PHYSIOLOGY OF IMMUNE SYSTEM **by Asiyanbola I. D.**

1.0 Introduction

Immune system is a team effort that involves many different players interacting together to provide a powerful defence against invaders. It is made up of a network of players who cooperate to get things done.

1.1 Players of the Immune System

1.1.1 Physical barriers/ External defence

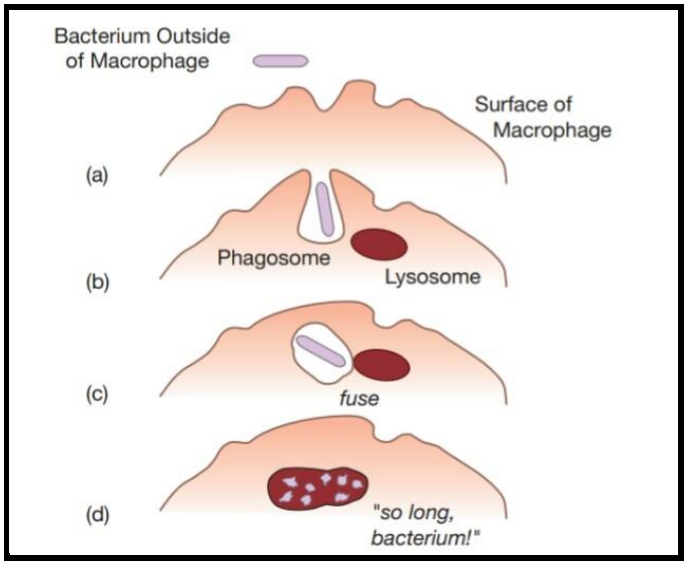
They are the first line of defence against invaders. For viruses, bacteria, parasites, and fungi to invade, they must penetrate these shields. They include the skin and mucous membrane.

1.1.2 Innate immune system

They are the next barrier faced by any invader that breaches the skin or mucosa layer. It is our second line of defence. It is called "innate" because it is a defence that all animals naturally seem to have. The most famous player of the innate immune system is a defender cell called 'Macrophage': it senses the presence of an invader e.g., bacteria, and reaches out to grab it. Its antennae acts as receptor and is tuned to recognise danger molecules, which are membranes that surround bacteria. These molecules are made of certain fats and carbohydrates that are not normally found in the human body.

When macrophages detect danger molecules, they begin to crawl toward the microbe which is emitting these molecules. When it encounters a bacterium, the macrophage engulfs it in a pouch (vesicle) called 'Phagosome'. The vesicle containing the bacterium is then taken inside the macrophage, where it fuses with another vesicle termed 'Lysosome'. Lysosomes contain powerful chemicals and enzymes which can destroy bacteria. This whole process is called "Phagocytosis": it is a clever strategy through which the macrophage can destroy an invader.

Illustration of the Phagocytosic Process



During battle with bacteria, macrophages produce and give off secrete proteins called cytokines: these are hormone-like messengers which facilitate communication between cells of the immune system. Some of these cytokines alert monocytes and other immune system cells traveling in nearby capillaries that the battle is on i.e., an invader is around, and encourage these cells to exit the blood to help fight the rapidly multiplying bacteria. As the innate immune system battles to eliminate the invaders, a vigorous inflammatory response comes up in the affected part of the body. In addition to the professional phagocytes like macrophages, which make it their business to eat invaders, the innate system also includes the 'Complement proteins': that can punch holes in bacteria; and natural killer (NK) cells: that are able to destroy bacteria, parasites, virus-infected cells, and some cancer cells.

1.1.3 The Adaptive immune system

After the natural barrier and innate immune system, the adaptive immune system is the third level of defence for us, the vertebrate. This is a defence system which actually can adapt to protect us against almost any invader. It works on the principle that: if the human immune system were given time to prepare, it could produce weapons that could provide protection against an intruder it had once seen before or an intruder similar to the one it has seen before. The objective of the adaptive immune system is to adapt to defend against specific invaders. Immunity is conferred by special proteins that circulate in the blood. These proteins are called 'Antibodies' and the agents causing the antibodies to be made are called 'Antigens'.

1.1.3.1 Antibodies and B Cells

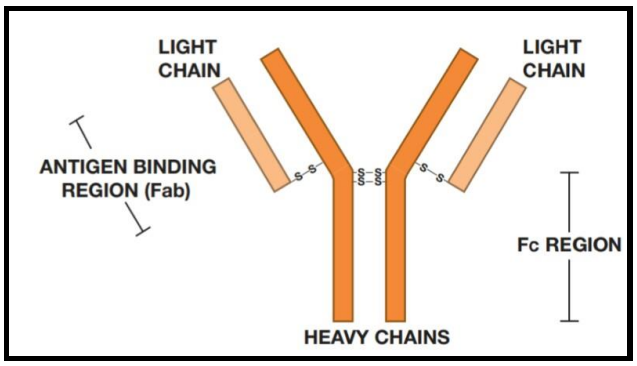
Antibodies are special proteins circulating in the blood of an individual that has been immunized against an infection. The agent that caused the antibodies to be made is called 'Antigen'. There are 5 different classes of antibodies in the blood, they are: IgA, IgD, IgE, IgG and IgM. IgG makes up about 75 % of the antibodies in the blood. It is the most abundant antibody in the serum. Each kind of antibody is produced by B cells: white blood cells that are produced in the bone marrow.

Human Immunoglobulin (Ig) Antibodies

Ig antibodies	Function
IgM	First Ig expressed during B cell development • tags antigen for destruction • Complement fixation
IgG	Main Ig during secondary immune response • Only antibody capable of crossing the placental barrier • Neutralization of toxins and viruses • tags antigen for destruction • Complement fixation
IgD	Function unclear; appears to be involved in homeostasis
IgA	Mucosal response; protects mucosal surfaces from toxins, viruses and bacteria through either direct neutralization or prevention of binding to mucosal surface
IgE	Associated with hypersensitivity and allergic reactions • Plays a role in immune response to parasites

Warrington *et al*., 2011

A Prototype Antibody, Immunoglobulin G (IgG)

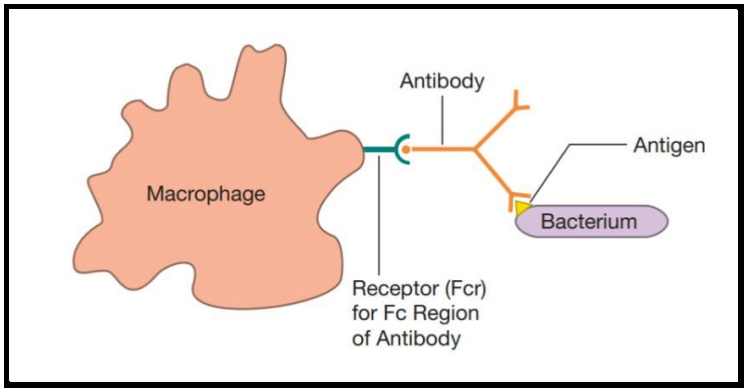


An IgG antibody molecule is made up of two pairs of two different proteins, the heavy chain (Hc) and the light chain (Lc). Each molecule has two identical 'hands': the Fab regions that can bind to antigens and a constant region known as the 'Fc-tail' that binds to receptors (Fc receptors) on the surface of cells such as macrophages. Fc region is the special structure of antibody that determines its class (e.g., IgG vs. IgA), which immune system cells it will bind to, and how it will function. The hands of each antibody bind to a specific antigen (e.g., a protein on the surface of a bacterium).

1.1.3.1.1 What do Antibodies do?

Although antibodies are very important in the defence against invaders, they really don't kill anything. Their job is to tag an invader for destruction. In other words, what antibody does is to opsonize or decorate an invader and leave the rest of the job to other Players. When antibodies opsonize bacteria or viruses, they do so by binding to the invader with their Fab regions, leaving their Fc tails available to bind to Fc receptors on the surface of cells such as macrophages. Using this strategy, antibodies form a bridge between the invader and the phagocyte, bringing the invader closely, and preparing it for phagocytosis.

Antibody, a Bridge between Macrophage and Antigen



The ability of antibody to form a bridge between a macrophage and an invader allows a macrophage to increase its catalogue of enemies to include any invader to which an antibody can bind. In effect, antibodies focus a macrophage's attention on invaders, some of which a

macrophage would otherwise ignore (especially the uncommon antigens). For viral attack, antibodies work a little differently: they can bind to a virus while it is still outside of a cell, and keep the virus from entering the cell or from reproducing. Antibodies with these properties are called neutralizing antibodies: they prevent a virus from "docking" on the surface of a cell by binding to the part of the virus that normally would plug into the cellular receptor. When this happens, the virus is tagged and ready to be eaten by phagocytes.

1.1.3.2 T cells

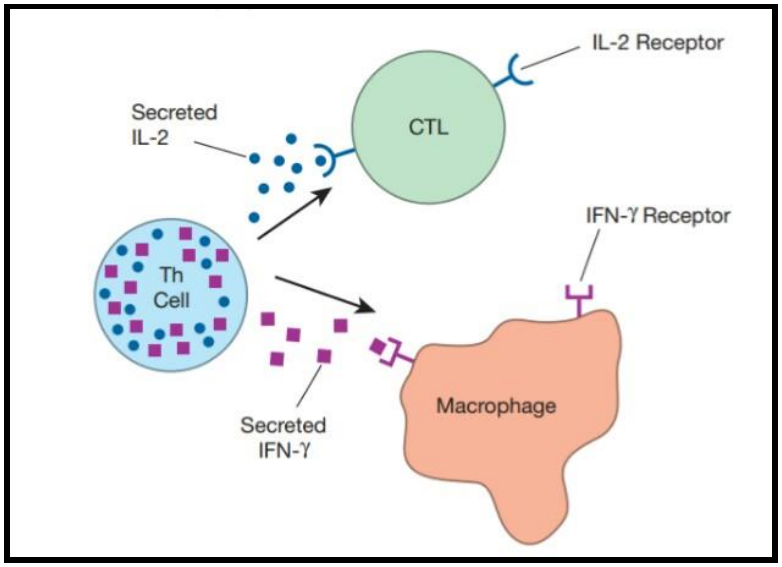
They are of 3 different types:

a) Killer T cells, also known as Cytotoxic lymphocytes (CTLs)
b) Helper T cells
c) Regulatory T cells.

Although antibodies can tag viruses for phagocytic ingestion, and can help keep viruses from infecting cells, there is a flaw in the antibody defence against viruses: once a virus gets into a cell, antibodies can't get to it, so the virus is safe to make thousands of copies of itself. The immune system tackles this through the invention of 'Killer T cells', one of the players of the adaptive immune system team. T cells are produced in the bone marrow, and on their surface they display antibody-like molecules called T cell receptors (TCRs). Like the B cells receptors, TCRs also are made by a mix-and-match, modular design strategy. As a result, TCRs are as diverse as BCRs. T cells also obey the principle of clonal selection: When a T cell receptor bind to their cognate antigen, the T cell proliferates to build up a clone of T cells with the same specificity. This proliferation stage takes about a week to complete. Like the antibody response, the T cell response is slow and specific. As B cells make antibodies that can recognize any organic molecule, T cells are specialized in recognizing protein antigen only if it is properly presented by another cell. The killer T cell is a potent weapon that can destroy virus-infected cells. The way a killer T cell destroys virus-infected cells is by making contact with the target and then triggers the cell to commit suicide. This assisted suicide is a great way to deal with viruses that have infected cells: because when a virus-infected cell dies, the viruses within the cell die also.

The helper T cell (Th cell) acts by secreting chemical messengers, known as cytokines. These chemicals have activating effects on other immune system cells. They include: interleukin 2 (IL-2), interferon gamma (IFN-γ), etc. Helper T cells are basically regarded as the 'Cytokine factories'. The role of regulatory T cell (Treg) is to help keep the immune system from overreacting.

Illustration of the Role of Helper T-Cell



1.1.3.3 Antigen Presentation for T cells

There is an organised mechanism through which antigen is presented to T cells. This is done by a special protein called 'Major histocompatibility complex' (MHC), while T cells use their receptors to view the presented antigen. There are two types of MHC molecules, they are:

a) Class I MHC molecules
b) Class II MHC molecules

Class I MHC molecules are found in varying amounts on the surface of most cells in the body. They function as billboards, informing killer T cells about what is going on in a particular cell. For example, when a human cell is infected by a virus, fragments of viral proteins called peptides are loaded onto class I MHC molecules, and transported to the surface of the infected cell. By inspecting these protein fragments displayed by class I MHC molecules, killer T cells can use their receptors to scan the cell. If the cell is found infected, it will be destroyed.

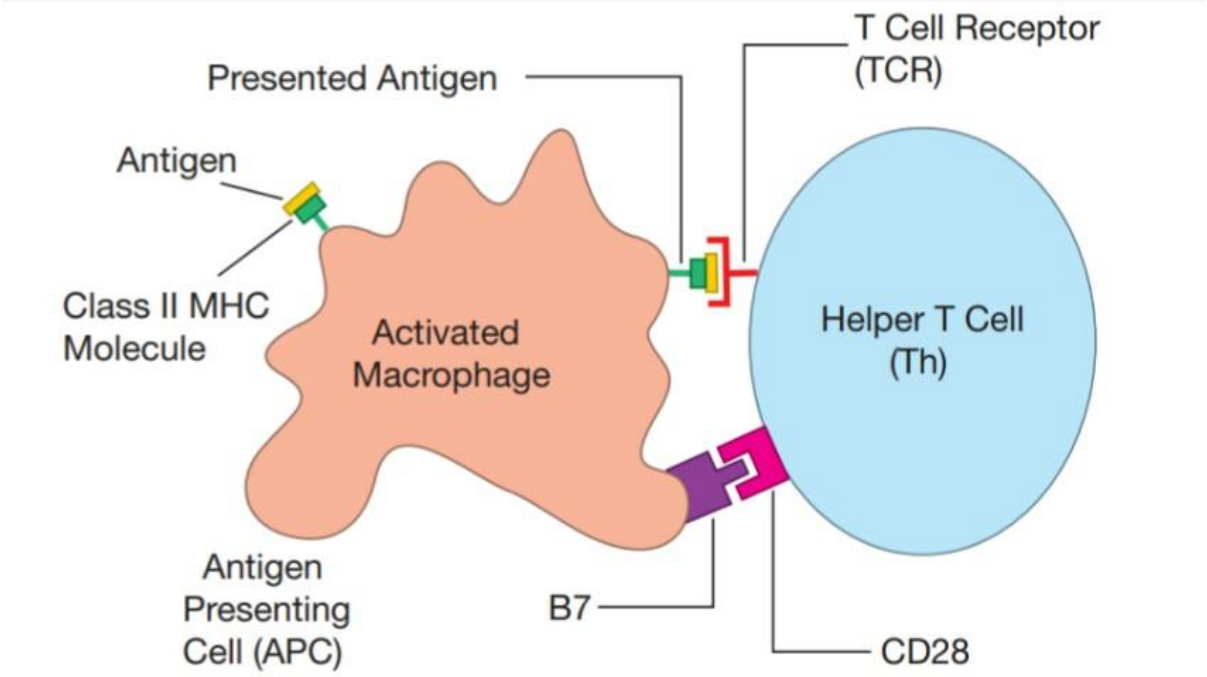
Class II MHC molecules also function as billboards: their display is intended for the activation of helper T cells. Only certain cells in the body make class II MHC molecules, and these are called antigen presenting cells (APCs). Macrophages, for example, are excellent antigen presenting cells. During a bacterial infection, a macrophage will digest bacteria through the phagocytic process, and will load fragments of ingested bacterial proteins onto class II MHC molecules for display. Then, using their T cell receptors, helper T cells can scan the macrophage's class II MHC billboards for news of the bacterial infection and for further action to be taken.

1.1.3.4 Activation of the Adaptive Immune System

The B and T cells are potent weapon. They have to be activated before they can function. Collectively, both cells are called 'Lymphocytes'. The first step in the activation of a helper T cell is recognition of its cognate antigen (e.g., a fragment of a bacterial protein) displayed by class II MHC molecules on the surface of an antigen presenting cell (APC). A second signal

or “key” also is required for activation. This second signal is non-specific (it’s the same for any antigen), and it involves a protein B7 on the surface of an antigen presenting cell that plugs into its receptor CD28 on the surface of the helper T cell.

Illustration of the 2 key System of Helper T-cells



Like T cells, other cells of the adaptive immune system make use of the 2 key system for activation. This is because they are powerful weapons that must only be activated at the appropriate time and place. Once a helper T cell has been activated by this two-key system, it proliferates to build up a clone composed of many helper T cells whose receptors recognize the same antigen. These helper cells then mature into cells that can produce the cytokines needed to direct the activities of the immune system. B cells and killer T cells also require two-key systems for their activation.

1.2 Immunological Memory

After B and T cells have been activated, that is, proliferated to build up clones of cells with identical antigen specificities, and have vanquished the enemy, most of them die off. The leftover B and T cells are called Memory cells: they are experienced B and T cells that stick around, just in case we are exposed to the same invaders again; that way, the adaptive immune system wouldn’t have to start from scratch. In addition to being more numerous than inexperienced B and T cells, memory cells are easier to activate. As a result of this immunological memory, during a second attack, the adaptive system usually can spring into action so quickly without the manifestation of any symptom.

1.3 Tolerance of Self

B cell receptors and T cell receptors are so diverse that they should be able to recognize any potential invader. However, this diversity raises a problem: many of them are certain to recognize our own self molecules (e.g., the molecules that make up our cell, or proteins like insulin that circulate in our blood). If this were to happen, our adaptive immune system might attack our own bodies, and we could die from autoimmune disease. Fortunately, Mother-nature has devised ways to educate B cells and T cells to discriminate between ourselves and dangerous invaders; the education which B and T cells receive is sufficiently rigorous that autoimmune disease is relatively rare.

1.4 Comparison of the Innate and Adaptive Immune System

The players of the innate system (like the macrophage) are already in place, and are ready to defend against a relatively small attack by invaders we are likely to meet on a day-to-day basis. Indeed, in many instances, the innate system is so effective and so fast that the adaptive immune system never even kicks in. In other cases, the innate system may be insufficient to deal with an invasion, and the adaptive system will need to be mobilized. This takes time because the B and T cells of the adaptive system must be custom-made through the process of clonal selection and proliferation. Consequently, while these "designer cells" are being produced, the innate immune system must do its best to hold the invaders in check.

The adaptive immune system's antigen receptors (BCRs and TCRs) are so diverse that they can probably recognize any protein molecule in the universe. However, the adaptive system is clueless as to which of these molecules is dangerous and which is not. So how does the adaptive system distinguish friend from foe? The answer is that it relies on the judgment of the innate system. In contrast to the antigen receptors of the adaptive immune system, which are totally "unfocused", the receptors of the innate system are precisely tuned to detect the presence of the common pathogens we encounter in daily life: viruses, bacteria, fungi, and parasites. In addition, the innate system has receptors that can detect when uncommon pathogens kill human cells. Consequently, it is the innate system which is responsible for evaluating the danger and for activating the adaptive immune system. In a real sense, the innate system gives permission to the adaptive system to respond to an invasion.

The innate system does more than just turn the adaptive system on: it actually integrates all the information it has collected about an invader and formulates a plan of action. This "game plan", which the innate system delivers to the adaptive immune system, tells the weapons to be mobilized (e.g., B cells or killer T cells) and the exact location in the body these weapons should be deployed.

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