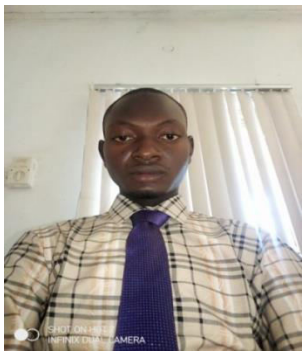
CHAPTER-9

AUTHORS' INFORMATION



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Open Access Full Text Article
https://doi.org/10.26524/royal.37.9

CHAPTER-9

IMMUNE RESPONSE TO COVID-19 INFECTION

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ABSTRACT

Corona viruses are diverse group of viruses belonging to the order Nidovirales and family Coronaviridae. In 2002, there was an outbreak of a virus with pneumonia-like symptoms. The virus that causes that illness is Systemic Acute Respiratory Syndrome Corona virus (SARS-Cov), which belongs to the genus β-Corona virus and was believed to have originated from bats. Later on in 2003, the outbreak of Middle East Respiratory Syndrome Corona virus (MERS-Cov) had been experienced. MERS-Cov originated from camels. In December, 2019, there was an outbreak of Systemic Acute Respiratory Syndrome Corona virus type-2 (SARS-Cov-2) in Wuhan province, China. The virus causes a disease known as Corona Virus Disease-19 (COVID-19). COVID-19 has an incubation period of 2-14 days and the only factor that delays the onset of the symptoms is the immune system as there is no approved vaccine or drug for the virus. Two kinds of immune responses have been exploited in COVID-19 infection: Innate (which include Cilia, Action of Phagocytic and Natural Killer cells, Interferon, Complement proteins, Cytokines) as well as

Keywords

CORONAVIRUS
IMMUNE SYSTEM
VACCINE
INNATE-IMMUNE
RESPONSE

Adaptive (which include Action of T-lymphocytes and Humoral Immune Response). Immunoglobulin of M class (IgM) was detected in the serum of COVID-19 patients barely 3 days after exposure; whereas immunoglobulin of G class (IgG) was not detected until 6 days after exposure to the virus. This chapter will explain the host defensive mechanisms involved in the pathogenesis of COVID-19 infection.

1. Introduction

Immunology is the study of the immune system and the term was derived from two Latin words: *Immunos* (meaning safe) and *Logos* (which means study). In broad terms, Immunology is the study of defensive mechanisms to foreign invaders [1]. The immune system consists of proteins, cells and organs that are concerned with defense of the individual, primarily against the threat of disease caused by infectious organisms. An infectious organism that causes disease is called a pathogen and the individual (person or animal) that is infected by a pathogen is called the host [2]. The word *immunity* refers to the ability of a living organism to resist infection. This happens due to various complex processes occurring in the body whenever the immune system is activated by infectious microbes or other foreign (non-self) substances [1]. *Corona viruses* are diverse group of viruses belonging to the order *Nidovirales* and family *Coronaviridae* [3].

In 2002, there was an outbreak of a virus with pneumonia-like symptoms. The virus that causes that illness is Systemic Acute Respiratory Syndrome Corona virus (SARS-Cov), which belongs to the genus β-Corona virus and was believed to have originated from bats. Later on in 2003, the outbreak of Middle East Respiratory Syndrome Corona virus (MERS-Cov) had been experienced. MERS-Cov originated from camels. In December, 2019, there was an outbreak of Systemic Acute Respiratory Syndrome Corona virus type-2 (SARS-Cov-2) in Wuhan province, China. The virus causes a disease known as Corona Virus Disease-19 (COVID-19) [4]. The genome of COVID-19 virus is single-stranded RNA (positive sense) with approximately 30, 000 base pairs. It encodes five structural proteins; these are the

Spike (S), Membrane (M), Envelope (E) glycoproteins, Hemagglutinin Esterase (HE) and Nucleocapsid (N) protein. All envelope proteins and N proteins are present in all virions but HE is only present in some beta coronaviruses [5]. For effective understanding of the immune response to this infection, it is important to review the strategy this virus uses to replicate.

2. Replication and Pathogenesis of COVID-19 Virus

The replication of coronaviruses occurs in host cell cytoplasm. The viruses primarily bind to the receptor which is Angiotensin Converting Enzyme -2 (ACE-2) on the surface of alveolar cells via the spike (S) protein. When S protein is bound to the receptor, a conformational structure occurs in the structure and the process of entry into the virus cell begins [6, 7]. This process with endocytosis is dependant of P^H[8]. After entering the cytoplasm, the virus particle releases the RNA genome. This genome is a single-stranded, non-segmented RNA, which is approximately 26-32 kb [9, 10]. The genome consists of seven genes. It is organized into 5' non-structural protein coding regions comprising the replicase genes (gene 1), which are two-thirds (2/3) of the genome, and 3' structural and nonessential accessory protein coding regions comprising gene 2-7 [11, 12]. The replicase gene 1 products are encoded two very large open reading frames ORF1a and 1b, which are translated into two large polypeptides pp1a and pp1b, which are synthesized directly from the 5' two-thirds of the genomic RNA of CoV. After synthesis of these proteins, they are then cleaved by viral proteases in to sixteen (16) units (nsp1-nsp16) [13, 14].

These 16 proteins form Double-Membrane Vesicles (DMV). At the same time, this DMV is virus Replication and Transcription Complex (RTC) [15]. These nsp proteins, especially non-structural protein3 (nsp3), have an important role in the virion structure, the replication and transcription of CoV [16]. Genes 2 to 7 are translated from sub genomic mRNA. Sub genomics RNAs encode the major viral Structural proteins: Spike protein (S), Envelope protein (E), Membrane protein (M), Nucleocapsid protein (N), and the accessory proteins, which are essential for virus-cell receptor binding. The newly synthesized structural proteins are released into the endoplasmic reticulum. All of these proteins, along with the N protein, are linked to the viral genomic RNA and localized in the ERGIC region [15, 17]. Although, N protein is

known to be necessary for coronavirus replication, the specific role that this protein plays in this process remains unknown. But, many studies suggest that N protein when interacted with nsp3 plays a critical role in the viral replication in early infection [3].

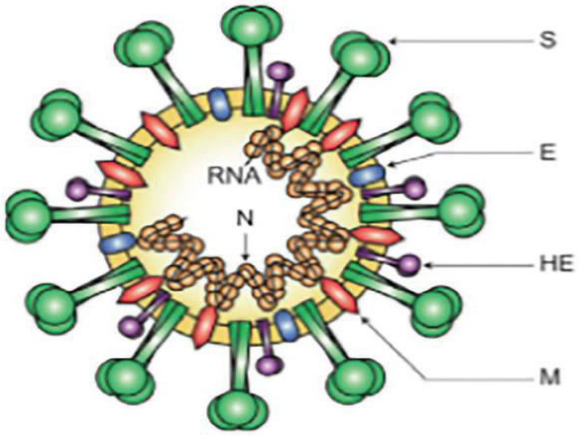

Figure1.1 Structure of Coronavirus Showing Structural Proteins**: Source:** (Susan and Julian, 2011)

3. TYPES OF IMMUNE RESPONSE TO COVID-19 INFECTION

Two types of immune response have been identified in COVID-19 infection. These are:

1. ***Innate (non specific) immune response***: The innate (non specific) immune response provides a first line of defense that can often prevent infectious agents from gaining access into the body. These defenses are described as nonspecific because they do not target any specific pathogen; rather, they defend against a wide range of potential pathogens in a similar way. They are called innate because they are built-in mechanisms of the human organism. Broadly speaking, nonspecific (innate) defenses provide an immediate (or very rapid) response against potential pathogens. Furthermore, this type of response does not have immunological memory [18].

The mechanisms involved in innate response include:

- Cilia
- Action of immune cells (Phagocytic and Natural Killer cells)
- Interferons
- Complement proteins

- Interleukins
- Tumor Necrosis Factor-α

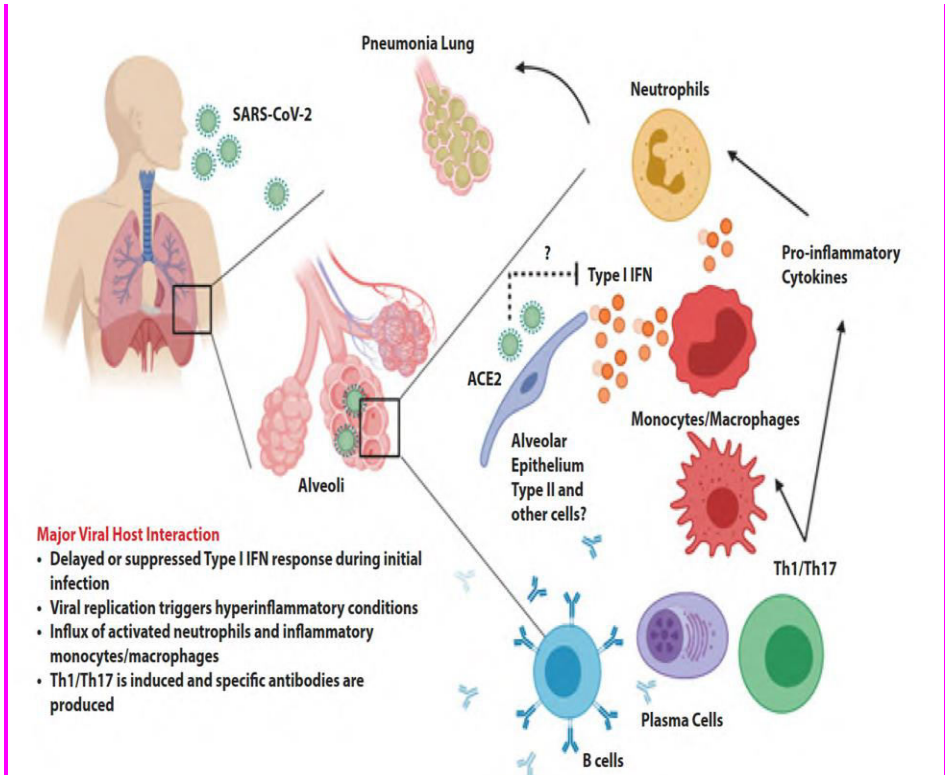

Figure 2.1: Pathogenesis of COVID-19 (Prompetchara *et al.,* 2020)

Cilia

COVID-19 virus enters the body through mouth or nose via infected droplets and moves through trachea (wind pipe) into the lungs, then alveoli [19]. The most important anatomical structure that could flush the virus out of the body is the *cilia*. Cilia are a hair-like structures found on epithelial cells in many parts of the body (such as respiratory and digestive tracts).

Mechanical actions of cilia serve to flush mucus (along with trapped or dead microbes) out of the body or away from potential sites of infection. In the respiratory system, inhalation can bring microbes, dust, mold spores, and other small air borne debris into the lungs. This debris becomes trapped in the mucus lining the respiratory tract, a layer known as the muco-ciliary blanket. The epithelial cells lining the upper parts of the respiratory tract are called ciliated epithelial cells because they have hair

like appendages known as cilia. Movement of the cilia removes mucus away from the lungs. The expelled mucus is then swallowed and destroyed in the stomach, coughed up, or sneezed out.

This system of removal is often called the *mucociliary escalator*. The mucociliary escalator pushes mucus away from the lungs, along with any debris or microorganisms that may be trapped in the sticky mucus, and the mucus moves up to the esophagus where it can be removed by swallowing. The mucociliary escalator is such an effective barrier to microbes that the lungs, the lowermost (and most sensitive) portion of the respiratory tract, were considered to be a sterile environment in healthy individuals [18].

Action of Immune Cells

The cells responsible for both specific and nonspecific immune response are the *leukocytes* (white blood cells) [20]. The major leukocytes that participate in COVID-19 response are the *Macrophages* and *Natural Killer* (NK)cells. However, it is important to have a quick glance at the *cells of the immune system*. Cells involved in immune response can be categorized in to *Granulocytes and Agranulocytes*.

Granulocytes

Granulocytes have visible sand-like structures (granules) when viewed under light microscope after they are stained with acidic or basic dyes. The neutrophils, also called polymorphonuclear neutrophils (PMNs), have a nucleus with three to five lobes and small, numerous, lilac-coloured granules. Each lobe of the nucleus is connected by a thin strand of material to the other lobes. The eosinophils have fewer lobes in the nucleus (typically 2–3) and larger granules that stain reddish-orange. The basophils have a two-lobed nucleus and large granules that stain dark blue or purple [18].

Neutrophils:

Stain readily at a neutral pH, have a nucleus with three to five lobes connected by slender threads of chromatin, and contain fine primary and secondary inconspicuous granules. Neutrophils have receptors for antibodies and complement proteins and are highly phagocytic cells. However, neutrophils do not reside in healthy tissue but rapidly migrate to the site of tissue damage and infection where they are the principal phagocytic and microbicidal cells. The lytic enzymes and bactericidal substances in

neutrophils are contained within large primary and smaller secondary granules. Primary granules contain peroxidase, lysozyme, and various hydrolytic enzymes, whereas secondary granules have collagenase, lactoferrin, and lysozyme. Both of these granules help accomplish intracellular digestion.

Neutrophils also use oxygen-dependent and oxygen-independent pathways that generate antimicrobial substances and defensins to kill ingested microorganisms [20]. As neutrophils fight an infection, a visible accumulation of leukocytes, cellular debris, and bacteria at the site of infection can be observed. This build-up is called pus. The presence of pus is a sign that the immune defences have been activated against an infection [18].

Eosinophils:

Eosinophils are granulocytes that protect against protozoa and helminths; they also play a role in allergic reactions. The granules of eosinophils, which readily absorb the acidic reddish dye eosin, contain histamine, degradative enzymes, and a compound known as major basic protein (MBP). MBP binds to the surface carbohydrates of parasites, and this binding is associated with disruption of the cell membrane and membrane permeability [18].

Basophils:

Basophils have cytoplasmic granules of varied size and are named for their granules' ability to absorb the basic dye methylene blue. Their stimulation and degranulation can result from multiple triggering events. Activated complement fragments C3a and C5a, produced in the activation cascades of complement proteins, act as anaphylatoxins by inducing degranulation of basophils and inflammatory responses. This cell type is important in allergic reactions and other responses that involve inflammation. One of the most abundant components of basophil granules is histamine, which is released along with other chemical factors when the basophil is stimulated. These chemicals can be chemotactic and can help to open the gaps between cells in the blood vessels. Other mechanisms for basophil triggering require the assistance of antibodies [18].

Mast Cells:

Hematopoiesis also gives rise to mast cells, which appear to be derived from the same common myeloid progenitor cell as neutrophils, eosinophils, and basophils. Functionally, mast cells are very similar to basophils, containing many of the same components in their granules (e.g., histamine) and playing a similar role in allergic responses and other inflammatory reactions. However, unlike basophils, mast cells leave the circulating blood and are most frequently found residing in tissues. They are often associated with blood vessels and nerves or found close to surfaces that interface with the external environment, such as the skin and mucous membranes in various regions of the body [18].

Dendritic Cells:

These cells can recognize specific pathogen-associated molecular patterns on microorganisms and play an important role in nonspecific resistance. They can differentiate between potentially harmful microorganisms and "self" molecules. After the pathogen is recognized, it binds to the dendritic cell's pattern recognition receptors and then is phagocytosed. These cells are also stimulated by endogenous activators such as interferon-α, heat-shock proteins, and tumour necrosis factor that are released in response to microbial infection. After stimulation, dendritic cells migrate to the bloodstream or lymphatic system and present antigens to T cells. Thus dendritic cells also play an important role in the specific immune response [20].

Agranulocytes:

As their name suggests, agranulocytes lack visible granules in the cytoplasm. Agranulocytes can be categorized as lymphocytes or monocytes. Among the lymphocytes are natural killer (NK) cells, which play an important role in nonspecific innate immune defences. Lymphocytes also include the B cells and T cells. The monocytes differentiate into macrophages which are collectively referred to as the mononuclear phagocytes [18].

Natural Killer (NK) Cells:

These are large mononuclear lymphocytes that kill viral infected cells or tumour cells by direct cell-cell contact. These cells are non specific (fights all cells infected by any of the numerous viral species in a similar manner) and have no

memory. NK cells have specific receptors that bind to the infected cells. Tumour cells and cells infected with viruses display abnormal proteins on their surfaces. When NK cells are in circulation, they can recognise such cells displaying abnormal surface proteins and therefore bind to them. The NK cell then injects its granules which eventually kills the infected cell by cytotoxicity or causes the cell to kill itself (apoptosis) [1].

Monocytes:

The largest of the white blood cells, monocytes have a nucleus that lacks lobes and they also lack granules in the cytoplasm. Nevertheless, they are effective phagocytes, engulfing pathogens and apoptotic cells to help fight infection .When monocytes leave the bloodstream and enter a specific body tissue, they differentiate into tissue-specific phagocytes called macrophages and dendritic cells. They are particularly important residents of lymphoid tissue, as well as non lymphoid sites and organs. Macrophages and dendritic cells can reside in body tissues for significant lengths of time. Macrophages in specific body tissues develop characteristics suited to the particular tissue. Not only do they provide immune protection for the tissue in which they reside but they also support normal function of their neighbouring tissue cells through the production of cytokines [18].

4. Macrophages engulf and destroy particulate pathogens by a process called phagocytosis.

Phagocytosis can be described in the following steps:

1. Attachment of the phagocyte to the particle being phagocytosed, which may be COVID-19 viral particle, a dead or damaged host cell or a piece of tissue. Attachment is mediated when Pattern Recognition Receptors (PRRs) found on the surface of the phagocytic cells bind to some structures on the pathogens. Such structures on the pathogen recognised by phagocytic cells are called Pathogen Molecular Associated Patterns (PAMPs) [2]. In case of COVID-19, the PAMP is the spike protein.
2. Ingestion. By extending membrane protrusions called pseudopodia around the particle, the phagocyte is able to engulf the particle, which is taken into the cell in a phagocytic vacuole [2].

3. Killing. If the ingested particle is a live cell of a pathogen (e.g. a bacterium) the phagocyte will normally kill the cell by one of the number of mechanisms [2].
4. Degradation. The phagocytosed particle, whether it is a dead cell or a piece of tissue, is broken down by enzymes in the phagocytic vacuole [2].

Lymphocytes: Are the major cells of the specific immune system. Lymphocytes can be divided into two populations: T cells and B cells. B cells or B lymphocytes reach maturity within the bone marrow, circulate in the blood, and also settle in various lymphoid organs.

T cells or T lymphocytes mature in the thymus gland; they can remain in the thymus, circulate in the blood, or reside in lymphoid organs such as the lymph nodes and spleen [20]. B lymphocytes differentiate in to memory cells and plasma cells (which in turn produce antibodies) that play key role in humoral immune response.

T lymphocytes are responsible for tissue or organ rejection during transplant. There are 3 types of T lymphocytes: T helper (Th) lymphocytes, Cytotoxic T-lymphocytes (Tc) and Supressor T-lymphocytes (Ts).

Interferons

Interferons are a diverse group of immune signaling molecules and are especially important in our defence against viruses. Type I interferons (interferon-αand interferon-β) are produced and released by cells infected with virus. These interferons stimulate nearby cells to stop production of mRNA, destroy RNA already produced, and reduce protein synthesis. These cellular changes inhibit viral replication and production of mature virus, slowing the spread of the virus. Type I interferons also stimulate various immune cells involved in viral clearance to more aggressively attack virus-infected cells. Type II interferon (interferon-γ) is an important activator of immune cells [18]. Production of IFN-α and IFN-β is stimulated by COVID-19 single-stranded RNA molecule. Effective innate immune response against viral infection relies heavily on the interferon (IFN) type I responses and its downstream cascade that culminates in controlling viral replication and induction of effective adaptive immune response. While SARS-CoV and SARS-CoV-2 seem to share the entry receptor of ACE2, MERS-CoV uses dipeptidyl peptidase-4 (DPP-4) as a specific receptor [21].The putative receptor of SARS-CoV-2, ACE2, is mainly expressed in a small subset of cells

in the lung called type 2 alveolar cells [22]. It has been reported that SARS-Co-V directly infects macrophages and IFN-stimulated genes (ISGs) under the control of IFN-stimulated response element (ISRE) containing promoters [23]. A successful mounting of this type I IFN response should be able to suppress viral replication and dissemination at an early stage. IFNs have many other functions in addition to inhibiting viral replication, two of which are to activate macrophages and natural killer cells. IFN-α was found in the serum of many COVID-19 patients.

Complement Proteins

Complement system: Is a group of inactive proteins present in low concentration in serum. They can be activated by enzyme cascade (when products of the first reaction become the substrate of the subsequent reactions) [1]. The complement system is composed of more than 30 proteins (including C1 through C9) that normally circulate as precursor proteins in blood. These precursor proteins become activated when stimulated or triggered by a variety of factors, including the presence of pathogens. Complement proteins are considered part of innate non-specific immunity because they are always present in the blood and tissue fluids, allowing them to be activated quickly. Also, when activated through the alternative pathway, complement proteins target pathogens in a nonspecific manner. The process by which circulating complement precursors become functional is called complement activation. This process is a cascade that can be triggered by one of three different mechanisms, known as the *alternative, classical, and lectin pathways*. The alternative pathway is initiated by the spontaneous activation of the complement protein C3. The hydrolysis of C3 produces two products, C3a and C3b. When no invader microbes are present, C3b is very quickly degraded in a hydrolysis reaction using the water in the blood. However, if invading microbes are present, C3b attaches to the surface of these microbes. Once attached, C3b will recruit other complement proteins in a cascade. The classical pathway provides a more efficient mechanism of activating the complement cascade, but it depends upon the production of antibodies by the specific adaptive immune defences. To initiate the classical pathway, a specific antibody must first bind to the surface of the Corona virus to form an antibody-antigen complex. This activates the first protein in the complement cascade, the C1 complex.

The C1 complex is a multipart protein complex, and each component participates in the full activation of the overall complex. Following recruitment and activation of the C1 complex, the remaining classical pathway complement proteins are recruited and activated in a cascading sequence. Although each complement activation pathway is initiated in a different way, they all provide the same protective outcomes: opsonization, inflammation, chemotaxis, and cytolysis. The term opsonization refers to the coating of a pathogen by a chemical substance (called an opsonin) that allows phagocytic cells to recognize, engulf, and destroy it more easily.

Opsonins from the complement cascade include C1a, C3b, and C4b. Additional important opsonins include nnose-binding proteins and antibodies. The complement fragments C3a and C5a are well-characterized anaphylatoxins with potent proinflammatory functions. Anaphylatoxins activate mast cells, causing degranulation and the release of inflammatory chemical signals, including mediators that cause vasodilation and increased vascular permeability. C5a is also one of the most potent chemoattractants for neutrophils and other white blood cells. The complement proteins C6, C7, C8, and C9 assemble into a membrane attack complex (MAC), which allows C9 to polymerize into pores in the membrane of COVID-19 [18].

Cytokines

Cytokines are soluble proteins that act as communication signal between cells. In a nonspecific (innate) immune response, various cytokines may be released to stimulate production of chemical mediators or other cell functions, such as cell proliferation, cell differentiation, inhibition of cell division, apoptosis, and chemotaxis. When cytokines are released from mononuclear phagocytes, these proteins are called monokines; when released from T lymphocytes they are called lymphokines; when produced by a leukocyte and the action is on another leukocyte, they are interleukins; and if their effect is to stimulate the growth and differentiation of immature leukocytes in the bone marrow, they are called colony stimulating factors (CSFs). When a cytokine binds to its target receptor, the effect can vary widely depending on the type of cytokine and the type of cell or receptor to which it has bound. The function of a particular cytokine can be described as autocrine, paracrine, or endocrine. In autocrine function, the same cell that releases the cytokine is the recipient of the signal; in other

words, autocrine function is a form of self-stimulation by a cell. In contrast, paracrine function involves the release of cytokines from one cell to other nearby cells, stimulating some response from the recipient cells. Last, endocrine function occurs when cells release cytokines into the bloodstream to be carried to target cells much farther away [18]. In a report where 99 cases were investigated in Wuhan, increased IL-6 in and C-reactive protein were detected in the serum of COVID-19 patients as reported by Zhou *et al.,* 2020. Furthermore, patients needing ICU care had higher plasma levels of many innate cytokines like TNF-α [24].This clinical feature suggested the likelihood of involvement of highly pro-inflammatory condition in the disease progression and severity. This early high rise in the serum levels of pro-inflammatory cytokines were also observed in SARS-CoV and MERS-CoV infection, suggesting a potential similar cytokine storm-mediated disease severity [25, 26].

5. Adaptive (Specific) Immune Response

Adaptive immunity is defined by two important characteristics: specificity and memory. Specificity refers to the adaptive immune system's ability to target specific pathogens, and memory refers to its ability to quickly respond to pathogens to which it has previously been exposed. Specificity and memory are achieved by essentially programming certain cells involved in the immune response to respond rapidly to subsequent exposures of the pathogen. This programming occurs as a result of the first exposure to a pathogen or vaccine, which triggers a primary response. Subsequent exposure (secondary response) is faster and stronger as a result of the body's memory of the first exposure. This secondary response, however, is specific to the pathogen in question. Adaptive (specific) immunity involves the actions of two distinct cell types: B lymphocytes (B cells) and Tlymphocytes (T cells). Although B cells and T cells arise from a common hematopoietic stem cell differentiation, their sites of maturation and their roles in adaptive immunity are very different. B cells mature in the bone marrow and are responsible for the production of proteins called antibodies, or immunoglobulins. Antibodies are involved in the body's defence against pathogens and toxins in the extracellular environment. Mechanisms of adaptive immunity that involve B cells and antibody production are referred to as humoral immunity [18]. There are two types of specific immune response:

a. **Antibody Mediated (humoral) immune response**
b. **Cell mediated immune response**

Antibody Mediated (Humoral) Immune Response

This is also called humoral immune response. The cells responsible for the synthesis of antibodies are the B-lymphocytes. Each B-lymphocyte has an immunoglobulin of appropriately coded specificity on its surface that is determined at the genetic level 1.

Activation of B-lymphocyte by antigen can be:

i T-cell independent

ii T-cell dependent

Both i and ii depend on the nature of the antigen.

T-Cell Independent Activation

Polymeric antigens such as spike proteins, Membrane glycoproteins, Envelope proteins and other SARS-Cov-2 antigens can directly induce B-lymphocytes to produce antibodies against the specific antigens that induced their production. The antigen subunit binds to a side on the specific surface immunoglobulins on B-lymphocytes to proliferate in to clone of identical cells. These clone of cells later mature in to plasma cells that produce and secrete antibody molecules into body fluids. There are 3 characteristics of T-cell independent activation [1]:

1. It can only produce immunoglobulin of M class (IgM) which were detected in the serum of most COVID patients barely 2-3 days following exposure to the virus
2. It does not require help from T-helper (T_H) cell
3. No memory cells are produced from this type of response

T-Cell Dependent Activation

This is a mechanism that stimulates the production of antibodies induced by many antigens. The characteristics of this response are:

1. It can produce immunoglobulin of any class (IgG, IgM, IgE, IgD and IgA). IgG were detected in the serum of some patients 6 days after infection with the SARS-Cov-2 virus [27]. IgG also serves as indicator immunoglobulin in diagnosing most COVID-19 cases by serological tests.
2. It requires a help from T_H lymphocytes

3. This response produces memory cells; such that in the subsequent exposure to the same pathogen, the memory cells produced can proliferate and mature in to plasma cells.

6. Mechanism of Antibody Production

The mechanism of antibody production is explained in the following steps:

1. When an antigen (coronavirus) comes in contact with macrophages, it will be phagocytosed. Within the macrophages, enzymes partially degrade the virus in such a way that its antigenic determinants are exposed.
2. The partially degraded antigen is placed on the macrophage surface next to the Ia marker, which is the genetically determined class II antigen or Human Leukocyte Antigen (HLA) system
3. T_H cell has a receptor, specific for each antigen on their surface in association with CD3 molecule. When such T_H comes in contact with a macrophage having the Ia-antigen complex, they bind each other.
4. At this stage, the resting T_H cell is activated by monokine (interleukin-1/ IL-1) produced by macrophage. The activated T_H then undergo some biochemical changes resulting in cell stimulatory responses by production of large quantities of lymphokines including interleukin-2 (IL-2)
5. The activated T_H cell also produce IL-4, IL-5 and IL-6 which participate later in B-cell proliferation and differentiation.
6. B-lymphocytes can come in contact with antigen in 3 ways:

   A: Direct binding of antigen to the specific surface immunoglobulin molecule on B-cell

   B: Presentation of antigen by activated T_H cell to B cell

   C: Presentation of the antigen by macrophages or other B-cells possessing bound antigens on their surface
7. At this stage, only antigens capable of initiating B-cell proliferation without the influence of T_H cell can induce antibody production independently. Other antigens can only do so under the influence of IL-5 and IL-4 released by T_H cell
8. After proliferation of B-cells, IL-5 and IL-6 trigger differentiation of B-cells into plasma cells to secrete antibody molecules specific for inducing antigens. Some

stimulated B-cells will transform into memory B-cells instead of plasma cells. These memory cells have a very long life span and can be activated upon exposure to the same antigen [1].

7. Cell Mediated Immune Response

The T in T lymphocyte stands for thymus. While B cells complete their maturation in the bone marrow, T lymphocyte precursors migrate to the thymus where they develop into mature T lymphocytes. The mature T lymphocytes then leave the thymus and circulate through the bloodstream and lymphoid tissue. T cells can be categorized into three distinct classes: helper T cells, regulatory T cells, and cytotoxic T cells. These classes are differentiated based on their expression of certain surface molecules, their mode of activation, and their functional roles in adaptive immunity. All T cells produce cluster of differentiation (CD) molecules, cell surface glycoproteins that can be used to identify and distinguish between the various types of white blood cells. Although T cells can produce a variety of CD molecules, CD4 and CD8 are the two most important used for differentiation of the classes. Helper T cells and regulatory T cells are characterized by the expression of CD4 on their surface, whereas cytotoxic T cells are characterized by the expression of CD8.Classes of T cells can also be distinguished by the specific MHC molecules and APCs with which they interact for activation.

Helper T cells and regulatory T cells can only be activated by APCs presenting antigens associated with MHC II. In contrast, cytotoxic T cells recognize antigens presented in association with MHC I, either by APCs or by nucleated cells infected with an intracellular pathogen [18]. T cell response in SARS-CoV was extensively investigated. In one study using 128 convalescent samples, it was reported that CD8+ T cell responses were more frequent with greater magnitude than CD4+ T cell responses. Furthermore, the virus specific T cells from the severe group tended to be a central memory phenotype with a significantly higher frequency of polyfunctional CD4+ T cells and CD8+ T cells, as compared with the mild-moderate group. Strong T cell responses correlated significantly with higher neutralizing antibody while more serum Th2 cytokines (IL-4, IL-5, and IL-10) were detected in the fatal group as per the scientific literatures.

Conclusion and Future Perspectives

COVID-19 does not respect wealth status or border and presently, there is no approved vaccine or treatment protocol for COVID-19. However, many vaccines are on trial and some countries have approved the use of Chloraquine, Remedisivir, Hydroxychloraquine and Ritonavir. Recently, Ivemectin (anti parasitic drug used in the treatment of onchocerciasis) had been found to effectively inhibit SARS-Cov-2 in vitro. Many scientists have proposed that specific antibodies (IgG) from the sera of recovered patients should be isolated and mass produced by hybridoma method and then administered to those with active infection. However, this would not confer immunity for a life-time but it could provide a solution before a vaccine is produced and approved. International Society for Stem Cell Research (ISSCR) has proposed the use of stem cell in COVID-19 treatment due to their immunomodulatory and tissue repair activities.

Furthermore, scientists and pharmaceutical industries should share their findings to the scientific community, as they should remember that this is struggle to save humanity, not struggle for fame.

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