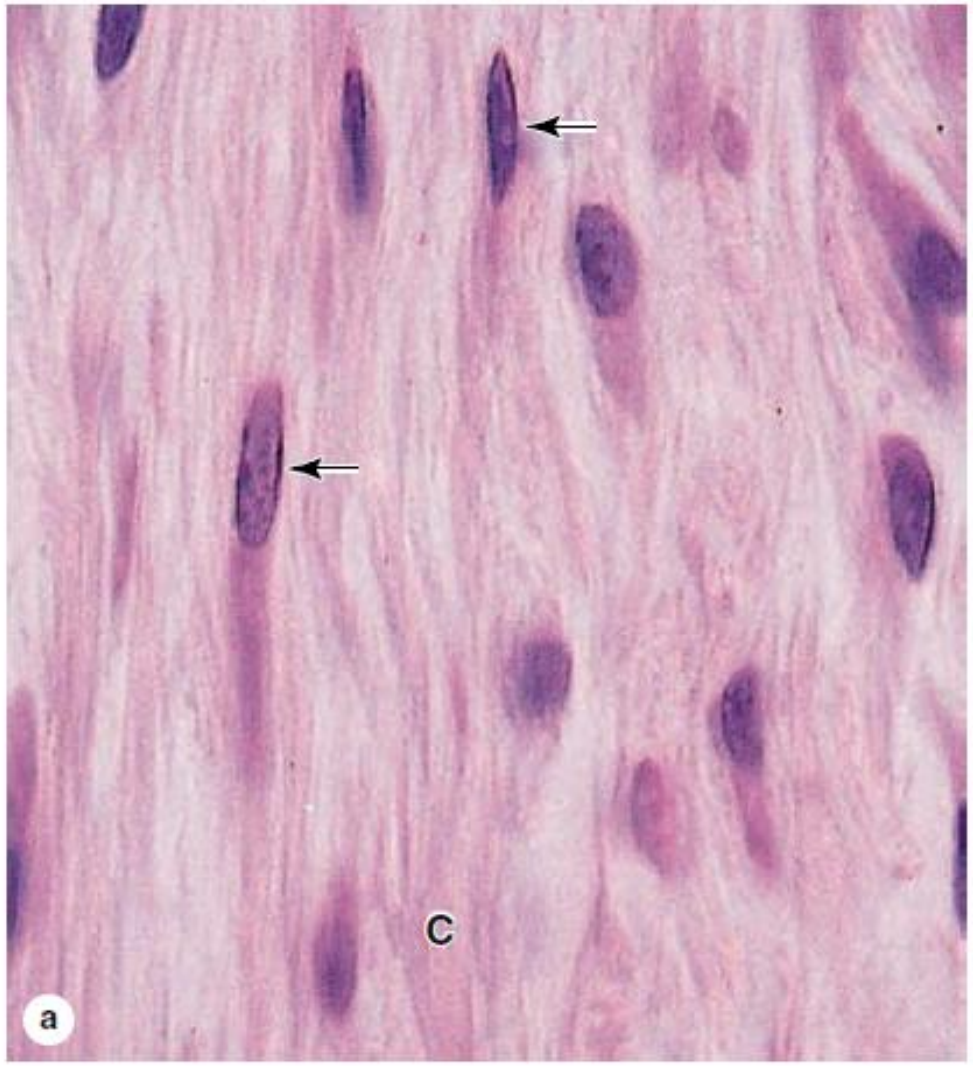
Cells of Connective Tissue

- **Permanent (resident) cells**
  - **Fibroblasts**
  - **Adipocytes**
  - **Macrophages**
- **Transient cells (**they perform various functions in connective tissue for a short period as needed and then die by apoptosis
  - **Mast cells**
  - **Leukocytes (white blood cells)**
  - **Plasma cells**

Fibroblasts

- **Fibroblasts** are the key cells in connective tissue proper
- Fibroblasts originate locally from mesenchymal cells
- They are the most common cells in connective tissue proper
- They produce and maintain most of the tissue's extracellular components.

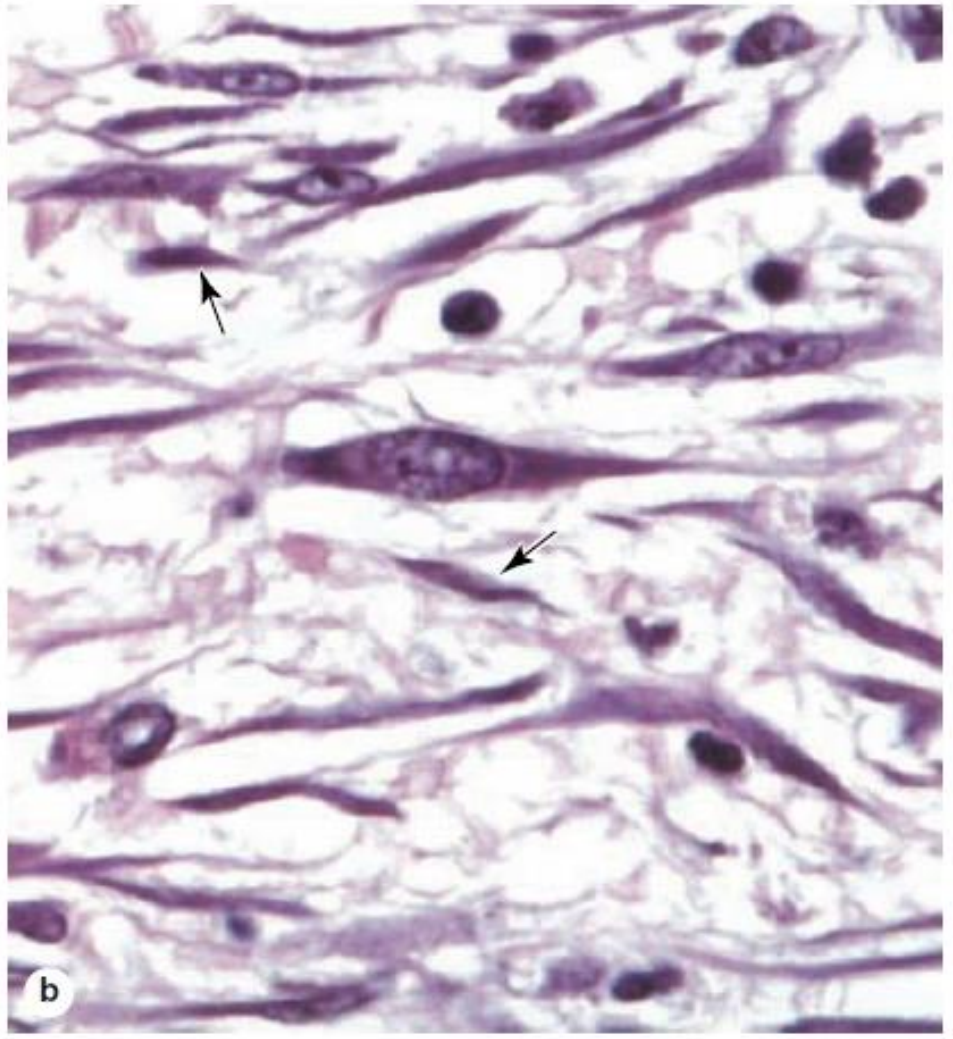
- Fibroblasts typically have large active nuclei and eosinophilic cytoplasm that tapers off in both directions along the axis of the (spindle-shaped)
- Nuclei (**arrows**) are clearly seen, but the eosinophilic cytoplasmic processes resemble the collagen bundles (**C**) that fill the ECM and are difficult to distinguish in H&E-stained sections



Fibroblast vs Fibrocyte

- Cells with intense synthetic activity are morphologically different from the quiescent fibroblasts that are scattered within the matrix they have already synthesized.
- Some histologists reserve the term “fibroblast” to denote the active cell and “fibrocyte” to denote the quiescent cell.
- The active fibroblast has more abundant and irregularly branched cytoplasm, containing much rough endoplasmic reticulum (RER) and a well-developed Golgi apparatus, with a large, ovoid, euchromatic nucleus and a prominent nucleolus.
- The quiescent cell is smaller than the active fibroblast, is usually spindle-shaped with fewer processes, much less RER, and a darker, more heterochromatic nucleus

- Both active and quiescent fibroblasts may sometimes be distinguished
- Active fibroblasts have large euchromatic nuclei
- Inactive fibroblasts (or fibrocytes) are smaller with more heterochromatic nuclei (**arrows**).
- The round, very basophilic round cells are in leukocytes.

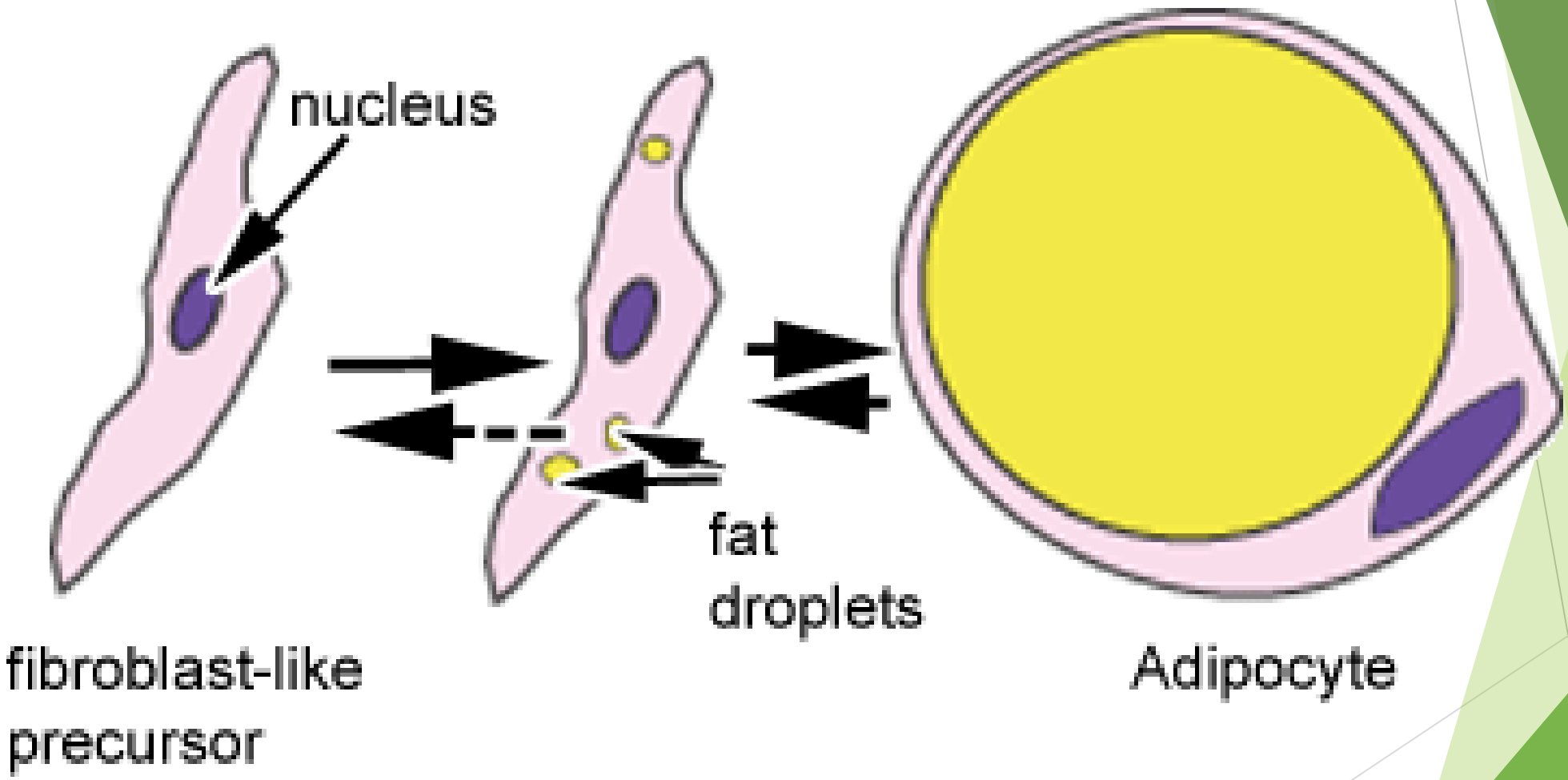


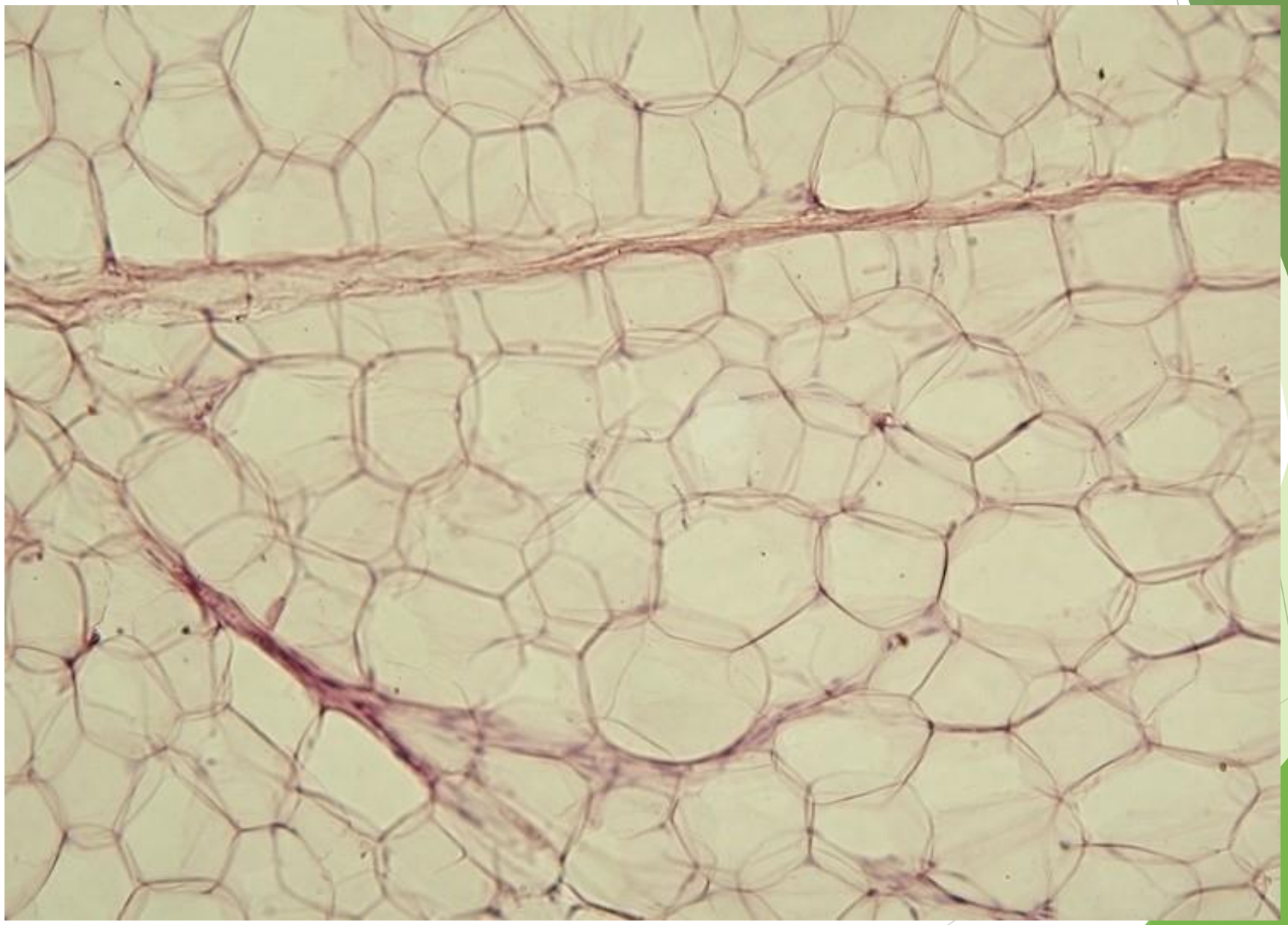
Myofibroblast

- **Myofibroblasts** are fibroblasts involved in wound healing
- They have a well-developed contractile function
- They are enriched with a form of actin also found in smooth muscle cells

Adipocyte

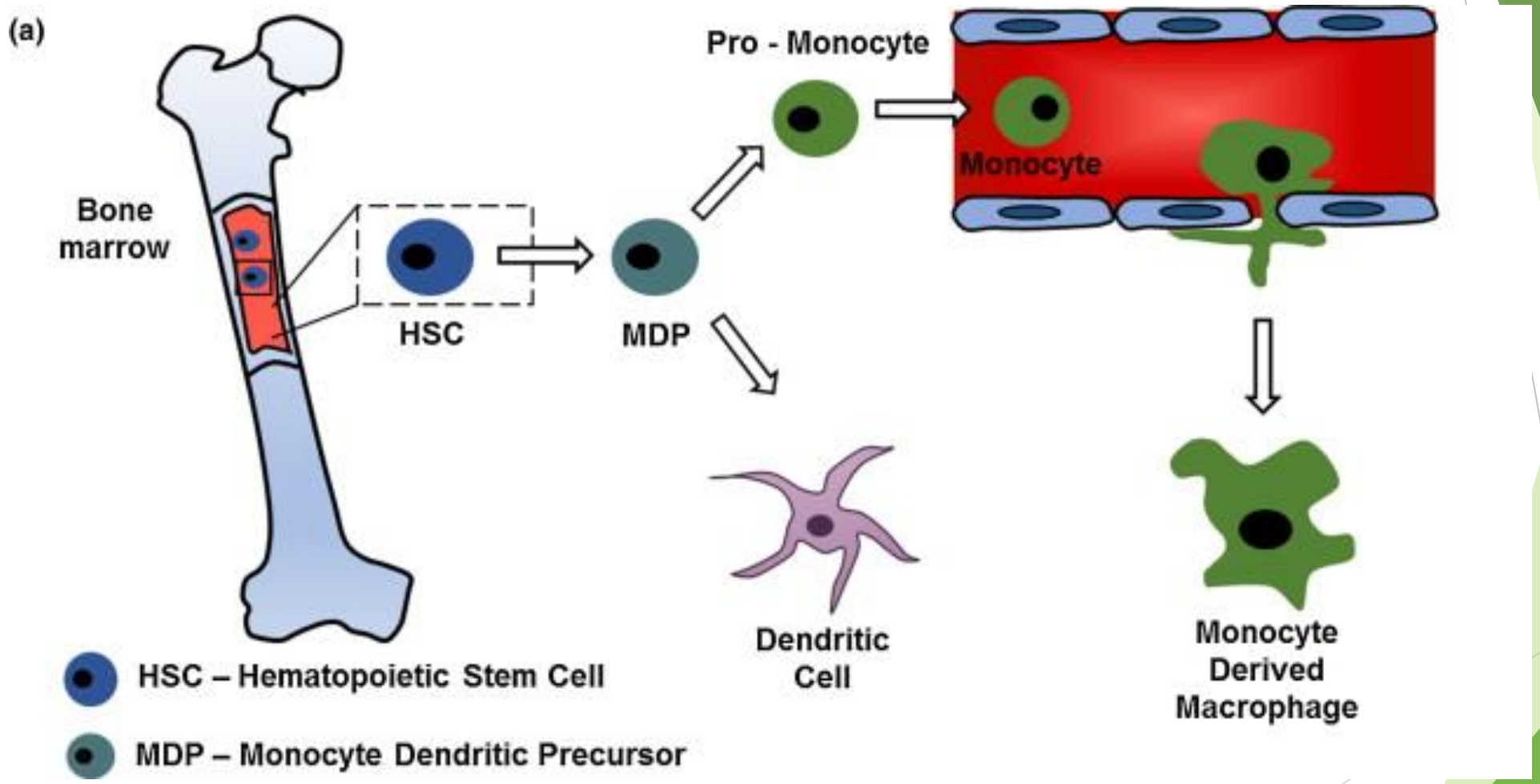
- **Adipocytes** or fat cells, are found in the connective tissue of many organs.
- They are specialized for cytoplasmic storage of lipid as neutral fats
- Tissue with a large population of adipocytes, called adipose connective tissue, serves to cushion and insulate the skin and other organs.

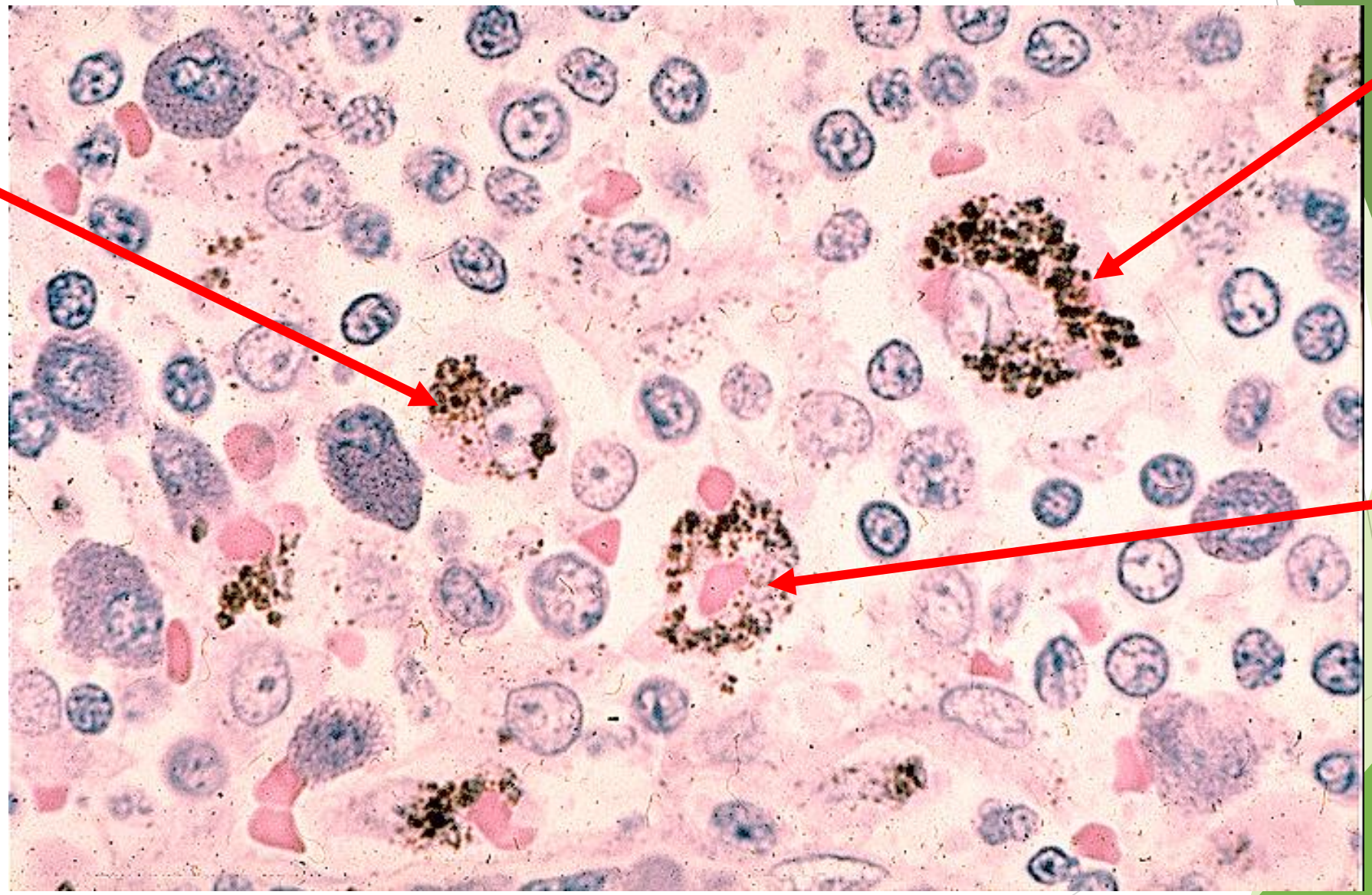

nucleus
fat
droplets
fibroblast-like
precursor
Adipocyte



Macrophage

- **Macrophages** have highly developed phagocytic ability
- They specialize in removal of dead cells and tissue debris
- They are abundant at sites of inflammation
- A macrophage has an eccentrically located, oval or kidney-shaped nucleus
- Macrophages are present in the connective tissue of most organs and are sometimes referred to by pathologists as “histiocytes”
- Macrophages derive from bone marrow precursor cells called **monocytes** that circulate in the blood


(a)
Bone marrow
HSC
MDP
Pro - Monocyte
Monocyte
Dendritic Cell
Monocyte Derived Macrophage
HSC – Hematopoietic Stem Cell
MDP – Monocyte Dendritic Precursor



- Macrophages have prominent nucleus (**N**) and nucleolus (**Nu**) and numerous secondary lysosomes (**L**).
- The arrows indicate phagocytic vacuoles near the protrusions and indentations of the cell surface.

Mononuclear Macrophage System

- Macrophages are distributed throughout the body and are normally present in the stroma of most organs.
- They comprise a family of cells called the **mononuclear phagocyte system**.
- All of these macrophage-like cells are derived from monocytes
- They have different names in various organs:
  - Kupffer cells in the liver
  - Microglial cells in the central nervous system
  - Langerhans cells in the skin
  - Osteoclasts in bone
- Macrophages are long-living cells and may survive in the tissues for months.
- These cells are highly important for the uptake, processing, and presentation of antigens for lymphocyte activation

Mononuclear Phagocyte System

TABLE 5–2 Distribution and main functions of the cells of the mononuclear phagocyte system.

Cell Type	Major Location	Main Function
Monocyte	Blood	Precursor of macrophages
Macrophage	Connective tissue, lymphoid organs, lungs, bone marrow, pleural and peritoneal cavities	Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing, and presentation
Kupffer cell	Liver (perisinusoidal)	Same as macrophages
Microglial cell	Central nervous system	Same as macrophages
Langerhans cell	Epidermis of skin	Antigen processing and presentation
Dendritic cell	Lymph nodes, spleen	Antigen processing and presentation
Osteoclast (from fusion of several macrophages)	Bone	Localized digestion of bone matrix
Multinuclear giant cell (several fused macrophages)	In connective tissue under various pathological conditions	Segregation and digestion of foreign bodies

Mast cells

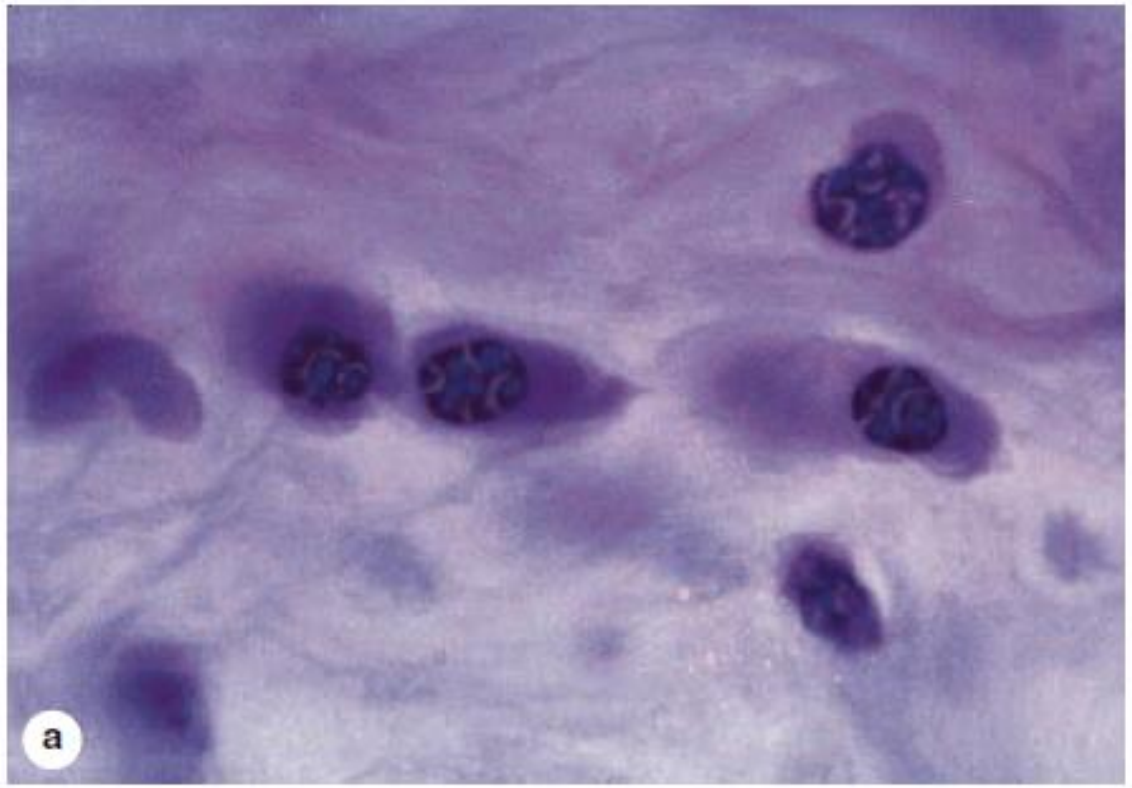
- **Mast cells** are oval or irregularly shaped cells of connective tissue
- They are filled with basophilic secretory granules which often obscure the central nucleus
- These granules are electron-dense and of variable size
- Mast cell granules display **metachromasia**, which means that they can change the color of some basic dyes (eg, toluidine blue) from blue to purple or red.
- Mast cells function in the localized release of many bioactive substances important in the local inflammatory response
- The main molecules they release are heparin (an anticoagulant) and histamine (increases vascular permeability)
- They are involved in allergic reactions known as immediate hypersensitivity reactions

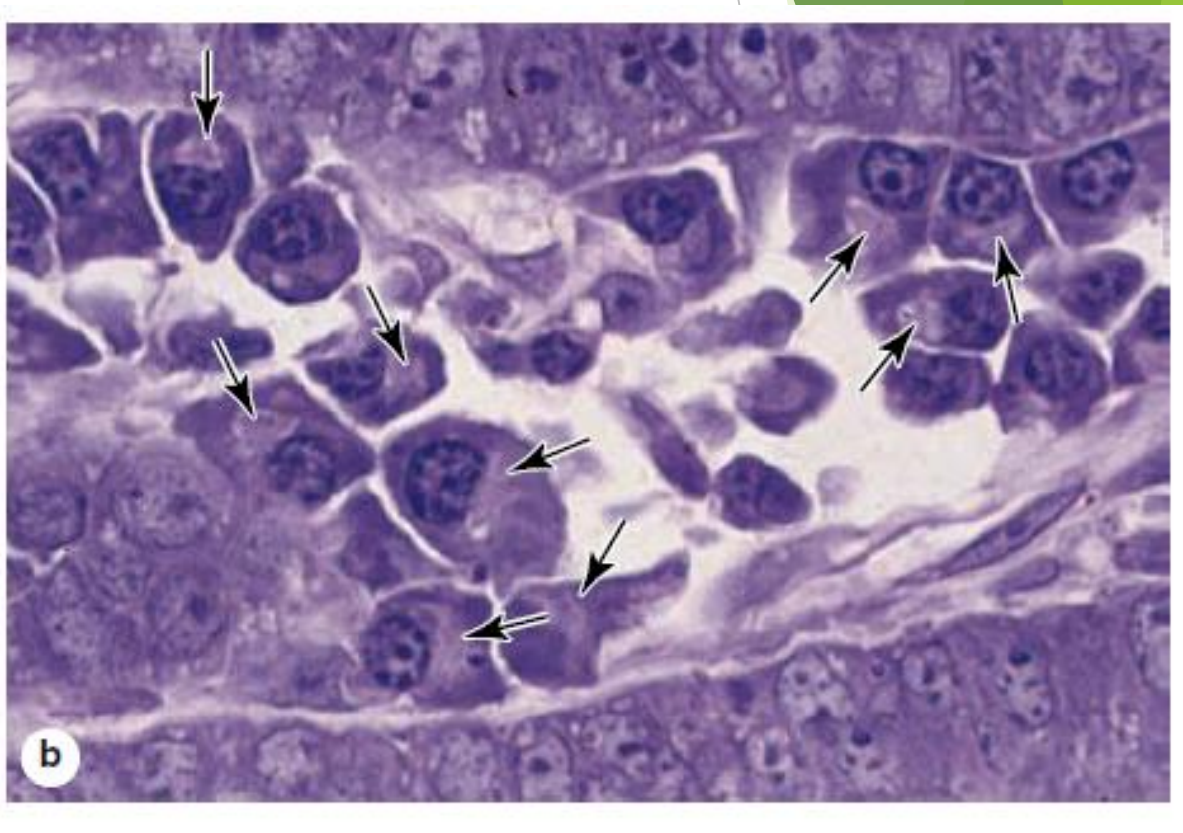

BV
a


E
G
M
N
C
b

Plasma cells

- **Plasma cells** are lymphocyte-derived, antibody-producing cells.
- They are relatively large ovoid cells with basophilic cytoplasm rich in RER and a large Golgi apparatus near the nucleus that may appear pale in routine histologic preparations (negative Golgi staining)
- The nucleus of the plasma cell is generally spherical but eccentrically placed.
- Many of these nuclei contain compact, peripheral regions of heterochromatin alternating with lighter areas of euchromatin (**clock-face or cart-wheel appearance**).


a


b

Medical Application

- Plasma cells are derived from B lymphocytes and are responsible for the synthesis of immunoglobulin antibodies. Each antibody is specific for the one antigen that stimulated the clone of B cells and reacts only with that antigen or molecules resembling it. The results of the antibody-antigen reaction are variable, but they usually neutralize harmful effects caused by antigens. An antigen that is a toxin (eg, tetanus, diphtheria) may lose its capacity to do harm when it is bound by a specific antibody. Bound antigen-antibody complexes are quickly removed from tissues by phagocytosis.

Leukocytes

- Other white blood cells, or **leukocytes**, besides macrophages and plasma cells normally comprise a population of wandering cells in connective tissue.
- Derived from circulating blood cells, they leave blood by migrating between the endothelial cells of venules to enter connective tissue.
- This process increases greatly during inflammation, which is a vascular and cellular defensive response to injury or foreign substances, including pathogenic bacteria or irritating chemical substances.

Leukocytes in CT

- Most leukocytes function in connective tissue only for a few hours or days and then undergo apoptosis.
- However, some lymphocytes and phagocytic antigen-presenting cells normally leave the interstitial fluid of connective tissue, enter blood or lymph, and move to selected lymphoid organs.

Medical Application

- Increased vascular permeability is caused by the action of vasoactive substances such as histamine released from mast cells during **inflammation**. Classically, the major signs of inflamed tissues include “redness and swelling with heat and pain”.
- Increased blood flow and vascular permeability produce local tissue **swelling (edema)**, with increased redness and warmth. **Pain** is due mainly to the action of the chemical mediators on local sensory nerve endings. All these activities help protect and repair the inflamed tissue.
- **Chemotaxis**, the phenomenon by which specific cell types are attracted by specific molecules, draws much larger numbers of leukocytes into inflamed tissues.