Scott Wang
sxw847@case.edu
CWRU School of Dental Medicine, Class of 2026

Body as Host

Problem Set A: Innate Immunity

This study guide will go over big points covered in lectures pertaining to innate immunity.

1. Identify the type of cell based on the statement.
    a. Most prominent leukocyte in the blood.
    b. Release histamines and have high affinity IgE receptors; primary mediator of allergies.
    c. Primary defense against multicellular microbes and parasites.
    d. Differentiated monocyte once it has arrived at a tissue.
    e. Non-phagocytic leukocyte that comprises 0-1% of blood and functions similarly to mast cells.

2. List and differentiate the primary and secondary lymphoid organs.

3. What is the first line of defense in innate immunity? What type of metabolites are among the first inflammatory signals?

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4. What is the first cell to call for help upon injury? What is inside that cell that gets released upon injury? What is the second cell to call for help and how do they respond?

5. Describe how a cell performs rolling and extravasation via transendothelial migration.

6. Fill in the table regarding cytokines.

Cytokine	IL-1	Class I Hematopoietic	TNF	IL-17	Chemokines
Structure					
What stimulates them?					
Who produces them/induces them?					
What do they do locally?					
What do they do systemically?					

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7. Fill in the table regarding IL-1 subclasses.

	Activation	Function/Expression
IL-1 alpha		
IL-1 beta		

8. Fill in the table regarding Class I Hematopoietic subclasses.

	Function
IL-2	
IL-4	
IL-6	
GM-CSF and G-CSF	

9. Fill in the table regarding IFN subclasses.

	Greek letters	Who secretes them?	What do they do?
Type I			
Type II			
Type III			

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10. Fill in the table regarding TNF subclasses.

	Who secretes them?	What do they do?
TNF-alpha		
TNF-beta		

11. Starting with C3b and factor B, explain the steps of the alternate pathway that lead to the formation of C3 convertase.

12. Starting with C1q, C4, and C2, explain the steps of the classical pathway that lead to the formation of C3 convertase.

13. Starting with MASP-1, MASP-2, C4, and C2, explain the steps of the mannose-lectin pathway that lead to the formation of C3 convertase.

14. Explain how C5 convertase is formed and how it eventually helps form MAC.

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ANSWER KEY

1. Identify the type of cell based on the statement.
    a. Most prominent leukocyte in the blood. (Neutrophil)
    b. Release histamines and have high affinity IgE receptors; primary mediator of allergies. (Mast cell)
    c. Primary defense against multicellular microbes and parasites. (Eosinophil)
    d. Differentiated monocyte once it has arrived at a tissue. (Macrophage)
    e. Non-phagocytic leukocyte that comprises 0-1% of blood and functions similarly to mast cells. (Basophil)

2. List and differentiate the primary and secondary lymphoid organs.

- Primary- thymus and bone marrow
- Secondary- lymph nodes, GALT/MALT, spleen

3. What is the first line of defense in innate immunity? What type of metabolites are among the first inflammatory signals?

(Physical and chemical barriers; arachidonic acid)

4. What is the first cell to call for help upon injury? What is inside that cell that gets released upon injury? What is the second cell to call for help and how do they respond?

(Dead cell; IL-1 alpha; neighboring cells release cytokines)

5. Describe how a cell performs rolling and extravasation via transendothelial migration.

–First, Induction of weak adhesion molecule on endothelium, constitutive weak counter-adhesion molecule on phagocyte
–Rolling / jumping
–Next, Constitutive strong adhesion molecule on endothelium; activation of strong counter-adhesion molecule on phagocyte

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6. Cytokines Table

Cytokine	IL-1	Class I Hematopoietic	TNF	IL-17	Chemokines
Structure		Four-helix bundle structure	Dimer, may be soluble or membrane bound Short intercellular N-terminus; long extracellular C-terminus	Transmembrane homodimers	Highly conserved disulfide bonds Share 2, 4, or 6 conserved cysteine residues
What stimulates them?	Bacterial, viral, and parasitic antigens	Binding to the alpha chain	LPS bound TLRs in macrophages	Receptors found on neutrophils, keratinocytes, and other non-lymphoid cells	Transduce signals via G-protein coupled receptor
Who produces them/induces them?	Many immune cells- mainly dendritic cells, monocytes, and macrophages		Activated macrophages and T cells	Receptors found on neutrophils, keratinocytes, and other non-lymphoid cells	
What do they do locally?	Increase capillary permeability and bring in leukocytes		(2) Recruits neutrophils and macrophages to site of inflammation Stimulates neutrophils and macrophages to produce chemokines		
What do they do systemically?	(4) Liver produces acute phase proteins and other cytokines Destruction of viral RNA Systemic fever Activates adaptive immunity	Mediate proliferation, differentiation, and antibody secretion	(2) Potent pyrogen→ systemic fever Production of acute phase proteins	Work at interface of innate and adaptive immunity	Direct leukocyte migration

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Subclasses

7. IL-1

	Activation	Function/Expression
IL-1 alpha	Cleavage by calpains Synthesized in the absence of cellular stress as precursors	Dual function cytokine-nuclear transcription factor and ligand for plasma membrane
IL-1 beta	Cleavage by caspase-1 Synthesized during cellular stress	Expressed induced by NF-kB and alarmins Binds IL-1R1 and IL-1R3→ tells them to produce IL-1 and TNF-alpha Pyrogen, T cell activation, fibroblast proliferation, and collagen production

8. Class I Hematopoietic

	Function
IL-2	Stimulate B and T cell proliferation
IL-4	Regulate Helper T cell function
IL-6	Stimulate differentiation of B cells to plasma cells
GM-CSF and G-CSF	Differentiation of leukocyte lineages

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9. IFN

	Greek letters	Who secretes them?	What do they do?
Type I	Alpha and beta	Activated macrophages and dendritic cells	Induce ribonucleases and inhibit protein synthesis
Type II	Gamma	Activated T/NK cells	Potent modulator of adaptive immunity
Type III	Lambda	Plasmacytoid dendritic cells	Upregulate genes controlling viral proliferation and host cell proliferation

10. TNF

	Who secretes them?	What do they do?
TNF-alpha	Activated macrophages	Proinflammatory
TNF-beta	Activated lymphocytes	Deliver signals to leukocytes and endothelial cells

11. Starting with C3b and factor B, explain the steps of the alternate pathway that lead to the formation of C3 convertase.

C3b binds to factor B that is cleaved by factor D to Bb. The C3bBb complex then acts as the C3 convertase and generates more C3b through an amplification loop.
Cleavage of C3 reveals a thio-ester bond that can react with bacteria surface, if it is available.
Tickover reaction allows for some active, soluble C3 convertase to be available all the time (C3*Bb: Soluble C3 Convertase).
C3bBb is the alternate (oldest) convertase.

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12. Starting with C1q, C4, and C2, explain the steps of the classical pathway that lead to the formation of C3 convertase.

C1q is a six-headed structure that can bind to antibodies only when antibodies are bound to a surface.
C1r and C1s (proteases) can only bind to C1q when it is bound to antibodies to become the complex C1qrs.
Then C4 comes in and has a thioester bond (so it's structurally similar to C3), and C4 gets cleaved to C4a and C4b by C1qrs, and C4b binds to the pathogen membrane.
C4b binds to C2 and exposes it to the action of C1s. C1s cleaves C2, creating C3 convertase= C4bC2a.

13. Starting with MASP-1, MASP-2, C4, and C2, explain the steps of the mannose-lectin pathway that lead to the formation of C3 convertase.

MASP-1 and MASP-2 are proteases that bind to the 6-headed structure.
Activated MASP-2 cleaves C4 to C4a and C4b. C4b is bound to the pathogen surface.
Next, activated MASP-2 also cleaves C2 to C2a and C2b. C2a binds to surface C4b forming the classical convertase C3= C4bC2a.
C4bC2a binds to C3 and cleaves into C3a and C3b.

14. Explain how C5 convertase is formed and how it eventually helps form MAC.

C3b binds both to C4b2a and C3bBb, forming the active C5 convertases: C4bC2aC3b and (C3b)2Bb.
The C3b, a component of C5 convertase binds C5, permitting C4bC2a to cleave C5.
C5b binds C6, initiating the formation of the membrane attack complex, which spontaneously adds C7, which spontaneously adds C8.
C8 binds to the complex and inserts into the cell membrane. C9 molecules bind to the complex and polymerize. 10-16 molecules of C9 bind to form a pore in the membrane.