Introduction to Immunology Lectures 1-3

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TheComponents Of The Immune System and Innate Immunity:

Ref: Immunobiology-5th edition. Janeway et al. Chapters-1 & 2.

Immune System can be broadly divided into:

Innate immune system: Born with it
Adaptive Immune system: Acquired during life

Both innate and adaptive immunity depend on leukocytes/WBCs.
Innate immunity is mediated by ***granulocytes*** (also called PMNs), ***macrophages*** and ***neutrophils*** (a type of granulocytes), which are the primary phagocytic cells

We are constantly exposed to microbes, which are effectively cleared by the innate immune system. If necessary, the adaptive immune system is recruited.

Cells of the immune system ***originate in bone marrow*** and then ***migrate to periphery*** through blood and lymphatic system.

All white blood cells (WBC) are derived from a common precursor cell
Hemetopoietic stem (pluripotent) cells give raise to all blood cells

Myeloid progenitor cells give raise to (Fig 1-3):

Neutrophils – Phagocytic cells most important component of the innate IS
Granulocytes – Phagocytic cells
Macrophages – Phagocytic cells
Dendritic cells – Professional antigen presenting cells (APCs)
Mast cells – Allergic responses
Basophils – Similar to eosinophils and mast cells but are distinct
Eosinophils – Play important role in the clearance of parasitic infections

Myeloid cells play important role in innate immunity **(Fig 1-4)**

Common lymphoid progenitor cells give raise to (Fig 1-3):

B cells – differentiate into plasma cells
T cells – cytotoxic (CD8+) and helper (CD4+) T cells
Natural killer (NK) cells **(Fig 1-6)**

Resting B and T cells have large nuclei with very little cytoplasm **(Fig 1-5)**
Upon Ag encounter lymphocytes proliferate and differentiate.
They mount specific immune responses against virtually all foreign Ags
They recognize Ags through cell surface receptors.
B cells have membrane immunoglobulins, which serve as BCRs (B cell receptor).
T cell antigenic receptors are called T cell receptors (TCRs)
BCR and TCR are structurally related but are distinct

NK cells lack Ag receptor-therefore is part of the innate immune system.

Maturation of Lymphocytes

Lymphoid system is organized into (Fig 1-7):
Central/primary lymphoid organs – where lymphocytes are generated.
Peripheral/secondary lymphoid organs-where adaptive immune response is initiated and lymphocytes are maintained.

The central lymphoid organ consists of thymus and bone marrow where T cells and B cells undergo maturation

The peripheral lymphoid organs are designed to trap Ag
Allow initiation of adaptive immune response
Sustain re-circulating lymphocytes.

Lymph node: has a highly organized structure **(Fig 1-8)**.
Lymph is extracellular fluids from the tissue.
Lymph is brought into the lymph node through ***afferent lymphatic vessels***.
The Ag in the lymph is trapped in the lymph node
B cells are localized in the follicles
T cells are diffused throughout in paracortical (T cell zone) area
B cell follicles contain germinal centers-where B cells & T cells interact and proliferate
Lymphocytes move out of lymph nodes through efferent lymphatic vessels

Spleen: Consists of red and white pulp **(Fig 1-9)**
Red pulp collects and disposes senescent RBCs
White pulp consists of T and B cells
Inner region consists of periarteriolar lymphoid sheath consisting of T cells
Coronal region contains B cells

GALT: Consists of tonsils, adenoids and appendix **(Fig 1-10)**
Specialized structures called Pyer's patches in the small intestine.
Ag is captured by multi-fenestrated (M) cells
BALT: Bronchial Associated Lymphoid Tissue
MALT: Mucosal Associated Lymphoid Tissue
SALT: Skin Associated Lymphoid Tissue

B lymphocytes that have matured in BM and T cells that have matured in the thymus that have not yet encountered the Ag are called ***naïve lymphocytes***
They circulate **(Fig 1-11)** from blood into peripheral organs by squeezing through capillary wall
Migrate from tissue through afferent lymphatic vessels into lymph node
Lymphocytes get back into blood through ***efferent lymphatic vessels***

Principles of innate and Adaptive Immunity:

Cells of the innate immune system provide the 1st line of defense
Sometimes they cannot clear infection
Adaptive immune system is more versatile
Cells of the innate immune system are involved in activating adaptive immune system
There is a delay of 4-7 days before the adaptive immune system is activated
Therefore, cells of the innate immune system play a critical role

Infection results in inflammation by activating innate immune system (Fig 1-12):

Phagocytic cells ***recognize patterns*** on microbes
Macrophages engulf bacteria, which in turn induce cytokines
Cytokines are proteins that affect cells that express their cognate receptor
Macrophages also release chemokines
Chemokines attract neutrophils and monocytes from blood
Inflammation in initiated by Chemokines
Inflammation can also be initiated by activation of complement

Complement in a system of plasma proteins that activate proteolysis on microbes but not on host cells.
They coat the microbial surface and bind to receptors and activate macrophages.
They release small peptides (chemokines***)*** that cause inflammation

Inflammation: *Heat, Pain, Redness and Swelling*

Reflect effects of inflammatory mediators on blood vessels
Results in ***increased blood*** flow
Causes ***increased permeability***
Leakage of fluid from blood vessels and tissues causes ***edema***
Leukocytes migrate into the site through endothelial wall
Initially neutrophils-the principal cells that engulf and destroy bacteria appear
Later in the process monocytes migrate and differentiate into macrophages
Further down in the process ***lymphocytes*** might be involved
This increases lymph flow into the lymph node
Lymph brings Ag into the lymph node where it is trapped
Activates adoptive immune system via ***dendritic cells***

A variety of inflammatory mediators such as ***Prostaglandins, Leukotrienes, platelet activating factor (PAF)*** are produced by macrophages, followed by ***tumor necrosis factor-α (TNF- α).*** If bleeding occurs, ***the kinin and the coagulation*** systems are activated which increase permeability and clot formation respectively.

Activation of specialized APCs is necessary for induction of adaptive immune response **(Fig 1-13):**

Pathogens are ingested by immature dendritic cells (DCs)
DCs are resident phagocytic cells in tissues
DCs interact with naïve T cells in lymph nodes
If DCs fail to be activated, they induce tolerance
DCs recognize patterns through receptors and take up a wide variety of microbes
Upon stimulation through receptors, they engulf the microbe
They also engulf microbes in a receptor independence mechanism called ***macropinocytosis***
Primary function of DCs is to carry Ags to lymph nodes and not phagocytosis
Upon activation DCs mature into APCs and activate Ag specific T cells

Innate Immunity:

Innate immune responses-early induced responses activated by microbial infections that are not long lasting-followed by adaptive immunity **(Fig 2-1).**

Different microbes use different routes of infection **(Fig 2-2)**
Different mechanisms of protection are active at different stages of infection **(Fig 2-3)**
Epithelial cells act as intrinsic barriers to infection **(Fig 2-4)**
Macrophages bear receptors that recognize microbial components and induce phagocytosis **(Fig 2-5)**
Phagocytes release bactericidal agents following ingestion of microbes **(Fig 2-6)**

Complement system will be covered later by Dr. Ucker (Figs 2-7 to 2-26)

Innate immune system uses receptors to recognize microbes:

Innate immune system has receptors that are distinct from those of the adaptive immune system **(Fig 2-27).** These are called ***"pattern recognition molecules" Examples include:***

Macrophage mannose receptor **(Fig 2-5)**
Mannan-biding lectin **recognizes properly spaced mannose/fucose residues (Fig 2-28)**

LPS/LPS-BP bind to ***CD14*** and interact with ***Toll-like receptors*** and activate NFκB, which in turn activates genes involved in host defense **(Fig 2-29)**

This activates DCs or Langerhans' cells to undergo activation and migrate to LNs **(Fig 2-30).**

Induced Innate responses:

Activated macrophages secrete a range of cytokines-***IL1, TNF-a, IL-6, IL-8 and IL-12 (Fig 2-31),*** that play distinct roles in host defense.

Chemokines produced by phagocytic cells act as chemoattractants, they have similar structure and bind to chemokine receptors **(Fig 2-33)**

Cell-adhesion molecules (leukocyte functional antigens-***LFA-1,-2,-3,***) expressed on leukocytes initiate interactions with ***selectins*** expressed on endothelial cells.
Subsequently, LFAs interact with ICAMs (intercellular adhesion molecules) allow

leukocytes to cross the blood vessel **(Fig 2-36).**

Cytokines activate acute phase response **(Fig 2-38)**

Interferons are anti-viral proteins produced in response to viral infection **(Fig 2-40)**

NK (natural killer) cells appear early after viral infection (Fig 2-41 and -42)

CD5 positive B cells might respond to carbohydrate antigens on bacteria (Fig 2-43)

Ag mediated activation of lymphocytes give raise to clones of Ag specific cells:

Cells of the innate immune system recognize patters on microbes
Whereas, T and B cells recognize specific peptide/epitopes
They bear Ag receptors with a single specificity
This specificity is determined by genetic mechanism
Specificity of each lymphocyte is different
This ensures millions of different specificities-***lymphocyte-receptor-repertoire***

Ag binds - activates lymphocytes-results in identical progeny - ***clone*** **(Fig 1-14)**
Secrete ***clonotypic*** Abs, which are identical to the surface receptor

Clonal selection theory McFarlane Burnett **(Fig 1-15)**

Clonal Selection is the Central Principal of Adaptive Immunity:

T cells are selected in thymus
B cells are selected in BM
When cells encounter self-antigens-***clonal deletion*** occurs. This is also known as negative selection. When cells are positively selected it is called ***clonal selection***

Basic principals of clonal selection are shown in Fig. 1-15

The Structure of Ab illustrates the Central Puzzle of Adaptive Immunity:

Antibody (Ab) consists of two regions
Constant region - can only take 4 or 5 distinct forms
Variable region - can take infinite variety that can bind to a vast variety of Ags
Abs has two fold axis of symmetry **(Fig 1-16 & 17)**
Consist of two identical heavy and light chains
Both heavy and light chains have variable and constant regions
Variable regions of H & L chains combine to form Ag binding site
Immunoglobulins act as Ag receptors on B cells

Each developing lymphocyte can generate a unique Ag receptor by receptor gene rearrangement:

Antigenic (Ag) receptors with infinite range of specificities are encoded by a finite number of genes
Variable regions are inherited as sets of gene segments **(Fig 1-18)**
Through DNA recombination a complete region in encoded

Once a productive rearrangement has occurred, further rearrangement is prohibited

Gene rearrangement has 3 important consequences:
Vast diversity in generated with very few genes
Each cell expresses unique receptor specificity
All progeny inherit the same gene

Lymphocyte development and Survival are determined by signaling through their Ag receptor:

T cells receive signals from ***thymic epithelium***
B cells receive signals from ***stromal cells in BM***
Both continually receive signal in the lymphoid tissues for their survival
Self reactive cells and cells that fail to receive signal die by apoptosis or programmed cell death

Lymphocytes proliferate in peripheral lymphoid tissues to form effector and memory cells:

Upon Ag stimulation lymphocytes undergo clonal expansion
Small lymphocytes change and become lymphoblasts **(Fig 1-19)**
Lymphoblasts divide and differentiate into effector cells
Most effector cells undergo apoptosis but some become memory cells
Memory cells are the basis for Immunological memory and for vaccination **(Fig 1-20)**

Interactions with other cells and the Ag is required for lymphocyte activation:

Naive B cells are activated by T cells and Ag **(Fig 1-21)**
Naive T cells are activated by DCs and Ag **(Fig 1-22)**

Recognition of antigen and mechanisms of adaptive immunity:

Different pathogens require different responses **(Fig 1-23)**
There are two types of antigen receptors; surface Ig for B cells & TCR for T cells
Surface Igs recognize antigen that are outside of the cell. (eg. Bacteria)
TCRs recognize antigens that are generated in the cell. (eg. Virus)

Effector mechanisms used to clear pathogens is similar to those of innate immunity
Please see figure 1-24

Immunity mediated by antibodies is called humoral (Humor:body fluids) immunity
There are 5 different classes of antibodies with different functions
Different classes (isotypes) are found in different compartments of the body
Stem of the "Y" determines the class and function of the antibody
Antibodies protect by ***neutralization, opsonization or complement activation*** **(Fig 1-24)**

Pathogens bound by antibody are delivered to phagocytic cells for clearance from body
Antibodies are the sole contribution of B cells to adaptive immunity (unlike T cells)
T cells have a variety of effector actions

T cells are required for immune responses against intracellular pathogens and for B cell activation:

Antibodies cannot detect pathogens that grow inside the cell (eg. Viruses)
Cell-mediated (T cell) responses are required for their clearance
T cell responses require direct interactions with infected cells
If a cytotoxic T cell (CD8+) recognizes the antigen, it kills the infected cell **(Fig 1-25)**
If helper T cells (CD4+) recognize the antigen they carryout different functions
Th1 CD4+ cells clear intracellular pathogens; *M. tuberculosis* and *M. leprae* **(Fig 1-26)**
Th2 CD4+ cells primarily activate B cells to produce antibodies

T cells recognize foreign antigens as peptides bound to MHC proteins

Antigen is produced in the cell or is internalized through phagocytosis
Antigenic peptides are generated within the cell
Peptides are presented on the cell surface by cellular proteins called MHC molecules
Major **H**istocompatibility **C**omplex (MHC) genes encode MHC molecules
There are two major types of MHC molecules; MHC class I and MHC class II **(Fig 1-27)**
MHC class I present peptides acquired in the cytosol to CD8+ T cells **(Figs 1-28/30)**
MHC class II present peptides acquired in the vesicles to CD4+ T cells **(Figs 1-29/31)**
Antigen specific activation of T cells is aided by co-receptors
CD8 binds to class I and CD4 binds to Class II
Upon activation CD8+, CD4+Th1 and CD4+Th2 cells release different cytokines

Defects in immune system results in increased susceptibility to infection:

Inherited immune deficiency diseases (Eg. severe combined immunodeficiency)
Acquired immune deficiency disease (Eg. HIV infection)

Harmful immune responses: Allergies, autoimmune diseases and graft rejection **(Fig 1-32):**

Allergy is induced by innocuous substances (eg. food, chemicals, pollen)
Autoimmune responses are directed against self-antigens (eg. TSH receptor and β-cells)
Graft rejection is due to immune response to alloantigens
These are usually treated with immunosuppressive drugs
Antigen specific immune regulation might become treatment of choice.

Vaccination is the most effective way of controlling infectious diseases:

Many childhood disease have been eradicated through vaccination **(Fig 1-33)**
Vaccines against many other infectious agents are under development

Practice questions:

1. Which mechanism is likely to be effective against bacteria that grow inside macrophages?

1. Antibody neutralization
2. Complement activation
3. T_H2 activation
4. Activation of T_H1 producing lymphokines
5. Lysozyme

2. Which of the following mechanisms or agents is an effective chemical barrier against infection?

1. High pH of the skin
2. Low pH of vagina
3. Cilia of the respiratory tract
4. Lysozyme of the intestinal tract
5. Urine flow

3. Which of the following cell populations are not represented by clones with specific receptors for antigens and do NOT undergo blast transformation and proliferation?

1. T_H1 cells
2. B cells
3. Macrophages
4. T_H2 cells

4. The heavy chain of an IgG molecule is genetically controlled by:

1. V genes and C genes
2. V, D, J and C genes
3. V, J and C genes
4. V and J genes

5. The cells which present antigens to T_H cells are:

1. Macrophages and polymorphonuclear cells
2. Polymorphonuclear cells containing bacteria
3. Macrophages only
4. Macrophages and B cells
5. All of the above can present antigens.

6. The difference between innate and adaptive immune response is mainly in the:

1. Ability fights bacterial infections.
2. Ability to fight viral infections.
3. Memory of the response.
4. Number of cells involved.
5. Speed of the response.

7. Allergies (type I hypersensitivity) develop mainly because the patient
    1. Makes more IgG than IgM antibodies.
    2. Makes mainly IgM and IgA antibodies.
    3. Makes IgE inappropriately.
    4. Has a T cell deficiency
    5. Is unable to fight infections.

8. For an effective response antigen fragments are presented to T cells in association with:
    1. Surface antibodies on B cells.
    2. Molecules controlled by the major histocompatibility complex.
    3. Adhesion molecules.
    4. Polysaccharides.
    5. Acute phase reactants.

9. In AIDS patients the cells primarily destroyed are:
    1. The neutrophils.
    2. Tc cells
    3. Th cells
    4. B cells
    5. Macrophages

10. The process of elimination of self-reactive clones of B and T cells is called:
    1. Positive selection.
    2. Antigen elimination.
    3. Selective apoptosis.
    4. Negative selection.
    5. Selective differentiation.

11. Complement molecules help antibodies in defense by:
    1. Creating a whole in bacterial cell wall.
    2. Opsonizing bacteria.
    3. Attracting polymorphonuclear cells
    4. All of the above
    5. None of the above

12. Which of the following cells are essential to activate macrophages and make them kill ingested Mycobacterium tuberculosis?

    1. T_H2 cells
    2. B cells and TH1 cells
    3. Tc cells
    4. B cells
    5. T_H1 cells.

13. Primary follicles contain mainly:

    1. Macrophages.
    2. Tc cells
    3. TH1 cells
    4. B cells

5. Neutrophils.

14. Lacking which cells in a patient may lead to widespread infection with Staphylococcus aureus?

1. B cells.
2. T_H1 cells.
3. Tc cells.
4. Any of the above.

15. The essential factors involved in inflammation caused by type III hypersensitivity are:

1. Complement molecules.
2. Complement molecules, immune complexes and polymorphonuclear cells.
3. Polymophonuclear cells activated by IFNγ.
4. macrophages and IFNγ.
5. Antibodies and complement.

16. Early induced responses are characterized by:

1 Their appearance immediately after infection
2. Their appearance after early innate immune responses
3. Their appearance after adaptive immune responses are exhausted
4. Lasting protective immunity
5. Their antigen specificity

17. Intrinsic epithelial barriers for infection include:

1. Mechanical
2. Fatty acids
3. Enzymes
4. Normal microbial flora
5. All of the above

18. Activated macrophages produce:

1. Chemokines
2. IL-1, IL-6 and IL-8
3. IL-8
4. TNF-
5. All of the above

Correct answers.1(4); 2(2); 3(3); 4(2); 5(4); 6(3); 7(3); 8(2); 9(3); 10(4); 11(4); 12(5); 13(4) 14(1), 15 (2). 16 (2), 17 (5), 18 (5).