

Allergy and Immunology Review Corner: *Cellular and Molecular Immunology, 8th Edition*

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Chapter 2 (pages 22–33): Cells and Tissues of the Immune System

Prepared by Kristen Dazy, MD, Scripps Clinic Medical Group

1. Which of the following surface proteins is highly expressed on effector T cells and indicative of recent activation?
 - A. IL-2R (CD25)
 - B. L-selectin (CD26L)
 - C. IL-7R (CD127)
 - D. CCR7
2. The epithelial component of the thymus is derived from invaginations of what germ cell layer?
 - A. Endoderm
 - B. Mesoderm
 - C. Ectoderm
 - D. Neural crest
3. The thoracic duct and right lymphatic duct drain return fluid to the blood stream via which major vessel?
 - A. Aortic arch
 - B. Superior vena cava
 - C. Inferior vena cava
 - D. Subclavian vein
4. Where does B-cell proliferation and generation of memory B cells take place within the lymph nodes?
 - A. Germinal center
 - B. Paracortex
 - C. Subcapsular sinus
 - D. Medulla
5. Chemokines promote naïve T cells to enter the T cell zones of the lymph node via which of the following?
 - A. Afferent lymphatic vessels
 - B. Medullary sinus lymphatic vessels
 - C. High endothelial venules
 - D. Marginal sinus
6. The chemokines CCL19 and CCL21 promote the migration of naïve T cells into the T cell zones of the lymph node by binding to which receptor located on the surface of naïve T cells?

- A. CCR7
 - B. CXCR5
 - C. IL-7R
 - D. IL-2R
7. Circulating naïve B cells enter lymph nodes and are attracted into the follicles by which chemokine?
- A. CCL19
 - B. IL-3
 - C. IL-7
 - D. CXCL13
8. During fetal life, which cell types are responsible for the development of lymph nodes as well as other secondary lymphoid organs?
- A. Fibroblastic reticular cells (FRCs)
 - B. Lymphoid tissue-inducer cells
 - C. Follicular dendritic cells (FDCs)
 - D. Naïve T cells
9. Which of the following is not a true statement regarding the spleen?
- A. The spleen is responsible for removing aging and/or damaged blood cells from the circulation.
 - B. Asplenic patients are susceptible to disseminated infections with encapsulated bacteria, including pneumococci and meningococci.
 - C. Blood is carried out of the spleen through the splenic vein, which drains into the portal circulation.
 - D. The spleen recognizes and removes un-opsonized microbes from the circulation.
10. The anatomic arrangement of antigen presenting cells, B cells, and T cells within the spleen helps to promote the interactions required for the efficient development of humoral immune responses. In which part of the spleen do these actions take place?
- A. Red pulp
 - B. White pulp
 - C. Hilum
 - D. Vascular sinusoids
 - E.

Answers

1. A, pages 22–23, Table 2-3.

Both CD4 and CD8 effector T cells usually express surface proteins indicative of recent activation, including CD25 (a component of the receptor for T cell growth factor IL-2), and altered patterns of adhesion molecules (selectins and integrins). Choices B, C, and D are all highly expressed on naïve T cells rather than effector T cells.

2. C, page 27.

The epithelial component of the thymus is derived from invaginations of the ectoderm in the developing neck and chest of the embryo, forming structures called branchial pouches.

3. B, page 28.

The efferent lymph vessel at the end of a lymph node chain joins other lymph vessels, eventually culminating in a large lymphatic vessel called the thoracic duct. Lymphatics from the right upper trunk, right arm, and right side of the head drains into the right lymphatic duct. The thoracic and right lymphatic ducts both empty into the superior vena cava, thus returning fluid to the blood stream.

4. A, pages 28–30.

Germinal centers develop in response to antigenic stimulation. They are sites of remarkable B cell proliferation, selection of B cells producing high-affinity antibodies, and generation of memory B cells and long-lived plasma cells. The T lymphocytes are located mainly beneath and more central to the follicles, in the paracortical cords, often called the paracortex.

5. C, page 30.

T cell rich zones, called the paracortex, contains a network of fibroblastic reticular cells (FRCs), many of which form the outer layer of tube-like structures called FRC conduits. These conduits begin at the subcapsular sinus and extend to both medullary sinus lymphatic vessels and cortical blood vessels, call high endothelial venules (HEVs). Naïve T cells enter the T cell zones through the HEVs, specifically promoted by chemokines produced by stromal cells in the T cell zones of the lymph node.

6. A, page 30.

Naïve T cells express a receptor called CCR7 that binds the chemokines CCL19 and CCL21 produced by stromal cells in the T cell zones of the lymph node. These chemokines promote naïve T cell movement from the blood, through the walls of the high endothelial venules (HEVs), and into the T cell zone. The chemokine CXCL13 and its receptor CXCR5 are responsible for B cell migration into the follicles.

7. D, page 30.

Naïve B cells express high levels of the receptor CXCR5, which recognizes a chemokine, CXCL13, produced only in follicles by follicular dendritic cells (FDCs). Studies of CXCR5 knockout mice lack B cell-containing follicles in lymph nodes and spleen.

8. B, pages 30–31.

The development of lymph nodes, as well as peripheral lymphoid organs, depends on lymphoid tissue-inducer cells and the coordinated actions of several cytokines (e.g., lymphotoxin- α , lymphotoxin- β), chemokines, and transcription factors. These cells are a subset of innate lymphoid cells. Cytokines produced by these cells go on to activate stromal cells, such as FRCs and FDCs, to secrete additional cytokines, which help organize the structure of lymphoid organs.

9. D, page 31.

The spleen is a highly vascularized organ whose major functions are to remove aging and damaged blood cells and particles (such as immune complexes and opsonized microbes) from the circulation and to initiate adaptive immune responses to blood-borne antigens. Macrophages within the red pulp of the spleen serve as an important filter for the blood and remove antibody-

coated (opsonized) cells and microbes. Individuals lacking a spleen are therefore susceptible to disseminated infections with encapsulated bacteria, such as pneumococci. Blood enters the spleen via the splenic artery and leaves via the splenic vein, which drains into the portal circulation.

10. B, pages 31–32.

The splenic parenchyma is anatomically and functionally divided into red pulp, which is composed mainly of blood-filled vascular sinusoids, and lymphocyte-rich white pulp. The white pulp is arranged into T cell (periarteriolar lymphoid sheath) and B cell (follicles) zones. This segregation is a highly regulated process and is dependent upon the production of different cytokines and chemokines in the stromal cells in these different areas, analogous to the case for lymph nodes. This arrangement is crucial to initiate the development of the adaptive humoral immune response to blood-borne antigens.

Review Questions

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Chapter 3 (pages 38–45): Leukocyte Circulation and Migration into Tissues

Prepared by Kara Wada, MD, Ohio State University/Nationwide Children's Hospital

1. Which molecule found on leukocytes promotes their adhesion to endothelial cells?
 - A. Sialomucin
 - B. P-selectin
 - C. L-selectin
 - D. E-selectin
2. Which best describes the properties of integrins?
 - A. They mediate adhesion of cells to other cells or to the extracellular matrix through non-specific binding interactions with various ligands.
 - B. They normally are present in a high-affinity state on the endothelial surface.
 - C. They have the ability to respond to intracellular signals by decreasing their affinity for ligands.
 - D. Chemokines induce membrane clustering of integrins.
3. The HIV virus uses which chemokine receptors as co-receptors?
 - A. CCR5 and CXCR4
 - B. CCR5 and Mac-1
 - C. LFA-1 and CXCR4
 - D. Mac-1 and LFA-1
4. Chemokines are a large family of cytokines with diverse functions. Which best describes a property of chemokines?

- A. Chemokines are large molecules with three or more external disulfide bonds.
 - B. Chemokines are only produced by leukocytes.
 - C. Chemokines are essential for the recruitment of leukocytes from blood vessels to extravascular sites.
 - D. Chemokines are not involved in lymphoid organ development.
5. Selectins, integrins and chemokines work together to regulate migration of leukocytes into the tissues. What best describes this process?
- A. Selectin-mediated rolling on the endothelium, chemokine-mediated increased in integrin affinity, stable integrin-mediated adhesion of leukocytes to the endothelium and transmigration between endothelial cells.
 - B. Selectin-mediated adhesion on the endothelium, chemokine-mediated increased in integrin affinity, stable integrin-mediated rolling of leukocytes to the endothelium and transmigration between endothelial cells.
 - C. Selectin-mediated rolling on the endothelium, chemokine-mediated decreased in integrin affinity, stable integrin-mediated adhesion of leukocytes to the endothelium and transmigration between endothelial cells.
 - D. Selectin-mediated rolling on the endothelium, chemokine-mediated increased in integrin affinity, stable integrin-mediated adhesion of leukocytes to the endothelium and transmigration through endothelial cells.
6. The interplay of selectins, integrins and chemokines in leukocyte migration is essential in normal host defense. What defect is responsible for leukocyte adhesion deficiency type 1 (LAD-1)?
- A. A deficiency in the α subunit of LFA-1 and Mac-1
 - B. A lack in the golgi fucose transporter needed to express the carbohydrate ligands for E-selectin and P-selectin.
 - C. A mutation in the signaling pathways linking chemokine receptors to integrin activation.
 - D. A deficiency in the β subunit of LFA-1 and Mac-1.
7. Migration of the inflammatory infiltrate generally follows the same pattern and is directed by chemokines and their receptors. Which pairing of cell types and chemokine receptor is correct?
- A. Monocytes & CCR7
 - B. Neutrophils & CXCR1
 - C. Monocytes & CCL2
 - D. Neutrophils & CXCL2
8. Migration of naïve T cells depends on efficient homing mechanisms.
- A. Naïve T cells are delivered through venous blood flow into the high endothelial venules (HEVs).
 - B. Rolling of naïve T cells on the HEVs is mediated by P-selectin.
 - C. Firm adhesion of naïve T cells is mediated by LFA-1.
 - D. Chemokines that deactivate the naïve T cell integrins to a low-affinity state are CCL19 and CCL21.

9. How is S1P responsible for the exit of naïve T cells from the lymph nodes?
- A. S1P is in higher concentrations in the tissues attracting naïve T cells away from the lymph node.
 - B. S1P binds to S1PR1 on T cells directing movement toward higher concentrations of S1P.
 - C. S1P lyase degrades S1P and is responsible for the higher levels in the tissues.
 - D. Naïve T cells are coated in S1PR1 receptors allowing for immediate interaction with the S1P.
10. Central memory T cells are characterized by what phenotype?
- A. CD45RO⁺ with high expression of CCR7 & L-selectin
 - B. CD45RO⁺ with low expression of CCR7 & L-selectin
 - C. CD45RO⁺ with high expression of CXCR5
 - D. CD45RO⁺ with low expression of CXCR5

Answers

1. C, page 38.

L-selectin is expressed on leukocytes. Their ligands are sialomucins on endothelial cells, whose expression is increased by cytokine activation of the cells. E-selectin and P-selectin are also found on endothelial cells.

2. D, pages 38–39.

Integrins mediate adhesion through specific binding interactions. They are normally present in a low-affinity state. They will respond to intracellular signaling by increasing their affinity for ligands and chemokines will induce clustering on the membrane surface.

3. A, page 39.

CCR5 and CXCR4 act as co-receptors for the HIV. Mac-1 and LFA-1 are integrins and not chemokine receptors.

4. C, pages 39–41.

Chemokines are 8-10-kD polypeptides that contain two internal disulfide bonds, which are produced by leukocytes, endothelial cells, epithelial cells and fibroblasts. They are essential for the recruitment of leukocytes from blood vessels to extravascular sites and are involved in the development of lymphoid organs.

5. A, pages 41–42.

Selectin-mediated interactions slow down the leukocyte, release of chemokines increase integrin affinity allowing the stronger integrin-mediated adhesion to occur. This allows the leukocyte to then migrate between the endothelial cells by transiently disrupting the adherens junction proteins.

6. D, page 42.

Patients with LAD-2 lack the golgi fucose transporter thus are unable to express the carbohydrate ligands for E-selectin and P-selectin. LAD-3 is characterized by a mutation in the signaling

pathways. LAD-1 is characterized by an autosomal recessive deficiency in the b subunit of LFA-1 and Mac-1.

7. B, page 42, Table 3.2 on page 40.

In the nomenclature, all chemokine receptors contain the letter R whereas chemokines contain the letter L. CCR7 is responsible for T and dendritic cell migration in the lymph nodes. CXCR1 and CXCR2 are responsible for neutrophil migration.

8. C, page 44.

Naïve T cells are delivered through arterial blood flow to the HEVs where rolling is mediated by L-selectin and firm adhesion is mediated by LFA-1. CCL19 and CCL21 are chemokines that activate the naïve T cell integrins to a high affinity state.

9. B, page 45.

S1P is a lipid chemoattractant which binds to S1PR1 on T cells. S1P is found in higher concentrations in the blood and lymph. It is degraded by S1P lyase in the tissues. The binding of S1P to S1PR1 results in directed movement of T cells along the S1P concentration gradient and out of the lymph node parenchyma. Circulating T cells have very little S1PR1 due to high blood levels causing internalization of this receptor. It takes several hours for S1PR1 to be re-expressed thus allowing naïve T cells to interact with antigen presenting cells in the lymph node before exiting back into the circulation via the efferent lymphatic.

10. A.

Central memory T cells are CD45RO⁺ with high expression of CCR7 & L-selectin. Effector memory T cells are defined as CD45RO⁺ with low expression of CCR7 & L-selectin. CXCR5 is a chemokine receptor found on B cells, which is found on mature naïve B cells.