USMLE Step 1 Lecture Notes 2019: Immunology and Microbiology (Kaplan Test Prep Book 4)

Publisher: Kaplan Publishing (December 4, 2018)
Format: pdf, epub
Language: English

USMLE® Step 1: Immunology and Microbiology

Lecture Notes 2019

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Published by Kaplan Medical, a division of Kaplan, Inc.

750 Third Avenue

New York, NY 10017

10 9 8 7 6 5 4 3 2 1

ISBN: 978-1-5062-3615-5

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The editors would like to acknowledge **Masood Sadaat, MD** and **Aditya Patel, MD** for their contributions.

We want to hear what you think. What do you like or not like about the Notes? Please email us at **medfeedback@kaplan.com**.

Part I Immunology

1 The Immune System Learning Objectives Define and describe the components of the immune system Discriminate between innate and acquired immunity The Immune System

The immune system is designed to recognize and respond to non-self antigen in a coordinated manner. Additionally, cells that are diseased, damaged, distressed or dying are recognized and eliminated by the immune system.

The immune system is divided into 2 complementary arms: the **innate** and the **adaptive** immune systems. Innate Immunity

Innate immunity provides the body's first line of defense against infectious agents. It involves several defensive barriers: Anatomic and physical (skin, mucous membranes and normal flora) Physiologic (temperature, pH, anti-microbials and cytokines) Complement Cellular: phagocytes and granulocytes Inflammation

Innate immune defenses have the following characteristics in common: Are **present intrinsically** with or without previous stimulation Have **limited specificity** for shared microbe and cellular structures (pathogen-associated molecular patterns [PAMPs] and damage-associated molecular patterns [DAMPs]) Have **limited diversity** as reflected by a limited number of pattern recognition receptors Are not enhanced in activity upon subsequent exposure—**no memory** Adaptive Immunity

The components of the adaptive immune response are B and T lymphocytes and their effector cells.

Adaptive immune defenses have the following characteristics in common: Each B and T lymphocyte is **specific** for a particular antigen As a population, lymphocytes have extensive diversity Are enhanced with each repeat exposure-—**immunologic memory** Are capable of **distinguishing self** from **non-self** Are **self-limiting**

The features of adaptive immunity are designed to give the individual the best possible defense against disease. **Specificity** is required, along with **immunologic memory,** to protect against persistent or recurrent challenge. **Diversity** is required to protect against the maximum number of potential pathogens. **Specialization** of effector function is necessary so that the most effective defense can be mounted against diverse challenges. The ability to **distinguish between self** (host cells) **and non-self** (pathogens) is vital in inhibiting an autoimmune response. **Self-limitation** allows the system to return to a basal resting state after a challenge to conserve energy and resources and to avoid uncontrolled cell proliferation resulting in leukemia or lymphoma. Table I-1-1. Innate versus Adaptive Immunity

Characteristics

Innate

Adaptive

Specificity

For pathogen-associated molecular patterns (PAMPs)

For specific antigens of microbial and nonmicrobial agents

Diversity

Limited

High

Memory

No

Yes

Self-reactivity

No

No

Components

Anatomic and physiologic barriers

Skin, mucosa, normal flora, temperature, pH, antimicrobials, and cytokines

Lymph nodes, spleen, mucosal-associated lymphoid tissues

Blood proteins

Complement

Antibodies

Cells

Phagocytes, granulocytes and natural killer (NK) cells

B lymphocytes and

T lymphocytes Function

The innate and adaptive arms of the immune response work in collaboration to stop an infection. Once a pathogen has broken through the anatomic and physiologic barriers, the innate immune response is immediately activated, oftentimes it is able to contain and eliminate the infection.

When the innate immune response is unable to control the replication of a pathogen, the adaptive immune response is engaged and activated by the innate immune response in an antigen-specific manner. Typically, it takes 1-2 weeks after the primary infection for the adaptive immune response to begin clearance of the infection through the action of effector cells and antibodies.

Once an infection has been cleared, both the innate and adaptive immune responses cease. Antibodies and residual effector cells continue to provide protective immunity, while memory cells provide long-term immunologic protection from subsequent infection. Figure I-1-1. Timeline of the Immune Response to an Acute Infection

The innate and adaptive immune responses do not act independently of one another; rather, they work by a positive feedback mechanism. Phagocytic cells recognize pathogens by binding

PAMPs through various pattern-recognition receptors leading to phagocytosis. Phagocytic cells process and present antigen to facilitate stimulation of specific T lymphocytes with subsequent release of cytokines that trigger initiation of specific immune responses. T lymphocytes produce cytokines that enhance microbicidal activities of phagocytes. Cytokines released by phagocytes and T lymphocytes will drive differentiation of B lymphocytes into plasma cells and isotype switching. Antibodies will aid in the destruction of pathogen through opsonization, complement activation and antibody-dependent cellular cytotoxicity. Figure I-1-2. Interaction between Innate and Adaptive Immune Responses Recall Question

Which of the following is most likely to cause a faster and stronger immunologic response against the same infectious agent after re-exposure?

Innate immunity, as adaptive immunity takes 1-2 weeks Natural killer cells Innate immunity because macrophages recognize PAMPS and DAMPS Adaptive immunity and immunological memory

Complement activation

Answer: D

2 Ontogeny of the Immune Cells Learning Objectives Explain information related to origin and function of cells of the immune system Explain information related to antigen recognition molecules of lymphocytes Answer questions about the generation of receptor diversity Origin

Hematopoiesis involves the production, development, differentiation, and maturation of the blood cells (erythrocytes, megakaryocytes and leukocytes) from **multipotent stem cells**. The site of hematopoiesis changes during development.

During embryogenesis and early fetal development, the yolk sac is the site of hematopoiesis. Once organogenesis begins, hematopoiesis shifts to the liver and spleen, and finally, to the bone marrow where it will remain throughout adulthood. Figure I-2-1. Sites of Hematopoiesis during Development

These **multipotent stem cells** found in the bone marrow have the ability to undergo asymmetric division. One of the 2 daughter cells will serve to renew the population of stem cells (**self-renewal**), while the other can give rise to either a common lymphoid progenitor cell or a common myeloid progenitor cell (**potency**). The multipotent stem cells will differentiate into the various lymphoid and myeloid cells in response to various cytokines and growth factors. The **common lymphoid progenitor cell** gives rise to B lymphocytes, T lymphocytes and natural killer (NK) cells. The **common myeloid progenitor cell** gives rise to erythrocytes, megakaryocytes/thrombocytes, mast cells, eosinophils, basophils, neutrophils, monocytes/macrophages and dendritic cells.

Function

The white blood cells of both the myeloid and lymphoid stem cells have specialized functions in the body once their differentiation in the bone marrow is complete. Cells of the myeloid lineage,

except erythrocytes and megakaryocytes, perform non-specific, stereotypic responses and are members of the innate branch of the immune response. B lymphocytes and T lymphocytes of the lymphoid lineage perform focused, antigen-specific roles in immunity. Natural killer cells are also from the lymphoid lineage but participate in innate immunity.

Although B lymphocytes and T lymphocytes in the bloodstream are almost morphologically indistinguishable at the light microscopic level, they represent 2 interdependent cell lineages. **B lymphocytes** remain within the **bone marrow** to complete their development. **T lymphocytes** leave the bone marrow and undergo development within the **thymus.**

Both B and T lymphocytes have surface membrane receptors designed to bind to specific antigens; the generation of these receptors will be discussed in chapter 4. The **natural killer (NK) cell** (the third type of lymphocyte) is a large granular lymphocyte that recognizes tumor and virally infected cells through non-specific binding. Figure I-2-2. Ontogeny of Immune Cells Table I-2-1. White Blood Cells

Myeloid Cell

Tissue Location

Physical Description

Function

Neutrophil or polymorpho- nuclear (PMN) cell

Most abundant circulating blood cell

Granulocyte with a segmented, lobular nuclei (3–5 lobes) and small pink cytoplasmic granules

Phagocytic activity aimed at killing extracellular pathogens

Lymphoid Cell

Tissue Location

Physical Description

Function

Lymphocyte

Bloodstream,

secondary lymphoid tissues

Large, dark-staining nucleus with a thin rim of cytoplasm

Surface markers: B lymphocytes CD19, 20, 21 T lymphocytes
CD3 Helper T cells CD4 CTLs CD8

No function until activated in the secondary lymphoid tissues

Plasma cell

Bloodstream, secondary lymphoid tissue and bone marrow

Small eccentric nucleus, intensely staining Golgi apparatus

Terminally differentiated B lymphocyte that secretes antibodies

Natural killer cell

Bloodstream

Lymphocyte with large cytoplasmic granules

Surface markers:

CD16, 56

Kills virally infected cells and tumor cells

Myeloid Cell

Tissue Location

Physical Description

Function

Monocyte

Circulating blood cell

Agranulocyte with a bean or kidney-shaped nucleus

Precursor of tissue macrophage

Macrophage

Resident in all tissues

Agranulocyte with a ruffled cytoplasmic membrane and cytoplasmic vacuoles and vesicles
Phagocyte Professional antigen presenting cell T-cell activator

Dendritic cell

Resident in epithelial and lymphoid tissue

Agranulocyte with thin, stellate cytoplasmic projections Phagocyte Professional antigen presenting cell T-cell activator

Eosinophil

Circulating blood cell recruited into loose connective tissue of the respiratory and GI tracts

Granulocyte with bilobed nucleus and large pink cytoplasmic granules Elimination of large extracellular parasites Type I hypersensitivity

Mast cell

Reside in most tissues adjacent to blood vessels

Granulocyte with small nucleus and large blue cytoplasmic granule Elimination of large extracellular parasites Type I hypersensitivity

Basophil

Low frequency circulating blood cell

Granulocyte with bilobed nucleus and large blue cytoplasmic granules Elimination of large extracellular parasites Type I hypersensitivity

Laboratory evaluation of patients commonly involves assessment of white blood cell morphology

and relative counts by examination of a blood sample. Changes in the morphology and proportions of white blood cells indicate the presence of some pathologic state. A standard white blood cell differential includes neutrophils, band cells, lymphocytes (B lymphocytes, T lymphocytes, and NK cells), monocytes, eosinophils and basophils. Table I-2-2. Leukocytes Evaluated in a WBC Differential

Cell Type

Adult Reference Range (%)

Neutrophils (PMNs)

50–70

Band cells

0–5

Lymphocytes

20–40

Monocytes

5–10

Eosinophils

0–5

Basophils

<1

Recall Question

Which cytokine differentiates the myeloid stem cell into a granulocyte that contains a bilobed nucleus and pink cytoplasmic granules?

IL-11 IL-5 Thrombopoietin GM-CSF and IL-3 IL-7

Answer: B

3 Lymphocyte Development and Selection Learning Objectives Answer questions about selection of T and B lymphocytes Solve problems concerning innate immunity and components/barriers Antigen Recognition Molecules of Lymphocytes

Each cell of the lymphoid lineage is clinically identified by the characteristic surface molecules that it possesses. The mature, naïve **B lymphocyte**, in its mature ready-to-respond form, expresses 2 isotypes of antibody or immunoglobulin called IgM and IgD within its surface membrane. The mature, naive **T cell** expresses a single genetically related molecule, called the **T-cell receptor (TCR)**, on its surface.

Both of these types of antigen receptors are encoded within the immunoglobulin superfamily of genes and are expressed in literally millions of variations in different lymphocytes as a result of complex and random rearrangements of the cells' DNA. Figure I-3-1. Antigen Receptors of Mature Lymphocytes

The antigen receptor of the B lymphocyte, or **membrane-bound immunoglobulin**, is a 4-chain glycoprotein molecule that serves as the basic monomeric unit for each of the distinct antibody molecules destined to circulate freely in the serum. This monomer has 2 identical halves, each composed of a **heavy chain** and a **light chain**. A cytoplasmic tail on the carboxy-terminus of each heavy chain extends through the plasma membrane and anchors the molecule to the cell surface. The 2 halves are held together by disulfide bonds into a shape resembling a "Y." Some flexibility of movement is permitted between the halves by disulfide bonds forming a **hinge region**.

On the N-terminal end of the molecule where the heavy and light chains lie side by side, an antigen binding site is formed whose 3-dimensional shape will accommodate the noncovalent binding of one, or a very small number, of related antigens. The unique structure of the antigen binding site is called the **idiotype** of the molecule. Although 2 classes **(isotypes)** of membrane immunoglobulin (IgM and IgD) are coexpressed on the surface of a mature, naïve B lymphocyte, only one idiotype or **antigenic specificity** is expressed per cell (although in multiple copies). Each individual is capable of producing hundreds of millions of unique idiotypes. Figure I-3-2. B-Lymphocyte Antigen Recognition Molecule (Membrane-Bound Immunoglobulin)

The antigen receptor of the T lymphocyte is composed of 2 glycoprotein chains, a beta and alpha chain that are similar in length. On the carboxy-terminus of the chains, a cytoplasmic tail extends through the membrane for anchorage. On the N-terminal end of the molecule, an antigen-binding site is formed between the 2 chains, whose 3-dimensional shape will accommodate the binding of a small antigenic **peptide complexed to an MHC molecule** presented on the surface of an antigen-presenting cell. This groove forms the idiotype of the TCR. There is no hinge region present in this molecule, and thus its conformation is quite rigid.

The membrane receptors of B lymphocytes are designed to bind **unprocessed antigens** of almost any chemical composition, i.e., polysaccharides, proteins, lipids, whereas the TCR is designed to bind only **peptides complexed to MHC**. Also, although the B-cell receptor is ultimately modified to be secreted **antibody**, the TCR is never released from its membrane-bound location.

In association with these unique antigen-recognition molecules on the surface of B and T cells, accessory molecules are intimately associated with the receptors that function in signal transduction. Thus, when a lymphocyte binds to an antigen complementary to its idiotype, a cascade of messages transferred through its **signal transduction complex** will culminate in intracytoplasmic phosphorylation events leading to activation of the cell. In the B cell, this

signal transduction complex is composed of 2 invariant chains, Ig-alpha and Ig-beta, and a B-cell co-receptor consisting of CD19, CD21 and CD81. The B-cell co-receptor is implicated in the attachment of several infectious agents. CD21 is the receptor for EBV and CD81 is the receptor for hepatitis C and *Plasmodium vivax*. In the T cell, the signal transduction complex is a multichain structure called CD3. Figure I-3-3. Lymphocyte Signal Transduction

Table I-3-1. B- versus T-Lymphocyte Antigen Receptors

Property	B-Cell Antigen Receptor	T-Cell Antigen Receptor
Molecules/Lymphocyte	100,000	100,000
Idiotypes/Lymphocyte	1	1
Isotypes/Lymphocyte	2 (IgM and IgD)	1 (α/β)
Is secretion possible?	Yes	No
Number of combining sites/molecule	2	1
Mobility	Flexible (hinge region)	

Rigid

Signal-transduction molecules

Ig-α, Ig-β, CD19, CD21

CD3

The Generation of Receptor Diversity

Because the body requires the ability to respond specifically to millions of potentially harmful agents it may encounter in a lifetime, a mechanism must exist to generate as many idiotypes of antigen receptors as necessary to meet this challenge. If each of these idiotypes was encoded separately in the germline DNA of lymphoid cells, it would require more DNA than is present in the entire cell. The generation of this necessary diversity is accomplished by a complex and unique set of rearrangements of DNA segments that takes place during the maturation of lymphoid cells.

It has been discovered that individuals inherit a large number of different segments of DNA which may be recombined and alternatively spliced to create unique amino acid sequences in the N-terminal ends (**variable domains**) of the chains that compose their antigen recognition sites. For example, to produce the **heavy chain variable domains** of their antigen receptor, B-lymphocyte progenitors select randomly and in the absence of stimulating antigen to recombine 3 gene segments designated variable (V), diversity (D), and joining (J) out of hundreds of germline-encoded possibilities to produce unique sequences of amino acids in the variable domains (VDJ recombination). Note

VDJ rearrangements in DNA produce the diversity of heavy chain variable domains.
Note

mRNA molecules are created which join this variable domain sequence to μ or δ constant domains.

An analogous random selection is made during the formation of the beta-chain of the TCR.
Figure I-3-4. Production of Heavy (B-Cell) or Beta (T-Cell) Chains of Lymphocyte Antigen Receptors Note

VJ rearrangements in DNA produce the diversity of light chain variable domains.
Note

K or λ constant domains are added to complete the light chain. Bridge to Pathology

Tdt is used as a marker for early stage T- and B-cell development in acute lymphoblastic leukemia.

Next, the B-lymphocyte progenitor performs random rearrangements of 2 types of gene segments (V and J) to encode the **variable domain amino acids of the light chain.** An analogous random selection is made during the formation of the alpha-chain of the TCR. The enzymes responsible for these gene rearrangements are encoded by the genes *RAG1* and *RAG2*. The *RAG1* and *RAG2* gene products are 2 proteins found within the recombinase, a protein complex that includes a repair mechanism as well as DNA-modifying enzymes. Figure I-3-5. Production of Light (B-Cell) or Alpha (T-Cell) Chain of a Lymphocyte Antigen Receptor

While heavy chain gene segments are undergoing recombination, the enzyme **terminal**

deoxyribonucleotidyl transferase (Tdt) randomly inserts bases (without a template on the complementary strand) at the junctions of V, D, and J segments (**N-nucleotide addition**). The random addition of the nucleotide generates junctional diversity.

When the light chains are rearranged later, Tdt is not active, though it is active during the rearrangement of all gene segments in the formation of the TCR. This generates even more diversity than the random combination of V, D, and J segments alone. Figure I-3-6. Function of Tdt

Needless to say, many of these gene segment rearrangements result in the production of truncated or nonfunctional proteins. When this occurs, the cell has a second chance to produce a functional strand by rearranging the gene segments of the homologous chromosome. If it fails to make a functional protein from rearrangement of segments on either chromosome, the cell is induced to undergo **apoptosis** or programmed cell death.

In this way, the cell has 2 chances to produce a functional heavy (or β) chain. A similar process occurs with the light (or α) chain. Once a functional product has been achieved by one of these rearrangements, the cell shuts off the rearrangement and expression of the other allele on the homologous chromosome—a process known as **allelic exclusion**. This process ensures that B and T lymphocytes synthesize only **one specific antigen-receptor per cell**.

Because any heavy (or β) chain can associate with any randomly generated light (or α) chain, one can multiply the number of different possible heavy chains by the number of different possible light chains to yield the total number of possible idiotypes that can be formed. This generates yet another level of diversity. Table I-3-2. Mechanisms for Generating Receptor Diversity

Mechanism

Cell in Which It Is Expressed

Existence in genome of multiple V, D, J segments

B and T cells

VDJ recombination

B and T cells

N-nucleotide addition

B cells (only heavy chain)

T cells (all chains)

Combinatorial association of heavy and light chains

B and T cells

Somatic hypermutation

B cells only, after antigen stimulation (*see* Chapter 7)

Downstream on the germline DNA from the rearranged segments, are encoded the amino acid sequences of all the constant domains of the chain. These domains tend to be similar within the classes or isotypes of immunoglobulin or TCR chains and are thus called **constant domains**.

Figure I-3-7. Immunoglobulin Heavy Chain DNA

The first set of constant domains for the heavy chain of immunoglobulin that is transcribed is that of IgM and next, IgD. These 2 sets of domains are alternatively spliced to the variable domain product at the RNA level. There are only 2 isotypes of light chain constant domains, named κ and λ, and one will be combined with the product of light chain variable domain rearrangement to produce the other half of the final molecule. Thus, the B lymphocyte produces IgM and IgD molecules with identical idiotypes and inserts these into the membrane for antigen recognition.

Table I-3-3. Clinical Outcomes of Failed Gene Rearrangement

Clinical Syndrome

Genetics

Molecular Defect

Symptoms

Omenn syndrome

Autosomal recessive

Missense mutation in *RAG* genes

The *RAG* enzymes have only partial activity

Lack of B cells (below limits of detection)

Marked decrease in predominantly Th2

Characterized by early onset, failure to thrive, red rash (generalized), diarrhea, and severe immune deficiency

Severe combined immunodeficiency (SCID)

Autosomal recessive

Null mutations in *RAG1* or *RAG2* genes

No *RAG* enzyme activity

Total lack of B and T cells

Total defects in humoral and cell-mediated immunity Recall Question

Which of the following mechanisms is involved in generation of the receptor diversity in B and T cells?

Rearrangement of V(D)J segments

N-nucleotide addition at junctions of V, D, and J segments

Combinatorial association of heavy and light chains

A recombinase enzyme All mechanisms are involved

Answer: E

Selection of T and B Lymphocytes

As lymphoid progenitors develop in the bone marrow, they make random rearrangements of their germline DNA to produce the unique idiotypes of antigen-recognition molecules that they will use throughout their lives. The bone marrow, therefore, is considered a **primary lymphoid organ** in humans because it supports and encourages these early developmental changes. B lymphocytes complete their entire formative period in the bone marrow and can be identified in their progress by the immunoglobulin chains they produce. Recall Question

What is the cause of Omenn syndrome? Null mutations in RAG1 and RAG2 genes
Missense mutation in Tdt enzyme Missense mutation in RAG genes

Heterozygous deletion of 22q11

Somatic hypermutation

Answer: C B Lymphocyte Development

In essence, the rearrangement of the gene segments and the subsequent production of immunoglobulin chains drive B-cell development.

Because these gene segment rearrangements occur randomly and in the absence of stimulation with foreign antigen, it stands to reason that many of the idiotypes of receptors produced could have a binding attraction or **affinity** for normal body constituents. These cells, if allowed to develop further, could develop into self-reactive lymphocytes that could cause harm to the host. Therefore, one of the key roles of the bone marrow stroma and interdigitating cells is to remove such potentially harmful products. Cells whose idiotype has too great an affinity for normal cellular molecules are either deleted in the bone marrow (**clonal deletion)** or inactivated in the periphery (**clonal anergy**). Anergic B cells express high levels of IgD on their surface rendering them inactive. The elimination of self-reactive cells in the bone marrow is intended to minimize the number of self-reactive B-lymphocytes released to the periphery, only those cells that are **selectively unresponsive** (**tolerant**) to self-antigens are allowed to leave the bone marrow.

Figure I-3-8. B-Cell Differentiation T Lymphocyte Development

Immature lymphocytes destined to the T-cell lineage leave the bone marrow and proceed to the **thymus**, the second **primary lymphoid organ** dedicated to the maturation of T cells. These pre-thymic cells are referred to as **double negative** T lymphocytes since they do not express CD4 or CD8 on their surface. The thymus is a bilobed structure located above the heart; it consists of an outer **cortex** packed with immature T cells and an inner **medulla** into which cells pass as they mature. Both the cortex and medulla are laced with a network of epithelial cells, dendritic cells, and macrophages, which interact physically with the developing thymocytes. Figure I-3-9. Structure of the Thymus

Within the cortex, the thymocytes will begin to rearrange the beta and alpha chains of the T-cell receptor (TCR) while coexpressing the CD3 complex as well as the CD4 and CD8 co-receptors; these thymocytes are collectively referred to as being **double positive**. As the developing thymocytes begin to express their TCRs, they are subjected to a rigorous 2-step selection process. Because the TCR is designed to bind antigenic peptides presented on the surface of **antigen-presenting cells** (APCs) in the body, a selection process is necessary to remove those cells that would bind to normal self-antigens and cause **autoimmunity,** as well as those that have no attraction whatsoever for the surfaces of APCs. This is accomplished by exposure of developing thymocytes to high levels of a unique group of membrane-bound molecules known as **major histocompatibility complex** (MHC) antigens.

The MHC is a collection of highly polymorphic genes on the short arm of chromosome 6 in the human. There are 2 major classes of cell-bound MHC gene products: I and II. Both class I and class II molecules are expressed at high density on the surface of cells of the thymic stroma. MHC gene products are also called human leukocyte antigens (HLA). **Class I** MHC gene products: HLA-A, HLA-B, HLA-C **Class II** MHC gene products: HLA-DM, HLA-DP, HLA-DQ, HLA-DR
Table I-3-4. Class I and II Gene Products

Class I Gene Products	Class II Gene Products
HLA-A	
HLA-B	
HLA-C	
	HLA-DM*
	HLA-DP
	HLA-DQ
	HLA-DR

*HLA-DM is not a cell surface molecule but functions as a molecular chaperone to promote proper peptide loading.

Class I molecules are expressed on all nucleated cells in the body, as well as platelets. They are expressed in **codominant** fashion, meaning that each cell expresses 2 A, 2 B, and 2 C products (one from each parent). The molecules (A, B, and C) consist of an α heavy chain with 3 extracellular domains and an intracytoplasmic carboxy-terminus. A second light chain, β2-microglobulin, is not encoded within the MHC and functions in peptide-loading and transport of the class I antigen to the cell surface. A groove between the first 2 extracellular domains of the α chain is designed to accommodate small peptides to be presented to the TCR.
Figure I-3-10. Class I MHC Molecule (left) and X-Ray Crystallographic Image (right) of Class I MHC Peptide-Binding Groove

Class II MHC molecules are expressed (also **codominantly**) on the professional antigen-presenting cells of the body (primarily the macrophages, B lymphocytes, and dendritic cells). The molecules are 2 chain structures of similar length, called α and β, each possessing 2 extracellular domains and 1 intracytoplasmic domain. A groove that will accommodate peptides to be presented to the TCR is formed at the N-terminal end of both chains. Figure I-3-11. Class II MHC Molecule (left), and X-ray Crystallographic Image (right) of Class II MHC Peptide-Binding Groove

Within the thymus, each of these MHC products, loaded with normal self-peptides, is presented to the developing double positive thymocytes. Those that have TCRs capable of binding with low affinity will receive a **positive selection** signal to divide and establish clones that will eventually mature in the medulla. Those that fail to recognize self-MHC at all will not be encouraged to mature (**failure of positive selection**). Those that bind too strongly to self MHC molecules and self-peptide will be induced to undergo apoptosis (**negative selection**) because these cells would have the potential to cause autoimmune disease.

Although double positive thymocytes co-express **CD4** and **CD8**, the cells are directed to express only CD8 if their TCR binds class I molecules, and only CD4 if their TCR binds class II molecules. At this point in T-cell development, the thymocytes are referred to as being **single positive**.

This selection process is an extraordinarily rigorous one. A total of 95–99% of all T-cell precursors entering the thymus are destined to die there. Only those with TCRs appropriate to protect the host from foreign invaders will be permitted to exit to the periphery: CD4+ cells that recognize class II MHC are destined to become **â€œhelperâ€• T cells** (Th), and CD8+ cells that recognize class I MHC are destined to become **cytotoxic T lymphocytes** (CTLs).

While most self-reactive T cells will be deleted in the thymus, a small population of these T cells will instead differentiate into regulatory T cells (Tregs). Tregs inhibit self-reactive Th1 cells in the periphery. Identified by their constitutive expression of CD25 on the surface and by the expression of the transcription factor FoxP3 Secrete IL-10 and TGF-β which inhibit inflammation Shown to be critical in the prevention of autoimmunity

Tregs will leave the thymus and serve in a peripheral tolerance. Figure I-3-12. Identification of Treg Cells Figure I-3-13. Human T-Cell Differentiation

Recall Question

What is the function of MHC class II? Presenting intracellular peptides to Tregs

Presenting extracellular peptides to CD8+ cells

Presenting intracellular peptides to CD4+ cells Presenting intracellular peptides to CD8+ cells

Presenting extracellular peptides to CD4+ cells

Answer: E

4 Periphery: Innate Immune Response Learning Objectives Describe the structure and function of secondary lymphoid organs Describe the structure of lymph nodes Answer questions about chemokines and adhesion molecules Innate Immunity

The innate immune system is an important part of any immune response. It is responsible for reacting quickly to invading microbes and for keeping the host alive while the adaptive immune system is developing a very specific response. The innate immune defenses are all present at birth; they have a very limited diversity for antigen, and they attack the microbes with the same basic vigor no matter how many times they have seen the same pathogen.

The innate immune system handles pathogens in 2 general ways: Figure I-4-1. Pathogen Clearance by the Innate Immune System

Microbes may gain access to the tissues if the physical barriers are breached. In the tissues, they come in contact with phagocytic cells such as neutrophils, macrophages and dendritic cells, which will produce chemical messengers called **cytokines** that can initiate an inflammatory response.

Many times the innate immune components are enough to eliminate the pathogen, but not always. The pathogens may gain access to the blood, in which the alternate pathway for complement activation may provide some additional help. But this is where the adaptive immune system may have to take over to resolve the infection and eliminate the pathogen.
Figure I-4-2. Entry Sites for Pathogens
Innate Immune Components/Barriers

There are several components to the innate immune response that are essential for this early defense against pathogens. They will be introduced here and discussed in more depth later in this chapter. They include **physical (anatomic) barriers, physiologic barriers, innate cellular response**, and **inflammation**. Anatomic Barriers

The main portals of entry for most pathogens are the skin, the respiratory tract, and the GI tract. All of these surfaces are lined with epithelial cells that can produce a few antimicrobial products such as defensins and interferons. They may also contain a number of specialized intra-epithelial lymphocytes (IEL) called γδ T cells. These specialized T cells are considered part of innate immunity as they can only recognize shared microbial structures. The skin is a great physical barrier as most pathogens can't invade intact skin. The pH of the skin is also slightly acidic and can retard the growth of pathogenic organisms. The respiratory tract is lined with cilia that physically attempt to remove microbes as they enter. Saliva and mucous are also difficult environments for microbes to live in, as there are many antimicrobial enzymes and chemicals within those entities. The GI tract is also a mucous membrane with similar properties to the respiratory tract; however, pathogens that enter here must first survive a trip through the stomach with a highly acidic pH that kills many microorganisms. Physiologic Barriers

Physiologic barriers include the following components: **Temperature** Many microbial pathogens can't survive much past human body temperature. When the inflammatory response is

initiated in the local tissues, cytokines may act systemically to alter the temperature set point in the hypothalamus resulting in fever. **pH** The acidic pH of the stomach impedes the growth and transmission to the gut of many pathogens. The skin is also acidic and retards the growth of many microorganisms. **Chemical** Lysozyme present in secretions such as tears, saliva, breast milk and mucous can break down the cell wall peptidoglycan of bacteria. Defensins found within phagocytes can form pores in bacteria and fungi. **Interferons** IFN-α and IFN-β are anti-viral interferons. They have a direct anti-viral effect by transiently inhibiting nascent protein synthesis in cells. Innate Cellular Response

Phagocytic cells (monocytes/macrophages, neutrophils and dendritic cells) are part of the first line of defense against invading pathogens. They recognize pathogens via shared molecules that are not expressed on host cells. They are responsible for controlling the infections and sometimes are even capable of eradicating them.

Receptors of the innate immune system are referred to as **pattern recognition receptors (PRRs)**. PRRs recognize **pathogen-associated molecular patterns (PAMPs)**, molecules that are shared by pathogens of the same type (bacterial LPS, n-formyl peptides etc.) or **damage-associated molecular patterns (DAMPs)** released from dying or damaged cells. These receptors are present intrinsically, encoded in the germline genes, and are not generated through somatic recombination as the lymphocyte receptors are generated.

The innate immune system can recognize <1,000 patterns on various pathogens, compared to the adaptive immune system (B and T cells) which can recognize over 1 billion specific sequences on pathogens. Inflammasome

The inflammasome is an important part of the innate immune system. It is expressed in myeloid cells as a signalling system for detection of pathogens and stressors. Activation of the inflammasome results in the production of IL-1β and IL-18, which are potent inflammatory cytokines.

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