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Immunology 3rd stage / Microbiology 2020-2021

*****Cells of Immune Systems*****

Cells of the Innate, and Adaptive Immune System

OVERVIEW

White blood cells or leukocytes serve as sentinels and defenders against infection by patrolling the tissues and organs of the body. They move around the body via the lymphatic and blood circulatory systems and can leave and reenter the circulation to move through body tissues. As "soldiers" of the immune system, leukocytes have specialized roles in defense of the body. Leukocytes are classified by morphology, including the number of lobes that their nuclei possess and the presence or absence of microscopically visible granules in their cytoplasm (Fig.1&2).

Histologic structure is often a helpful clue to the cell's function. Some Leukocytes may combat invasive organisms directly; others produce soluble molecules that serve as deterrents to microbial invasion throughout the body.

Some leukocytes are autonomous, wielding lethal blows against invaders with out intervention from other cells. Others are poised for "combat,"

awaiting "orders" from their superiors. Still others serve as field marshals by regulating the assault. Leukocytes may be found as individual cells throughout body, as accumulations within lymphoid organs (e.g., spleen, lymph nodes) and at sites of infection or inflammation. Knowledge of the role that each leukocyte plays is important to understanding immune function.

All bloodborne cells ultimately derive from pluripotent hematopoietic stem cell. They are called pluripotent because each stem cell has the capacity to produce all leukocytes as well as red blood cells(erythroid lineage) and platelets (thrombocytic lineage). Pluripotent stem cells resident in the bone marrow are the source of lymphocytes and plasma cells; macrophages, monocytes, and dendritic cells; and granulocytes (neutrophils, eosinophils, and basophils).

Cells of the myeloid lineage, especially those containing cytoplasmic granules (eosinophils,basophils, and neutrophi) , together with agranular phagocytic cells monocytes, macrophages, and dendritic cells) are involved in innate defenses. Other myeloid lineage-derived cells are involved in transport of oxygen and carbon dioxide (erythrocytes or red blood cells) and in blood clotting (platelets). Most of the cells derived from the lymphoid lineage (lymphocytes and plasma cells) are responsible for adaptive immune responses. Other cells (natural killer or NK cells and the phagocytes) bridge both innate and adaptive immune systems .

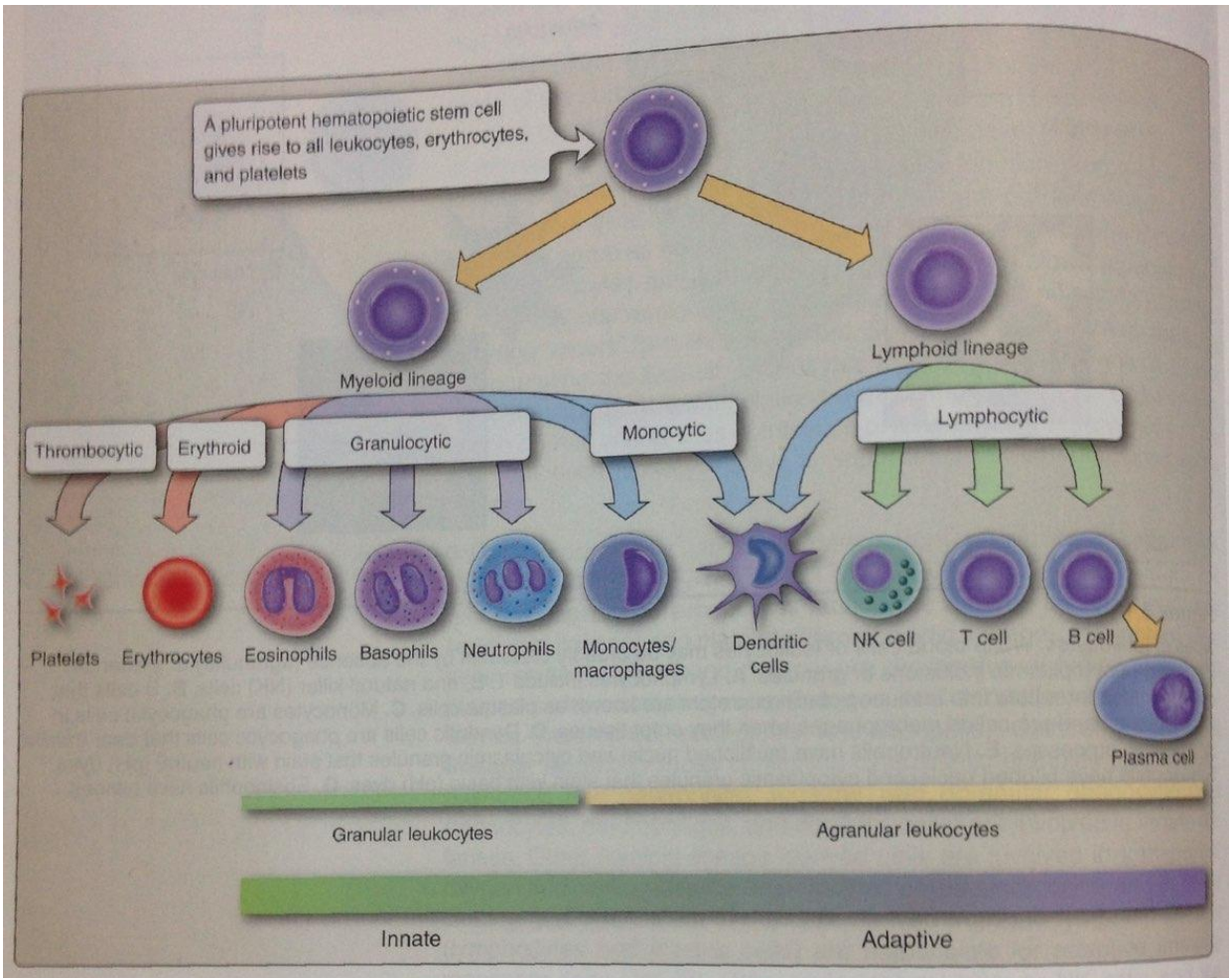

Figure 4.2
Hematopoietic lineages. Pluripotent stem cells within the bone marrow give rise to all the cells found in the blood. Cells of the myeloid lineage differentiate further into platelets, erythrocytes, eosinophils, basophils (and mast cells), neutrophils, monocytes/macrophages, and some dendritic cells. Cells of the lymphoid lineage differentiate further into T and B lymphocytes, NK cells, and some dendritic cells.

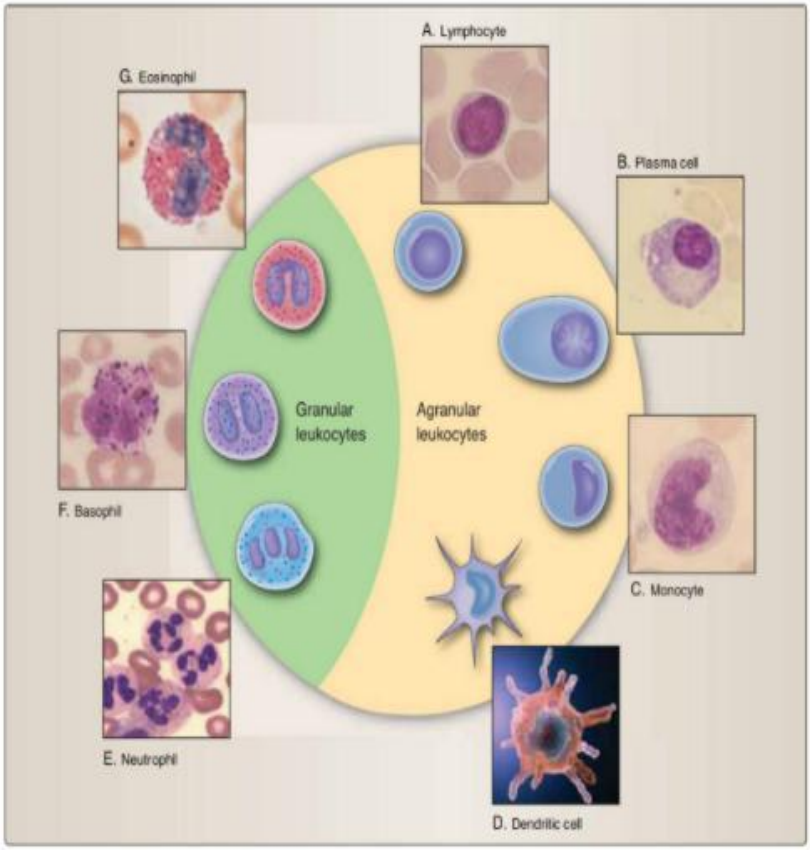

Figure 4.1
Types of leukocytes. White blood cells or leukocytes may be broadly classified by the absence (agranular) or presence (granular) of cytoplasmic inclusions or granules. **A.** Lymphocytes include T, B, and natural killer (NK) cells. **B.** B cells that enlarge and differentiate into immunoglobulin secretors are known as plasma cells. **C.** Monocytes are phagocytic cells in the circulation and are called macrophages when they enter tissues. **D.** Dendritic cells are phagocytic cells that bear treelike cytoplasmic processes. **E.** Neutrophils have multilobed nuclei and cytoplasmic granules that stain with neutral (pH) dyes. **F.** Basophils have bilobed nuclei and cytoplasmic granules that stain with basic (pH) dyes. **G.** Eosinophils have bilobed nuclei and cytoplasmic granules that stain with acidic (pH) dyes.

***GRANULAR and AGRANULAR LEUKOCYTES

** Granular leukocytes

Leukocytes that contain conspicuous cytoplasmic granules are known as granulocytes. These cells have multi lobed nuclei and cytoplasmic granules that contain amines (stained by basic dyes) , basic proteins (stained with acidophilic or eosinophilic dyes) , or both (neutral staining).

1. Neutrophils

Comprising approximately 60% of the peripheral blood leukocytes, neutrophils are the most numerous leukocyte population. They are also called polymorphonuclear (PMN) cells because of their variable number of nuclear segments (two to five) . With a half-l ife of approximately 7 hours, more than 1 00 billion neutrophils enter the circulation daily in normal adults. It takes about 2 weeks for metamyelocytes (an intermediate stage neutrophil with a kidney-shaped nucleus) to differentiate from the juvenile or band form (with an elongating nucleus) , to the staff or stab (German, meaning "staff") form, and then to the segmented or mature stage (Fig3).

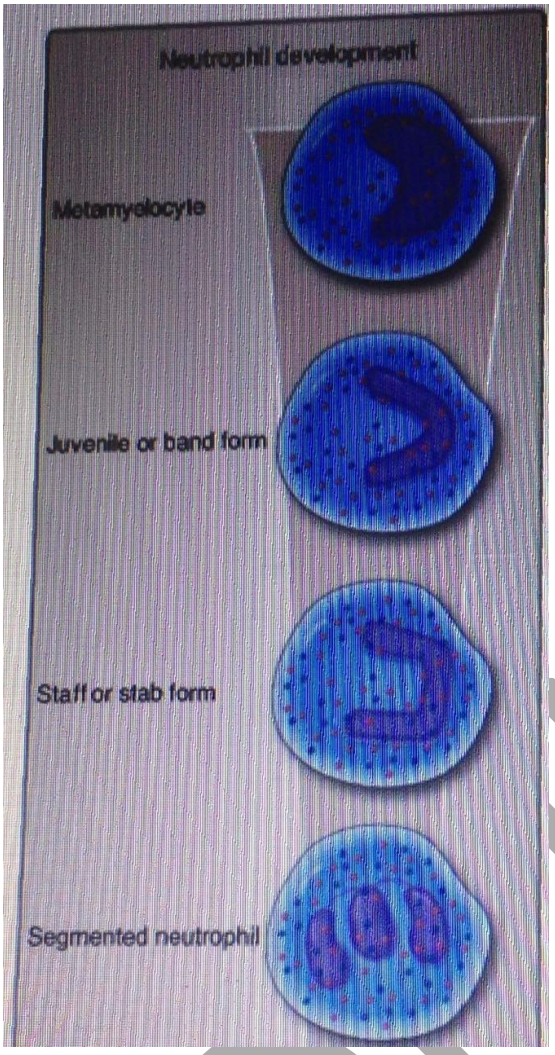

Figure 3:

Neutrophil development. Neutrophils are the most numerous leukocytes and play a vital role in policing the body against microbial invasion. They require about 2 weeks to mature from metamyelocytes through intermediate stages and become mature-segmented neutrophils.

Neutrophils are very effective at killing bacteria. An increase in the number of Peripheral blood neutrophils is often an indication of acute infection.

As reserves of PMNs within the bone marrow become exhausted during an infectious disease, several metamyelocytes and juvenile forms increase in the circulation.

2. Basophils and mast cells

The acidic cytoplasmic granules of basophils contain vasoactive amines (e.g., histamine) that cause smooth muscle contraction and are readily stained with "base-loving" dyes (Fig.4). These bilobed cells are found in low numbers in the peripheral blood (0% to 1 %) or in their tissue resident form, known as mast cells. Both basophils and mast cells are important in allergic reactions of the adaptive immune response .

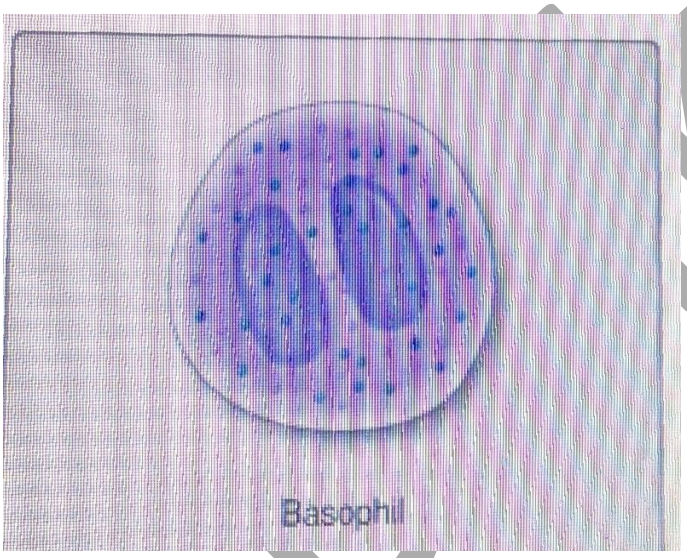

Figure :4

Basophils. Release of their cytoplasmic granules (degranulation) disseminates vasoactive amines and other molecules associated with allergic reactions.

3. Eosinophils

So named because of their "eosin-loving" granules (eosin is a dye used in histology), eosinophils are bilobed granulocytes with cytoplasmic granules that contain basic proteins. Although they comprise 0% to 5% of the peripheral blood

leukocytes, eosinophils are active participants in innate and adaptive immune responses to parasitic helminth (worm) infections (Fig.5)

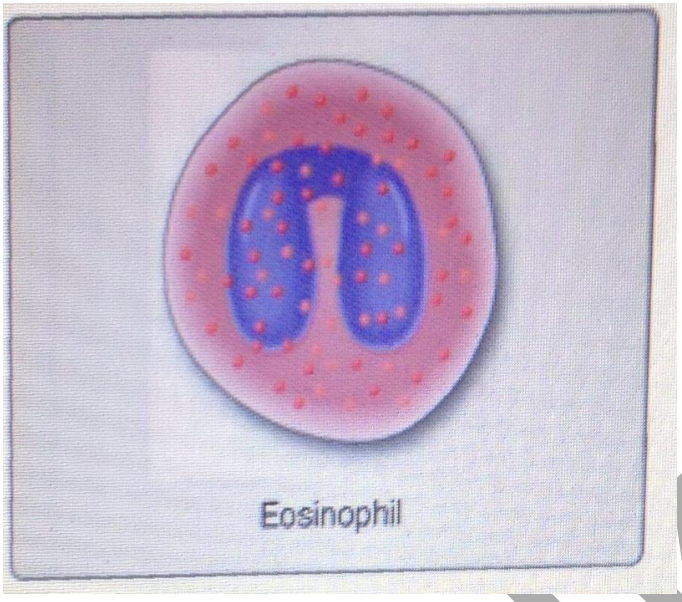

Figure 5:

Eosinophils. Release of cytoplasmic granules by eosinophils provides molecules that are potent weapons against parasitic worms.

***** Agranular Leukocytes

Other White blood cells with a single, unlobed nucleus and cytoplasm that contains few or no granules are known as agranular leukocytes. Agranular leukocytes derive from lymphoid or myeloid lineage precursors and account for approximately 35% to 38% of the leukocytes in circulation.

A) Monocytic lineage cells

Mononuclear cells that differentiate from myeloid precursors are known as monocytes in the circulation or macrophages once they leave the circulation

and enter the tissues. These cells are the scavengers of the body. They phagocytize or pick up cellular debris, foreign cells, and particles and degrade them enzymatical ly. Another group of phagocytic cells with both myeloid and lymphoid origins is collectively known as dendritic cells, so named for their branchlike cytoplasmic projections.

1. Monocytes and macrophages: Monocytes are large mononuclear cells and account for approximately 5% to 7% of the leukocytes in the peripheral blood (Fig. 6). Monocytes spend 1 to 2 days in the circulation (their half-life is approximately 8.4 hours) , then cross the endothelium to enter tissues throughout the body, where they reside for up to several months as macrophages. Both monocytes and macrophages actively sample their environment by phagocytosis and serve as scavengers to remove cellular debris.Ingested materials are enzymatically degraded.

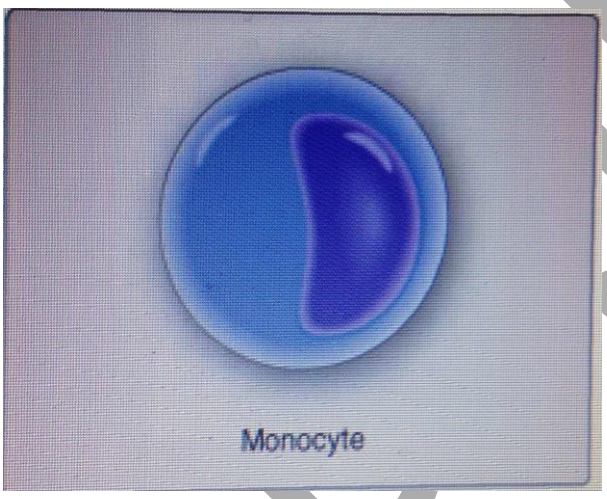

Figure 6:

Monocytes. Circulating mononuclear phagocytes are called monocytes. When they leave the circulation and enter tissues they are called macrophages.

2. Dendritic cel ls: Found throughout the body but predominantly in potential portals of microbial entry (e.g., skin, lung, gastrointestinal tract), these cells are named for their branchlike cytoplasmic projections (Fig.7). Like other

phagocytes, dendritic cel ls actively engulf cells and particles in their environment by phagocytosis). In addition , dendritic cells sample copious quantities of extracellular fluids by macropinocytosis, in which their cytoplasmic projections encircle and engulf tissue fluids, and the molecules, and particles contained within. Dendritic cells may arise from either myeloid or lymphoid (also called plasmacytoid) lineage cells. As actively phagocytic cells, dendritic cells are important in innate immune defenses.

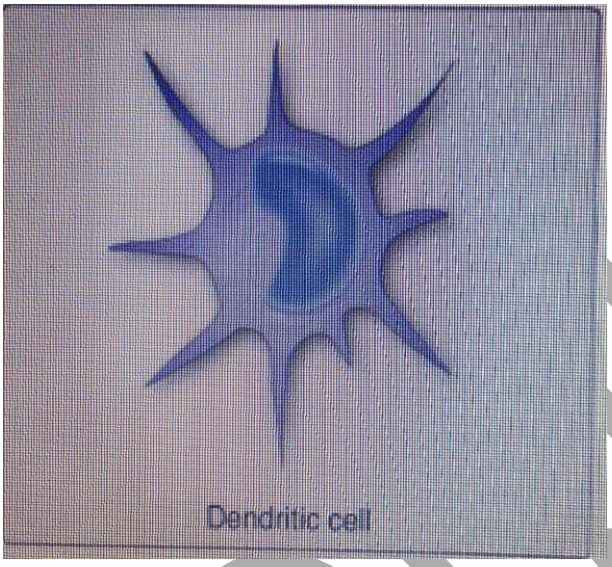

Figure 7:

Dendritic cells. As professional phagocytes, dendritic cells use their cytoplasmic extensions to sample their environment.

B) Lymphoid lineage cells

Cells that differentiate along one of several of the lymphocytic pathways are known as lymphocytes). B lymphocytes or B cells reside in the bone marrow and are able to synthesize immunoglobulin molecules. In fact, B cells and their further differentiated progeny,plasma cells, are the only cells that are capable

of immunoglobulin synthesis. Other lymphoid lineage cells of bone marrow origin migrate to, differentiate, and are vetted within the environment of the thymus. Those cells (thymocytes) that exit the thymus are known as thymus-derived lymphocytes or T lymphocytes (T cells). We will address the differentiation and function of B cells, plasma cells, and T cells and their roles in adaptive immune function .

A third lymphoid lineage cell distinct from B and T cells, and their progeny is the natural killer (NK) cell. These large, nonphagocytic, granular lymphocytes are named for their ability to kill abnormal (e.g.,infected or malignant) host cells . They account for 5% to1 0% of all lymphocytes in the circulation.

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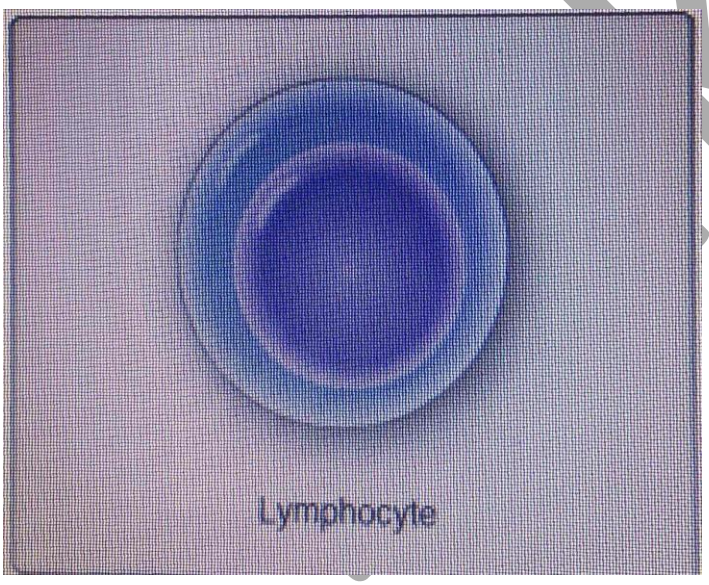

Figure 8:

Lymphocytes. Except for differing in size (4- to 1 5·1m range), lymphocytes generally look alike although they may vary functionally.

A. Thymus-derived cells

T cells are the key players in most adaptive immune responses. They participate directly in immune responses as well as orchestrating and regulating the activities of other cells. T cells arise from hematopoietic stems cells in the bone marrow. Immature T cells called prothymocytes migrate to the thymus, where, as thymocytes, they develop TCRs and are screened for their abil ity to distinguish self from nonself. Although most thymocytes fail the screening process and are eliminated, those that pass scrutiny and survive are able to further differentiate and mature to become thymus-derived lymphocytes or T cells and enter the circulation. Although T cells show a wide diversity in adaptive immune function, all can be identified by the presence of the CD3 (cluster of differentiation 3) molecule that is associated with the TCR on the T-cell surface. Two other CD molecules are also used to identify CD3+ T-cell subsets, CD4 and CD8, and to readily distinguish their potential immune function.

1. CD4 + T cel ls: These cells account for approximately two-thirds of mature CD3+ T cells. CD4 molecules displayed on the su rfaces of these T cells recognize a nonpeptide-binding portion of MHC class II molecules (Fig. 9). As a result, CD4 + T cells, also known T helper(Th) cells are restricted to recognize PMHC class II complex.

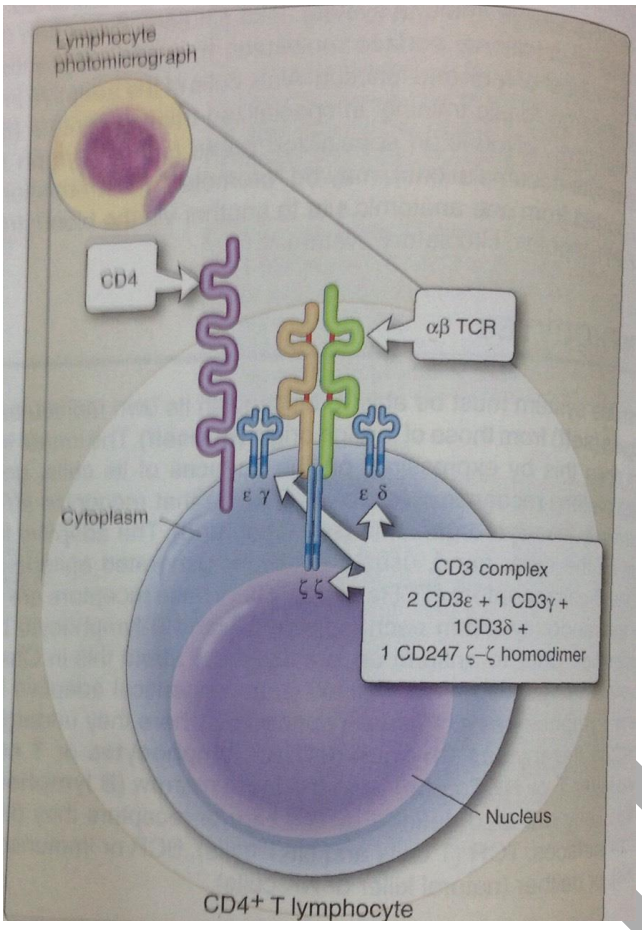

Figure 9:

CD4+ T lymphocyte Comprising approximately two-thirds of all T lymphocytes, CD4+ T cells arethe workhorses of the adaptive immune system. They display T-cell receptors (TCRs), associated CD3 signaling complex molecules, and CD4 molecules on their cell surfaces.

2. CD8+ T cells account for approximately one-third of all mature C03+ T cells. CO8 molecules displayed on the sufaces of these T cells recognize the nonpeptide-binding portion of MHC class I molecules. As a result, CD8+ T cells are "restricted" to the recognition of pMHC I complexes (Fig10). Functionally, CD8+ T cells are also known as cytotoxic T (Tc) and some act as suppressor T(Ts) cells. Tc cells identify body cells that are infected with intracellular organisms, such as viruses and intracellular bacteria, and eliminate the cells harboring

these organisms. Ts cells function to downregulate and thus control adaptive immune responses.

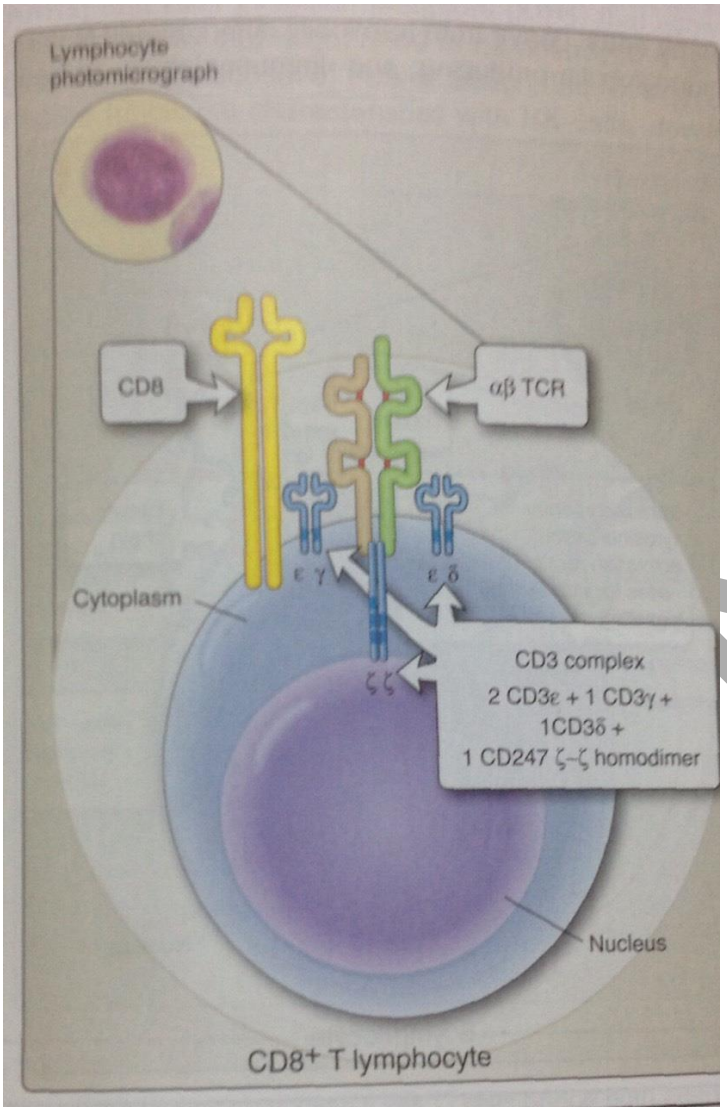

Fig. 10: CD8+ T lymphocyte

Approximately one-third of the T cells are found in peripheral blood, CD8+ T cells display T-cell receptors (TCRs), associated CD3 molecules, and CD8+ dimers on their cell surfaces.

B. Bone marrow-derived cells

Not all lymphocytes of bone marrow origin are destined for thymic education. Certain cells of lymphoid lineage remain and develop within the bone marrow and are the precursors of immunoglobulin-producing Lymphocyte ymphocytes. These bone marrow-derived lymphocytes, also known as B lymphocytes or B cells, synthesize immunoglobulin and display it on their surfaces, where it functions as their BCR. Plasma cells are derived from differentiated, mature B cells and both synthesize and secrete immunoglobulin.

1. B cells arise from pluripotent hematopoietic stem cells in the bonemarrow. They do not migrate to the thymus but develop within the bone marrow (Fig.11). B cells arise from two distinct lineages:

B-1 and B-2 cells. So named because they are the first to develop embryologically; B-1 cells are a self-renewing population that dominates the plural and peritoneal cavities. In contrast, conventional or B-2 cells arise during and after the neonatal period, are continuously replaced from the bone marrow, and are widely distributed throughout the lymphoid organs and tissues. Each B cell is specific, that is, it produces immunoglobulin of only one antibody specificity that recognizes only one epitope.

2. Plasma cells derive from terminally differentiated B cells and are immunoglobulin-producing and immunoglobulin-secreting cells. They cease to use immunoglobulin as a membrane receptor and instead secrete it into the fluids around the cells. Plasma cells, with increased size and metabolic activity, are factories that produce large quantities of immunoglobulin during their short life span of less than 30 days. They are characterized by basophilic cytoplasm, a nucleus that has a stellate (starlike) pattern within it, and non-staining Golgi (Fig.12) .

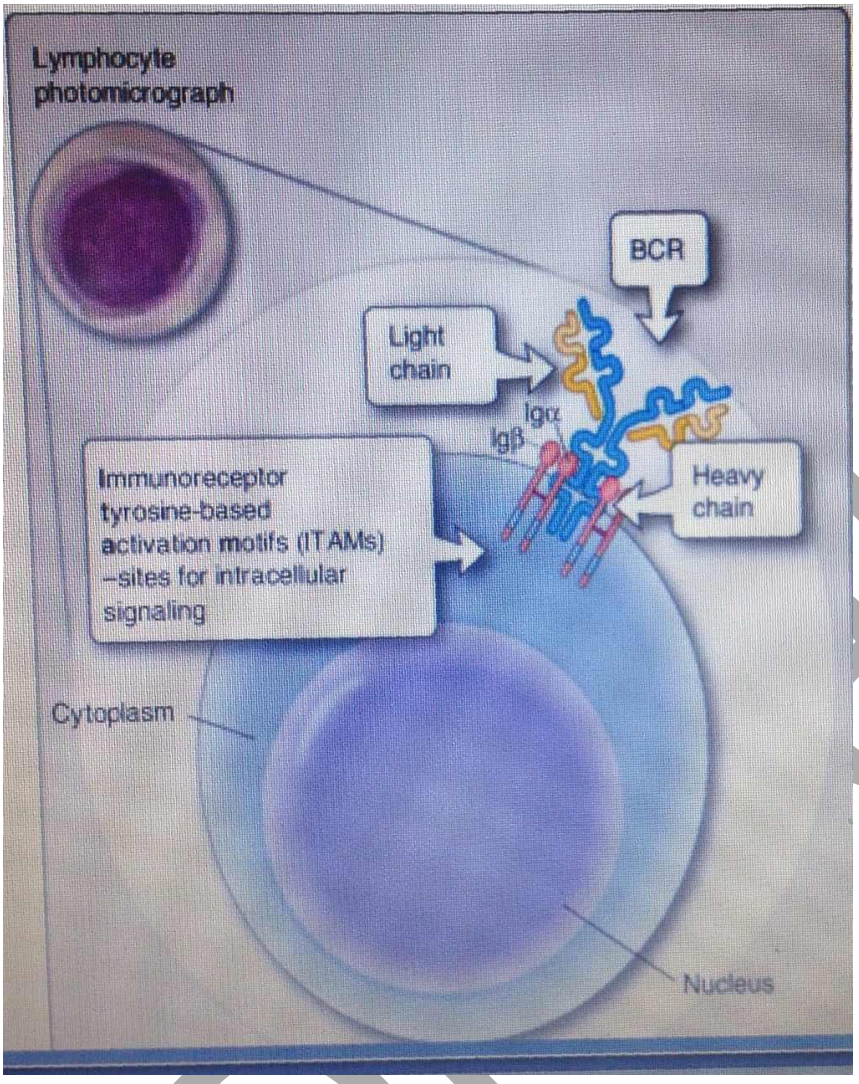

Figure 11:

B Lymphocyte Bone marrow-derived lymphocytes or B cells synthesize immunoglobulinmolecules that are displayed on their cell surface. On the surface, they function as the B-cell epitope-specific receptor (BCR)

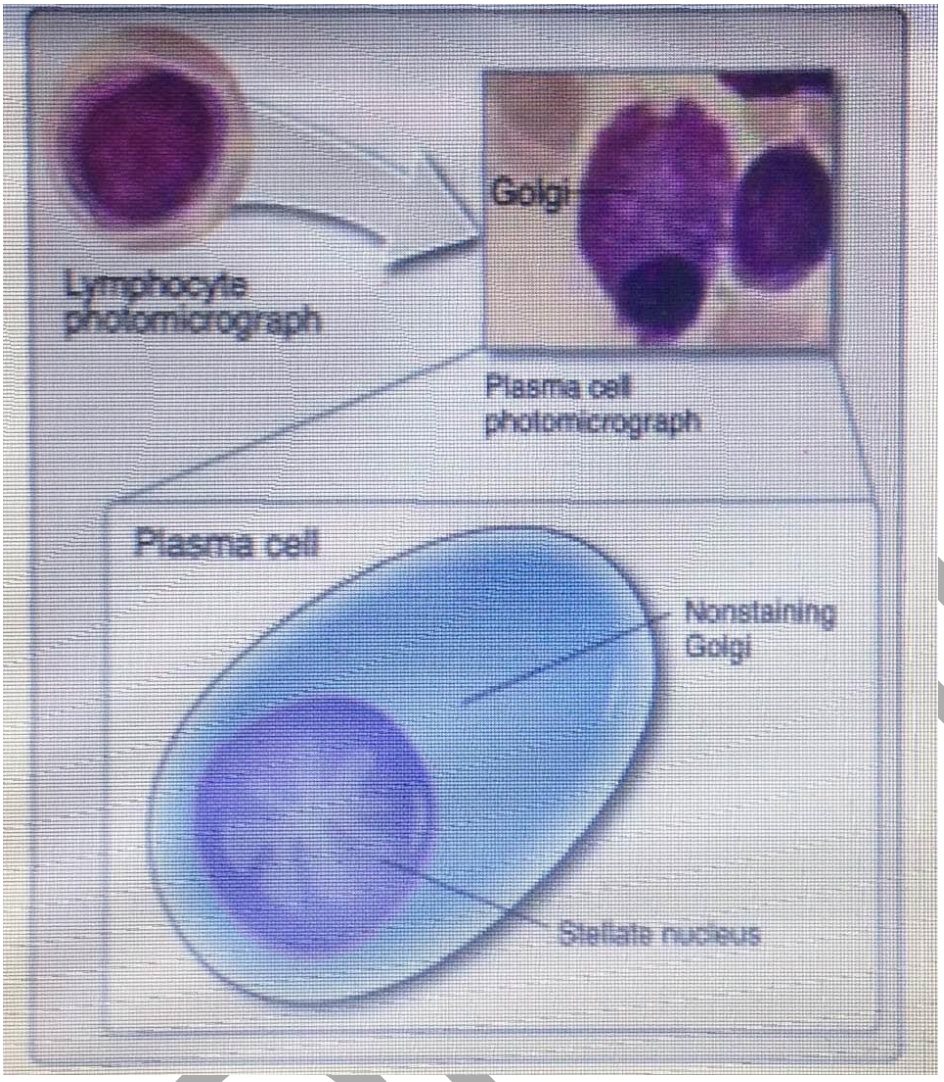

Fig. 12: Plasma cell

Plasma cells are terminally differentiated B cells that both synthesize and secrete immunoglobulin. Anatomically distinguishable from lymphocytes, their cytoplasm reflects increased ribosomes and endoplasmic reticulum. Immunoglobulin molecules are assembled within their (nonstaining) Golgi prior to export to the fluids surrounding the cell.

C. Natural killer cells

Approximately 5% to 1 0% of peripheral blood lymphocytes lack both T-cell (CD3) and B-cell (su rface immunoglobulin) markers. These cells are known as natural kil ler (NK) cells to reflect their abil ity to kill certain virally infected cells and tumor cells without prior sensitization. Their granular appearance is caused by the presence of cytoplasmic granules containing perforin and granzyme that can be released to damage the membranes of the cells they attack. NK cells develop within the bone marrow and lack TCR produced by rearrangement of TCR genes (see Chapter 8). However, they do bear another set of receptors called killer activation receptors (KARs) and ki ller inhibition receptors (KIRs) that allow them torecognize host cells that might need to be destroyed (Fig.13) .

In addition, a unique subset of T cells, designated NKT because they share some functional characteristics with NK cells, develop within the thymus and express a rearranged TCR of extremely limited repertoire (Fig.13) . Unlike conventional T cells, NKT cells respond to lipids, glycolipids, or hydrophobic peptides presented by a specialized, nonclassical MHC class I molecule, CD1d, and secrete large amounts of cytokines, especially interleukin-4 (IL-4) .

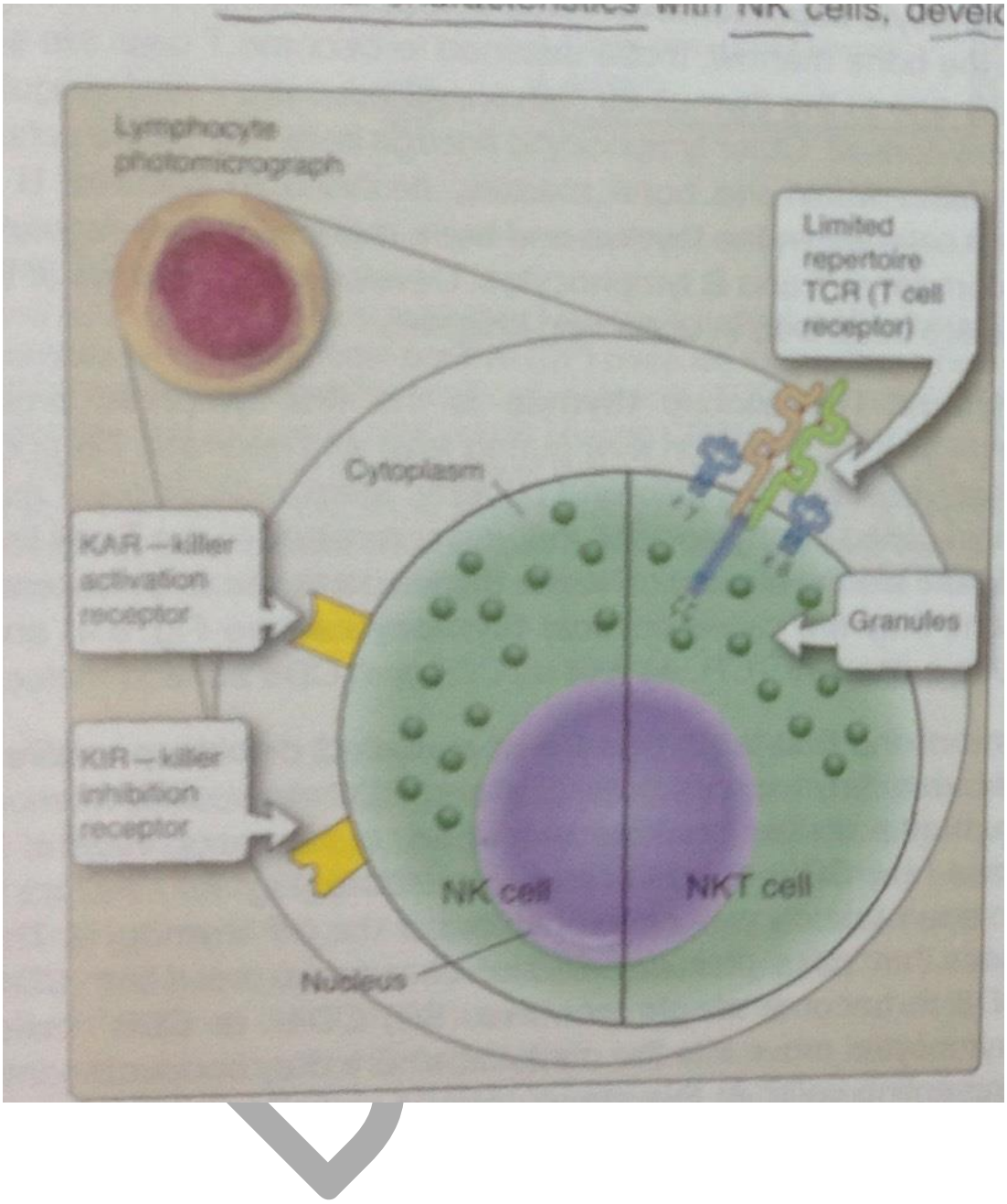

Fig.13: NK, and NKT

Natural killer (NK) and natural killer T (NKT) cells bridge both adaptive and innate immune systems. NK cells are characteristically large granular lymphocytes that express neither TCRs nor BCRs and bear receptors forstress molecules (killer activation receptors or KARs) and for MHC classI molecules (killer inhibition receptors or KIRs). Unlike NK cells, NKT cells express low levels of TCRs with extremely limited repertoires.

HOME WORK

Write about each of the following;

1) CDCC

2) IgE mediated hypersensitivity

GOOD LUCK