Immunology Chap 2

Wednesday, February 6, 2013
3:59 PM

The Early Defense Against Infections

- Defense mechanisms that are always present are the innate immunity.
- Shared characteristic of innate mechanisms is that they recognize and respond to microbes, NOT nonmicrobial substances.
- Innate immunity provides the early defense against infections and also instructs the adaptive immune system to respond differently to each microbe, making the adaptive response more effective.
- **Recognition of Microbes by the Innate Immune System**
    - **Innate immunity components recognize structures that microbes share but that are not on host cells.**
        - Phagocytes have receptors for bacterial lipopolysaccharide (LPS),also called endotoxin, which is found in the cell wall of many bacteria but NOT in mammalian cells.
            - Also recognize double-stranded RNA, found in viruses but not in mammalian cells.
        - Microbial molecules that are targets of innate are sometimes called *pathogen-associated molecular patterns.*
    - **The structures recognized are often essential for survival and infectivity of microbes.**
        - If these structures are mutated the microbe cannot infect and colonize the host.
        - Antigens which are recognized by antigens can be mutated because they are not required for life.
    - **Innate Immune System (IIS) also recognized molecules from stressed or necrotic cells, *damage-associated molecular patterns.***
    - **Receptors of IIS are encoded in the germline and are not reproduced by somatic recombination of genes.**
        - This means that the IIS receptors have a predetermined specificity for certain things.
        - Gene recombination can generate more structurally different receptors but they cannot have the predetermined specificity for microbes like the IIS.
            - Adaptive is more diverse and recognizes more chemically distinct structures.
        - Adaptive receptors are CLONALLY distributed: each clone of lymphocytes (B cells or T cells) has a different receptor specific for an antigen.
        - IIS receptors are NONCLONALLY distributed: identical receptors are expressed on all cells of a particular type.
    - **IIS does NOT react against the host.**
        - Due to inherent specificity for microbial structures and to the expression of regulatory molecules by mammalian cells.
        - AIS produces self antigens but these die or are inactivated.
    - **IIS responds the same way to repeat encounters with a microbe whereas the AIS responds more efficiently each time.**
        - Known as Immunologic Memory, not seen in IIS.
    - **IIS has two main reactions: Inflammation and Anti-viral Defense**
        - Inflammation recruits and activates leukocytes while the anti-viral defense is mainly with NK cells and cytokines (interferons)
    - **Cellular Receptors for Microbes**
        - **Toll-Like Receptors (TLRs)**
            - Specific for different compounds of microbes.
                - TLR2 - bacterial lipoglycans
                - TLR3,7, and 8 for viral nucleic acids

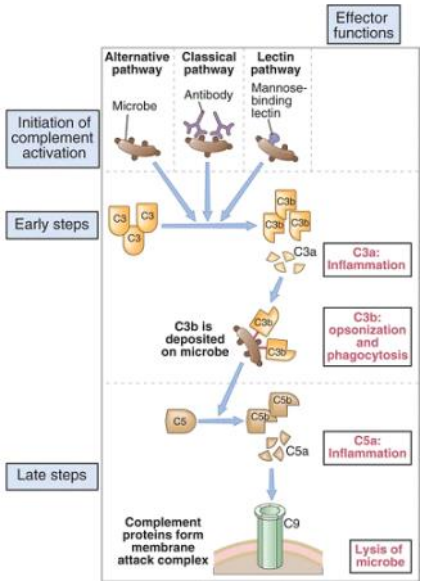
        - TLR4 for bacteral LPS (endotoxin)
        - TLR5 for flagella called flagellin
        - TLR9 for unmethylated CG-rich (CpG) oligonucleotides
    - Signals generated by engagment of TLRs activate transcription factors that stimulate expression of genes encoding cytokines, enzymes, and other proteins involved in the antimicrobial functions of activated phagocytes and dendritic cells.
        1. NF-κB (nuclear factor κB) - promotes expression of cytokines and endothelial adhesion molecules.
        2. IRF-3 (Interferon Response Factor 3) - stimulates production of type I Interferons (cytokines that block viral replication)
- **Interleukin-1 (IL-1) is a powerful inducer of the inflammatory reaction to microbes and damaged tissues.**
    - Gain-of-Function mutations affecting inflammasomes are the cause of rare human diseases called autoinflammatory syndromes.

- **Components of Innate Immunity**
    - **Epithelial Barriers**
        - Three major interfaces are the skin, gastrointestinal tract, and the respiratory tract.
            - Epithelium provides physical boundary but also produces peptide antibiotics to kill bacteria.
                - Also contains intraepithelial lymphocytes belonging to T cell family that express certain receptors.
                    - Recognize microbial lipids/other structures shared by the same type of microbe.
    - **Phagocytes: Neutrophils and Monocytes/Macrophages**
        - Neutrophils are the most abundant and are the first cell type to respond to infection, especially bacterial and fungal.
            - Production stimulated by cytokines (colony-stimulating factors) secreted in response to infection and that act on bone marrow stem cells.
        - Monocytes that enter extravascular tissue survive a long time and differentiate into macrophages.
    - **Neutrophils and Monocytes migrate by binding to endothelial adhesion molecules and in response to chemoattractants.**
        - Resident macrophages in tissues produce cytokines when they encounter a microbe.
            - Tumor Necrosis Factor (TNF) and interleukin-1 (IL-1) stimulate the endothelium to express E-selectin and P-selectin.
        - Neutrophils bind to the selectins with surface carbohydrates. This causes rolling and eventual stopping of the neutrophil.
        - Leukocytes, like monocytes, express integrins that bind with the selectins.
            - Tissue macrophages that stimulated TNF and IL-1 also produce chemokines which increase the affinity (or attraction) of the integrins for their ligands (selectins) on the epithelium.
            - These bonds stop the rolling of the leukocytes, which allows them to spread out and move
            - This accumulation of leukocytes at the site of infection, with vascular dilation and increased fluid/proteins, is called **inflammation.**
    - **Several types of receptors are used for microbes to initiate destroy functions.**
        - The process of coating microbes for efficient recognition by phagocytes is called opsonization.
    - **After ingestion, destruction of the microbe takes place in intracellular vesicles.**
        - As the microbe is being "eaten" signals are sent to enzymes within the phagolysosome.
            - Phagocyte oxidase converts molecular oxygen into superoxide anion and free

radicals.
        - Inducible Nitric Oxide Synthase catalyzes the conversion of arginine to nitric oxide, which is microbicidal.
        - Lysosomal proteases break down microbial proteins.
    - Chronic Granulomatous Disease:
        - Inherited deficiency of phagocyte oxidase.
        - Unable to get rid of intracellular microbes.
        - The cell tries to contain the infection by calling in more macrophages which results in collections of cells called granulomas.
- **Macrophages**
    - Produce cytokines to recruit and activate leukocytes.
    - Secrete growth factors and enzymes to repair injured tissue and replace it with connective tissue.
    - Stimulate T lymphocytes and enhance adaptive immunity.
    - Respond to products of T cells and function as effector cells of cell-mediated immunity.
- **Dendritic Cells**
    - Produce cytokines that recruit leukocytes and initiate adaptive immune responses.
    - Antigen display is a major function.
- **Natural Killer Cells**
    - **Lymphocytes that recognize infected and stressed cells, respond by killing them and secreting macrophage activating cytokine IFN-γ.**
        - Do NOT express immunoglobulins or T cell receptors.
        - NK cell granule proteins enter infected cells and activate apoptotic enzymes.
        - IFN-γ activates macrophages to become more effective at killing phagocytosed microbes.
        1) Macrophages ingest microbes and produce IL-12
        2) IL-12 activates NK cells to secrete IFN-γ
        3) IFN-γ activates macrophages to kill the ingested microbes.
    - **Activation of NK cells is a balance between activating and inhibitory factors.**
        - When a cell is infected or irreparably injured, it expresses activating receptors for NK cells so it can be killed.
            - Recognition of antibody-coated cells results in killing of these cells, called *antibody-dependent cellular cytotoxicity (ADCC)*.
        - Activating Receptors contain immunoreceptor tyrosine-based activation motifs (ITAMs) which stimulate phosphorylation and later release of cytotoxic granule exocytosis and production of IFN-γ.
    - **Inhibitory receptors of NK cells are specific for self class I MHC molecules, which are expressed on healthy nucleated cells.**
        - Inhibiting Receptors contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) which are phosphorylated and later block signaling molecules to block NK cell activation.
            - When the inhibitory receptors of NK cells encounter self MHC molecules, the NK cells are shut off.
            - Viruses turn off the production of these self MHC molecules, marking those cells for destruction.
        - The host uses cytotoxic T lymphocytes (CTLs) to recognize viral antigens displayed by MHC molecules while NK cells have evolved to recognize the ABSENCE of MHC molecules.
- **The Complement System**
    - Many of these proteins are proteolytic enzymes and the complement activation is a sequential activation, or enzymatic cascade, of these enzymes.
    - Three Pathways

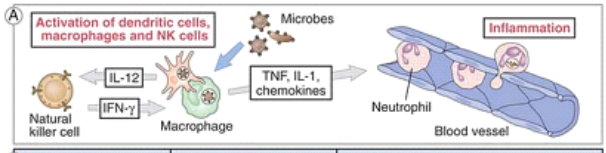
- Alternative Pathway:
  - Component of Innate Immunity
  - Triggered when some complement proteins are activated on microbial surfaces and cannot be controlled because regulatory proteins aren't present on microbes.
- Classical Pathway
  - Humoral Arm of Adaptive Immunity
  - Triggered after antibodies bind to microbes or other antigens.
- Lectin Pathway
  - Component of Innate Immunity OR Adaptive Immunity
  - Triggered when a plasma protein (mannose-binding lectin) binds terminal mannose residues on the surface glycoproteins of microbes.
  - This lectin activates proteins of the classical pathway, but because it is initiated by a microbial product, in the absence of an antibody, it is a component of innate immunity.

- Central part of complement is C3 whose major fragment is called C3b.
  - Becomes covalently attached to microbes and activates downstream complements.



- Complement System Serves Three Functions
  1) C3b coats microbes and promotes binding by phagocytes (Opsonization)
  2) C5a and C3a are chemoattractants for phagocytes and promote leukocyte recruitment (inflammation) at site of activation.
  3) Formation of polymeric protein complex that inserts into the microbial cell membrane to induce either osmotic lysis or apoptotic death of the microbe.

○ **Cytokines of Innate Immunity**
- Most cytokines are called interleukins, implying that they are produced by leukocytes and act on leukocytes.
- Principle source are dendritic cells and macrophages activated by recognition of microbes.
- Also produced in cell-mediated immunity.
  - Major source here (in adaptive immunity) is helper T lymphocytes.



B

Cytokine	Principal cell source(s)	Principal cellular targets and biologic effects
Tumor necrosis factor (TNF)	Macrophages, T cells	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Liver: synthesis of acute phase proteins Muscle, fat: catabolism (cachexia) Many cell types: apoptosis
Interleukin (IL-1)	Macrophages, endothelial cells, some epithelial cells	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever Liver: synthesis of acute phase proteins T cells: T_H17 differentiation
Chemokines	Macrophages, dendritic cells, endothelial cells, T lymphocytes, fibroblasts, platelets	Leukocytes: Increased integrin affinity, chemotaxis, activation
Interleukin-12 (IL-12)	Dendritic cells, macrophages,	NK cells and T cells: IFN-γ production, increased cytotoxic activity T cells: T_H1 differentiation
Interferon-γ (IFN-γ)	NK cells, T lymphocytes	Activation of macrophages Stimulation of some antibody responses
Type I IFNs (IFN-α, IFN-β)	IFN-α: dendritic cells, macrophages IFN-β: fibroblasts	All cells: anti-viral state, increased class I MHC expression NK cells: activation
Interleukin-10 (IL-10)	Macrophages, dendritic cells, T cells	Macrophages, dendritic cells: inhibition of IL-12 production, reduced expression of costimulators and class II MHC molecules
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T cells	Liver: synthesis of acute phase proteins B cells: proliferation of antibody-producing cells T cells: T_H17 differentiation
Interleukin-15 (IL-15)	Macrophages, others	NK cells: proliferation T cells: proliferation
Interleukin-18 (IL-18)	Macrophages	NK cells and T cells: IFN-γ production
TGF-β	Many cell types	Inhibition of inflammation T cells: differentiation of T_H17, regulatory T cells

- Most cytokines have autocrine or paracrine actions.
  - Only during large scale activation may cytokines act through endocrine actions.
- TNF, IL-1 and chemokines principally recruit neutrophils and monocytes to the site of infection.
  - TNF promotes thrombus formation on the endothelium and reduces blood pressure through reduced myocardial contractility and vascular dilation/leakiness.
    - Septic Shock
      - Caused by severe, disseminated gram-negative bacterial infections
      - Characterized by low blood pressure (defining feature), disseminated intravascular coagulation, and metabolic disturbances.
      - Early clinical and pathologic manifestations caused by high levels of TNF.
  - IL-12 activates NK cells, which produces IFN-γ to activate macrophages.
- In viral infections, dendritic cells, macrophages, etc, produce cytokines called type I interferons, which inhibit viral replication and prevent spread of infection.
  - Type I IFN called IFN-α is used to clinically treat viral hepatitis.

- **Other Plasma Proteins of Innate Immunity**
  - Plasma mannose-binding lectin (MBL) recognizes microbial carbs and opsonizes the microbes for phagocytosis or activates the complement cascade by the lectin pathway.
  - C-reactive protein (CRP) binds to phosphorylcholine on microbes and coats the microbes for phagocytosis by macrophages, which express a receptor for CRP.
    - Response known as **acute phase response.**
  - Extracellular bacteria and fungi are combated by phagocytes, the complement system, and by acute phase proteins.
  - Intracellular bacteria and viruses are combated by phagocytes, dendritic cells, and NK cells with cytokines providing the communication between leukocytes.

- **Evasion of Innate Immunity by Microbes**

-

Mechanism of immune evasion	Organism (example)	Mechanism
Resistance to phagocytosis	Pneumococci	Capsular polysaccharide inhibits phagocytosis
Resistance to reactive oxygen species in phagocytes	Staphylococci	Production of catalase, which breaks down reactive oxygen intermediates
Resistance to complement activation (alternative pathway)	*Neisseria meningitidis*	Sialic acid expression inhibits C3 and C5 convertases
	Streptococci	M protein blocks C3 binding to organism, and C3b binding to complement receptors
Resistance to antimicrobial peptide antibiotics	*Pseudomonas*	Synthesis of modified LPS that resists action of peptide antibiotics

- **Role of Innate Immunity in Stimulating Adaptive Immune Responses**
  - IIS generates molecules that act as second signals together with antigens to activate T and B lymphocytes.
  - The requirement for microbe-dependent second signals ensures that lymphocytes respond to infectious agents and not to harmless, noninfectious substances.
    - In experiments you can induce the adaptive response only with antigens, as long as you have an **adjuvant**, which elicits the same innate immune reactions as microbes do.
  - Microbes stimulate two types of second signals to activate T lymphocytes.
    1. Dendritic Cells and Macrophages express surface molecules called costimulators that work with antigens to activate T lymphocytes.
    2. Dendritic cells and Macrophages secrete IL-12 to stimulate differentiation of naïve T cells into effector cells.
  - The combination of antigen recognition and C3d recognition initiates the process of B cell differentiation into antibody-secreting cells.