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Review Article

Lymphocytes: A Brief Review

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ABSTRACT

This review summarizes the various forms of lymphocytes and their immunomodulatory roles in health and diseases. Lymphocytes are found in blood and lymph, which is the colorless fluid in lymphatic vessels that connect lymph nodes to each other and to the bloodstream. However, lymphocytes are still found in lymphoid organs such as the thymus, lymph nodes, spleen, and appendix (in man). Natural killer (NK) cells, T cells and B cells are the different forms of lymphocytes. Each of these cells play fundamental role in immune system's function. These cells influence responses of the immune system to foreign substances such as invading microorganisms, tumor cells as well as tissues following organ transplant. Furthermore, a deviation in lymphocytes count from the reference values may indicate an abnormal condition and hence, prompt diagnosis is required. Therefore, proper interpretation of lymphocytes abnormalities in the form of lymphocytosis and lymphopaenia would assist a clinician in the adequate description, diagnosis and management of physiological and pathological conditions.

Keywords: Lymphocytes; Blood; Lymph; Lymphocytosis; Lymphopaeni

INTRODUCTION

Lymphocytes play fundamental role in the immune system due to their influence on immune responses to infectious microorganisms and other foreign substances [1]. They provide a specific response to attack by invading microorganisms [2], protection against tumors such as multiple myeloma [3] as well as cause rejection of tissues following organ transplants [4] as they perceive these tissues as foreign invaders. They occur in blood and lymph (the colorless fluid in the lymphatic vessels that connect the lymph nodes in the body to each other through the bloodstream) [5]. They also occur in lymphoid organs, such as the thymus, lymph nodes, spleen, and appendix (in man) [6]. In this paper, the various forms of lymphocytes as well as their roles in health and disease has been reviewed.

STRUCTURE AND CHARACTERISTICS OF LYMPHOCYTES

The size of lymphocytes ranges from 7-20 micrometres in diameter [7]. Microscopically, normal lymphocytes are characterized by large, dark purple/blue-staining nucleus (using Wright's stain) with little to no eosinophilic cytoplasm [8]. However, larger forms of lymphocytes with abundance of cytoplasm containing several bright reddish/purplish, grain-like particles have been reported [1]. In health, the coarse, dense nucleus of lymphocytes approximates the size of red blood cells [7]. Some lymphocytes possess clear perinuclear zone (or halo) around the nucleus and could exhibit a small clear zone to one side of the nucleus [5]. Polyribosomes which are a prominent feature in lymphocytes have been demonstrated with the aid of electron microscope [9]. These ribosomes are suggested to be involved in protein synthesis thus, allowing the generation of large quantity of cytokines and immunoglobulins by lymphocytes [5].

However, there is difficulty in distinguishing between T cells and B cells in peripheral blood smears, specific lymphocyte population counts have been demonstrated by flow cytometric test [1]. Furthermore, other scientific techniques such as Enzyme Linked Immuno Spot Assay (ELISPOT) and secretion assay techniques have been utilized in the study of functions of lymphocytes using the proteins they generate [5]. Enzyme-Linked Immuno Spot Assay represents one of the earliest assays to monitor immune responses by the detection of cytokine producing cells such as lymphocytes as well as the frequency of production in a heterogeneous population of cells [10,11].

ORIGIN AND DEVELOPMENT OF LYMPHOCYTES

The various forms of lymphocytes originate from a common lymphoid progenitor before differentiating into their distinct lymphocyte types [6]. The maturation of B cells have been reported to occur in the bursa of Fabricius (in birds) [12] and in the Gut Associated Lymphoid Tissue (GALT) located in the Peyer's patches of the intestine (in mammals) [13]. The cells that migrate to and mature in the thymus form the T cells [14]. After maturation, there is entry of lymphocytes into circulation and peripheral lymphoid organs [2,3].

TYPES OF LYMPHOCYTES

These include T cells, B cells and natural killer (NK) cells.

T Cells

T cells or T lymphocytes play central role in cell-mediated immunity [8]. T cells mature in the thymus from thymocytes, although some T cells maturation in the tonsils have been reported [15]. The presence of T-cell receptor on the cell surface has been used to distinguish T cells from B cells and natural killer cells [9]. In humans, rearrangement of majorities of T cells alpha and beta chains on cell receptor to form alpha beta T cells (αβ T cells) involved in the adaptive immune system have been demonstrated [16]. In ruminants, specialized gamma delta T cells, which have invariant T cell receptors with limited diversity for effective antigen presentation to other T cells have been reported and thus, are considered to be part of the innate immune system [17].

The suggested processes involved in T cells development in the thymus include beta selection (involving the formation of a functional β-chain (DN stage) and a functional α-chain (DP stage) to ultimately produce a functional αβ T cell receptor) [16,18], positive selection (involving the production of a signal by double-positive precursors that express either Major Histocompatibility (MHC) Class I or II restricted receptor) [19] and negative selection (involving the removal thymocytes capable of triggering autoimmunity) [20].

The activation of T cells occurs through the simultaneous engagement of the T cell receptor and a co-stimulatory molecule (like CD28) on the T cell by the Major Histocompatibility Complex (MHC II) peptide [21] and co-stimulatory molecules on the Antigen Presenting Cells (APC) [22] (Table 1).

Disorders of T cells:

a. **T cells deficiency:** this could result from

Lymphocytopaenia of T cells and/or defects on function of individual T cells.

Acquired Immune Deficiency Syndrome (AIDS), and hereditary conditions such as Chromosomal Breakage Syndromes (CBSs), and B-cell and T-cell combined disorders (partial insufficiencies of T cell function) [5].

Pathogens including *Herpes simplex virus, Mycobacterium* and *Listeria* as well as fungal infections [27].

b. **Cancer**

Cancer of T cells is termed as T-cell lymphoma, and accounts for perhaps one in ten cases of non-Hodgkin lymphoma [28]. The main forms of T cell lymphoma include extranodal T cell lymphoma, cutaneous T cell lymphomas (Sézary syndrome and Mycosis fungoides), anaplastic large cell lymphoma and angioimmunoblastic T cell lymphoma [28]

c. **T cell exhaustion**

T-cell exhaustion is the progressive loss of T-cell function [29] and could result from sepsis and after other acute or chronic infections [27]. T-cell exhaustion has been reported to be mediated by inhibitory receptors including programmed cell Death Protein 1 (PD1) and Lymphocyte Activation Gene 3 Protein (LAG3) [30,31].

B Cells

B cells (or B lymphocytes) function in the humoral immune responses through the production of antibodies [32,33]. They also present antigen and secrete cytokines [12]. The maturation of B cells takes place in the bone marrow in mammals [8] and in the bursa of Fabricius in birds [12]. B cells express B Cell Receptors (BCRs) on their cell membrane thus, allowing them to bind a specific antigen in order to initiate an antibody response [32] (Table 2).

B Cells related pathology: Autoimmune diseases that have been correlated with B cell activity include scleroderma, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and rheumatoid arthritis [32,39]. The malignant transformation of B cells and their precursors have been associated with chronic Lymphocytic Leukemia (CLL) [40], Acute Lymphoblastic Leukemia (ALL) [41], hairy cell leukemia [42], follicular lymphoma, non-Hodgkin's lymphoma [28], and Hodgkin's lymphoma [43].

Table 1: Forms of T cells.

T Cells	Description and Functions
Helper T cells (T_H cells)	-They express the CD4 glycoprotein on their surfaces [5]. -Assist other white blood cells in maturation of B cells into plasma cells and memory B cells [9], and activation of cytotoxic T cells and macrophages [23]. -They can differentiate into one of several subtypes, including T_H1, T_H2, T_H3, T_H17, T_H9, or Follicular T-helper cells (T_{FH}) stimulated by certain cytokines such as interleukin(IL)-2, IL-4, IL-6, IL-12 and Transforming growth factor (TGF-β) [20].
Cytotoxic (killer) T cells (T_C cells, CTLs, T-killer cells, killer T cells)	-They express the CD8 glycoprotein at their surfaces [5]. -Through IL-17, adenosine, and other molecules secreted by regulatory T cells, the $CD8^+$ cells can be inactivated to an anergic state to prevent autoimmune diseases [23]. -Destroy virus-infected cells [24] and tumor cells [3], and are also implicated in transplant rejection [4].
Memory T cellss	-Persist long-term after an infection has resolved and quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections [25].
Regulatory (suppressor) T cells	-Crucial for the maintenance of immunological tolerance by shutting down T cell-mediated immunity toward the end of an immune reaction and suppressing autoreactive T cells that escaped the process of negative selection in the thymus [8].
Mucosal associated invariant T cells	-they are associated with the gastrointestinal tract [26].
Gamma delta T cells (γδ T cells)	-Possess a distinct T Cell Receptor (TCR) on their surfaces comprising of one γ-chain and one δ-chain [17].

Table 2: Forms of B cells.

B Cells	Description and functions
Plasmablast	-Short-lived, proliferating antibody-secreting cell arising from B cell differentiation [34].
Plasma cell	-Long-lived, non-proliferating antibody-secreting cell arising from B cell differentiation [33].
Memory B cell	-Dormant B cell arising from B cell differentiation [33]. -Function to circulate through the body and initiate a stronger, more rapid antibody response (secondary antibody response) following detection of antigen that had activated their parent B cell [35].
Follicular (FO) B Cell (or B-2 cell)	-Most common type of B cell found mainly in the lymphoid follicles of SLOs when not circulating through the blood [36]. -Responsible for generating the majority of high-affinity antibodies during an infection [5].
Marginal Zone (MZ) B cell	-Found mainly in the marginal zone of the spleen [36]. -Serves as a first line of defense against blood-borne pathogens, as the marginal zone receives large amounts of blood from the general circulation [37].
Regulatory B (Breg) cell	-An immunosuppressive B cell type that stops the expansion of pathogenic, pro-inflammatory lymphocytes through the secretion of IL-10, IL-35, and TGF-β [38].

Natural killer cells

Natural killer (NK) cells are Large Granular Lymphocytes (LGL) and constitute the third kind of cells differentiated from the common lymphoid progenitor generating B and T lymphocytes [44]. NK cells have been known to differentiate and mature in the bone marrow, lymph nodes, spleen, tonsils, and thymus, from which they then enter into the circulation [45]. Natural killer cells have been reported to provide rapid responses to viral-infected cells and respond to tumor formation [46]. Also, they have been demonstrated to recognize stressed cells in the absence of antibodies and MHC, thus allowing for a much faster immune reaction [47].

Functions of natural killer cells:

- Cell apoptosis mediated by cytolytic granule [46].
- Antibody-dependent cell-mediated cytotoxicity [8].
- Tumor cell surveillance [48,49].
- Adaptive features of NK cells-"memory-like" and memory NK cells [50].
- NK cell function in pregnancy [51] (Table 3).

LYMPHOCYTOSIS

This is an abnormal increase in lymphocytes counts in the circulation. Increased circulatory lymphocytes count greater than 40% of total white blood cells is considered to be abnormal [53].

Causes of lymphocytosis

- Viral infections such as influenza, chicken pox, rubella, varicella, herpes simplex, hepatitis, cytomegalovirus [54].
- Bacterial infections such as tuberculosis [55], brucellosis [56], whooping cough [57].

Table 3: Lymphocytes reference values in domestic animals.

Animals	Lymphocytes Count (cells/µl)
Dog	1,000-4,000
Cat	1,000-7,000
Horse	1,600-5,800
Foal	700-2,900
Cattle	1,700-5,600
Sheep	2,000-5,700
Goat	2,500-12,000
Alpaca	2,130-6,410

[52] Reference values were established using adult animals (> 1 year). Foal reference values were established using animals < 24 hours old. Cattle are adult dairy cows at mid-lactation. Alpaca age range 6mths-7yrs/male & female.

- Protozoal infections such as toxoplasmosis [54].
- Medications such as Dilantin, mephenytoin [58].
- Cancers such as Acute Lymphoblastic Leukemia (ALL) [41], chronic lymphocytic leukemia (CLL) [40].
- Post-splenectomy state [59].
- Smoking [60].

LYMPHOCYTOPAENIA OR LYMPHOPAENIA

Lymphocytopaenia is an abnormally low level of lymphocytes in the circulation [5,61]. When the complete blood count reveals lymphocyte count lower than the age-appropriate reference interval, lymphocytopaenia is reported [12,61].

Causes of lymphocytopaenia

- Infections caused by bacteria and fungi [5]
- Viral infections such as influenza, feline leukemia, HIV, infectious bursal disease [62]
- Malnutrition [5]
- Corticosteroid use [63]
- Systemic lupus erythematosus [64]
- Severe stress, intense/prolonged physical exercise, pregnancy [63]
- Rheumatoid arthritis [5]
- Sarcoidosis [65]
- Advanced Hodgkin's disease [66]

CONCLUSION

Lymphocytes have been demonstrated to play vital body functions such as immunity, tumor cells surveillance and rejection reaction during organ transplant. However, any increase or decrease in lymphocytes count outside the reference values may indicate an abnormal condition and prompt diagnosis. Therefore, a proper interpretation of lymphocytes abnormalities in the form of lymphocytosis and lymphopenia would assist a clinician in the adequate description of physiological and pathological conditions.

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