IMMUNOLOGY

Definitions:

- Pathogen: organism has ability to cause disease
- Virulence: degree of pathogenicity of a given strain of MO
- Attenuation: reduction in the normal virulence of a pathogen
- Avirulent organism: organism losing its virulence completely
- Exaltation: ↑ in virulence

Non-Specific Defense Mechanisms (Innate Immune System)

Skin & mucus membrane:

- Intact skin is virtually impregnable to MO
- When damage occurs → invasion take place
- Many MOs fail to survive on skin surface due to inhibitory effects of FAs & lactic acid in sweat & sebaceous secretions
- Mucus, secreted by membranes lining inner surfaces of the body, acts as a protective barrier by trapping MOs & other foreign particles → removed by ciliary action (e.g. respiratory tract: coughing & sneezing)
- Many body secretions contain substances exert bactericidal action. Examples:
    - Lysozyme in tears, nasal secretions, & saliva
    - HCl in stomach → low pH
    - Basic polypeptides (such as spermine in semen)
- Normal bacterial flora

Phagocytosis:

- Phagocytes responsible for engulfment & digestion of MOs
- 2 types of phagocytic cells, both derived from totipotent bone marrow stem cell:
    - **Monocytes:** migrate into tissues → mature into macrophages
    - **Neutrophils** (also called polymorphonuclear leukocytes, PMNs)
- Another group of phagocytic cells are **macrophages:** large, longlived cells found in most tissues & lining serous cavities & lung
- Other macrophages recirculate to 2ry lymphoid organs, spleen, & lymph nodes
- Total body pool of macrophages constitutes **reticuloendothelial system (RES)**
- Phagocytosis: adherence of MO on surface of phagocyte → engulfment in vacuole (phagosome). Lysosomal granules fuse with it → phagolysosome
- Phagocytosis is enhanced by a family of proteins called complement

Complement system & other soluble factors:

- Group of heat-labile serum proteins
- When activated → destruction of bacteria
- Present in low conc in serum
- Virus-infected cells → interferons (glycoproteins) → interfere with viral replication & activate leucocytes (NK cells) → kill these cells & also tumor cells
- Interferons known collectively as “acute phase proteins”

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- Some interfeons enhance phagocytosis in conjunction with complement & upregulate Class I MHC → make infected cells more visible to Tc cells
- Main complement component is C3 & C5a
- Complement ⊕ B cells & regulate memory of immune system

Interferon (INF)	Source
α-INF	Leukocytes
β-INF	Fibroblasts
γ-INF	T lymphocytes & NK cells

Inflammation:

- Early symptom of injury to tissue due to microbial infection
- Dilatation of local arterioles & capillaries → ↑ blood flow to area → redness
- ↑ capillary permeability → fluid accumulation → localized edema → promote bacterial growth & pressure on nerves → pain
- Fibrin deposited → limit spread of MO
- Inflam mediators: lymphokines, derivatives of arachidonic acid, (PGs, LTs, TXs), & release of vasoactive amines (histamine & serotonin) from damaged cells
- Fever is the most common manifestation
- Thermoregulatory centre in hypothalamus regulates body temp affected by endotoxins (heat-stable lipopolysaccharides) of Gm -ve bacteria & by monokine secreted by monocytes & macrophages called IL-1 (endogenous pyrogen)
- ↑ body temp → ↑ Ab production & T-cell proliferation (beneficial effect of fever)

Host damage:

- MOs that escape phagocytosis in → regional lymph nodes via lymphatic vessels → thoracic duct → bloodstream → bacteraemia (indicate failure of 1ry defense)
- How MO overcome 1ry defense?
    - Hyaluronidase & streptokinase (by hemolytic streptococci):
        - Hyaluronidase dissolves hyaluronic acid (intercellular cement)
        - Streptokinase dissolves blood clots
    - Coagulase (by many *staph*) → coagulation of plasma surrounding MO → barrier protection against phagocytosis (coagulase = pathogenic MO)
    - Capsule outside cell wall serves a similar function
    - Lecithinase (by *Clostridium perfringens*) is Ca^{2+}-dependent → hydrolysis of erythrocytes & necrosis of other tissue cells
    - Collagenase (by *Cl. Perfringens*) → spread of infection
    - Leucocidins (by many strains of *streptococci*, most strains of *Staph aureus*, & most strains of Gm -ve bacteria) → kill leucocytes

Specific Defense Mechanism

- 2ry defense
- Appearance in serum of modified serum globulins (immunoglobulins; antibodies)
- Ag: proteins, polysaccharides, lipids, or mixtures. Have high molecular wt
- Release of free Ab into blood & body fluid ➔ **humoral immune response**
- Ag induce a 2nd type of response ➔ **cell-mediated immune response** → ⊕ appearance of 'sensitized' lymphocytes in the body → protection against MO that have ability to live & replicate inside cells of host
- Certain of these lymphocytes are also involved in rejection of tissue grafts
- 3 groups of bacterial Ag:
    - H-antigens: flagella. Chemical composition can vary b/w bacteria → different Abs
    - O-antigens: surface of bacterial cell wall (somatic Ag)
    - Surface Ag: polysaccharide capsule

Cells involved in immunity:

- Found mainly in lymphoreticular organs
- Divided into:
    - Primary lymphoid organs: thymus & BM
    - Secondary or peripheral organs: lymph nodes, spleen, Peyer's patches (lymphoid tissue in the submucosa of small intestine), & tonsils
- The predominant cell is lymphocyte
- Also, monocytes-macrophages, endothelial cells, eosinophils, & mast cells
- 2 types of immunity (humoral & cell-mediated) dependent on 2 distinct lymphocytes, B cells & T cells, respectively

Humoral immunity (B cells & T_{H1} cells):

- Ab-mediated immunity, is due rx b/w Ab & Ag. May involve complement
- Ag may possess multiple epitopes → each ⊕ Ab → Ab react with epitope
- B cell activation supplied by secretion of peptide molecules (cytokines or lymphokines) & T-cells (helper T cells)
- These peptide molecules (IL 2,4,5, & 6) ⊕ B cells proliferation → mature into longer-living, non-dividing memory cells (IgA, E, G) & plasma cells that secrete Ab
- Ags require assistance of TH cells termed T-dependent (TD) Ags
- Ags induce Ab synthesis without assistance of TH cells known as T-independent (Ti) Ags. Only one class of Ig (IgM) is synthesized with weak memory response
- 5 classes of Ig. Each type distinguished by polypeptide chain: one pair of heavy (large) chains & one pair of light (small) chains joined by disulphide bonds
- Ig: Fab fragment (Ag binding site) & FC fragment

Immunoglobulin classes: ***All have 2 Ag binding sites EXCEPT IgM has 10 sites

- **IgM:**
    - Synthesis after 1ry Ag stimulation
    - Largely confined to bloodstream, because of large size (M. wt)
    - Appear early in response to infection (imp in bacteraemia)

  - Single molecule can initiate complement cascade (i.e, potent activator)
  - IgM (with IgD) is the major Ig expressed on surface of B cells where it acts as Ag receptor
  - Minor memory response
- **IgG:**
  - The major Ig synthesized during 2ry response (most abundant Ig)
  - Can cross placenta → protection of newborn
  - Diffuses readily into extravascular spaces → neutralize bacterial toxins
  - Bind to MO → enhancing phagocytosis (opsonization) due to presence of receptor for FC on phagocytic cell surface
  - Complexes of IgG with bacterial cell activate complement, macrophages, & NK cells (through FC region of IgG)
- **IgA:**
  - In seromucous secretions (saliva, tears, nasal secretions, sweat, & secretions of lung, urinogenital & GI tracts
  - Protects external surfaces of body from microbial attack & prevent adherence of MO to mucosal cells → preventing entering body tissues
  - Protected from proteolysis by combination with another protein
- **IgD:**
  - Very low serum levels
  - The predominant surface component of B cells (on immature lymphocyte)
  - After activation of B cells → surface IgD can no longer be detected
  - IgD may be involved with differentiation of B cells
  - Play important role in early immune response
- **IgE:**
  - Very minor serum level (< IgD)
  - The major class of Igs
  - Binds with very high affinity to mast cells & basophils → release of TNF-α, histamine, LTs, & other vasoactive compounds➔ associated with immediate hypersensitivity reactions (hay fever & extrinsic asthma)
  - Play a role in immunity to helminthic parasites
  - Allergic people are hypersecretors of IgE

Humoral Ag-Ab reactions:

- 4 types of reactions:
  - Neutralization: soluble complex
  - Precipitation: insoluble precipitates enable phagocytes to eliminate soluble Ag from the body
  - Agglutination: aggregation of bacterial cells into agglutinates enabling phagocytes to eliminate these cells rapidly from the body
  - Cytotoxic reactions: Ab & cell react → cell lysis. (presence of complement necessary for this rx)

Complement:

- Group of functionally linked 20 proteins that interact with each other to provide many functions of humoral immunity & inflammation
- Most of complement components present in serum as proenzymes

- Activation of a complement molecule occurs as a result of proteolytic cleavage of the molecule
- Many components of the system serve as substrate of a prior component and, in turn, activate a subsequent component
- This pattern of sequential activation ➔ **complement cascade**
- Complement can be activated by 2 pathways:
    (a) Classical pathway: activated by Ag-Ab complex (IgM & IgG)
    (b) Alternative pathway: activated (in absence of Ag-Ab complex) by agents such as bacterial polysaccharide
- Complement cause lysis of Gram -ve MO by allowing lysozyme to reach peptidoglycan layer of MO
- Generation of C3b complex on surface of cell facilitates phagocytosis (as the phagocytes possess a receptor for C3b)
- C3a & C5a → release of histamine →↑ vascular permeability → flow of serum Ab into infected area. Also attract phagocytic cells

Cell-mediated immunity:

- Localized rx occur to MO that have ability to live & multiply within cells of host
- These rx mediated by lymphocytes, phagocytes, & Ab
- Lymphocytes originate in BM & processed by thymus gland ➔ T cells
- T cells express CD4 & CD8 antigenic markers
- HIV → destruction of TH
- Immune system distinguish b/w Ags via MHC (major histocompatibility complex) molecules
- Human MHC gene located on chromosome 6. Known as HLA (human leukocyte Ag)
- MHC classes:
    - Class 1: integral membrane proteins on surface of all cells & platelets
    - Class 2: expressed on surface of B cells, macrophages, monocytes, various antigen-presenting cells (APCs), certain T cells
    - Class 3: several complement components
- **Helper T cells (TH cells):**
    - Central cells of immune system
    - Activate other immune cells by secretion of cytokines
    - Cytokines produced by macrophages & monocytes (monokines), whilst those produced by lymphocytes (lymphokines)
    - TH cells express CD4 on their surface
    - APC → IL-1 → ⊕ TH cells to → IL-2 → differentiation of B cells (humoral response)
    - T cells responsible for delayed-type hypersensitivity rx secrete the following lymphokines:
        (1) Macrophage chemotactic factor (MAC)
        (2) Macrophage migration inhibitory factor (MIF): encourages macrophages to remain in area
        (3) Macrophage-activating factor (MAF)
- **Supressor T cells (Ts cells):**

  - Inhibit activation phase of immune responses by:
    - Production of cytokines with inhibitory function
    - Ability to absorb necessary growth & differentiation factors
    - Possible lysis of cells bearing stimulatory Ag in association with MHC molecules
    - Possible release of specific soluble factors (TsF) directed at either TH cell or B cell
- **Cytotoxic T cells (Tc cells):**
  - ①Virus-infected cells & tissue grafts & ②TH cells → ⊕ Tc cells formation
  - Tc cells express CD8 on their cell surface
  - Kill virus-infected cells by TNF-β, granzymes, & granulolysins

Natural killer (NK) cells:
- Lymphocytes in blood & lymphoid tissue, esp. spleen
- Derived from BM
- Kill tumor & virus-infected cells
- Killing is not specific for viral antigenic epitopes & not restricted by MHC mol
- Express CD2, CD 16, & CD56 with low-affinity for FC portion of IgG
- The most important role of NK cells is to provide a 1st line of defense against viral infections as they do not require prior exposure to Ag in order to respond
- ➔ effective before production of Ab & Tc cells
- NK cells possess receptor for Fc → adhere to target cells coated in Ab → destruction of that cell
- This phenomenon is known as "antibody-dependent cell-mediated cytotoxicity (ADCC)"

Autoimmunity:
- Causes:
  1. Evasion of tolerance to self antigens (e.g. lens or spermatozoa). These are confined to anatomical sites & do not have access to lymphoid tissue. So,exposure of to lymphoid cells as a result of surgery or accident → production of corresponding Abs
  2. Breakdown of tolerance mechanisms

Hypersensitivity:
- First 3 types involve interaction b/w Ag & Ab, and as onset of rx is rapid ➔ immediate hypersensitivity
- 4th type (delayed hypersensitivity) involves T cells & symptoms appear after 24 hr
- 5th type: Ab ⊕ cell function
- <u>Type I (anaphylactic) reactions:</u>
  - Mechanism: cAMP → cGMP → Phospholipase C → ↑ cytosolic Ca^{2+}
  - Rx b/w Ag & Ab on surface of mast cells → degranulation → release of vasoactive amoines → skin (urticaria), nasal mucosa (rhinitis), eyes (edema), bronchioles (extrinsic asthma), CVS (anaphylactic shock)
  - Ab are **IgE**, sometimes IgG Desensitization goal: ↓ IgE & ↑ IgG

- Type II (cytolytic or cytotoxic) reactions:
  - Rx b/w Ag & Ab on surface of cells → destruction by phagocytosis
  - Activation of complement system → lysis
  - ADCC reactions involving NK cells may also occur
  - E.g. AB0 & Rh incompatibility, cells whose surface altered by sensitizing drugs
  - Signs & symptoms: hemolytic anemia & thrombocytopenia
  - Ab are IgG & IgM
  - E.g. Rh fever, Haschimoto's thyroiditis, Goodpasture's syndrome, hemolytic anemia, Phimphigus, drugs (penicillin, cephalosporin, methyldopa)
- Type III (complex-mediated) reactions:
  - Due to presence of immune complexes in circulation or extravascular space
  - Complexes may localize in capillary networks (lungs, kidney, joints) → extensive tissue damage
  - Ab are IgM & IgG in large amounts in circulation
  - Two types:
    - Arthus reaction: local rx. Xss of Ab to AG
    - Serum sickness: xss of Ag to Ab → formation of soluble complexes → circulate & cause systemic reactions or deposited in kidneys, joints, & skin. E.g repeated admin of foreign (horse) serum
  - Other e.g. Subacute bacterial endocarditis, SLE, response to drugs (weeks after ttt)
- Type IV (delayed hypersensitivity) reactions:
  - Slow rx (1-3 d after exposure to Ag)
  - Rx b/w Ag-specific T cells (memory T_{H1} & Tc cells) & Ag → release of lymphokines & immunity
  - E.g. bacteria, viruses, fungi, graft rejection, contact dermatitis, Tuberculin test, Lepromin test, Celiac disease
- Type V (stimulatory hypersensitivity) reactions [Autoimmunity; autoimmune disorders]:
  - Cells possess surface receptor sites for chemical messengers of the body
  - If autoantibody produced against this site → it can combines with it → cause same effect as chemical messenger
  - E.g. thyrotoxicosis caused by autoantibody to receptor site to TSH

Types of immunity:
[Natural immunity]:

- Species immunity:
  - Humans are susceptible to diseases to which other animals are immune & vice versa
  - This is due to body temperature, biochemical differences, etc.
- Individual immunity:
  - Variation in natural immunity b/w individuals depend on state of health, age, hormonal balance, etc.

[Acquired immunity]:
Subdivided into actively acquired & passively acquired immunity, each of which may be induced naturally or artificially

- Active acquired immunity:
    - Produced as a result of an antigenic stimulus
    - This stimulus may occur:
        (a) *Naturally:* by clinical or subclinical infection
        (b) *Artificially:* by admin of Ag in the form of vaccine or toxoid
    - Long-lasting immunity
- Passive acquired immunity:
    - Admin of preformed Ab (there is no antigenic stimulus)
    - This can occur:
        (a) *Naturally:* by transplacental passage of Ab from mother to child & in breast milk
        (b) *Artificially:* by admin of Ab preformed in another human or in animals (horses), which are used for production of antitoxic sera (antitoxins, such as tetanus, diphtheria)
    - Produces immediate protection of short duration (depending on rate of degradation of Ab)

Hemolytic disease of newborn:

- When mother develops immune response against calls of fetus (alloimmune response)
- E.g. Mother is Rh -ve & fetus is Rh +ve (ttt in pregnancy: Rhogam)
- → hemolysis of fetal blood → anemia & jaundice

Hyposensitivity:

- Administration of allergen to desensitize the patient
- ➔ IgE & IgG (exposure to allergen → bypass IgE & activate IgG)
- Desensitization goal: ↓ IgE & ↑ IgG