

**Allergy and Immunology Review Corner:** Chapter 2, Part I of *Janeway's Immunobiology* 8th Edition by Kenneth Murphy.

**Chapter 2, Part I (pages 37-52): Innate Immunity: The First Lines of Defense**

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1. Innate immunity cannot use which of the following mechanisms to remove infectious agents?
  - A. Gene segment rearrangements resulting in variable antigen-specific receptors
  - B. Recognition of preformed, nonspecific and broadly specific effectors such as lysozymes and defensins
  - C. Recognition of PAMPs
  - D. Activation of the complement system
2. Which of the following is considered a property of the cathelicidin family?
  - A. They are made of dendritic cells in the skin in response to infection.
  - B. They are made as active propeptides composed of two linked domains and are processed after secretion
  - C. They are stored in primary granules and are activated by fusion of these primary granules into secondary granules
  - D. They lack disulfide bonds that stabilize molecules such as defensins
3. The following is the correct series of stages for response to an infection by the immune system:
  - A. Pathogens adhere to tissues → antimicrobial defenses such as lysozymes and defensins released → activation of memory B cells → complement destroys microorganisms
  - B. Pathogens adhere to epithelium → complement destroys microorganisms → antimicrobial defenses such as lysozymes and defensins released → adaptive immunity initiated
  - C. Pathogens adhere to epithelium → local infection and penetration of epithelium → local infection of tissues → adaptive immunity initiated
  - D. Pathogens adhere to tissues → local infection and penetration of epithelium → complement destroy microorganism → local chemical factors result in phagocytosis of remaining organisms
4. Which of the following is the critical step in complement activation leading directly or indirectly to all of the initial effector activities of the complement system?
  - A. C1q interaction with pathogen surface
  - B. Cleavage of C5 resulting in generation of C5b important for opsonization
  - C. Cleavage of C3 into C3a and C3b
  - D. Hydrolysis of C3 to C3 (H<sub>2</sub>O) to initiate deposition of C3 convertase on microbial surfaces
5. The following all are direct mechanisms of tissue damage produced by pathogens via endotoxins, **except** which pathogen listed below?
  - A. *E. coli*
  - B. *H. flu*

- C. Shigella
- D. C.tetani

6. Surface epithelia provide mechanical, chemical, and microbiological barriers to infection. Which of the following is an example of a **chemical** barrier?

- A. Movement of mucus by cilia
- B. Tears
- C. Normal microbiota
- D. Pulmonary surfactant

7. Which of the following antimicrobial proteins leads to the formation of pores and a loss of membrane integrity in microbial cell membranes?

- A. Defensins
- B. Histatins
- C. Cathelicidins
- D. Lectins

8. The recognition domain of the complement protein C1 is which of the following:

- A. C1r
- B. C1s
- C. C1q
- D. C1qrs complex

9. The crucially important highly reactive thioester bond, which allows for complement to bind covalently to the pathogen surface, is found in which complement protein?

- A. C5
- B. C5b
- C. C3b
- D. C1

10. Which of the following B-cell receptors is also a complement receptor?

- A. CD21
- B. CD19
- C. CD81
- D. CD 21 and CD19

### Answers

1. A, page 37

Adaptive immunity involves gene segment rearrangements resulting in variable antigen-specific receptors, which innate immune system cannot utilize. Recognition of preformed nonspecific effectors, recognition of PAMPs, activation of the complement system, and recognition of germline encoded broadly specific effectors are all part of the innate immune response.

2. D, page 46

Cathelicidins are made constitutively by neutrophils, macrophages, and keratinocytes in the skin in response to infection. They are made as inactive propeptides composed of two linked domains

and are processed before secretion. Cathelicidins are stored in secondary granules and are activated by proteolytic cleavage when these granules fuse with the phagosome. This family of antimicrobial peptides lack disulfide bonds that stabilize molecules such as defensins.

3. C, page 43

The immune system fights off infection by first allowing pathogens adhere to epithelium → local infection and penetration of epithelium → local infection of tissues → adaptive immunity initiated

4. C, page 50

Cleavage of C3 is the critical step in complement activation leading directly or indirectly to all of the effector activities of the complement system. C5 cleavage is involved in “late events” including formation of MAC.

5. D, page 41

Endotoxins include E.coli, Shigella, and H. flu, but C. tetani is in the category known as exotoxin production.

6. D, page 43, Figure 2.6

7. A, pages 45-46

The hydrophobic region of defensins inserts itself into the membrane bilayer and forms a pore that makes the membrane leaky. Key to note, neutrophils produce alpha-defensins which are stored in primary granules.

8. C, page 50

C1 is made up of three parts: C1q is the recognition domain while C1r and C1s function as proteases. C1q can bind to Ag:Ab complexes and directly to pathogen surfaces. Binding of C1q initiates the classical pathway.

9. C, pages 351-52, Figure 2.13

The KEY feature of C3b is its ability to form a covalent bond with microbial surfaces, which allows the innate recognition of microbes to be translated into effector responses. Covalent bond formation is due to a highly reactive thioester bond that is hidden inside the folded C3 protein AND cannot react until C3 is cleaved.

10. A, page 50, and see page 259

CD21 is also known as CR2 (complement receptor 2) and enhances B cell responses to complement-coated antigens.

**Allergy and Immunology Review Corner:** Chapter 2, Part II of *Janeway's Immunobiology* 8th Edition by Kenneth Murphy.

**Chapter 2, Part II (pages 53-71):** Innate Immunity: The First Lines of Defense

*Prepared by Hannah Walford, MD, University of California, and Andrew Nickels, MD, Mayo School of Graduate Medical Education*

1. Which of the following are highly conserved structures on microbial organisms that trigger the innate immune system?
  - A. Toll like receptors (TLRs)
  - B. Collectins
  - C. Pathogen associated molecular patterns (PAMPs)
  - D. Mannose-binding lectins
  
2. The three complement-activation pathways (Mannose-Binding Lectin, Classical and Alternative pathways) converge with the formation of which of the following protein complexes?
  - A. C1 complex
  - B. C3 convertase
  - C. C5 convertase
  - D. Membrane attack complex (C5-C9)
  
3. Leukocyte adhesion defect (LAD - type 1) is a primary immunodeficiency due to impaired leukocyte chemotaxis resulting in recurrent bacterial infections early in life. It results from a mutation in the Beta-subunit of which of the following complement receptors?
  - A. CR1 (CD35)
  - B. CR2 (CD21)
  - C. CR3 (Mac-1 or CD11b/CD18)
  - D. CRIg (Complement receptor of immunoglobulin family)
  
4. Genetic deficiency in which of the following membrane protein(s) results in paroxysmal nocturnal hemoglobinuria (PNH) due to unregulated complement activation?
  - A. Protectin (CD59) and Decay-accelerating factor (DAF or CD55)
  - B. Factor H
  - C. Factor B and Factor D
  - D. Membrane cofactor of proteolysis (MCP or CD46)
  
5. An 18-year-old college student living in the dormitory develops acute meningitis. CSF cultures grow *Neisseria meningitidis*. She recalls having bacterial meningitis on two occasions previously. Complement studies are sent. Both total complement (CH50) and alternative complement (AH50) are absent. Which of the following complement defects is likely?
  - A. C2
  - B. Properdin
  - C. C5
  - D. C1 inhibitor
  
6. Which of the following component of the lectin pathway with a general specificity for oligosaccharides containing acetylated sugars is synthesized and secreted by the lung?
  - A. Factor I
  - B. MBL-associated serine proteases
  - C. M-ficolin

D. Collectins

7. Factor I is synthesized mainly in the liver and complete deficiency of Factor I, while rare, leads to recurrent severe infections, glomerulonephritis or autoimmune diseases. Which of the following statement best characterized the role of Factor I in the complement cascade?

- A. Cleaves C3b bound to the microbial surface to removed C3f, leaving the inactive iC3b from bound to the surface.
- B. Activates C5a receptor to allow bacteria to be phagocytosed via CR1.
- C. Co-activated C3a receptor with C3a to active g-protein coupled receptor to promote phagocyte activation.
- D. Terminates the compliment cascade after activation of C9

8. Which component of the classical pathway allows this pathway to function in both innate and adaptive immunity?

- A. C1r
- B. C1s
- C. C4
- D. C1q
- E. Factor D

9. Which of the following receptor has seven membrane spanning domains that transduce signals via intracellular guanine-nucleotide-binding proteins (G-protein-coupled receptor) and facilitates bacterium being phagocytize via bacterial bound C3b interacting with macrophage CR1?

- A. CRig receptor
- B. CR2 receptor
- C. CR4 receptor
- D. C5a receptor

10. Hereditary angioedema is caused by a deficiency in C1 inhibitor (C1INH) and presents with extensive soft tissue swelling. Which of the following product builds up and is responsible for this clinical manifestation?

- A. C4
- B. C2 kinin
- C. C1r
- D. C1s

**Answers**

1. C, Part 2-6 on pages 52-53

Microorganisms bear patterns of molecular structures on their cell surface, which are known generally as pathogen-associated molecular patterns, and are recognized by our innate immune system. Examples of this include the lipoteichoic acids of gram-positive bacterial cell walls, the lipopolysaccharide of the outer membrane of gram-negative bacteria, and the glycans of yeast surface proteins. Mammalian toll like receptors (TLRs) recognize these molecular patterns. Mannose-binding lectin (MBL) is a type of collectin protein, which may trigger the lectin complement pathway.

2. B, Figure 2.12 on p. 51

All three pathways converge with the formation of a C3 convertase, which cleaves C3 to produce the active complement component C3b.

The classical pathway is initiated by activation of the C1 complex, which is composed of a large subunit (C1q), which acts as the pathogen sensor, and two serine proteases (C1r and C1s). The C1 complex is similar in overall structure to the MBL-MASP complex of the lectin pathway, and has identical function, cleaving C4 and C2 to form the C3 convertase (C4b2a). The alternative pathway of complement can amplify the classical or lectin pathway by forming an alternative C3 convertase C3bBB and depositing more C3b molecules on the pathogen, which allows it to be recognized by phagocytic cells.

3. C, page 63, Figure 2.26

LAD-1 (Leukocyte Adhesion Defect, type 1) is a primary immunodeficiency in leukocyte chemotaxis that results from a heterogeneous mutation in the Beta-subunit of CD18, which is common to the complement receptors CR3 (Mac-1) (CD11b/CD18) and CR4 (glycoprotein 150, 95) (CD11c/CD18). CR3 and CR4 are both integrins; CR3 is especially important for leukocyte adhesion and migration.

4. A, pages 70-71

Paroxysmal nocturnal hemoglobinuria is a disease characterized by episodes of intravascular red blood cell lysis by complement. It is an acquired (rather than inherited) intrinsic defect in the [cell membrane](#) that results from deficiency of [glycophosphatidylinositol](#) (GPI). The main proteins that protect red blood cells from destruction are Decay accelerating factor (DAF/CD55) and Protectin (CD59), which are both peripheral membrane proteins linked to the cell surface by a GPI tail. DAF (CD55) competes with Factor B for binding of C3b on the cell surface and disrupts the formation of the C3 convertase. Protectin (CD59) inhibits the binding of C9 to the C5b678 (MAC complex) on autologous or allogeneic cells.

5. C, page 59

Patients with terminal complement defects (C5-C9) are especially prone to infection with *Neisseria meningitidis* and *N. gonorrhoeae*. In order to understand the appropriate diagnostic tests for working up congenital complement deficiency, one must understand the unique components of the classical and alternative complement pathways. A deficiency in both pathways, as indicated by both low CH50 and low AH50, suggests the defect lies in the terminal complement components common to both pathways (C5-C9) or the membrane attack complex (MAC). Of the complement components listed C5 is the most likely to be deficient.

A defect in Properdin would result in a normal CH50 but an abnormal AH50.

A defect in C2 would result in a normal AH50 but an abnormal CH50.

Finally, deficiency in C1 inhibitor esterase results in hereditary angioedema and not complement deficiency.

6. C, pages 53-54

Ficolins are a class of pathogen receptor molecules used by the lectin pathway and have a general specificity for oligosaccharides containing acetylated sugars, but do not bind mannose-containing carbohydrates. H- and L-ficolin are synthesized by the liver and circulate in the blood. M-ficolin is synthesized in the lung.

7. A, pages 63-64

Factor I cleaves C3b bound to the microbial surface to the inactive iC3b from bound to the surface. iC3b is recognized by several complement receptors

Nilsson SC et al. Complement factor I in health and disease. *Mol Immunol.* 2011 Aug;48(14):1611-20.

8. C, page 56

The C1 complex allows the classical pathway to function both in the innate immunity and adaptive immunity. In the C1 complex, C1q can attach itself to the surface pathogens in several different ways. One is binding directly to the pathogen surface. Secondly, it can bind with C-reactive protein to phosphocholine residues in the bacterial surface molecules. Thirdly, C1q binds to the constant regions of antibodies (the Fc regions) that have bound pathogens via their antigen binding sites. Thus, C1q links the effector functions of complement to recognition provided by adaptive immunity.

9. D, pages 62-63

C3b bound to bacterium binds to the CR1 receptor on many types of immune cells including macrophages and neutrophils. Binding of C3b to CR1 cannot by itself stimulate phagocytosis, but requires other receptor activation. C5a receptor (and C3a receptor) are seven membrane spanning domains that transduce signals via intracellular guanine-nucleotide-binding proteins (G-protein-coupled receptor) and facilitates bacterium being phagocytized via bacterial bound C3b interacting with macrophage CR1.

10. B, pages 67-68

C1 inhibitor is a plasma serine protease inhibitor (or serpin) that binds the active enzymes C1r:C1s and causes them to dissociate from C1q and decreases complement activity. In C1INH deficiency, there is a chronic spontaneous complement activation that leads to the production of excess cleaved fragments of C4 and C2. The small fragment of C2, C2b, is further cleaved into a peptide, C2a, which causes extensive swelling. C1INH also inhibits kallikrein and lack of kallikrein inhibition leads to an increase in bradykinin as well.