Allergy and Immunology Review Corner: Chapter 3, Part I of *Janeway's Immunobiology* 8th Edition by Kenneth Murphy.

Chapter 3, Part 1 (pages 75-98): Basic Concepts in Immunology

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1. Which of the following cell types are major producers of antiviral interferons and are considered to be part of innate immunity?
A. Eosinophils
B. Macrophages
C. Conventional dendritic cells
D. Plasmacytoid dendritic cells

2. Which of the following receptors recognizes a unique feature of bacterial polypeptides?
A. Dectin-1
B. Mannose receptor
C. fMet-Leu-Phe receptor
D. CD36

3. Which of the following TLRs recognizes DNA with unmethylated CpG?
A. TLR-2
B. TLR-2:TLR-6
C. TLR-9
D. TLR-7

4. Which of the following cascade of events represents the correct initial signaling pathway that uses MyD88?
A. MyD88 death domain → IRAK4/IRAK1 → TRAF-6/TRICA1 → polyubiquination of TRAF-6 and NEMO → recruitment of TAK1
B. MyD88 TIR domain → IRAK4/IRAK1 → TRAF-6/TRICA1 → polyubiquination of TRAF-6 and NEMO → recruitment of TAK1
C. MyD88 death domain → TRAF-6/TRICA1 → IRAK4/IRAK1 → polyubiquination of TRAF-6 and NEMO → recruitment of TAK1
D. MyD88 death domain → IRAK4/IRAK1→ polyubiquination of TRAF-6 and NEMO → activation of IKK complex

5. Which of the following NOD-like receptors (NLRs) is strongly expressed in the Paneth cells of the gut?
A. NLRP3
B. AIM2
C. NOD1
D. NOD2

6. Which of the following is NOT a characteristic of receptors of the innate immune system?

A. Expressed by all cells of a particular type (i.e. Macrophages)
B. Recognizes broad classes of pathogens
C. Requires gene rearrangement
D. Specificity inherited in the genome

7. What is the correct sequence of the respiratory burst?
A. Superoxide production, fusion of phagosome and granules, NADPH oxidase assembly, acidification with release of proteases
B. NADPH oxidase assembly, acidification with release of proteases, Superoxide production, fusion of phagosome and granules
C. Fusion of phagosome and granules, Superoxide production, NADPH oxidase assembly, acidification with release of proteases
D. Fusion of phagosome and granules, NADPH oxidase assembly, superoxide production, acidification with release of proteases

8. Which of the following immune deficiencies is caused by a genetic deficiency of NADPH oxidase?
A. Chronic granulomatous disease
B. Leukocyte adhesion deficiency
C. Chediak-Higashi syndrome
D. Shwachman-Diamond syndrome

9. Which of the following is the ligand for Toll-Like receptor (TLR) 4?
A. Flagellin
B. LPS
C. Unmethylated CpG DNA
D. ssRNA

10. Which TLR's are expressed intracellularly, in the walls of endosomes?
A. TLR's 2, 5, and 6
B. TLR's 3, 5, and 7
C. TLR's 7, 8, and 9
D. TLR's 3, 7, and 9

Answers:
1. D, page 77
pDCs are major producers of antiviral interferons, in contrast to conventional DCs, which chiefly function to generate peptide antigens that can activate T cells.

2. C, page 79
The fMLP receptor is a G-protein-coupled receptor that recognizes the N-formylmethionine (fMet) residue at which protein synthesis is typically initiated at in bacteria. Dectin-1 and mannose receptors recognize B-1,3-linked glucans and mannosylated ligands, respectively. CD36 is a scavenger receptor that recognizes lipoproteins.

3. C, pages 86-88

TLR-9 is one of the intracellular TLRs, which recognizes unmethylated CpG in bacteria and viruses. TLR-9 is one of the endosomal TLRs, along with TLR-3 and TLR-7, and delivery of such TLRs to the endosome from the ER requires UNC93B1.

4. A, page 91
Next, TAK1 phosphorylates and activates the IkB kinase (IKK) complex, which is also known as NEMO. Activated NEMO then phosphorylates IkB, which then releases NFkB. This must occur in order for NFkB to enter the nucleus and induce the transcription of key pro-inflammatory cytokines TNF-alpha, IL-1B, and IL-6.

5. D, page 93
NOD2 is a part of the NOD subfamily, which contains a CARD in its structure (caspase recruitment domain). NOD1 senses gamma-glutamyl diaminopimelic acid (iE-DAP), a breakdown product of peptidoglycans of gram-negative bacteria. NOD2 recognizes muramyl dipeptide, which is present in the peptidoglycans o most bacteria. NOD2 regulates the expression of potent antimicorbila peptides such as the alpha- and beta-defensins in the gut. NOD1 is an important activator of the innate response in epithelial cells. **Loss of function of NOD2 may lead to Crohn's disease.**

6. C, page 76, Table 3.1
Receptors that require gene rearrangement are found in the adaptive immune system, not the innate immune system. Receptors of the innate immune system are inherited in the genome, expressed by all cells of a particular type, trigger immediate response, recognize broad classes of pathogens, and interact with a range of molecular structures of a given type.

7. D, page 81, Figure 3.5.
The phagosome fuses with primary and secondary granules. Rac induces assembly of NADPH oxidase in the phagolysosome membrane, this leads to generation of superoxide (O2-). Acidification resulting from ion influx leads to release of granule proteases from the granule matrix.

8. A, page 82
Chronic granulomatous disease is caused by genetic deficiency in NADPH oxidase, resulting in lack of the respiratory burst. It is most commonly associated with inactivating mutations on the X chromosome.

9. B, page 86
The ligands for TLR-4 are Lipopolysaccharide (LPS) from gram negative bacteria and lipoteichoic acids from gram positive bacteria.

10. D, page 87, Figure 3.10
TLR's 3, 7 and 9 are expressed intracellularly in the walls of endosomes. They recognize microbial components, such as DNA, that are only accessible after the microbe has been broken down. TLR 3 recognizes dsRNA, TLR 7 recognizes ssRNA, and TLR 9 recognizes unmethylated CpG DNA.

Allergy and Immunology Review Corner: Chapter 3, Part II of *Janeway's Immunobiology* 8th Edition by Kenneth Murphy.

Chapter 3, Part II (pages 99-103): Basic Concepts in Immunology

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1. Which of the following cytokines activates NK Cells and induces the differentiation of CD4 T Cells into TH1 Cells?
A. IL-1β
B. IL-6
C. IL-12
D. CXCL-8
E. TNF α

2. Cytokines are small proteins that are released by various cells in the body, usually in response to an activating stimulus and induce response through binding to specific receptors. Which term best describes a cytokine that affects behavior of adjacent cells?
A. Paracrine
B. Exocine
C. Autocrine
D. Endocrine

3. CXC chemokines have two cysteine residues separated by a single amino acid near their amino terminus. CXC chemokines are primarily responsible for what type of cells?
A. Lymphocytes
B. Neutrophils
C. Monocytes
D. Dendritic Cells
E. NK Cells

4. A 3-year-old boy is brought into the ER with a laceration on his left forearm two days ago, and you diagnose cellulitis. In an acute infection, neutrophils are typically the first cells to arrive in large numbers at the site of infection. Once present at the site of infection, what action does CXCL8 have on neutrophils?
A. Induce release of TNF α
B. Inhibit the migration of monocytes and dendritic cells
C. Induce release of CCL2
D. Activate neutrophils to produce the respiratory burst

5. Which of the following is best described as membrane glucoproteins with a distal lectin-like domain that binds *specific carbohydrate groups*?
A. CR3
B. Chemokines
C. P-selectin

D. CD11a:CD18 (complement receptor 4)

6. In the process of effector cell recruitment into infected tissue, leukocytes adhere to endothelial cell surfaces via selectins such as P-selectin and E-selectin. What portion of the leukocytes is recognized by the selectins to allow monocytes and neutrophils to adhere reversibly to the vessel wall, so that circulating leukocytes can marginate in the circulation?
A. IL-8 receptor
B. CD31
C. ICAM-1
D. Sialyl-Lewis^{x} moiety
E. LFA-1

7. A 68-year-old male is admitted to the intensive care unit with gram-negative bacteriemia and hypotension. Which of the following membrane associated cytokine is cleaved by a protease and released from the membrane as a soluble cytokine and released in massive amounts from macrophages in the liver, spleen and other sites?
A. IL-8
B. CCL5
C. CXCL8
D. IL-12
E. TNF α

8. TNF α, IL-1β, and IL-6 are important in initiating the acute phase response, in which these cytokines act on liver hepatocytes to cause decrease in some proteins and the increase of acute phase proteins. Which acute phase protein binds to phosphocholine portion of certain bacterial and fungal cell-wall lipopolysaccharides?
A. Mannose-binding lectin (MBL)
B. C-Reactive protein (CRP)
C. Surfactant protein SP-A
D. Surfactant protein SP-D

9. Plasmacytoid dendritic cells (pDC) (also called interferon-producing cells or natural interferon-producing cells) are peripheral blood class that accumulate in the peripheral lymphoid tissues during a viral infection and make abundant type 1 interferons (INF-α and INF-β). Which receptor is expressed on pDCs that interact with T Cell produced chemokines allowing pDCs to migrate from the blood to lymph nodes in which active inflammatory responses to a pathogen occurs?
A. ICAM-1
B. E-selectin
C. CXCR3
D. TLR3

10. Natural killer cells (NK cells) develop in the bone marrow from the same progenitor cells as T and B lymphocyte and are recognized in flow cytometry by being CD 16 and CD 56 positive. What cytokine do activated NK cells secrete in large amounts early in an immune response to

induce activated CD4 T-cells to differentiate into pro-inflammatory T_h1 cells, which are able to active macrophages?

A. IL-18
B. INF-γ
C. IL-12
D. CXCL9

Answers

1. C, page 101, Figure 3.21
IL-12 Activates NK Cells and induces the differentiation of CD4 T Cells into TH1 Cells.

2. A, page 99
Paracrine describes when a cytokine affects the behavior of adjacent cells. Endocrine describes effects on distant cells and Autocrine affects self.

3. B, page 103
CXC chemokine promote neutrophil migration. This is in contrast to CC Chemokines which promote the migration of monocytes, lymphocytes, and other cells.

4. D, page 103
CXCL8 activate neutrophils to produce the respiratory burst that generates oxygen radicals and nitric oxide and to release their stored antimicrobial granular contents.

5. C, page 105
Selectins are membrane glycoproteins with a distal lectin-like domain that binds specific carbohydrate groups. P-selective appears on the surfaces of local endothelial cells just minutes after macrophages have responded to the presence of microbes by producing TNF α.

6. D, page 106-107, Figure 3.25
Sialyl-Lewis^x moiety binds reversibly to E- and P- selectin to allow monocytes and neutrophils to adhere reversibly to the vessel wall, so that circulating leukocytes can be seen to 'roll' along endothelium that has been treated with inflammatory cytokines.

7. F, pages 108-109
In sepsis, TNF α is cleaved by a specific protease TACE (TNF α converting enzyme, formerly ADAM17) and release from the membrane as a soluble cytokine. The presence of infection in the blood stream, or sepsis, is accompanied by a massive release of TNF α into the blood stream causes vasodilation, which leads to a loss of blood pressure and increased vascular permeability.

8. B, page 110
C-Reactive protein is a member of the pentraxin protein family (they are formed from five identical subunits) and is an acute phase reactant that is induced by TNF α, IL-1β, and IL-6. CRP binds to phosphocholine portion of certain bacterial and fungal cell-wall lipopolysaccharides.

9. C, page 111

Plasmacytoid dendritic cells (pDC) express CXCR3. CXCR3 is a receptor for chemokines CXCL9, CXCL10, and CXCL11 produced by T Cells allowing pDCs to migrate from the blood to lymph nodes in which active inflammatory responses to a pathogen occurs.

10. B, page 113
INF-γ is secreted by NK cells in large amounts early in an immune response to induce activated CD4 T-cells to differentiate into pro-inflammatory T_h1 cells, which are able to active macrophages. See question 1 (IL-12 is responsible for activating NK cells).