THE IMMUNE SYSTEM, FOURTH EDITION
CHAPTER 2: INNATE IMMUNITY: THE IMMEDIATE RESPONSE TO INFECTION

2–1 Soluble effector molecules are effective when encountering pathogens in/on _____. (Select all that apply.)
a. extracellular spaces
b. cytoplasm
c. epithelial surfaces
d. interstitial spaces
e. vesicular compartments
f. lymph.

2–2 Which of the three complement pathways becomes activated soonest after an initial infection?
a. the classical pathway
b. the lectin pathway
c. the alternative pathway.

2–3 Identify the incorrectly paired molecular association.
a. iC3: factor B
b. CR4: iC3b
c. properdin: C3bBb
d. membrane cofactor protein: $C3b_2Bb$
e. decay-accelerating factor: C3bBb.

2–4 All of the following complement proteins help form a pore in the pathogen's membrane except _____.
a. C3b
b. C5b
c. C6
d. C7
e. C8
f. C9.

2–5 The importance of CD59 (also known as protectin) is to _____.
a. promote the speed of complement activation by protecting C3 convertase C3bBb from proteolytic degradation
b. prevent the recruitment of C9
c. dissociate the components of the alternative C3 convertase
d. prevent the attachment of C3b to host cell surfaces
e. inhibit the anchoring of C5b, C6, and C7 to host cell surfaces.

2–6 _____ are soluble complement fragments that mediate localized and systemic inflammatory responses.
a. cryptdins
b. defensins
c. anaphylatoxins
d. selectins
e. C-reactive proteins.

2–7 All of the following statements are correct regarding \alpha$_2$-macroglobulin except _____.
a. it binds covalently to its target via a thioester bond
b. it possesses a bait region to lure its target
c. it undergoes a conformational change that enables it to enshroud the target
d. when bound to its target it is cleared from the circulation by hepatocytes, fibroblasts, and macrophages bearing receptors specific for the complex
e. its target is the membrane-attack complex on human cells.

2–8 Although activation of the three different pathways of complement involves different components, the three pathways converge on a common enzymatic reaction referred to as complement fixation.
A. Describe this reaction.
B. Describe the enzyme responsible for this reaction in the alternative pathway.
C. Identify the three effector mechanisms of complement that are enabled by this common pathway.

2–9 Which of the following is the soluble form of C3 convertase of the alternative pathway of complement activation?
a. iC3
b. iC3b
c. C3b
d. iC3Bb
e. C3bBb.

2–10 Explain the steps that take place when a bacterium is opsonized via C3b:CR1 interaction between the bacterium and a resident macrophage in tissues.

2–11 In the early stages of the alternative pathway of complement activation there are complement control proteins that are soluble (factors H and I) and associated with the cell surface (DAF and MCP). Identify the (i) soluble and (ii) cell surface-associated complement control proteins that operate in the terminal stages of the alternative pathway of complement activation, and describe their activities.

2–12
A. Review the differences between the three pathways of complement (alternative, lectin, and classical) in terms of how they are activated.

B. Distinguish which pathway(s) are considered part of an adaptive immune response and which are considered part of innate immunity, and say why.

2–13 Which of the following does not accurately describe complement components?
a. soluble proteins
b. made by the spleen
c. located in extracellular spaces
d. some function as proteases once activated
e. activated by a cascade of enzymatic reactions.

2–14 Explain why a genetic deficiency of C3 leads to a type of immunodeficiency characterized by recurrent and severe infections.

2–15 Which of the following is the membrane-bound form of C3 convertase of the alternative pathway of complement activation?
a. iC3
b. C3a
c. C3b
d. iC3Bb
e. C3bBb.

2–16 Explain how the alternative C3 convertase on pathogen cell surfaces is (A) formed and (B) stabilized.

2–17 Why is it important to expose the hydrophobic sites of C7 and C8 during the formation of the membrane-attack complex?

2–18 The plasma proteins that counteract the activity of factor P by inactivating C3 convertase through the cleavage of C3b are _____.
a. factor B and factor H
b. factor H and factor I
c. factor B and factor I
d. decay-accelerating factor and factor H
e. decay-accelerating factor and membrane cofactor protein.

2–19 The membrane-bound proteins on human cells that dissociate and inactivate alternative C3 convertase to avoid complement activation are _____.
a. factor B and factor H
b. factor H and factor I
c. factor B and factor I
d. decay-accelerating factor and factor H
e. decay-accelerating factor and membrane cofactor protein.

2–20 Explain the similarities between membrane cofactor protein, factor H, and complement receptor 1 in terms of their complement control properties.

2–21 Explain how the anaphylatoxins C3a and C5a contribute physiologically to inflammation during complement activation.

2–22 Which of the following complement components is an opsonin that binds to complement receptor 1 (CR1) on macrophages?
a. C3b
b. C3a
c. Bb
d. Ba
e. C3bBb.

2–23 Which of the following polymerizes to form a transmembrane channel that compromises the integrity of cell membranes?
a. C5
b. C6
c. C7
d. C8
e. C9.

2–24 Which of the following are important in anchoring the membrane-attack complex to the membrane?
a. C3 and C5
b. C5 and C6
c. C6 and C7
d. C7 and C8
e. C8 and C9.

2–25 Which of the following does not contain a glycosylphosphatidylinositol (GPI) lipid tail?
a. decay-accelerating factor (DAF)
b. homologous restriction factor (HRF)
c. membrane cofactor protein (MCP)
d. protectin (CD59)
e. all of the above contain a GPI tail.

2–26 The ligand for CR3 and CR4 formed by the cleavage of C3b by the combined action of factors H and I is called _____.
a. C3bBb
b. C3a
c. $C3b_2Bb$
d. iC3b
e. C5b.

2–27 Which of the following does not describe the actions of the coagulation system?
a. blood clot formation
b. enhancement of dissemination of microbes into lymphatics and bloodstream
c. decrease in blood loss and fluid into interstitial spaces in tissues

d. release of inflammatory mediators by platelets
e. wound healing.

2–28 Damage to tissues triggers a cascade of plasma proteins involving bradykinin and is known as _____.
a. the alternative pathway of complement
b. the coagulation system
c. the kinin system
d. receptor-mediated endocytosis
e. the acute-phase response.

2–29 Which of the following does not describe defensins?
a. highly conserved with few variants
b. contain a large proportion of arginine residues
c. contain three intra-chain disulfide bonds
d. amphipathic, with hydrophobic and hydrophilic regions
e. disrupt pathogen membranes by penetrating them and disrupting their integrity.

ANSWERS

2–1 a, c, d, f

2–2 c

2–3 d

2–4 a

2–5 b

2–6 c

2–7 e

2–8

A. The cleavage of C3 into C3a and C3b and the covalent bonding of C3b to the pathogen surface is called complement fixation, and is the reaction on which the alternative, lectin, and classical pathways of complement activation converge.

B. The enzyme responsible for cleaving C3 into C3a and C3b is called C3 convertase, and it differs in composition depending on the particular complement pathway. The classical and lectin pathways use the classical C3 convertase (C4b2a), whereas the alternative pathway uses the alternative convertase (C3bBb).

C. C3 is the most abundant complement component in the plasma and circulates as a zymogen, an inactive enzyme. When cleaved into C3a and C3b, three different effector

mechanisms are armed: (1) C3b binds to and tags pathogens for destruction by phagocytes through binding to a C3b receptor, CR1; (2) C3b contributes to a multicomponent enzyme, C5 convertase, that catalyzes the assembly of the terminal complement components and the formation of the membrane-attack complex; and (3) C3a is an inflammatory mediator that serves as a chemoattractant and recruits inflammatory cells to the infection site.

2–9 d

2–10 The CR1 on the macrophage can bind to C3b that is coating a bacterial surface after complement activation, and the macrophage then engulfs the bacterium through receptor-mediated endocytosis. The macrophage membrane invaginates and forms an intracellular vesicle called a phagosome. The phagosome fuses with a lysosome to form a phagolysosome, where toxic mediators and degradative enzymes are localized. The bacterium is destroyed.

2–11

i. The soluble proteins include S protein, clusterin, and factor J, which all inhibit C5b, C6, and C7 from binding to cell membranes.

ii. The cell surface-associated proteins include homologous restriction factor (HRF) and CD59 (protectin), which both prevent the recruitment of C9 and thus block C9 polymerization.

2–12

A. (1) The classical pathway is activated in two ways, either by the presence of antibody bound to the surface of the microorganism (for example IgM bound to lipopolysaccharide of Gram-negative bacteria) or by the presence of C-reactive protein bound to a bacterium. (2) The lectin pathway requires the presence of mannose-binding lectin, an acute-phase protein made by the liver in response to interleukin-6 (secreted by activated macrophages) and which accumulates in plasma during infection. (3) The alternative pathway requires an activating surface of a pathogen, which stabilizes complement components.

B. Only the classical pathway is considered part of the adaptive immune response because of the requirement for antibody. However, the classical pathway is also considered part of innate immunity because of the ability of C-reactive protein, an acute-phase protein, to activate it. The other two pathways are considered part of innate immunity because they are initiated independently of antibody.

2–13 b

2–14 C3 is a key element in the initiation of the complement cascade in all three pathways of complement activation, namely the alternative, lectin, and classical pathways. Its cleavage into C3a and C3b occurs early in the complement cascade. C3a acts as an inflammatory mediator and recruits inflammatory cells to the site of infection. C3b becomes fixed to the pathogen surface and facilitates the opsonization of pathogens by phagocytes and the assembly of complement components for perforation of the pathogen membrane. In the absence of C3, all three pathways of complement activation would be arrested and extracellular pathogens would escape immune detection until adaptive immune mechanisms develop fully many days later.

2–15 e

2–16

A. Spontaneous hydrolysis of C3 without cleavage exposes its highly reactive thioester bond, forming iC3. Factor B binds to iC3, is cleaved by factor D, and consequently releases a small fragment called Ba. The larger fragment, Bb, remains associated with iC3 to form iC3Bb, a soluble C3 convertase, which cleaves C3 into C3a and C3b. The reactive thioester bond of C3b is attacked by R–OH and $R–NH_2$ groups on the surface of the pathogen, where it becomes anchored and binds to factor B. Factor D then cleaves factor B, releasing fragment Ba and forming C3bBb on the pathogen surface.

B. Factor P (properdin) binds to C3 convertase (C3bBb) bound to the pathogen surface, and inhibits the proteolytic degradation of C3bBb. This stabilizes the C3 convertase and enhances the rate of C3b deposition on the pathogen surface.

2–17 The hydrophobic sites of C7 and C8 enable anchoring of these two complement components into the membrane of the pathogen. Once anchored in the membrane, the hydrophobic site of C8 facilitates C9 polymerization, which completes the formation of the membrane-attack complex.

2–18 b

2–19 e

2–20 MCP, factor H, and CR1 all bind to C3b and render it susceptible to proteolytic cleavage by factor I. All three contain complement control protein (CCP) modules and are therefore considered regulators of complement activation (RCA).

2–21 G-protein-coupled receptors for the anaphylatoxins C3a and C5a are found on phagocytes, mast cells, and the endothelial cells of blood vessel walls. Anaphylatoxin bound to mast cells causes them to degranulate, releasing inflammatory mediators such as histamine and leading to increased vascular permeability. Through their action on endothelial cells, anaphylatoxins exert vasoactive effects on blood vessels, contributing to increased vascular permeability and increased blood flow, which facilitate the extravasation of plasma proteins, such as complement proteins and antibodies, and the recruitment of cells to infected tissues through increased adherence and chemotaxis. Phagocytic activity is enhanced by anaphylatoxins, which bring about increased levels of CR1 and CR3 and microbicidal activity. All these activities enhance inflammation.

2–22 a

2–23 e

2–24 d

2–25 c

2–26 d

2–27 b

2–28 c

2–29 a