Micro Ch 6: Innate Immunity

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Innate Immunity
Microbiology: Chapter 6

- Skin and Mucus membrane
  - mechanical barriers (skin) are covered with thick keratinized epithelium
  - linked through tight junctions - does not allow passage of microorganisms
  - mucus - cross-linked gel-like structure of glycoproteins, traps particles and prevents reach of mucus membrane
  - antimicrobial peptides
    - phospholipase A2 - destroys bacterial cytoplasmic membrane
    - defensin - adds pores to cell wall increasing permeability (cation attracted to negative cytoplasmic membrane)
    - lysozymes - hydrolyses peptidoglycan structures in cell walls
      - Gram (+)
    - Amidase - hydrolyses peptidoglycan structures in cell walls
- recognition strategies of innate immune system
  - Pattern recognition receptors - recognize characteristic structures in microbes
    - Toll-like receptors
      - TLR2 -
        - recognize lipoproteins, peptidoglycan, lipoteichoic acid (Gram (+)), zymosan
        - signal activation of macrophages and dendritic cells, increase proinflammatory mediators, and adaptive immunity
      - TLR4
        - recognize lipopolysaccharide (Gram (-))
        - same as TLR2
    - CD14 - alert host to presence of microbe, start

proinflammatory defense, start adaptive immune response
        - recognize lipopolysaccharide (Gram (-)), peptidoglycan, lipoteichoic acid
        - signal activation of macrophages to secrete proinflammatory mediators
    - Scavenger receptors
        - recognize negatively charged polymers of bacteria and fungi
        - signals phagocytosis by macrophages
    - Mannose receptors
        - recognize mannose-containing polymers
        - signal phagocytosis by macrophages
    - CLR (C-type lectin receptors)
        - recognize ß-glucan (fungi)
        - signal phagocytosis by macrophages and inflammation
    - RLR
        - recognize RNA (viruses)
        - signals expression of viral-inhibitory protein and interferon
    - NLRP1,2,3
        - recognize toxins (bacteria), RNA (bacteria + virus), uric acid crystals (humans)
        - signal secretion of IL-1ß, caspase-1
    - NLRC3,4,5
        - recognize flagella
        - same as NLRP
    - NOD1,2
        - recognize peptidoglycan (bacteria)
        - signal activation of macrophages and proinflammatory mediators
  - detect danger signs produced by tissue
  - detect missing or changed self
    - ex. NK cells/MHC interaction
- Consequences of recognition - effector mechanisms
  - Induced innate immune responses
    1. Increase production of antimicrobial peptides
    2. secretion of numerous mediators of inflammation
    3. activation of complement system

4. activation of clotting cascade and generation of bradykinin
5. chemotactic attraction of phagocytic cells and lymphocytes
6. acute phase response
7. inflammation

- Complement system
  - Cleavage of C3
    - start of common pathway from classic, lectin, and alternative pathway
    - C3 convertases convert C3 to C3a and C3b
    - C3a is an anaphylatoxin
    - C3b is an opsonin (binds membrane of bacteria)
      - binds complement receptor type 1 (CR1) on phagocytes enhancing binding of bacteria to phagocytes
      - binds CR2 on B cells enhancing production of antibodies
  - C3 convertase of the classical pathway
    - initiated by antigen-antibody complex
    - C1 complex (C1q,r,s)
      - **C1q binds Fc** portion of antibody-antigen complex (only one IgM needed, 2 IgG needed
      - **C1q converts C1r** to a protease which then cleaves C1s into active C1s enzymes
      - **C1s enzyme cleaves C2 and C4 to C4b2a** which binds to antigen and becomes **C3 convertase**
  - C3 convertase of lectin pathway
    - mannose-binding lectin binds mannose-containing polysaccharide (present on bacteria cell wall)
    - results in activation and complexing of MBL with MBL-associated proeases (MASP-1,2)
    - MASP-1,2 cleave C4 and C2 to C4b2a --> C3 convertase as in classic
  - C3 convertase of alternative pathway
    - C3 is constantly cleaved without complement activation (forms C3b and C3a)
    - C3b binds microorganism surfaces --> binds factor B to form C3bB
    - Factor D clease factor B from C3bB to form C3bBb which is

C3 convertase
        - Factor P binds C3bBb --> C3bBb complexes with another C3b to yield C3b3bBb --> splits C5
- Late steps in complement activation
    - membrane attack complex
        - C5 is cleaved to C5a and C5b
        - C5a is anaphylatoxin and powerful chemoattractant
        - C5b produces membrane attack complex (C9)
            - punches holes in cell membrane increasing permeability and lysis
- Regulation of complement system
    - suicide substrate mechanism
    - proteolytic digestion of active fragments
    - inhibition of association of complement components
    - defects in complement inhibitors
        - hereditary angioedema - genetic deficiency of C1 esterase inhibitors --> uncontrolled anaphylatoxin
        - paroxysmal nocturnal hemoglobinuria - intravascular hemolysis from complement induced host cell lysis
            - lack CD55 and CD59 causing C3b binding and red cell lysis
- Microbial view of complement
    - viruses and bacteria can activate complement and use C3b deposits their surface to enter host cells through C3b receptors
- Leukocyte chemotaxins: sounding the alarm

Micro Ch 7: Adaptive Immunity

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Adaptive Immunity
Microbiology Chapter 7

- innate vs adaptive immune system
  - adaptive
    - flexibility in cutting and joining genes (junctional diversity
    - small mutations (somatic hypermutation)
    - Memory
- Cells and molecules of adaptive immunity
  - immunoglobulin - synthesized by B cells (plasma cells)
    - diverse group of globular molecules
    - 2 heavy, 2 light chains linked by disulfide bonds
    - AA sequence determines class (isotype) of Ig
    - Light chain composition
      - variable (VL)
      - constant (CL)
    - Heavy chain composition
      - signel variable (VH)
      - 3-4 constant (CH)
    - Constant region determine Ig type
    - landmarks of Ig monomer
      - Fab - fragment produced by papain cleavage of monomer and contains only a single epitope-binding site (short chain + variable and 1 constant heavy chain)
      - Fc - fragments of constant heavy chain only
      - F(ab')2 - produced by pepsin cleavage of immunoglobulin monomer - contains 2 linked (disulfide) epotope-binding sites
      - Hinge region - proline-rich region allows flexibility of Fab
    - DNA chromosomal rearrangement is responsible for a significant portion of Ig diversity

        - Allelic exclusion - restriction of light and heavy chain expression to a single member of the chromosome pair either maternal or paternal
        - Ig synthesis by B-Cells
            - initial synthesis is IgM
            - change isotype via isotype switching
                - directs abs with identical specificity toward a variety of immune responses
        - IgG is only isotype able to enter fetal circulation (passive immunity protecting newborn)
        - IgA secreted in tears, saliva, milk and mucus
        - IgM and IgG activate compliment system
    - anitbody
        - immunoglobulin that binds a specific ligand
    - cluster of differentiation (CD molecules)
        - CD3,4,8 assist TCR in antigen recognition
- T Cell-associated molecules
    - composition very similar to Ig but do not increase diversity by incorporation of small mutations
    - contain 1 variable and only 1 constant region
- Cell surface and soluble molecules
    - CD3 - support TCR and involved in transmembrane signaling when TCR is engaged
    - CD4 - recognize nonpeptide-binding portion of MHC class II
        - T helper cells (Th) restricted to recognition of pMHC class II complexes
    - CD8 - recognize nonpeptide-binding portion of MHC class I
        - cytotoxic (Tc) restricted to recognition of pMHC class I complexes
    - cytokines
        - initiate growth, differentiation, and maturation of cells
        - promote or inhibit inflammation and tissue repair
        - chemokines stimulate leukocyte movement and migration
    - Adhesion molecules
        - provide stable cell-to-cell contact
        - critical for receptor-ligand interaction
- Lymphocyte development and receptor selection
    - T-cells

        - double-negative cells - immature thymocyte
        - double-positive cells - DN cells with alpha and beta TCR and CD4 and CD8 molecules
            - positive selection - die within 3-4 days if not activated by MHC I or II molecule from dendritic presentation
            - if CD recognition is too strong, apoptosis is triggered (negative selection)
    - B-Cells
        - B-1 cells - secrete IgM with strong reaction to carbohydrates (natural antibodies)
        - B-2 cells -
            - Pro-B cells - responsible for chromosomal rearrangement of V, D, and J genes from Vh domain
            - Early-stage pre-B cells - surrogate light chains on cell
            - Late-stage pre-B cells - k or L light chains replace surrogates
            - Immature B cells - if engage a epitope in bone marrow then destroyed
                - in circulation, short half-life unless signaled by lymph node to mature
                - in lymph node, begin Delta and mu chain synthesis
            - Mature B cells - coexpression of IgM and IgD
            - Plasma Cells - secrete mass amounts of Ig
- Lymphocyte activation
    - antigen presentation
        - phagocytosis - clathrin-coated pits bind content to engulf, induce actin-dependent phagocytosis and receptor internalization to form small phagosomes or endocytic vesicles
        - macropinocytosis - cytoplasmic ruffles encircle and enclose extracellular fluid to form endocytotic vesicle (do not require clathrin)
        - lysosomes - enzyme sack fuses with endocytic vesicle
        - Dendrite cells sense invasion
            - direct - recognition receptors recognize pathogen-associated molecular patterns (PAMPs) on invader
            - indirect - recognition of complement molecules on

invader
        - For phago/pinocytosis - MCH **class II** complexes are synthesized and combine with phagolysosome to load antigen
            - complex is moved to surface for **CD4** cells recognition
        - For direct host cells entry - tagged with ubiquitin, cleaved via proteasome to peptide fragments
            - enter ER and loaded to MCH **class I** via TAP-1 and TAP-2
            - pMHC class I sent to membrane for **CD8** recognition
    - T-cell activation
        - pMHC-TCR-CD4/CD8 complex signals CD3 complex --> stimulates naive T cells to proliferate and differentiate
        - costimulatory molecules (second signal) causes T-cell activation
            - without costimulatory --> anergy or apoptosis
        - Th1 cells - respond to **intracellular** pathogens by recruiting and **activating phagocytic** cells
        - Th2 cells - respond to **extracellular** pathogens by **stimulating B** cells to differentiate into antibody-secreting plasma cells
    - B-cell activation
        - bind and recognize soluble molecules (T-cells don't)