THE IMMUNE SYSTEM, FOURTH EDITION
CHAPTER 3: INNATE IMMUNITY: THE INDUCED RESPONSE TO INFECTION

3–1 C-type lectins are so called because of the role of _____ in facilitating receptor:ligand interactions.
a. carbohydrate
b. CR1
c. calcium
d. chemokines
e. caspases.

3–2 Lectins recognize microbial _____.
a. phosphate-containing lipoteichoic acids
b. nucleic acids
c. carbohydrates
d. flagellin
e. sulfated polysaccharides.

3–3 Scavenger receptor SR-B recognizes _____.
a. lipopolysaccharides
b. teichoic acid
c. filamentous hemagglutinin
d. CpG-rich bacterial DNA
e. lipids.

3–4 Macrophages bear on their surface receptors for all of the following except _____. (Select all that apply).
a. mannose
b. glucans
c. C3b
d. muramyl dipeptide
e. lipopolysaccharide
f. lipoteichoic acid
g. CpG-rich bacterial DNA.

3–5 _____ is a soluble protein. (Select all that apply.)
a. TLR4
b. CD14
c. lipopolysaccharide-binding protein (LBP)
d. CXCR1
e. mannose-binding lectin.

3–6 _____ are structurally similar membrane-bound proteins that aid in the adhesion between various types of human cell.
a. Interferons
b. Integrins
c. GTP-binding proteins
d. Pyrogens
e. Pentraxins.

3–7 All of the following induce fever except _____.
a. IL-12
b. IL-6
c. IL-1
d. TNF-\alpha.

3–8 Match the term in column A with its description in column B.

Column A	*Column B*
___a. interferon response	1. a notable rise or reduction of plasma proteins in response to IL-6
___b. apoptosis	2. stimulates inhibition of viral replication
___c. extravasation	3. temporary rise in oxygen consumption and toxic oxygen species production
___d. respiratory burst	4. cellular suicide characterized by DNA fragmentation
___e. acute-phase response	5. migration of neutrophils into inflamed tissues

3–9 Which of the following is not associated with mobilization of neutrophils to infected tissue?
a. TNF-\alpha production by macrophages
b. upregulation of selectins on blood vessel endothelium
c. interferon response
d. generation of a CXCL8 gradient
e. extravasation across endothelium
f. proteolysis of basement membrane of blood vessels.

3–10 Which of the following pairs is mismatched?
a. primary granules: azurophilic granules
b. secondary granules: unsaturated lactoferrin
c. azurophilic granules: myeloperoxidase
d. gelatinase: iron sequestration
e. tertiary granules: natural killer cells.

3–11 The pH of the phagosome increases following phagocytosis because _____.
a. the microbe delivers a significant number of hydroxyl ions in its cytosol that are released upon membrane disruption

b. hydrogen ions are eliminated by the activity of NADPH oxidase and superoxide dismutase
c. azurophilic granules deliver alkaline substances
d. catalase consumes hydrogen ions once activated.

3–12 C-reactive protein binds to _____.
a. phosphorylcholine
b. mannose-containing carbohydrates
c. lipoteichoic acid
d. flagellin
e. MASP-1/MASP-2.

3–13 The C3 convertase that functions in the lectin pathway of complement activation consists of _____.
a. C3bBb
b. C3b2a
c. C4b2a
d. C4b2b
e. $C3b_2Bb$.

3–14 Which of the following cleaves C2? (Select all that apply.)
a. Factor B
b. C1r
c. MASP-2
d. C1s
e. C4b.

3–15 With which of the following complement proteins does C-reactive protein interact?
a. factor D
b. C1
c. factor P
d. C4
e. C2.

3–16 All of the following are true of MyD88 except _____.
a. It binds to the TIR domains of all Toll-like receptors except TLR3.
b. It binds to IRAK4, a protein kinase, causing the kinase to phosphorylate itself.
c. It is an adaptor protein with similar function to TRIF.
d. A genetic deficiency of MyD88 causes the disease X-linked ectodermal dysplasia and immunodeficiency.

3–17 The name given to cytokines that recruit cells to move towards areas of inflammation is _____.
a. chemokines
b. caspase-recruitment domains (CARDs)
c. inflammakines

d. adhesion molecules
e. pyrogens.

3–18 In common with Toll-like receptors, NOD-like receptors also contain _____ that is/are used for pathogen-recognition of microbial ligands.
a. caspase-recruitment domains (CARD)
b. Toll interleukin 1 receptor (TIR) domain
c. variable extracellular domain
d. leucine-rich repeat regions (LRRs)
e. C-type lectin domain (CTLD).

3–19 Identify which of the following receptors does not lead to nuclear translocation of NF\kappaB through an activated IKK intermediate.
a. TLR4
b. IL-1 receptor
c. NOD1
d. NOD2
e. All of the above receptors culminate in nuclear translocation of NF\kappaB through an activated IKK intermediate.

3–20 Which of the following is most similar in its activity to that of IRF3?
a. IRAK4
b. NF\kappaB
c. TRAF6
d. I\kappa\kappa
e. GTP-binding (G) protein.

3–21 _____ help to prevent systemic bacterial dissemination by producing chromatin structures loaded with antimicrobial substances.
a. Inflammasomes
b. Neutrophil extracellular traps
c. RIG-1-like helicases
d. Granulomas
e. Plasmacytoid dendritic cells.

3–22 Match the condition/disease in column A with its description in column B. Use each answer only once.

Column A	*Column B*
___a. X-linked hypohidrotic ectodermal dysplasia and immunodeficiency (NEMO deficiency)	1. insufficient superoxide production in neutrophils compromises the respiratory burst
___b. septic shock	2. failure to translocate NF\kappaB and activate macrophages due to deficiency in IKK\gamma subunit
___c. chronic granulomatous disease	3. allelic polymorphism of TLR4 with glycine

	at position 299 causing reduced responsiveness to LPS of Gram-negative bacteria

3–23 _____ is/are needed to minimize the damaging effects to neighboring host cells during a respiratory burst.
a. Catalase activity
b. Complement control proteins
c. NADPH oxidase activity
d. Neutrophil mobilization
e. Superoxide dismutase activity.

3–24 Measurement of which of the following is commonly used when monitoring patients with autoimmune diseases as an indicator of inflammatory relapse?
a. IL-1RA
b. cryopyrin
c. C-reactive protein
d. proIL-1\beta
e. IL-15.

3–25 All of the following characterize serum amyloid protein except _____.
a. it contains approximately 100 amino acids
b. it interacts with CD36 scavenger receptor
c. it increases in concentration by 25% or more in response to infection
d. it associates with high-density lipoprotein particles
e. it activates the classical pathway of complement activation.

3–26 _____ is not an opsonin.
a. Mannose-binding lectin
b. IFN-\alpha
c. C-reactive protein
d. surfactant protein-A (SP-A)
e. surfactant protein-D (SP-D).

3–27 Toll-like receptors are located _____.
a. only on the plasma membrane
b. on the plasma membrane and the mitochondrial outer membrane
c. on the plasma membrane and endosomal membranes
d. only in the cytoplasm
e. inside inflammasomes.

3–28 Toll-like receptors differ from scavenger receptors in that they _____.
a. bind to common repetitive arrays on microbial surfaces
b. stimulate a pathway that causes enzymatic degradation of the microbe to which they bind
c. are soluble receptors that bind to microbes in extracellular spaces
d. mediate signal transduction pathways, causing cytokine production.

3–29 The Toll-like receptor that is able to signal through both the TRIF and MyD88 pathways is _____.
a. TLR3
b. TLR4
c. TLR5
d. TLR7
e. TLR8
f. TLR9.

3–30 Unlike inflammatory cytokines, Toll-like receptors _____.
a. are never secreted
b. participate only in adaptive immune responses
c. are expressed only by dendritic cells
d. stimulate the production of acute-phase proteins
e. induce fever.

3–31 All of the following statements regarding Toll-like receptors are true except _____.
a. They exist as either transmembrane homodimers or heterodimers.
b. The extracellular domain detects the microbial component.
c. They facilitate changes in gene expression.
d. They sense molecules not found in or on human cells.
e. The cytoplasmic signaling domain contains a variable number of leucine-rich repeat regions (LRRs).

3–32 _____ binds to and retains NF\kappaB in the cytosol.
a. MyD88
b. TRAF6
c. I\kappaB
d. I\kappa\kappa
e. IRAK4.

3–33 Plasmacytoid dendritic cells _____. (Select all that apply.)
a. detect viral infection by using TLR4
b. produce large amounts of the type I interferons when activated
c. are found exclusively in the blood
d. make up 10% of circulating leukocytes
e. have a cytoplasmic morphology resembling that of antibody-producing plasma cells.

3–34 All of the following are correct in reference to type I interferons except _____.
a. Type I interferons inhibit the replication of viruses.
b. In the presence of type I interferons, virus-infected cells undergo cell-surface changes that render them more susceptible to attack by NK cells.
c. Not only can most cells synthesize type I interferons, but they can also respond to them.
d. The receptor for type I interferons is abundant in the cytosol.
e. Type I interferons function in autocrine and paracrine fashions.

f. Type I interferons promote NK-cell proliferation and differentiation into cytotoxic cells.

3–35 Match the term in column A with its description in column B.

Column A	*Column B*
___a. oligoadenylate synthetase	1. activates endoribonucleases that degrade viral RNA
___b. plasmacytoid dendritic cell (PDC)	2. facilitates adhesion and information exchange between cells undergoing surveillance via activating and inhibitory receptors
___c. RIG-I-like helicase	3. synthesizes 1000 times more interferon than do other cells
___d. protein kinase R (PKR)	4. inhibits protein synthesis by phosphorylating eIF-2
___e. NK-cell synapse	5. contains domains that bind to viral RNA and mitochondrial-associated adaptor proteins

3–36 The following cytokines activate NK cells early in the course of a viral infection with the exception of _____.
a. IFN-\alpha
b. IFN-\beta
c. IFN-\gamma
d. IL-12
e. IL-15.

3–37
A. Describe the different functions performed by the two subpopulations of NK cells in the blood and how they are distinguished.
B. How does this compare with NK-cell subpopulations in other tissues?

3–38 The function of uterine NK cells (uNK) is to _____.
a. kill virus-infected cells
b. secrete growth factors that promote blood vessel growth to supply the placenta
c. activate resident macrophages by secreting inflammatory cytokines
d. secrete 1000 times more type I interferon than other cells to protect the fetus from viral infection.

3–39 NK cells express all of the following proteins either on endosome membranes or on their cell surface with the exception of _____. (Select all that apply)
a. CD3
b. type I interferon receptor
c. CR3
d. CD56
e. LFA-1

f. activating receptors
g. inhibitory receptors
h. TLR3
i. TLR4
j. IL-12R\beta1 and IL-12R\beta2.

3–40 Which of the following does not describe a safety mechanism to ensure that only infected cells are attacked by NK cells?
a. The default state is one of active inhibition, which must be overcome by activating signals before killing occurs.
b. Intimate contact with target cells is required.
c. Activating receptors are induced only after encountering an infected cell.
d. No single receptor–ligand interaction induces cytotoxicity, but instead many combinations of receptor–ligand interactions influence the decision to kill or not to kill a target cell.

3–41 Which of the following does not describe a feature observed when a target cell is induced to commit apoptosis by an NK cell?
a. DNA fragmentation by target cell nucleases
b. target cell shrinkage
c. shedding of membrane-enclosed vesicles by the target cell
d. chromatin extrusion in the form of decondensed DNA by the target cell
e. macrophage disposal of apoptotic remains of the target cell.

3–42 Which of the following Toll-like receptors are expressed exclusively in NK cells? (Select all that apply.)
a. TLR3
b. TLR4
c. TLR7
d. TLR8
e. TLR9.

3–43 Immediately after engagement of NK-cell Toll-like receptors, the NK cell _____.
a. discharges cytotoxic granules
b. ligates IL-12R\beta1 and IL-12R\beta 2
c. synthesizes and secretes IL-15
d. synthesizes and secretes IL-12
e. synthesizes and secretes type I interferons.

3–44 Stimulation of NK cells by IL-12 _____.
a. enhances their cytotoxic potential
b. skews their differentiation into effector NK cells
c. induces the synthesis and secretion of IL-15 by NK cells
d. turns off type I interferon production by NK cells
e. induces the NK cell to undergo programmed cell death.

3–45 _____ is a cytokine produced by both macrophages and dendritic cells that promotes the proliferation, differentiation, and survival of NK cells.
a. IL-15
b. IL-1\beta
c. CXCL8
d. TNF-\alpha
e. IL-6.

3–46 On the basis of laboratory experiments, a possible scenario for the activation of an adaptive immune response would involve _____ within an infected tissue. (Select all that apply.)
a. a balanced number of myeloid dendritic cells and NK cells
b. an abundance of NK cells compared with myeloid dendritic cells
c. a shortage of NK cells compared with myeloid dendritic cells
d. migration of myeloid dendritic cells to secondary lymphoid tissue
e. migration of NK cells to secondary lymphoid tissue.

3–47 After recognizing its ligand, a NOD receptor interacts with a signaling protein called _____, which is a serine–threonine kinase that phosphorylates TAKI.
a. CARD
b. NLRP3
c. RIPK2
d. MARCO
e. SR-A.

3–48 An adaptor protein in the inflammasome is required to link _____ to the NOD-like receptor NLRP3.
a. MyD88
b. procaspase-1
c. RIPK2
d. TAKI
e. IKK.

3–49 Chemokine receptors form complexes with _____ after binding to their ligands.
a. inflammasome components
b. pro-IL-1\beta
c. potassium channels
d. GTP-binding proteins
e. tertiary granules.

3–50 All of the following acute-phase proteins increase in concentration in the plasma during inflammation with the exception of _____.
a. albumin
b. serum amyloid A protein
c. fibrinogen
d. C3
e. mannose-binding lectin.

3–51 The ligands of endosomal Toll-like receptors are _____.
a. lipids of Gram-negative bacteria
b. flagellin proteins of bacteria
c. lipids of Gram-positive bacteria
d. zymosan of fungi
e. nucleic acids of viruses and bacteria.

3–52 Of the following Toll-like receptors, which is the most highly conserved and displays the smallest amount of allelic polymorphism?
a. TLR1
b. TLR8
c. TLR10
d. TLR6
e. TLR4.

3–53 Sensors for viral nucleic acid in the cytoplasm, called RLRs, possess domains that bind to _____. (Select all that apply.)
a. GTP-binding proteins
b. type 1 interferons
c. 5\prime-triphosphate of uncapped RNA
d. oligomerized procaspase-1
e. CARD domains of MAVS.

3–54 Match the innate immune receptor in column A with its ligand(s) in column B. More than one ligand may be used for each immune receptor.

Column A	*Column B*
___a. lectin receptor	1. iC3b
___b. scavenger receptor	2. lipophosphoglycan
___c. CR3	3. carbohydrates (for example mannose or glucan)
___d. CR4	4. filamentous hemagglutinin
___e. CR1	5. lipopolysaccharide (LPS)
___f. TLR4:TLR4	6. negatively charged ligands (for example sulfated polysaccharides and nucleic acids)
___g. TLR5	7. C3b
___h. TLR3	8. flagellin
	9. RNA

3–55 Other than their ligand specificity, what is a key difference between TLR5, TLR4, TLR1:TLR2, and TLR2:TLR6 compared to TLRs 3, 7, 8, and 9?

3–56 Explain why TLRs can detect many different species of microbes despite the limited number of different TLR proteins.

3–57 What is NF\kappaB and what is its role in mediating signals through TLRs?

3–58 What is the name given to the earliest intracellular vesicle that contains material opsonized by macrophages?
a. opsonome
b. membrane-attack complex
c. lysosome
d. phagosome
e. phagolysosome.

3–59
A. What induces the production of type I interferon by virus-infected cells?
B. Do normal cells produce this inducer? Why, or why not?
C. Discuss the mechanisms by which type I interferons exert their antiviral effects.

3–60 Which of the following activities are most closely associated with natural killer cells?
a. production of TNF-\alpha
b. lysis of virus-infected cells
c. phagocytosis of bacteria
d. release of reactive oxygen intermediates
e. production of IFN-\gamma.

3–61 The lectin pathway of complement activation is induced by _____.
a. C-reactive protein
b. antibodies bound to pathogens
c. mannose-binding lectin
d. iC3Bb
e. terminal components of the complement pathway.

3–62 Which of the following is not a characteristic of mannose-binding lectin?
a. acts as an opsonin by binding to mannose-containing carbohydrates of pathogens
b. synthesized by hepatocytes
c. induced by elevated IL-6 levels
d. a member of the pentraxin family
e. triggers the alternative pathway of complement activation.

3–63 Which of the following is not a characteristic of C-reactive protein?
a. acts as an opsonin by binding to phosphorylcholine of pathogens
b. synthesized by spleen
c. induced by elevated IL-6 levels
d. a member of the pentraxin family
e. triggers the classical pathway of complement activation.

3–64 Describe the two different domains of TLRs and their respective functions.

3–65 Explain the consequence of engagement of the TLR4, CD14, and MD2 complex with LPS in macrophages.

3–66 Which of the following TLRs do not use a signal transduction cascade involving MyD88?
a. TLR1:TLR2
b. TLR3
c. TLR4
d. TLR2:TLR6
e. TRL7.

3–67 Which of the following adaptor proteins participates in the activation pathway induced through either TLR3 or TLR4 that culminates in the synthesis of type I interferons?
a. C-reactive protein
b. MyD88
c. LPS-binding protein
d. TRIF
e. NF\kappaB.

3–68 Which of the following properties is common to macrophages and neutrophils in an uninfected individual?
a. life-span
b. anatomical location
c. ability to phagocytose
d. morphology
e. formation of pus.

3–69 Which of the following best describes an endogenous pyrogen?
a. cytokines made by pathogens that decrease body temperature
b. pathogen products that decrease body temperature
c. pathogen products that increase body temperature
d. cytokines made by the host that decrease body temperature
e. cytokines made by the host that increase body temperature.

3–70 Which of the following is an acute-phase protein that enhances complement fixation?
a. TNF-\alpha
b. mannose-binding lectin
c. fibrinogen
d. LFA-1
e. CXCL8.

3–71 During inflammation, host tissue may be damaged owing to the release of toxic oxygen derivatives produced by activated macrophages and neutrophils. Explain what cellular mechanisms limit these damaging bystander effects.

ANSWERS

3–1 c

3–2 c

3–3 e

3–4 d, g

3–5 c, e

3–6 b

3–7 a

3–8 a—2; b—4; c—5; d—3; e—1

3–9 c

3–10 e

3–11 b

3–12 a

3–13 c

3–14 c, d

3–15 b

3–16 d

3–17 a

3–18 d

3–19 e
3–20 b

3–21 b

3–22 a—2; b—3; c—1

3–23 a

3–24 c

3–25 e

3–26 b

3–27 c

3–28 d

3–29 b

3–30 a

3–31 e

3–32 c

3–33 b, e

3–34 d

3–35 a—1; b—3; c—5; d—4; e—2

3–36

A. (i) One subpopulation of NK cells is committed to killing virus-infected cells so as to interfere with virus replication and intercellular spread. They are the most abundant subpopulation in the blood, making up 90% of circulating NK cells, and express fewer CD56 molecules on their cell surface ($CD56^{dim}$) than does the other circulating subpopulation. (ii) The other subpopulation serves to maintain and exacerbate the inflammatory state in infected tissue by secreting inflammatory cytokines that activate resident macrophages. They comprise the remaining ~10% of circulating NK cells, and express higher numbers of CD56 molecules on their cell surface ($CD56^{bright}$).

B. In other tissues, the situation is reversed, with $CD56^{bright}$ cells predominating. In addition, in the uterus there exists a specialized subpopulation of NK cells called uterine NK cells (uNK), which comprise the predominant leukocytes in this tissue. They are essential to the provision of growth factors needed for expansion of maternal blood vessels to ensure that the placenta and fetus are supplied adequately with oxygen during pregnancy.

3–37 b

3–38 a, i

3–39 c

3–40 d

3–41 a, d

3–42 e

3–43 b

3–44 a

3–45 c, d

3–46 c

3–47 b

3–48 d

3–49 a

3–50 e

3–51 b

3–52 c, e

3–53 a—3; b—6; c—1, 2, 3, 4, 5; d—1, 2, 3, 4, 5; e—7; f—5; g—8; h—9.

3–54 TLR-4, TLR1:TLR2, and TLR2:TLR6 are transmembrane receptors anchored on the plasma membrane surface of human cells and interact with pathogens located in extracellular locations. In contrast, TLR3, 7, 8, and 9 are anchored in endosomal membranes located in the cytosol, where the intracellular degradation of pathogens takes place.

3–56 Because many pathogens possess features that are common to different groups of pathogens, for example LPS in Gram-negative bacteria, only a small number of TLRs are required to act as sensors of molecular patterns shared by pathogens.

3–57 NF\kappaB is a transcription factor, and some TLRs signal through an intracellular pathway that involves the activation of NF\kappaB. In the absence of stimulation of the TLR, NF\kappaB is found in an inactive form in the cytoplasm. Signaling through the TLR results in a phosphorylation cascade that converts NF\kappaB to its active form, which is then able to translocate into the nucleus and direct the transcription of specific genes that promote the cell's response to the infection.

3–58 d

3–59

A. Type I interferon genes (for interferons-\alpha and -\beta) are transcribed as a result of the presence of double-stranded RNA.

B. Normal cells not infected with virus do not contain double-stranded RNA; however, cells infected with virus often do. Some viruses either have double-stranded RNA genomes or use double-stranded RNA as an intermediate in the replication cycle.

C. Type I interferons (IFN-\alpha and -\beta) block virus replication in infected cells and protect uninfected cells nearby from becoming infected. This is accomplished by: (1) inducing cellular genes that destroy viral RNA through endonuclease attack; and (2) inhibiting protein synthesis of viral mRNA by modifying the initiation factors required for protein synthesis. In addition, IFN-\alpha and -\beta activate natural killer (NK) cells. NK cells kill virus-infected cells by releasing cytotoxic granules through a mechanism that involves the engagement of activating and inhibitory receptors; if inhibitory signals predominate, the target cell is not killed; however, if activating signals predominate, the target cell is killed.

3–60 b, e

3–61 c

3–62 e

3–63 b

3–64 The first domain of the TLR is an extracellular domain, also known as the pathogen-recognition domain, which contains a hydrophobic, leucine-rich repeat region (LRR) forming a horseshoe-shaped structure that binds specifically to arrays on microbial surfaces. The second domain of the TLR is the cytoplasmic signaling domain, also known as the Toll interleukin receptor (TIR) domain, which facilitates the transmission of information to the interior of the cell.

3–65 When TLR4 on the surface of macrophages is bound to its LPS ligand, a signal transduction cascade is initiated that mediates signaling between the cell surface and the nucleus. The macrophage in turn begins to express particular genes encoding cytokines and adhesion molecules that are needed to induce a state of inflammation in the infected tissue.

3–66 b

3–67 d

3–68 c

3–69 e

3–70 b

3–71 Toxic oxygen species including superoxide, hydrogen peroxide, singlet oxygen, hydroxyl radical, hypohalite, and nitric oxide are produced during the respiratory burst in macrophages and neutrophils. Simultaneous extraphagosomal production of enzymes that neutralize these compounds occurs. Specifically, superoxide dismutase metabolizes superoxide to hydrogen peroxide, which is further metabolized by catalase to innocuous water and molecular oxygen.