Introduction to cellular basis of Immunity

Introduction

Immunity is derived from a Latin word " ***immunitas***" which means "exempt" which is state of protection from infectious disease. Immunity generally means protection. In biological terminology, immunity is the natural process that is responsible for fighting microorganisms, which enter our bodies to damage the cells. Basically, when our body detects a pathogen, our immune system gets activated. Pathogens are the microorganisms that are either bacteria or viruses, which are capable of causing a disease.

So, immunity, is a natural process which keeps us safe from minor and major ailments. We all know that ailments are inevitable whatsoever but can we even guess the number of times our body escapes infections? How many times our body fights bacteria and viruses without even letting us know? Our immunity system is our Superman inside who saves us from diseases.

Organs of Immune system

The organs of the immune system, the lymphoid organs, are distributed throughout the body. They can be divided into **primary lymphoid organs**, where the lymphocytes—the central actors of the immune system—are generated, and secondary lymphoid organs, where the adaptive immune responses are initiated. The **primary organs** are the **bone marrow and the thymus**, whereas the **secondary** organs (also called the peripheral lymphoid organs) are the **lymph nodes, spleen and the mucosal- and gut-associated lymphoid tissues** (MALT and GALT, respectively), i.e. tonsils, adenoids, the appendix and the Peyer's patches of the small intestine (Fig 1).

Before knowing the details of immune cells, we should first recall the types of blood cells human body has; these are Red blood corpuscles (RBCs), blood platelets and White blood corpuscles (WBCs) or leucocytes. So, RBCs are involved in oxygen transport and blood platelets are the cells take part in blood clotting. WBCs or leucocytes are the cells which constitute the defense system of our body. It protects us

from foreign microbes and infections. They are granulocytes (granule bearing cells, neutrophils, basophils and eosinophils) and agranulocytes (without granules in cell cytoplasm, monocytes and lymphocytes) (Fig 2).

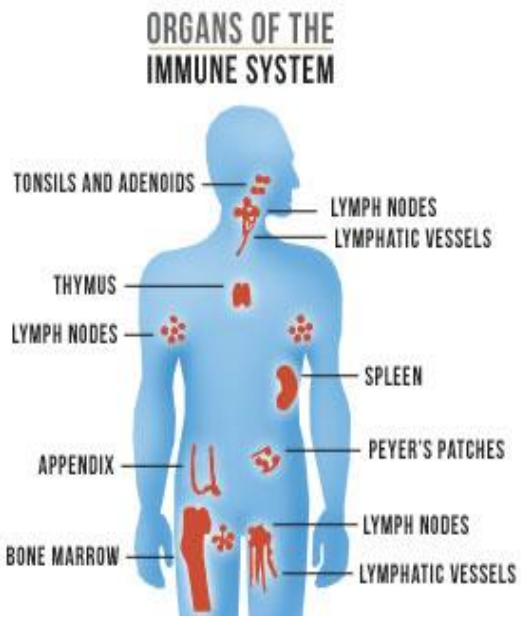


Fig. 1 showing organs of immune system

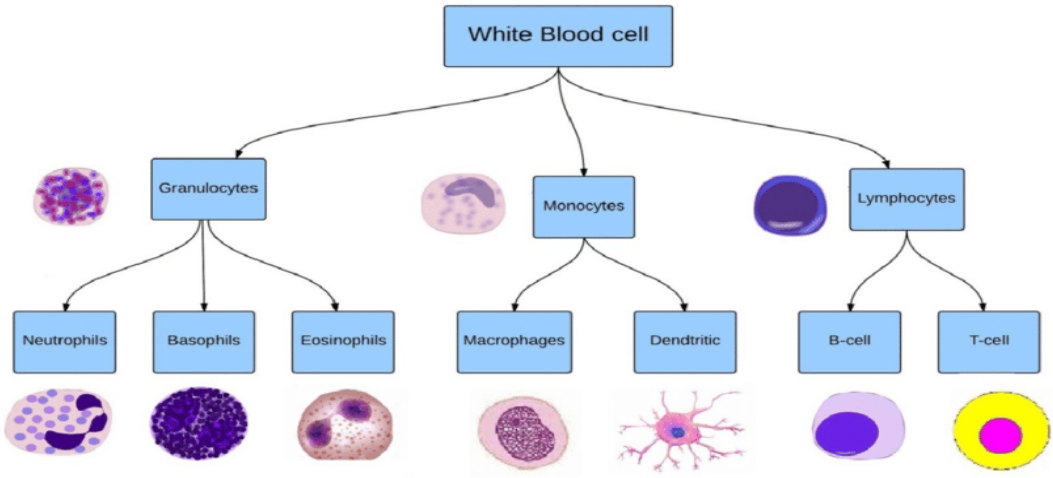


Fig. 2 showing types of leucocytes

Classification Immunity can be classified into two types: **Innate and Adaptive Immunity**

(i) Innate Immunity (natural/ non-specific/ present by birth)

Innate immunity represents the first line of host defense against pathogenic micro-organisms that have entered the body. This innate defense mechanism lacks memory and is mostly focused on a limited set of microbial determinants shared by a large number of pathogens. Innate responses are characterized by a lack of learning process and rapid kinetic, providing almost immediate protection against invading pathogens. It is non-specific and comprises four types of defensive barriers. Skin itself is a part of innate immunity as physical barrier. It is the primary defense of body that stops harmful organisms from entering the body. However, pathogens can still break into the body by means of air, food or water. The second defense of the body is in the form of mucus which attaches the pathogen to itself and kills it right there. It is destroyed by the complement system which involves a set of proteins.

Now let's assume the pathogen is even more powerful and it escapes from skin and then mucus as well. It further goes inside and confronts the cells called phagocytes and NK cells. Phagocytes are of three types: Macrophages, Neutrophils and Dendritic cells

All these cells detect the pathogen, attack and destroy it right there by a process called phagocytosis. The body sends a whole army of cells to fight the pathogen. NK stands for natural killer cells. These cells on the other hand fix the damage already caused to the host cells. It kills them so the pathogen is finally eradicated from the body. If the pathogen still survives phagocytes and NK cells, then our body activates the secondary immunity which is the adaptive immunity.

(ii) Adaptive Immunity (Acquired/specific)

It is the functional immune system and capable of recognizing and selectively eliminating foreign microorganisms and molecules. Adaptive immunity provides a second line of defense, often at a later stage of infection. Adaptive immunity is relatively slower as compared to innate immunity. Adaptive

responses are characterized by a very large set of effector molecules and cells, able to efficiently recognize and eliminate virtually any known pathogen. After elimination of the pathogen, the adaptive immune response establishes a state of "memory" characterized by the ability to efficiently protect the body from re-infection with the same agent. **Memory is the hallmark of the adaptive immune response and can be induced by both natural infection and vaccination.**

Our immune system produces proteins known as antibodies. They neutralize the pathogen There are two kinds of adaptive immunity, active and passive. The **active immunity** works by means of two kinds of cells: B lymphocytes and T lymphocytes where antibodies are produced in response to pathogen and memory cells are generated which remember the earlier exposure of the pathogen nd again ready to secrete antibodies. **Passive immunity** on the other hand involves the transfer/injection of antibodies which are acquired from another person.

Cells of adaptive Immunity

B and T lymphocytes which are derived from specific types of stem cells, called multipotent hematopoietic stem cells, in the bone marrow. After they are made in the bone marrow, they need to mature and become activated. Each type of cell follows different paths to their final, mature forms.

B Lymphocytes After formation and maturation in the bone marrow (hence the name "B cell"), the naive B cells move into the lymphatic system to circulate throughout the body. In the lymphatic system, naive B cells encounter an antigen, which starts the maturation process for the B cell. B cells each have one of millions of distinctive surface antigen-specific receptors that are inherent to the organism's DNA. For example, naive B cells express antibodies on their cell surface, which can also be called membrane-bound antibodies.

B cell and membrane-bound antibodies When a naive B cell encounters an antigen that fits or matches its membrane-bound antibody, it quickly divides in order to become either a *memory B cell* or an *effector B cell*, which is also called a *plasma cell*. Antibodies can bind to antigens directly. The antigen must effectively bind with a naive B cell's membrane-bound antibody in order to set off *differentiation*, or the process of becoming one of the new forms of a B cell.

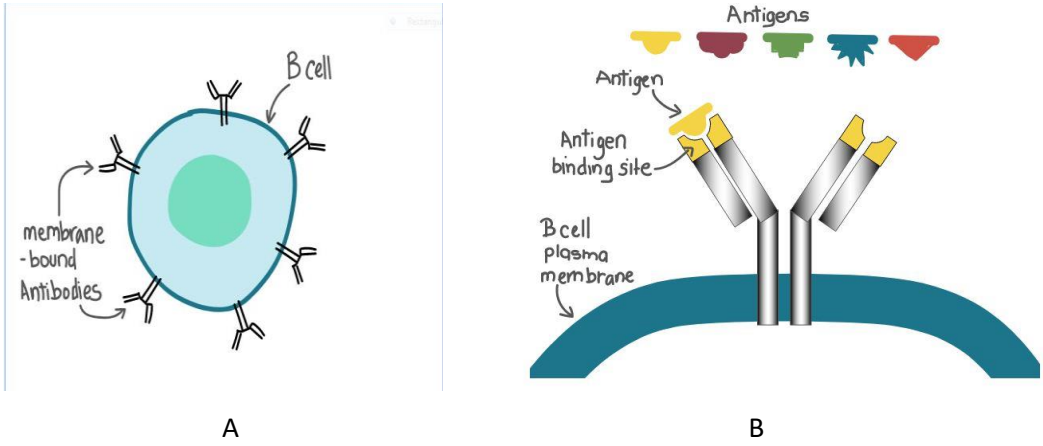
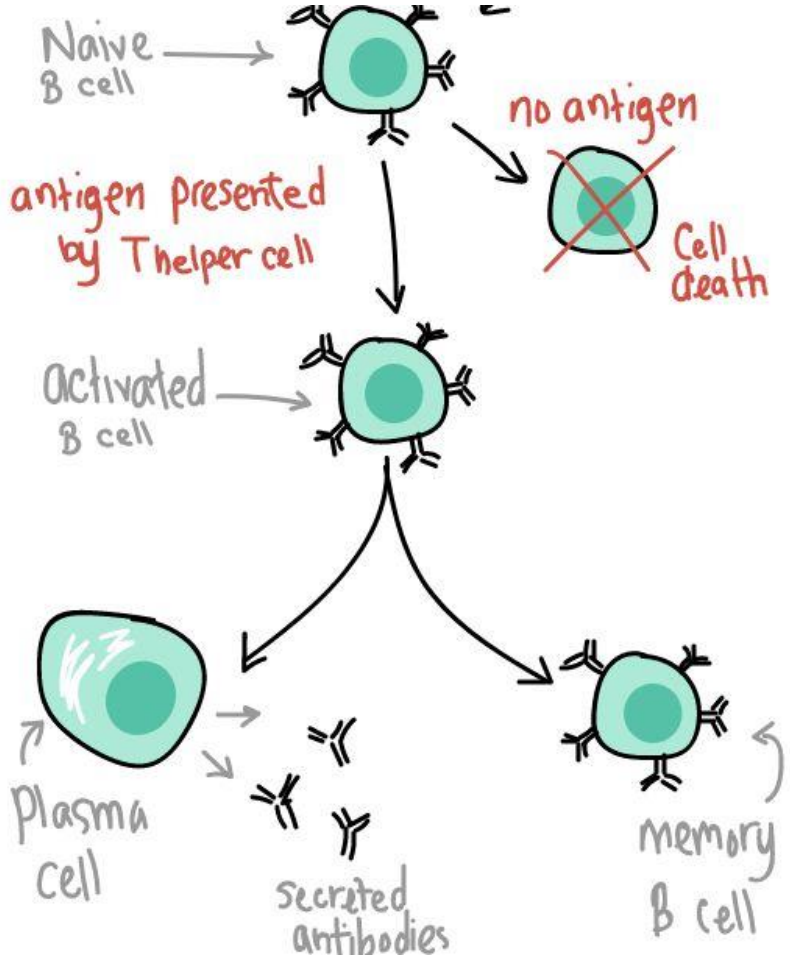


Fig: 3 (A) Surface bound antibodies on naïve B cells; (B) membrane bound antibodies and its interaction with antigen

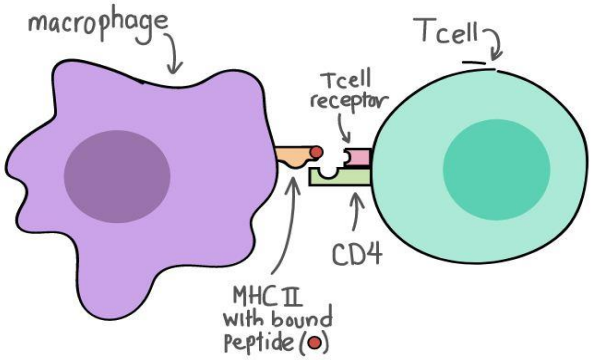
Memory B cells express the same membrane-bound antibody as the original naive B cell, or the "parent B cell". Plasma B cells produce the same antibody as the parent B cell, but they aren't membrane bound. Instead, plasma B cells can secrete antibodies. Secreted antibodies work to identify free pathogens that are circulating throughout the body. When the naive B cell divides and differentiates, both plasma cells and memory B cells are made. B cells also express a specialized receptor, called the *B cell receptor (BCR)*. B cell receptors assist with antigen binding, as well as internalization and processing of the antigen. B cell receptors also play an important role in signaling pathways.



T cells

Once formed in the bone marrow, *T* cell progenitors migrate to the thymus (hence the name "T cell") to mature and become T cells. While in the thymus, the developing T cells start to express *T cell receptors (TCRs)* and other receptors called *CD4* and *CD8* receptors. All T cells express T cell receptors, and either CD4 or CD8, not both. So, some T cells will express CD4, and others will express CD8. Unlike antibodies, which can bind to antigens directly, T cells (receptors) can only recognize antigens when they are bound with **Major Histocompatibility Complex class 1 (MHCI)** and **class 2 (MHCII).** MHC class 2 are membrane-bound surface receptors on **antigen-presenting cells,** like **macrophages, B cells and dendritic cells**. CD4 and CD8 play a role in T cell recognition and activation by binding to either MHCI

or MHCII. **MHC I** glycoproteins are present on cell membranes of all the nucleated cells whereas **MHCII** are present only on antigen presenting cells(APCs).



There are three types of T cells: Helper T cells **(T_H)**, Cytotoxic T cells (**T_{Cyt}**) and T regulatory cells (**T_{reg}**). Helper *T* cells express CD4, and help with the activation of B cells, and other immune cells. Cytotoxic *T* cells express CD8, and are responsible for removing pathogens and infected host cells. *T* regulatory cells express CD4 and another receptor, called CD25. T regulatory cells help distinguish between self and non-self molecules, and by doing so, reduce the risk of autoimmune diseases.

Humoral and Cell Mediated Immunity

There are two types of immunity that the adaptive immune system provides, and they are dependent on the functions of B and T cells, as described above. **Humoral immunity** is immunity from serum antibodies produced by plasma cells (effector B cells). More specifically, someone who has never been exposed to a specific disease can gain humoral immunity through administration of antibodies from someone who has been exposed, and survived the same disease (this is a type of passive immunity because antibodies are transferred from some other individual). "Humoral" refers to the bodily fluids where these free-floating serum antibodies bind to antigens and assist with elimination.

Cell-mediated immunity can be acquired through T cells from someone who is immune to the target disease or infection. "**Cell-mediated**" refers to the fact that the response is carried out by cytotoxic cells. Much like humoral immunity, someone who has not been exposed to a specific disease can gain cell-

mediated immunity through the administration of T_H cells and Tcyt cells from someone that has been exposed, and survived the same disease. The T_H cells act to activate other immune cells, while the Tcyt cells assist with the elimination of pathogens and infected host cells.

Immunological memory

Because the adaptive immune system can learn and remember specific pathogens, it can provide long-lasting defense and protection against recurrent infections. When the adaptive immune system is exposed to a new threat, the specifics of the antigen are memorized so we are prevented from getting the disease again. The concept of immune memory is due to the body's ability to make antibodies against different pathogens.

A good example of immunological memory is shown in vaccinations. A vaccination against a virus can be made using either active, but weakened or attenuated virus, or using specific parts of the virus that are not active. Both attenuated whole virus and virus particles cannot actually cause an active infection. Instead, they mimic the presence of an active virus in order to cause an immune response, even though there are no real threats present. By getting a vaccination, you are exposing your body to the antigen required to produce antibodies specific to that virus, and acquire a memory of the virus, without experiencing illness.

Some breakdowns in the immunological memory system can lead to autoimmune diseases. Molecular mimicry of a self-antigen by an infectious pathogen, such as bacteria and viruses, may trigger autoimmune disease due to a cross-reactive immune response against the infection. One example of an organism that uses molecular mimicry to hide from immunological defenses is *Streptococcus* infection.

Innate Immunity vs. Adaptive Immunity: A summary

The following chart compares and summarizes all of the important parts of each immune system:

Quality	Innate Immunity	Adaptive Immunity
Response Time	Fast: minutes or hours	Slow: days

Quality	Innate Immunity	Adaptive Immunity
Specificity	Only specific for molecules and molecular patterns associated with general pathogens or foreign particles	Highly specific! Can discriminate between pathogen vs. non-pathogen structures, and miniscule differences in molecular structures
Major Cell Types	Macrophages, Neutrophils, Natural Killer Cells, Dendritic Cells, Basophils, Eosinophils	T cells, B cells, and other antigen presenting cells
Key Components	Antimicrobial peptides and proteins, such as toxic granules	Antibodies
Self vs. Nonself Discrimination	Innate immunity is based on self vs. nonself discrimination, so it has to be perfect	Not as good as the innate immune system, but still pretty good at determining which is which. Problems in self vs. nonself discrimination result in autoimmune diseases
Immunological Memory	None	Memory used can lead to faster response to recurrent or subsequent infections
Diversity and Customization	Limited: Receptors used are standard and only recognize antigen patterns. No new receptors are made to adapt the immune response	Highly diverse: can be customized by genetic recombination to recognize epitopes and antigenic determinants.

III. BASIC STRUCTURE OF IMMUNOGLOBULINS

A. An antibody is composed of two heavy chains (50 KD each) and two light chains (25 KD each), which are joined by disulfide bonds to form a ‘Y’ shaped structure (150 KD). Antibodies are further divided into two regions: a variable region and a constant region.

B. The variable region is responsible for the antigenic specificity of an antibody. This region includes a fragment antigen binding (Fab) portion that binds the antigen with high specificity.

There are two Fab portions in each antibody, which can simultaneously bind two identical epitopes (a specific antibody-binding site of an antigen) of a particular antigen.

C. The constant region of an antibody includes a fragment crystallization (Fc) portion that binds cell surface receptors (Fc receptors) on circulating WBCs, macrophages, and natural killer cells. This binding is necessary to initiate an immune reaction. In addition, there are two hinge regions that join the Fab and Fc portions of an antibody.

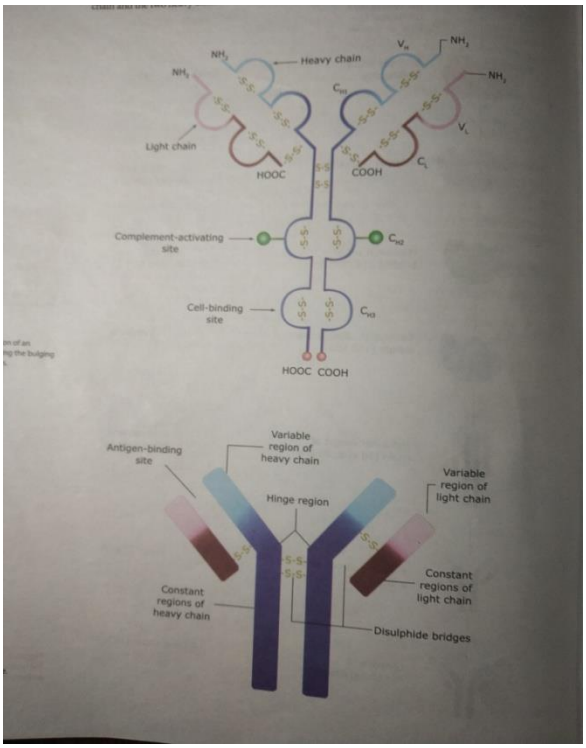


Fig 4 Antibody structure

GENERAL FUNCTIONS OF IMMUNOGLOBULINS

(a)**Antigen binding** Immunoglobulins bind specifically to one or a few closely related antigens. Each immunoglobulin actually binds to a specific antigenic determinant. Antigen binding by antibodies is the primary function of antibodies and can result in protection of the host. The valency of antibody refers to the number of antigenic determinants that an individual antibody molecule can bind. The valency of all antibodies is at least two and in some instances more.

b. **Effector functions** Frequently the binding of an antibody to an antigen has no direct biological effect. Rather, the significant biological effects are a consequence of secondary "effector functions" of antibodies. The immunoglobulins mediate a variety of these effector functions. Usually the ability to carry out a particular effector function requires that the antibody bind to its antigen. Not every immunoglobulin will mediate all effector functions. Such effector functions include:

1. **Fixation of complement** - This results in lysis of cells and release of biologically active molecules.
2. **Binding to various cell types** - Phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins. This binding can activate the cells to perform some function. Some immunoglobulins also bind to receptors on placental trophoblasts, which results in transfer of the immunoglobulin across the placenta. As a result, the transferred maternal antibodies provide immunity to the fetus and new born baby.

Types of antibodies

IgG

This isoform accounts for 70–75% of all human immunoglobulins found in the blood. Depending on the size of the hinge region, the position of disulfide bonds, and the molecular weight of the antibody, IgG can be further divided into 4 subclasses: IgG1, IgG2, IgG3, and IgG4.

In general, proteins are responsible for triggering IgG1 and IgG3 production, whereas IgG2 and IgG4 typically respond to foreign polysaccharides. IgG is the main component of the humoral immune system (immune response initiated by macromolecules present in the extracellular fluid) because of its abundance.

Due to its small size (monomeric) and high diffusibility, IgG is the prevalent type in the extracellular fluid that binds Fc receptors on phagocytic or other lytic cells and initiates the antibody-dependent cell-mediated cytotoxicity (ADCC) response – a cell-mediated defense mechanism wherein effector cells (phagocytes) destroy the target cell.

In addition, IgG triggers phagocytosis to initiate opsonization reaction – a process used to destroy foreign particles (e.g. bacteria) through phagocytosis. Apart from these functions, **IgG is the only antibody that can cross the placenta and provides passive immunity to the fetus and infants in the first few months of life.**

IgM

IgM is the largest antibody and the first one to be synthesized in response to an antigen or microbe, accounting for 5% of all immunoglobulins present in the blood. IgM typically exists as polymers of identical subunits, with a pentameric form as the prevalent one.

In its pentameric form, five basic antibody units are attached by disulfide bonds. Other forms include secretory IgM, which is synthesized by glandular-associated B cells, and monomeric form, which is present in the B cell membrane and functions as a B cell antigen receptor.

Due to its large size, IgM is mostly intravascular and has a lower affinity for antigens. However, since pentameric IgM has 10 antigen binding sites, it has higher avidity (overall binding strength) for antigens than IgG and acts as an excellent activator of the complement system and agglutination.

IgA

It accounts for 10–15% of all immunoglobulins and is prevalent in serum, nasal mucus, saliva, breast milk, and intestinal fluid. It has two subtypes namely IgA1 and IgA2, which mainly differ in terms of their hinge region characteristics. At mucosal surfaces, IgA provides the primary defense against inhaled and ingested pathogens.

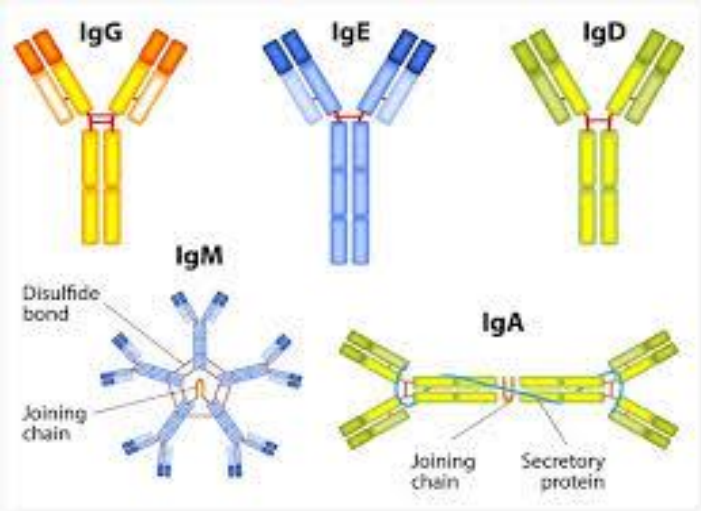
IgE

IgE is the least prevalent one, with a serum concentration 10,000 times lower than IgG. However, the concentration of IgE increases significantly in allergic conditions, such as bronchopulmonary aspergillosis, and parasitic diseases, such as schistosomiasis.

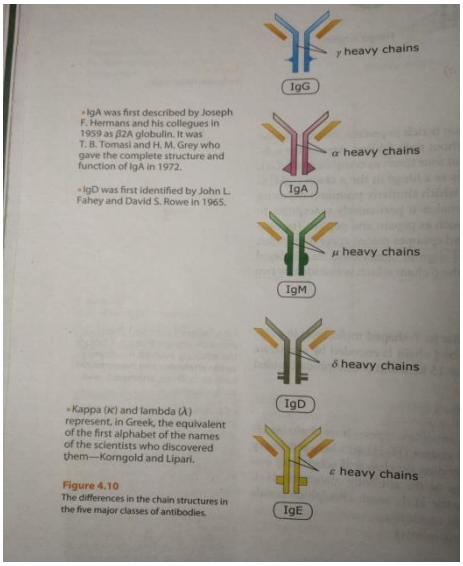
In response to pathogens, IgE binds to mast cells via specific receptors, followed by pathogen-mediated cross-linking of these receptors (degranulation). This causes recruitment of eosinophil at the site of infection and destruction of pathogens via ADCC-type mechanisms.

IgD

IgD functions as a B cell antigen receptor and may participate in B cell maturation, maintenance, activation, and silencing. Although the exact function is still unclear, IgD may be involved in humoral immune responses by regulating B cell selection and homeostasis.



S.no	Immunoglobulin type	Heavy chain
1.	IgG	Gamma (**γ**)
2.	IgM	Mu (**μ**)
3.	IgA	Alpha (**α**)
4.	IgD	Delta(**δ**)
5.	IgE	Epsilon(**ε**)



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