CELLS AND MEDIATORS OF CHRONIC INFLAMMATION

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Learning objectives:

- By the end of this lecture student should be able to;
- Discuss cells of chronic inflammation
- Discuss activation of cells and role of mediators in activation of cells.
- Understand interplay between these cells.

- Chronic inflammation is characterized by leukocyte infiltration, tissue damage and fibrosis.
- These effects brought about by different cell types.
- Three types of cells take part in chronic inflammation.

1. Macrophages
2. Lymphocytes
3. Plasma cells

- Others include Eosinophils and Mast cells.

- **Macrophages:**
- Macrophages, the dominant cells of chronic inflammation, are tissue cells derived either from circulating blood monocytes after their emigration from the bloodstream or directly from yolk sac and fetal liver (early development).

- Monocyte to macrophage transformation occurs in inflammatory response, skin and GIT.
- Those derived directly from yolk sac or liver are specific ones residing in liver, spleen, lungs etc.

- So macrophages come from two sources.

1. From blood monocytes, which reside in skin and GIT and take part in inflammation.

- The half-life of monocytes is about 1 day, whereas the life span of macrophages is several months or years.

2. Those directly arising from fetal liver and yolk sac, reside in spleen (sinus histiocytes),

in CNS (microglia), in liver (kupffer cells) and in lungs (alveolar macrophages) etc.

- These macrophages become resident and remain stable throughout the life in these tissues.
- During inflammation, monocytes emigrate and become macrophages very early.
- Within 48 hours become dominant cells of interstitial tissue.

- Macrophages form Mononuclear Phagocyte System (MPS) together with neutrophils.
- The older misnomer is reticuloendothelial system.
- Macrophages have got different names in different tissues

1. Kupffer cells (liver)

2. Sinus histiocytes (spleen and lymph nodes)
3. Microglia or Microglial cells (CNS)
4. Alveolar macrophages (lung)
5. Langerhan cells (skin)
6. Mesangial cells (kidney)

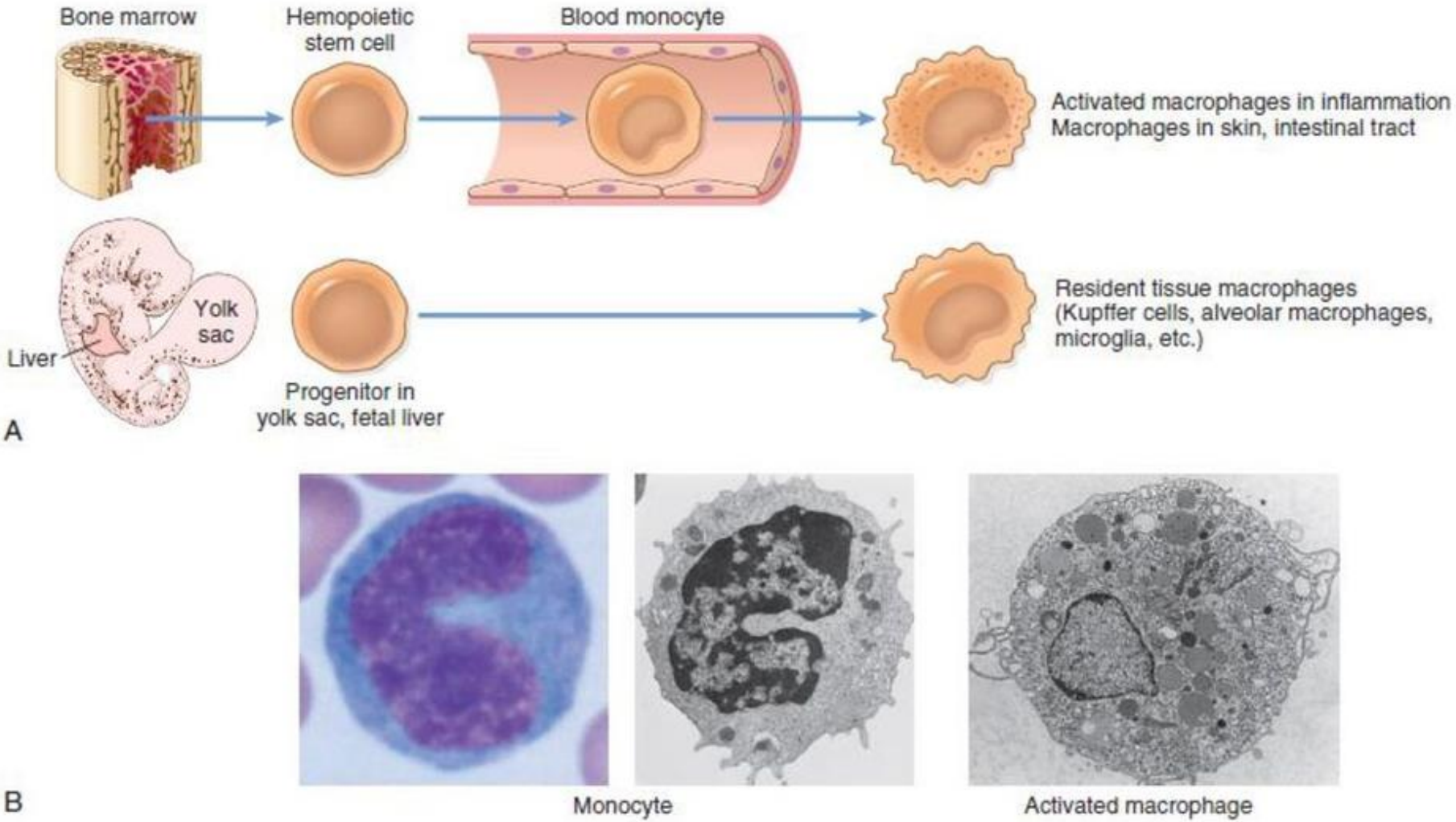
- Tumor-associated macrophages (TAMs) can recognize and lyse tumor cells.

- Macrophages perform different functions.

1. They are the professional phagocytes
2. Initiate the process of tissue repair and involved in fibrosis and scar formation.
3. Secrete mediators of inflammation, like TNF, IL-1, chemokines, and others.

- So contribute to the initiation and propagation of inflammatory reactions.

4. Act as antigen presenting cells and thus stimulate other cells like T lymphocytes


Bone marrow
Hemopoietic stem cell
Blood monocyte
Activated macrophages in inflammation
Macrophages in skin, intestinal tract
Yolk sac
Liver
Progenitor in yolk sac, fetal liver
Resident tissue macrophages (Kupffer cells, alveolar macrophages, microglia, etc.)
A
B
Monocyte
Activated macrophage

- There are two pathways of macrophage activation.

1. Classical
2. Alternative

- Macrophages activated by classical pathway are called M1 macrophages.
- Activated by;

a. Microbial products like endotoxin.
b. INFγ produced by CD4+ cells

- CD4+ cells secrete INF γ when they combine with macrophages (after antigen presentation) or

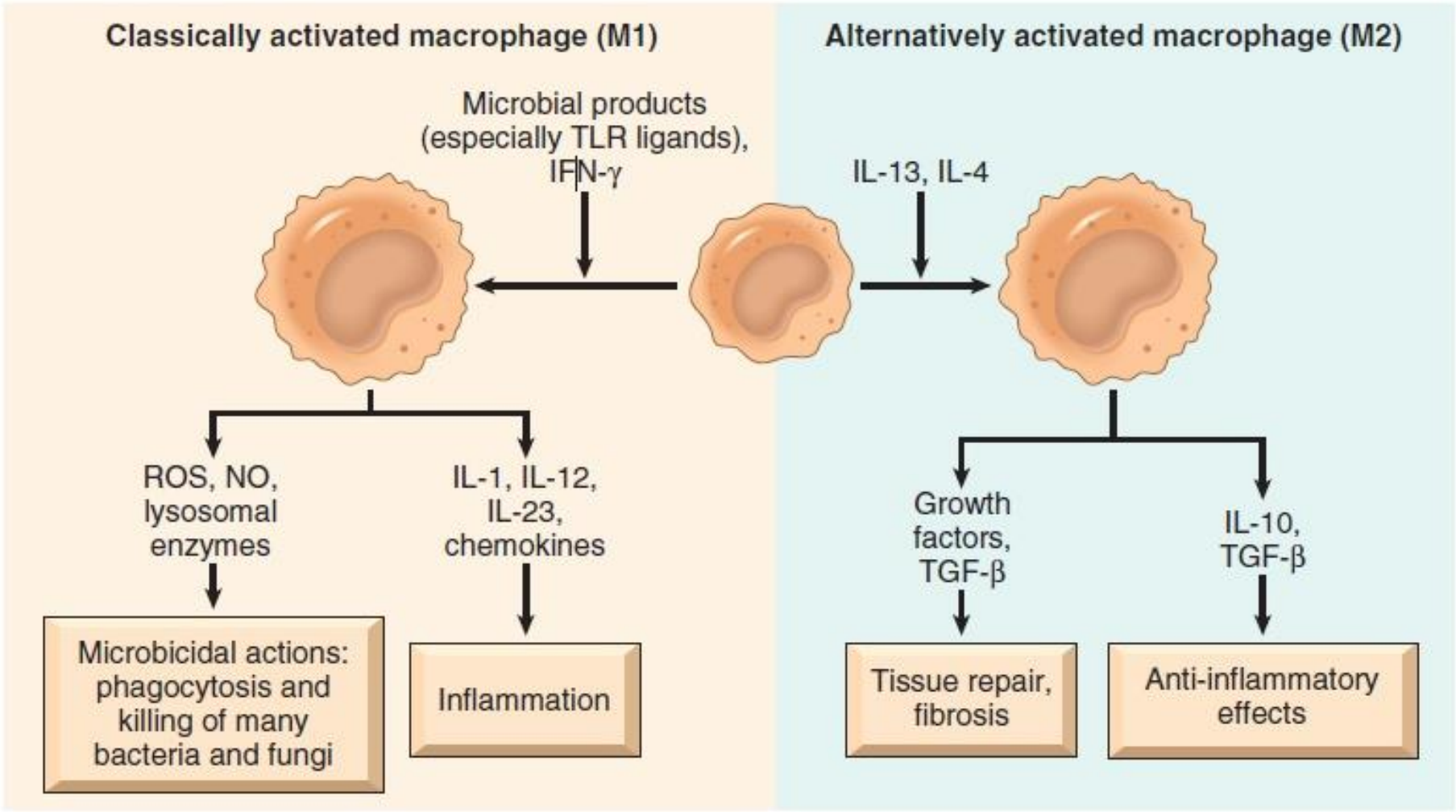
c. Foreign bodies like crystals and particulate matter.

- M1 macrophages produce NO, ROS and lysosomal enzymes.
- These substances then mount inflammatory response.
- So, M1 are involved in inflammation.

- Alternative pathway produces M2 macrophages.
- T lymphocytes produce IL-4 and IL-13 which in turn stimulate the macrophages.
- M2 cells take part in healing and repair and termination of inflammation.
- Not microbicidal.

- They secrete growth factors that promote angiogenesis, activate fibroblasts, and therefore collagen synthesis.
- It seems M2 are produced after M1.
- But such typical situation probably does not occur.
- There may be types in between M1 and M2.

- Macrophages play important role in inflammation due to mediators.
- Same mediators are the cause of tissue destruction (exaggerated activation of macrophages).
- So the routine tissue destruction in chronic inflammation is also due to macrophages and their mediators.


Classically activated macrophage (M1)
Alternatively activated macrophage (M2)
Microbial products (especially TLR ligands), IFN-γ
IL-13, IL-4
ROS, NO, lysosomal enzymes
IL-1, IL-12, IL-23, chemokines
Growth factors, TGF-β
IL-10, TGF-β
Microbicidal actions: phagocytosis and killing of many bacteria and fungi
Inflammation
Tissue repair, fibrosis
Anti-inflammatory effects

- Lymphocytes:
- They are mobilized to the site of inflammation.
- Both T and B lymphocytes migrate into inflammatory sites.
- Macrophages activate lymphocytes which in turn activate macrophages and so in this way the process of chronic inflammation continues.

- Lymphocytes are further classified into different types.

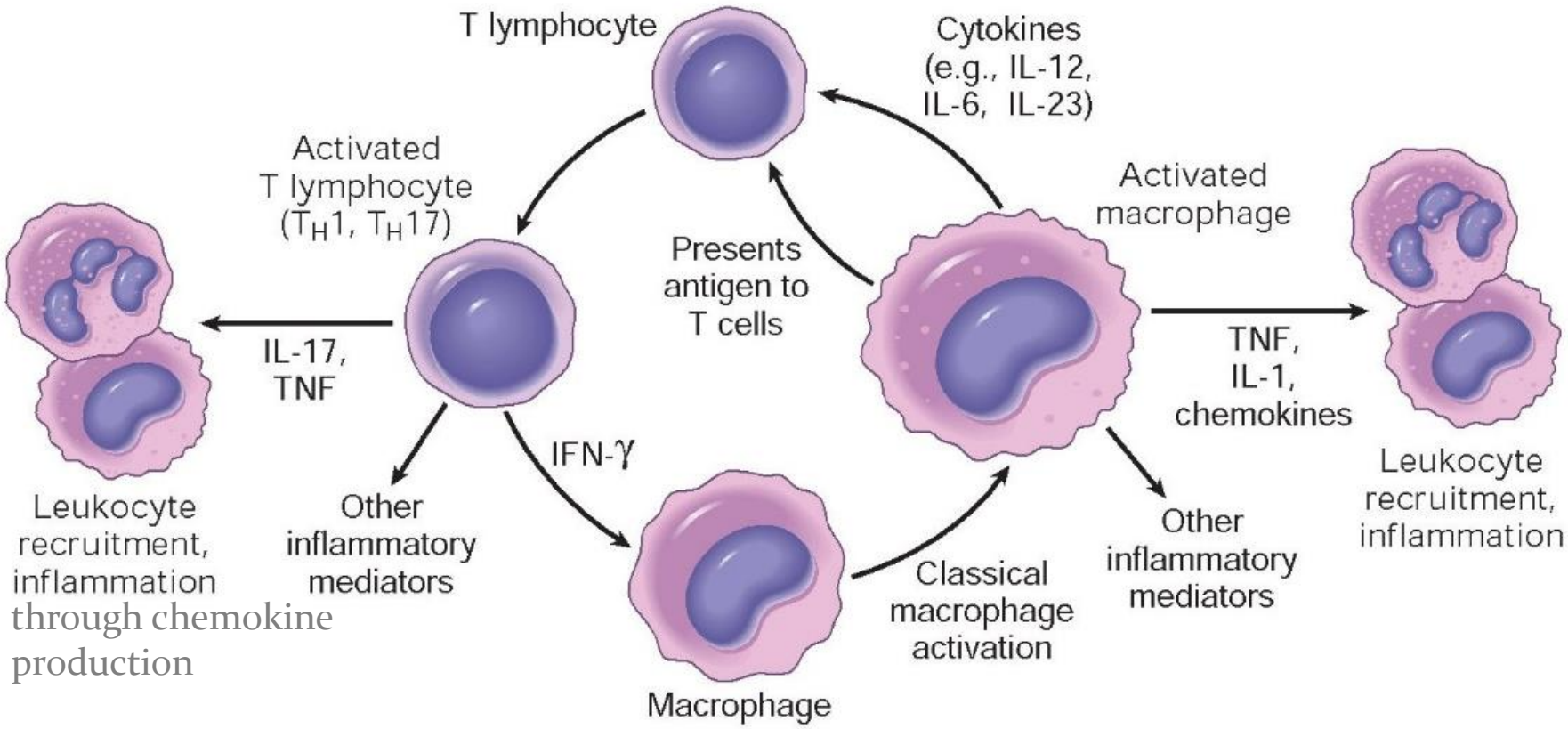
a. T lymphocytes
    i. Helper T cells (CD4+)
    ii. Cytotoxic T cells (CD8+)
    iii. Regulatory T cells
b. B lymphocytes
c. Natural killer cells

- T Lymphocytes:

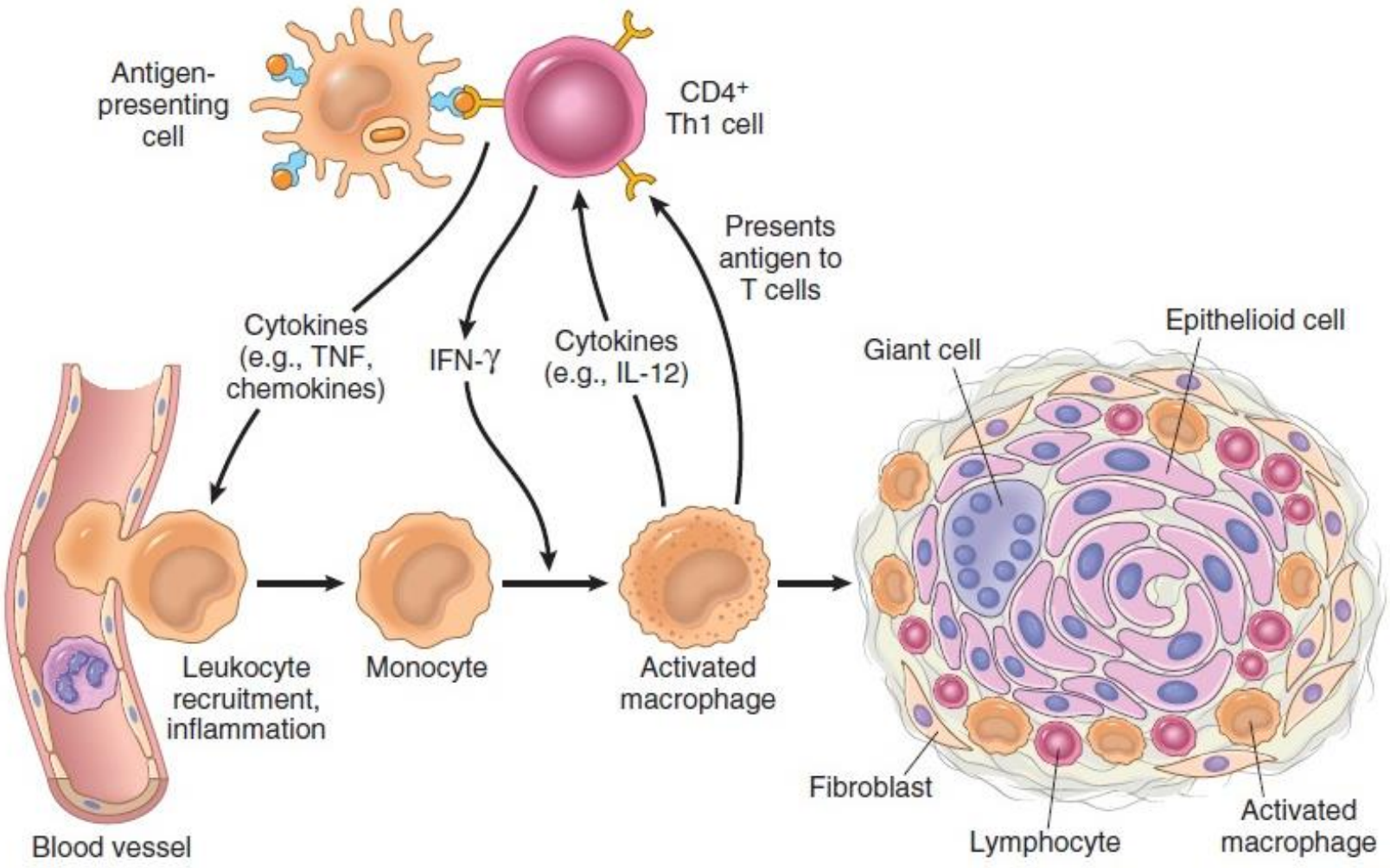
- Lymphocytes that have matured in the thymus.
- T cells make 60% to 70% of the lymphocytes in peripheral blood.
- Helper T cells (CD4+ T cells):
- There are three subsets of CD4+ T cells.

1. Th1 cells produce cytokine IFN-γ, which activates macrophages by classical pathway.

2. Th2 cells secrete IL-4, IL-5, and IL-13, which recruit and activate eosinophils and are responsible for alternative pathway of macrophage activation.
3. Th17 cells secrete IL-17 and other cytokines, which induce the secretion of chemokines responsible for recruiting neutrophils (and monocytes).



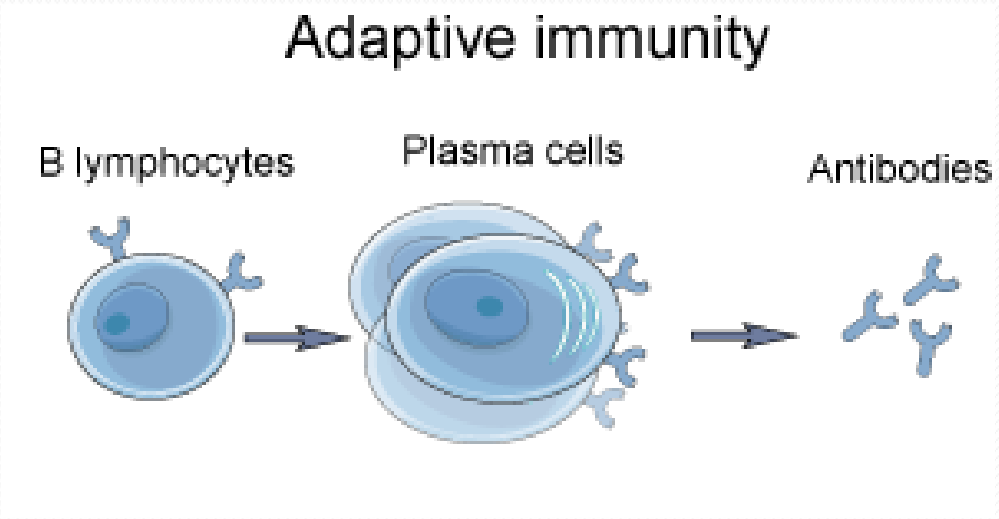
through chemokine production


Antigen-presenting cell
CD4+ Th1 cell
Presents antigen to T cells
Cytokines (e.g., TNF, chemokines)
IFN-γ
Cytokines (e.g., IL-12)
Epithelioid cell
Giant cell
Leukocyte recruitment, inflammation
Monocyte
Activated macrophage
Fibroblast
Lymphocyte
Activated macrophage
Blood vessel

- Cytotoxic T cells: can secrete cytokines, but their most important role is to directly kill virus-infected cells and tumor cells.
- Regulatory T lymphocytes function to suppress immune responses.
- Maintain tolerance to self-antigens and prevent autoimmune diseases.

- NK cells are lymphocytes that arise from the same common pool that gives rise to T lymphocytes and B lymphocytes.
- But, NK cells are cells of innate immunity as they are functional without prior activation.

- B Lymphocytes
- B (bone marrow–derived) lymphocytes are the cells that produce antibodies, the mediators of humoral immunity.
- B cells make up 10% to 20% of the circulating peripheral lymphocyte population.

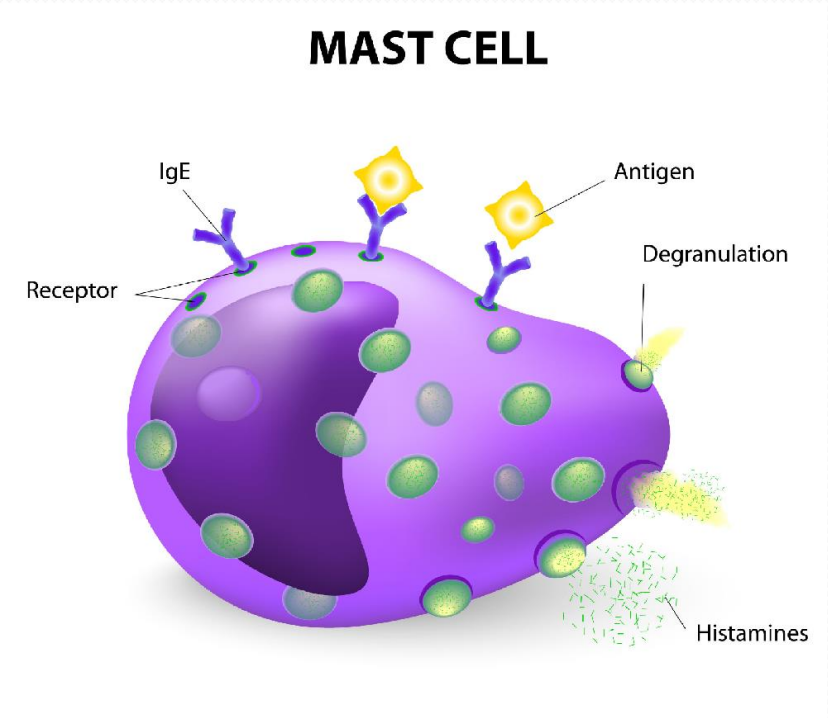


- **<u>Eosinophils</u>:**
- They are found in inflammatory sites around parasitic infections or as part of allergic reactions mediated by IgE.
- Their recruitment is driven by adhesion molecules (those used by neutrophils) and by specific chemokines (e.g. eotaxin)

- Eosinophil granules contain major basic protein, a highly charged cationic protein that is toxic to parasites and epithelial tissues as well.

- **Mast cells:**
- Are widely distributed in connective tissues throughout the body, and they can participate in both acute and chronic inflammatory responses.
- In atopic individuals (individuals prone to allergic reactions), mast cells are "armed" with IgE antibody specific for certain environmental antigens.

- Mast cells express on their surface the receptor (FcεRI) that binds the Fc portion of IgE antibody
- They release histamine when specific antigen/allergen comes in contact and bind IgE antibodies.



THANK YOU