LECTURE: 03

Title: CELLS INVOLVED IN THE IMMUNE RESPONSE

LEARNING OBJECTIVES:

The student should be able to:

- **Identify the organs where the process of the blood formation occurs.**
- **Identify the main cell type that produces all the immune cells.**
- **Determine the site of the first appearance of the stem cell.**
- **Enumerate the different given names of the stem cells.**
- **Identify the site of production, and maturation for all immune cells, and where each resides during the lifetime.**
- **Illustrate the immune cells classification, and the main function (s).**
- **Enumerate the different types of mononuclear and polymophonuclear phagocytes.**
- **Enumerate the different names given for the macrophages.**
- **Enumerate the most common antigen presenting cells.**
- **Compare between the mononuclear and polymophonuclear phagocytic cells in regarding to their functions.**
- **Differentiate between resting T, B, and NK cells.**
- **Describe the resting T- and B lymphocytes, and compare them to Natural killer cell.**
- **Identify the different accessory cells.**

LECTURE REFRENCE:

1. Visit my web site at www.Mlinjawi@kau.edu.sa

2. TEXTBOOK: ROITT, BROSTOFF, MALE
IMMUNOLOGY. 6th edition. Chapter 1. pp 1-4
Chapter 2. pp. 15-30
3. TEXTBOOK: Lauren Sompayrac
How the Immune system works. Chapter 1. pp 05-15

4. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR IMMUNOLOGY. 5TH EDITION. Chapter 2. pg 16-26.

CELLS INVOLVED IN THE IMMUNE RESPONSE

Allah the creator provides our bodies with different types of cells in order to protect us from microbes. These cells are called the immune cells, and all are formed during the development of our lives.

■ During our bodies development, all blood are formed

Haemopoiesis (blood formation)**, begins** in the **yolk sac (the major haematopoietic organ in the embryo),** then in the **liver** and shifts sometimes to the **spleen,** and **finally** in the **neonatal bone marrow ~ 16 weeks and continues after birth, for most life, until old ages, it is produced be the flat bones.**

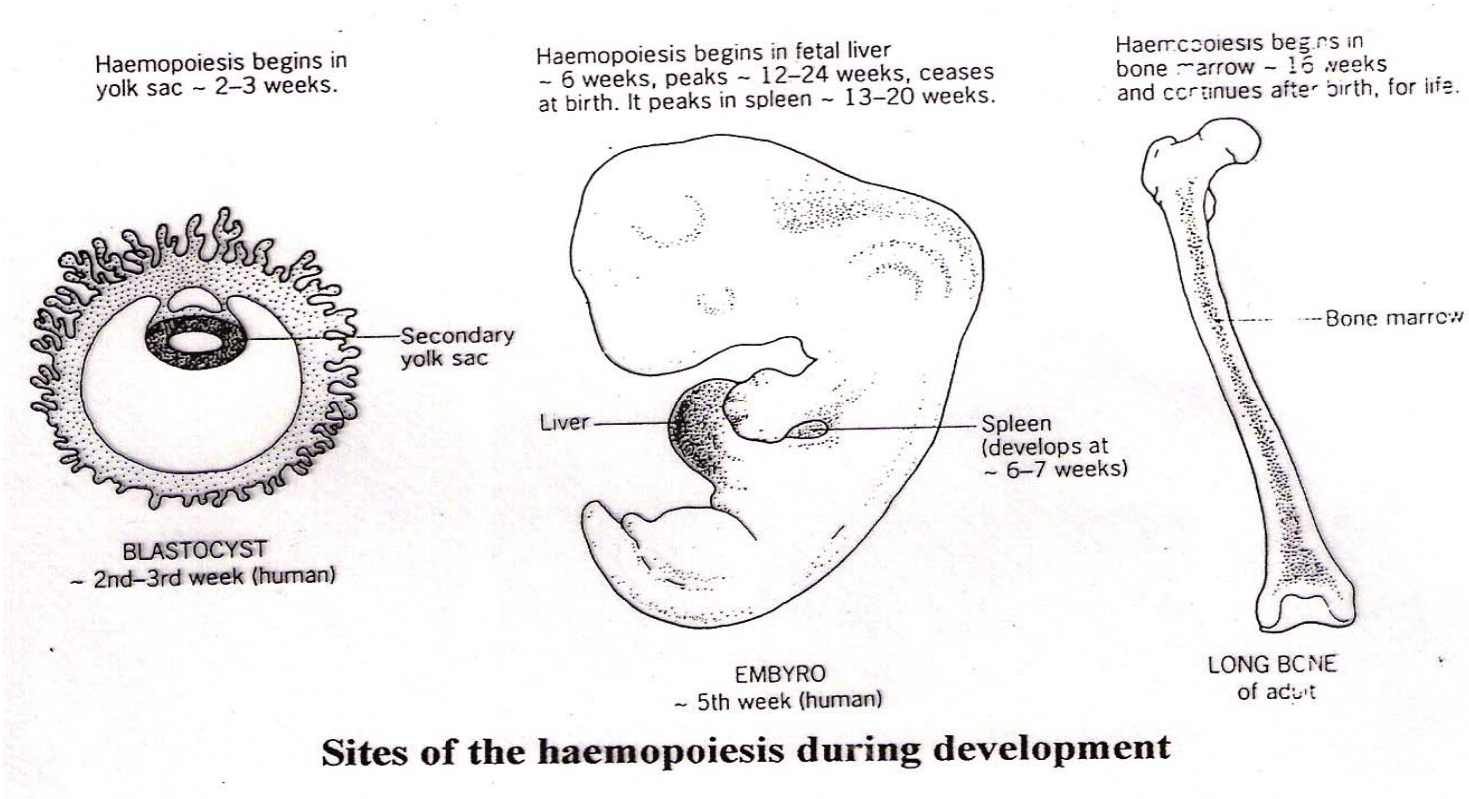


Figure 1.1 In embryo, blood starts to form in the yolk sac in a process known as Haemopoiesis, then with time the site of blood production change to the liver and sometimes shifts to the spleen, where at the end the site of blood formation is finally in the neonatal bone marrow ~ 16 weeks and continues after birth, for most life, until old ages, it is produced be the flat bones.

■ Origin of the immune cells and their classifications

All blood cells are produced from the Pluripotent stem cells, which is first produced in the yolk sac, then in the spleen and liver, and finally in the bone marrow produces two main lineages; one for lymphoid cells, and the other for the myeloid. The lymphoid progenitor is differentiated into the T, B, and NK-cells. The myeloid is differentiated into the granulocytes (eosinophil, neutrophils, and basophils). The exact origin of some APCs is unknown. Platelets are produced from the megakaryocytic that is driven from the common myeloid progenitor. After their production in the bone marrow, these immune cells leave the bone marrow and scattered all over the body, for example, in body tissues (to function, & further differentiation), in the thymus (for further differentiation, and to function), in the peripheral blood (to function), etc….. The **progenitor** stem cell **several names**:

1. Haemopoietic stem cell.
2. Totipotential (toti= all) **stem cell.**
3. Pluripotent (pluri= several) **stem cell.**
4. Multipotent (multi= several) **stem cell.**

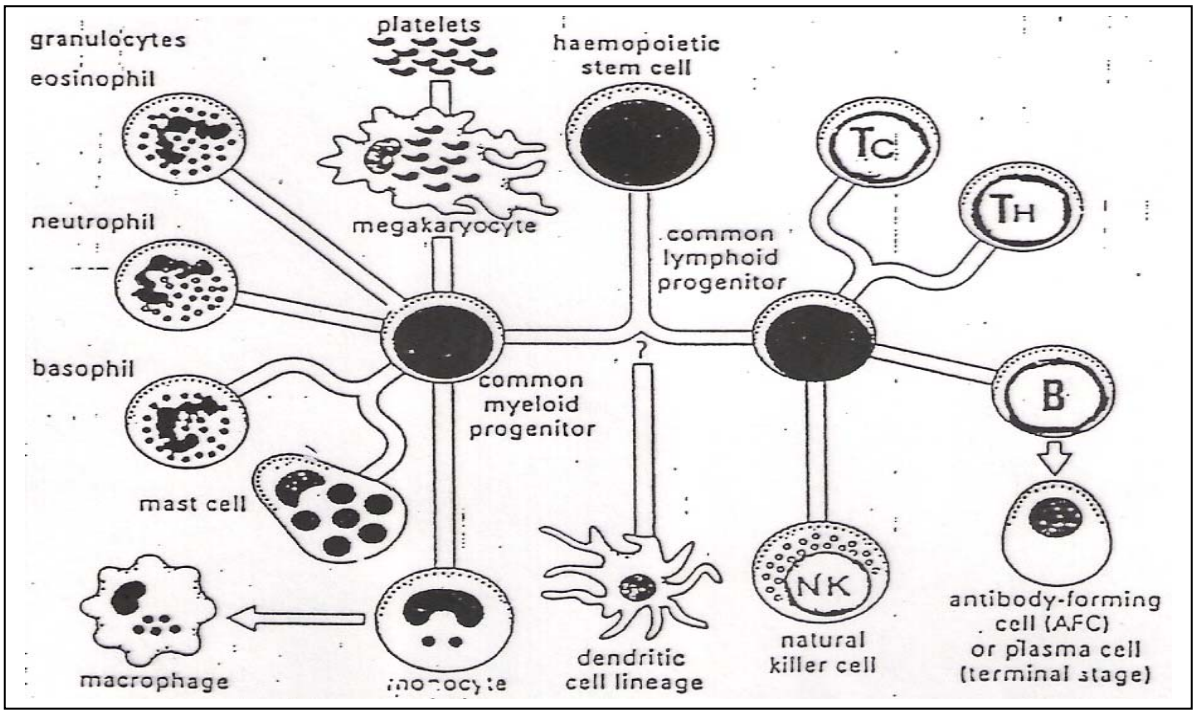


Figure 1.2 Haematopoietic stem cell is divided into two common immune cell family types, the lymphoid and myeloid lineages. The lymphoid progenitor includes T, B, and NK-cells, while the myeloid consists of the rest of the blood types and these are; the granulocytes (eosinophil, neutrophils, and basophils). Platelets are produced from the megakaryocytic that is driven from the common myeloid progenitor. The exact origin of some APCs (e.g., dendritic cells) is unknown.

■ Sites of immune cell maturation, and function during the life time

The immune cells are produced and mature in the bone marrow, but some such as the T-lymphocytes mature in the thymus. After they complete their maturation all immune cells are released into the blood circulation that carries them to the whole various parts of the body to perform their different functions. Megakaryocytes in the bone marrow secrete platelets into blood stream. All granulocytes; neutrophils, basophils, and eosinophils are secreted from the bone marrow into the blood circulation, and all migrates to the body's tissues to perform their functions if they are needed there. T and B- lymphocytes recirculate in the tissues especially in the secondary lymphoid organs where they meet their cognate antigens. While antigen presenting cells such as Interdigitating, macrophage and dendretic cells are found in the tissues (skin) and secondary lymphoid organs as well as Langerhans.

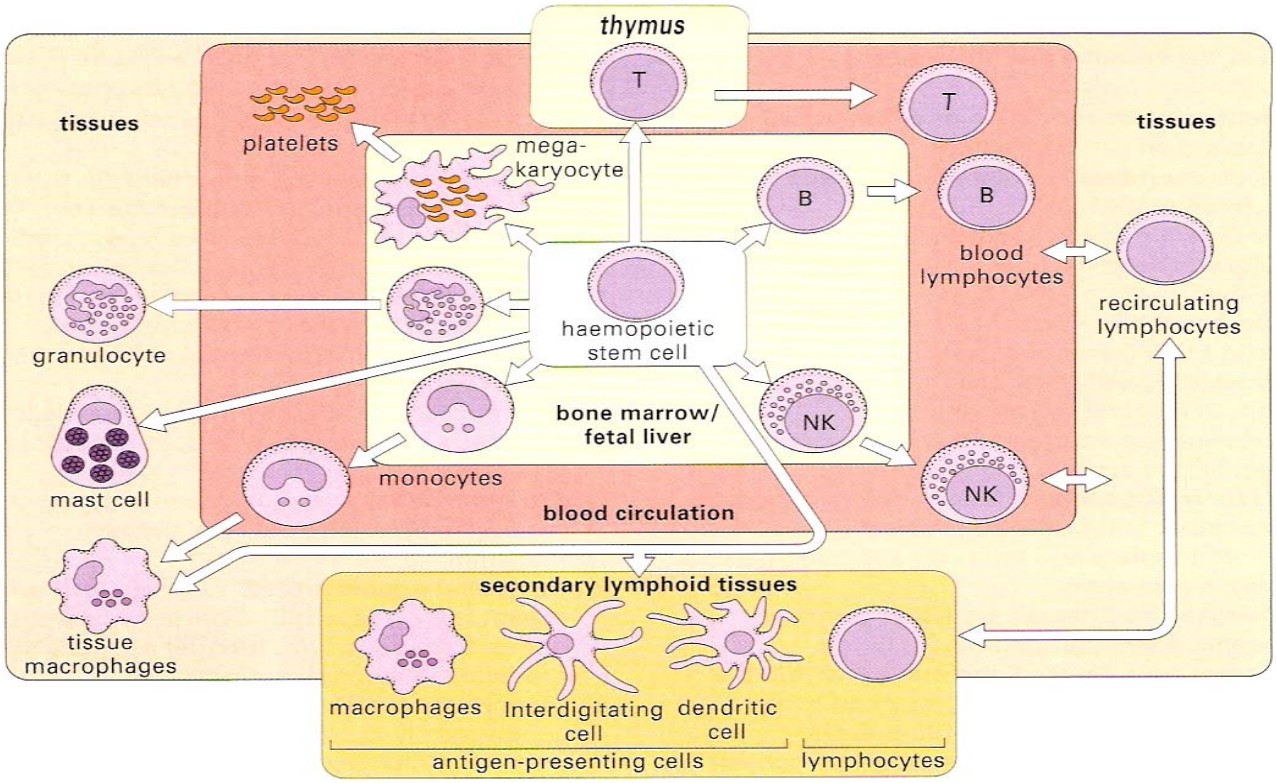
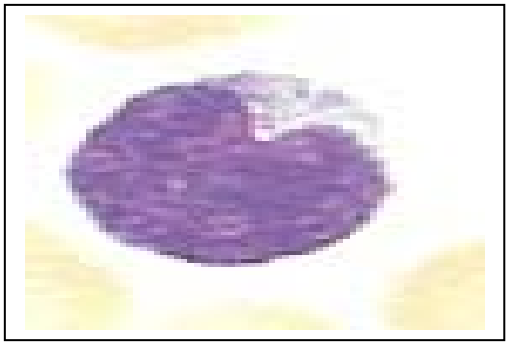


Figure 1.3 All immune cells are produced form the stem cell. Megakaryocytes produce platelets and release them into the blood stream. Neutrophils, Eosinophils, and Basophils (Granulocytes) migrate into body tissues from the blood circulation. T-lymphocytes are produced in the bone marrow, but migrate into the thymus for maturation and finally released into the blood circulation. B-lymphocytes are created and mature in the bone marrow. The main site of production of the natural killer cells, which is large granular lymphocytes (LGL) is not well determined. Monophagocytic cells include monocytes that circulate in the blood, and are developed into "macrophage" when they migrate into the tissues. Some of these macrophages are considered to be antigen presenting cells "APCs"). Lymphocytes circulate through the secondary lymphoid organs (lymph nodes, tonsils, Peyer's patch, and spleen, ….etc), where the other antigen presenting cells such as Langerhans, dendritic, and follicular dendritic cells are also found.

■ Phagocytic cells are of two types "Mono and Polymophonuclear" cells

Mononuclear Phagocytes

Mononuclear phagocytes are derived from the myeloid lineage, and have two main functions, performed by two different types of bone-marrow derived cells, these are circulating monocytes, and the tissue macrophage.



1.4 The monocyte shows the horseshoe shaped nucleus, N: C ratio is high, lysosomal granules, and mitochondria.

The network of phagocytic tissues macrophages, together with endothelial cells and polymorphs, was previously called “the reticuloendothelial system (RES). Phagocytic macrophages are found in many organs, examples of these phagocytic cells are:

- ♦ Circulating blood monocytes
- ♦ Kupffer cells in liver
- ♦ Intraglomerular measngium of the kidney
- ♦ Alveolar macrophages in lung
- ♦ Brain microglia
- ♦ Spleen sinus macrophages
- ♦ Lymph node sinus macrophages

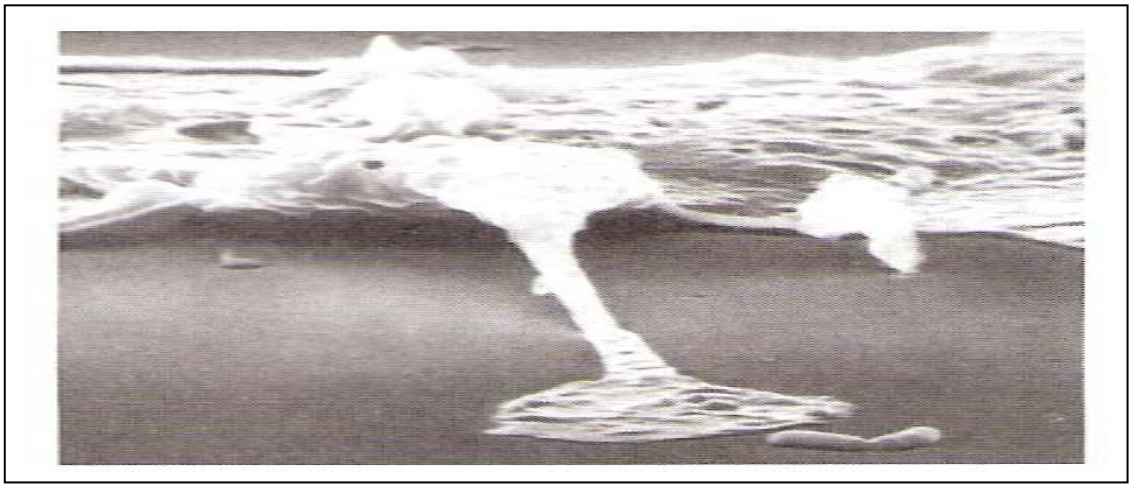


Figure 1.5 The mononuclear phagocytes are classified into two types depending on their functions, these two types are; **Professional phagocytic macrophages**, whose predominant role are to remove particular antigen, and **Antigen-presenting cells (APC)**, whose role is to take up, process and present antigen to T cells.

Polymophonuclear Granulocytes and Mast Cells

These cells have lobed, irregular shaped (polymorphic) nucleus. On the basis of how their cytoplasmic granules react with several types of staining agents, these cells (granulocytes) can are of three kinds; **neutrophils, basophils, and eosinophils**. The most numerous immune white cells in the blood stream are the neutrophils also called (PMN)**.** They are produced in the bone-marrow, at a rate of 80 million per minute and are short-lived (2-3 days) compared to mono/and macro which may live for months or years. PMNs represents about 60-70% of blood leukocytes. Like monocytes PMNs can adhere to endothelial cells lining the blood vessels and squeeze between them to scape from the blood vessels (this process is called diapedesis). The adhesion is mediated by the receptors on the granulocytes and ligands on the endothelial cells, and promoted by the chemo-attractant such as IL-8. Granulocytes play an important role in the acute inflammation; their predominant role is the phagocytosis. Figures 1.6-9 illustrate the different shapes of the granulocytes.

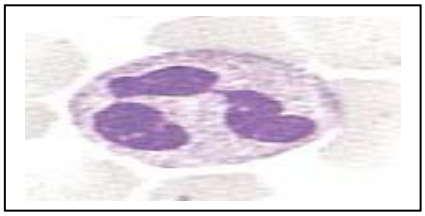


Figure 1.6 Neutrophil shows the azurophilic (primary) granules are larger than the secondary (specific) granules. The majority are specific granules. Neutrophils represent about 95 % of the circulating granulocytes. They have a characteristic of multilobed nucleus.

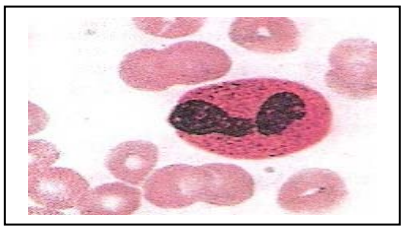


Figure 1.7 Eosinophil shows granules with crystalloids, the azurophilic (primary) granules are larger than the secondary (specific) granules. Eosinophils represent about 2-5 % of the circulating blood leukocytes in healthy non-allergic persons. Human blood eosinophil usually has bilobed nucleus and many cytoplasmic granules, stains with acidic dyes such as eosin.

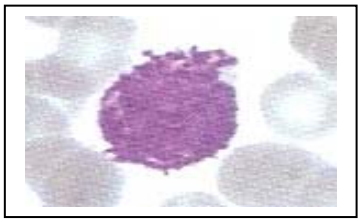


Figure 1.8 Basophil plays a role with the mast cell in immunity against parasites. They are found in very small number in the circulation and account for less than 0.2 % of leukocytes. The up above figure shows segmented nucleus and the large cytoplasmic granules.

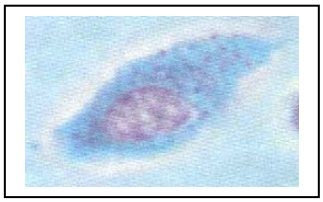


Figure 1.9 The connective tissue mast cell is not found in blood circulation, and it is indistinguishable from basophil in a number of characteristics, but displays some distinctive morphological features. It plays a role with parasitic infections. The micrograph shows dark blue cytoplasm with purple granules. Alcian blue and safranin stain.

■ Lymphocytes consist of T, B-lymphocytes, and natural killer cells (NK)

The two main types of lymphocytes are known as T and B cells. These two types of lymphoid cells are developed and differentiated in the primary lymphoid organs. For example, T cells are developed in the thymus, where as the B lymphocytes are differentiated in the adult bone marrow and fetal liver. In birds, B cells are differentiated in the bursa of Fabricius. Further more, in the primary lymphoid organs T and B cells precursors acquire the ability for recognizing antigens through the development of specific surface receptors. NK- cells do not express antigen receptors on their cell membranes. They are capable to lyse certain tumour cell lines in vitro without being sensitized. NK cells are large granular lymphocytes (LGLs)

LYMPHOCYTES

Lymphocytes are produced & maturate in the primary lymphoid organs (thymus and adult bone marrow) at a high rate 10^9 per day. Some of these cells migrate to the blood circulation via the secondary lymphoid tissues (spleen, lymph nodes, tonsils, and mucosa-associated lymphoid tissue). The average human adult has about 10^{12} lymphoid cell, and approximately 2% of the body weight is a lymphoid tissues. Lymphoid cells represent about 20% of the total leukocytes population in the adult circulation. Many mature lymphoid cells are long-lived, and may persist as a memory cells for several years, or even for the live time of the individual.

Lymphocytes are morphologically heterogeneous

Lymphocytes show several variations in the size (6-10 μm) and morphology. These variations are seen in the:
A. Nuclear to cytoplasmic ratio (N:C ratio).
B. The nuclear shape.
C. The presence or absence of azurophilic granules.

Resting lymphocytes

The conventional blood smear stained with Giemsa stain, show two distinct morphological types:

A. The first are relatively small, typically **a** granular lymphocytes with higher N:C ratio.
B. The second type is larger with lower N:C ratio, and contain intracytoplasmic azurophilic granules same as those found in the granulocytes (neutrophils, basophils, and eosinophils) or to that of the monocytes and macrophage, so it should not be confused with them. These lymphocytes are
known as the large granular lymphocyte (LGL).

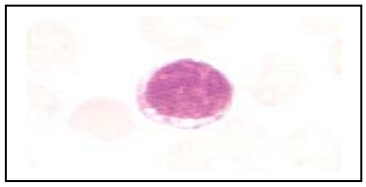


Figure 1.10 The small lymphocyte has no granules, a round nucleus, and a high N:C ratio.

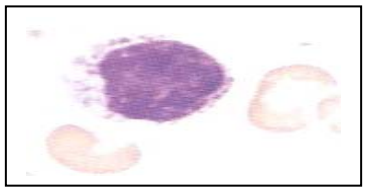


Figure 1.11 The large granular lymphocyte (LGL) has a lower N:C ratio, indented nucleus, and azurophilic granules in the cytoplasm (Giemsa stain).

Resting blood T cells

These cells can found in the blood smear with either the **LGL** form **or** the **small**, **granular** lymphocytes morphology. More than **90 %** of the **helper T lymphocytes (TH)** and more than **65 %** of the T **cytotoxic lymphocytes** are of the **smaller (non-granular with a high N:C ratio**). These T cells with **non-granular morphology** (small) include in their cytoplasm "**Gall body**" which is a **cluster of primary lysosomes associated with a lipid droplet**. Other morphological pattern shown by up to **10 %** of **Th cells** and of **35 % of Tc cells**, these cells show the **LGL morphology**, with **primary lysosomes dispersed in the cytoplasm** and a **well developed Golgi apparatus**. **Another set of the T cells with LGL morphology** is the **gamma/delta (γδ) or TCR-1^{+} lymphocytes**, which show a **dendritic morphology** in the **lymphoid tissues**.

Resting blood B cells

The cytoplasm of the resting B lymphocytes is filled with scattered single ribosome. Activated B cells are found with developing endoplasmic reticulum. These B cells **do not display** Gall **bodies** or **LGL morphology**.

NK cells-like γδ T cells and some Tc cells

These cells are characterized by LGL morphology. NK cells express a large number of azurophilic than T cells.

Figure 1.12 Scanning electron micrograph showing leucocytes adhering to the wall of a venule in inflamed tissue

■ The immune accessory cells

In addition to lymphocytes and phagocytes there are some other cells are also involved in the immune system, are called accessory cells:

A. Antigen presenting cells (APCs) Expose antigen to T cells.
B. Platelets are involved in blood clotting and inflammation.
C. Mast cells have structural and functional similarities to basophil polymorphs.
D. Endothelial cells express surface molecules capable of recognizing certain lymphocytes but not others, and then control lymphocytes traffic and distribution**.**

Dr. Mustafa Hasan Linjawi