

1. Lymphocytes

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Lymphocytes are white blood cells uniform in appearance but varied in function and include T, B, and natural killer cells. These cells are responsible for antibody production, direct cell-mediated killing of virus-infected and tumor cells, and regulation of the immune response. Advances in immunology have led to the characterization of newly appreciated effector populations such as IL-17–producing T cells, T cells with regulatory function, and natural killer T cells, thus revising established paradigms. This chapter provides an overview of the major lymphocyte populations with emphasis on their development, distinguishing characteristics, and functions. (J Allergy Clin Immunol 2008;121:S364-9.)

Key words: Lymphocyte, adaptive immune system, T cell, B cell, natural killer cell

Multicellular organisms evolved mechanisms to sense pathogens and rapidly mount protective responses; these first-line defenses are collectively called *innate immunity*. Vertebrates have evolved additional protective mechanisms including lymphocytes that respond to specific antigens using receptors generated from rearranged gene segments. In addition to providing an enormous repertoire of antigen-specific responses, these cells enable immunologic memory, allowing for robust immunity on re-encounter with the same pathogen. Collectively these functions make up adaptive immunity.

Lymphocytes are white blood cells that are uniform in appearance but varied in function and include T, B, and natural killer (NK) cells. Although T and B cells are the effectors of adaptive immunity, NK cells do not have recombined antigen receptors and are innate immune lymphocytes. This chapter provides a brief overview of the major lymphocyte populations with emphasis on their development, characteristics, and diverse roles.

HUMAN LYMPHOCYTE DEVELOPMENT

T, B, and NK cells and their respective subsets (Table I) originate from the bone marrow–derived progenitors. Progenitors that migrate to the thymus and receive signals through the Notch receptor commit to the T-cell lineage.¹ In human beings, lineage development is critically dependent on IL-7 for T cells² and IL-15 for NK cells.³ Lymphocyte specificity and diversity are gained during the process of T-cell receptor (TCR) or B-cell receptor (BCR) generation, key events in the adaptive immune system.

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Abbreviations used

APC:	Antigen presenting cell
BCR:	B-cell receptor
CSR:	Class switch recombination
D:	Diversity gene segment
DC:	Dendritic cell
DP:	Double-positive
GC:	Germinal center
iNKT:	Invariant natural killer T cell
ITAM:	Immunotyrosine-based activation motif
J:	Joining gene segment
NK:	Natural killer
nTreg:	Thymic-derived “natural” regulatory T cell
SHM:	Somatic hypermutation
T _{CM} :	Central memory T cell
T _{EM} :	Effector memory T cell
TCR:	T-cell receptor
Treg:	T-regulatory cell
V:	Variable gene segment

The receptor repertoire is determined by random variable (V), diversity (D), and joining (J) somatic gene segments that recombine with the imprecise addition of nucleotides at segment connections. The enzyme complex that performs this recombination is termed the V(D)J recombinase and includes the recombination-activating gene (RAG) proteins expressed in B and T cells. Successful recombination is determined by expression of a functional antigen receptor, which allows cell survival and continued development.

T-cell development

Early T-cell precursors do not express the CD4 or CD8 coreceptor (double-negative) and begin recombination of TCR gene segments, of which there are 4: α , β , γ , and δ . Recombination begins at the δ , γ , and β loci, and if expression of the $\gamma\delta$ TCR is successful, commitment to the $\gamma\delta$ T-cell lineage results.⁴ $\gamma\delta$ T cells remain double-negative and leave the thymus, populating lymphoid tissue and epithelia. Alternatively, successful β loci recombination results in β TCR expression, which pairs with the surrogate α receptor (pre-T α) and forms the pre-TCR. With the immunotyrosine-based activation (ITAM) motif-rich CD3 signaling machinery, the pre-TCR provides ligand-independent signals enabling commitment to the $\alpha\beta$ T-cell lineage and CD4/CD8 coexpression (double-positive; DP). An ITAM is a common motif in immunoreceptors that becomes phosphorylated, permitting interaction with intracellular signaling molecules. Assembly of the pre-TCR is followed by recombination at the α loci, which, if successful, generates the $\alpha\beta$ TCR. Ligand-dependent selection now occurs and is determined by DP cells binding peptide-loaded MHC molecules on thymic cortical epithelia. MHC molecules are heterodimeric proteins that display peptide

TABLE I. Major lymphocyte populations

Population	Phenotype*	Immune function
Naive $\alpha\beta$ T cells	$CD3^+CD45RA^+TCR\alpha\beta^+$	Cell-mediated adaptive immunity, specific peptide recognition restricted by MHCII/II
T_{EM}	$CD3^+CD45RO^+CD62L^-CCR7^-$	High peripheral precursor frequency, rapid effector response
T_{CM}	$CD3^+CD45RO^+CD62L^+CCR7^+$	High precursor frequency in lymphoid organs, rapid proliferation
T_H1	$CD3^+CD4^+(Tbet^+)$	Cell-mediated immunity, macrophage activation, produce: IFN- γ , TNF
T_H2	$CD3^+CD4^+(GATA3^+)$	B-cell help, allergic inflammation, produce: IL-4, IL-5, IL-13
T_H17	$CD3^+CD4^+(ROR\gamma t^+)$	Hyperinflammation, host defense, produce: IL-17, IL17F, TNF
Treg	$CD3^+CD4^+CD25^+(FOXP3^+)$	Contact-dependent suppression, produce: TGF β , IL-10
T-regulatory type 1	$CD3^+CD4^+$	Immune regulation, high IL-10 production
Cytotoxic T lymphocyte	$CD3^+CD8^+(Eomes^+Tbet^+)$	Cell-mediated immunity, antigen-specific cytotoxicity, produce: IFN- γ , TNF, perforin, granzyme
NKT	$CD3^+CD56^+$	Multiple roles in immune response, produce: IFN- γ /TNF or IL-4/IL-13
$\gamma\delta$ T cells	$CD3^+TCR\gamma\delta^+CD4^-CD8^-$	Component of epithelial immunity, some cytotoxicity, produce: IFN- γ , TNF
Naive B cells	$CD19^+IgM^+IgD^+$	Humoral adaptive immunity, natural antibodies, APC
Memory B cells	$CD19^+CD27^+IgM^+$	High-affinity BCR, rapid proliferation and differentiation on recall
Switched memory	$CD19^+CD27^+IgM^-$	High-affinity BCR, rapid recall, antibody with specific effector functions
Plasma cells	$CD38^+CD138^+$	Constitutive high-affinity antibody production
NK cells	$CD3^-CD56^+CD94^+$	Innate cytotoxicity, ADCC, produce: IFN γ , TNF, perforin, granzyme
CD56 ^{BRIGHT}	$CD56^{bright}CD16^{+/-}$	More cytokine production, less cytotoxicity
CD56 ^{DIM}	$CD56^{dim}CD16^+$	More cytotoxicity, less cytokine production

*Distinguishing surface markers with subset-specific intracellular transcription factors shown in parentheses.

antigen for recognition by T cells. DP cells that bind MHC with sufficient affinity are selected to survive (positive selection), whereas those that do not are deleted by apoptosis. The interaction with the TCR complex and MHC molecule is restricted by the specificity of the TCR and T-cell coreceptor (Fig 1); CD4 restricts interaction to class II MHC and CD8 to class I MHC. Surviving DP cells then lose the CD4 or CD8 coreceptor not involved in MHC recognition. These single-positive cells traffic to thymic medulla, and those that react too strongly with self-antigens presented by medullary epithelia and bone marrow–derived antigen-presenting cells (APCs) are deleted by apoptosis (negative selection). The autoimmune regulator gene (*AIRE*), discovered from study of autoimmune polyendocrinopathy syndrome type 1, is required for expression of tissue-specific antigens by medullary thymic epithelia, thus enabling central tolerance.⁵ *AIRE* is also involved in intrathymic regulatory T-cell differentiation.⁶

These processes of positive and negative selection promote viable T cells capable of recognizing and responding to peptide antigen in MHC while checking those that have autoreactivity. Although rigorous, with approximately only 2% of DP cells surviving, other mechanisms ensure tolerance in the periphery and are discussed.

B-cell development

B cells develop in the bone marrow but achieve maturity in peripheral lymphoid organs. Developmental stages are defined by the successful expression of heavy-chain and light-chain immunoglobulin genes. Early progenitors committed to the B-cell lineage (pro-B cells) begin recombination at the immunoglobulin heavy-chain loci.² Successful recombination leads to expression of μ heavy chain, distinguishing the pre-B cell. With the surrogate light chain and the Ig α/β signaling machinery, an immunoglobulin-like heterodimer is surface-expressed (pre-BCR). Pre-BCR signals halt μ heavy-chain recombination, and Ig κ or Ig λ light-chain recombination begins. Bruton's tyrosine kinase is important in transducing this signal because when deficient, B-cell development is arrested at early pre-B cells. The surrogate light chain is

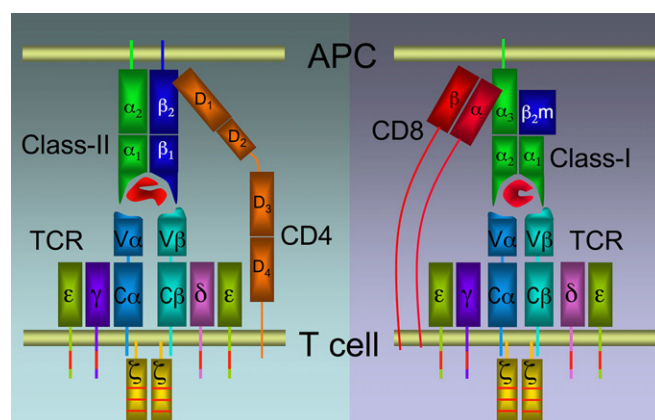


FIG 1. TCR complex and its restriction. The TCR consists of α and β chains that enable specificity through V regions and are anchored via C regions. Receptor signaling occurs through the CD3 subunits, δ , γ , ϵ , and ζ ; each is represented, but there are 2 ϵ and ζ chains. ITAMs (red rectangles) are key signaling elements, and each TCR complex contains 10. The 4 domain-containing CD4 coreceptor restricts TCR binding to class II MHC (left), whereas the α/β chain-containing CD8 coreceptor restricts TCR binding to class I MHC (right).

replaced by a successfully formed κ or λ light chain and the BCR expressed as surface IgM distinguishing the immature B cell. In mice, autoreactive immature B cells undergo receptor editing, deletion, and anergy induction to condition tolerance. Surviving cells exit the bone marrow homing to the spleen, where they undergo transitional stages of development and further selection. B-cell activating factor (BAFF) and related costimulatory signals positively influence transitional B-cell survival and promote mature B-cell development.⁷

T-CELL PRIMING

When T cells recognize their specific peptide:MHC ligand on APCs, TCR signals result in adhesion molecule changes that strengthen and prolong APC contact. During this cognate

interaction, activation and proliferation of naive T cells require a second costimulatory signal provided by CD28 on T cells binding B7 molecules on APCs. This initial antigen-specific activation and proliferation of naive T cells is referred to as *priming*. The molecular signals that mediate activation are beyond the scope of this review but are discussed in detail elsewhere.⁸

After costimulation, T-cell proliferation and differentiation are dependent on IL-2 produced by activated T cells themselves. Without costimulation, cognate interactions fail to activate naive T cells, and anergy results. Once anergic, T cells do not proliferate or produce IL-2 even after subsequent costimulatory signals. This mechanism helps maintain peripheral tolerance of self-reactive T cells. Furthermore, T cells express CD28-related molecules that negatively regulate activation.⁹ For example, signals transduced by the coinhibitory receptor cytotoxic T-lymphocyte antigen 4 (CTLA-4) limit proliferation of activated T cells and help maintain the steady state. Once primed, naive T cells differentiate into effector T cells that perform antigen-specific functions without the need for costimulation.

EFFECTOR T-CELL POPULATIONS

Clearance of intracellular pathogens and tumors depends on the cell-mediated immune response. CD8⁺ effector T cells are pivotal, and their function is distinguished by antigen-specific cytotoxicity restricted by MHC class I (Fig 1). On priming, CD8⁺ T cells produce cytotoxic proteins including perforin and granzymes and secrete them at the point of contact with the target cell, the immunologic synapse, resulting in specific killing without bystander cell damage. Perforin is a membrane-disrupting protein that facilitates the ability of granzymes to induce apoptosis in the target cell. In addition to cytolysis, CD8⁺ effectors produce IFN- γ and TNF. In mice, the transcription factors T-box expressed in T cells (T-bet) and Eomesodermin (Eomes) function in a cooperative and partially redundant way to regulate CD8⁺ T-cell differentiation.¹⁰

Unlike CD8⁺ T cell priming, CD4⁺ T-cell priming results in the differentiation of various subsets distinguished by the production of particular cytokines and effector functions. Classically, CD4⁺ effectors were viewed in the context of the T_H1-T_H2 paradigm, but other subsets have emerged, including IL-17-producing T cells (T_H17) and T cells with regulatory function (Tregs).¹¹ The factors that determine the differentiation of these subsets *in vivo* are not completely understood, although it seems the cytokine milieu may be the major factor.

T_H2 cells produce IL-4, IL-5, and IL-13, and specialize in facilitating B-cell antibody responses. They drive B-cell proliferation by IL-4 and contact-dependent CD40 ligand:CD40 binding, augmenting humoral defenses against extracellular pathogens. Furthermore, IL-4 and IL-5 enable IgE production and eosinophilic inflammation, important for the clearance of helminthic infestations, but highly relevant to the allergic response. T_H2 differentiation is initiated by weak TCR signals coupled with IL-4 receptor signaling and signal transducer and activator of transcription (STAT) 6 activation. This results in upregulation of GATA-3 transcription factor, the master regulator of T_H2 differentiation. GATA-3 enhances T_H2 cytokine production and inhibits T_H1 developmental pathways. The tissue factor thymic stromal lymphopoietin (TSLP), produced in thymus and epithelia, has been shown to activate dendritic cells (DCs) that drive development of inflammatory T_H2 cells.¹²

T_H1 cells specialize in macrophage activation by IFN- γ production and contact-dependent stimulation by using a variety of cell surface costimulatory ligands, thus playing a major role in intracellular pathogen clearance and delayed-type hypersensitivity. T_H1 differentiation is directed by IFNs generated by the innate response to infection, which ultimately leads to upregulation of T-bet, the master regulator of T_H1 differentiation. T-bet directs IFN- γ production and IL-12 receptor expression. The presence of IL-12 results in STAT4 activation, further enhancing IFN- γ production and T_H1 effector formation.

Experiments in mice revealed that loss of the T_H1-IFN- γ pathway does not confer resistance to inflammatory autoimmunity and suggested the presence of an additional pathogenic effector T-cell subset. T_H17 cells produce IL-17, IL-17F, IL-6, and TNF, and are now regarded as a distinct CD4⁺ T-cell subset in both mice and humans. IL-17 is a potent inflammatory cytokine involved in the recruitment and proliferation of neutrophils. Furthermore, data in mice implicate IL-17 as directly involved in the pathogenesis of autoimmune disease including experimental allergic encephalomyelitis (EAE) and collagen-induced arthritis, disease models of multiple sclerosis and rheumatoid arthritis, respectively.¹³ T_H17 differentiation and survival requires TGF- β , IL-6, IL-23, and the transcription factor retinoic acid–related orphan receptor (ROR) γ t.

CD4⁺ T cells can also differentiate into cells characterized by the ability to suppress T-cell responses and prevent autoimmunity, so-called *Tregs*.¹⁴ *Natural Tregs* (nTregs) develop in the thymus and constitutively express the high-affinity IL-2 receptor (CD25) in accordance with their high dependency on IL-2 for survival. The transcription factor Foxp3 is stably expressed by nTregs and is required for their suppressive function. Loss of function mutations in the *FOXP3* gene result in the inflammatory autoimmune disease immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX). Other Treg populations may develop extrathymically from naive CD4⁺ T cells under the influence of TGF- β , referred to as *induced Tregs*. These cells are Foxp3⁺ and are functionally indistinguishable from nTregs. So-called *T-regulatory type 1* cells do not express Foxp3, produce high amounts of IL-10, and develop outside the thymus under the control of IL-10-conditioned DCs.

MEMORY T CELLS

The features that typify memory T cells are the following: (1) persistence of an increased frequency of antigen-specific precursors (100-fold to 1000-fold more than naive host); (2) accelerated responsiveness and rapid effector molecule acquisition on encounter with specific antigen; and (3) antigen-independent steady-state maintenance (homeostatic proliferation) dependent on IL-7 and IL-15.¹⁵ Memory T cells are categorized into 2 subsets termed *central memory* (T_{CM}) and *effector memory* (T_{EM}). T_{CM} cells express CD45RO, CD62L, and CCR7, and are sequestered in lymphoid tissue. They respond to antigen by dividing rapidly and can differentiate into effector cells, but in and of themselves they have little or no effector function. T_{EM} cells express CD45RO but not CD62L or CCR7. They circulate to the peripheral tissues and have limited proliferative capacity but more pronounced effector function. Thus, T_{EM} cells provide peripheral surveillance and rapid effector responses, whereas T_{CM} cells quickly generate back-up effector cells when the immune response becomes more regional.

There are 2 main models of memory T-cell development. The conventional model of linear differentiation posits that memory

cells are derived from effector cells. Activated naive T cells undergo dramatic clonal expansion, but after the acute response, this is followed by apoptosis-induced contraction to maintain steady state; those that survive establish memory. The alternative model is a divergent pathway in which memory is established independent of an effector stage.¹⁵ Recent data show that asymmetric division of the naive T cell during antigen stimulation may be one mechanism of this divergence.¹⁶ During initial cognate stimulation, the formation of the immunologic synapse results in subcellular asymmetry. The daughter cell proximal to the immune synapse establishes a lineage toward effectors, and the daughter cell distal establishes a lineage toward memory.¹⁶

T CELLS USING NONCLASSIC MHC MOLECULES

Important subsets of T cells recognize antigen in the context of atypical MHC molecules. An atypical MHC is essentially any molecule other than MHC class I or II that can present antigen to a TCR. The best known T-cell subsets that use atypical MHC are NKT cells and $\gamma\delta$ T cells.

NK T cells are T cells that express characteristic NK cell receptors including CD56. A rare but important subset of NKT cells is the invariant NKT (iNKT) cell subset, which uses a restricted repertoire of TCR gene segments, V α 24/J α 18 and V β 11, to create a TCR. The iNKT cell recognizes glycolipid antigen in the atypical MHC molecule CD1d. Although little is known about the repertoire of glycolipids presented to the iNKT cell receptor by CD1d, they include α -galactosyl ceramide, a compound derived from aquatic sponges, certain bacterial products, and the endogenously derived glycosphingolipid iGb3.^{17,18} iNKT cells are CD4-positive or CD4-negative and generally do not express CD8. Their development requires the SH2 domain protein 1A (*SH2D1A*) gene (encoding the signalling lymphocyte activation molecule (SLAM)-associated protein [SAP] protein), and thus they are absent in the X-linked lymphoproliferative syndrome (XLP) caused by *SH2D1A* mutation.¹⁹ The function of iNKT cells includes the production of IFN- γ /TNF or IL-4/IL-13. Furthermore, they have been associated with a pathogenic role in asthma and are overrepresented in the bronchial lavage fluid of patients with asthma.²⁰

$\gamma\delta$ T cells use γ and δ TCR chains instead of α and β . Although not as extreme as iNKT cells, the diversity of the $\gamma\delta$ TCR is also limited because there are less than 20 γ and δ variable genes. These cells are present among peripheral blood lymphocytes but are found preferentially in epidermal tissues. $\gamma\delta$ T cells do not express CD4 or CD8 but recognize a variety of antigens, such as microbial phosphoantigens, in a number of different nonclassic MHC molecules. These include MHC I-chain related (MIC) molecules and the atypical MHC molecule CD1c. After TCR ligation and appropriate costimulatory signals, $\gamma\delta$ T cells can mediate cytotoxicity and produce cytokines, especially TNF and IFN- γ . They participate in protection against a variety of microbes and play important roles in stimulating APCs to induce more classic adaptive immunity.

B CELLS

B cells provide humoral immunity against extracellular pathogens through antibody production. Antibodies neutralize pathogens and toxins, facilitate opsonization, and activate complement. In addition to binding soluble peptides, the BCR is

capable of binding large conformational epitopes discontinuous in primary structure that include nonpeptide antigens such as polysaccharides and nucleic acids. In most cases, primary infection or vaccination results in prolonged production of high-affinity specific antibody, the basis of adaptive humoral immunity. Furthermore, so-called *natural* IgM antibodies are produced in the absence of infection, are of lower affinity, are often polyreactive and weakly autoreactive, and bind to many conserved pathogen-associated polysaccharides. These antibodies play a role in first-line defense against bacterial infection and assist in the clearance of endogenous cellular debris.

Naive follicular B cells reside in the follicles of secondary lymphoid tissues. Antigen arrives in lymphoid organs by circulation of soluble molecules or immune complexes or is transported by DCs.²¹ BCR cross-linking initiates receptor-mediated endocytosis, antigen processing, and presentation in MHC class II. Antigen-engaged follicular B cells migrate to the T-B interface, the border between the T-cell zone and B-cell follicle, increasing the probability of encounter with primed helper T cells of cognate specificity. On such an encounter, signals from T-cell-derived cytokines and CD40L:CD40 binding sustain B-cell activation and promote immunoglobulin class switch recombination (CSR). Lack of T-cell-expressed CD40L results in the X-linked hyper-IgM syndrome characterized by normal or high plasma IgM but low or absent IgG, IgA, and IgE.

Activated B cells migrate into the follicle and, with continued T-cell help, initiate the germinal center (GC) reaction, or migrate to the marginal zone and differentiate into short-lived plasma cells. Short-lived plasma cells secrete antibody for 2 to 3 weeks, providing a rapid but transient source of effector molecules. In contrast, B cells forming the GC undergo specificity diversification through somatic hypermutation (SHM), and high-affinity variants are selected by survival advantage, a process termed *affinity maturation*. SHM occurs through single base-pair substitution within the variable region of antibody gene segments. The enzymes activation-induced cytidine deaminase (AID) and uracil-DNA glycosylase (UNG) are essential for both SHM and CSR, and defects in these molecules also result in the hyper-IgM syndrome.²² Thus, within the GC, sequential cycles of proliferation, BCR diversification, and selection amplify high-affinity variants of the original activated B cell.²³

B cells that exit the GC reaction give rise to the memory compartment, which consists of affinity-matured memory B cells and long-lived plasma cells. Affinity-matured memory B cells are long-lived CD27⁺ cells that express surface immunoglobulin but do not secrete antibody. When these cells re-encounter antigen, they divide rapidly and expand their numbers or differentiate into antibody-secreting plasma cells. Long-lived plasma cells are CD138⁺, terminally differentiated B cells incapable of further division. They home to the bone marrow and constitutively secrete high-affinity class-switched antibody. In mice, the transcription factors B-lymphocyte-induced maturation protein 1 (Blimp-1) and X-box binding protein 1 (XBP-1) drive plasma cell differentiation and antibody secretion; B-cell maturation protein A (BCMA) is necessary for long-lived plasma cell survival.

T-cell-dependent and T-cell-independent responses

Follicular B cells present MHC-restricted protein antigens and receive T-cell help that promotes CSR, affinity maturation, and

memory differentiation. These antigen responses are referred to as *T-cell-dependent*. B cells also recognize nonprotein antigens including polysaccharides and glycolipids that cannot be presented in class II MHC molecules. B-cell responses to these antigens occur in the absence of cognate T-cell help and are termed *T-cell-independent*. These responses have a reduced propensity to support memory differentiation and produce IgM or IgG₂ subclass antibodies that have undergone little if any affinity maturation, although exceptions to these generalizations do exist. For instance, the adult response to pneumococcal capsular polysaccharide vaccine provides long-lasting protection, and revaccination results in large secondary responses typical of memory. Interestingly, children less than age 2 or splenectomized individuals do not respond well to vaccines composed of purified polysaccharide. These and other data suggest the immaturity or absence of a B-cell subset or accessory cell functioning within the spleen may play a major role in the T-cell-independent response.²⁴

Human marginal zone B cells primarily reside in the splenic marginal zone and are considered key players in the defense against polysaccharide encapsulated bacteria. These cells express high levels of IgM and CD21 and have a lower threshold for activation, capable of rapid differentiation into dividing, antibody-secreting cells known as *plasmablasts*. Human marginal zone B cells are found in sites other than the spleen, appear to undergo some degree of extrafollicular SHM independent of CD40L-mediated signals, and are phenotypically identical to IgM⁺ memory cells.²⁵ These cells are absent in congenital asplenia and are lost after splenectomy, although it is unclear why the spleen is necessary for generation or maintenance.

NK CELLS

NK cells are lymphocytes of the innate immune system, because they do not rearrange their germline DNA to gain specificity. They do not express TCR or immunoglobulin genes, but instead use a variety of germline-encoded receptors to induce their functions.²⁶ These include the natural cytotoxicity receptor family (NKp30, NKp44, NKp46, NKp80), the C-type lectin-domain containing receptor NKG2D, the CD2 superfamily receptor 2b4 (CD244), and the IgG receptor CD16. The ligands for some of these receptors are known and include molecules upregulated by cellular stress or infection. Important examples are MIC for NKG2D, viral hemagglutinin for NKp46, CD48 for CD244, and IgG for CD16.

Ligation of NK cell activating receptors can induce NK cell functions, which include perforin-dependent cytotoxicity, cytokine production (especially IFN- γ , IL-5, and IL-13), and induction of costimulatory molecules. In this capacity, NK cells participate in antiviral and anticancer responses and can facilitate adaptive immunity. NK cells also have a well defined system of restraining their functions by using several families of inhibitory receptors. The best known of these are the killer cell immunoglobulin-like receptors (KIR), which are highly polymorphic and recognize specific MHC class I molecules and inhibit NK cell functions through the induction of phosphatases. These receptors define an essential feature of NK cells, which is the routine sampling of healthy cells in search of abnormal cells that have lost determinants of self.

Two major subsets of NK cells are distinguished by their low or high expression of CD56 (CD56^{bright} and CD56^{dim}). CD56^{dim} NK

cells constitute the majority of NK cells among PBMCs and excel in cytotoxicity. CD56^{bright} NK cells are less effective in cytotoxicity but are very potent cytokine producers. Interestingly, a different subset of NK cells that express very high levels of CD56 are the major lymphocyte present in the pregnant uterine decidua and are likely involved in immunologic tolerance of the fetus, defense against fetal infection, and decidualization.²⁷

Conclusion

Lymphocytes are a diverse population of cells that participate in both innate and adaptive immunity. Our evolving understanding of lymphocyte populations and their multiple effector functions underscores the sophistication of the immune response. In addition to their essential functions in host defense against microbes and tumors, lymphocytes perpetuate inflammatory autoimmunity and atopy, thus contributing to human disease. Newly appreciated lymphocyte subsets, the signals required for their differentiation, and their effector molecules all provide targets for development of novel therapeutic strategies.

The length of this review has required numerous generalizations and thus has excluded some important exceptions and challenges to the paradigms presented. We refer the reader to the cited literature for a more specific and comprehensive treatment of the subject matter.

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Lymphocytes

Instructions for category 1 Continuing Medical Education credit

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Learning objectives: "Lymphocytes"

1. To achieve familiarity with the major subpopulations of lymphocytes and their respective functions.
 2. To broadly appreciate the developmental influences that give rise to different types of lymphocytes.
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CME items

Question 1. Which transcription factor do T_H2 cells rely on to distinguish themselves from T_H1 cells?

- A. GATA-3
- B. Eomes
- C. T bet
- D. ROR γ t

Question 2. Which MHC molecule is the ligand for T cells bearing the specific T-cell receptor containing V α 24/J α 18 and V β 11?

- A. CD1d
- B. HLA-E
- C. HLA-G
- D. MHC class I

Question 3. Tumor cells and other "stressed" cells can express MICA, which serves as a "danger ligand" to induce natural killer (NK) cell cytotoxicity through which of the following NK cell activation receptors?

- A. NKp30
- B. NKp46
- C. NKG2A
- D. NKG2D

Question 4. Which of the following T-cell subsets are best associated with functional responses in lymphoid tissues?

- A. $\gamma\delta$ T cells
- B. central memory T cells
- C. effector memory T cells
- D. invariant NK T cells