



CONNECTIVE TISSUE CELLS

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Connective Tissue Cells

Resident cells in connective tissue

- **Fibroblasts** and related cells
myofibroblasts,
- **Macrophages,**
- **Adipocytes,**
- **Mast cells, and**
- **Adult stem cells**

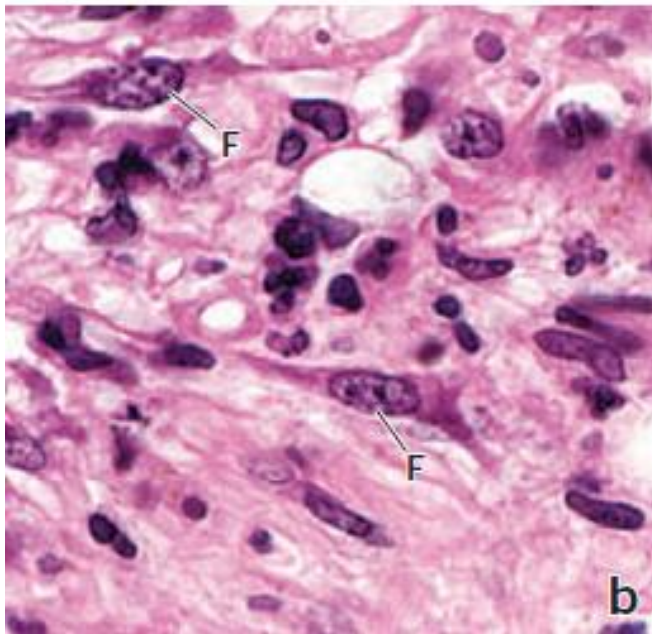
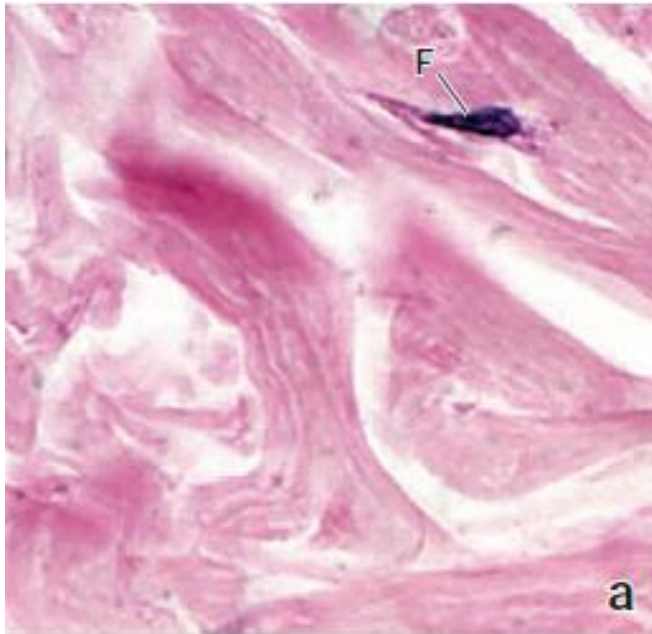
Transient cells in connective tissue

- **Lymphocytes,**
- **Plasma cells,**
- **Neutrophils,**
- **Eosinophils,**
- **Basophils,**
- **Monocytes.**

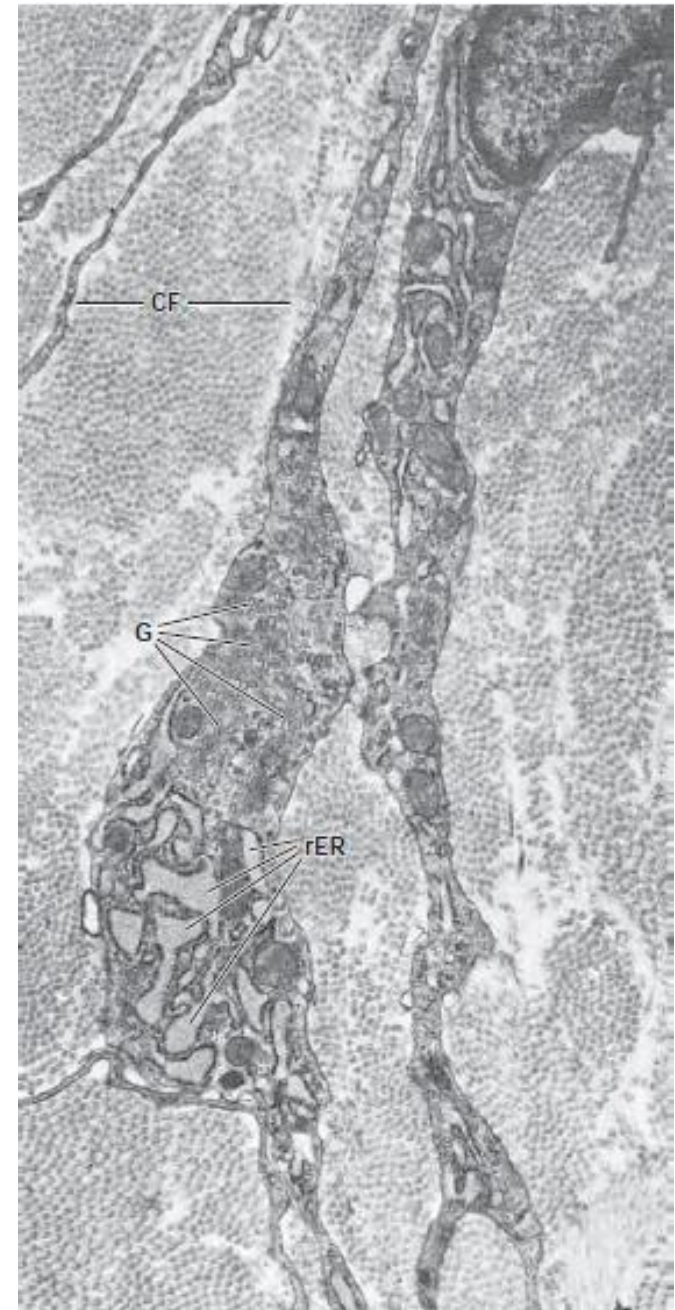
migrated into the tissue
from the blood in response to
specific stimuli

Fibroblasts

- It is the primary cell of the connective tissue.
- Production of collagen, elastic and reticular **fibers**, and complex carbohydrates of the **ground substance**
- A single fibroblast can synthesize all ECM elements.
- It is observed adjacent to collagen in H&E preparations and can be distinguished by its nucleus. Thin, branching, cytoplasm extensions are masked by collagen.
- When cell's synthesis function reach to a minimum level, it is called **fibrocytes**.

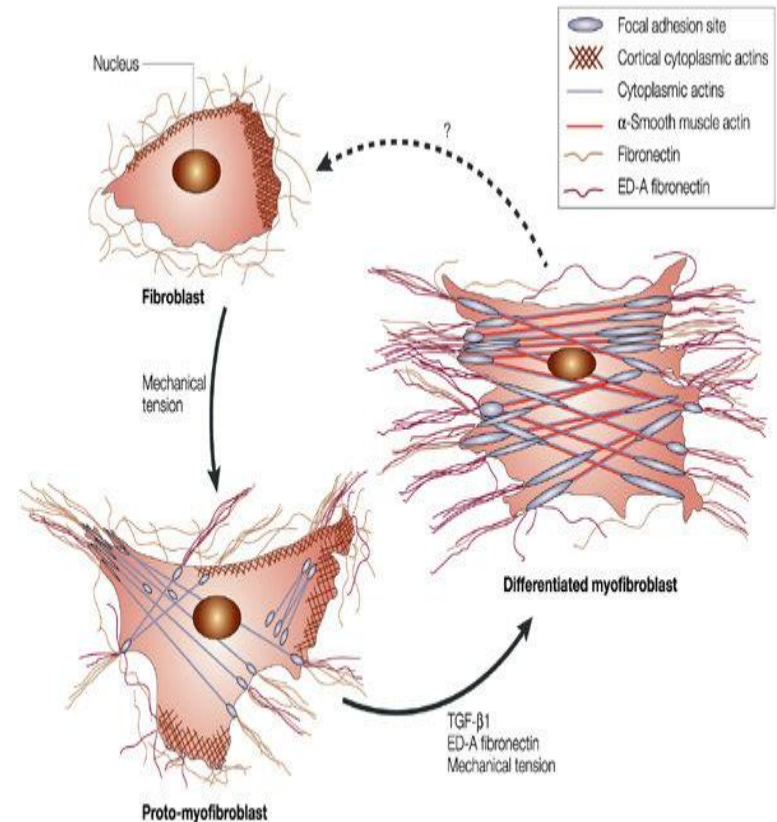


- Since the amount of GER in active fibroblasts increases due to protein synthesis, their cytoplasm appears more basophilic and can be distinguished between collagen fibers. (eg wound healing zone)



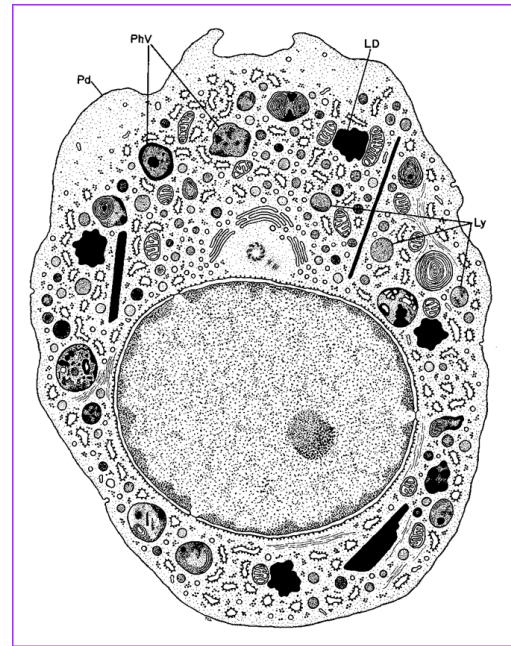
Myofibroblasts

- They are both fibroblast and smooth muscle cells.
- They can be seen in wound healing areas....
Contraction: wound closure
- Contains actin motor proteins such as filament bundles and myosin.
- It expresses α -smooth muscle actin (α -SMA) and is controlled by TGF- β 1.
- In addition to smooth muscle cell properties, TEM shows plenty of Golgi and GER
- There is no external lamina (basal lamina) unlike smooth muscle cells.

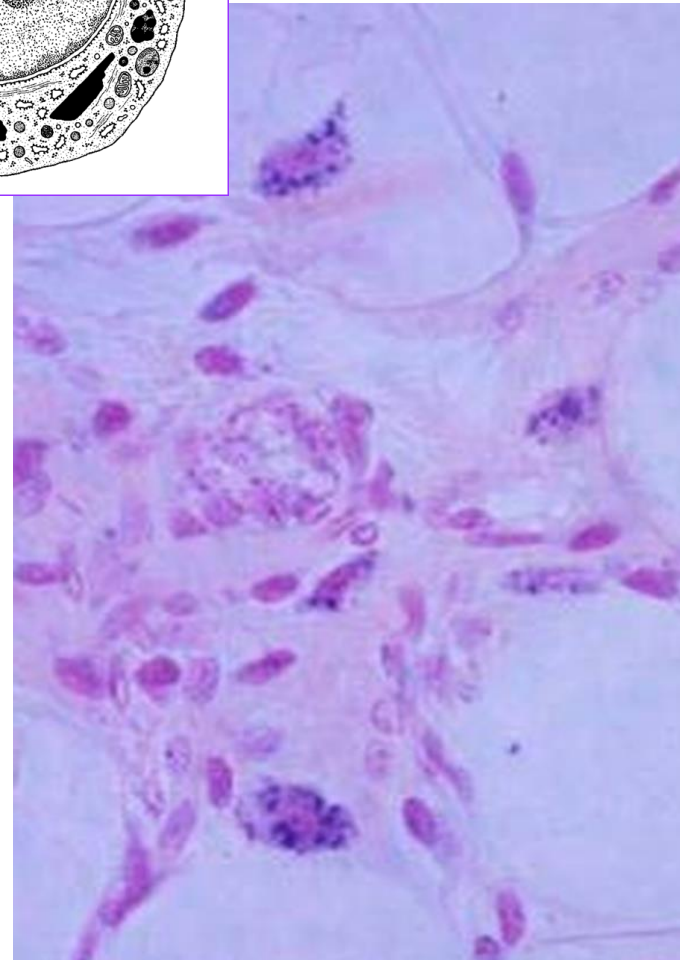


Macrophages

- Phagocytic cells originating from monocytes.
- **Monocytes migrate from blood to connective tissue, where they become macrophages.**
- Also called **histiocyte**.
- They have kidney-shaped nucleus.
- Due to the material that they phagocytize (inclusion), they can be noticed under the microscope.
- They have dense lysosomes and can be stained using acid phosphatase activity.
- There are plenty of Golgi, GER, SER, mitochondria, secretory vesicles and lysosomes in the cytoplasm.



The best way to show macrophages is vital staining. (Trypan blue or Indian ink)

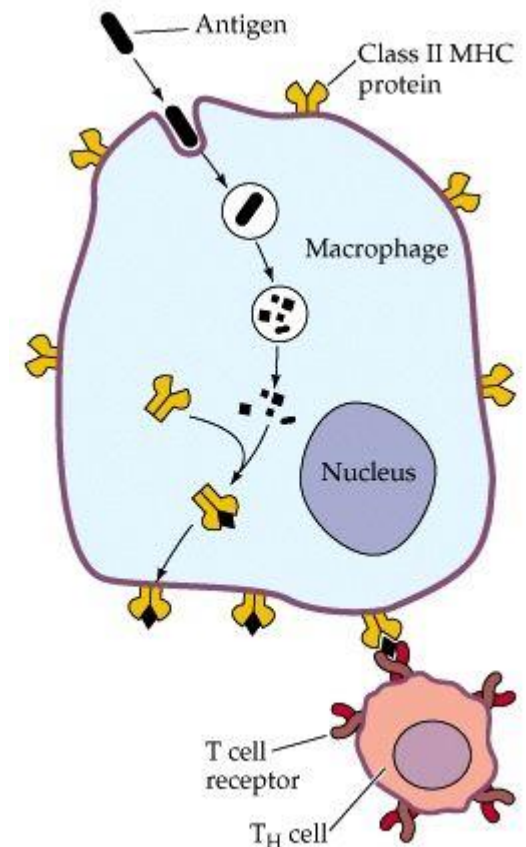


Macrophages

- The cell surface contains short blunt cytoplasmic extensions (Filopodia).
- Their cytoplasm is slightly basophilic and contains many small dense granules and vacuoles.
- Cell activity includes; providing phagocytosis, lymphokines caused by lymphocytes, immune complexes, complement.
- They secrete substances that stimulate the **immune response**, **anaphylaxis** and **inflammation**, and **enzymes** that break down GAGs and open space in connective tissue for movement.
- In addition to fighting and cleaning pathogens and foreign bodies with phagocytosis, they have another very important task = **Antigen-presentation**.

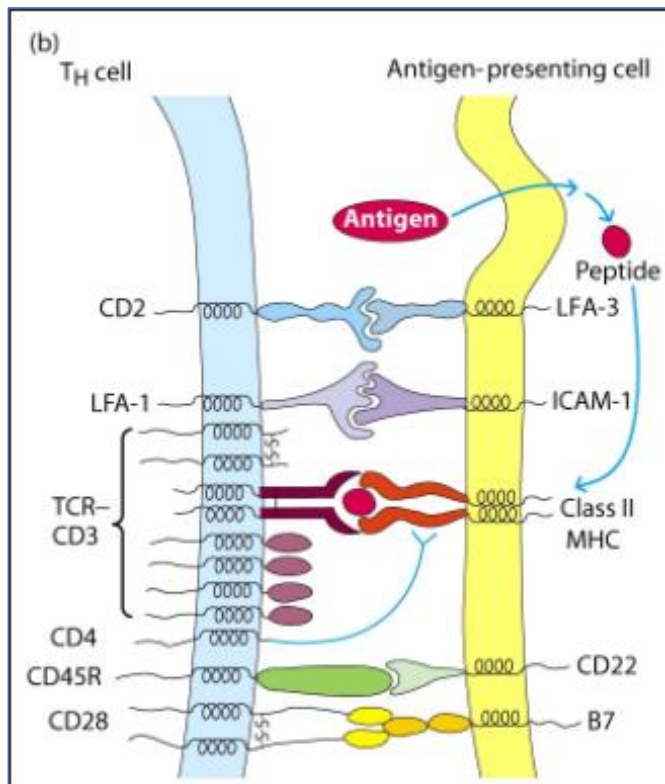
Antigen-presentation- MHC Class II

- Macrophages express a unique protein in their cell membranes: Major Histocompatibility Complex II (MHC II)
- After a pathogen has been phagocytosed and digested, its polypeptide antigens are presented to **helper CD4 + T lymphocytes** by the **MHC II** on the cell surface.

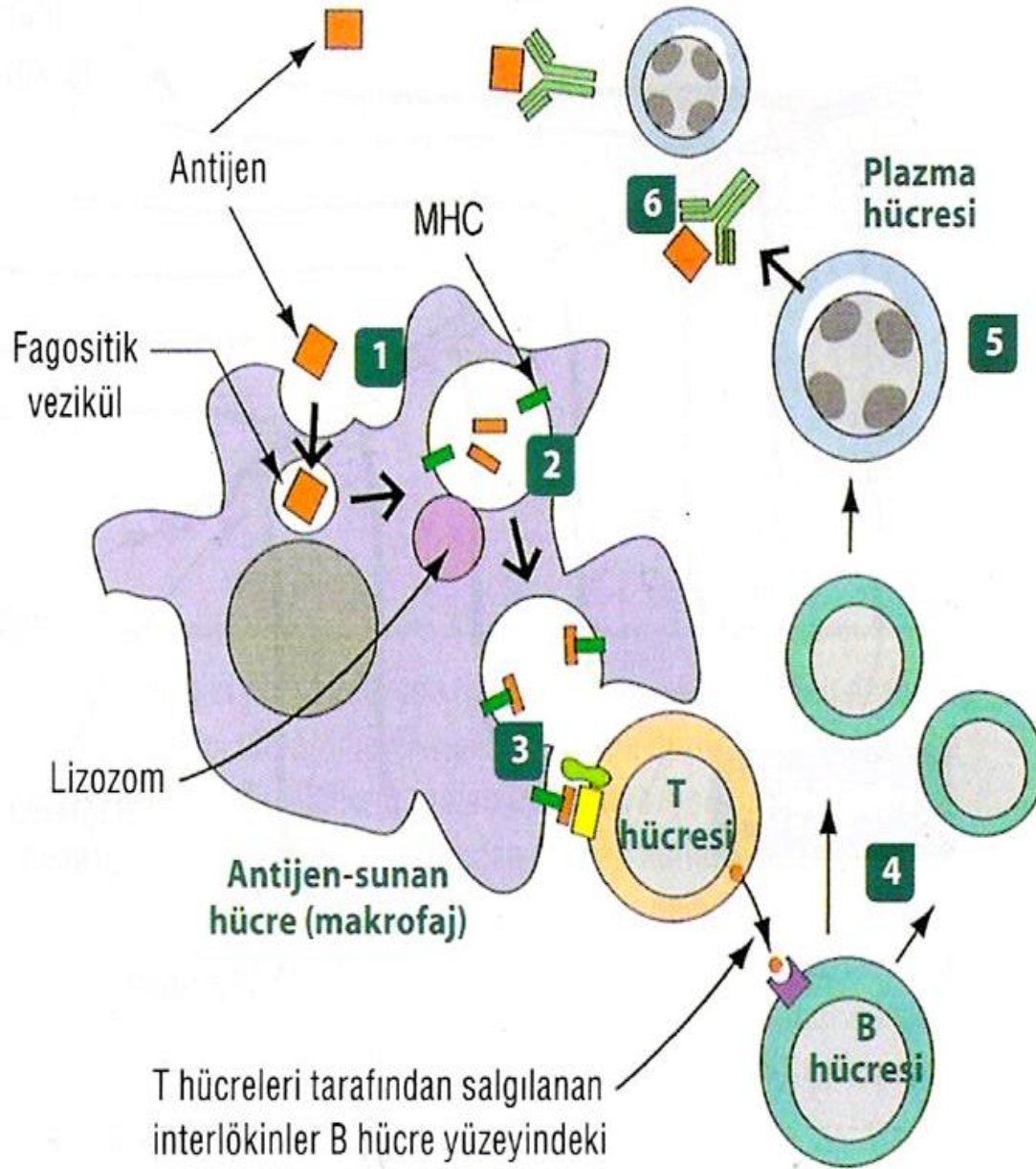


Antigen Presenting Cells

- Critical in initiating an immune reaction against a foreign antigen



- MHC-II-bound antigen is introduced by an «antigen-presenting cell» (macrophage) to CD4
- Activated Th lymphocytes attract more T cells by secreting IL-2 and differentiate B cells into plasma cells. Plasma cells produce antibody.

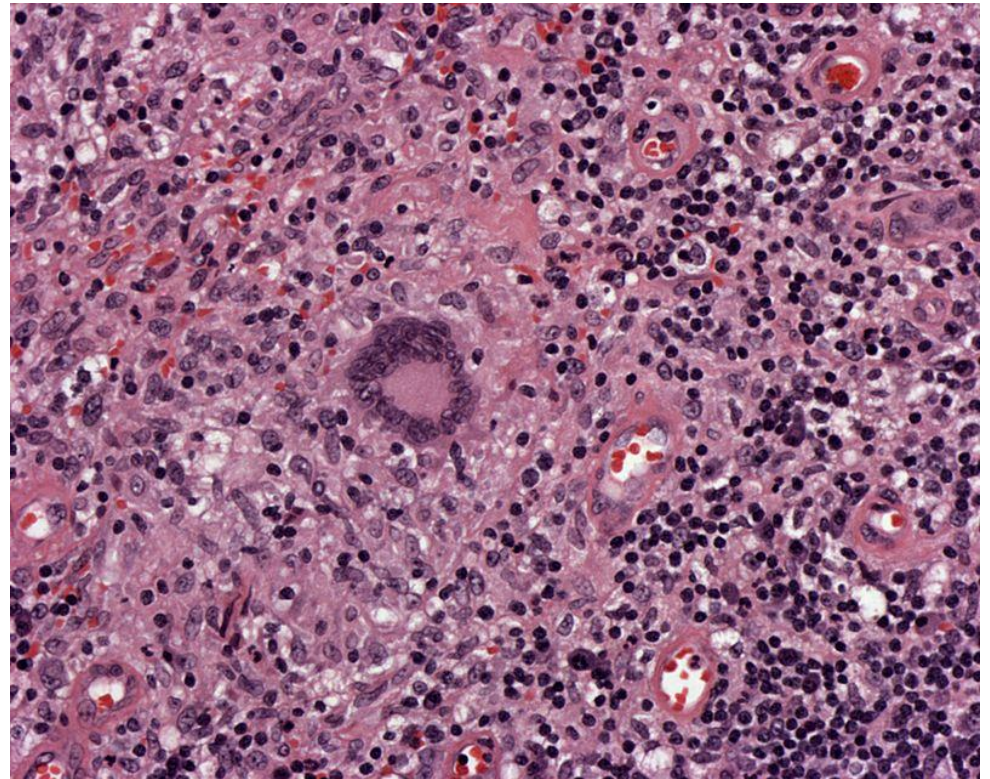


T hücreleri tarafından salgılanan interlökinler B hücre yüzeyindeki bir interlökin reseptörüne bağlanır

Langhans giant cells

No confusion with Langerhans cells

- In chronic, granulomatous diseases such as sarcoidosis, tuberculosis, macrophages are transformed into large, multi-nucleated (about 100) cells.

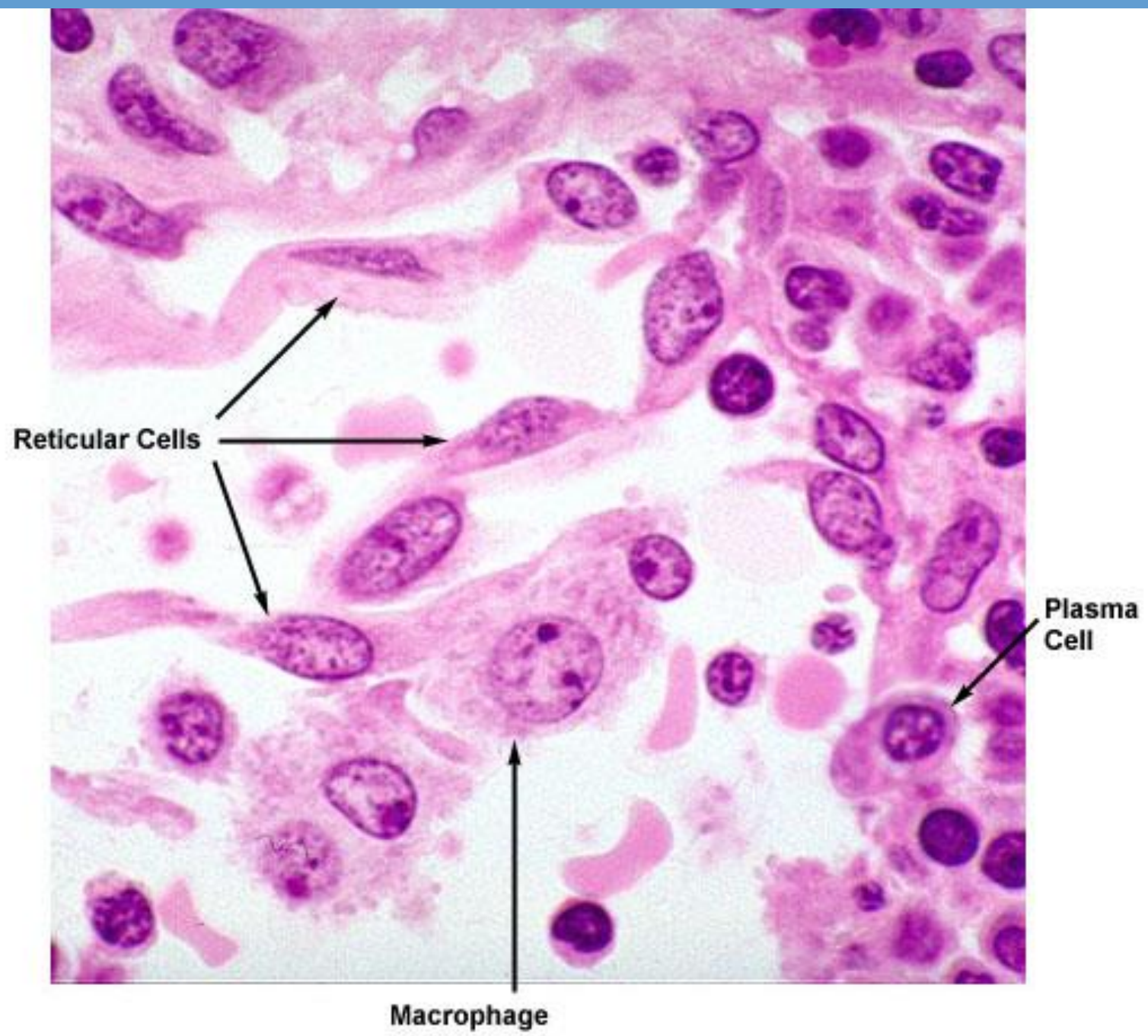




Antigen Presenting Cells

Mononuclear Phagocytic System Cells

Name of Cell	Location
Macrophage (histiocyte)	Connective tissue
Perisinusoidal macrophage (Kupffer cell)	Liver
Alveolar macrophage	Lungs
Fetal placental antigen-presenting cell (Hofbauer cell)	Placenta
Macrophage	Spleen, lymph nodes, bone marrow, and thymus
Pleural and peritoneal macrophage	Serous cavities
Osteoclast	Bone
Microglia	Central nervous system
Langerhans' cell	Epidemis
Fibroblast-derived macrophage	Lamina propria of intestine, endometrium of uterus
Dendritic cell	Lymph nodes, spleen

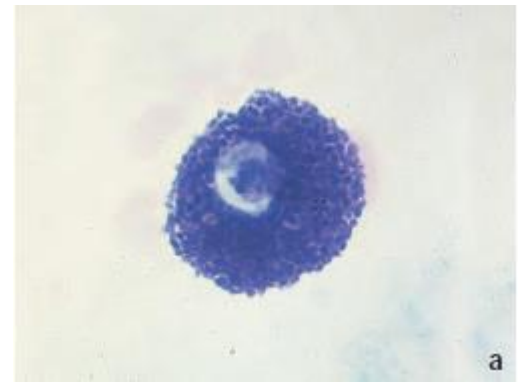


Reticular Cells

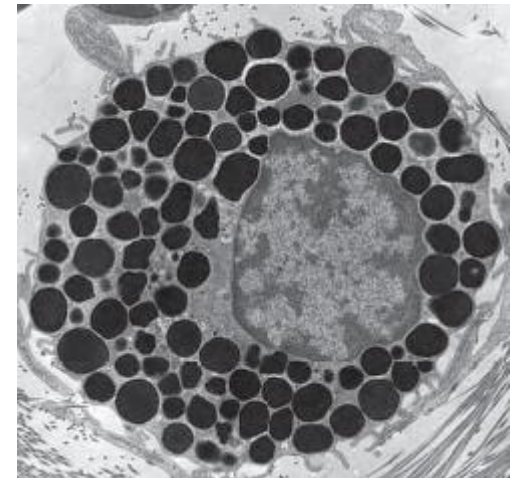
Plasma Cell

Macrophage

Mast Cells



- Connective tissue cells of bone marrow origin.
- Large, oval cells with a diameter of 20-30 μm
- Basophilic granules in the cytoplasm with round nucleus
- These granules are stained metachromatic with toluidin blue after gluteraldehyde fixation. This is caused by heparin and highly sulphated proteoglycans.



Mast Cells

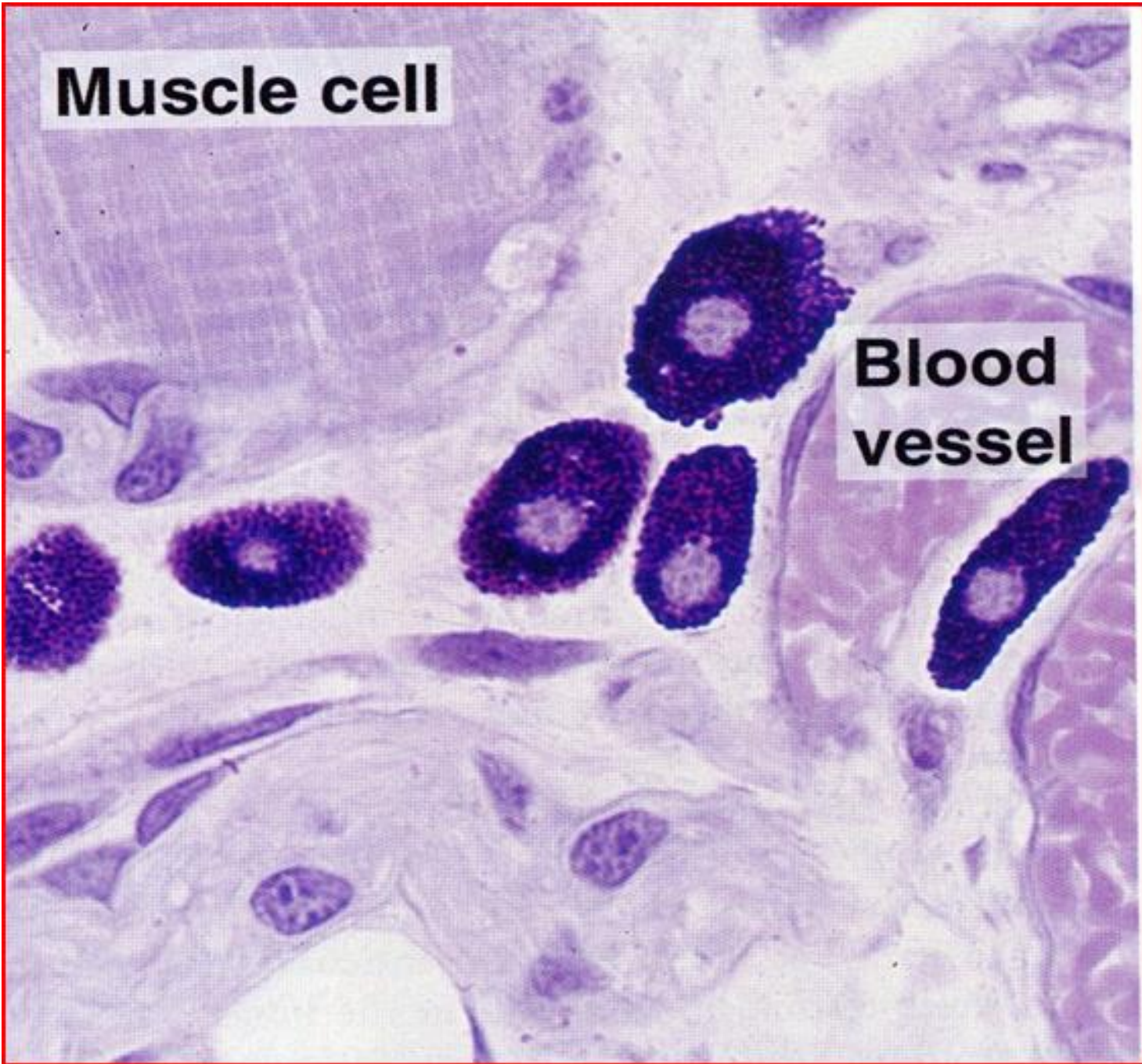
- They are similar but not the same as basophils.
- Both originate from bone marrow, from hematopoietic stem cells.
- The basophils mature in the circulation and remains in the circulation

Mast cell;

- When come out from the bone marrow, they have a monocyte-like, agranular appearance.
- When they migrate to the tissue, they mature and synthesize their granules. They have a life of 1-2 months.
- It contains high affinity Fc receptors for IgE and IgE binding activates emptying its granules to ECM

Muscle cell

Blood vessel



Mast Cells

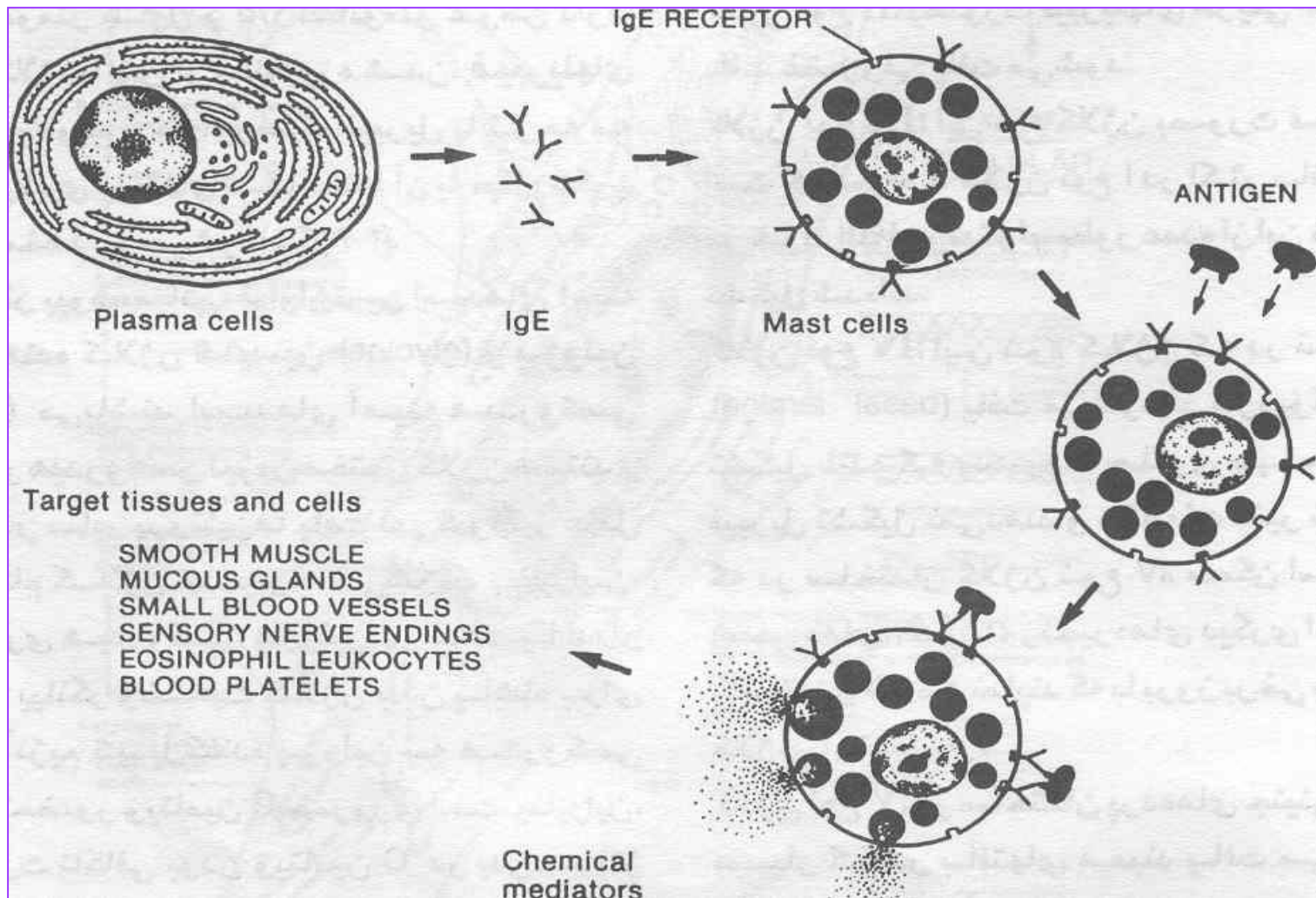
- Mast cells are abundant in the connective tissue of the skin and mucous membranes, but not in the brain and medulla spinalis (protecting CNS from edema and allergy)
- It is located around the small vessels in the skin, around the hair follicle, sebaceous glands and sweat glands.
- They are observed abundantly especially in the dermis, respiratory and digestive system mucosa.
- Abundant in thymus and other lymphatic organs, but not in the spleen

Mast cell granules

- Mediators that act on inflammation
- Secreted granules are two kind:
 - Produced and stored granules that are secreted after a stimulus
 - Immediately produced and secreted granules

- Granules that are stored in advanced:
- **Histamin:**
 - Increases permeability in small blood vessels
 - Increases edema and itching in skin and surrounding tissue
 - Increases mucus production in bronchi, contracts smooth muscles
- **Heparin:**
 - It is a sulfated GAG with anticoagulant properties.
 - Only produced in mast and basophil cells
 - Combines anti-thrombin III and FIV to stop clotting
- **Serine proteases:**
 - Tryptase; secreted from human mast cells, not secreted from the basophil. Activation marker of mast cells.
 - Chymase; Stimulates angiotensin II production in vascular injury and is responsible for apoptosis in the pathogenesis of atherosclerosis.
- **Eosinophil chemotactic factor (ECF) and neutrophil chemotactic factor (NCF)**

- Immediately produced and secreted granules
- **Leukotriene C:**
 - LTC₄ is secreted from the mast cell, degraded in ESM to form two metabolites: LTD₄ and LTE₄
 - They are secreted in anaphylactic reactions
 - Similar to histamine, they perform bronchoconstriction but do not respond to antihistamines.
- **Tumor Necrosis Factor α (TNF- α)**
 - It is a major cytokine produced by mast cells.
 - It increases the adhesion molecules in endothelial cells and has antitumor effects.
- **Interleukins (IL-4, -3 -5, -6, -8 and -16)**
- **Growth factors (GM-CSF)**
- **Prostaglandin D₂ (PGD₂)**



Mast cell secretion; it can be released by mechanical, chemical trauma, or sometimes released after contact with an antigen the body has already recognized.

FcεRI reseptörüne bağlanmış IgE

FcεRI reseptör

Antijen (allerjen)

1

1 Özgün (spesifik) bir antijen (allerjen de denen) FcεRI reseptörüne bağlanmış iki bitişik IgE reseptör molekülüne köprü yapar.

2 Sitosolik kalsiyum harekete geçer.

Ca²⁺

2

3 Granül ve lipid mediyatörleri ve sitokinler salınır

1-5 dakika

Granül mediyatörler

Histamin
Heparin
Triptaz
Kimaz

5-30 dakika

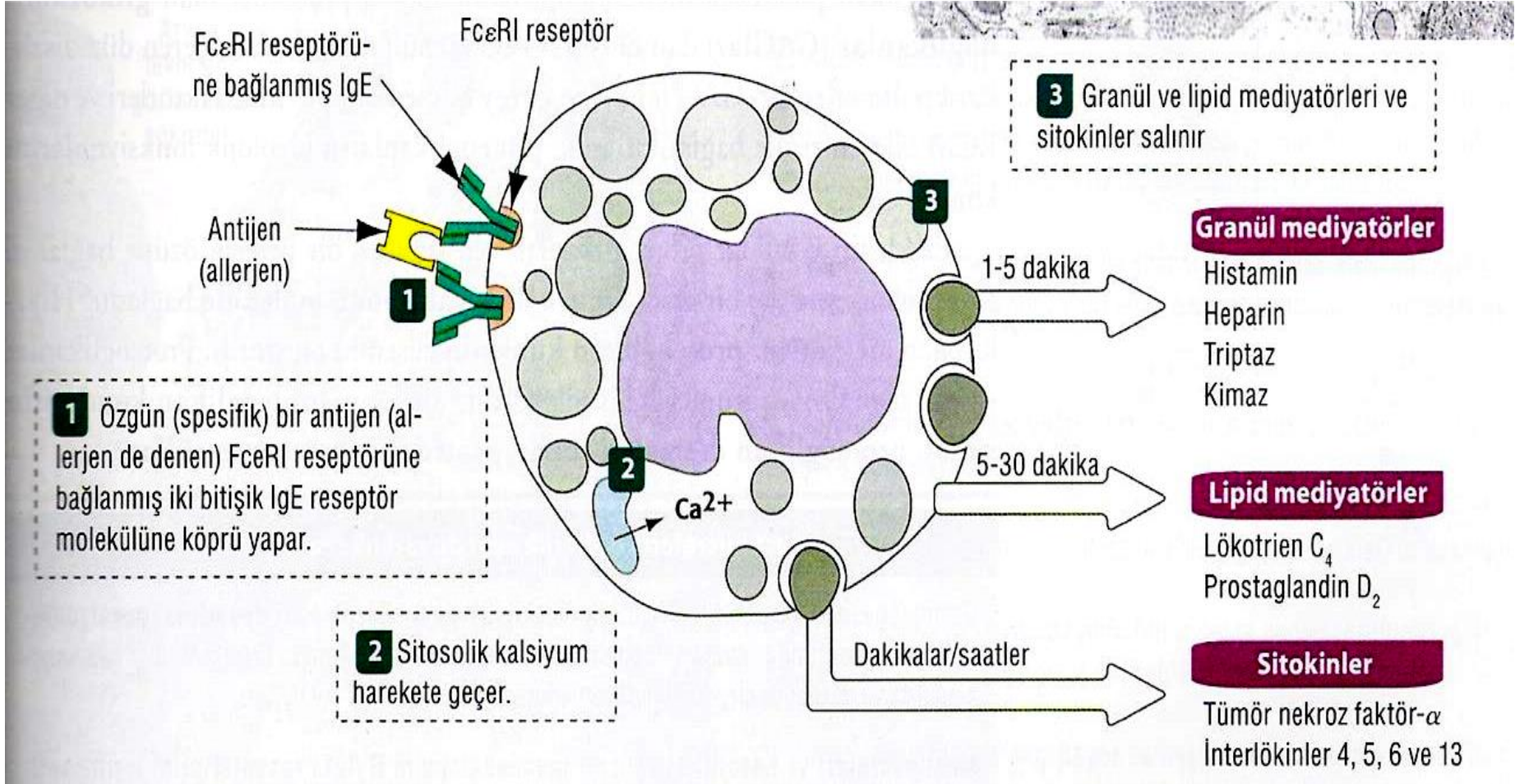
Lipid mediyatörler

Lökotrien C₄
Prostaglandin D₂

Dakikalar/saatler

Sitokinler

Tümör nekroz faktör-α
İnterlökinler 4, 5, 6 ve 13



Basophils

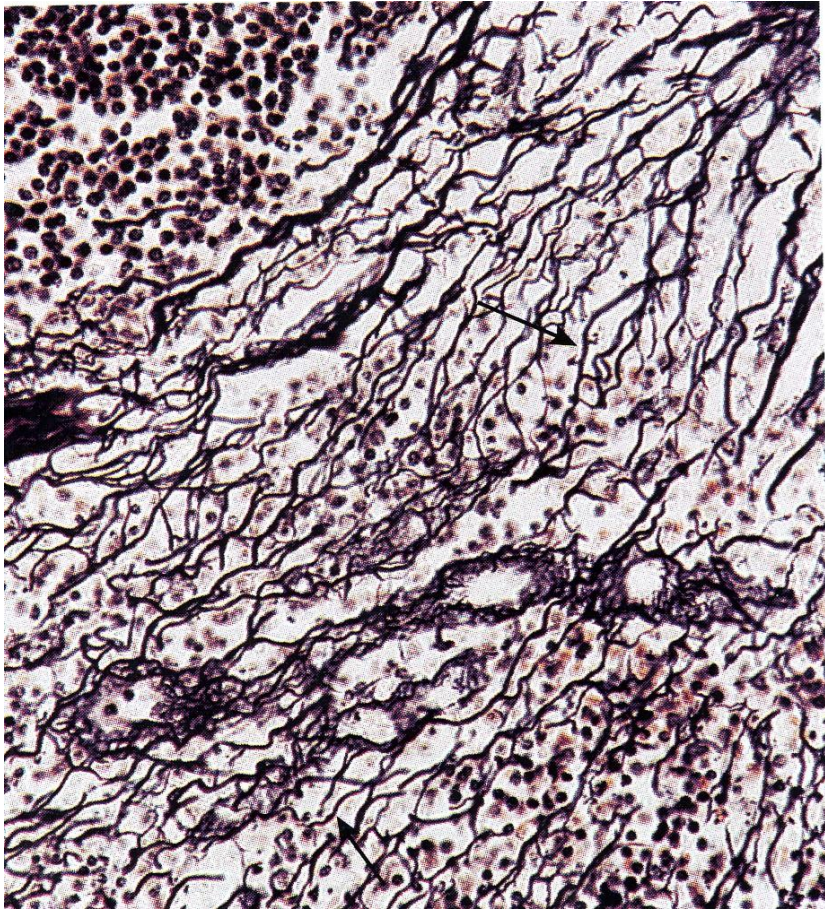
- Can penetrate into tissue and participate in inflammatory events
- There are Fc receptors that show affinity for IgE, like mast cells
- Release histamine, heparin, heparan sulfate, ECF, NCF
- They do not produce PGD₂ and IL-5, different from mast cells.

CHARACTERISTIC FEATURES	MAST CELLS	BASOPHILS
ORIGIN	Hemopoetik stem cell	Hemopoetik stem cell
DIFFERANTIATES IN	Connective tissue	Bone marrow
CELL DIVISION	Sometimes	None
LIFE SPAN	Weeks-Months	Days
SIZE	20-30 μm	7-10 μm
SHAPE OF NUCLEI	Round	Segmented Usually 2 lobes
GRANULES	Plenty, large, metachromatic	Few, small, basophilic
SURFACE Fc RECEPTORS	present	Present for Ig E antibody
MARKER OF CELL ACTIVATION	Tryptase	Not identified yet

Adipocytes

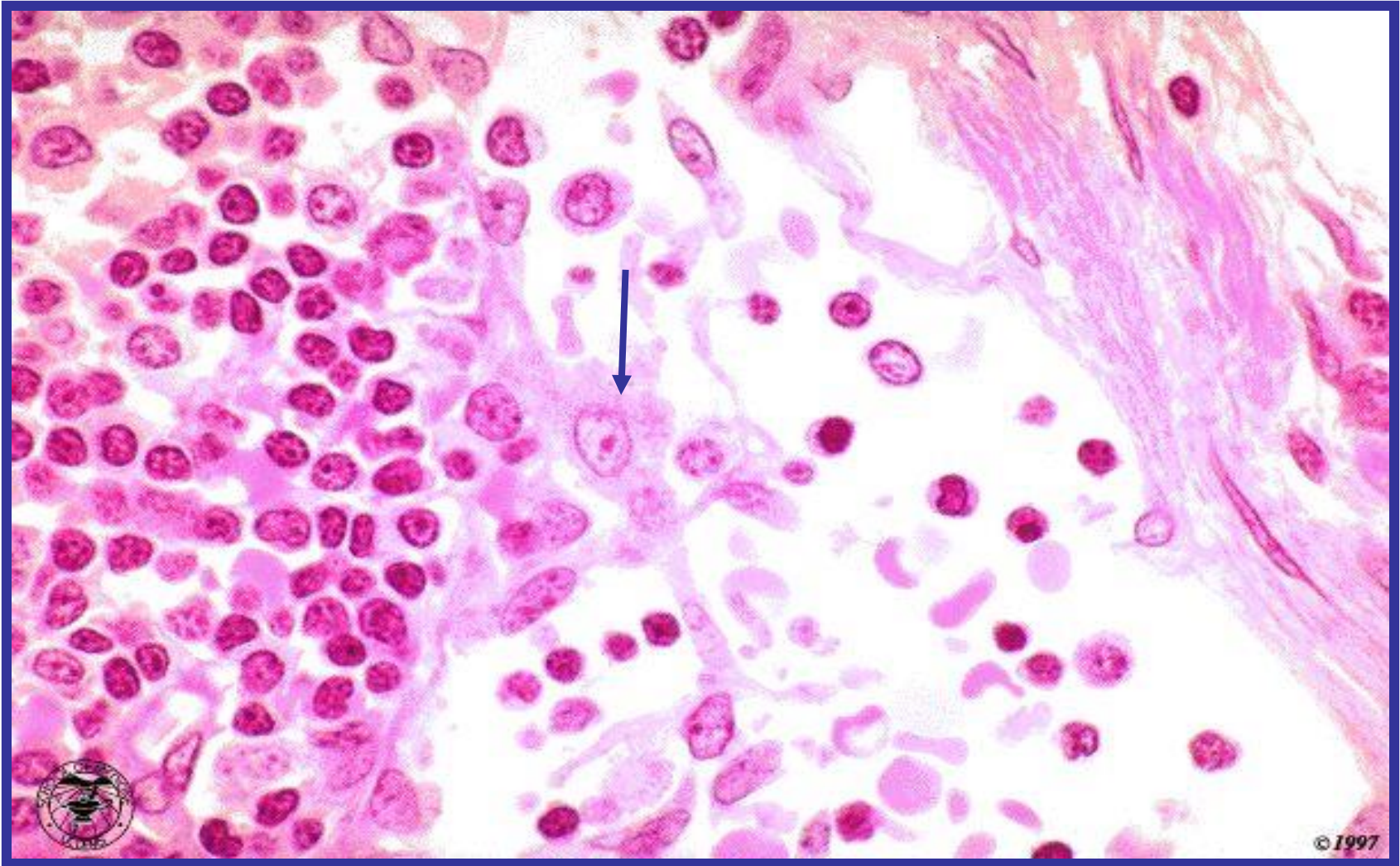
- Cells that are responsible for storing fat in the connective tissue and secreting some hormones
- They are differentiated from mesenchymal stem cells and store fat in their cytoplasm
- They can be found in connective tissue in single or group form.
- Named after adipose tissue when abundantly clustered

Reticular cells



- Star-shaped cells
- It is actually a modified fibroblast
- Has large euchromatic nuclei
- Ability to differentiate into different cells and **phagocytosis**
- They are found in the reticular connective tissue (lymph node, spleen, etc.).

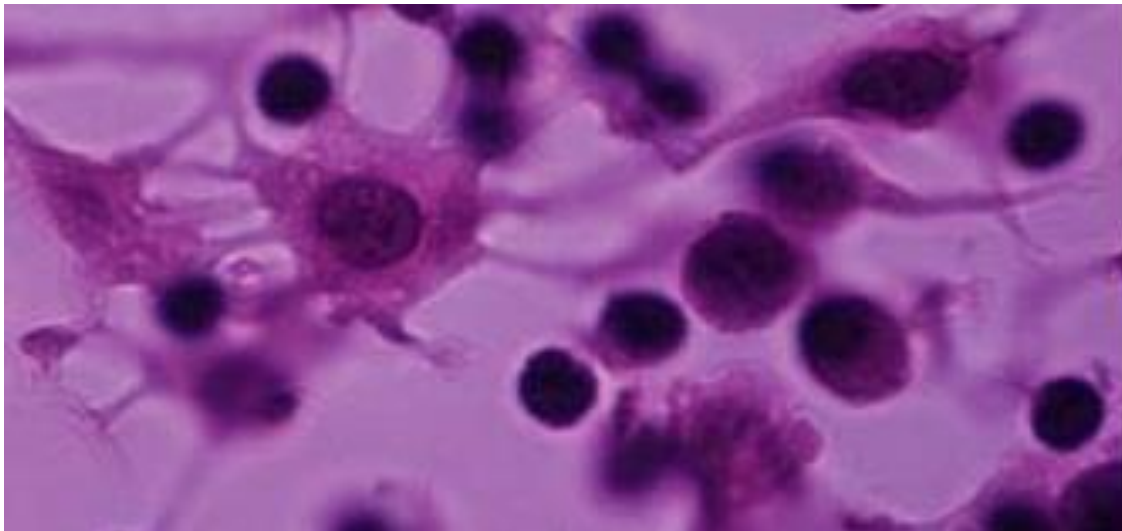
Reticular cells



Reticular cells; are divided into two subgroups considering their morphology and functions:

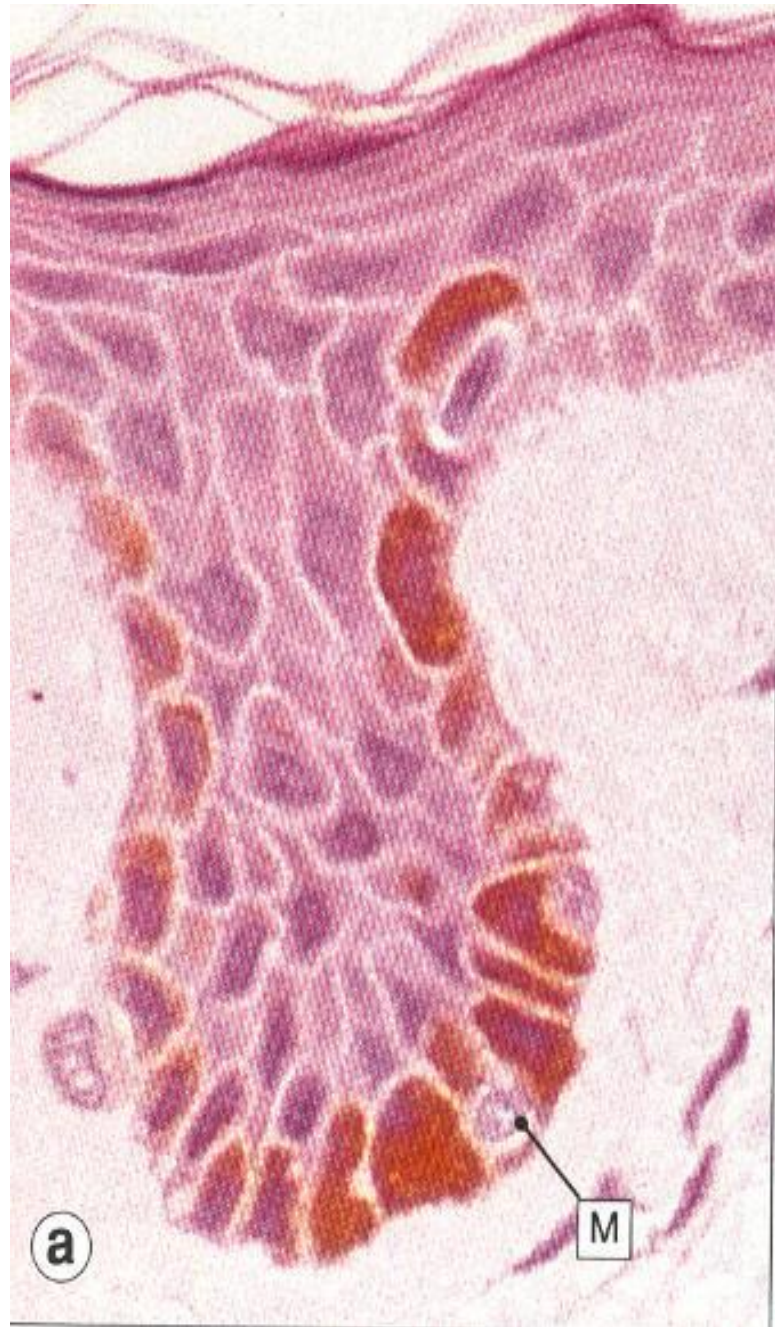
Primitive Reticular Cells: This type, which can differentiate into different cells, sometimes synthesizes reticular fibrils, but does not have a phagocytic function.

Phagocytic Reticular Cells: They are fixed macrophages. It has marked phagocytosis.



- **PIGMENT CELLS**

- Pigment-bearing cells (**Chromotophores**) are rarely found in loose connective tissue, but abundant in the tight connective tissue of the skin, pia mater, and eye.
- Cells carrying melanin pigment are called **melanocytes**.
- These cells, which originate from neural crista (ectodermal), not from the mesenchym, have irregular cytoplasmic extensions.
- Both the cytoplasm and its extension have abundant granules called **melanosomes**.
- Melanosomes are ovoid endogenous inclusions surrounded by membranes



Adult stem cells

- Tissue stem cells are unipotent and are located in areas called niches (except bone marrow)
- In bone marrow, there are 2 types of stem cell groups except hematopoietic stem cells;
 - multipotent adult progenitor cells
 - Bone marrow stroma cells
- Adult stem cell niches are called mesenchymal stem cells and are located in loose connective tissue

Pericytes

- **Pericytes**, also called **adventitial cells** or **perivascular cells**, are found around capillaries and venules
- Several observations support the interpretation that vascular pericytes are indeed **mesenchymal stem cells**.
- The pericyte is typically wrapped, at least partially, around the capillary, and its nucleus is similar to that of endothelial cells
- They can differentiate into **smooth muscle cells** during novel vessel formation
- In different studies they are noticed to differentiate into **osteoblasts, adiposites, chondrocytes, fibroblasts** as mesenchymal stem cells

Immune cells in connective tissue

Lymphocytes:

- Among the variable cells in the connective tissue, lymphocytes are the **smallest** in size.
- Dark stained **heterochromatic** nucleus surrounded by a thin cytoplasm rim
- They are normally found in small numbers, but their numbers increase with the presence of a pathogen.
- Patrol lymphocytes are common in the respiratory and gastrointestinal tract **lamina propria**, the main entry gate of pathogens.

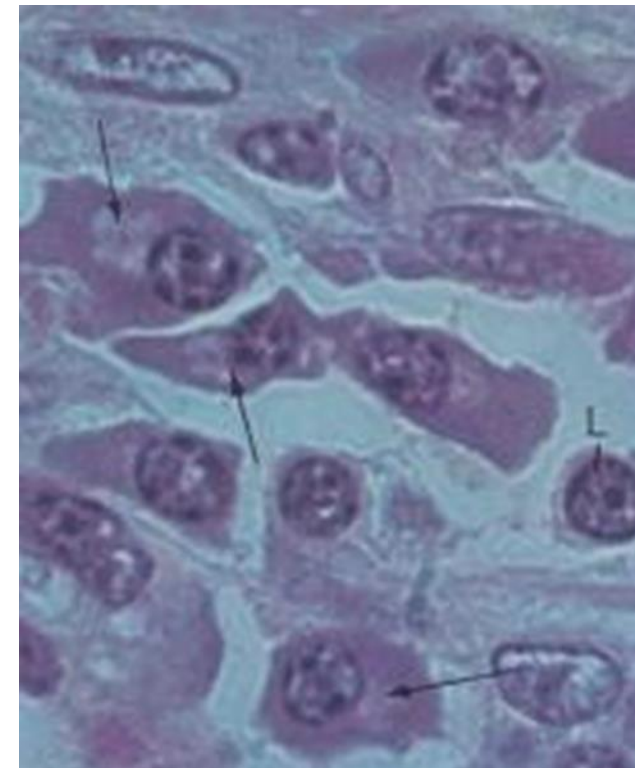
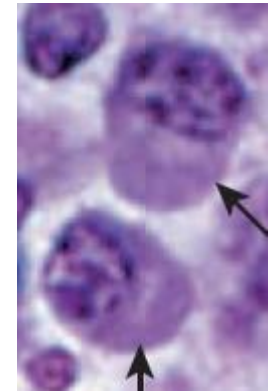
CD: cluster of differentiation

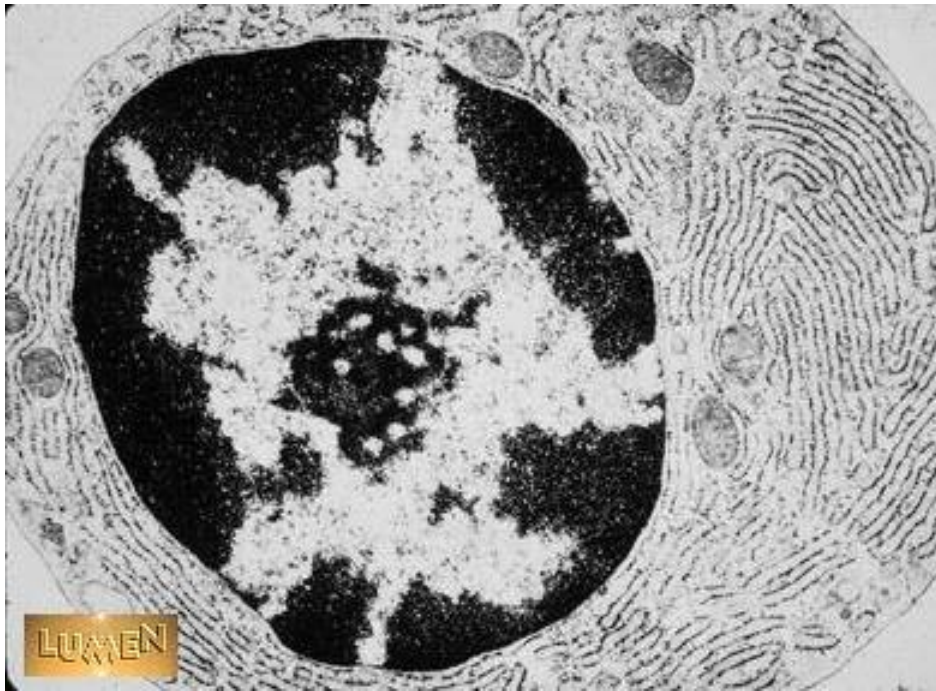
Lymphocytes

- **T-lymphocytes** : CD2, CD3, CD5 ve CD7. Cellular immunity
- **B-lymphocytes** : CD9, CD19 ve CD20. Superfacial IgM and IgD bindings. They differantiate into **Plasma cells**.
- **NK cells**: CD16, CD56 ve CD94. They do not act antigen specific, they destroy virus-infected cells and some tumor cells by cytotoxic mechanism.

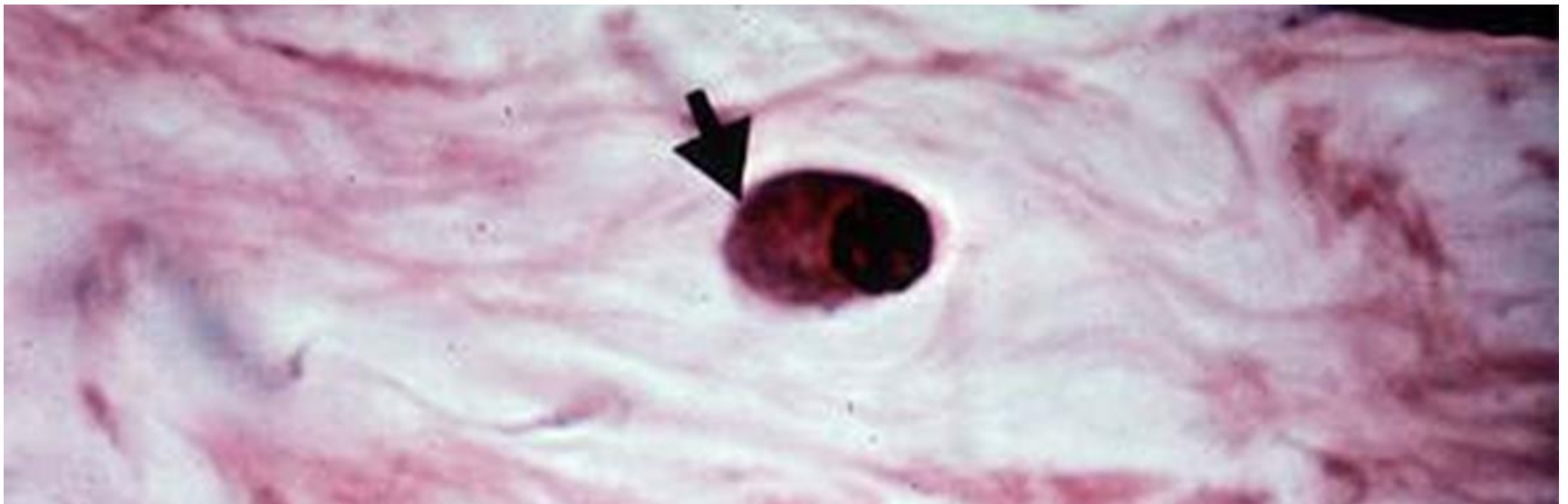
Plasma cells

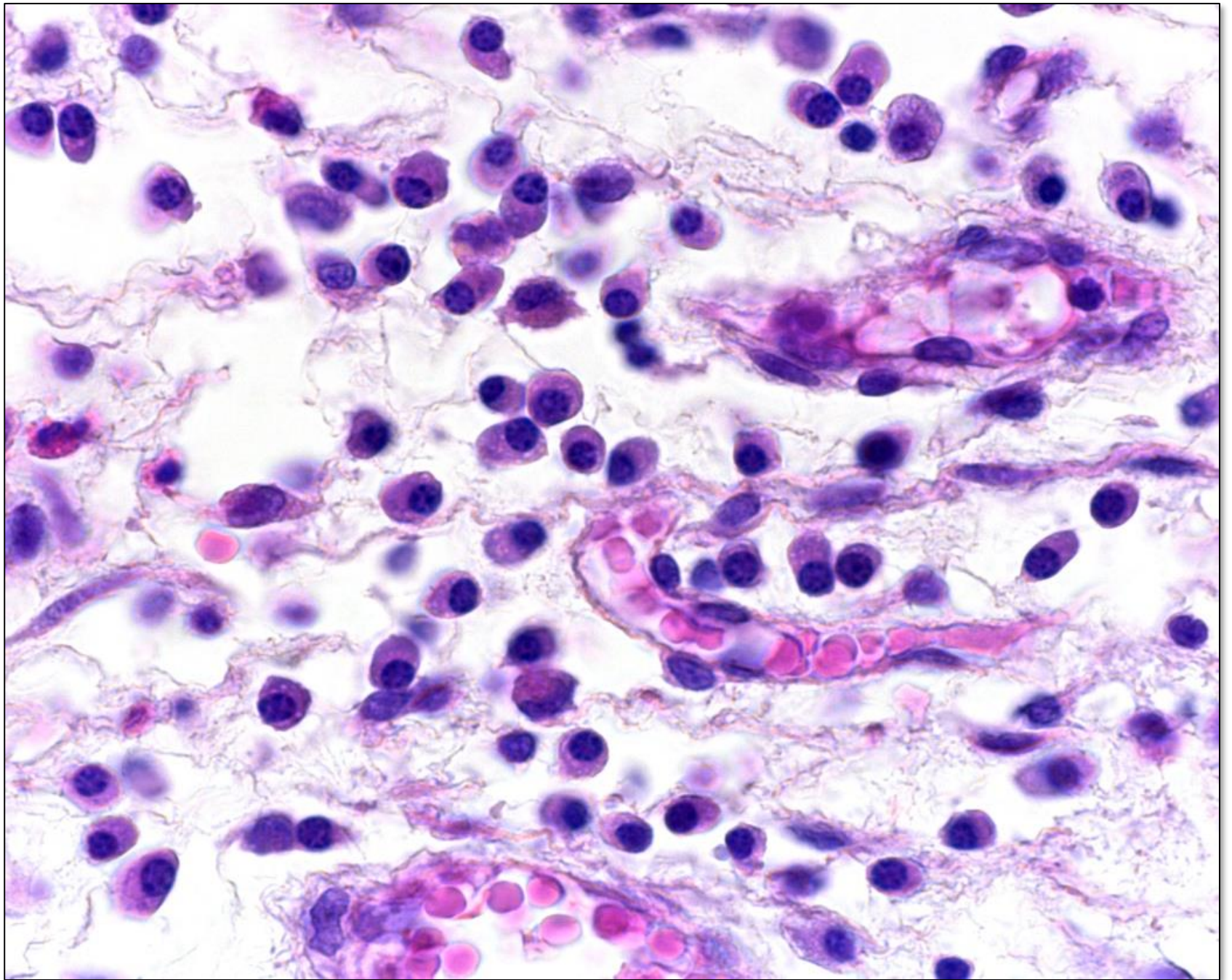
- Antibody producing cells originated from B-lymphocytes
- They are found abundant in loose connective tissue (lamina propria) of respiratory and GIS, where antigens mostly enter
- They are also found in lymph node, salivary gland and hematopoietic tissue.
- After conversion from B-lymphocyte, the plasma cell does not move much and has a life span of about 10-30 days.
- They are large, oval cells. The cytoplasm is basophilic due to intense GER. Golgi body stands out as a clear area in the basophilic cytoplasm.
- The nucleus is round, eccentric and heterochromatic. Although it synthesizes intense protein synthesis, chromatin is dense since it synthesizes uniform protein. Nucleus is stained like a horse carriage wheel





Electron microscopic image of plasma cell. The alignment of the chromatins in the nucleus looks like a carriage wheel. GER is quite abundant in the cytoplasm.





Other defence cells

- With antigenic stimulation, the defense cells in the blood, especially neutrophils and monocytes, pass into the connective tissue.
- The presence of these cells means acute inflammation.
- Monocytes will turn into macrophages
- Eosinophils may be involved in connective tissue, especially in allergic and parasitic diseases and chronic infections.

