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BT302 PPT Slide 01 TO 167

New Merged File date 2020

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Immunology

Overview of the Immune System as the Body's main Defense Mechanism

Immunology

Immunology, Immunity , Immune System & Immune Response

Terminologies

- Immunity
- Immune System
- Immune Response
- Immunology

Immunology

Infectious vs Non-Infectious diseases

Infections Vs Non-Infections

Infections

- Contagious
- Transmissible
- Communicable
- Pathogens (Bacteria, Virus, Fungus & Parasites) *e.g* Hepatitis

Non-Infections

- Non-Communicable
- Metabolic disorders
- Genetic Factors *e.g* Diabetes Mellitus

Immunology

Importance of Immune System

Importance of Immune System

Role of Immune System

- Defense against infections: AIDS
- Responsive against tissue grafts & newly introduced proteins: Barrier for tissue transplantation & gene therapy

Importance of Immune System

Role of Immune System

- Surveillance against cancers (Tumors)
- Immune Products *e.g* Antibodies use in diagnostics & therapeutics

Immunology

Difference between Innate & Adaptive Immune system

Difference B/W Innate & Adaptive Immune System

Two (02) types of Immunity

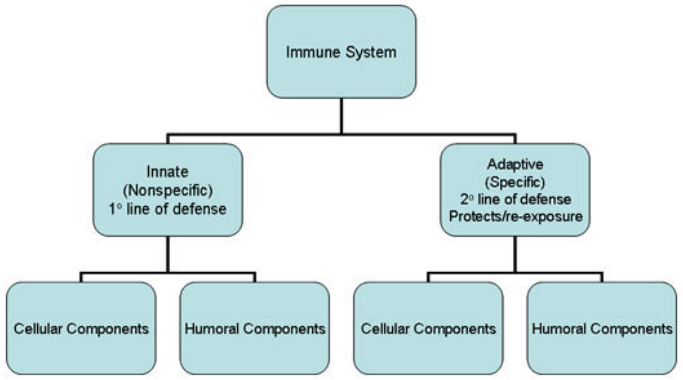
Innate Immune system

- Non-Specific
- First line of defense
- Readily available

Adaptive Immune System

- Specific
- Second line of Defense
- Needs to be activated

Difference B/W Innate & Adaptive Immune System



Difference B/W Innate & Adaptive Immune System

Differences B/W Innate & Adaptive Immune System

Innate Immune System	Adaptive Immune System
Response is antigen-independent	Response is antigen-dependent
There is immediate maximal response	There is a lag time between exposure and maximal response
Not antigen-specific	Antigen-specific
Exposure results in no immunologic memory	Exposure results in immunologic memory

Immunology

Components of Innate Immune System

Components of Innate Immune System

Three (03) components or barriers of Immunity against infections

- Anatomical (Physical) barriers
- Humoral (Secretory) barriers
- Cellular barriers

Immunology

Physical barriers of Innate Immune system

Physical Barriers of Innate Immune System

Anatomical Barriers

Mechanical Factors

- Skin
- Epithelium membrane (Squamous)
- Desquamation (Flushing of microbes)
- Peristalsis/ Cilliary movement (GIT)
- Flushing actions of tears & saliva
- Trapping actions of mucus lining of respiratory & GIT

Physical Barriers of Innate Immune System

Anatomical Barriers

Chemical Factors

- Fatty acids in skin
- Lysozymes & Phospholipases in tears, saliva, nasal secretions
- Defensins show antimicrobial peptides (GIT/Lungs)
- Low pH of sweat & GIT secretions
- Surfactants act as opsonins (Lungs)

Physical Barriers of Innate Immune System

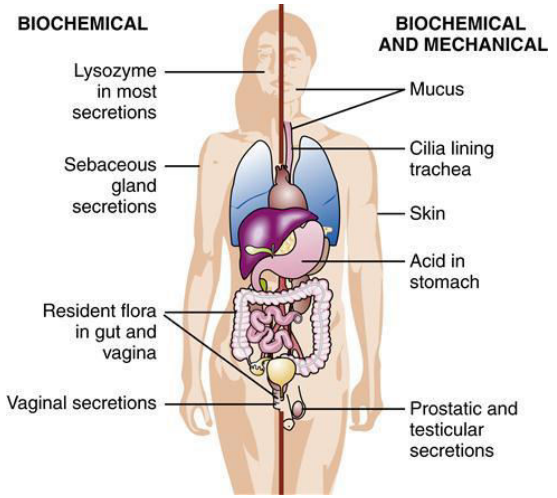
Anatomical Barriers

Biological Factors

- Normal flora of skin & GIT
- Prevents the colonization of bacteria
- By secreting toxins against foreign microbes
- Physical potential for utilization of nutrients by competing the pathogenic bacteria

Physical Barriers of Innate Immune System

Anatomical Barriers



http://www.onlinebiologynotes.com/anatomical-physico-chemical-barriers-immune-system/

Immunology

Secretory molecules of Innate Immune System

Secretory Molecules of Innate Immune System

Humoral barriers

- After breaching anatomical barriers, infectious agent penetrate the deep tissues
- Inflammation: tissue response
- Humoral (Secretory) barriers mediate the inflammatory process
- Signs of inflammation: pain, heat, redness, swelling & loss of tissue functions

Secretory Molecules of Innate Immune System

Humoral barriers

1)Complement System

- Complement Proteins
- Plasma proteins
- After activation, mediate the lysis of infectious agent

2)Coagulation System

- Coagulation Factors
- Plasma Proteins
- Chemotactic agent
- Antimicrobial acitivity e.g β-Lysins

Secretory Molecules of Innate Immune

Humoral barriers

3) Lactoferrin & transferrin

- Plasma proteins
- Ability to bind iron
- Deprive bacteria from iron

4) Interferons

- Plasma proteins
- Inhibit viral replication in cells

Secretory Molecules of Innate Immune System

Humoral barriers

5) Lysozymes

- Present in saliva, nasal secretions & tears
- Has ability to lyse bacterial cell wall after digesting peptidoglycan

6) Interlukin-1 (IL-1)

- Cytokine
- Released by immune cells after activation
- Induce fever & antimicrobial acute phase proteins

Immunology

Cells of Innate Immune system

Cells of Innate Immune System

Cellular barriers

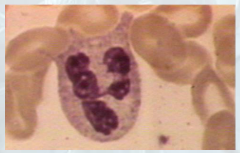
- In inflammatory process during infections, under the action of various humoral substances immune cells recruit towards the site of infection (Chemotaxsis)
- Immune cells from blood
- Immune cells from the inflamed tissues

Cells of Innate Immune System

Cellular barriers

1) Neutrophils

- Polymorphonuclear leucocytes (PMNs)
- Phagocytose the invading agent & kill intracellularly
- Immune cells from the inflamed tissue



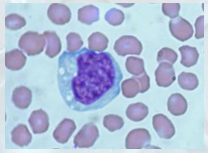
http://www.microbiologybook.org/ghaffar/neutrophil.jpg

Cells of Innate Immune System

Cellular barriers

2) Macrophages

- Phagocytic cells
- Tissue macrophages: Histocytes
- Circulating macrophages: Monocytes
- Involved in phagocytosis & intracellular killing



http://undergraduate.vetmed.wsu.edu/images

Cells of Innate Immune System

Cellular barriers

3) Natural Killer (NK) Cells

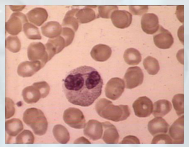
- Have the ability to kill viral infected cells non-specifically
- Also kill transformed or Tumorous cells
- Role in tumor surveillance

Cells of Innate Immune System

Cellular barriers

4) Eosinophils

- Blood Granulocytes
- Contain granules which are effective against parasitic infections
- Also cause the cytotoxicity of parasitic infected cells via receptors non-specifically



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Immunology

Phagocytosis

Phagocytosis

Phagocytosis

- The process of engulfing the invading or infectious agent by phagocytes
- Professional phagocytes
- Polymorphonuclear Phagocytes e.g Neutophils
- Mononuclear Phagocytes e.g monocytes, histocytes, Kupffer cells

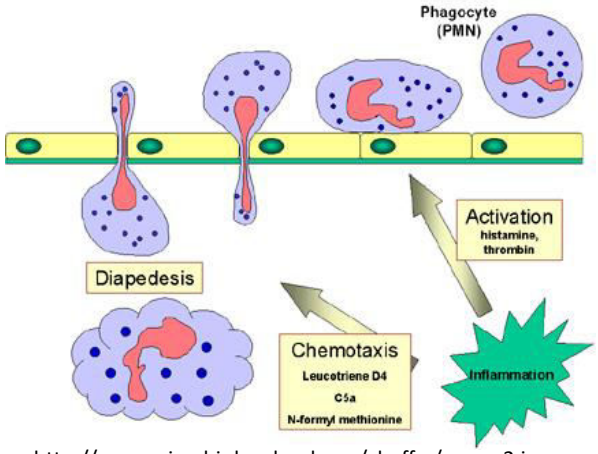
Phagocytosis

Process of Phagocytosis 1) Chemotaxis

- Chemo: Chemical, Taxis: Movement
- SOS signals from bacteria
- Secretory molecules like coagulation peptides, complement
- Migration of phagocytes across the capillary wall (Diapedesis)

Phagocytosis

Chemotaxis of Phagocytes



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Phagocytosis

Process of Phagocytosis 2) Attachment

- Phagocytes carry receptors for binding with bacterial surface components
- Fc receptors
- Complement receptors
- Scavenger receptors
- Toll like receptors (Pattern Recognition Receptors)

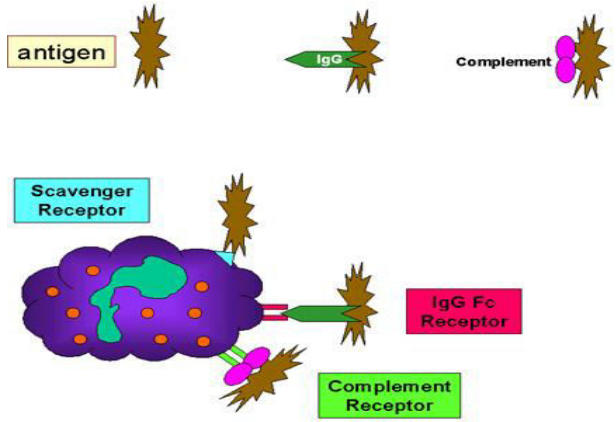
Phagocytosis

Process of Phagocytosis
2) Attachment

- On bacterial surface phagocyte's receptors interact with following components
- Opsonization
- IgG (Opsonins)
- Complement proteins
- Pathogen Associated Molecular Patterns (PAMPs) e.g LPS, flagellin etc

Phagocytosis

Attachment of Bacteria to Phagocytes



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Phagocytosis

Process of Phagocytosis
3) Phagosome Formation

- Once bacteria attach with its corresponding receptor on phagocyte
- Pseudopod extends around the bacterium to form a vesicle called as Phagosome
- Phagosome contains the trapped bacteria inside

Phagocytosis

Process of Phagocytosis
4) Phagolysosome Formation

- Phagosome with trapped bacteria fuse with secretory vesicles of phagocytes called "Lysosomes"
- Phagolysosome formation result in the action of hydrolytic enzymes i.e Lysozyme

Immunology

Intracellular killing

Intracellular killing

Intracellular Killing

- After phagocytosis the ingested bacteria is being killed by a process called as Intracellular Killing
- Two ways of intracellular killing
- Oxygen independent
- Oxygen dependent

Intracellular killing

Intracellular Killing

1) Oxygen Independent

- No need of oxygen for such kind of intracellular killing of bacteria
- Granules & Vesicles of phagocytes secrete hydrolytic proteins
- Those proteins are bacteriocidal in nature according to their modes of action

Intracellular killing

Mechanisms of Oxygen Independent Killing

Effector Molecule	Function
Cationic proteins (including cathepsin)	Damage to microbial membranes
Lysozyme	Splits mucopeptide in bacterial cell wall
Lactoferrin	Deprives proliferating bacteria of iron
Proteolytic and hydrolytic enzymes	Digestion of killed organisms

Intracellular killing

Intracellular Killing

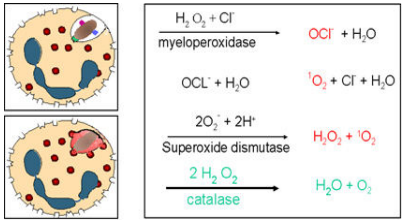
2) Oxygen Dependent

- Requirement of oxygen for such kind of intracellular killing of bacteria
- Also called "Respiratory Burst" as requirement of glucose & oxygen increased after phagocytosis
- Oxygen containing bacteriocidal radicals are produced

Intracellular killing

Intracellular Killing

2) Oxygen Dependent



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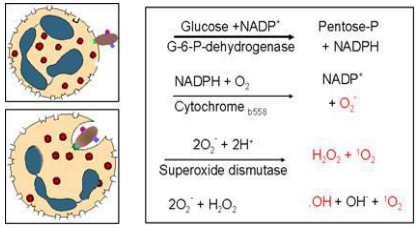
- Myeloperoxidase (MPO)dependent
- MPO from granules of phagocytes
- Halide ions (OCl-) are formed which are bacteriocidal

Intracellular killing

Intracellular Killing

2) Oxygen Dependent



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- Myeloperoxidase independent
- Involvement of Hexose monophosphate shunt
- Reactive Oxygen Species (ROS) e.g Superoxide radicals, hydrogen peroxide & singlet oxygen

Immunology

Complement System

Complement System

Complement System

- Serum Proteins
- Heat labile inactivated at 56°C for 30 minutes
- Lyse the bacterial cell
- Exist as Proenzymes which become activated after a cascade reaction

Complement System

Complement Functions of complement Proteins System

- Act as opsonin
- Chemoattractant for Polymorphonuclear Leucocytes (PMNs)
- Pro-Inflammatory: detrimental for host

Complement System

Complement System Activation

- Complement proteins are activated by following three pathways
- Classical Pathway
- Alternate Pathway
- Lectin Pathway

Immunology

Classical Pathway of Complement Activation

Classical Pathway of Complement Activation

Classical Pathway for Complement activation

- Activated by antibodies attached on pathogen (bacteria) Surface
- C1 protein is activated after interacting with Fc region of IgG or IgM
- C2 & C4 are activated after the C1 complex
- C3 is finally activated after the action of C2 & C4 in a cascade manner

End

Immunology

Alternate Pathway of Complement Activation

Alternate Pathway of Complement Activation

Alternate Pathway for Complement activation

- No need of antibody
- C3 is directly converted in the absence of antibodies
- Various co-factors of serum facilitate the activation of C3 sequentially
- Finally C3 helps in the lysis of bacterial cell

End

Immunology

Lectin Pathway of Complement Activation

Lectin Pathway of Complement Activation

Lectin Pathway for Complement activation

- Very similar to classical pathway
- In place of antibodies, mannose on the surface of specific pathogens are involved in activation

Lectin Pathway of Complement Activation

Lectin Pathway for Complement activation

- Mannose binding Lectins (MBL) in serum bind to surface of pathogen containing mannose in their cell wall e.g Fungus
- C3 proteins are produced after interaction of mannose & Lectins

Immunology

Effector Functions of Complement Proteins

Effector Functions of Complement Proteins

Effector Functions of Complement Proteins

- Opsonization (Opsonins)
- Chemoattraction (Chemoattractants)
- Anaphylaxsis (Anaphylatoxins)
- Pro-Inflammatory

End

Immunology

Pathology related to Complement Proteins

Pathology Related to Complement Proteins

Pathology related to Complement system

- Acute Inflammatory response
- Capillary dilatation
- Exudation of plasma proteins & fluids (Edema)
- Bronchoconstriction
- Mast cells degranulation (Allergic reaction)

End

Immunology

Cells & Organs of the Immune System

Immunology

Tissues of Immune System

Tissues of Immune System

Tissues of Immune System

- Two (02) major types of tissues of immune system based on their functions

1. Primary (Generative) or Central Lymphoid Organs
2. Secondary or Peripheral Lymphoid Organs

Immunology

Peripheral Lymphoid Organs

Peripheral Lymphoid Organs

Primary Lymphoid Organs

- Generative or Central Lymphoid Organs
- Involved in maturation of Lymphocytes
- Contain Stem cells for division and maturation
- Bone Marrow
- Thymus

Immunology

Secondary Lymphoid Organs

Secondary Lymphoid Organs

Secondary Lymphoid Organs

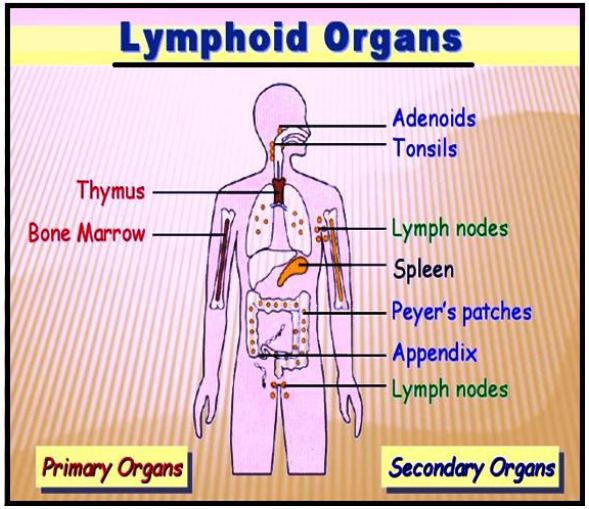
- Peripheral Lymphoid Organs
- Involved in providing adaptive immune response
- Site of interaction of antigen, antigen presenting cells & lymphocytes
- Various Anatomical Location

Secondary Lymphoid Organs

Secondary Lymphoid Organs

- Lymph Nodes
- Spleen
- Tonsils
- Adenoids
- Appendix
- Peyer's patches

Secondary Lymphoid Organs



http://exxamm.com/blog/Blog/14380/zxcvbnm4?

Immunology

Cell of Immune Systems

Cell of Immune Systems

Cells of Immune System

- Hematopoietic Stem Cells of Bone marrow (Primary Lymphoid Tissue) are the progenitor cells
- Two (02) main lineage originated from stem cells for immune cells

1. Lymphoid Lineage
2. Myeloid Lineage

Immunology

Lymphoid Lineage of Immune Cells

Lymphoid Lineage of Immune Cells

Lymphoid Lineage

- Lymphoid lineage progenitor cells give rise to the following immune cells
- B-Lymphocytes (Plasma cells or antibodies forming cells)
- T-Lymphocytes (T-Helper & Cytotoxic T-Cells)
- Natural Killer (NK) cells

Immunology

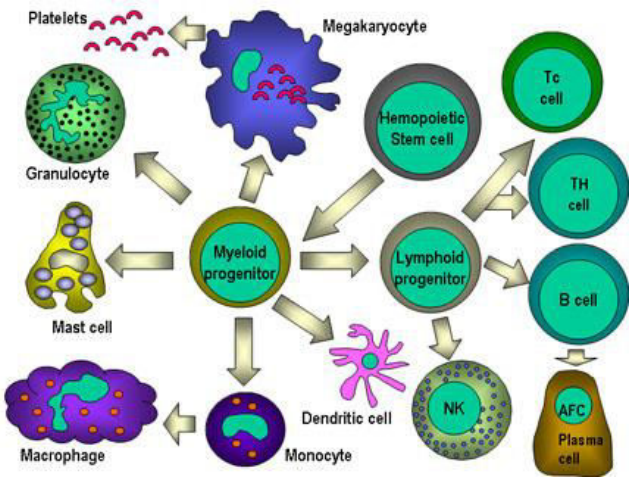
Myeloid Lineage of Immune Cells

Myeloid Lineage of Immune Cells

Myeloid Lineage

- Myeloid lineage progenitor cells give rise to the following immune cells
- Monocytes & Macrophages
- Dendritic cells
- Megakaryocytes
- Granulocytes

Cells & Organs of the immune system



http://www.microbiologybook.org/ghaffar/innate.htm

Immunology

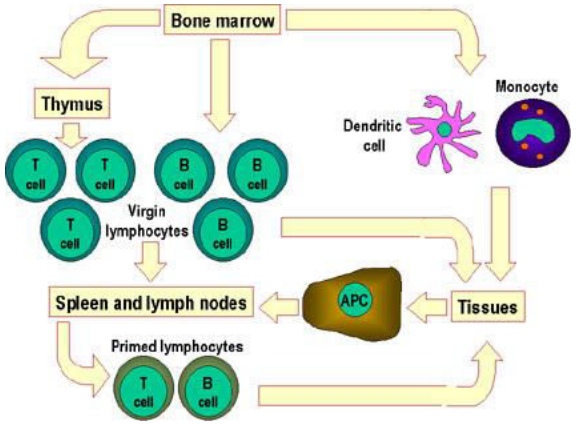
Lymphocyte Recirculation

Lymphocyte Recirculation

Lymphocyte Recirculation

- Naïve (Virgin) lymphocytes from primary lymphoid tissues move to secondary tissues
- Priming of lymphocytes
- Lymphocytes in blood enter in lymph node and percolate
- 1-2% of lymphocytes recirculate every hour

Lymphocyte Recirculation



http://www.microbiologybook.org/bowers/immune%20cells.htm

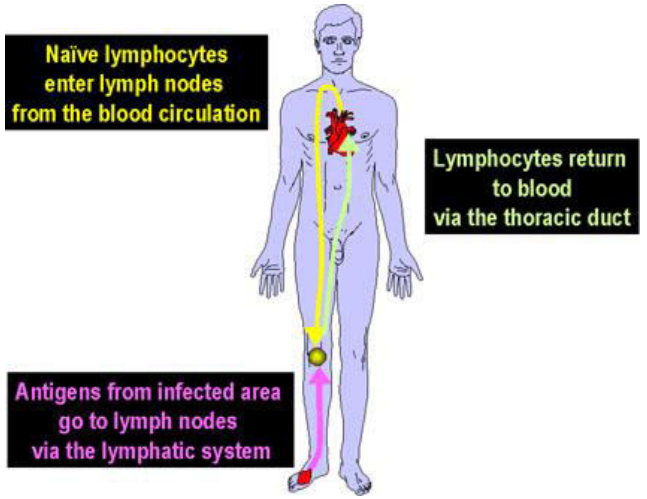
Immunology

Lymphocyte Migration & Localization

Lymphocyte Migration & Localization

- Chances of successful encounter of specific B & T lymphocytes with appropriate antigen is low
- By lymphocytes migration, chances of successful encounter may increase
- Lymphocytes from blood enter in lymph nodes and percolate through lymph nodes

Lymphocyte Migration & Localization



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Immunology

Clonal Selection of Lymphocyte

Clonal Selection of Lymphocyte

- T-Cell Receptors (TCR)
- Receptor Specificity
- Lymphocyte Repertoire
- After maturation, selection of lymphocytes which are non-reactive to self antigens

Clonal Selection of Lymphocyte

- Four principles

1) Unique Receptor Specificity

2) Lymphocyte Activation: Interaction with foreign molecule

3) Differentiation of lymphocyte: from single clone

4) Selection of lymphocytes bearing receptors against non-self molecules

Immunology

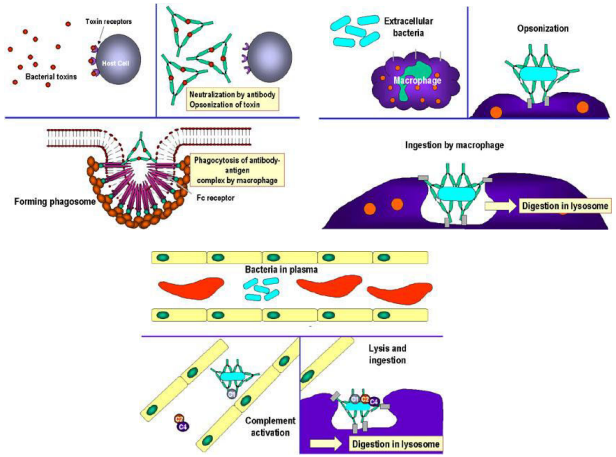
Control of Extracellular Pathogens

Control of Extracellular Pathogens

- Secretory immune molecules are effective against extracellular pathogens like antibodies & complement proteins
- Three ways of controlling

1) Neutralization
2) Opsonization
3) Complement activation

Control of Extracellular Pathogens



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Immunology

Control of Intracellular Pathogens

Control of Intracellular Pathogens

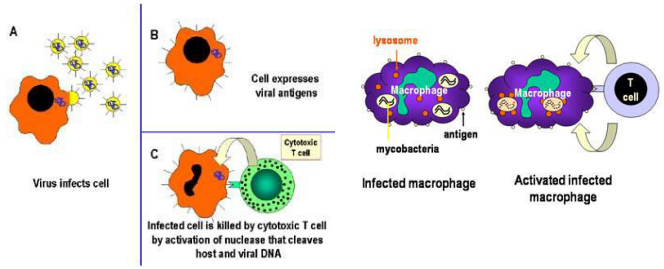
- Secretory immune molecules are ineffective against intracellular pathogens like viruses & intracellular bacteria
- Cell mediated immune response is the primary defense against intracellular pathogens
- T-Lymphocytes play role in cell mediated immunity

Control of Intracellular Pathogens

- Cell mediated immune response varies according to the residing site of the pathogen

1) Cytosolic site- Cytotoxic T-Cells e.g Viruses
2) Vesicular site- Helper T-cells e.g *Mycobacterium tubercluosis*

Control of Intracellular Pathogens



Control of Cytosolic Pathogens

Control of Vesicular Pathogens

http://www.microbiologybook.org/bowers/myco-macro2.jpg

Immunology

Properties of antibodies and antigens together with their structure, functions & interactions

Immunology

Comparison B/W Antigen, Immunogen & Hapten

Comparison B/W Antigen, Immunogen & Hapten

- **Antigen**

A substance that reacts with the products of specific immune response

- **Immunogen**

A substance that induces specific immune response

- **Hapten**

A substance that is non-immunogenic but can react with products of specific immune response

Comparison B/W Antigen, Immunogen & Hapten

- **Hapten/Carrier**

Hapten has the property of antigenicity but in combination with carrier molecule it become immunogen

- **Epitope/Antigenic determinant**

The portion of antigen that combines with products of immune system

Immunology

Factors influencing Immunogenicity (Contribution of the Immunogen)

Contribution of the Immunogen

- **Contribution of the Immunogen**

Following factors contribute in immunogenicity of Immunogen

1) Foreignness

Non-Self (Foreign) molecules induce immune response

2) Chemical Composition

Complex structured are more Immunogenic

Contribution of the Immunogen

- **Contribution of the Immunogen**

3) Physical Form

Particulate antigens: More immunogenic

Soluble antigens: Less immunogenic

4) Degradability

Easily degradable antigens are more immunogenic

Immunology

Factors influencing Immunogenicity (Contribution of the Biological System)

Contribution of the Biological System

1) Genetic factors

- Some substances are immunogenic in some species but not in others
- Responders vs Non-Responders
- Altered genes which encode for B & T cells receptors

2) Age

Very young & old individuals have diminished immune response

Immunology

Factors influencing Immunogenicity (Method of Administration)

Method of Administration

Administration of Immunogen

1) Dose

- Optimal dose of immmunogen causes immune response
- Above or below of optimal dose remain insufficient for appropriate immune response

Method of Administration

Administration of Immunogen

2) Route

- Route of immunogen administration alter the nature of immune response
- Subcutaneous route: more immunogenic
- Intravenous & Gastric route: less immunogenic

Method of Administration

Administration of Immunogen

3) Adjuvants

- Substances which increase the immune response of an immunogen
- Used with vaccine in vaccination
- Alum or Aluminium hydroxide
- Show undesirable side effects i.e fever

Immunology

Chemical Nature of Immunogen

Chemical Nature of Immunogen

Chemical nature of Immunogen

1) Proteins

- Good Immunogens
- Most immunogens
- Pure & Conjugated

2) Polysacchrides

- Pure & Lipopolysacchrides are good immunogenss

Chemical Nature of Immunogen

Chemical nature of Immunogen

3) Nucleic Acids

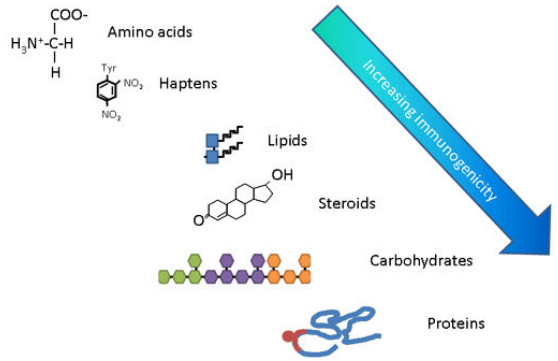
- Poor Immunogens
- Immunogenic in single stranded form
- Complex with proteins

4) Lipids

- Non-Immunogenic
- Can be haptens

Chemical Nature of Immunogen

Immunogenicity



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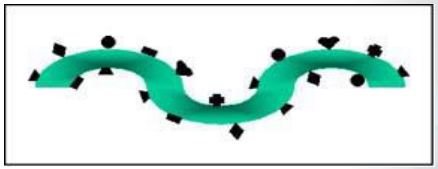
Immunology

Types of Antigens

(T-Cell dependent & Independent)

Types of Antigens

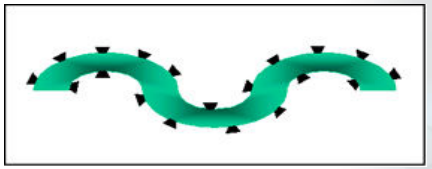


http://www.microbiologybook.org/mayer/ag-2a.jpg

T-dependent antigens

- Require T-cells
- B-cells are activated with the help of T-cells for antibodies production
- Protein in nature
- Contain variety of epitopes with few copies

Types of Antigens



http://www.microbiologybook.org/mayer/ag-1.jpg

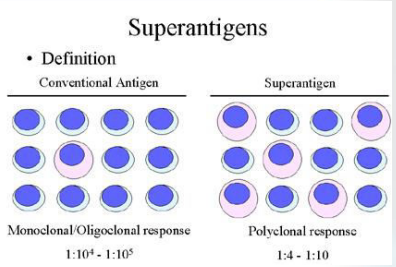
T-independent antigens

- Not Require T-cells
- B-cells are activated directly without the help of T-cells for antibodies production
- Polysacchride in nature
- Contain same kind of epitopes in polymeric form
- More resistant to degradation

Immunology

Sperantigens

Superantigens



http://www.microbiologybook.org/mayer/antigens2000.htm

Superantigens

- T-dependent antigens
- Conventionally activate small fraction of T-cells
- Superantigens can activate 25% of T-cells polyclonally
- Hyperactivation of T-cells by superantigens
- Bacterial antigens e.g Staphlococcal entertoxin (Food Poisoning)

Superantigens

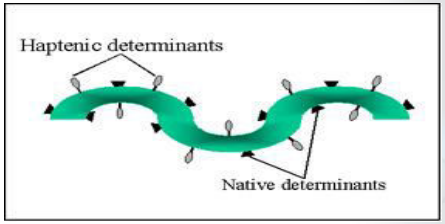
Superantigens

- Bacterial antigens e.g Staphlococcal entertoxin (Food Poisoning), Staphloccocal Exfoliatin toxin (Scalded Skin Syndrome), Staphlococcal Toxic shock toxin (Toxic Shock Syndrome)
- Viral & other microorganisms antigens can also be superantigns

Immunology

Hapten-Carrier Conjugate

Hapten-Carrier Conjugate



http://www.microbiologybook.org/mayer/ag-3.jpg

- Immunogenic molecules to which hapten is non-immunogenic
- Carrier is immunogenic in nature
- Hapten bounded with carrier covalently
- Structurally contain Haptenic determinants & Carrier determinants
- Immune response is being determined by Carrier determinant

Immunology

Antigenic determinants recognized by Innate Immune System

Antigenic determinants/Innate Immune

- No specificity
- Broad Molecular pattern called Pathogen associated molecular patterns (PAMPs) present on different pathogens
- PAMPs are recognized by Pattern recognition Receptors (PRRs) on the surface of immune cells

Antigenic determinants/Innate Immune

PAMPs	PRRs	Effector Function
LPS	Toll Like Receptors-4 (TLR-4)	Macrophage activation
Flagellin	TLR-5	Macrophage activation
Microbial cell wall components	Complement	Opsonization, Complement activation

Immunology

Characteristics of Immunoglobulins (Antibodies)

Characteristics of Immunoglobulins

Immunoglobulins

- Glycoproteins
- Produced by plasma cells in response to immunogens
- Globular proteins responsible for immunity (Humoral)
- Has ability to combine specifically with antigens

Characteristics of Immunoglobulins

Characteristics

Antigen (Ag) binding

- Primary function
- To bind specifically with epitopes of antigens
- Paratope: Binding site

Valency

- Number of antigenic determinants which can bind with immunoglobulin
- Minimum is two (02)

Characteristics of Immunoglobulins

Characteristics

Effector functions

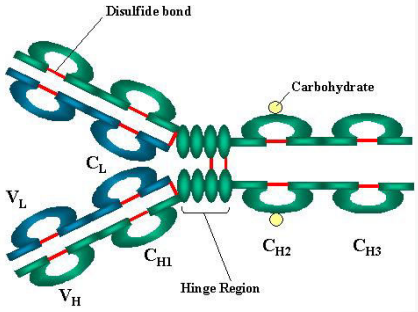
- After binding with antigen, there is no primary direct biological function
- Secondary effector functions

1) Complement activation
2) Binding to various cell types via defined receptors(Fc receptors)

Immunology

Basic Structure of Antibodies

Basic structure of Antibodies



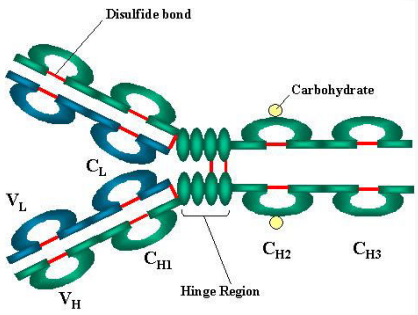
http://www.microbiologybook.org/mayer/stru-2.jpg

Immunoglobulins

- Composed of following structures

1) Heavy & Light chains: Four chains, 02 identical light chains, 02 identical heavy chains
2) Disulfide bonds: Interchain & Intrachain
3) Variable & constant regions: based on amino acid sequences

Basic structure of Antibodies



http://www.microbiologybook.org/mayer/stru-2.jpg

Immunoglobulins

4) Hinge region: makes antibodies flexible to change its shape while performing function

5) Domains: Folded regions which contain an intra-chain disulfide bond

6) Oligosaccharides: attached on CH2 domain in most of immunoglobulins

Immunology

Structure of the Variable Region

Structure of the Variable Region

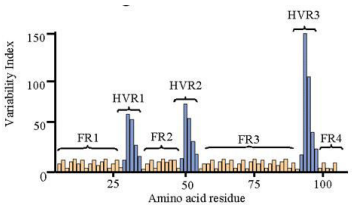
Variable region

- Present on heavy & light chains of Immunoglobulins
- Two sub-regions

1) Hypervariable (HVR)

- Based on variability of amino acid sequences
- Complementarity determining region

Structure of the Variable Region



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Variable Region

2) Framework Regions

- Regions between hypervariable regions
- Groups & sub-groups of immunoglobulins
- Products of different variable region genes

Immunology

Antibodies Fragments Structure/Function

Antibodies Fragments

Antibodies Fragments

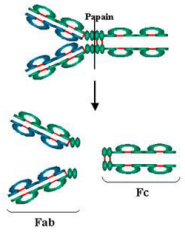
- Produced by proteolytic enzymes i.e papain
- Two fragments are produced which have structure & function relationship

1) Fab
2) Fc

Antibodies Fragments

Immunoglobulin Fragments: Structure/Function Relationships

- Fab
  - Ag binding
  - Valence = 1
  - Specificty determined by V_H and V_L
- Fc
  - Effector functions



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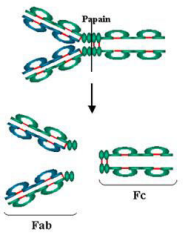
1) Fab

- Fragment for antigen binding (Fab)
- Papain causes the cleavage at hinge regions to produce two identical fragments containing one heavy & one light chain
- Having monovalent valency for antigen binding

Antibodies Fragments

Immunoglobulin Fragments: Structure/Function Relationships

- Fab
  - Ag binding
  - Valence = 1
  - Specificty determined by V_H and V_L
- Fc
  - Effector functions



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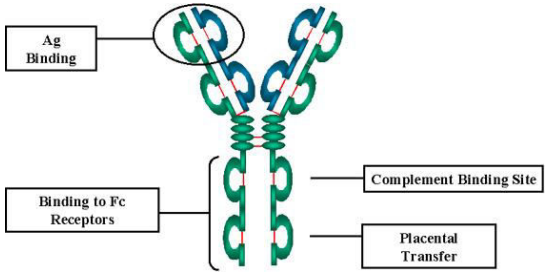
2) Fc

- Crystalizable Fragment (Fc)
- Contain two heavy chains with CH2 & CH3 domains
- Performed effector functions

Antibodies Fragments

Immunoglobulin Fragments:
Structure/Function Relationships



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Immunology

Classes of Antibodies

Classes of Antibodies

Classes

- Classes of antibodies: based on amino acid sequences in the constant region of heavy chains
- Five different heavy chains on which classes of antibodies are based

Classes of Antibodies

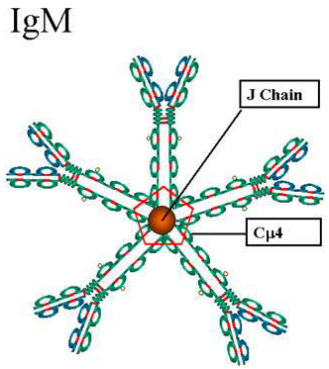
Classes

1) Gamma chain- IgG
2) Mu chain- IgM
3) Alpha chain-IgA
4) Delta chain-IgD
5) Epsilon chain-IgE

Immunology

IgM/IgG Properties & Functions

IgM & IgG Properties & Functions



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IgM

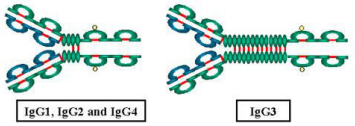
- Carry Mu heavy chain
- Structurally, IgM exist in pentamer generally as secretory form
- Monomer form also exsist but membrane bounded on B-Cells
- All five molecules are joined through J-chain

IgM & IgG Properties & Functions

IgM

- Third most common serum antibody
- First antibody made by virgin B-cells
- Due to structure, IgM is a good complement fixing antibody
- Bind to surface of microorganisms for removal by phagocytosis

IgM & IgG Properties & Functions



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IgG

- Carry Gamma heavy chain
- Structurally, IgG exist in monomer
- Has subclasses like IgG1,IgG2,IgG3 & IgG4 based on number of disulphide bonds & length of hinge region

IgM & IgG Properties & Functions

IgG

- Major antibody of serum-75% of total antibodies
- Also major in extravascular space
- Complement fixing
- Role in placental transfer: by FcR on placental cells
- Good opsonin

Immunology

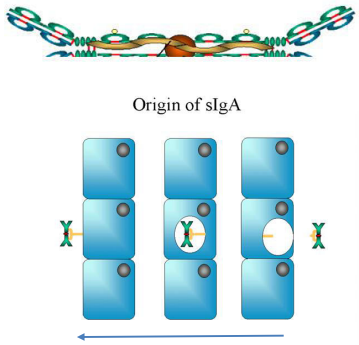
IgA/IgE/IgD Properties & Functions

IgA/IgE/IgD Properties & Functions

IgA

- Second most common serum antibody
- In Serum, IgA exist as monomer
- Mostly IgA is present in secretions i.e saliva, tears, mucus & colostrum
- Responsible for "Mucosal Immunity"

IgA/IgE/IgD Properties & Functions



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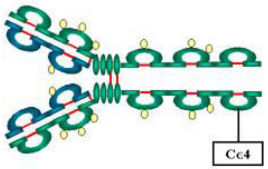
IgA

- In secretions. two molecules of IgA are linked with J chain
- sIgA contains secretory piece
- Secretory piece is added to IgA in epithelial cells
- IgA doesn't fix complement unless aggregated

IgA/IgE/IgD Properties & Functions

IgE



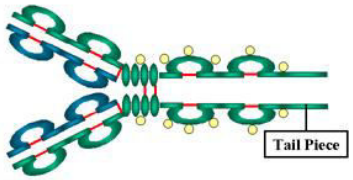
http://www.microbiologybook.org/mayer/stru-14.jpg

IgE

- Least common serum antibody
- IgE exist as monomer
- Involved in allergic reactions (Anaphylaxis)
- Degranulation of basophils after IgE binding
- Responsible for parasite killing: IgE mediated
- Not fix complement

IgA/IgE/IgD Properties & Functions

IgD



http://www.microbiologybook.org/mayer/stru-13.jpg

IgD

- Very low level serum antibody
- Role in serum is unknown
- Primarily found on B-cells as receptor for antigen with help of tail piece
- Exist as monomer
- Doesn't fix complement

Immunology

Types vs Sub-types of Antibodies

Types vs Sub-Types of Antibodies

Types

- Based on kind of light chains of antibodies
- Following two light chains

1) Kappa light chains
2) Lambda light chains

- Based on differences in amino acid sequences in constant regions of light chains e.g IgG Kappa, IgG Lambda

Types vs Sub-Types of Antibodies

Sub-Types

- Light chains are divided into subtypes based on differences in amino acid sequences in constant region
- Following Subtypes of light chains
- Lambda chains: 4 subtypes e.g L1, L2,L3 & L4
- Kappa chains: 2 subtypes e.g K1 &K2

Immunology

Antigen & Antibody Reactions

Antigen & Antibody Reactions

Nature of Ag & Ab reactions

- Interactions B/W antigen & antibody (Epitope & Paratope)
- Serological reactions
- One is known & one is unknown
- Lock & Key Concept

Antigen & Antibody Reactions

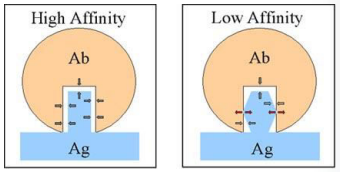
Nature of Ag & Ab reactions

- Non-Covalent bonding
- Hydrogen bonds
- Vander Wall forces
- Electrostatic forces
- Reversibility

Immunology

Factors Effecting on Antigen & Antibody Tests

Factors effecting on Ag & Ab Tests



http://www.microbiologybook.org/mayer/rx-2.jpg

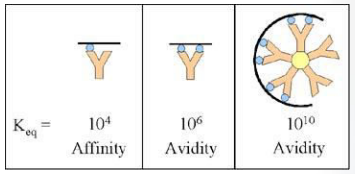
Factors

- Easily detectable Ag & Ab reactions

1) Affinity

- Strength of binding B/W single antigenic determinant & single antibody site
- Sum of attractive & repulsive forces
- Higher the affinity of Ab for Ag, more stable interaction

Factors effecting on Ag& Ab Tests

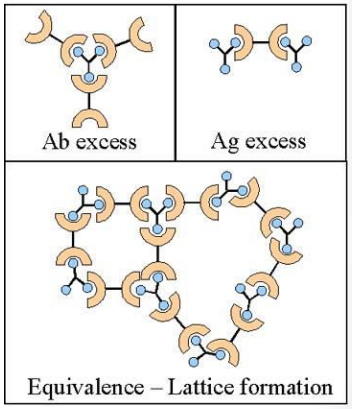


http://www.microbiologybook.org/mayer/rx-4.jpg

2) Avidity

- Strength of binding of antigen with many antigenic determinant & multivalent antibody
- Overall strength B/W multivalent antigens & antibodies
- Avidity is influenced by valency of both Ag & Ab
- More avidity more stable & easy to detect

Factors effecting on Ag& Ab Tests



http://www.microbiologybook.org/mayer/rx-6.jpg

3) Ag & Ab ratio

- Ag & Ab ratio determines the nature of complex
- Lattice formation: Equivalence B/W Ag & Ab ratio
- Larger Ag & Ab complex: Easily detectable

Factors effecting on Ag& Ab Tests

4) Physical form

- Physical form of antigen determines the nature of Ag & Ab reaction
- Particulate form of Ag: Agglutination reactions
- Soluble form of Ag: Precipitation reactions

Immunology

Agglutination Reactions

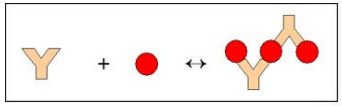
Agglutination Reactions

Agglutination

- Particulate nature of antigen causes the reaction of antibody to form visible clumps (Agglutinate).
- Antibodies: Agglutinins
- Nature of particle

1) RBC: Hemagglutination
2) Bacteria: Bacterial agglutination
3) Latex: Latex Agglutination

Agglutination Reactions



http://www.microbiologybook.org/mayer/rx-7.jpg

Hemagglutination

- Qualitative: Blood group typing (ABO & Rh)
- Quantitative: For determining the quantity of antibodies
- Titer: the lowest conc. Of Ab which causes agglutination or the max. dilution of serum which causes agglutination

Agglutination Reactions

Applications of Agglutination

- Blood grouping: ABO & Rh for both either on the basis of antigens of RBC or antibodies of serum
- Assessing bacterial infections e.g Widal test for diagnosis of Typhoid fever

Immunology

Precipitation Reactions

Precipitation Reactions

Precipitation (Diffusion)

- Soluble nature of antigen causes the reaction of antibody to form precipitate in a medium
- Immunoprecipitation
- Antibodies: Precipitins
- Medium used for visualization of Ag & Ab reaction e.g Agar
- Both Ag & Ab are soluble form in serum

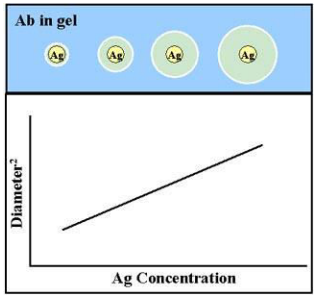
Precipitation Reactions

Precipitation

- On the basis of diffusion of each molecule i.e Ag & Ab, two types of precipitation reactions

1) Single immunodiffusion or precipitation
2) Double immunodiffusion or precipitation

Precipitation Reactions



http://www.microbiologybook.org/mayer/rx-13.jpg

Single Immunodiffusion

- Also called Radial Immunodiffusion
- Antibody is already incorporated in agar
- Serum containing antigen is added
- Antigen diffuses in agar & react with Ab to form visible precipitate
- Used for determining the level of serum immunoglobulins e.g IgA

Precipitation Reactions

Double Immunodiffusion

- Both antigen & antibody is added in the medium separately
- Ag & Ab are allowed to react together and reached at equivalence to form precipitate
- Qualitative analysis of complex mixture of Ag can be determined
- Purity of isolated serum proteins can be checked

Immunology

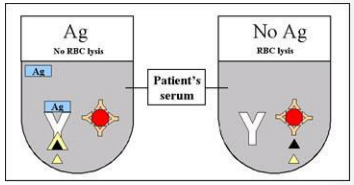
Complement Fixation Tests

Complement Fixation Test

Complement Fixation

- Ag & Ab reaction which can be detected on the basis of ability to fix or consume complement
- Used for determining good complement fixing antibodies e.g IgG or IgM
- Unknown Ag : Known Ab
- Complement proteins
- Presensitized RBC with anti RBC antibodies

Complement Fixation



http://www.microbiologybook.org/mayer/rx-24.jpg

Complement Fixation Interpretation

- Lysis of RBC: No Complement fixation by Ag & Ab complex: No Ag: Negative CFT
- No Lysis: Complement fixation by AG & Ab complex: Ag is present: Positive CFT
- CFT is used for determining Gonococcal Ab in serum

Immunology

Enzyme Linked Immunosorbent Assay (ELISA)

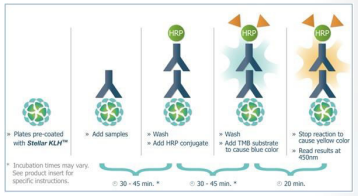
ELISA

ELISA

- Ag & Ab reaction which can be detected on the basis of substrate utilization by enzyme
- Solid phase Immunoassay
- Used for determining either unknown Ag or Ab

1) Direct ELISA
2) Indirect or Sandwich ELISA

ELISA

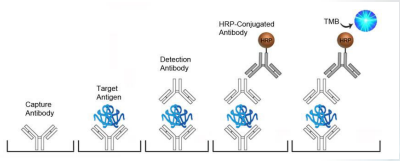


https://www.stellarbiotechnologies.com/products/order-stellar-klh-elisa-kits

Direct ELISA

- Unknown Ab can be determined
- Known Ag is coated on solid phase (Glass surface)
- Serum containing unknown Ab is added
- Another ab which is precoated with enzyme e.g horseradish peroxidase
- Substrate:H_2O_2

ELISA



https://www.lsbio.com/elisakits/human-f7-factor-vii-elisa-kit-sandwich-elisa-ls-f10416/10416

Indirect (Sandwich) ELISA

- Unknown Ag can be determined
- Known Ab is coated on solid phase (Glass surface)
- Serum containing unknown Ag is added
- Another Ab which is precoated with enzyme e.g horseradish peroxidase
- Substrate: H_2O_2

ELISA

Applications

- Used for determining viral antigens in patient's serum e.g Hepatitis B surface Antigens (HbsAG)
- For determination of antibodies against viruses e.g Anti HCV antibodies
- For serum cytokine levels e.g IL-1, TNF-a etc

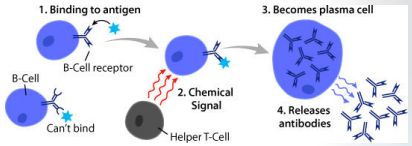
Immunology

Genetics of Antibody Structure & Diversity

Immunology

Antibody Formation

Antibody Formation



https://www.quora.com/What-are-the-differences-between-B-Cells-and-T-Cells

Antibody Formation

- A process of immune response against antigen or immunogen
- Can be T-independent or dependent
- B-cells recognize the Ag with its specific receptor
- Transformation of B-cells into plasma cells
- Plasma cells secrete antibodies

Immunology

General Characteristics of Antibody Response

General Characteristics of Antibody Formation

General Characteristics

- Antibody formation process is well controlled mechanisms with following characteristics

1) Self/Non-Self Discrimination

- Antibodies would be reactive against non-self antigens
- Reactivity against self Ag: Autoimmunity

General Characteristics of Antibody Formation

General Characteristics

2) Memory

- Remembering the nature of antigen
- Illicit memory response against same antigen
- Anamnestic response
- Robust way of clearing antigen
- B memory cells

General Characteristics of Antibody Formation

General Characteristics

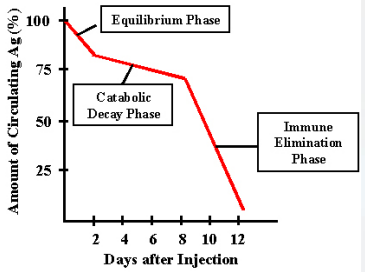
3) Specificity

- High degree of specificity of antibodies against specific antigens
- Less chances of cross reactivity
- Characteristic of adaptive immune response

Immunology

Fate of Immunogen

Fate of Immunogen



http://www.microbiologybook.org/mayer/ab1-1.jpg

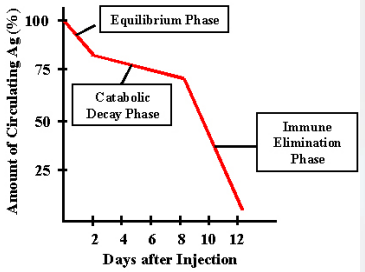
Fate of Immunogen Primary Injection

- Immunogen enters in the body first time (Primary Injection)
- Following four phases for kinetics of immunogen clearance

1) Equilibrium Phase

- Rapid diffusion process
- As equilibrates B/W vascular & extravascular components by diffusion

Fate of Immunogen



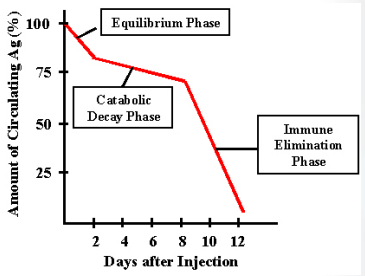
http://www.microbiologybook.org/mayer/ab1-1.jpg

Fate of Immunogen Primary Injection

2) Catabolic decay phase

- Host immune cells cause the decay of Ag
- Cells & enzymes involved in this phase
- Macrophages & phagocytic cells
- Duration depends upon the nature of immunogen & host

Fate of Immunogen



http://www.microbiologybook.org/mayer/ab1-1.jpg

Fate of Immunogen Primary Injection

3) Immune Elimination phase

- Newly synthesized antibodies combines with Ag to form Ag/Ab (Immune) complexes
- Immune complexes: eliminated by phagocytosis
- Ab appears in serum only after this phase get over

Fate of Immunogen

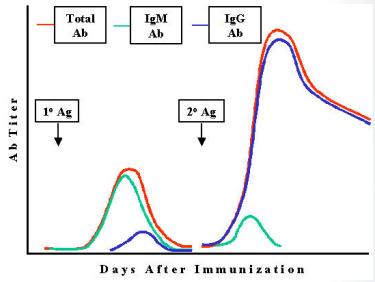
Fate of Immunogen Secondary Injection

- If there is circulating Ab: rapid immune elimination of Ag
- No circulating Ab: All three phases occur but immune elimination phase will be rapid

Immunology

Primary & Secondary Antibody Response

Primary & Secondary Ab Response



http://www.microbiologybook.org/mayer/ab1-4a.jpg

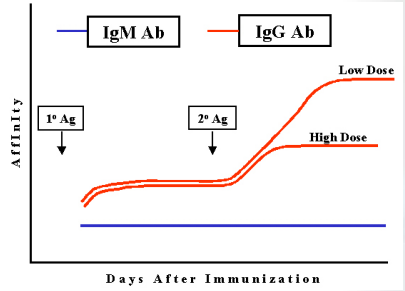
Primary Ab response

- First kind of antibody response against antigen
- Major class of antibody is IgM
- Ab are with less affinity & Less persistent

Secondary Ab response

- Second kind of antibody response against antigen
- Major class is IgG but may IgE or IgA but less IgM

Primary & Secondary Ab Response



http://www.microbiologybook.org/mayer/ab1-5.jpg

Primary Ab response

- Ab are with less affinity

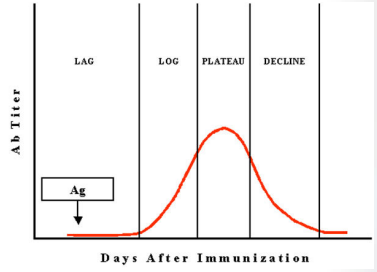
Secondary Ab response

- Ab with high affinity
- With low dose of Ag, Ab have high affinity as compare to high dose (Affinity maturation)

Immunology

Kinetics of antibody response against T-dependent antigens

Kinetics of Ab/T-dependent Ag



http://www.microbiologybook.org/mayer/ab1-2.jpg

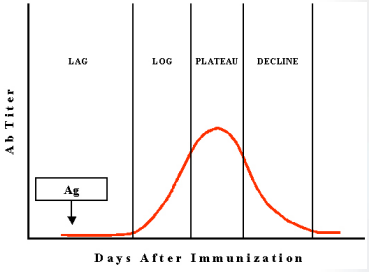
Primary Ab response

- Four phases

1) Inductive or Lag phase

- Antigen is recognized as foreign
- Immune cells start to proliferate & differentiate in response to antigen
- Duration: Usually 5-7 days

Kinetics of Ab/T-dependent Ag



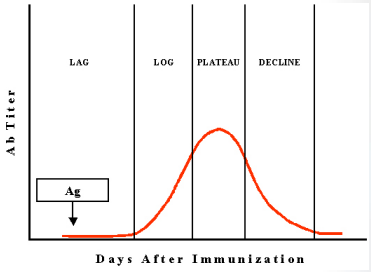
http://www.microbiologybook.org/mayer/ab1-2.jpg

Primary Ab response

2) Log or Exponential phase

- Ab conc. Increase rapidly
- B-cells proliferation
- B-cells differentiation into plasma cells to secrete more antibodies

Kinetics of Ab/T-dependent Ag



http://www.microbiologybook.org/mayer/ab1-2.jpg

Primary Ab response

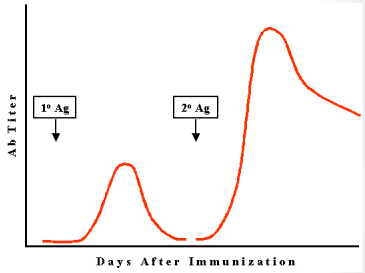
3) Plateau or Steady State phase

- Ab synthesis is balanced by Ab decay
- No net increase in Ab concentration

4) Decline or Decay Phase

- Rate of Ab decay exceeds
- Fall in Ab level
- Base line Ab level

Kinetics of Ab/T-dependent Ag



http://www.microbiologybook.org/mayer/ab1-3.jpg

Secondary Ab response

- Second time (Anamnestic) exposure would also induce the same four phases but with different kinetics

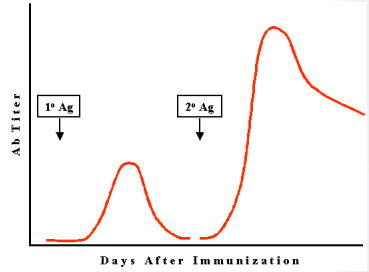
1) Lag phase

- Shorter as compare to primary exposure

2) Log phase

- More rapid & sharp
- Higher levels of Ab in short time

Kinetics of Ab/T-dependent Ag



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Secondary Ab response

3) Plateau or Steady state phase

No plateau

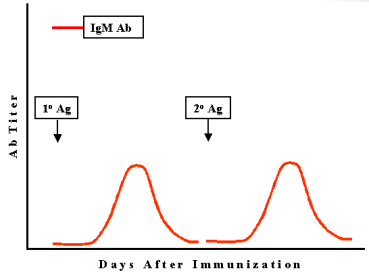
4) Decline phase

- Less rapid & sharp
- Antibodies may persist for days, months or even yeas due to memory response

Immunology

Kinetics of antibody response against T-independent antigens

Kinetics of Ab/T-independent Ag



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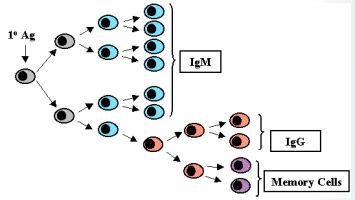
T-independent Ag

- Mainly IgM production
- All those phases in primary response
- No secondary response as same phases in second time exposure to Ag
- No memory response

Immunology

Cellular Events during Antibody Response

Cellular events during Ab Response



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Primary Response

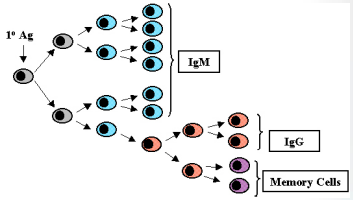
Lag phase

- Clones of B & T-cells bind to antigens with receptor
- B-Cells differentiate into plasma cells
- Plasma cells start to secrete Ab

Log Phase

Plasma cells initially secrete IgM as Mu chains gene is close to rearranged VDJ regions

Cellular events during Ab Response



http://www.microbiologybook.org/mayer/ab1-7.jpg

Primary Response

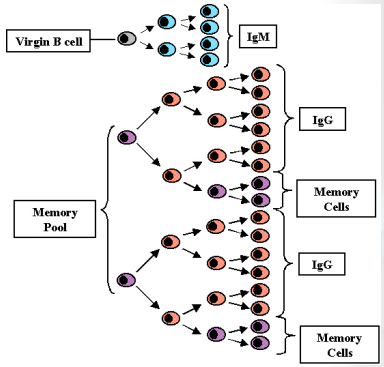
Plateau phase

- Due to Ag depletion & T-cells are no longer active
- Plasma cells begin to die
- Newly synthesized Ab equilibrates

Decline Phase

- No new Ab formation
- Most of plasma cells die

Cellular events during Ab Response



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Secondary Response

- Memory cells pool: Comprised of T & B cells activated during primary response
- Mostly memory pool cells are activates
- Ab class switching: IgM to IgG
- Mostly IgG in secondary response
- Some plasma cells differentiate into memory

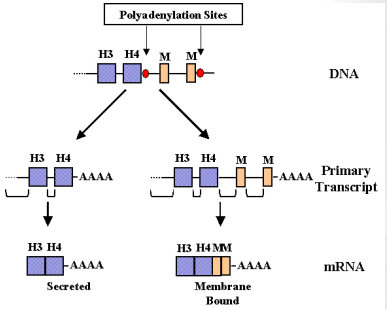
Immunology

Membrane & Secreted Antibodies

Membrane & Secreted Antibodies

- Membrane bounded & secreted Ab from a same B-cell have same specificity
- Role of Immunoglobuin gene in determining the specificity
- Polyadenylation sites in gene for Ig determine the nature of immunoglobulin

Membrane & Secreted Antibodies



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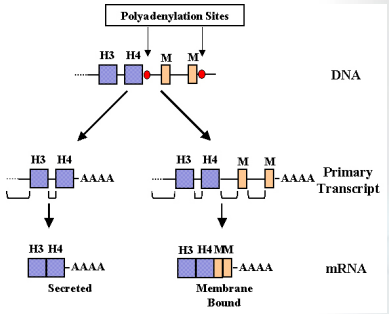
- There are two kinds of polyadenylation sites present in gene of Ab

1) After the exons of last heavy chain (H)
2) After the exons which encode for trans-membrane domain (M)

- If the first sites is used the pre-mRNA processed for secretory form of immunoglobulin

Membrane & Secreted Antibodies



http://www.microbiologybook.org/mayer/ab1-11.jpg

- If the second polyadenylation site is used the pre-mRNA processed for membrane bounded form of immunoglobulin
- As the gene contain same VDJ region that's why specificity remain same

Immunology

Expression of Immunoglobulin Genes & V(D)J Recombination

Immunology

Structure of Human Antibody Gene (Loci)

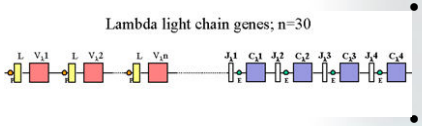
Structure of Human Antibody Gene

Antibody Gene

- Gene: Protein
- Immunoglobulin repertoire is encoded by multiple germ line gene segments
- These segments undergo somatic recombination during development of B-Cells
- Basic component of gene is inherited but alteration during lifetime

Structure of Human Antibody Gene

Located at Chromosome 22



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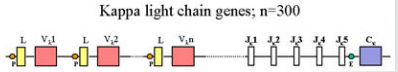
Light Chain Gene Family

1) Lambda Light Chains

- Composed of 4 C region genes. One for each subtype of Lambda
- 30 Variable genes
- Each of V gene composed of L (Ladder) exons
- V (variable) Exons
- J (Joining) exons
- Introns in between Exons

Structure of Human Antibody Gene

Located at Chromosome 2



http://www.microbiologybook.org/mayer/gen-1.jpg

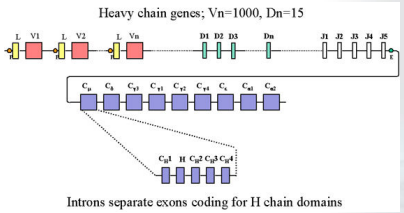
Light Chain Gene Family

2) Kappa Light Chains

- Composed of only single C region gene for a single type of Kappa
- 300 Variable genes
- Each of V gene composed of L (Ladder) exons
- V (variable) Exons
- J (Joining) exons
- Introns in between Exons

Structure of Human Antibody Gene

Located at Chromosome 14



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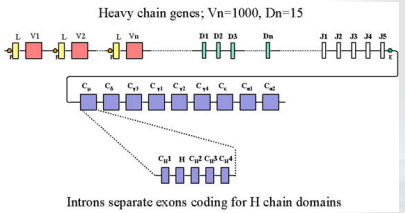
Heavy Chain Gene Family

- Located at chromosome 14
- Composed of many C region gene for a each class & sub class
- Each of C contain exons for hinge region & domains
- 1000 Variable genes

Structure of Human Antibody Gene

Located at Chromosome 14



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Heavy Chain Gene Family

- Each of V gene composed of L (Ladder) exons
- V (variable) Exons
- Additional D (diversity) Exons
- J (Joining) exons
- Introns in between Exons

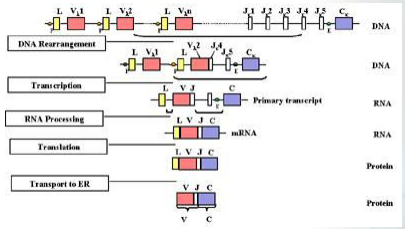
Immunology

Somatic Recombination

Somatic Recombination

- Recombination involves rearrangement of DNA in somatic cells
- The newly recombined genes are not inherited in contrast to germ cells
- Primary Ig repertoire differ slightly from one individual to next one
- Also differ in individual's lifetime by their exposure to different antigens

Somatic Recombination



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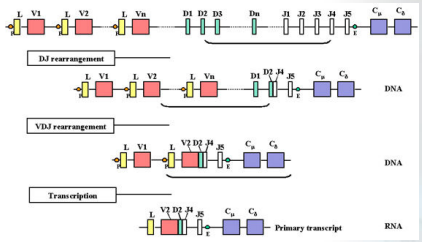
- As B-cell differentiate into mature one, it make light chain (Kappa)
- There is rearrangement of genes(exons) as introns are removed and genes start to express
- In this recombination, V genes become close to J genes by removing introns
- Recombined DNA processed into mature RNA by splicing

Somatic Recombination



http://www.microbiologybook.org/mayer/gen-4.jpg

- As B-cell differentiate into mature one, it make heavy chains
- There is rearrangement of genes(exons) as introns are removed and genes start to express
- In this recombination, D genes become close to J & then V recombines with DJ
- Recombined DNA processed into mature RNA by splicing

Immunology

Somatic Hypermutation

Somatic Hypermutation

- The enhanced rate of point mutation in the Ig V region genes
- Somatic hypermutation occurs particularly in V gene which codes for 2nd hypervariable region
- Increase in Ig diversity after various antigenic stimulation
- Also increase the affinity of Ig in order to compete for limited amount of Ag present

Immunology

Role of Somatic Hypermutation in diversity of antibodies

Role of Somatic Hypermutation

Antibody Diversity

- Sum of all the possible Ab specificities that an organism can make
- Humans can make 10^7-10^8 different Ab molecules
- Increase in Ig diversity after various antigenic stimulation
- So increase in Ab specificities due to somatic mutation

Role of Somatic Hypermutation

Antibody Diversity

- Somatic hypermutation occurs at high rate approx. 10^6 times higher
- The exact mechanism by which mutation occurs in V region gene without effecting the C region is still under research
- Activation induced cytidine deaminase (AID): essential role in DNA deamination

Immunology

V(D)J combinational Diversity

V(D)J Combinational Diversity

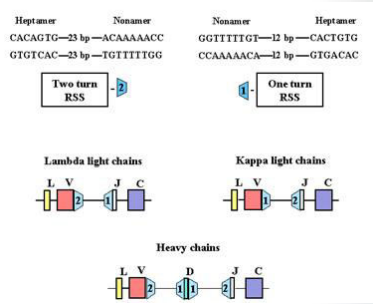
Combinational Diversity

- The component of Ab diversity that is generated by joining of various gene segments
- In Light chain genes: V & J region genes combination
- In Heavy Chain: V, D & J region genes combination
- D combines first J and then V to form heavy chain

Immunology

Regulation of V(D)J Recombination

Regulation of V(D)J Recombination



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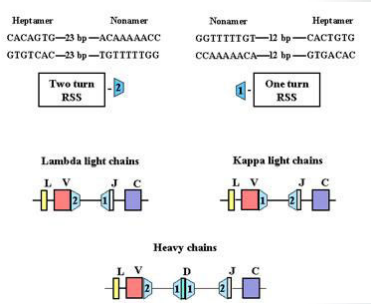
Regulation

- Recombination Signal Sequence (RSS): Flanked B/W V, D & J exons
- Composed of conserved haptamer & nonamer separated by 2 & 1 turn signals
- Recombination occurs B/W 2 & 1 turn

Regulation of V(D)J Recombination



http://www.microbiologybook.org/mayer/gen-6.jpg

Regulation

- Recombination occurs after the removal of introns B/W V & J in case of light chain
- Recombination occurs after the removal of introns B/W V, D & J in case of heavy chain
- RAG1 & RAG2: Enzymes responsible for this recombination
- SCID

Immunology

Affinity Maturation

Affinity Maturation

Affinity Maturation

- Increase in average affinity of Immunoglobulins
- Following Ag activation, V regions of heavy & light chains are diversified by somatic hypermutation
- This results in increase in binding affinity of BCR for its cognate ligand

Affinity Maturation

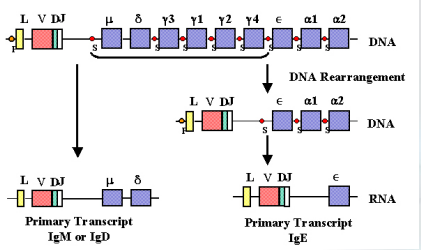
Affinity Maturation

- B-cells with higher affinity Ig can compete better for limited amount of Ag
- Increase in binding strength of Ab produced by immune response with Ag
- Affinity maturation occurs during secondary Ab response

Immunology

Class Switching or Class Switch Recombination

Class Switching



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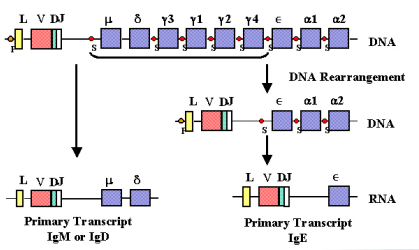
Class Switching

- The process by which a B-Cell changes the class of Ab but not specificity
- Switching occurs from IgM to IgG or IgA & IgE
- Class switching occurs as a result of recombination at gene of Immunoglobulin
- Class switch recombination (CSR)

Class Switching



http://www.microbiologybook.org/mayer/ab1-10.jpg

Class Switching

- Recombination occur B/W the rearranged VDJ & the switch site called S mu before the C mu(μ)
- This recombination causes to bring VDJ region to constant regions of other heavy chains except delta
- CSR occurs due to cytokines secreted by activated T-cells

Immunology

Antigen Processing & Presentation

Immunology

Review of B & T-Cell Receptors for Antigens

Review of B&T-cell Receptors

B-Cell Receptors (BCR)

- B & T cells recognize various form of substances as antigens in different & unique ways
- The role of receptors is very significant in such form of antigen recognition
- BCR is composed of surface immunoglobulin molecule with a certain specificity for antigen

Review of B&T-cell Receptors

B-Cell Receptors (BCR)

- BCR can recognize following antigens in soluble form
- Proteins (Both Native & Denatured determinants)
- Nucleic acids
- Polysacchrides
- Some lipids
- Small molecules i.e haptens

Review of B&T-cell Receptors

T-Cell Receptors (TCR)

- TCR recognize mainly those antigens which are protein in nature
- Antigens in fragmented form (Processed)
- Not soluble form
- Processed proteins in association with Major Histocompatibility Complex (MHC)
- MHC expressed on all nucleated cells

Review of B&T-cell Receptors

T-Cell Receptors (TCR)

- T-cells are grouped functionally on the basis of associated MHC with fragmented protein fragments
- Cytotoxic T-Cells- MHCI
- Helper T-Cells- MHC II

Immunology

Introduction to Antigen Processing & Presentation

Antigen Processing & Presentation

Ag Processing

- Processes that occur within the cell for fragmentation of antigens (Proteolysis)
- Association of fragmented peptide with Major Histocompatibility Complex (MHC) molecule expressed on the surface of Ag presenting Cells (APC) e.g Macrophages

Antigen Processing & Presentation

Ag Processing

- Presentation of processed Antigen with MHC molecule to T-cell determine the function of T-cell too
- Cytotoxic T-Cells: MHC I
- Helper T-Cells- MHC II

Immunology

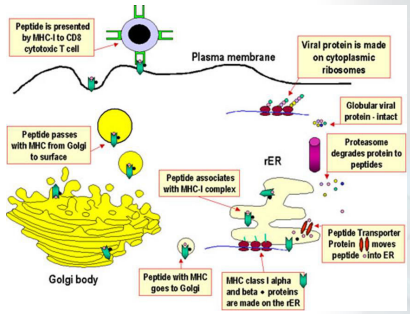
Antigen Processing & Presentation of Endogenous antigens

Antigen Processing of Endogenous Ag

Endogenous Antigens

- Intracellular source of antigen: Endogenous Ag residing in cytosol e.g Viruses
- MHC I present such kind of Ag
- MHC I express on all nucleated cells
- Ag are processed in proteasome:a complex having proteolytic activity

Antigen Processing of Endogenous Ag



http://www.microbiologybook.org/bowers/MHCInew.jpg

Endogenous Antigens

- Fragmented proteins move across the membrane of ER using transporter membrane
- Synthesis & assembly of MHC I complex inside ER
- Within ER MHC I form a stable complex with fragmented peptide & express on the surface of cell membrane

Immunology

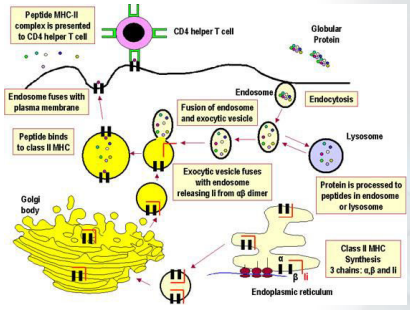
Antigen Processing & Presentation of Exogenous antigens

Antigen Processing of Exogenous Ag

Exogenous Antigens

- Exogenous antigens e.g bacteria are taken up by the process of endocytosis
- MHC II present such kind of Ag
- MHC I express on limited number of cells like antigen presenting cells (APC)
- APC include macrophages, dendritic cells & B-cells

Antigen Processing of Exogenous Ag



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Exogenous Antigens

- Exogenous proteins are processed in endosomes by proteases
- Synthesis & assembly of MHC II complex inside ER and transported across Golgi complex
- Trans GC combines with endosomes containing fragmented peptides
- MHC II complexed with peptides present on cell

Immunology

Major Histocompatibility Complex (MHC)

Immunology

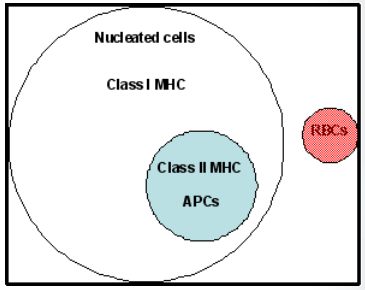
Introduction to MHC

Introduction to MHC

MHC

- Adaptive Immunity: Cell to cell interaction or Cell mediated immunity
- Cell to cell interaction orchestrated by immunological synapses
- TCR: T-cells
- MHC with processed peptides: on APC
- Two classes of MHC
- Class I & Class II

Introduction to MHC



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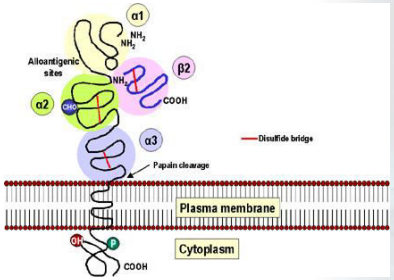
MHC

- MHC encoded by genes which are highly polymorphic
- MHC genes were first identified in case of tissue transplant rejection
- Class I MHC: on all nucleate cells of body
- Class II MHC: limited to APC

Immunology

Structure of Class I MHC molecules

Structure of Class I MHC molecules



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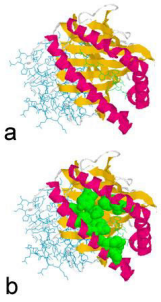
Class I MHC

- Composed of two polypeptide chains

1) A long alpha chain
2) A short beta chain

- A Cytoplasmic region
- A trans membrane region
- A highly conserved α3 region
- A highly polymorphic peptide binding region

Structure of Class I MHC molecules



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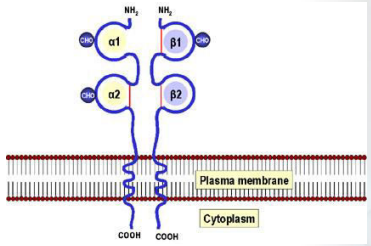
Antigen binding Groove of Class I MHC

- Composed of α1 & α 2 domain
- Antigenic peptide reside within the Ag binding groove
- Within groove peptide make contact with residue peptide (highly polymorphic)
- 8-10 amino acids can accommodate

Immunology

Structure of Class II MHC molecules

Structure of Class II MHC molecules

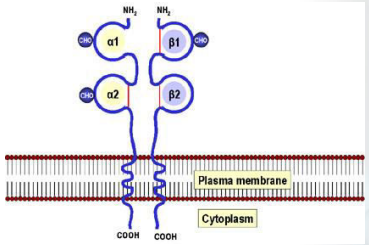


http://www.microbiologybook.org/bowers/mhc2.jpg

Class II MHC

- Composed of two polypeptide chains α & β chains of equal length
- A Cytoplasmic region for phosphorylation & Binding to cytoskeleton
- A trans membrane region for anchoring the membrane

Structure of Class II MHC molecules



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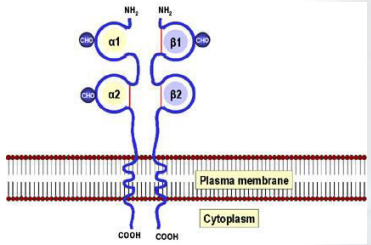
Class II MHC

- A highly conserved α2 & β2 domain for binding to CD4
- A highly polymorphic peptide binding region formed of α1 & β1
- Ag peptide accommodates in Ag binding groove

Structure of Class II MHC molecules



http://www.microbiologybook.org/bowers/mhc2.jpg

Class II MHC

- Peptide also remain in contact with residues which are highly polymorphic
- As groove is open it can accommodate approx. 13-25 amino acids long
- Can bind different amino acids due to its polymorphic nature

Immunology

Important Aspects of MHC

Important Aspects of MHC

Class II MHC

- MHC molecules are membrane bounded
- Recognized by T-cells with antigen as a result of cell to cell interaction
- For an immune response, peptide must be bounded with MHC (One level control)

Important Aspects of MHC

Class II MHC

- Mature T-cell must have a TCR which recognize MHC bounded peptide (second level control)
- Cytokines increase the expression of MHC
- Peptides from cytosol: Class I MHC
- Peptides from vesicle: Class II MHC
- Polymorphism in MHC

Immunology

Role of MHC in Tissue Matching

Role of MHC in Tissue Matching

Tissue Matching

- Prospective donor & recipient tested for compatibility prior to transplantation
- MHC also called as Human leucocyte antigen (HLA)
- HLA molecules are the primary target of immune responses to allogeneic transplants

Role of MHC in Tissue Matching

Tissue Matching

- HLA molecules are highly diverse in human population
- HLA typing or tissue matching detects & classifies this diversity
- Extensive polymorphism of HLA: less chances of HLA matched donors for transplants
- Appx.25% of siblings inherit same HLA type

END

Immunology

Self MHC Restriction

Self MHC Restriction

- For an appropriate immune response, T-cells should recognize & respond to foreign Ag
- Foreign Ag presented to T-cells must be self MHC
- Ag: Foreign
- MHC: Self

Self MHC Restriction

- Cytotoxic T-Cells recognize Ag in context of Self Class I MHC
- Helper T-Cells recognize Ag in context of Self Class II MHC
- This process whereby T-cells become restricted to recognize self-MHC occur in thymus

Self MHC Restriction

- For an appropriate immune response, T-cells should recognize & respond to foreign Ag
- Foreign Ag presented to T-cells must be self MHC
- Ag: Foreign
- MHC: Self
- Cytotoxic T-Cells recognize Ag in context of Self Class I
- Cytotoxic T-Cells recognize Ag in context of Self Class I

Self MHC Restriction

- Cytotoxic T-Cells recognize Ag in context of Self Class I MHC
- Helper T-Cells recognize Ag in context of Self Class II MHC
- This process whereby T-cells become restricted to recognize self-MHC occur in thymus

Immunology

Differences B/W Monoclonal & Polyclonal Antibodies

Differences B/W Mono & Polyclonal Ab

Monoclonal Ab

- Antibody from a single antibody producing B-cell
- Also able to bind with single & unique epitope
- Mainly consist of single subtype of IgG e.g IgG1, IgG2 & IgG3

Differences B/W Mono & Polyclonal Ab

Polyclonal Ab

- Collection of Antibodies from a different antibody producing B-cell
- Also able to bind with multiple epitopes on a same antigen
- Obtained in serum with antibodies having different affinities
- Mainly belong to IgG class

Immunology

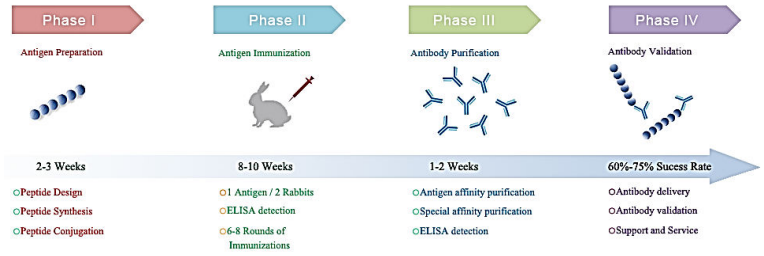
Generation of Polyclonal Antibodies

Generation of Polyclonal Antibodies

Polyclonal Ab

- The general procedure for generation of polyclonal antibodies include following phases
- Antigen preparation/Antigen & Adjuvant conjugate
- Antigen Immunization
- Antibody Purification from animal's serum
- Antibody Validation

Generation of Polyclonal Antibodies



https://www.novoprolabs.com/custom-polyclonal-antibodies/

Immunology

Role of Adjuvants in Polyclonal Antibodies Production

Role of Adjuvants/Polyclonal Antibodies

Adjuvants

- Potentiates immune response to antigen
- Modulates towards desired immune response
- Also have undesirable effects like toxicity
- Selection would made in order to get maximum immunostimulation

Role of Adjuvants/Polyclonal Antibodies

Adjuvants

- For polyclonal antibodies production following adjuvants are used
- Freund's Adjuvants
- Freund's complete adjuvant (FCA): water-in-oil emulsion containing antigen with heat killed *Mycobacterium tuberculosis*
- Stimulate both humoral & Cell mediated immune response for Ab

Role of Adjuvants/Polyclonal Antibodies

Adjuvants

- Freund's Incomplete adjuvant (FIA): water-in-oil emulsion containing antigen without heat killed *Mycobacterium tuberculosis*
- Used as booster antigen dose
- Freund's adjuvant is used by mixing with equal parts of antigen

Immunology

Production of Monoclonal Antibodies

Production of Monoclonal Antibodies

Monoclonal Antibodies

- Production of monoclonal antibodies is done using Immortal clone of cell with single Ab specificity
- Immortal cell: Not proliferate indefinitely
- Fusion of normal Ab producing cell with an appropriate B-cell tumor line (Hybrid Cell)
- Large production of Ab

Immunology

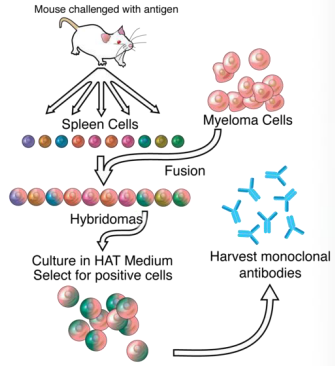
Hybridoma Formation

Hybridoma Formation

Hybridoma

- Hybrid cell line: Fusion of Lymphoid tumor cell with normal B-Lymphocyte with single specificity
- Dual function: Immortality of tumor cell & production of Ab with single specificity
- Principle involves
- Injection of mice with an antigen

Hybridoma Formation

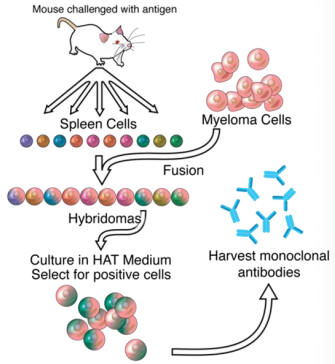


https://en.wikipedia.org/wiki/File:Monoclonals.png

Hybridoma

- Isolation of B-lymphocyte from spleen of mice
- Fusion of that B-lymphocyte with lymphocyte immortal cell i.e Myeloma cell
- Fused cell: Hybridoma
- Selection Hybridoma cell: Using HAT (Hypoxanthine, aminopterin, thymidine)

Hybridoma Formation



https://en.wikipedia.org/wiki/File:Monoclonals.png

Hybridoma

- Only hybridoma cell can grow on HAT medium
- Propagation of hybridoma cell: for large amount of monoclonal Ab
- Dual function: Ab production plus exaggerated longevity

Immunology

Usage of Monoclonal Antibodies

Usage of Monoclonal Antibodies

- Usage in prevention, diagnosis & treatment of disease
- Immunophenotyping of Immune cells: Monoclonal Ab used against cell surface molecules like Cluster of Differentiation (CD)
- Typing of various tumors e.g Leukemia
- Immunohistchemistry of solid tumors

Usage of Monoclonal Antibodies

- Use in Immunotherapy: Against various tumor marker e.g CD20 B-Cell lymphoma
- Use in Fluorescence Activated cell sorting (FACS)

Immunology

T-Lymphocyte Receptors, Maturation, Activation & Differentiation

Immunology

Structure of T-Cell Receptor (TCR)

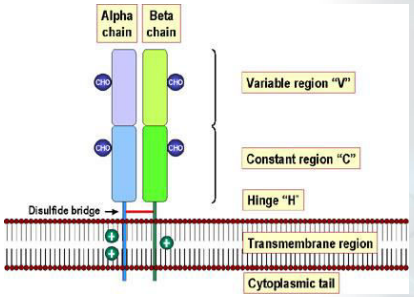
Structure of TCR

TCR

- Surface receptor for binding with Ag bounded with MHC
- Like immunoglobulin: Part of Ig Superfamily
- TCR is a heterodimer surface receptor
- Composed of two chains of equal length

1. A Chain
2. B Chain

Structure of TCR

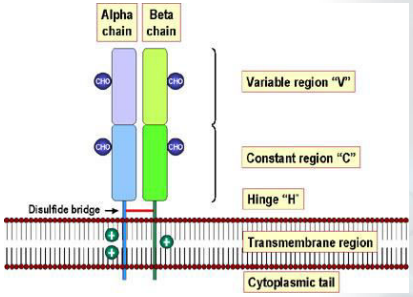


http://www.microbiologybook.org/bowers/tcr.jpg

TCR

- Short Cytoplasmic tail: Not sufficient for signal transduction
- Transmembrane region: for anchoring cell membrane (due to hydrophobic amino acids)
- Disulfide bridge B/W two chains
- Both chains contain carbohydrate moiety

Structure of TCR



http://www.microbiologybook.org/bowers/tcr.jpg

TCR

- Both chains contain constant (C) & Variable (V) Regions
- Variable regions: Hypervariable regions in both chains
- Specificity of TCR: Variable region of both chains
- Each TCR carry single specificity

Immunology

Diversity of T-Cell Receptor (TCR)

Diversity of TCR

- Genetic basis: Diverse array of TCR
- Joining of Various Gene segments
- T-cell maturation: Thymus
- Germ line gene for α chain: V & J segments
- Germ line gene for αβ chain: V, D & J segments
- Combinational diversity: For V, D & J

Diversity of TCR

- Specificity of TCR: Combination of α & β chains
- Small population T-cells: Carrying TCR with γ (Gamma) & δ (Delta) chains
- T-cells predominates mucosal epithelium: for certain bacteria & viral antigens

Diversity of TCR

- Repertoire of γδ T-cells : Joining gene segment
- Gamma chain gene contain V & J segment
- Delta chain germline gene: V, D & J segments
- Combinational diversity
- γδ T-cells recognize antigens independent of MHC association

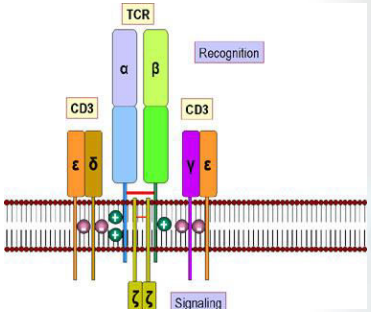
Immunology

CD3 complex
Structure & Functions

CD3 Structure & Function

- CD3: Cluster of differentiation 3
- Adjacent to TCR
- Transducing element of TCR
- Exist as a complex
- Composed of 5 proteins:CD3 complex
- One Gamma(γ)
- One delta(δ)
- Two Epsilon (ε)
- Two Zeta (**ζ**)

CD3 Structure & Function



http://www.microbiologybook.org/bowers/cd3.jpg

- CD3 complex: Invariant Proteins
- No role in specificity of T-Cell
- Necessary for surface expression of TCR during development of T-cell
- Role in transducing signals: Signal transduction
- After engaging with Ag with TCR in association with MHC complex

Immunology

Cell Surface Molecules involved in T-Cell & Other Interaction

Cell Surface Molecules

Immunological Synapse

- Interface B/W Antigen presenting cell (Target Cell) & T-lymphocyte
- Interaction B/W TCR & MHC molecules are not strong
- Cell surface molecules on T-cells & their interacting molecule on antigen presenting cells

Cell Surface Molecules

Immunological Synapse

- T-cells also express co-receptor for MHC Molecule(e.g CD8 & CD4)
- Expression of supporting molecules increased by cytokines: Modulators of immune system
- In addition to these molecules, some molecules are also required for T-cell activation

Cell Surface Molecules

Immunological Synapse

- Activation of T-cells require two signals
- Signal 1: Engagement of TCR with Ag/MHC complex
- Signal 2: Engagement of supporting molecules with their ligands
- Co-stimulatory molecules are also required for activation e.g C28 on T-cell & its ligand on APC i.e B7-1

Cell Surface Molecules

Immunological Synapse

- Lack of co-stimulation: No activation of T-cells
- Cellular Anergy
- Full activation of T-cells: Engagement of Immunological synapse
- APC must possess & present peptides to T-cells

Immunology

Accessory Molecules

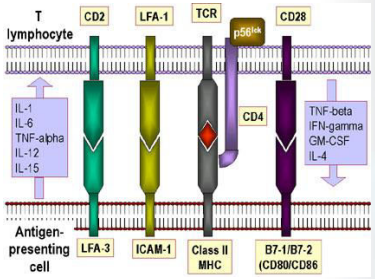
Accessory Molecules

- Weak interaction B/W TCR & Ag/MHC complex
- Accessory molecules: Stabilize this interaction
- Invariant molecules
- No role in the specificity of T-cells
- Can modulate immune system in either positive or negative manner

Accessory Molecules

- Critical to success or failure of controlling the immune response to foreign antigen like infectious agent
- Aberrant response to self-antigen: In autoimmune diseases & response to tumors
- Promote or suppress the immune response
- Nomenclature: according to function

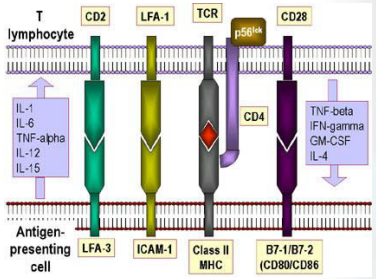
Accessory Molecules



http://www.microbiologybook.org/bowers/apc.jpg

- Followings are important accessory molecules
- Nomenclature: according to function
- CD4: binding to class II MHC: ensures the binding of Th cells to APC
- CD8: Binding to Class I MHC: ensures the binding of Tc cells to target cell
- CD2: Leucocyte Function Antigen 3 (LFA-3)

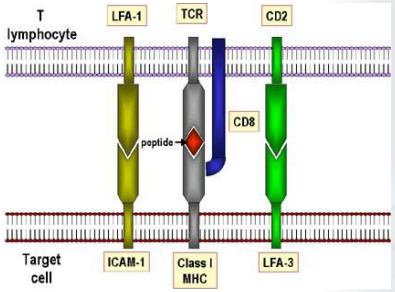
Accessory Molecules



http://www.microbiologybook.org/bowers/apc.jpg

- Leucocyte Function Antigen 1 (LFA-1): Intracellular Adhesion Molecule (ICAM-1)
- CD28: B7-1/B7-2

Accessory Molecules



http://www.microbiologybook.org/bowers/target.jpg

- CD8: Class I MHC
- Leucocyte Function Antigen 1 (LFA-1): Intracellular Adhesion Molecule (ICAM-1)
- CD2: LFA-3

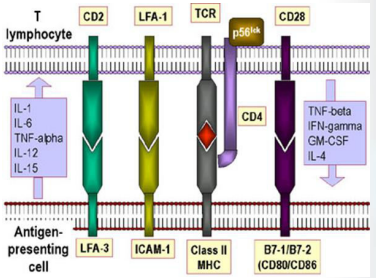
Immunology

Co-Stimulatory Molecules for Activation & Maturation of T-Cells

Co-Stimulatory Molecules

- Molecules required for activation of T-Cells after binding to its ligands
- Two signals required for T-cells activation
- Engagement of TCR with Ag which is associated with MHC
- Second comes from engagement of co-stimulatory molecules with their ligands

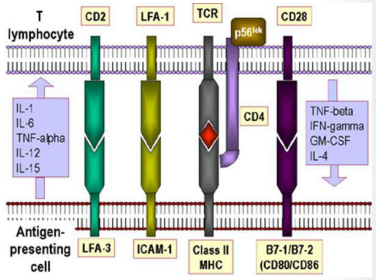
Co-Stimulatory Molecules



http://www.microbiologybook.org/bowers/apc.jpg

- Molecules which transmit the signals to a cell to enhance the response of that cell in positive manner
- CD 28 is the co-stimulatory molecule of both types of T-cells
- Ligand for C28 is B7-1 or B7-2 present on the surface of APC

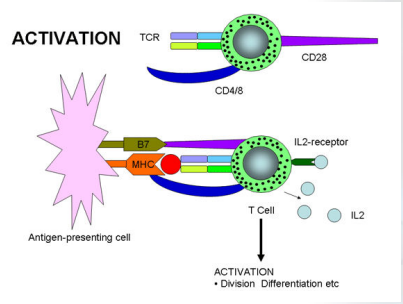
Co-Stimulatory Molecules



http://www.microbiologybook.org/bowers/apc.jpg

- Immunological Synapse: Multiple interaction of TCR,MHC, accessory & co-stimulatory molecules
- Co-stimulatory molecules are also invariant
- No involvement in determining the specificity of interaction

Co-Stimulatory Molecules

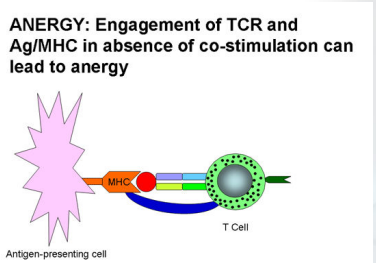


http://www.microbiologybook.org/bowers/apc.jpg

T-cell activation

- Engagement of TCR with MHC containing Ag
- Engagement of co-stimulatory molecule
- Engagement of accessory molecules
- Secretion of cytokines after T-cell activation
- Maturation & differentiation of T-Cells

Co-Stimulatory Molecules

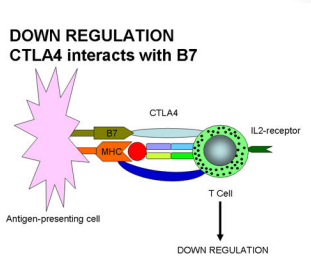


http://www.microbiologybook.org/bowers/apc.jpg

T-cell activation

- Engagement of TCR, MHC with Ag
- Lack of co-stimulation: leads to anergy
- No responsiveness to Ag
- No T-Cell activation

Co-Stimulatory Molecules

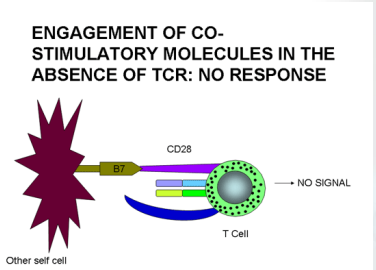


http://www.microbiologybook.org/bowers/antigen-pres2.gif

T-cell activation

- Engagement of TCR, MHC with Ag
- Lack of co-stimulation: leads to down regulation of T-Cell activation
- Absence of CD28
- Expression of CTLA-4
- No responsiveness to Ag
- No T-Cell activation

Co-Stimulatory Molecules



http://www.microbiologybook.org/bowers/antigen-pres4.gif

T-cell activation

- No Engagement of TCR, MHC with Ag
- Interaction of CD28 with B7
- No signal for activation

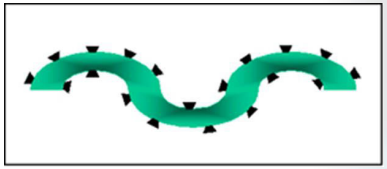
Immunology

B-Lymphocytes Receptors, Maturation, Activation & Differentiation

Immunology

Antigens Responding to B-Cells

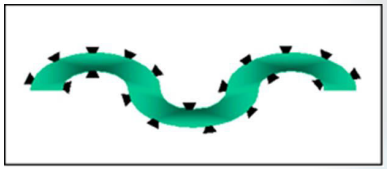
Antigens Responding to B-Cells



http://www.microbiologybook.org/mayer/ag-1.jpg

- T-Independent Antigens: Directly stimulate the B-cells
- No requirement of T-Cells
- Polysaccharides e.g *Pneumococcus*
- Polymeric structure: Ag are characterized by the same antigenic determinants
- Antigenic determinates are repeated many times

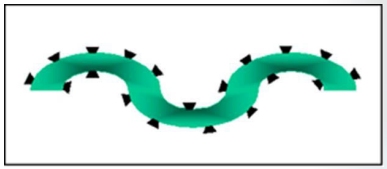
Antigens Responding to B-Cells



http://www.microbiologybook.org/mayer/ag-1.jpg

- Polyclonal activation of B-Cells
- Many of these Ag can activate B-Cell clones specific for other antigens
- 2 types of T-Independent Ag
- Type 1: are polyclonal activator
- Type 2: are not polyclonal activator

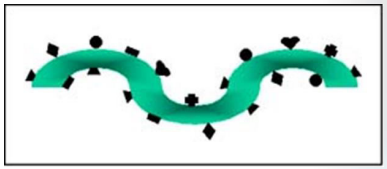
Antigens Responding to B-Cells



http://www.microbiologybook.org/mayer/ag-1.jpg

- Ag are more resistant to degradation by phagocytic cells
- Persist for longer time
- Consistent stimulation of immune system
- Have mitogenicity

Antigens Responding to B-Cells



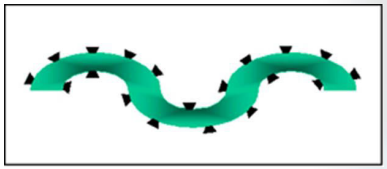
http://www.microbiologybook.org/mayer/ag-2a.jpg

- T-dependent antigens
- Requires the help of T-cells for B-cell activation
- Can't fulfil the molecular requirements for direct stimulation
- Readily degraded by phagocytes
- Ag is presented to T-cells with class II MHC
- Protein in nature
- Contain variety of epitopes with few copies

Immunology

Antigens Processing by B-Cells

Antigens Processing by B-Cells

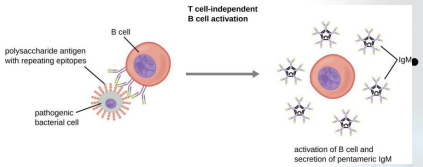


http://www.microbiologybook.org/mayer/ag-1.jpg

T-independent antigens

- Directly stimulate the B-cells
- Have the ability to activate a substantial proportion of the B-cell pool
- Polyclonal activation: without reference to Ag specificity of the surface receptor hypervariable regions e.g Type I Ag

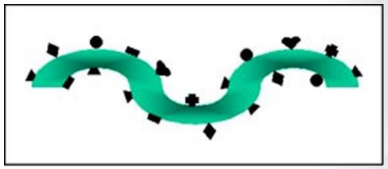
Antigens Processing by B-Cells



https://courses.lumenlearning.com/microbiology/chapter/b-lymphocytes-and-humoral-immunity/

- High conc. Of Ag e.g bacterial liposacchrides
- Binding to a surface molecule
- Bypasses the early part of the biochemical pathway mediated by specific Ag receptor
- Repeating Ag determinants cross link Ig receptor
- Transformation into plasma cell for Ig secretion

Antigens Processing by B-Cells

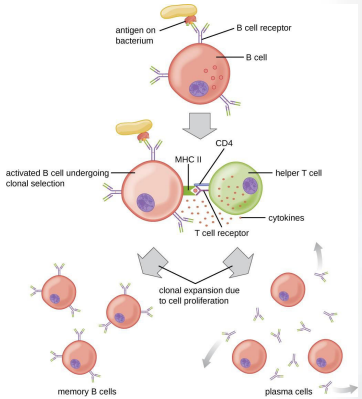


http://www.microbiologybook.org/mayer/ag-2a.jpg

T-dependent antigens

- No direct stimulation of B-cells
- Require T-cells help as can't fulfil the molecular requirement for direct stimulation
- T-dependent Ag are recognized by surface Ig receptor
- Are univalent with respect to specificity of each determinant

Antigens Processing by B-Cells



https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/1094/2016/11/03172718/OSC_Microbio_18_04_BCellact.jpg

- Ag are internalized within endosomes
- Processed by fusion with Lysosomes into simple peptides
- Peptides are expressed on the surface of B-cells with Class II MHC
- Presentation of Ag to Helper T-cells with co-stimulatory molecules
- Clonal expansion & Differentiation into Plasma cells

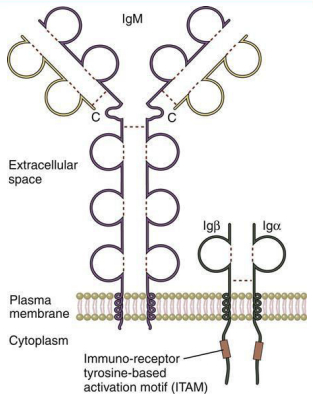
Immunology

Nature of B-Cell Activation

Nature of B-Cell Activation

- Similar to T-cells, naïve or resting B-cells are non- dividing
- Activation occur through BCR
- Like T-cell, BCR (surface Ig) doesn't process any intrinsic enzymatic activity
- Accessory molecules associated with Ag receptor : Propagate activation signals into B-cells

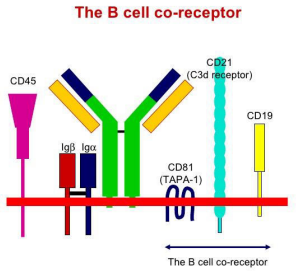
Nature of B-Cell Activation



https://oncohemakey.com/b-cell-activation-and-signaling/

- BCR Complex: Composed of membrane anchored immunoglobulin
- Is associated with disulfide linkage Igα & Igβ heterodimer
- Cytoplasmic tail of Igα & Igβ contain a single ITAM motif
- Cross linking of BCR results in the initiation of PTK driven signal, seeded by ITAM

Nature of B-Cell Activation



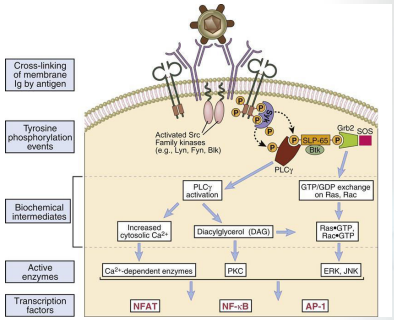
https://oncohemakey.com/b-cell-activation-and-signaling/

- B-Cells also require co-stimulation to mount efficient effector responses
- Like C28 in case of T-cells, a complex of co-stimulatory molecules perform this function
- Composed of
- CD81
- CD21
- CD19

Immunology

B-Cell Receptor & Co-stimulation For Maturation

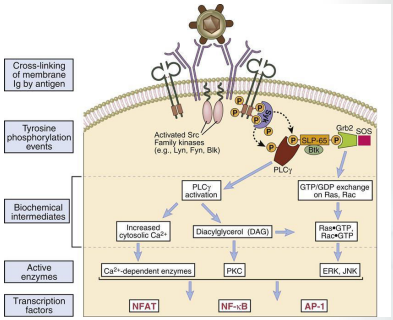
B-Cell Receptor for Maturation



https://oncohemakey.com/b-cell-activation-and-signaling/

- Cross linking of BCR by Ag
- By cross linking, there is activation of Src for cellular signaling
- Src phosphorylates tyrosine on ITAM of Igα & β
- Phosphorylated ITAM act as docking site for Syk
- Downstream signaling for antibody synthesis

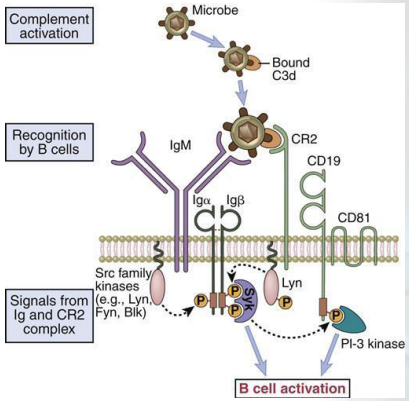
B-Cell Receptor for Maturation



https://oncohemakey.com/b-cell-activation-and-signaling/

- Two biochemical processes are activated
- Activation of Phospholipase C (PLCγ)
- Phosphorylastion of adapter protein SLP: activation of Ras & Rac
- In turn, mitogen activation proteins (MAP) e.g JNK are activated
- AP-1 moves to nucleus: for B-cell proliferation & differentiation

B-Cell Receptor for Maturation



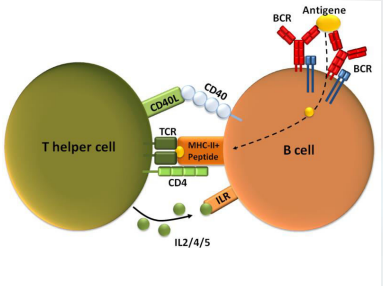
https://oncohemakey.com/b-cell-activation-and-signaling/

- Second signal required after BCR engagement
- Accessory molecules: Amplification of B-cell signals
- Amolification occur: Multivalent Ag with C3d engage CR2 with BCR
- Signals from Ig & CR2: Phosphorylation of Syk
- CD19 also reorients for PI-3 kinase
- B-cell activation & differ.

Immunology

Role of CD40 in B-Cell Activation

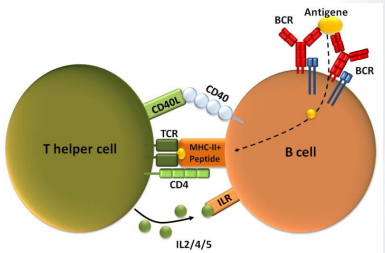
Role of CD40



https://en.wikipedia.org/wiki/CD154#/media/File:T-dependent_B_cell_activation.png

- T-dependent antigen: Univalent
- B-cell process & present such antigens
- Upregulation of co-stimulatory molecule on B-cell i.e CD40
- Engagement of CD 40 with its ligand on T-cells: CD40 ligand
- B-cells activation ensured with co-stimulatory signals

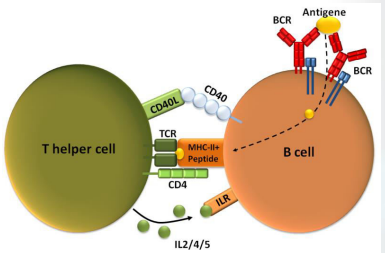
Role of CD40



https://en.wikipedia.org/wiki/CD154#/media/File:T-dependent_B_cell_activation.png

- Co-stimulatory signal: CD40 & CD40 ligand interaction
- B-cell activation by cytokines from T-cell like IL-2/4/5
- These cytokines cause B-cell proliferation & differentiation
- Class switching
- Affinity maturation

Role of CD40



https://en.wikipedia.org/wiki/CD154#/media/File:T-dependent_B_cell_activation.png

- Absence of CD40L
- Defect in gene of CD40 L
- Absence of class switching
- Hyper IgM globunemia
- No IgG: recurrent infections & immunodeficiency

Immunology

Complement System

Immunology

Introduction to Complement System

Introduction to Complement System

- Heat Labile serum proteins
- Able to destroy or lyse pathogen (one way of host defense)
- Become Inactive by heating serum at 56C for 30 min
- Composed of more than 20 proteins
- Produced by variety of cells: Hepatocytes, macrophages & gut epithelial cells

Introduction to Complement System

- Some complement proteins bind Immunoglobulins
- Some on the membrane component of cell
- Others are Proenzymes
- Need activation into active form
- When activated cleave one or more other complement proteins

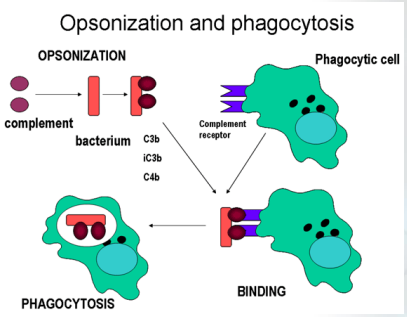
Immunology

Functions of Complement Proteins

Functions of Complement Proteins

- Complement System: Specific & Non-specific resistance against infections
- Primary function: To kill or lyse infectious agent i.e bacteria
- Secondary or Effector functions: Effects on other functions of immune system

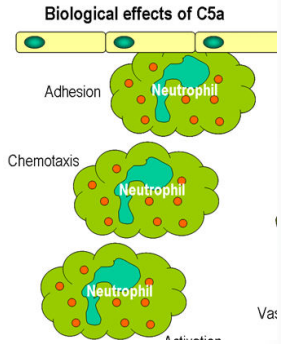
Functions of Complement Proteins



http://www.microbiologybook.org/ghaffar/opson-phago.gif

- Opsonization: some complement proteins are good opsonins
- C3b, iC3b and C4b attach to microorganism first
- This complex of complement protein binds with complement receptor on the surface of phagocytic cell
- Phagocytosis of microbe

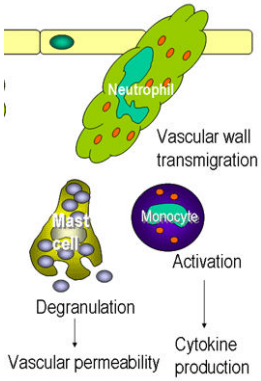
Functions of Complement Proteins



http://www.microbiologybook.org/ghaffar/c5a-effects.gif

- Chemotaxis: some complement proteins are good chemotactic factors
- C5a: Potent activator of Neutrophils, basophils & macrophages
- Causes induction of adhesion molecules on surface of blood vessel endothelial cells
- Membrane attack complex (MAC) C5bC6C7: chemotactic factor

Functions of Complement Proteins



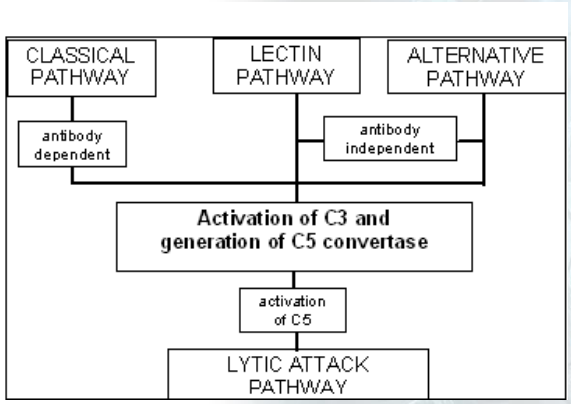
http://www.microbiologybook.org/ghaffar/c5a-effects.gif

- Anaphylaxsis: some complement proteins are anaphylatoxins
- C4a, C3a & C5a: Potent anaphylatoxins
- Cause basophils/mast cells degranulation
- Smooth muscles contraction
- Vasodilatation
- Bronchoconstriction

Immunology

Classical Pathway of Complement Activation

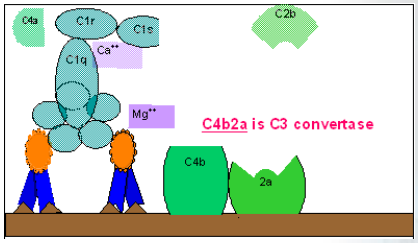
Complement Activation



Classical Pathway

- Antibody dependent complement activation
- Antibody bind to microbe: link the first molecule of classical pathway
- C1 activation
- C1 a multi subunit protein containing three proteins
- C1q, C1r & C1s
- Followings are important events of this pathway

Classical Pathway

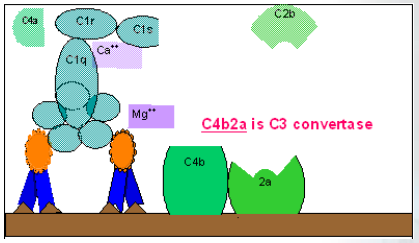


http://www.microbiologybook.org/ghaffar/comp2.gif

1) Activation of C1

- Binding of C1q to Fc portion of Immunoglobulin (IgM& IgG) which have bounded with antigens on bacterial surface
- Binding of C1q in turn activates C1r and then C1s
- Activated C1qrs act as enzyme for C4 to cleave it in C4a & C4b

Classical Pathway

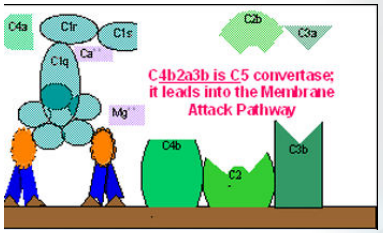


http://www.microbiologybook.org/ghaffar/comp2.gif

2) Generation of C3 convertase

- Activated C1qrs also act on C2
- C2 cleaves into C2a & C2b
- C2a binds on bacterial surface with C4b
- C4b & C2a act as C3 convertase

Classical Pathway

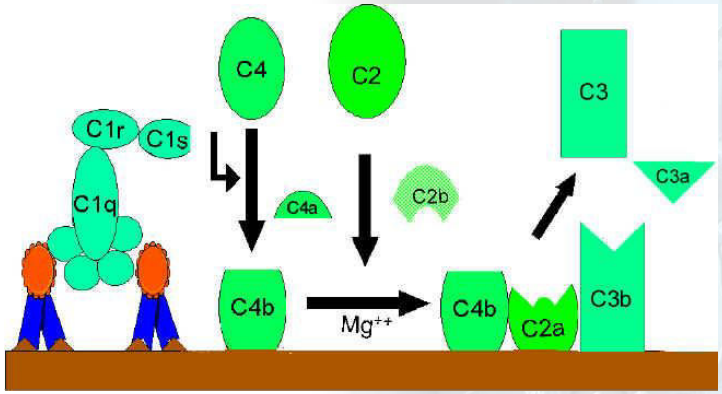


http://www.microbiologybook.org/ghaffar/comp3.gif

3) Generation of C5 convertase

- Activated C3 convertase (C4b&C2a)
- Act on C3 to convert into C3a & C3b
- C3a moves into microenvironment while C3b binds with C4b &C2a
- C4bC2aC3b is called as C5 convertase

Classical Pathway



http://www.microbiologybook.org/ghaffar/C1class.JPG

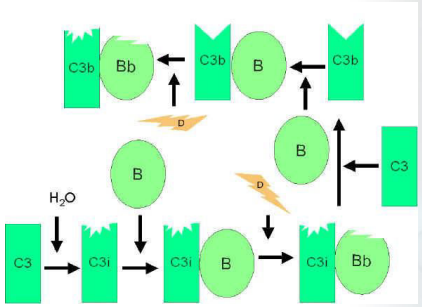
Immunology

Alternative Pathway of Complement Activation

Alternative Pathway

- Antibody independent complement activation
- Initiation by direct conversion of C3 into C3a & C3b
- Various serum proteins & factors required
- Factor B, D & Mg^{++} ions
- In serum, there is low level spontaneous hydrolysis of C3 to produce C3i

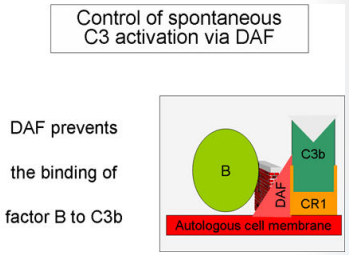
Alternative Pathway



http://www.microbiologybook.org/ghaffar/C3Alt.JPG

- Factor B binds with C3i
- Become susceptible to factor D which cleaves B into Bb
- C3iBb acts as C3 convertase which converts C3 into C3a & C3b
- Resulting C3b reacts again with factor B and become susceptible to factor D
- C3bBb acts as C3 convertase

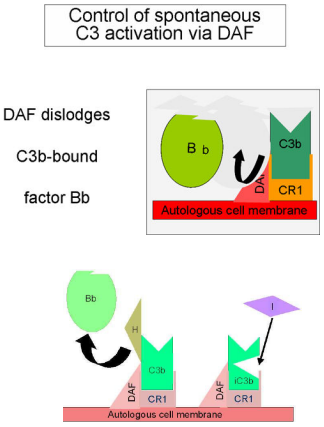
Alternative Pathway



http://www.microbiologybook.org/ghaffar/C3Alt.JPG

- C3b amplification loop for more production of C3b
- LPS of Gram negative, Cell wall of bacteria & yeasts: Activator of Alternative pathway
- Control of C3b amplification by Decay accelerating factor (DAF) by
- Blocking the formation of C3 convertase

Alternative Pathway

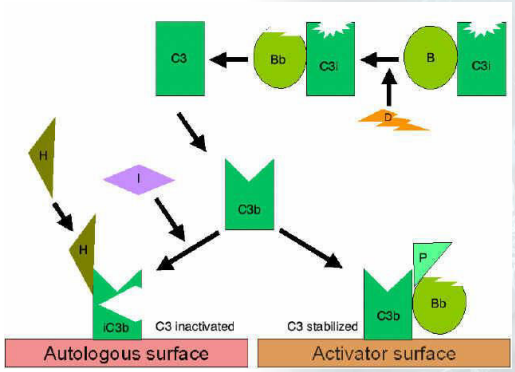


http://www.microbiologybook.org/ghaffar/alt2.gif

- By dissociating C3 convertase after cleavage of Bb from C3b
- Amplification of C3b loop is controlled by enzymatic degradation of C3b by serum factor i.e factor H & I
- Deficiency of Factor H & I leads to increased susceptibility to various infections

Alternative Pathway

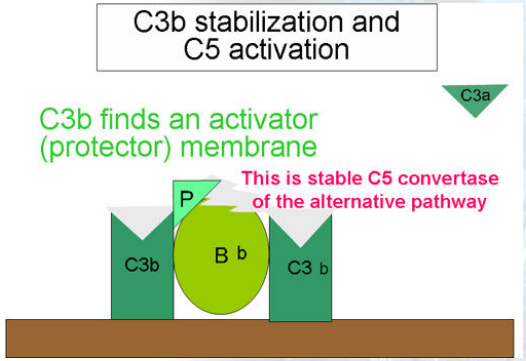
Stabilization of C3 on Activator surface by Protector Protein



http://www.microbiologybook.org/ghaffar/C6C3stab.JPG

Alternative Pathway

Generation of C5 Convertase



http://www.microbiologybook.org/ghaffar/alt3.gif

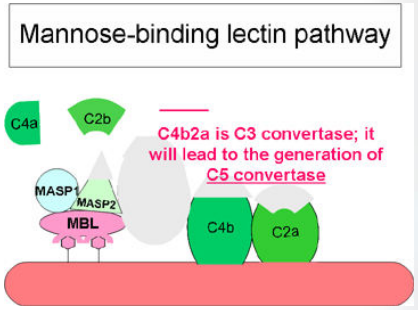
Immunology

Lectin Pathway of Complement Activation

Lectin Pathway

- Antibody independent complement activation
- Initiation by mannose binding Lectins (MBL) on bacterial surface with mannsoe containing polysaccharides (Mannans)
- After binding of MBL on bacterial surface, there is association of two serine proteases called mannose-associated serine proteases (MASP)

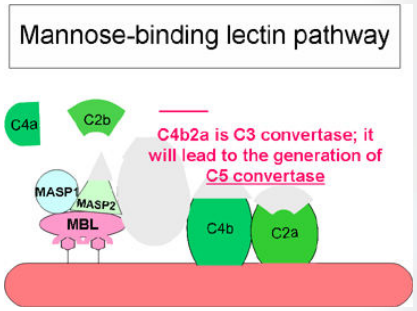
Lectin Pathway



http://www.microbiologybook.org/ghaffar/lect1.gif

- Two types of MASPs
- MASP-1 & MASP-2
- MASP-1 corresponds like C1r & MASP-2 like C1s of classical pathway
- While MBL like C1q
- Formation of MBL/MASP-1 & MASP-2 tri molecular complex: Activation of MASPs
- Cleavage of C4 & C2 into C4b & C2a respectively

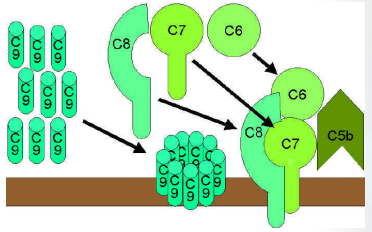
Lectin Pathway



http://www.microbiologybook.org/ghaffar/lect1.gif

- Binding of C4b & C2a on pathogen surface: Act as C3 convertase
- Cleavage of C3 into C3b: generation of C5 convertase (C4b, C2a & C3b complex)
- Biological activities of C4a, C2b & C3a & regulatory proteins are same like classical pathway

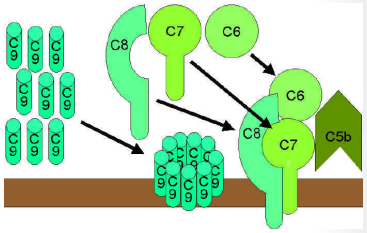
Lytic (Common)Pathway



http://www.microbiologybook.org/ghaffar/C7lyt.JPG

- Also called as Membrane attack complex (MAC) pathway
- C5 convertase from all three pathways
- Classical:C4b2a3b
- Alternative:C3bBb3b
- Lectin:C4b2a3b
- Converts C5 into C5b &C5a
- C5b rapidly associates C6 &C7 and insert into membrane

Lytic (Common)Pathway



http://www.microbiologybook.org/ghaffar/C7lyt.JPG

- Subsequently C8 binds followed by several molecules of C9
- C9 make pore in the membrane
- Leakage of cellular contents cause cytolysis
- C5bC6C7C8C9 is called as membrane attack complex (MAC)

Immunology

Biological Active Products of Complement

Biological Active Products

- Complement System: Specific & Non-specific resistance against infections
- Activation of complement: Production of various biological active molecules
- Cause resistance, anaphylaxis & inflammation

Biological Active Products

- Kinnin production
- C2b produced in classical pathway is called as Pro-Kinnin
- Pro-Kinnin is activated by serum factor called as Plasmin
- Excess C2b production cause undesirable effects
- Smooth muscles contraction
- Vasodilatation

Biological Active Products

- Anaphylaxsis: Components of complement proteins in microenvironment
- C4a, C3a & C5a: Potent anaphylatoxins
- Cause basophils/mast cells degranulation
- Smooth muscles contraction
- Vasodilatation
- Bronchoconstriction

Biological Active Products

- Inflammation: Tissue response against infection
- Chemotaxsis: movement of inflammatory cells to site of infection
- C5a: Potent activator of Neutrophils, basophils & macrophages
- Causes induction of adhesion molecules on surface of blood vessel endothelial cells

Biological Active Products

- Opsonization: some complement proteins are good opsonins
- C3b, iC3b and C4b attach to microorganism first
- This complex of complement protein binds with complement receptor on the surface of phagocytic cell
- Phagocytosis of microbe

Immunology

Hypersensitivity

Immunology

Introduction to Hypersensitivity

Introduction to Hypersensitivity

- Also known as Hypersensitivity reaction or intolerance
- Undesirable reaction by normal immune system
- Overreaction of immune system
- Damaging, uncomfortable and fetal state
- Require pre-sensitize state of host

Introduction to Hypersensitivity

- Protective role of immune system become harmful
- Allergy: abnormal response against the otherwise harmless environment stimulus (e.g food, pollen & animal dander)
- Autoimmune disorder: Abnormal response against self tissues

Immunology

Classification of Hypersensitivity

Classification of Hypersensitivity

- Based on following two factors
- Kind of immune reaction involved
- Time required for reaction
- Four different types of hypersensitivity
- Type I
- Type II
- Type III
- Type IV

Immunology

Type I Hypersensitivity

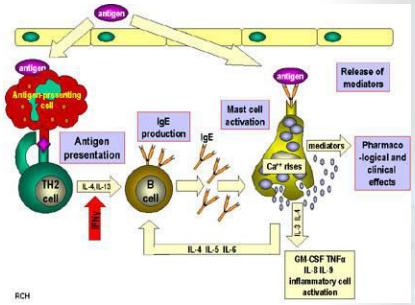
Type I Hypersensitivity

- Also known as Immediate or Anaphylactic reactions
- Involve various tissues
- Skin: Urticaria & Eczema
- Eyes: Conjunctivitis
- Nose: Rhinorrhea, Rhinitis
- Lungs: Asthma
- GIT: Gastroenteritis
- Symptoms: Minor inconvenience to death

Type I Hypersensitivity

- Usually reaction is quick:15-30 minutes
- Sometimes can be 10-12 hours
- Mediated by IgE
- Primary cells involved: Basophils, Mast cells
- Reaction is amplified by involvement of platelets, Neutrophils & Eiosinophils

Type I Hypersensitivity



http://www.microbiologybook.org/ghaffar/antigen.jpg

- Allergen: Preferential involvement of IgE
- Class switching
- Mediated by IgE
- Sensitization of mast cells with IgE via FcR receptor
- Cross linking of IgE with allergen
- Degranulation of mast cells
- Release of mediators

Type I Hypersensitivity

Pharmacological Mediators of Immediate Hypersensitivity

Preformed mediators in granules	
Histamine	Bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
Tryptase	Proteolysis
Kininogenase	Kinins and vasodilatation, vascular permeability, edema
ECF-A (tetrapeptides)	Attract eosinophil and neutrophils

Type I Hypersensitivity

- Diagnosis of Type I Hypersensitivity
- By Skin (Prick & Intradermal) test: Administration of allergen
- Measurement of total IgE levels
- Also allergen specific IgE levels

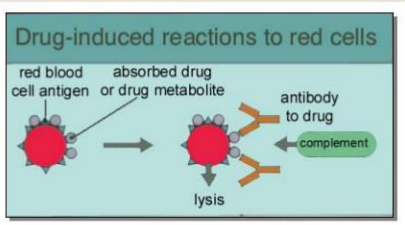
Immunology

Type II Hypersensitivity

Type II Hypersensitivity

- Also known as cytotoxic hypersensitivity
- Effect various organs & tissues (Tissue specific)
- Antigens are usually endogenous
- Exogenous: Chemicals in the form of haptens
- Binds to the surface of cell membrane
- Antibodies against antigens: IgM or IgG

Type II Hypersensitivity



https://www.google.com/search?q=type+ii+hypersensitivity&client=firefox-b&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjC2vDLpJDdAhXUfSsKHZC0DcEQ_AUICigB&biw=1366&bih=654#imgrc=raxf5lj46XJCwM:

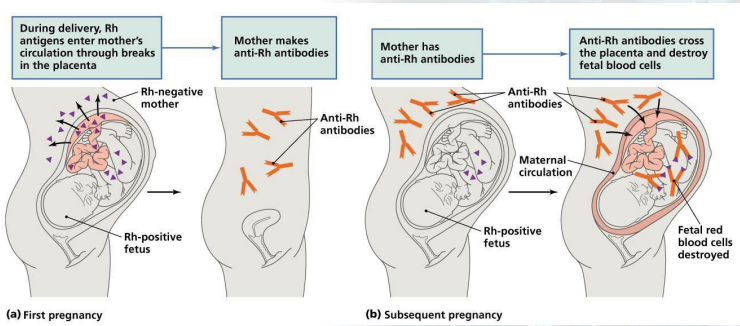
- Example of exogenous antigen: Drug induced hemolytic anemia, granulocytopenia & thrombocytopenia
- Ag-Ab reaction on the surface of RBC
- Complement fixation on immune complex on RBC surface
- Reaction time is minutes to hour
- Lysis of RBC

Type II Hypersensitivity

- Example of endogenous antigen: Erythroblastosis Fetalis
- Also called as Hemolytic disease of newborn (HDN)
- Rh incompatibility B/W mother & fetus
- Development of anti-Rh antibodies in maternal serum (IgG)
- Cross placenta in subsequent pregnency

Type II Hypersensitivity

Hemolytic Disease of Newborn

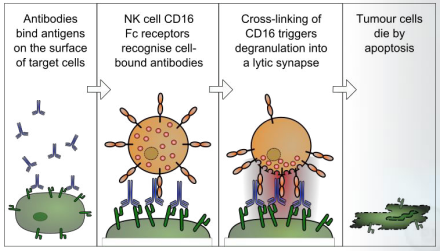


https://southernbloodservices.com/faq/

Type II Hypersensitivity

- Other Examples of endogenous antigen: Autoimmune Tissues disease
- Goodpasture's Syndrome: Autoantibodies against glomerulus basement membrane
- Hashimoto's thyroiditis: Autoantibodies against thyroid

Type II Hypersensitivity



https://en.wikipedia.org/wiki/Antibody-dependent_cell-mediated_cytotoxicity#/media/File:Antibody-dependent_Cellular_Cytotoxicity.svg

- Antibody dependent Cellular Cytotoxicity (ADCC): Another form of Type II hypersensitivity
- Independent of complement system
- Effector immune cell lyse the target cell coated with antibody
- NK cells are the primary effector cells
- Neutrophils, macrophages & Eiosinophils

Immunology

Type III Hypersensitivity

Type III Hypersensitivity

- Also known as immune complex hypersensitivity
- Time required: 3-10 hours after exposure to antigen
- Soluble immune complex formation
- Immune complex effect generally (Serum sickness)
- Specific to various organs

Type III Hypersensitivity

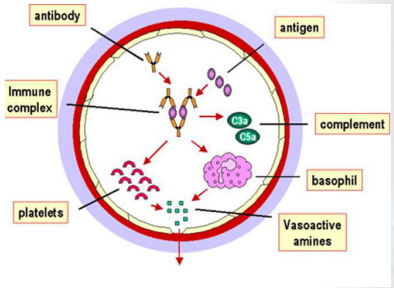
https://www.rheumatologyadvisor.com

- Skin: Systemic Lupus erythematous (SLE), Arthus reaction
- Kidney: Lupus nephritis
- Lung: Aspergillosis
- Blood vessels: Polyarteritis
- Joints: Rheumatoid Arthritis
- Pathogenesis: Involvement of microorganisms

Type III Hypersensitivity

- Antigens can be of two types in these reactions
- Exogenous: Chronic bacterial, viral & parasitic infections
- Endogenous: Non-organ specific autoimmunity e.g SLE
- Antigens are soluble
- Antibodies: Mostly IgG but IgM also involved

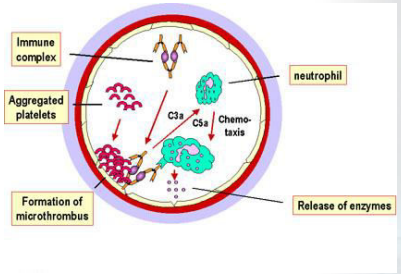
Type III Hypersensitivity



http://www.microbiologybook.org/ghaffar/capil2.jpg

- Primary components: Soluble Immune complexes with complement (C3a & C5a)
- Platelets & Neutrophils are involved in damage
- Lesion contain: Primarily Neutrophils with immune complex & complement
- Infiltrating macrophages: later in healing process

Type III Hypersensitivity



http://www.microbiologybook.org/ghaffar/capil2.jpg

- Affinity of antibodies
- Size of immune complex
- Type of tissue involved
- Aggregated platelets form micro thrombus
- Increased vascular permeability
- Diagnosis: Presence of immune complex with complement in tissue biopsies by Immunofluorescence

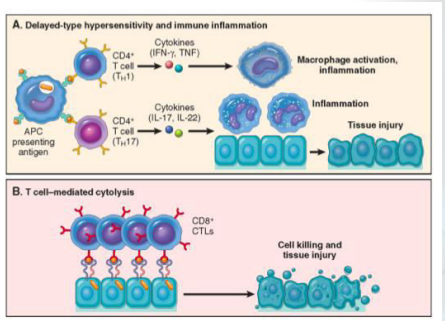
Immunology

Type IV Hypersensitivity

Type IV Hypersensitivity

- Also known as cell mediated hypersensitivity
- Time required: 48-72 hours
- Delayed type of hypersensitivity
- T-cells, Macrophages & monocytes are involved
- Response is against intracellular pathogens
- Antibody independent

Type IV Hypersensitivity



- CD8 (Cytotoxic)T-cells cause direct damage to target cells
- CD4 (Helper)T-cells: Th1 cells recognize foreign antigen with MHC class II
- Secretion of Cytokines
- Macrophage activation & Inflammation
- Tissue injury & damage

Type IV Hypersensitivity

Type	Reaction type	Clinical Appearance	Histology	Antigen & Site
Contact	48-72 hrs	Eczema	Lymphocytes, followed by macrophages; edema of epidermis	Epidermal (organic chemicals, poison ivy, heavy metals, *etc.*)
Tuberculin	48-72 hrs	Local induration	Lymphocytes, monocytes, macrophages	Intradermal (tuberculin, lepromin, *etc.*)
Granuloma	21-28 days	Hardening	Macrophages, epitheloid and giant cells, fibrosis	Persistent antigen or foreign body presence (tuberculosis, leprosy, *etc.*)

Immunology

Comparison of different Type Hypersensitivity

Comparison of Hypersensitivity

Characteristics	Type-I (anaphylactic	Type-II (cytotoxic)	Type-III (immune complex)	Type-IV (delayed type)
Antibody	IgE	IgG, IgM	IgG, IgM	None
Antigen	Exogenous	Cell surface	Soluble	Tissues and organs
Response time	15-30 minutes	Minutes-hours	3-8 hours	48-72 hours
Appearance	Weal and flare	Lysis and necrosis	Erythema and edema, necrosis	Erythema and induration
Histology	Basophils and eosinophil	Antibody and complement	Complement and neutrophils	Monocytes and lymphocytes
Transferred with	Antibody	Antibody	Antibody	T-cells
Examples	Allergic asthma, hay fever	Erythroblastosis fetalis Goodpasture's nephritis	SLE, farmer's lung disease	Tuberculin test, poison ivy, granuloma

Immunology

Cytokines

Immunology

Overview about Cytokines

Overview about Cytokines

- Diverse group of non-antibody proteins
- Act as mediators between cells
- Initially these were considered as products of immune cells
- Also considered to act as mediator for immune cells
- Also produced from non-immune cells & mediators for them

Overview about Cytokines

- Used as biological response modifier for treatment of various diseases
- Cytokine is a general term but more specific term used according to their cell of origin
- Monokines: produced by mononuclear phagocytic cells
- Lymphokines: produced by activated lymphocytes

Overview about Cytokines

- Interleukins: are mediators between leucocytes
- Chemokines: are responsible for leucocytes migration
- Cytokines function as cascade signaling in the form of cytokine network
- Act in additive or synergistic manner: enhance the effects of other cytokines

Overview about Cytokines

- Also act as antagonistic way: suppress the effects of other cytokines
- Are not as preformed proteins like Ab
- Produced by gene transcription as needed
- mRNA for cytokines are short lived
- Individual cytokine can act on many cells: pleotropic response

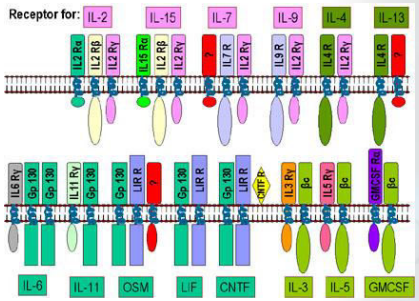
Immunology

Mechanism of acting of Cytokines

Mechanism of acting of Cytokines

- Cytokines act through specific receptors present on various cells
- Cytokines are considered as redundant
- Redundancy: is due to the nature of cytokine receptors
- Complex interaction between cells & cytokines: Through cytokine network

Mechanism of acting of Cytokines



http://www.microbiologybook.org/bowers/imm-reg-ver2.htm

- Different cells can respond to same cytokine due to structural similarities among cytokine receptors
- Cytokine signaling is flexible: Can have protective & damaging effects
- Influence the synthesis of other cytokines

Mechanism of acting of Cytokines

- Cytokines bind to specific receptors with high affinity & respond in following three ways
- Autocrine: effect on same cell which secrete cytokine
- Paracrine: effect on nearby cells to cells which secrete cytokine
- Endocrine: effect on distant cells through circulation

Immunology

Categories of Cytokines

Categories of Cytokines

- Cytokines are categorized on following two basis
- Their source of origin
- Their functions
- Categories based on source cells
- Monokines: produced by mononuclear phagocytic cells e.g Interferon gamma & Interleukin (IL-1) from macrophages & Monocytes

Categories of Cytokines

- Lymphokines: produced by activated lymphocytes e.g IL-3, IL-4 & IL-5
- Interleukins: are mediators between leucocytes e.g IL-1, IL-10& IL-18
- Chemokines: are responsible for leucocytes migration e.g IL-8

Categories of Cytokines

- Based on functions
- Cytokines which act for Innate (non-Specific) immune system e.g TNF-α, IL-1, Il-10 etc
- Cytokines which act for Adaptive (Specific) immune system e.g Il-2,IL-4 & IL-5

Immunology

Cytokines of Innate Immune System

Cytokines of Innate Immune System

- Cytokines which act primarily for Innate (non-Specific) immune system

1) Tumor Necrosis Factor-Alpha (TNF-α)

- Produced by activated macrophages in response to microbes or their products e.g LPS of Gram –ve bacteria
- It's a mediator of acute inflammation

Cytokines of Innate Immune System

- Recruits neutrophils & macrophages at the site of infection either by stimulating endothelial cells to secrete adhesion proteins
- Or by secreting chemokines
- TNF-a induces fever and acute phase proteins

Cytokines of Innate Immune System

2) IL-1

- Inflammatory cytokine as like TNF-a
- Produced by activated macrophages
- Also help to activate T-cells

3) IL-10

- It's a inhibitory cytokine
- Inhibits the cytokine production of cytokines from macrophages

Cytokines of Innate Immune System

4) IL-12

- Produced by dendritic cells & macrophages
- Enhance the cytolytic activity of cytotoxic T-cells

5) Type I interferon

- Include Interferon α & β
- Inhibit viral replication in cells
- Increase the expression of class I MHC making susceptible to CTL

Cytokines of Innate Immune System

6) IFN-γ

- Produced primarily by Th1 cells
- Enhance the cytolytic activity of NK cells
- Induction of class I & II MHC

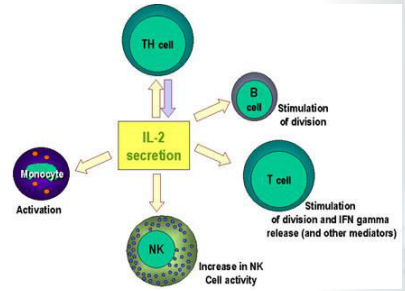
7) Chemokines

- Chemotactic cytokines produced by many leucocytes
- Recruits inflammatory cells at site of infection

Immunology

Cytokines of Adaptive Immune System

Cytokines of Adaptive Immune System



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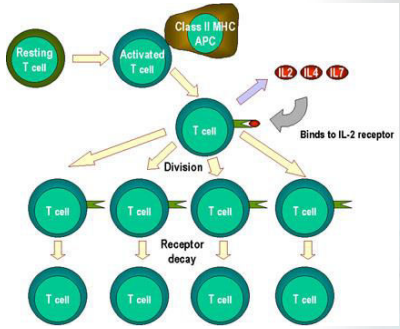
- Cytokines which act primarily for Adaptive (Specific) immune system

1) IL-2

- Produced by Th cells but Tc also produced in lesser extent
- Stimulate B-cell division
- Can also activate NK cells & monocytes
- IL-2 acts in autocrine manner on T-cells

Cytokines of Adaptive Immune System



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- Activation of T-cells result in expression of IL-2R & production of IL-2
- IL-2 binds to IL-2R and promotes cell division
- IL-2R decay if T-cells are not activated & eventually proliferative phase ends

Cytokines of Adaptive Immune System

2) IL-4

- IL-4 is produced by macrophages &Th2 cells
- Promotes the development of Th2 from naïve Th cells
- Differentiated Th2 cells result in the production of antibodies
- IL-4 involves in the class switching of antibody into IgE

Cytokines of Adaptive Immune System

3) IL-5

- IL-4 is produced by Th2 cells
- Promotes the development of B-cells & eosinophiles
- Also activates mature eosinophiles

Cytokines of Adaptive Immune System

4) TGF-β

- TGF- β is produced by T cells and many other cells types
- Acts as inhibitory cytokine
- Inhibits the proliferation of T-cells & activation of macrophages
- Also acts on neutrophils & endothelial cells to block the effects of pro-inflammatory cytokines

Immunology

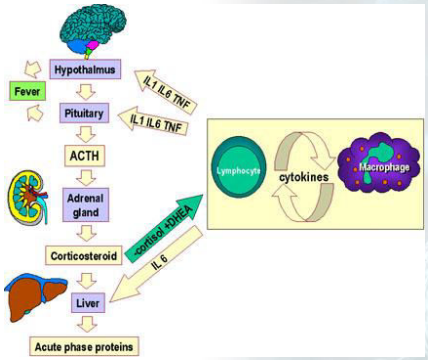
Cytokine Network

Cytokines Network

- A complex series of overlapping & inter-related connections among cytokines
- As cytokines secreted from one kind of cells have effect on other type of cells & organs
- Within this network, some cytokines have synergistic effects on other cytokines
- Some have antagonistic effects

Cytokines Network

Communication B/W Lymphocytes, Macrophages, Hypothalamus, Kidney & Liver



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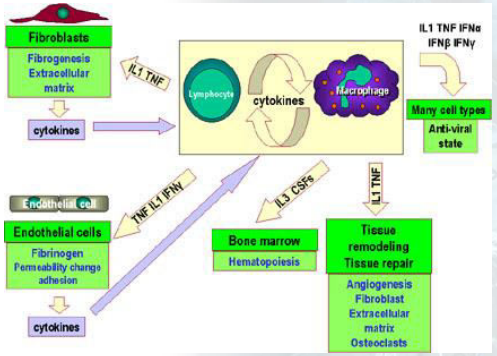
Cytokines Network

Communication B/W Lymphocytes, Macrophages & Other Tissues



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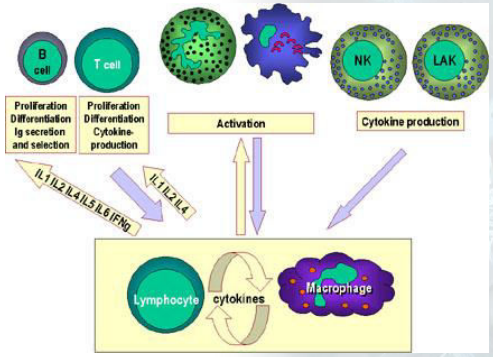
Cytokines Network

Communication B/W Lymphocytes, Macrophages & Other Components of Immune System



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Immunology

Immuno-Regulation by Cytokine

Immunoregulation by Cytokines

- The control of immune response B/W Lymphocytes & macrophages
- Balance is required B/W antigen driven activation of lymphocytes & negative regulatory influences
- Immunoregulation occur at following three phases of immune responses

Immunoregulation by Cytokines

1) Recognition phase
2) Activation Phase
3) Effector Phase

- Cytokines are considered as positive or negative regulator of Immune response
- Cytokines can act on many stages of immune responses

Immunoregulation by Cytokines

- Activity dependent on presence of other cytokines in microenvironment
- Receptor expression on effector cells
- Regulate the type & extent of immune response generated

Immunology

Resistance & Immune Response to Infectious diseases

Immunology

What is Immune Evasion?

Overview about Immune evasion

- Strategies used by pathogenic organisms and tumor cells to evade host immune's system
- Immune surveillance: Protection against pathogenic organisms & transformed cells
- Maximizes the ability of organism to flourish and develop infection
- Enhance the ability of tumor cells to evade & sustain inside the body

Overview about Immune evasion

- Immune-evasion occurs either by weak immune response
- Or by strategies devised by pathogens
- Immune system can be bypassed by evading humoral immunity
- Cell mediated immunity can also evaded by pathogenic microbes & transformed cells

Immunology

Mechanisms of Immune Evasion

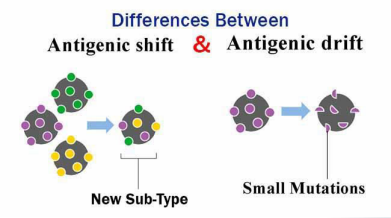
Mechanisms of Immune evasion

- Escape from immune system is caused by different microbes differently
- Extracellular organisms usually inactivate the humoral components of immune system
- Intracellular organisms bypass by inactivating intracellular killing & other cell mediated immune mechanisms

Mechanisms of Immune evasion

- **Antigenic Variation**
- Antigenic variation: Organisms mutate their antigenic surface molecules
- No longer protection by antibodies produced as a result of previous form of antigen
- Antigenic shift: Major form of change in antigenic structure results in new strains of microbe

Mechanisms of Immune evasion



https://microbiologyinfo.com/differences-between-antigenic-shift-and-antigenic-drift/

- **Antigenic Variation**
- Antigenic drift: Minor form of antigenic variation within the same strain
- Influenza (Flu) virus exhibits antigenic shift & drift for pandemic & seasonal flu respectively
- *E.coli*, *Neisseria gonorrhoeae* & *Salmonella typhimurium*

Mechanisms of Immune evasion

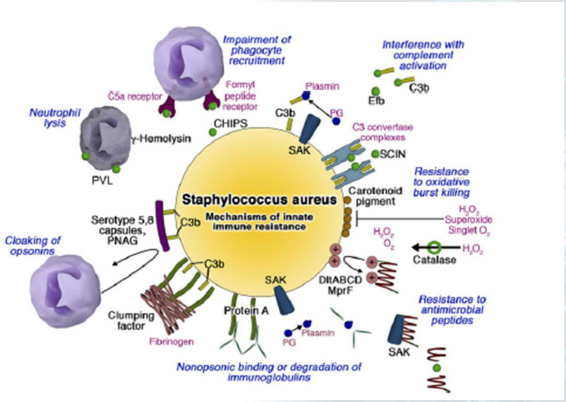
- **Inhibition of Complement activation**
- Degradation of complement proteins by complement deviation
- Complement deviation occurs by deviation the complement activation site on bacterial cell
- Resistance to insertion of Membrane Attack Complex (MAC) in bacterial due to thick cell wall & capsule

Mechanisms of Immune evasion

- **Resistance to Phagocytosis**
- Inhibition of phagocytosis process due to cell surface molecules of bacteria e.g capsule of bacteria (Pnemocccus)
- Trapping of bacteria e.g Coagulase by *S. aureus*
- Killing of phagocytes due to toxins e.g Leucocidin & Lysins (*S. aureus* & Streptococci)

Mechanisms of Immune evasion

Strategies of Immune evasion by *S. aureus*



Victor Nizet., J Allergy Clin Immunol 2007;120:13-22.

Mechanisms of Immune evasion

Mechanisms of Immune Evasion by intercellular Bacteria

Mechanism of Immune Evasion	Examples
Inhibition of phagolysosome formation	*Mycobacterium tuberculosis, Legionella pneumophila*
Inactivation of reactive oxygen and nitrogen species	*Mycobacterium leprae* (phenolic glycolipid)
Disruption of phagosome membrane, escape into cytoplasm	*Listeria monocytogenes* (hemolysin protein)

9

Immunology

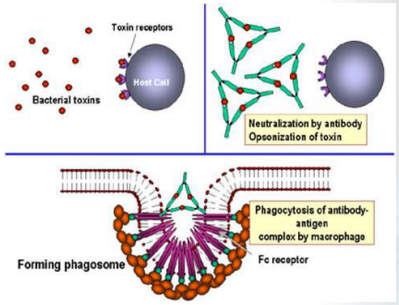
Immune Response against Extracellular Pathogens

Control of Extracellular Pathogens

- Secretory (humoral) immune molecules are effective against extracellular pathogens
- Molecules like antibodies & complement proteins
- Three ways of controlling

1) Neutralization
2) Opsonization
3) Complement activation

Control of Extracellular Pathogens



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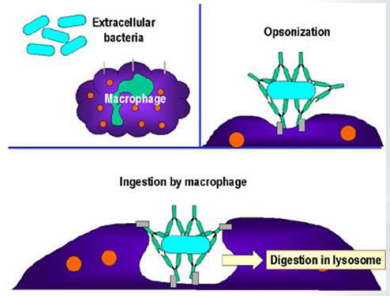
1) Neutralization

- Infectivity of bacteria or secreted molecules of bacteria like toxins
- By specific antibodies against toxins in a form of antitoxins
- Binding of antibodies with toxins (immune complex)
- Clearance of immune complex by process of phagocytosis

Control of Extracellular Pathogens



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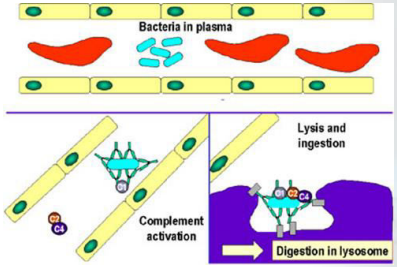
2) Opsonization

- Enhancement of process of phagycytosis by phagocytes
- Opsonin: Antibodies which bind specifically with extracellular bacteria e.g IgG or IgM
- Formation of immune complex
- Binding of immune complex with specific receptors against Fc fragment of Ab

Control of Extracellular Pathogens



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3) Complement activation

- Inactive complement proteins are activated by extracellular bacteria in combination with specific antibody
- Complement proteins are fixed on antibody which is already bounded with bacterial Ag
- Lysis of bacteria: Primary function by forming MAC

Immunology

Immune Response against Intracellular Pathogens

Control of Intracellular Pathogens

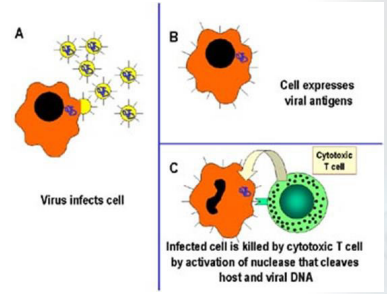
- Secretory immune molecules are ineffective against intracellular pathogens like viruses & intracellular bacteria
- Cell mediated immune response is the primary defense against intracellular pathogens
- T-Lymphocytes play role in cell mediated immunity

Control of Intracellular Pathogens

- Cell mediated immune response varies according to the residing site of the pathogen

1) Cytosolic site
2) Vesicular site

Control of Intracellular Pathogens



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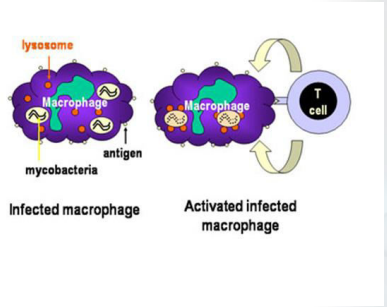
Control of Cytosolic Pathogens

- Exogenous Pathogens: Used to reside in the cytosol of infected cell
- Antigens are presented in combination with class I MHC
- Cytotoxic T-Lymphocytes: Recognize such antigens
- Viruses are controlled through such mechanism

Control of Intracellular Pathogens



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Control of Vesicular Pathogens

- Endogenous Pathogens: Used to reside in the vesicle (phagosomes) of infected cell
- Antigens are presented in combination with class I MHC
- Helper T-Lymphocytes: Recognize such antigens
- Intracellular bacteria e.g *Mycobacterium, Liesteria*

Immunology

Cell Mediated Effector Response

Immunology

Cell Mediated Immunity

Cell Mediated Immunity

- Immune response: Independent of antibodies
- Activation of phagocytes, antigen specific cytotoxic T-lymphocytes
- Release of cytokines from activated cell in response to antigen
- Humoral immunity: Cell free body fluid like serum contain protective molecules

Cell Mediated Immunity

- Cellular Immunity: Association of cells for protective functions of immunization
- Innate & Adaptive immune system both have humoral & cellular immunity
- Naïve & mature T-cells convert into effector T-cells after interacting with antigens via antigen presenting cells

Cell Mediated Immunity

- Cellular Immunity: Provides protection in following ways
- T-cell immunity: By activating cytotoxic T-cells for killing infected & transformed cells
- By activating macrophages for destroying pathogens
- Activating NK cells for killing transformed & viral infected cells

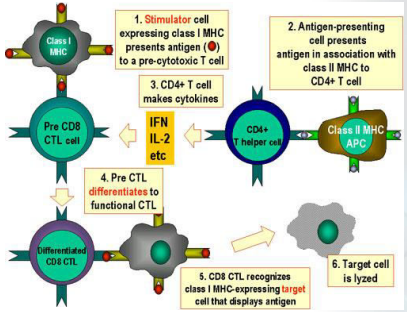
Immunology

Role of Cytotoxic T-Lymphocytes in Cell Mediated Immunity

Role of Cytotoxic T-Cells

- Cytotoxic T-Lymphocytes: CD8+ve
- Also called as CTL
- CTLs are not mature after exiting thymus
- Have functional TCR which can recognize antigens but cannot kill the target cells
- Needs differentiation for fully activation of CTL

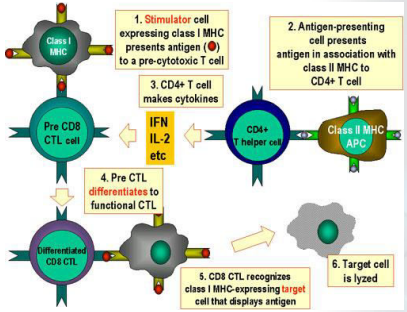
Role of Cytotoxic T-Cells



http://www.microbiologybook.org/bowers/ctl-8.jpg

- CTL differentiates from Pre-CTLs in response to two signals
- Specific antigen in context of Class I MHC
- Cytokines produced from Th1 cells especially IL-2 & INF-γ
- CTL cause killing of target cells
- CTL killing is antigen specific: Target cell must bear same antigen with class I MHC

Role of Cytotoxic T-Cells



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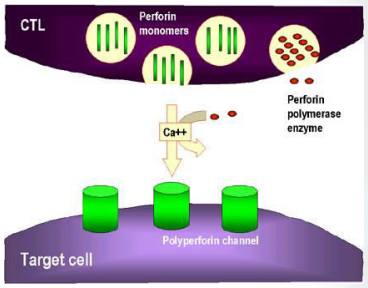
- CTL killing is antigen specific: Target cell must bear same antigen with class I MHC
- CTL killing requires cell to cell contact: Target cell should contain cell surface MHC molecule
- CTL are not injured while targeting the target cell
- One CTL can kill sequentially numerous target cells

Role of Cytotoxic T-Cells



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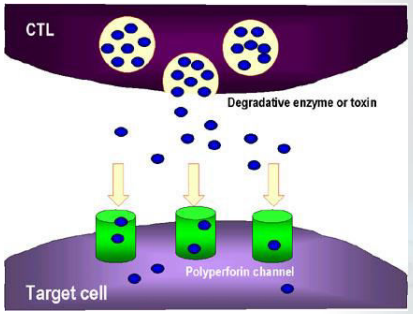
Mechanisms of CTL killing

- Granule-mediated killing: Fully differentiated CTL have numerous granules which contain perforin & graenzymes
- Upon CTL degranulation: Polymerization of perforin monomers
- Polyperforin channels are developed in the presence of Ca^{++}

Role of Cytotoxic T-Cells



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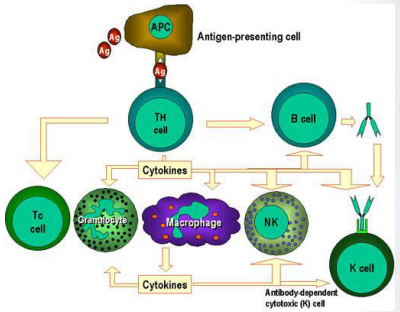
Mechanisms of CTL killing

- CTL release degradative enzyme or toxins
- Travel through perforin channels towards target cells
- Killing of target cells with the help of degradative enzymes
- Cytokines like TNF-a & INF-γ from CTL bind to target cells and induce apoptosis

Immunology

Role of Helper T-Lymphocytes in Cell-Mediated Immunity

Role of Helper T-Cells



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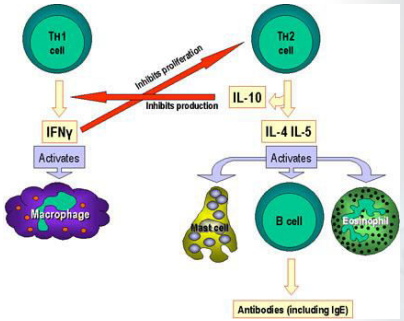
- Helper T-Lymphocytes: CD4+ve
- Th cells are at the center of cell mediated immunity
- Th cells recognize specific antigens presented with class II MHC
- Activate B-cells with the help of Th cells
- Release of cytokines which activate other immune cells

Role of Helper T-Cells



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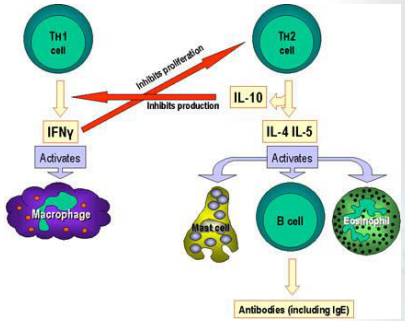
- Two major subtypes of Th cells

1) Th1 cells
2) Th2 cells

- Th1 cells release cytokine like IFNγ upon activation & activate macrophages
- In turn macrophages participate in generation of CTL for cell mediated immunity
- IFNγ: inhibitory for Th2

Role of Helper T-Cells



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- Th2 cells upon activation secrete cytokines like IL-4 & IL-5 which activate B-cells
- Promotes humoral immunity
- Class switching into IgE class
- Also activate mast cells & eosinophils
- IL-10 : Inhibitory for IFNγ production from Th1 cells

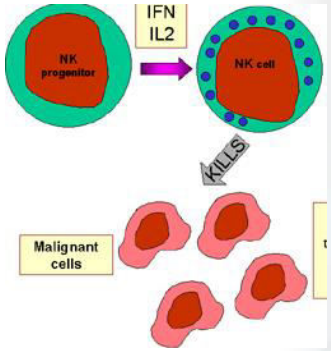
Immunology

Role of NK cells in Cell Mediated Immunity

Role of Natural Killer Cells

- NK cells also called as Large Granular Lymphocytes (LGL)
- Resemble with Lymphocytes except that they are larger & have numerous granules
- Have surface molecule C16 & CD56 and lack CD3
- Capable of killing virus infected & malignant cells
- Need activation

Role of Natural Killer Cells



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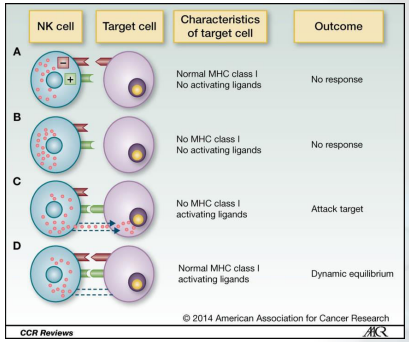
- Upon exposure to cytokines like IL-2 & IFNγ NK cells are activated
- NK cells recognize the infected & malignant cells
- Recognition is based on the absence of class I MHC molecule from infected cells in contrast to normal cells
- NK cells kill the target cell like CTL using perforin & graenzymes

Role of Natural Killer Cells



http://clincancerres.aacrjournals.org/content/20/13/3390.figures-only

- NK cells need cell to cell interaction for its effector function
- NK cell cannot kill normal cells (Self) due to normal expression of Class I MHC
- Infected & malignant cells are recognized due absence of Class I MHC
- In this way viral infected & tumor cells are rejected

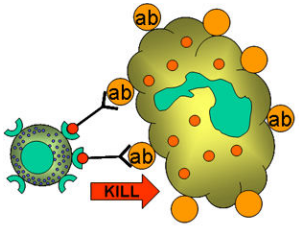
Immunology

Antibody dependent Cellular Toxicity by Killer Cells

ADCC by Killer Cells

- Antibody dependent Cellular Cytotoxicity (ADCC)
- K cells are not morphologically distinct type of cells
- Any cell which can mediate ADCC like NK cell, macrophages & PMNLs
- Antibody act as to bring K cell close to target cell
- Cell to cell interaction

ADCC by Killer Cells

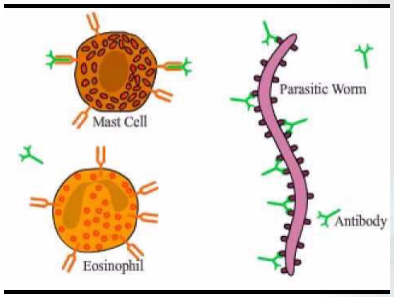


NK cell Target cell

http://www.microbiologybook.org/ghaffar/nk-target.gif

- K cells have Fc receptors on their surface
- Antibodies like IgG bind to target cell
- Coated target cell binds to Fc receptor for IgG present on NK, LAK cells & macrophages
- Target cell is killed by perforin/graenzyme mediated mechanism
- Cell to cell interaction

ADCC by Killer Cells



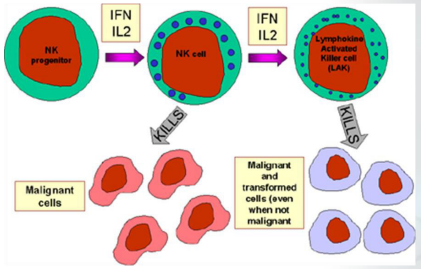
http://www.microbiologybook.org/ghaffar/nk-target.gif

- IgE mediated ADCC
- Mast cells & Eosinophils have Fc recetors for IgE
- IgE coat the parasite surface
- IgE bring coated parasitic cell to mast cells
- Degranulation of mast cells/eosinophils for killing of parasite

Immunology

Lymphokine Activated Killer Cells in Cell Mediated Immunity

Lymphokine Activated Cell



http://www.microbiologybook.org/ghaffar/ns6.jpg

- LAK cell
- Are NK cells which are differentiated by continuous exposure to IL-2 & IFN
- LAK cells kill transformed & malignant cells
- Killing process is selective for sparing normal cells
- Cell to cell interaction

Lymphokine Activated Cell

- Killing is executed as tumor cells lack class I MHC
- LAK cells are specific for tumor cells
- LAK cells are responding to those tumor cells which are resistant to NK cells killing
- LAK cell therapy for treating various tumors

Immunology

Leucocytes Migration & Inflammation

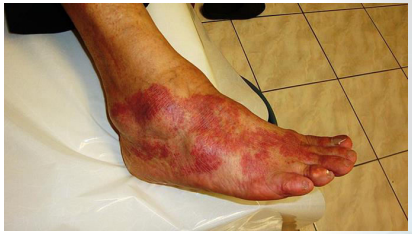
Immunology

Inflammation vs Infection

Inflammation vs Infection

- Inflammation is the body's attempt: To protect the body from harmful stimulus
- Complex Tissue response
- Part of body's immune system
- Inflammatory response: series of events for inflammation
- For wound healing
- For clearance of infections

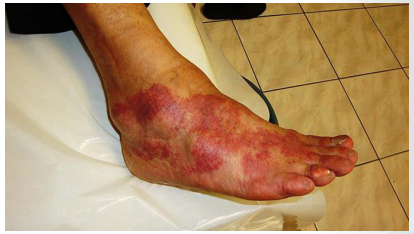
Inflammation vs Infection



https://en.wikipedia.org/wiki/File:Allergy_to_Antibiotic_Cefaclor.JPG

- Inflammation can be beneficial for host in order to remold the damaged tissue
- Undesirable effects: in the form of signs of inflammation
- Dolor (Pain)
- Calor (Heat)
- Rubor (Redness)
- Tumor (Swelling)
- Functio laesa (Loss of function)

Inflammation vs Infection



https://en.wikipedia.org/wiki/File:Allergy_to_Antibiotic_Cefaclor.JPG

- Inflammation is indicated with suffix "It is" e.g Appendicitis
- Outcome of Inflammation:
- Restoration of normal tissue
- Large amount of tissue destruction: Fibrosis
- Pus formation (Abscess formation)
- Chronic inflammation

Inflammation vs Infection

- Infections is not synonym to inflammation
- Invasion of body's tissue by pathogen
- Pathogens: Disease causing microbes e.g Bacteria, Viruses, Parasites, Fungi etc.
- Infectious disease: Transmittable
- Should comply Koch's postulates

Inflammation vs Infection

- Infectious agent: in patients suffering from infection not in healthy individuals
- Infectious agent: grow as pure culture
- Infection can be
- Epidemic: Sudden outbreak
- Endemic: constant occurrence
- Pandemic: global occurrence

Inflammation vs Infection

- Infections also describes the action of body after invasion in the form of inflammation
- Infection can be various kinds according to anatomical locations
- Respiratory tract infections
- GIT infections
- Skin infections
- Genital tract infections

Immunology

Role of Phagocytes in Inflammation

Role of Phagocytes in Inflammation

- Phagocytes: are inflammatory cells
- Macrophages & Neutrophils
- Recognition of infectious agent by receptors on phagocytes called Pattern Recognition receptors (PRRs)
- Toll like receptors
- Fc receptors
- Complement receptors
- Scavenger receptors

Role of Phagocytes in Inflammation

http://www.microbiologybook.org/gh affar/macrophage-dk-13.jpg

- PRRs recognize various molecular patterns on pathogens: Pattern associated Molecular Patterns (PAMPs)
- LPS: recognized by TLRs
- Flagellins: also recognized by TLRs
- Cell wall component: through complement receptor after binding with complement
- Phagocytes ingest infectious agent

Role of Phagocytes in Inflammation

http://www.microbiologybook.org/gh affar/alv-macrophage-dk-13.jpg

- Neutrophils ingest & kill the pathogens intracellularly
- During inflammation collateral tissue damage
- Macrophages: also ingest & kill the infectious agent
- Tissue macrophages: Inflammatory response
- Also contribute in tissue repair & antigen presentation

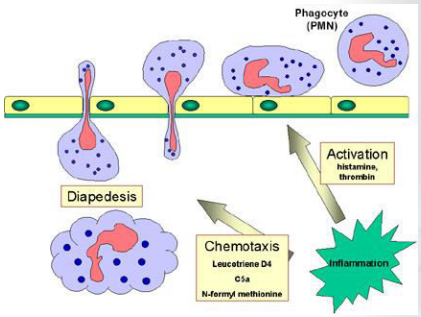
Immunology

Chemotaxis & Diapedesis of Leucocytes in Inflammation

Chemotaxsis & Diapedesis

- Leucocytes provide response against infection
- Chemotaxsis: movement of circulating phagocytes to the site of infection
- Chemotactic agents: SOS signals from bacteria like N-formylmethionine containing peptides
- Clotting system peptides
- Complement proteins
- Cytokines: Macrophages

Chemotaxsis & Diapedesis



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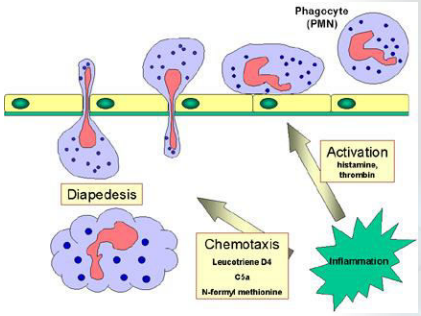
- SOS signals also activate endothelial cells of blood vessels
- Increased expression of adhesion molecules like ICAM-1 & selectins
- Binding of phagocyte to adhesion molecules: adherence of phagocytes on endothelial surface
- Rolling of phagocytes
- Release of vasodilators: loosen the gap B/W endothelial cells

Chemotaxsis & Diapedesis



http://www.microbiologybook.org/ghaffar/newns2.jpg

- After loosening of endothelial cells: Squeezing of phagocytes
- Diapedesis: crossing the endothelial barrier after squeezing & movement extravascularly
- Extravascular site: site of infection
- Infected Tissues sites: attraction of phagocytes (Chemotaxsis)
- Activation of phagocytes

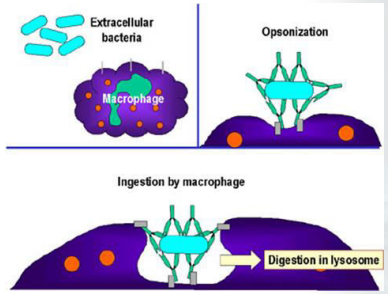
Immunology

Opsonization of Bacteria

Opsonization of Bacteria

- Enhancement of phagocytic process
- Pathogen is marked for ingestion by phagocytes
- Marking of bacteria by opsonin: molecule which enhance phagocytosis
- Opsonins: like immunoglobulin (IgG & IgM) & complement proteins
- Opsonin bind with bacterial surface

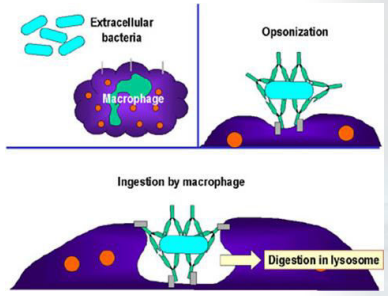
Opsonization of Bacteria



http://www.microbiologybook.org/bowers/bact-comp.jpg

- Under normal inflammatory circumstances, PAMPs of bacteria bind with PRRs of phagocytes
- Mediates neutrophil or macrophage phagocytosis
- PRRs also cause the expression of opsonin receptor on phagocytes like Fc receptor & complement receptor

Opsonization of Bacteria



http://www.microbiologybook.org/bowers/bact-comp.jpg

- Interaction of opsonin receptor on phagocytes with opsonin on bacterial surface
- After binding, bacteria is internalized in phagosome
- Killing of bacteria by intracellular killing

Immunology

Intracellular Killing by Leucocytes during Inflammation

Intracellular killing

Intracellular Killing

- During inflammation, ingested bacteria are killed by phagocytes
- After phagocytosis the ingested bacteria is being killed by a process called as Intracellular Killing
- Two ways of intracellular killing

1) Oxygen independent
2) Oxygen dependent

Intracellular killing

1) Oxygen Independent

- No need of oxygen for such kind of intracellular killing of bacteria
- Granules & Vesicles of phagocytes secrete hydrolytic proteins
- Those proteins are bacteriocidal in nature according to their modes of action

Intracellular killing

Mechanisms of Oxygen Independent Killing

Effector Molecule	Function
Cationic proteins (including cathepsin)	Damage to microbial membranes
Lysozyme	Splits mucopeptide in bacterial cell wall
Lactoferrin	Deprives proliferating bacteria of iron
Proteolytic and hydrolytic enzymes	Digestion of killed organisms

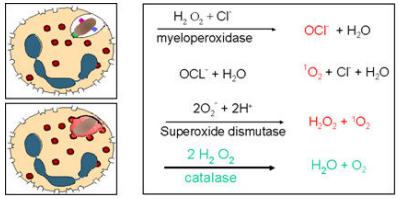
Intracellular killing

2) Oxygen Dependent

- Requirement of oxygen for such kind of intracellular killing of bacteria
- Also called “Respiratory Burst” as requirement of glucose & oxygen increased after phagocytosis
- Oxygen containing bacteriocidal radicals are produced

Intracellular killing

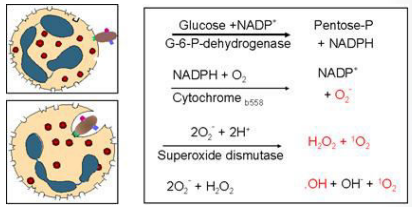
2) Oxygen Dependent



- Myeloperoxidase (MPO)dependent
- MPO from granules of phagocytes
- Halide ions (OCl^-) are formed which are bacteriocidal

http://www.microbiologybook.org/ghaffar/ns2000-3a.jpg

Intracellular killing



2) Oxygen Dependent

- Myeloperoxidase independent
- Involvement of Hexose monophosphate shunt
- Reactive Oxygen Species (ROS) e.g Superoxide radicals, hydrogen peroxide & singlet oxygen

http://www.microbiologybook.org/ghaffar/ns2000-3.jpg

Immunology

Role of Cytokines in Inflammation

Role of Cytokines in Inflammation

- Cytokines: Mediators of Inflammation
- Complex variety of mediators in acute inflammatory response
- Some cytokines directly act on smooth muscles wall surrounding the arterioles: to alter the blood flow
- Others act on venules to cause contraction of endothelial cells: opening of junctions

Role of Cytokines in Inflammation

- Migration of leucocytes from bloodstream
- Up regulate the expression of adherence molecules on endothelial cells
- Also adherence molecules on the surface of Leucocytes
- Cytokines also lead the leucocytes towards the inflamed site through chemotaxsis

Role of Cytokines in Inflammation

- Pro-Inflammatory cytokines: involved in up regulation of inflammatory process
- Predominantly produced by activated macrophages & Th cells
- Include IL-1β, IL-6 & TNF-α, IL-12 & INF-γ
- Role in mediating innate immune response
- Inflammatory diseases like atherosclerosis, cancer & depression

Role of Cytokines in Inflammation

- Anti-Inflammatory cytokines: involved in down regulation of inflammatory process
- Control pro-inflammatory cytokine response
- Include IL-4, IL-10 , IL-11 & IL-13
- Pathological role in systemic inflammatory states
- Balance B/W Pro & anti inflammatory cytokines

Immunology

Inflammosomes in Inflammation

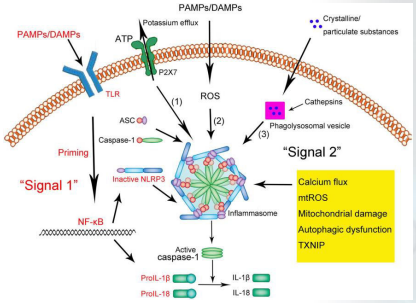
Inflammosomes in Inflammation

- A multi-protein oligomer
- Responsible for activation of inflammatory responses
- Promotes the maturation & secretion of pro-inflammatory cytokines like IL-1β & IL-18
- Inflammosomes expressed in myeloid cells
- Component of innate immune system

Inflammosomes in Inflammation

- Secretion of cytokines upon inflammasomes activation cells lead towards death process
- Pyroptosis: type of death induced after inflammosomes
- Pyroptosis mediates the inflammatory process by killing infected cells in physiological state
- Pathologically increased pyroptosis leads towards inflammatory diseases

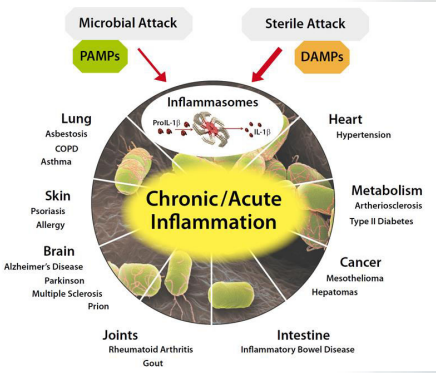
Inflammosomes in Inflammation



https://www.frontiersin.org/files/Articles/167682/fphar-06-00262-r2/image_m/fphar-06-00262-g001.jpg

- Germline encoded PRRs of immune cells like TLRs, Nod like receptors (NLRs)
- PRRs recognize PAMPs on pathogens lead the assembling of inflammosomes
- As a results, Caspase-1 get matured
- Caspase-1 cleaves the pro or inactive forms of pro-inflammatory cytokines like IL-1β & IL-18

Inflammosomes in Inflammation



https://adipogen.com/inflammasomes/

- Deregulated Inflammosomes activity leads to pathological states like autoimmune disorders e.g Rheumatoid arthritis, Inflammatory bowel disease
- Inflammatory disorders
- Metabolic disorders
- Cancer

Immunology

Acute vs Chronic Inflammation

Acute vs Chronic Inflammation

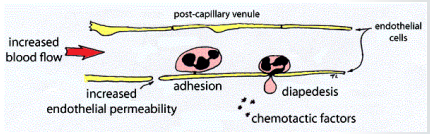
- Acute Inflammation: Short term process occurring in response to tissue injury
- Appear in minutes to hours
- Purely physical damage
- Activation of immune system
- Three main processes involved in acute inflammation

Acute vs Chronic Inflammation

1) Increased blood flow
2) Increased permeability
3) Migration of Leucocytes

- Increased blood flow
- Dilatation of blood vessels in the effected region
- Redness of the effected area
- Increased in temperature of effected area

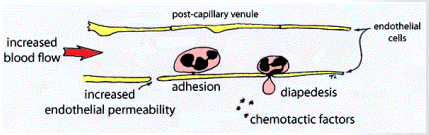
Acute vs Chronic Inflammation



https://courses.washington.edu/conj/inflammation/acuteinflam.htm

- Increased Permeability
- Permeability causes the leakage of plasma into tissue interstetium
- Accumulation of fluid in tissue
- Edema: swelling of the effected area due to additional accumulation of fluid into interstitial space of the region
- Endothelial cells separate

Acute vs Chronic Inflammation



- Migration of Leucocytes
- Chemotaxsis: increased movement of Leucocytes towards the site of infection
- Accumulation of fluid in tissue

https://courses.washington.edu/conj/inflammation/acuteinflam.htm

Immunology

Adverse Effects of Inflammation

Adverse Effects of Inflammation

- Inflammation is associated with general flu like symptoms including
- Fever
- Chills
- Fatigue/Lethargy/Loss of energy
- Headaches
- Loss of appetite
- Body pains
- Muscle stiffness

Immunology

Vaccines

Immunology

Introduction to Vaccination (Immunization)

Introduction to Vaccination

- Ways of providing specific protection against many common & damaging pathogens
- Stimulation of organism's or individual's immune system
- Stimulation of humoral immunity for production of antibodies against pathogen
- Cell mediated immunity activation by providing specific T-cells

Introduction to Vaccination

- Neutralization of specific pathogens
- Depending upon the nature of pathogenesis & site of infection by pathogen
- Toxin production is neutralized by specific antibodies (antitoxins)
- Toxins get masked by antitoxins, not able to bind its specific receptor on target cell

Introduction to Vaccination

- Antibodies against pathogens also bind complement and lead to lysis of pathogen
- Complement mediated intracellular killing of pathogen
- Intracellular pathogens: no neutralization by antibodies
- Immunization against intracellular pathogen by cell-mediated immunity

Immunology

Types of Vaccination

Types of Vaccination

- Two modes of providing specific protection against many common & damaging pathogens
- These modes of immunization can be natural or artificial in their nature

1) Active Immunization

1) Passive Immunization

Introduction to Vaccination

- Active Immunization: is the induction of immunity after exposure to antigen
- Antigenic exposure is mandatory
- Active immunization can occur naturally by exposing to microbe or other antigen
- No prior exposure before the entry of antigen
- No pre made antibodies

Introduction to Vaccination

- Immune system develops antibodies against the microbe
- Slow process of antibodies generation
- Memory response: antibodies remained in use for longer time
- Artificial Active Immunization: Injection of microbe before natural exposure
- Treated microbes or toxins

Introduction to Vaccination

- Passive Immunization: is the induction of active humoral immunity
- Antibodies are mandatory
- Active immunization can occur naturally by transfer of maternal antibodies to fetus by placenta
- Artificial induction: injecting gamma globulins from other individuals or animals

Immunology

Cells of Innate Immune system

Cells of Innate Immune System

Cellular barriers

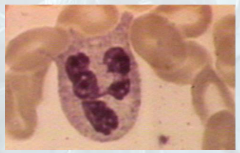
- In inflammatory process during infections, under the action of various humoral substances immune cells recruit towards the site of infection (Chemotaxsis)
- Immune cells from blood
- Immune cells from the inflamed tissues

Cells of Innate Immune System

Cellular barriers

1) Neutrophils

- Polymorphonuclear leucocytes (PMNs)
- Phagocytose the invading agent & kill intracellularly
- Immune cells from the inflamed tissue



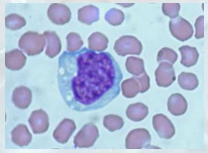
http://www.microbiologybook.org/ghaffar/neutrophil.jpg

Cells of Innate Immune System

Cellular barriers

2) Macrophages

- Phagocytic cells
- Tissue macrophages: Histocytes
- Circulating macrophages: Monocytes
- Involved in phagocytosis & intracellular killing



http://undergraduate.vetmed.wsu.edu/images

Cells of Innate Immune System

Cellular barriers

3) Natural Killer (NK) Cells

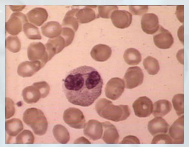
- Have the ability to kill viral infected cells non-specifically
- Also kill transformed or Tumorous cells
- Role in tumor surveillance

Cells of Innate Immune System

Cellular barriers

4) Eosinophils

- Blood Granulocytes
- Contain granules which are effective against parasitic infections
- Also cause the cytotoxicity of parasitic infected cells via receptors non-specifically



http://www.microbiologybook.org/ghaffar/eosinophil.jpg

Immunology

Artificial Passive Immunization

Artificial Passive Immunization

- Transferred by injecting specific gamma-globulins from other individual
- Or from other immune animals
- Artificial passive immunity is used against various acute infections
- Diphtheria
- Tetanus
- Measles
- Rabies

Artificial Passive Immunization

- Artificial passive immunity is also used against various poisoning conditions like
- Insects or sting biting e.g immunization against various strains of Malaria producing Plasmodium
- Reptiles e.g anti-venom administration in case of snake biting
- Food poisoning (Botulism)

Artificial Passive Immunization

- Artificial passive immunity is also used as prophylactic (preventive) measure against various infections
- Vaccination against Influenza & Poliomyelitis
- Antibodies: are usually human origin (Homologous antisera)
- Also raised in other species or animals after immunization (Heterologous antisera)

Artificial Passive Immunization

- Heterologous antibodies provide immediate protection
- Also complications like serum sickness & anaphylaxis
- Homologous antisera: potential risk of transmitting HIV & Hepatitis
- Passive transfer of cell mediated immunity: for cancer & immunodeficiency

Immunology

Artificial Active Immunization

Artificial Active Immunization

- Transferred by injecting live, dead or other components of microbes
- Vaccines used as artificial active immunization include

1) Live (attenuated) organisms
2) Killed organisms
3) Sub-unit vaccines

Artificial Active Immunization

- Live (attenuated) Vaccines
- Produced after inactivation of organism by heat
- Loss of virulence
- Used against various viral infections like Smallpox, measles, mumps, hepatitis A virus
- Live bacterial vaccine against tuberculosis: Bacille Calmette-Guerin vaccine: BCG

Artificial Active Immunization

- Killed Vaccines
- Produced after killing of organism by heat, chemical treatment or UV irradiation
- Used against various viral infections like Polio, rabies & influenza
- Most bacterial vaccines are also killed: typhoid, cholera, plague & pertussis

Artificial Active Immunization

- Subunit Vaccines
- Consist of various components of microbes
- Like polysaccharides from capsule & proteins (surface)
- Polysaccharides: T-independent Ag
- Proteins: T-dependent Ag
- Used for reducing the toxicity
- Pneumococcus

Immunology

Novel Vaccines

Novel Vaccines

- Novel ways of designing vaccines
- Reduction in toxicity
- Can provoke both humoral & cell-mediated immunity
- Mainly used in experimentally
- Would available for clinical use in future

Novel Vaccines

1) DNA vaccines

- Cloned viral peptides
- Transfected into host cell
- Generation of humoral & cell-mediated response like live attenuated vaccine
- Anti HIV-DNA vaccine
- No efficiency in experimental stage

Novel Vaccines

2) Immunodominant Peptides

- Simple & easy to prepare
- Incorporated with MHC to induce humoral & cell-mediated response

3) Anti-Idiotype antibodies

- Antibodies against polysaccharide antibodies
- Long lasting immune response with memory

Immunology

Role of Adjuvant in Vaccination

Role of Adjuvants in Immunization

- Adjuvants: substances which increase the antigenicity of weak antigens
- Can be of two forms

1) Chemicals
2) Biological

- Chemical: Aluminum salt (Alum)
- Only chemical suitable for human use
- Used in DTP (Diphtheria, Tetanus & Pertussis)

Role of Adjuvants in Immunization

- Alum causes slow release of antigen
- Increase TLR interaction
- Increase the activation of mononuclear phagocytes
- Also induce the increased cytokine secretion
- Appropriate immune response generation

Role of Adjuvants in Immunization

- Biological adjuvants: Certain bacteria used as biological adjuvant
- Bacterial products
- *B. pertussis* used as adjuvant
- *M. bovis* (BCG and others)
- Used in combination with oil & detergent
- Activation of mononuclear phagocytes & cytokine secretion

Immunology

Adverse Effects of Vaccination

Adverse Effects of Vaccination

- Adverse effects :Live microbe
- Most severe effects are rare, mild & moderate
- Active immunization: causes fever, malaise & discomfort
- Joint pains (Arthritis): Rubella vaccination
- Can be fetal: in case of Pertussis
- Neurological disorders: Influenza vaccination

Adverse Effects of Vaccination

- DPT vaccination:
- Local effects: Redness, swelling & pain
- Mild/Moderate effects: fever, drowsiness. Vomiting & anorexia
- Severe effects: persistent crying, fever, Convulsions, collapse, acute encephalopathy, permanent neurological deficit
- Due to pertussis components

Immunology

Tolerance, Diseases of Immune System- Autoimmunity

Immunology

Introduction to Tolerance

Introduction to Tolerance

- Specific Immunological unresponsiveness
- Non-reactivity to an antigen resulting from a previous exposure to same antigen
- Mostly unresponsiveness against self antigens
- Non-reactivity to non-self antigen can be induced
- Tolerogen: antigen which induce tolerance

Introduction to Tolerance

- Self tolerance: Physiologically no immune response against self antigens
- Autoimmunity: immune response against self antigens (Pathology)
- Immune system recognize self-antigens & mount strong immune response
- Discrimination B/w Self & Non-self antigens: Self MHC recognition

Introduction to Tolerance

- Tolerance: can be against non-self antigens
- Immune response should be against non-self antigens
- Modification of antigens: Leads towards tolerance
- Most bacteria & viruses develop tolerance: exploit or evading host immune system
- Lepromatus type of leprosy: Tolerance against *M.leprae*

Introduction to Tolerance

- Tolerance to tissue & cell antigens can be induced artificially
- Injecting hemopoietic stem cells in neonatal or severely immunocompromised animals
- Chimeras animals: transferring of allogeneic primary lymphoid tissues at early life
- Induction of tolerance against allogeneic tissues

Immunology

Immunological features of Tolerance

Immunological features of Tolerance

- Tolerance: different from non-specific immunosuppression & immunodeficiency
- Active antigen dependent process in response to antigen
- Tolerance: Specific & has immunological memory like immune response
- Tolerance to T-cells is longer as compare to B-cells

Immunological features of Tolerance

- Induction of tolerance to T-cells: easier & require small amount of antigen (Tolerogen)
- B-cell tolerance requires larger amount of tolerogen
- Maintenance of tolerance: persistence of antigen
- Lack of persistence leads to breach tolerance

Immunological features of Tolerance

- Tolerance can be break in following two ways

1) Naturally: In case of autoimmune disorders e.g Rheumatoid Arthritis, SLE etc.
2) Artificially: exposure to immunosuppressive drugs or X-ray irradiation e.g in case of experimental animals for bone marrow transplantation

Immunology

Mechanisms of Tolerance Induction

Mechanisms of Tolerance Induction

- Two forms of immunological tolerance

1) Central Tolerance
2) Peripheral Tolerance

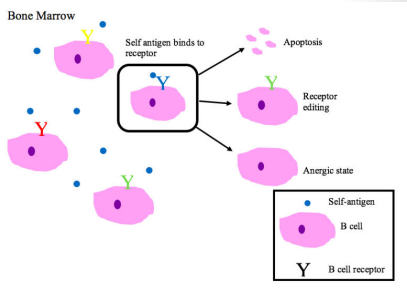
- Central Tolerance: occur in primary lymphoid organs e.g bone marrow & thymus
- Peripheral tolerance: occur at secondary lymphoid organs e.g spleen, lymph nodes, tonsils etc

Mechanisms of Tolerance Induction

Central Tolerance

- Mechanism involved: Clonal deletion
- Also called as Negative selection
- Self reactive B & T-lymphocytes are deleted in bone marrow & thymus respectively
- Clones of auto reactive cells are deleted by programmed cell death (Apoptosis)

Mechanisms of Tolerance Induction



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Central Tolerance

- B-cells during development in bone marrow: encounter with self soluble or cell surface associated antigen
- Negative selection: By apoptosis
- Self reactive B-cells are deleted from bone marrow

Mechanisms of Tolerance Induction

Central Tolerance

- T-cells develop in thymus express CD8 & CD4
- Acquire βα TCR
- Positive selection after interacting with self MHC
- Negative selection: for self reactive T-cells with either class I or II
- Auto-reactive T-cells are controlled to escape from central lymphoid tissues

Mechanisms of Tolerance Induction

Peripheral Tolerance

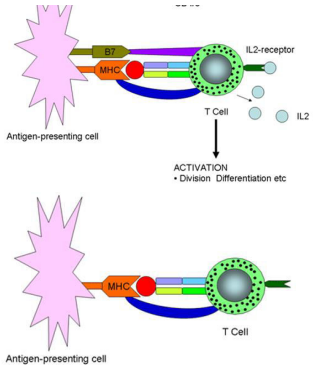
- Clonal deletion: Not fool proof system
- B & T cells fail to undergo deletion (escape from Central tolerance)
- Auto-reactive immune cells reach peripheral lymphoid organs
- Specific Un-responsiveness occur in peripheral lymphoid tissues

Mechanisms of Tolerance Induction

Peripheral Tolerance

- Activation induced cell death: Death of auto reactive T-cell upon activation
- Secretory cytokines from activated T-cells cause the expression of Fas ligand on T-cells
- Apoptosis after engagement of FasL with Fas
- Deletion of self reactive T-cells in periphery

Mechanisms of Tolerance Induction



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Peripheral Tolerance

- Clonal Anergy: Exposure of T-cells to self antigens lead to functional inactivation
- Loss of co-stimulation upon interacting with self antigen on APC
- No interaction of C28 on T-cells with CD80(B7-1) or CD86(B7-2) on APC
- Functional unresponsiveness

Mechanisms of Tolerance Induction

Peripheral Tolerance

- Clonal Ignorance: Lack of interaction with appropriate antigen
- After maturation in thymus, auto reactive T-cells reach the periphery
- Sequestration of these self-reactive T-cells in inaccessible tissues
- Death of such clones due to continuous ignorance

Mechanisms of Tolerance Induction

Peripheral Tolerance

- By Regulatory T-cells (Suppressor T-cells): CD4 & CD25 +ve cells
- Secretion of immunosuppressive cytokines like TGF-β & IL-10
- These cytokines cause the inactivation of auto-reactive cells

Immunology

Tolerance to Tissues & Cells

Tolerance to Tissues & Cells

- Specific unresponsiveness against various cells & tissues
- Inhibition of immune response against antigens of cells & tissues
- These antigens are foreign to immune system (Allogeneic antigens)
- Occur in tissue graft :Allogenic graft

Tolerance to Tissues & Cells

- Induction of Tolerance against tissues & cells: by injecting hematopoietic stem cells at neonatal stage
- Early stage: no development of fully matured lymphoid tissues
- Tolerance induction: by immunosuppression e.g lethal irradiation for killing of host's own stem cells in primary organs

Tolerance to Tissues & Cells

- Also by using immunosuppressive drugs: in order to inactivate immune cells of host
- Chimeras: animals with hybrid nature of immune cells with host's own cells & donor's cells
- Both transplantation of donor's bone marrow & thymus in early age or by immunosuppression
- Functional inactivation

Immunology

Introduction to Autoimmunity

Introduction to Autoimmunity

- Autoimmunity: all mechanisms responsible for breakdown of self tolerance against self antigens
- Generation of immune response against components of self tissues
- Harmful or aberrant immune response
- Products of immune system damage the host tissues

Introduction to Autoimmunity

- Both antibodies & T-cells are involved in autoimmunity
- Genetic predisposition: Certain genes of Immunoglobulins, TCR & MHC are associated with various autoimmune diseases
- Environmental factors: responsible for autoimmunity e.g drug & infection induced autoimmune diseases

Immunology

Etiology of Autoimmunity

Etiology of Autoimmunity

- Exact mechanism is still unknown
- Various theories have been proposed for understanding the mechanism of autoimmunity
- Sequestered antigens
- Escape of auto reactive cellular clones
- Lack of regulatory T-cells
- Cross reactive antigens

Etiology of Autoimmunity

Sequestered antigens

- Lymphoid cells may not be exposed to certain self antigens during differentiation
- Certain self antigens are confined to specialized organs (Testis, brain & eyes etc)
- Release of such antigens from tissues due to any injury or accident
- Initiation of autoimmune diseases

Etiology of Autoimmunity

Escape of auto reactive clones

- Loss of central tolerance
- Auto-reactive T-cells escape from thymus to periphery
- Not all self-antigens are presented to T-cells in thymus
- Auto-reactive B-cells also escape from clonal deletion or negative selection

Etiology of Autoimmunity

Lack of regulatory T-cells

- Few regulatory T-cells in autoimmune diseases
- Absence of regulatory (Suppressive) T-cells
- Absence of immunosuppressive cytokines like TGF-β & IL-10

Etiology of Autoimmunity

Cross Reactive antigens

- Antigens on certain pathogens have determinants
- Those determinants cross react with self antigens
- Generation of antibodies against those determinants cross react with self antigens
- Post-streptococcal nephritis & carditis (M-proteins)

Immunology

General Classification of Autoimmunity

Classification of Autoimmunity

- Autoimmunity: Classification based on tissues or organs involved
- Two following categories
- Organ-specific autoimmunity
- Non-organ Specific autoimmunity

Etiology of Autoimmunity

Organ Specific autoimmunity

- Immune response against organ associated specific antigens
- Antibodies against organ associated antigens damage the organ
- Target organs
- Skin
- Thyroid gland
- Muscles

Etiology of Autoimmunity

Organ Specific autoimmunity

Disease	Organs	Antibody to
Hashimoto's thyroiditis	Thyroid	Thyroglobulin, thyroid peroxidase (microsomal)
Primary Myxedema	Thyroid	Cytoplasmic TSH receptors
All hemolytic anemia	RBC	RBC antigens
Good Pasteur's Syndrome	Kidney, Lung	Renal & Lung basement membrane
Ulcerative colitis	Colon	Colon Lipopolysaccharide

Etiology of Autoimmunity

Non-Organ Specific autoimmunity

- Immune response not against organ associated specific antigens
- Antibodies against not organ associated antigens
- Systemic autoimmune diseases
- Mainly target organs: skin, joints, soft tissues etc

Etiology of Autoimmunity

Non-Organ Specific autoimmunity

Disease	Organs	Antibody to
Rheumatoid Arthritis	Skin, kidney, Joints etc	IgG
Systemic Lupus Erythematous (SLE)	Skin, joints	DNA, RNA, Nucleoproteins
Sjogren's syndrome	Moister-producing glands	Basement membrane
Scleroderma	Skin, blood vessels, muscles & internal organs	DNA, RNA, Nucleoproteins
Sarcodosis	Lung, skin, hear, nervous system	Auto reactive T-cells

Immunology

Diagnosis of Autoimmune Diseases

Diagnosis of Autoimmune diseases

- Diagnosis of autoimmune diseases is based on symptoms & detection of autoantibodies
- Autoantibodies can be against two kinds of antigens

1) Self cell or cell associated antigens
2) Soluble antigens
3) Biochemical test

Diagnosis of Autoimmune diseases

Autoantibodies against self cell/Cell associated antigens

- Using tissues section like kidney, skin etc
- By Immunofluorescence: Detection of autoantibodies
- Linear Pattern (Goodpastuer Syndrome)
- Granular Pattern (Systemic Lupus Erythramatous)

Diagnosis of Autoimmune diseases

Autoantibodies against Soluble Antigens

- Using serum for auto-antibodies by following techniques
- Agglutination e.g Anti nuclear antibodies (ANA) for SLE & RA
- ELISA e.g Rheumatoid factor for Rheumatoid Arthritis
- RIA for detection of anti-thyroid antibodies

Diagnosis of Autoimmune diseases

Biochemical Assays

- For Intrinsic factor (IF) in case of Pernicious anemia
- Competition for TSH receptors in case of Graves disease
- Auto-reactive T-cells can also be detected by Flowcytometry

Immunology

Treatment of Autoimmune Diseases

Treatment of Autoimmune diseases

- With goal of reducing symptoms
- Control of autoimmune response
- Increasing the ability of immune system to fight against infections
- Treatment varies based on specific disease & symptoms
- Treatment for reducing inflammatory process & immune response

Treatment of Autoimmune diseases

- Anti-Inflammatory drug therapy
- Corticosteroid: particularly inhibit the cellular signaling for production of pro-inflammatory cytokines
- Relieve from the symptoms of inflammatory process like pain, redness and fever
- Less inflammatory process

Treatment of Autoimmune diseases

- Immunosuppressive drug therapy
- Cyclosporine
- Cyclophosphamide
- Azathioprine
- Reduce immune response against self antigens
- Relieving from the symptoms of immune response

Treatment of Autoimmune diseases

- Specific approaches: using specific antibodies against receptor blocking the effects
- Mainly in research
- Anti-TNFα receptor antibodies
- Anti IL-2 receptor antibodies
- Anti CD4 antibodies
- Anti TCR antibodies
- Anti-Idiotype antibodies against autoantibodies

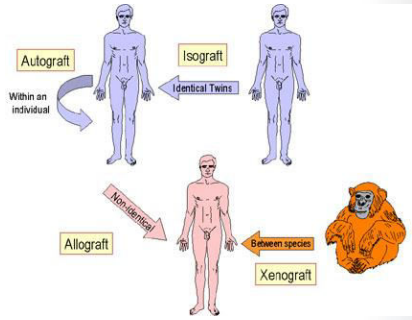
Immunology

Transplantation Immunology

Immunology

Immune Response against Transplants

Immune Response against Transplants



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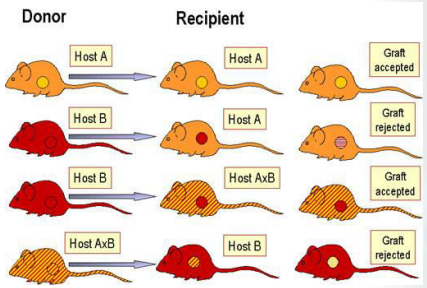
- Transplantation: is the process of moving cells, tissues & organs from one site to another
- One person (donor) to other person (recipient)
- Isograft: Between individuals of same genetic makeup (Twins)
- Allograft: One person to other non-identical person
- Xenograft: across the species

Immune Response against Transplants

- Immune system plays an important role in transplantation
- Act as a barrier for transplantation
- Identifies as foreign and mount an immune response
- Destruction or damage of transplanted tissue
- Transplantation Rejection: Recipient's immune system activation against donor

Immune Response against Transplants



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- Immunocompetent host recognize foreign antigens on grafted tissues
- As a result immune response generated against: graft rejection
- Tissue transplants in immunocompromised individuals leads to immune response by immunocompetent cells in graft
- Host antigens as foreign

Immunology

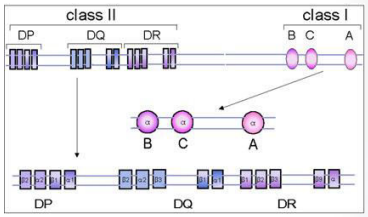
Transplantation Antigens

Transplantation Antigens

- Transplantation antigens: Major Histocompatibility Complex (MHC)
- Also called as Human Leucocytes Antigens (HLA)
- MHC complex: encoded by gene as Haplotype
- Responsible to influence allograft rejection
- Two major types of MHC

1) Class I MHC
2) Class II MHC

Transplantation Antigens



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Class I MHC

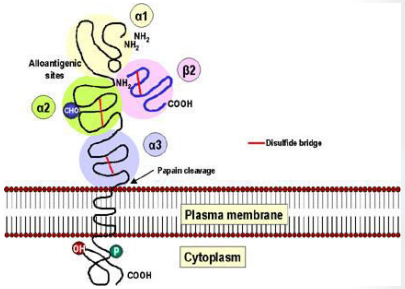
- Genes for Human MHC located at chromosome 6
- Contain three major loci

1) Locus B
2) Locus C
3) Locus A

- Each major locus encode for polypeptide
- α-chain that contains antigenic determinants

Transplantation Antigens

Class I MHC



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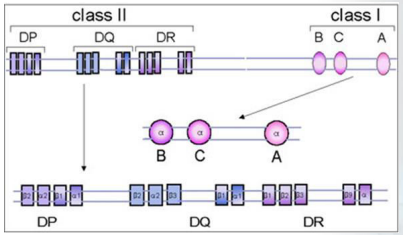
- Polymorphic: contains many alleles of α-chains
- β2-microglobulin (β-chain) is encoded by outside of MHC I haplotype
- β-2 chain has role in expression of class I MHC on cell surface
- Defect in β-2 chain: no expression of Class I MHC
- Deficiency of CTLs

Transplantation Antigens



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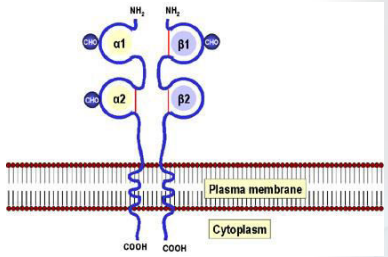
Class II MHC

- Genes for Human MHC located at chromosome 6
- Class II complex also composed of three major loci

1) DP
2) DQ
3) DR

- Each of these loci code foe one alpha & one beta

Transplantation Antigens



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- Both alpha & beta chains associate together to form class II MHC
- Like class I, class II antigens are polymorphic: contains many alleles of α-chains
- DR locus contain more than one beta chain genes: possibly four
- Class II MHC: express on B-cells & antigen presenting cells (APC)

Immunology

Induction of Immune Responses against Transplants

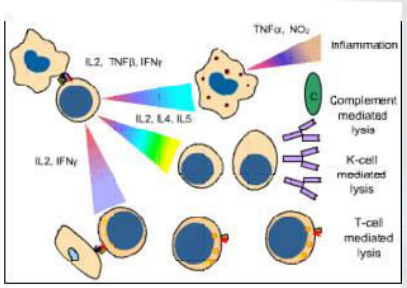
Immune Responses against Transplants

- Clinical significance of MHC : in tissue transplantation
- Cells and tissues are transplanted for the treatment of various diseases
- Generation of immune response against transplant: rejection or destruction of transplant
- Immune response can be of two types based on kind of rejection

Immune Responses against Transplants

- Host vs Graft Rejection: Antigens on graft recognize as foreign by host immune system
- Graft vs Host Rejection: Lymphoid tissues in graft recognize host immune system as foreign
- Both of these immune responses lead towards graft rejection
- Rejection is based on antigenic nature of graft & host immune status

Immune Responses against Transplants



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- Induction of immune response is mediated by
- Inflammatory process by inflammatory cells
- Antibodies against antigens of graft: Complement mediated lysis of graft
- Antibody mediated Cellular cytotoxicity (ADCC) of graft tissue
- T-cell mediated lysis of graft tissue

Immunology

Immune Mechanisms of Graft Rejection

Immune Mechanisms of Graft Rejection

- Reaction of host against allo-antigens of graft: Host vs Graft (HVG) Rejection
- Main obstacle in organ transplantation
- Immune mechanisms in graft rejection based on

1) Time of rejection
2) Nature of allo-antigens of graft
3) Immune status of host

Immune Mechanisms of Graft Rejection

- According to time of rejection: graft rejection can be of following types with distinct immune mechanisms

1) Hyper acute rejection

1) Accelerated rejection

1) Acute Rejection

1) Chronic Rejection

Immune Mechanisms of Graft Rejection

Hyper-acute Rejection

- Very quick onset on tissue rejection
- Occurs within minutes to hours
- High titer of pre-formed antibodies against antigens of graft
- Antigen/antibody reaction on the tissue surface
- Fixation of complement: leads to graft destruction

Immune Mechanisms of Graft Rejection

Accelerated Rejection

- Also called as secondary or 2nd set rejection
- Occurs after transplantation of second graft
- Sharing of antigenic determinants with the first one
- Occur within 2-5 days
- Sensitized T-cells during first graft
- Lymphokines, CTLs

Immune Mechanisms of Graft Rejection

Acute Rejection

- Also called as primary or 1st set rejection
- Occurs during first graft with allo-antigen
- Time span: 1-3 weeks
- Mediated by sensitized T-cells to class I & II of allo-graft
- Secretion of Lymphokines
- Activation of monocyte/macrophages

Immune Mechanisms of Graft Rejection

Chronic Rejection

- Delayed rejection within months to years
- After transplantation: graft remains normal for months to years but sudden rejection
- Unknown mechanisms
- Hypotheses: due to infection
- Loss of immunological tolerance by grafted tissue

Immunology

Prevention & Treatment of Graft Rejection

Prevention of Graft Rejection

- Decrease in tissue rejection: Increase in survival of graft
- Successful graft: Mostly in case of kidney & cornea
- Better understanding of Immune response, MHC
- Success of graft based on

1) Donor selection
2) Recipient preparation
3) Immunosuppression

Prevention of Graft Rejection

Donor Selection

- MHC compatibility with recipient
- Identical twin is the ideal donor: Isograft
- HLA matched siblings have 95-100% chance of graft success
- One haplotype parent or sibling must HLA-D matched
- ABO compatibility is also essential

Prevention of Graft Rejection

Recipient Preparation

- Should be in good health
- With no infection
- No active malignancy
- Absence of any systemic diseases: for better rehabilitation
- Not be hypertensive
- One to five transfusions of 100-200 ml of donor's blood at 1-2 weeks interval

Prevention of Graft Rejection

Immunosuppression

- Most essential component of allo-transplantation
- Use of immunosuppressive drugs
- Cyclosporin A: inhibit IL-2 synthesis following Ag
- Rapamycin: Inhibits signal transduction
- Inhibition of T-cells proliferation & activation

Immunology

Transplantation of Blood Cells & Bone Marrow

Transplantation of Blood Cells & Bone Marrow

- Decrease in tissue rejection: Increase in survival of graft
- Successful graft: Mostly in case of kidney & cornea
- Better understanding of Immune response, MHC
- Success of graft based on

1) Donor selection
2) Recipient preparation
3) Immunosuppression

END

Immunology

Tumor Immunology

Immunology

Evidence of Immune Reactivity to Tumor

Evidence of Immune Reactivity to Tumor

- Tumor: mass containing un-controlled proliferating cells
- A lot of evidences: Tumors elicit immune response
- Young & old populations have increased incidence of tumors
- Tumors having mononuclear infiltration have better prognosis as compare to those which lack mononuclear cells

Evidence of Immune Reactivity to Tumor

- Certain tumors regress spontaneously e.g melanomas, neuroblastomas
- Tumor regression: occur due to immune response
- Some tumors metastases: removal of primary tumor regress metastatic tumor due to decrease in tumor load
- Immune system facilitate the regression of metastatic tumor

Evidence of Immune Reactivity to Tumor

- There is increased incidence of tumor in immune deficient patients
- Patients suffering from AIDS are susceptible to Kaposi Sarcoma
- Patients receiving transplants also get Epstein-Barr virus (EBV) induced lymphoma
- Tumor specific antibodies & T-lymphocytes

Immunology

Tumor Associated Antigens

Tumor Associated Antigens

- For reacting against immune system, tumor must have antigens
- Tumorigenesis: alteration in number of gene expression
- Expression of new antigens on the surface of tumor (neo-antigens)
- Alteration in existing antigens which are present on normal cells

Tumor Associated Antigens

- These antigens are membrane bounded receptors, regulators of cell cycle & apoptosis and molecules of signal transduction
- There are two main types of tumor associated antigens

1) Tumor specific transplantation antigens
2) Tumor Associated transplantation antigens

Tumor Associated Antigens

1) Tumor specific transplantation antigens

- Are unique to tumor cells
- Not expressed on normal cells
- Responsible for rejection of tumor
- In most cases, these antigens cannot be easily identified

Tumor Associated Antigens

1) Tumor Associated transplantation antigens

- Are expressed by tumor & normal cells
- Various chemicals, UV & viruses are responsible for expression of neo-antigens
- Majority of these tumors are weakly immunogenic or on-immunogenic

Immunology

Tumor Associated Transplantation Antigens

Tumor Associated Transplantation Antigens

- Tumor antigens which are also expressed by normal cells
- Expressed high levels by tumor cells as compare to normal cells
- Also called as onco-fetal antigens
- Expressed during early development & lost during adult life
- Re-expressed on tumor cells

Tumor Associated Transplantation Antigens

- These antigens also called as tumor markers
- These are important in the diagnosis & prognosis of cancers
- There are following two types of onco-fetal antigens

1) Alpha-fetoproteins (AFP)
2) Carcino-embryonic antigens (CEA)

Tumor Associated Transplantation Antigens

1) Alpha-fetoproteins (AFP)

- Found as secretory protein in serum
- Level raised: during hepatocellular carcinoma

2) Carcino-embryonic antigens (CEA)

- Found both in secretory & cell associated form
- Increased levels in colon cancer

Immunology

Immunity Against Tumors

Immunity Against Tumors

- Immune system provides anti-tumor activity in humans
- Evidence for immunity against malignancy mainly come from experimental studies with animals
- Mice can be immunized with irradiated tumor cells
- Removal of primary tumor challenged with the same live tumor

Immunity Against Tumors

- There would be resistance against same tumor upon re-challange
- Antibodies play important role against various cancers for their neutralization
- Cell-mediated immunity also play pivotal role in tumor rejection
- Th cells process the tumor antigen like shed from tumor and present with Class II MHC

Immunity Against Tumors

- Th-cells also help B-cells to produce antibodies against tumor antigens
- Role of CTL is also very critical for tumor regression
- Th-cells also help in activation & differentiation of CTLs
- NK cells: also kill the tumor cells due to lack of class I MHC
- Cytokines: IFN-γ for tumorocidal activity

Immunology

Escape of Tumor from Immuno-Surveillance

Escape of Tumors from Immuno Surveillance

- Immuno-Surveillance: responsible for tumor rejection in host
- Tumor cells develop strategies for evading immune surveillance
- Tumors escape from immune response by following mechanisms
- Tumor cells may not express neo-antigens which are immunogenic in nature

Escape of Tumors from Immuno Surveillance

- Tumor cells may fail to express co-stimulatory molecules for activation of T-cells
- Certain tumors may lack or poor expression of MHC for proper immune response generation
- At early development of tumor, there is low level of antigens which are in sufficient for activation of immune system; Low dose tolerance

Escape of Tumors from Immuno Surveillance

- Overwhelming of immune system, after sudden maturation & expression of neo-antigens on tumor cells; high dose tolerance
- Certain tumors secrete immunosuppressive molecules for inactivation of immune cells
- Some tumors shed their antigens for neutralization of antibodies

Immunology

Use of Tumor Neo-antigens in Immuno-diagnosis & Immunotherapy

Use of Tumor Neo-Antigens

- Tumor neo-antigens on tumor cells used for both immune-diagnosis & immunotherapy
- *In-vivo* detection of relatively small tumor foci: radiolabelled monoclonal antibodies against tumor antigens
- *In-vitro* use for finding the cell origin of undifferentiated tumor particularly lymphocytic origin

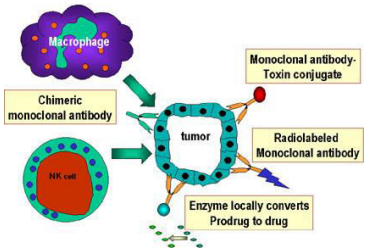
Use of Tumor Neo-Antigens

- Immuno-histochemical use of monoclonal antibodies against metastatic foci
- Immunotherapy: for treating various tumors in different ways
- Active immunotherapy: host actively participates against tumors
- Active immunotherapy is achieved by inducing immune response

Use of Tumor Neo-Antigens

- Non-specific active immunotherapy: for activation of immune response against neo-antigens e.g BCG for activation of macrophages against tumors
- Specific active immunotherapy: killed tumor cells or their antigens for killing of tumor cells

Use of Tumor Neo-Antigens



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- Passive immunotherapy: use of pre-formed antibodies against specific neo-antigens of tumor
- Specific monoclonal antibodies against tumor antigen can be served for
- As a vehicle for delivering anti-cancer drug
- Activation of components of innate immune system

Immunology

Immunodeficiency

Immunology

Introduction to Immunodeficiency

Introduction to Immunodeficiency

- Failure of immune system
- Deficiency of immune response
- State of complete absence of immunity
- Defects regarding generation of immune reactivity against infectious agents
- No immune response against transformed cells like tumors or malignancy

Introduction to Immunodeficiency

- Persons having immunodeficiency is also called as immunocompromised patients
- Increased vulnerability for opportunistic infections in addition to normal infections
- Decrease surveillance against tumors
- More chances of getting tumors

Immunology

Classification of Immunodeficiency

Classification of Immunodeficiency

- Immunodeficiency is classified into two main categories based on mode of acquiring

1) Primary Immunodeficiency

1) Secondary Immunodeficiency

Classification of Immunodeficiency

Primary Immunodeficiency

- Inherited defects of the immune system
- These defects can be either in specific or non-specific immunity
- These are classified on the basis of the site of lesion in the developmental or differential pathway of immune system

Classification of Immunodeficiency

Primary Immunodeficiency

- Susceptibility to variety of infections
- Type of infection depends on the nature of immunodeficiency
- It can be of two kinds

1. Immunodeficiency in specific immune system
2. Immunodeficiency in non-specific immune system

Classification of Immunodeficiency

Primary Immunodeficiency

- Specific immune system
- Defects in stem cell differentiation
- Reticular dysgenesis: absence or severe deficiency of lymphocytes & granulocytes
- Disorders of lymphoid stem cells: Severe combined immunodeficiency(SCID)

Classification of Immunodeficiency

Primary Immunodeficiency

- SCID: absence of T & B cell immunity
- Susceptible to variety of bacterial, viral, mycotic & protozoan infections
- Disorders of T-cells: DiGeorge Syndrome
- Due to congenital thymic aplasia/hypoplasia
- Live vaccines also cause infections

Classification of Immunodeficiency

Primary Immunodeficiency

- Disorders of B-Lymphocytes
- X-linked hypo gammaglobulinemia
- IgA deficiency: susceptible to GIT, eye & nasopharyngeal infections
- Selective IgG deficiency
- Hyper IgM immunodeficiency

Classification of Immunodeficiency

Primary Immunodeficiency

- Non-Specific immune system
- Cyclic Neutropenia: low number of circulating Neutrophils
- Chronic Granulomatous disease (CGD):defect in phagocyte function
- Complement deficiency: susceptible to infections particularly *Neisseria*

Classification of Immunodeficiency

Secondary Immunodeficiency

- Associated with infections e.g AIDS
- Associated with aging: hypo-cellularity
- Associated with malignancies e.g in case of Leukemia, Myeloma
- Associated with other diseases e.g diabetes, renal malfunction etc

Immunology

Acquired Immunodeficiency Syndrome (AIDS)

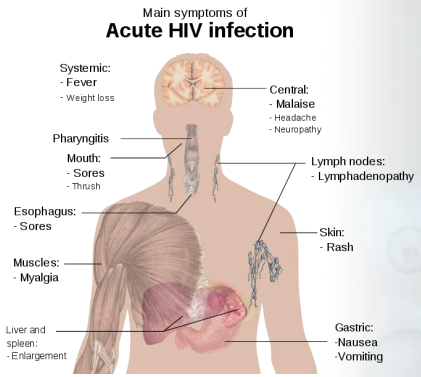
Acquired Immunodeficiency Syndrome

- Caused by human immunodeficiency virus (HIV)
- Initial infections with influenza like illness
- Disease progress with defects in immune system
- Opportunistic infections like tuberculosis
- Chance of getting tumor
- Circular abnormalities of lymphocytes

Acquired Immunodeficiency Syndrome

- Decrease in number of helper ($CD4^+$ve) cells
- Consequently reversal in $CD4^+/CD8^+$ T-cell ratio
- Normal NK cells with reduced activity
- AIDS patients have increased susceptibility to infections with opportunistic pathogens like Cryptococcus, herpes simplex, herpes zoster, Mycobacterium etc

Acquired Immunodeficiency Syndrome



https://en.wikipedia.org/wiki/File:Symptoms_of_acute_HIV_infection.svg

- Initial or primary infection: Systemic fever, Lethargy & malaise
- Localized tissue involvement
- AIDS patients have increased susceptibility to various following tumors
- Kaposi sarcoma
- Burkitt's lymphoma
- Primary central nervous system lymphoma

Acquired Immunodeficiency Syndrome

- HIV infection is transmitted by two modes
- Horizontal transmission: by person to person contact either sexually or through body fluids like blood
- Vertical transmission: from mother to fetus during
- Pregnancy
- Delivery & breast feeding

Immunology

Immunodeficiency: Disorders of T- Cells

Disorders of T-Cells

- Immunodeficiency associated with T-cells disorders effects both cell mediated & humoral immunity
- Complete absence & functional abnormality in T-cells
- More chances of getting viral, protozoal & fungal infections
- Viral infections like cytomegalovirus virus & measles

Disorders of T-Cells

DiGeorge Syndrome

- Primary immunodeficiency
- Complete absence of T-cells
- Also called as thymic aplasia or hypoplasia
- Immunodeficiency linked with hypoparathyroidism
- Due to abnormal development of fetus
- Poor development of heart, thymus & parathyroid

Disorders of T-Cells

- Abnormal development of heart, thymus & parathyroid
- All patients have thymic aplasia
- Autosomal dominant caused by deletion in chromosome 22
- Deletion is of variable size doesn't correlate with severity of disease
- Treatment: Thymic graft

Disorders of T-Cells

- T-cells deficiency with variable degree of B-cells deficiency
- Ataxia-telangiectasia: deficiency of T-cells with less movement of blood vessels
- Wiskott-Aldrich syndrome: normal number of T-cells with reduced functions
- Worst immunodeficiency with also low levels of antibodies

Immunology

Immunodeficiency: Disorders of B- Cells

Disorders of B-Cells

- Immunodeficiency associated with normal T-cells
- B-cells number may be low or normal
- Immunoglobulin levels are low
- More chances of getting pyogenic infections like bacterial infections

Disorders of B-Cells

X-linked hypo-gammaglobulinemia

- B-cells numbers are very low
- Immunoglobulin levels are also very low
- Defect is associated with B-cell maturation
- Patients suffer from recurrent bacterial infections

Disorders of B-Cells

IgA deficiency

- Commonest form of immunoglobulin deficiency
- Defect in class switching
- Patients are prone to GIT, eye & nasopharyngeal infections
- Diagnosis: measurement of IgA by various immunological methods

Disorders of B-Cells

X-linked hyper IgM - Immunodeficiency

- Very high levels of IgM
- Low level of IgG & IgA concentration
- Defect in class switching due to defect in CD40L on CD4 cells
- Patients are susceptible to pyogenic infections
- Treatment: with intravenous gamma globulins

Immunology

Immunodeficiency: Defects of Phagocytic Cells

Defects of Phagocytic Cells

- Primary immunodeficiency associated with cells of non-specific immune system including
- Phagocytic cells like neutrophils, monocytes & macrophages
- Also killer cells like NK cells

Defects of Phagocytic Cells

Congenital Agranulomatosis

- Decreased neutrophil count
- Defect in myeloid progenitor differentiation into neutrophils
- Patients are prone to pyogenic infections like bacterial

Defects of Phagocytic Cells

Chronic Granulomatous disease (CGD)

- Decreased neutrophil function wit normal number
- Defect is due to poor intracellular killing ability of neutrophils
- Deficiency of NADPH oxidase & other co-factors for respiratory burst
- Susceptibility to bacterial infections

Defects of Phagocytic Cells

Leukocyte Adhesion deficiency

- Defect in integrin molecules
- Decreased process of diapediesis & defective neutrophils movement towards chemotactic signals
- Defective phagocytic function leading towards recurrent bacterial infections

Immunology

Immunodeficiency: Defects of Complement System

Defects of Complement System

- Abnormalities in complement proteins (Hypo-complementemia)
- Are genetic abnormalities
- Inherited defects in the synthesis of various complement proteins
- Major defect in the synthesis of C3 due to defective C3 synthase
- Also defects in various regulatory proteins like Factor H & I

Defects of Complement System

- Majority of complement deficiency is autosomal recessive
- Properdin deficiency: X-linked inheritance
- MBL deficiency can be both
- Recurrent bacterial infections particularly Neisseria & Streptococcus infections
- Also cause autoimmune disorders like SLE, vasculitis etc

Immunology

Immunodeficiency: Defects of Complement System

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