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Immune System

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I. Introduction

Immunology is a broad field encompassing both basic and clinical applications and deals with antigens antibodies and cell mediated host defenses especially as they relate to immunity to disease, hypersensitivity, allergies and rejection of foreign tissue.

Classification of Immunity

The ability of the body to defend against invading agents is called immunity. It is of the following types:

A. Innate immunity:

1) Non specific defenses

2) Relatively specific defenses by NK cells

B. Acquired (adaptive) immunity.

1) Naturally acquired

a) Active immunity (usually through infections)

- Cellular immunity
- Humoral immunity

b) Passive immunity (transfer of antibody from mother)

- IgG via placenta
- IgA via breast feeding

2) Artificially acquired

a) Active immunity

Vaccination (antigens in vaccines area immunogenic but not pathogenic, stimulate immune responses and produce memory cells.

b) Passive immunity

I.V injection of antibodies such as anti-D immunization of Rh-ve mother.

A) Innate immunity

Natural, non adaptive and nonspecific immunity is innate immunity.

Physiological barriers such as skin and mucous membranes.

Nonspecific defenses such as.

i) Reticulo endothelial system

Mononuclear phagocyte cells in blood lymphoid tissue liver , spleen, bone marrow ,lung and other tissue.

ii) Alternative complement pathways such as C3 parasite, endotoxins, microbial surface C5, C6, C7, C8, C9 (opsonization) lysis of bacteria)

iii) Phagocytosis – Engulfment and killing of microbes by phagocytic cells which include microphage (granulocytes, polymorphs) and microphages.

iv) Inflamatory response.

2) Specific defenses

i) Nk cells lyse tumour cells and virus infected cells.

ii) Interferons are virus induced protein that have antiviral activity after 48 hrs of viral infection.

Ex: IFNa, IFNb, INFg

B. Acquired Immunity

This type of immunity occurs in response to infection called adaptive as the immune system must adapt itself to previously unseen molecules. It forms the 3rd line of defence.

a) Active immunity
Active immunity is of two types natural and antificial.
Natural – through clinical or sub clinical infection.
Artificial – Induced by vaccination.
It is the resistance developed by an individual as a result of contact with antigen. It leads to the stimulation of antibodies. Active immunity develops after a latent period and lasts longer.
Active immunity stimulates humoral immunity and cell mediated immunity.
i) Humoral immunity.
It is antibody mediated immunity. It depends on the synthesis of antibodies by plasma cells. These antibodies bindes with antigens and cause phagocytosis ,remove toxins and lyse cells
ii) Cell mediated immunity
It depends an T-lymphocytes developed against certain antigens. They are mediated by sensitised T lymphocytes. In these chronic infections organisms can multiply and survive in phagosome.
Ex: tuberculosis, leprosy

b. Passive immunity
Antibodies received by the host from the other person. The host's immune system does not participate.
It is of two types
i) Natural – through trans placental maternal IgG antibodies.Transfer of IgA antibodies through milk (colostrums).
ii) Artificial
It is through placental administrative of antibodies. The agents used for artificial passive immunity are hyper immune sera of animal or human origin.

Ex: Antitetamus serum (ATs) which is prepared by injecting series of doses of tetanus toxoid to horse and bleeding them for serum. Convalescent sera (sera obtained from patients recovering from infectious diseases) contain high doses of antibody. Antigens
Antigens are proteins (or) large polysaccharides which evokes immune response to produce antibodies. They are of two types.

A) Complete antigen
B) Haptens
A) **Complete antigen**
These antigens are substances which can induce antibody formation by themselves and can react specifically with these antibodies.
B) **Haptens**
Haptens are substances unable to induce antibody formation an its own but can become immunogenic

Epitopes
Antibody molecule do not kind to the whole of an infectious agent. Each antibody kinds to a restricted part of antigen can epitope. A single antigen has several different epitopes. T-cell and B-cell epitopes.

Antigen processing and presentation

The antigen is 1st degraded into short peptides of by antigen presenting cells and the process is called antigen processing. These peptides bind with MHC I (or) MHC II molecules within the Antigen presenting cells (APCs). This process is collect antigen presentation. Class II MHC molecules deliver costimulatory signal for TH cell activation are called antigen presenting cells.
These are two pathways.
1) Cytosolic pathway Intra cellular antigens are eliminated by cytotic T lymphocytes.
2) Endocytic pathway Extra cellular antigens are eliminated by antibodies.

Primary Immune defences
It is innate which offers protection to all pathogens Ex: Skin, Mast cells, Sudoriferous glands which produce sweat, Sebaceous glands goblet cells Lacrimal glands.

Secondary immune defences
Phagocytosis is by monocytes, Macrophages and inflamatory responses by Eosinophils, Basophils and neutrophils.

B-cell and T-cell receptors
B-lymphocytes are simply B cells
T-lymphocytes are T cells

B-cells are produced in bone marrow and also mature there. Each B-cell and T-cell is specific for a particular antigen. B cells bind to specific antigen T helper cells recognize the antigens are induce maturation and proliferation. A mature B cell may produce 100000 antigenic receptors. B cells are of two types.

Memory cells

B cells differentiate into long lived memory cells. When these cells encounter same antigen (even decades later) they rapidly differentiate into antibody producing plasma cells.

Plasma cells
They produce antibodies.

T cells
They are produced in bone marrow and mature in thymus. They are of 4 types.

T helper cells (T_H cells)
Activate cytotoxic T-cells and also necessary for B-cell activation.

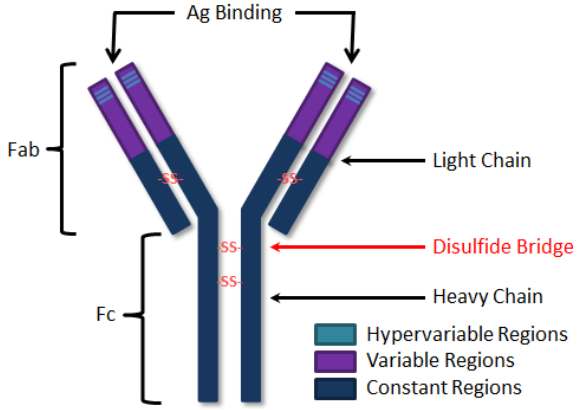
Cells for delayed hypersensitivity (TD cells)
causes transplant rejection and inflammation in allergic reactions.

T suppressor cells (TS cells)
Regulates immune system by turning it off

Cytotoxic T cells (TC cells)
Destroys target cells on contact, recognizes tumor (or) virus infected cells by their MHC markers and antigens.

Structure of antibodies
Most antibodies has 4 polypetide chains. The two of them are heavy chaines (H) and the other two are light (L) chains.
1) Antibodies are glycoproteins and their carbohydrates residue is attached to heavy chains.
2) Disulphide bonds bridge the L and H chains are attached to each of them at the middle by disulphide bonds. At this point H chains display flexibility. Therefore this region of H chain is called hinge region.
3) The tip of H and L chains is called variable region, as this region is different for each type of antibody. The variable region contains antigen binding site. This part of antibody recognizes the specifically attach to a particular antigen (F(ab)2). F ab digested by papain breaks at hinge region.
4) The flexibility at hinge region allows the antibody to bind to two antigenic determinents.
5) The rest of the H and L chain is called constant region (Fc) as it is constant in all antibodies FC region is digested into small fragment by pepsin.

Structure of Antibody



Types and functions of antibodies.

IgG	Complement fixation by classical pathway. IgG is the only antibodies that crosses placenta
IgA	Localized protection in body sections like tear, salivary glands intestinal secretions colostrums. IgA antibody is present in mother's milk.
IgM	Complement fixation by classical pathway. IgM is the 1st Ig made by the fetus and first Ig to be made by Virgin B cells.
IgD	Antigen recognition by B cells
IgE	Histamine releases from most cells and basophiles when IgE bind to them. IgE causes allergic symptoms. IgE plays an important role in helmuth diseases

Monoclonal Antibodies
Monoclonal antibodies are antibodies prepared from a single clone of B cells a plasma cells. They are used for immunotherapy of different diseases.

Method of production (mAbs)
An mice are immunized by injecting antigens then they are euthanized and antibody producing cells are extracted from spleem.
1) The antibody producing cells are fused with myeloma cells that are obtained from B lymphocyte tumor.
2) This fusion of myeloma cell with antibody results in formation of hybridism which become antibody producing tumor.
3) Fusion is done through cocentrifuging myeloma cells and spleen cells with polyethylene glycol. The cells are plated in the medium containing Hypoxanthine Aminopterin Thymidine (HAT) acts as inhibitor of Aminopterin which blocks nucleotide synthesis.So, only fused cells grow on murine bone marrow.
4) A mouse is inoculated with the fused cell and there by becomes a factory of mabs.
5) Screened and purified mAbs are specific for Ag binding.

Uses of monoclonal antibodies
1) Diagnosis of allergic diseases, hepatitis, STDs and drug level.
2) Detection of Cancer in early stage.
3) Prevention of transplant rejection.
4) Treatment of auto immune diseases.

Major histocompatibility complex
Transplants from other individuals are rejected. Gorer identified antigens responsible for graft rejection in mice that lead to the discovered of MHc. He identified two antigens. Antigen 1 is common for all strains in mice and antigens 2 are present in certain strains only which are responsible for allograft rejection. This was named as H2 antigen. H2 antigen is found to be major histo compatibility antigen and coded by closely linked genes. The MHc in humans is known as human leucocyte antigen (HLA) complex.

HLA means antigens that evoke immune response resulting in graft rejection. All of antigens are coded by a set of genes namely ALA complex. They are locataed a short arm of chromosane 6. The no menclatue of HLA system is regulated by World health organizaton. The antigens are this gens are divided into 3 classes.

1) Class I MHC Antigens (A,B,C)
The MHC class I antigens are present on all nucleated cells. They are involved in graft rejection and cytolysis. The cytoloxic T cells (CD8) recognize MHC class I antigens.

2) Class II MHC Antigens (DR, DQ and DP)
They are present on monocytes and macrophages and are activated by T lymphocytes (CD4) and B lymphocytes. They are responsible for graft vs host response.

3) Class III Antigens
Class III gens encode C_2, C_4 complement components of classical pathway and properdin factor B of alternative pathway.

The complement system
In classical path way antibody binds to an antigen and immune system is activated. This is antibody dependent.

In alternative pathway it does not require antibody. This is antibody independent. It constitute humoral component which operate without antibodies. The six proteins responsible for the formation of C_3/C_5 convertase re C_3, B, D, H, I and P. Both pathways contain initial enzyme that catalyses C_3 converters which geuerates C_5 convertase. This results in membrane attack complex (MAC). Mac binds to target membrane owing to hydrophobic interaction with lipid bilayer. Final events are the unfolding the polymerization of C9 which causes weakening of membrane structure and osmolytic lysis. This system lyses many cells like bacteria, viruses erythrocytes etc.,

Cytokines
Cytokines are the chemicals produced by the cells that regulate immune response. Cytokines produced by the lymphocytes are called lymphokines.

Important cytokines and their activity

Cytokine	Representative activity
Intuleukin I	Stimulates TH cells in the presence of antigens chemically attracts phagocytes
Intuleukin II	Involved in proliferation of antigen stimulated TH cells, proliferation and differentiation of B cells and activation of Tc cells and NK cells
Gamma interferons	Inhibits intra cellular viral replication. Increase the activity of Macrophases against microves and tumour cells.
Tumour Necrosis facta B	Cytotoxic Tc tumour cells enhances phagocytosis.
Gramulo cyte macrophage coloney stimulating facta (CIM – CSF)	Stimulates the formation of red and white blood cells

Hypersensitivity

It is an excessive immune response which leads to severe consequences like organ damage (or) disfunction. There are 4 types of hypersensitivity reactions.

Type I Reaction (or) Anaphylaxis.

It usually occurs when individual is exposed to allergen for the 2^{nd} time. Antigen antibody complexes release histamine from mast cells and basophiles which causes vasodilatation, hypotension and bradicardia.

Type II Reaction (or) Cytoloxic Reaction.

Caused by IgG and IgM antibody which are directed against persons red cells, blood transfusions, autoimmune anemias and erythroblastsis foetalis are examples.

Type III Reaction (or) Immune complex diseases

Antigen antibody from complexes is deposited on the basement membrane of the blood vessels. They induce inflammation. Rheumatoid arthritis is the example.

Type IV Reaction (or) Delayed hypersensitivity

They are mediated by macrophages that are activated by T cells.

Allergens (antigens) are taken up by APCs and presented to T cells which cause its proliferation. They migrate to the location of allergen and release cytokines which causes inflammatory response Ex. Skin test for tuberculosis.

Auto immunity

Auto immunity is a condition that occurs when the immune system mistakenly attacks and destroys healthy tissue. It may be due to persistant T cells and B cells against auto-antigens and failure of the process that removes antibodies against self antigens.

It is classified into two clusters.

Organ specific	**Systemic**
1. Diabetes mellitus	1. Rheumatoid arthritis
2. Good pasture's syndrome	2. Systemic lupus
3. Hashimoto's thyroiditis	3. Erythematosus

Immunodeficiency

Immuno deficiency is a state in which its ability to fight infections is compromised (or) absent. It is of two types.

1) Primary Immuno deficiency

It is due to severe combined immune deficiency (SCID) occurs due to defects in alular (or) humoral immunity.

2) Secondary immune deficiency

Acquired immune deficiency syndrome (AIDS) is caused due to immune deficiency Virus (HIV). It is a retrovirus that binds to CD_4 protein are the surface of helper T cells T_H cells which leads to decrease in its number. T_H cells are useful for humoral and cellular immunities. T_H cell destruction leads to serious infections and malignancies.

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