Abbas: Basic Immunology, 5th Edition

Chapter 02: Innate Immunity

Test Bank

MULTIPLE CHOICE

1. Which of the following statements about the innate immune system is NOT true?
   A. Innate immunity is present in all multicellular organisms, including plants and insects.
   B. Deficiencies in innate immunity markedly increase host susceptibility to infection, even in the setting of an intact adaptive immune response.
   C. Innate immunity is better suited for eliminating virulent, resistant microbes than is adaptive immunity.
   D. The innate immune response can be divided into recognition, activation, and effector phases.
   E. The innate immune response against microbes influences the type of adaptive immune response that develops.

ANS: C
Innate immunity is the first line of defense against infections, yet many pathogenic microbes have evolved strategies to resist innate immunity. Adaptive immunity, being more potent and specialized, plays a critical role in defending against these virulent microbes. Innate immunity is the phylogenetically oldest mechanism of microbial defense, and it is present in all multicellular organisms, including plants and insects. Studies have shown that hampering effector mechanisms of innate immunity renders hosts much more susceptible to infection, even with a functional adaptive immune system. It is also true that, like the adaptive response, the innate immune response consists of recognition, activation, and effector phases. Although it provides the initial, rapid response against microbes, innate immunity can influence adaptive immune responses to tailor them against particular microbes.

2. A 4-year-old girl stepped on a rusty nail in her backyard. Two days later, she is taken to the pediatrician because her heel is painful, red, and swollen and is warm to the touch. All of the following are mechanisms of innate immunity that may be protecting the patient against pathogenic microbes in the heel wound EXCEPT:
   A. Epithelial barrier function of the skin of her foot
   B. Intraepithelial lymphocytes present in the skin
   C. Circulating neutrophils migrating to the site of the wound
   D. Soluble cytokines that induce a local inflammatory response
   E. Circulating anti-tetanus toxin antibodies

ANS: E
Secreted antibodies against protein antigens are effectors of humoral immunity, a component of the adaptive immune system. All other mechanisms listed are part of the innate immune system. Intact epithelial surfaces prevent microbial entry, and epithelial cells express anti-microbial factors, such as defensins. Neutrophils are effector cells that function in early phagocytosis and

killing of microbes. Cytokines that mediate inflammation (e.g., tumor necrosis factor, interleukin-1, chemokines) are components of innate immunity. Intraepithe-lial T lymphocytes present in the epidermis and mucosal epithelia express a limited diversity of antigen receptors; as such, they are considered effector cells of innate immunity and function in host defense by secreting cytokines, activating phagocytes, and killing infected cells.

3. Which of the following comparisons of the innate and adaptive immune systems is FALSE?
   A. The innate immune system is more likely to recognize normal self, and therefore cause autoimmunity, than is the adaptive immune system.
   B. Receptors used for recognition in innate immunity are encoded in the germline, whereas those of the adaptive immune system are encoded by genes generated via somatic recombination of germline receptor gene loci.
   C. The innate and adaptive immune systems share some of the same effector mechanisms.
   D. Both the innate and adaptive immune systems can recognize nonmicrobial substances.
   E. The innate immune system does not have memory but the adaptive immune system does.

ANS: A
Innate immune system receptors are encoded by germline genes that have evolved to recognize microbial structures or molecules produced by stressed self, and therefore there is little chance of innate immune responses to normal self. Because the specificities of adaptive immune system receptors (Ig or T cell receptor molecules) are randomly generated by somatic recombination and junctional-diversity mechanisms, there is a greater chance that the adaptive immune system receptors may recognize normal self molecules, leading to autoimmunity. Mechanisms of tolerance minimize this possibility, but these mechanisms can fail. The adaptive immune system receptors can recognize nonmicrobial structures. Although most innate immune system receptors recognize microbial structures, some Toll-like receptors and activating receptors of natural killer cells do recognize nonmicrobial self proteins expressed by stressed, damaged, or infected cells. Memory is a unique property of the adaptive and not the innate immune system.

4. Toll-like receptors (TLRs) are a family of homologous receptors expressed on many cell types and are involved in innate immune responses. Ten different mammalian TLRs have been identified, and several ligands for many of these receptors are known. Which of the following is a TLR ligand?
   A. Single-stranded RNA
   B. Transfer RNA
   C. Double-stranded DNA
   D. Unmethylated CpG DNA
   E. Heterochromatin

ANS: D
More than 10 mammalian Toll-like receptors (TLRs) have been identified, and each appears to recognize a different set of structures that are found in pathogenic microbes but not in mammalian cells. Such structures are called pathogen-associated molecular patterns (PAMPs). Unmethylated cytosine guanosine (CpG) motifs are typical of bacterial and protozoan DNA, but not mammalian DNA, and are therefore PAMPs. TLR9 binds CpG DNA. Transfer RNA, single-stranded RNA, double-stranded DNA, and heterochromatin are all normal components of

mammalian cells and are not recognized by TLRs. Double-stranded RNA is produced by some viruses but not by mammalian cells and is recognized by TLR3.

5. A 67-year-old homeless man is brought to the emergency department after being found behind a neighborhood bar in freezing weather. On arrival, he has a shaking chill, fever, and cough productive of blood-tinged sputum. A chest radiograph shows lobar consolidations consistent with bacterial pneumonia. Blood cultures are positive for *Streptococcus pneumoniae.* Which of the following molecular patterns recognized by Toll-like receptors expressed on the surface of this patient's phagocytes is important for activating his innate immune system against this gram-positive bacterial infection?

A. Peptidoglycan
B. Double-stranded RNA
C. Lipopolysaccharide (LPS)
D. Lipoarabinomannan
E. Phosphatidylinositol dimannoside

ANS: A
Gram-positive bacteria contain cell walls rich in peptidoglycan. When shed by bacteria such as *Streptococcus pneumoniae,* peptidoglycan serves as a ligand that binds Toll-like receptor 2 (TLR2), stimulating an innate immune response. The other choices listed are also ligands that stimulate TLRs, but they are not present in gram-positive bacteria. Double-stranded RNA is found in replicating viruses, lipopolysaccharide (LPS) is a component of the outer cell wall of gram-negative bacteria, and both lipoarabinomannan and phosphatidylinositol dimannoside are present in mycobacteria.

6. The signaling pathways triggered by Toll-like receptors typically result in activation of which of the following pairs of transcription factors?

A. NFAT and T-bet
B. AP-1 and GATA-3
C. Fos and STAT-6
D. NFκB and AP-1
E. Lck and Jun

ANS: D
The predominant signaling pathway used by Toll-like receptors (TLRs) results in the activation of the NF-κB transcription factor. Ligand binding to the TLR at the cell surface leads to recruitment of several cytoplasmic signaling molecules through specific domain-domain interactions, resulting in degradation of IκB and subsequent activation of NFκB. In some cell types, certain TLRs also engage other signaling pathways, such as the MAP kinase cascade, leading to activation of the AP-1 transcription factor. T-bet and GATA-3 are transcriptional regulators involved in helper T cell differentiation. Fos is a component of AP-1, and STAT-6 is a transcription factor activated by IL-4 binding to cells. Lck is not a transcription factor, but rather a tyrosine protein kinase involved in antigen-receptor signaling in T cells.

7. Toll-like receptors and other receptors are potent activators of various components of the innate immune system. All of the following proteins are expressed in response to signaling by these receptors EXCEPT:

A. Interleukin-12
B. E-selectin
C. Tumor necrosis factor
D. Inducible nitric oxide synthase (iNOS)
E. CD28

ANS: E
CD28, the activating receptor for B7-1 and B7-2 costimulatory molecules, is constitutively expressed on the surface of many T cells and is not induced by Toll-like receptor (TLR) signaling. TLR signaling does induce expression of B7-1 and B7-2 on antigen-presenting cells. Other genes expressed in response to TLR signaling encode proteins important in many different components of innate immune responses. These include inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-12; endothelial adhesion molecules such as E-selectin; and proteins involved in microbial killing mechanisms, including inducible nitric oxide synthase (iNOS). The specific genes expressed depend on the cell type of the responding cell.

8. Which of the following is a receptor on macrophages that is specific for a structure produced by bacteria but not by mammalian cells?
A. CD36 (scavenger receptor)
B. Fc receptor
C. Complement receptor
D. Mannose receptor
E. ICAM-1

ANS: D
The macrophage mannose receptor binds to terminal mannose and fucose residues on bacterial glycoproteins and glycolipids. Mammalian cells do not typically contain these residues. CD36 binds many different ligands, including microbial and self molecules. Fc receptors, complement receptors, and ICAM-1 are receptors for mammalian complement fragments, Ig, and LFA-1, respectively.

9. Which one of the following comparisons between neutrophils and macrophages is true?
A. Neutrophils that enter inflammatory sites can survive for days, but macrophages are very short lived and only survive for hours.
B. Both neutrophils and macrophages are phagocytic and can kill internalized microbes.
C. Neutrophils proliferate at inflammatory sites, but macrophages are terminally differentiated and cannot proliferate.
D. Neutrophils, but not macrophages, express the high-affinity FcγRI receptor, which recognizes specific opsonins bound to microbes and facilitates phagocytosis.
E. Both neutrophils and macrophages contain abundant cytoplasmic granules containing lysozyme, collagenase, and elastase.

ANS: B
Neutrophils and macrophages can both actively phagocytose and kill microbes, and both express opsonin receptors, such as FcγRI or complement receptors that enhance phagocytosis. Neutrophils are short lived, whereas macrophages can survive for days or weeks. Macrophages

are not terminally differentiated and can undergo cell division at inflammatory sites, but neutrophils cannot. Only neutrophils have cytoplasmic granules filled with enzymes, including lysozyme, collagenase, and elastases; these are called specific granules.

10. A 43-year-old man with a history of kidney transplantation is on immunosuppressive drugs. He presents to the emergency department 84 days after transplantation with a slight fever, accompanied by violent shaking chills, rapid heart rate, and dangerously low blood pressure. Blood cultures are positive for gram-negative bacteria, including *Klebsiella* and *Pseudomonas.* Although the patient was initially alert and responsive to fluids and antibiotic therapy, his condition rapidly deteriorates into disseminated intravascular coagulation (DIC), hypoglycemia, and cardiovascular failure. Which of the following is an essential mediator of this patient's condition?

A. Transforming growth factor-β
B. Tumor necrosis factor-α
C. Interleukin (IL)-2
D. IL-10
E. IL-3

ANS: B
This patient is suffering from septic shock, characterized by the clinical triad of disseminated intravascular coagulation (DIC), hypoglycemia, and cardiovascular failure. This condition is most often initiated by endotoxin, also known as lipopolysaccharide (LPS), a component of the outer cell walls of gram-negative bacteria. LPS is a potent stimulus for tumor necrosis factor (TNF)-α secretion by mononuclear phagocytes and other cell types. Most of the biologic effects of LPS are mediated through TNF-α. Transforming growth factor-β (TGF-β) and interleukin (IL)-10 are anti-inflammatory cytokines, IL-2 is a T cell growth factor, and IL-3 is a hematopoietic cytokine. These cytokines are not mediators of septic shock.

11. Macrophages and neutrophils express several enzymes that are involved in biochemical mechanisms that kill ingested microbes. Which of the following is NOT an enzyme expressed by these cells?

A. Inducible nitric oxide synthase (iNOS)
B. Granzyme B
C. Phagocyte oxidase
D. Myeloperoxidase
E. Lysozyme

ANS: B
Granzyme B, a proteolytic enzyme component of cytolytic T lymphocyte (CTL) and natural killer (NK) cell granules, is involved in initiating caspase-dependent CTL killing of target cells. Granzyme B is not involved in phagocyte killing of ingested microbes. Inducible nitric oxide synthase (iNOS) generates NO in macrophages, and NO is toxic to microbes. Phagocyte oxidase and myeloperoxidase are involved in generating free radical species that kill ingested microbes in phagocytes. Lysozyme is a proteolytic enzyme in neutrophil granules that contributes to microbial killing.

12. All of the following molecules are opsonins that facilitate efficient phagocytosis of microbes by neutrophils and macrophages EXCEPT:

A. C3b
B. C5a
C. C-reactive protein
D. IgG
E. Mannose-binding lectin

ANS: B

C5a is a peptide released after cleavage of C5 protein during the complement cascade. It stimulates the influx of neutrophils to the site of infection, thus acting as a chemoattractant, not as an opsonin. C3b (covalently bound to microbes on which complement activation has taken place) and IgG bound to antigen, are particularly potent opsonins, because phagocytes have receptors for both C3b and the Fc region of IgG. C-reactive protein and mannose-binding lectin also can coat microbes and be recognized by phagocyte receptors; thus they serve as opsonins.

13. A 3-year-old boy, who is small for his age, has a history of pyogenic (pus-producing) infections and cutaneous skin abscesses. Physical examination is remarkable for high fever, enlarged liver and spleen, and swollen cervical lymph nodes. A culture from an abscess on his arm reveals *Staphylococcus aureus,* a gram-positive bacteria that is also catalase-positive. Immunoglobulin and complement levels are normal. Results of the nitroblue tetrazolium test are consistent with a diagnosis of chronic granulomatous disease (CGD). The boy's immunodeficiency involves impaired generation of which of the following?

A. C5a
B. C-reactive protein
C. Mannose-binding lectin
D. Reactive oxygen intermediates
E. Membrane attack complex

ANS: D

Chronic granulomatous disease (CGD) is a rare, inherited immunodeficiency disease associated with a defective intracellular respiratory burst in phagocytes. It consists of a group of heterogeneous disorders of oxidative metabolism in which the pathways required for generation of toxic reactive oxygen species (ROIs) are impaired. In patients with CGD, phagocytosis occurs normally, but the engulfed microbes are not killed and they multiply within the cell. In this way, patients are susceptible to recurrent infections with organisms such as *Staphylococcus,* which are of low virulence in normal hosts.

14. A 4-year-old-girl sees her physician because of a severe necrotizing, oropharyngeal herpes simplex viral (HSV) infection. She has a past medical history of cytomegalovirus (CMV) pneumonitis and cutaneous HSV infection. Phenotypic analysis of her blood cells shows an absence of $CD56^+$ and $CD16^+$ cells. There are normal numbers of $CD4^+$ and $CD8^+$ cells in the blood, and serum antibody titers are normal. The patient's $CD8^+$ T cells were able to kill virally infected target cells in vitro. Which of the following is NOT characteristic of this girl's immunodeficiency disease?

A. Lack of cells whose activation is normally inhibited by self class I major histocompatibility complex (MHC)

B. Impaired granzyme B–dependent killing of virally infected target cells
C. Lack of cells that are activated by IL-15
D. Impaired interferon (IFN)-γ production during early phases of viral infection
E. Failure to form viral peptide-class I MHC complexes

ANS: E

The presence of normal numbers of $CD8^+$ T cells and the ability of these cells to kill virally infected target cells indicates that the class I major histocompatibility complex (MHC) pathway of viral peptide antigen presentation is intact. The patient's immunodeficiency is due to a lack of natural killer (NK) cells. NK cells express CD56 and/or CD16. NK cells are activated by interleukin-15 (IL-15) and IL-12, are normally inhibited by recognizing class I MHC on other cells, kill target cells with altered class I MHC expression through a granzyme B–dependent mechanisms (similar to cytolytic T lymphocyte killing), and produce interferon-γ as part of the early innate response to viral infection.

15. Which one of the following statements about inhibitory receptors on natural killer (NK) cells is true?

A. Inhibitory receptors on NK cells express ITAM motifs in their cytoplasmic tails.
B. Some inhibitory receptors on NK cells recognize HLA-A or HLA-C.
C. Some inhibitory receptors on NK cells are members of the integrin family.
D. Some inhibitory receptors on NK cells are members of the Toll-like receptor family.
E. Inhibitory receptors on NK cells are not expressed on the same NK cells that express activating receptors.

ANS: B

Natural killing (NK) inhibitory receptors recognize class I MHC molecules that are normally and constitutively expressed, including various alleles of HLA-A and HLA-C. The cytoplasmic tails of NK inhibitory receptors contain immunoreceptor tyrosine-based *i*nhibitory motifs (ITIMs), but not immunoreceptor tyrosine-based *a*ctivation motifs (ITAMs). Some inhibitory receptors on NK cells are members of the Ig superfamily, but not the integrin or TLR families. NK cells usually express both activating and inhibitory receptors, and activation is regulated by a balance between signals generated from both types of receptors. The inhibitory receptors on NK cells bind to self class I MHC molecules, which are expressed on most normal cells. When activating and inhibitory receptors are simultaneously engaged, the inhibitory receptor signals dominate and the NK cell is not activated.

16. Complement activation in the innate immune system can be initiated in the absence of antibody. Which of the following molecular components of the complement system is involved in initiation of antibody-independent complement activation?

A. C1
B. C9
C. Mannose binding lectin
D. CR2
E. Mannose receptor

ANS: C

Mannose-binding lectin (MBL) is a soluble serum component that is structurally similar to C1 of the classical complement pathway. MBL binds to mannan residues on microbial surfaces and triggers proteolytic cleavage and activation of downstream components of the complement system. C9 is not involved in initiation of complement activation but is part of the common final membrane attack complex (MAC) pathway. CR2 is a cell surface receptor for complement fragments. A mannose receptor is a cell surface receptor on phagocytes that binds mannan residues and promotes phagocytosis of microbes.

17. Which of the following is an example of how the innate immune response stimulates or modifies adaptive immunity?

A. Tumor necrosis factor (TNF) secreted by helper T cells enhances adhesion molecules on endothelial cells and promotes recruitment of inflammatory cells.
B. Interferon (IFN)-γ produced by T helper cells is a potent activator of macrophages, allowing killing of phagocytosed microbes.
C. B7-1 expression on antigen-presenting cells is up-regulated in response to signaling through Toll-like receptors, thus enabling costimulation of T cells.
D. Infected cells coated by IgG3 are recognized by Fc receptors on natural killer cells, allowing efficient killing of the infected cells.
E. Double-stranded RNA of replicating viruses potently stimulates IFN-β expression by fibroblasts, inducing an “antiviral state” in neighboring, uninfected cells.

ANS: C

Innate immune responses are important stimulators of adaptive immunity. Increased expression of B7-1 and B7-2 on antigen-presenting cells after microbial activation of Toll-like receptors (innate immunity) is critical in providing costimulatory signals for T cell activation (adaptive immunity) via binding to CD28 receptors on T cells. T helper cell–mediated endothelial or macrophage activation is an example of adaptive immunity using the effector mechanisms of innate immunity. Neither IgG3 opsonization facilitating natural killer cytolytic activity nor double-stranded RNA stimulating interferon-β secretion involve innate immunity enhancing adaptive immunity.