AN INTRODUCTION TO IMMUNE SYSTEM WITH SPECIAL FOCUS ON VACCINES FOR SARS-COV-2: PART I

Chong Shimray
Associate Professor
Department of Education in Science and Mathematics
National Council of Educational Research and Training
New Delhi - 110 016
Email: cshimray@gmail.com

Shrishail E Shirol
Junior Project Fellow
Department of Education in Science and Mathematics
National Council of Educational Research and Training
New Delhi - 110016

COVID-19, the deadly pandemic caused by the coronavirus, SARS-CoV-2 hit the world hard but at the same time brought out the never-seen-before capabilities and capacities of the scientific community, the manufacturing companies and other stakeholders as the world engaged in its search for a vaccine to subdue the virus. Keeping the nature of COVID-19 pandemic and its impact on the immune system in view, this paper, the first part of the two-part article, attempts to provide a broad idea on a the various aspects related to immune system such as what pathogens do to our body and how our immune system works. The sequence of events that happens during SARS-CoV-2 will also be discussed in brief.

Keywords: Immune system, pathogens, SARS-CoV-2, vaccine.

Introduction

Vaccines are a symbol of triumph of the scientific community's indomitable spirit against nature's vicissitudes and vagaries. Since the first dose of vaccine administered by Edward Jenner, millions of lives have been saved by numerous vaccines at different times. For example, smallpox vaccine in the early 1800s, followed by tetanus, diphtheria pertussis vaccines, polio, measles, rubella, mumps, and more recently hepatitis B, rotavirus vaccine, etc. However, it is during the current COVID-19 pandemic caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) that we saw science and technology exploited and used like never before. We saw an extraordinary effort invested by the global scientific community backed by various philanthropists, investors, governments, etc. As a result, in just thirteen months after the identification of the SARS-CoV-2 virus and its genome, several vaccine initiatives have led to the development of over 300 vaccine projects. As of writing this paper, 175.3 million vaccine doses have already been administered using 11 approved vaccines. Nine more are in phase III clinical trials (Ref. 4). Theoretical and technical platforms that have been explored for this vaccine are diverse and innovative; new ones have been approved for the first time in history, changing the world of vaccines once and for all. As for COVID-19, most of the vaccines developed aim to induce neutralizing antibodies against the spike protein (antigen of the SARS-CoV-2). That is, vaccination causes the production of neutralising antibodies which bind to the spike protein of the virus and thereby blocking it from attaching to other cells and preventing it from causing infection. However, the vaccines developed for different diseases

do not respond in the same way. How they are developed and how they act in the body is different for different diseases. But one underlying principle that is common in all of the vaccines is that they are administered so as to provide us immunity from particular diseases caused by pathogens or infectious agents. It is, therefore, imperative to understand how our immune system works in general and the role of vaccines in immunity.

In this article, which is part I of the two-part article, focus will be on what pathogens do to our body and how our immune system responds in general.

Pathogens — the Infectious Agents

A pathogen is simply an infectious agent, also referred to as germ. These disease-causing organisms are all around us. They could be virus, bacterium, protozoan, prion, viroid, or fungus. There are several pathways through which pathogens can invade hosts to survive and thrive. Hosts could be plants, animals, humans and ironically bacteria themselves could sometimes be the host. Transmission of pathogens occurs through many different routes, including air, water, direct and indirect contact, sexual contact, through breast milk, blood, and other body fluids. So why exactly are these harmful? These pathogens are tiny little vehicles that carry instructions on how to make more of themselves. To reproduce, they smuggle this instruction into the host's cells and force the host's cellular mechanism to make more and more of themselves. They spread through the body and hijack more cells, damaging them in the process, which eventually makes us sick to the extent that a person might die. But we are not defenseless; we have our immune system. While other hosts like plants and animals also have developed mechanisms to defeat these pathogens, the human body's immune response is investigated and understood in much detail. The intelligence that is functioning at the micro-level in the human body is something phenomenal and miraculous.

How does our Immune System Work?

Each pathogen is made up of several subparts or molecules, which are unique to that specific pathogen. The subpart, typically proteins, that is immediately recognized as foreign and, as a result, triggers immune response is called an antigen. Immune response is gradual and happens in stages. It can be broadly grouped into two — the Innate Immune Response and the Adaptive (Acquired) Immune Response.

Innate Immune Response

The first line of defense always is innate immune response. The innate immune system is made of defenses against infection that can be activated immediately once a pathogen attacks. The innate immune system is always general or non-specific, meaning anything identified as foreign or non-self is a target for the innate immune response and it has the same mechanism for all pathogens. Essentially made up of barriers, it aims to keep viruses, bacteria, parasites out of our body or limit their ability to spread and move throughout the body. Immune response can also be triggered by foreign particles like dust and other irritants. Skin, tears, sweat, saliva, mucus and cilia

(hair-like projections) that move debris away from the lungs, the gastrointestinal tract, the respiratory tract, the nasopharynx, eyelashes, and other body hair, all work as a physical barrier. If the pathogen breaches this barrier, it prompts general immune responses such as inflammation, complement (a collective term that describes a system of about 20 proteins), etc. The inflammatory response actively brings immune cells to the site of an infection by increasing blood flow to the area. Complement is an important component of innate immune response as it defends our body against the antigens through opsonization, chemotaxis and by activating phagocytic cells or phagocytes, a type of leukocyte (White Blood Cells) that engulf and destroy pathogens through a process called phagocytosis (Hall, 2016). The macrophage is an example of phagocytes. They are also antigen presenting cells. Another type of cell involved is dendritic cells. These do not directly kill pathogens but form a bridge between the innate and adaptive immune systems, meaning that these cells pass information relevant for the adaptive immune response to kick in.

Adaptive Immune Response

Since innate immunity is general and non-specific, it may fail to defeat the pathogen; that's when adaptive immunity (also called acquired immunity), which is much more specific to the invading pathogen, comes into play. The adaptive or acquired immune response takes much longer, sometimes days and even weeks to become established if the system has encountered the pathogen for the first time. However, if the system encounters the same pathogen again, it will mount an immediate and quick response. The adaptive immune response activates when the innate response insufficiently controls an infection. In fact, without information from the innate immune system, the adaptive immune response cannot be mobilized.

There are two major types of Adaptive immunity: Humoral Immunity (HI) and Cell-mediated Immunity (CMI). These processes involve the activities of T and B lymphocytes, another category of leukocytes besides phagocytes. Whether an immature lymphocyte becomes a B cell or T cell simply depends on where in the body it matures. Those lymphocytes that remain in the bone marrow to mature are coined as B Cells ("B" comes from Bursa of Fabricius, a sac-like structure in birds whose only function is production and maturation of B cells). In contrast, those lymphocytes that move and mature in the thymus are coined T cells (Hence the name "T" for Thymus). The maturation of T or B cells involves becoming immunocompetent, meaning that they can bind to the specific antigen on the pathogen. This recognition which is fundamental to the functioning of the adaptive immune response, results from the presence of highly specific receptors on the surface of B and T cells. Receptors are unique chemical structures composed of proteins found on the cell membrane that is capable of binding to specific antigen (LibreTexts, 2021). B lymphocytes or B cells have on the surface of its cell membrane about 1,00,000 antibody molecules that will react highly specifically with only one specific type of antigen. Therefore, when the appropriate antigen comes along, it immediately attaches to the antibody in the cell membrane; this leads to the activation process. In the case of the T lymphocytes, there are surface receptor

proteins (or T-cell markers) on the surface of the T-cell membrane which are also highly specific for one specified activating antigen. There are as many as 1,00,000 receptor sites on a single T cell (Hall, 2016).

Both the Humoral and Cell-mediated Response follow certain general steps that can be broken down into the following (Payne, 2007).

(a) Antigen is trapped

(b) The antigen is recognized by T and B Cells.

(c) Antigen is eliminated

(d) Memory is established due to the presence of long-lived T and B cells

Humoral Immunity

When a foreign antigen enters the body, the macrophages in the lymphoid tissue phagocytize the antigen and then present it to the B cells. The antigen is also presented to the T cells thus becoming helper T cells which also contribute to the activation of the B cells.

Such activated B cells enlarge and form lymphoblasts. Some of these lymphoblasts further differentiate to form plasmablasts, which are the precursors of plasma cells. The plasmablasts then divide as a result of which about 500 cells are formed from each original plasmablast. The mature plasma cell then produces the antibodies at an extremely rapid rate — about 2000 molecules per second for each plasma cell. This is the primary response. These antibodies are secreted into the lymph and carried to the circulating blood. This process continues for several days or weeks until finally exhaustion and death of the plasma cells occur. The antibodies inactivate the invading agent by one of the many ways such as agglutination (by binding the antigens together into a clump), precipitation (by rendering the antigen insoluble and precipitates), neutralization (by covering the toxic sites of the foreign agent) or lysis (rupturing the agent by directly attacking the membranes) (Hall, 2016).

Some of the lymphoblasts form moderate numbers of new B lymphocytes similar to the original lymphocytes. They also circulate throughout the body and populate the lymphoid tissue. But these are immunologically dormant till they are exposed to or activated by the same antigen again. These B cells or B lymphocytes are called memory cells. As a result, on subsequent exposures to the same antigen, there are increased number of B lymphocytes circulating in the body which will eventually produce increased number of antibodies at a faster rate on subsequent exposure to the same antigen. This will be the secondary response (Hall, 2016). The same principle is being followed in vaccination or immunization wherein multiple doses of the antigen are administered with periods ranging from several weeks to several months between the two. Formation of plasma cells and memory cells are presented in the form of flow chart in Fig. 1.

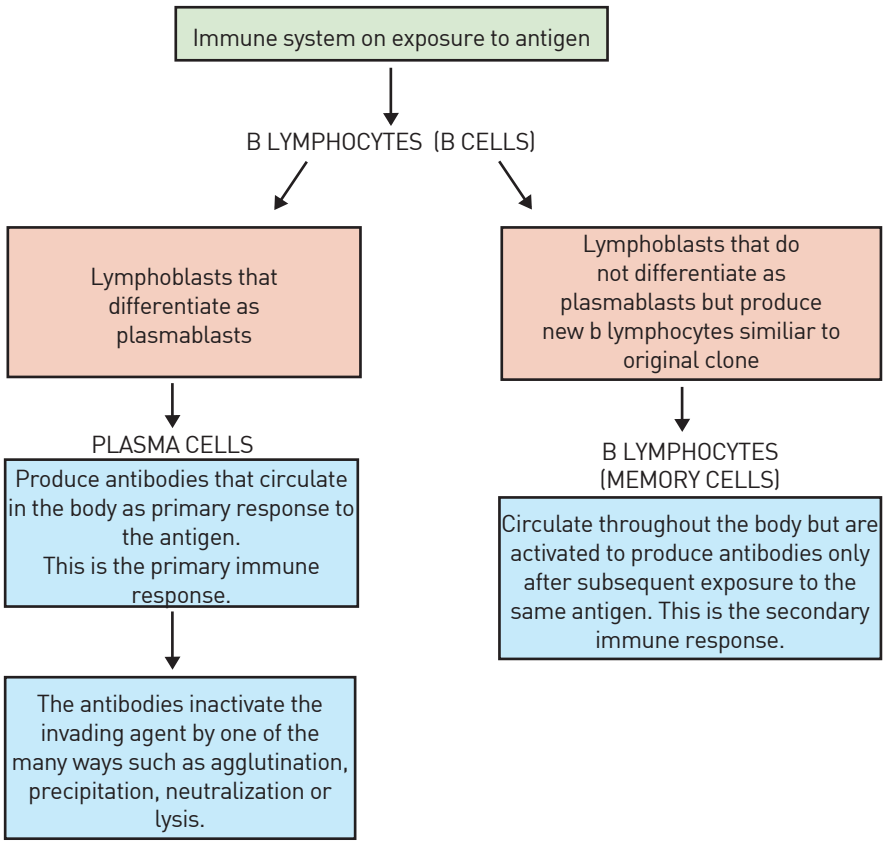

Fig. 1. Hummoral Immune Response

Cell-Mediated Immunity

Cell-mediated immunity involves T cells. On exposure to specific antigen, as presented by the antigen presenting cells (APCs), the specific T lymphocytes proliferate and release large numbers of activated, specifically reacting T cells as in the case of B cells. It may be mentioned that unlike B lymphocytes that recognise intact antigens, T lymphocytes respond to antigens only when they are bound to specific molecules called Major Histocompatibility Complex (MHC) proteins on the surface of APCs. There are three major types of APCs — macrophages, B lymphocytes and dendritic cells. The dendritic cells, the most potent of the APCs, are located throughout the body, and their only known function is to present antigens to T cells. The principal function of the MHC is to present antigen to T cells to discriminate between self (our cells and tissues) and non-self (the invaders or modified self)(Immunopedia.org). There are two types of MHC proteins: (1) MHC I proteins, which present antigens to cytotoxic T cells, and (2) MHC II proteins, which present antigens to T helper cells (Hall, 2016).

These activated T cells are released into the lymph from where they circulate throughout the body reaching the tissue spaces and then back into the lymph and blood again. This lasts for months or even years. As in the case of B memory cells, T-lymphocyte memory cells are also formed. Many of the newly formed lymphocytes are preserved in the lymphoid tissue to become additional T lymphocytes specific for an antigen. As in the case of B memory cells, subsequent exposure to the same antigen, activated T cells are released very rapidly and much more robustly than during the first exposure.

Cell-mediated immunity majorly involves helper T cells (or T-helper cells) and cytotoxic T cells. The role of the helper T cell is to activate cytotoxic T cell (Alberts et al., 2002). They also activate the macrophages to cause far more efficient phagocytosis by forming lymphokines. Cytotoxic T cells directly attack and kill the foreign agent (e.g., cell attacked by SARS-CoV-2). Helper T cell also stimulate B cells. They do this by secreting hole-forming proteins called perforins that literally punch round holes in the membrane of the attacked cell. Because of this, cytotoxic T cells are also called killer cells (Hall, 2016) (Fig. 2).

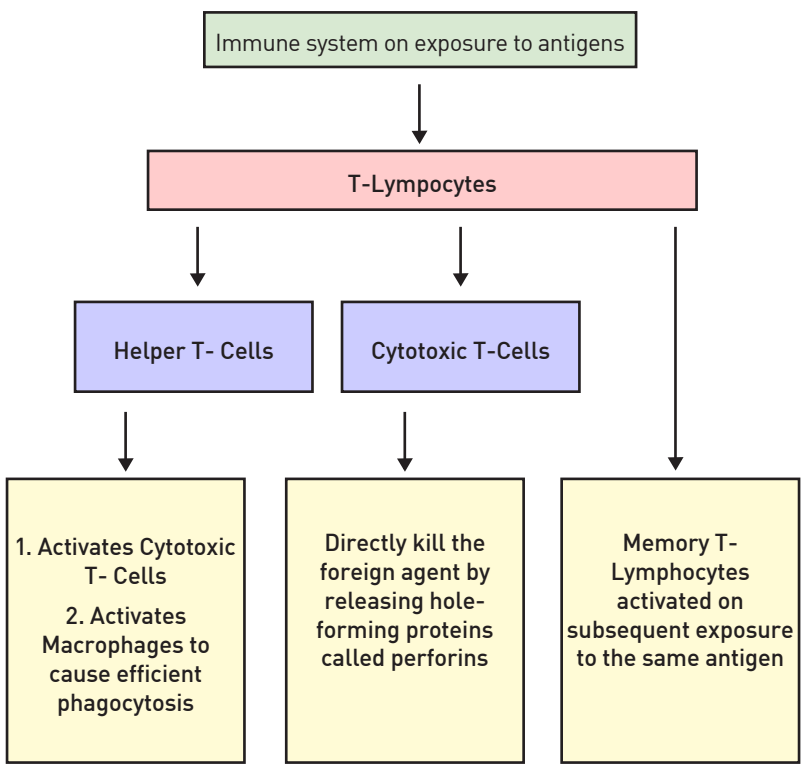

Fig. 2. Cell-mediated Immune R esponse

SARS-CoV-2 Infection and the Immune Response

In the case of SARS-CoV-2, infection begins with the entry of the virus through our nasal cavity, eyes or mouth. Following this, they come in contact with Angiotensin Converting Enzyme 2 (ACE2) receptors in the lining such as in the lining of respiratory tract and binds with them. The virus enters the cells through this receptor, hijacks the cell's machinery making large number of copies of itself and invades new cells. The events that occur during SARS-CoV-2 infection and the immune response against the infection is presented diagrammatically in Fig. 3.

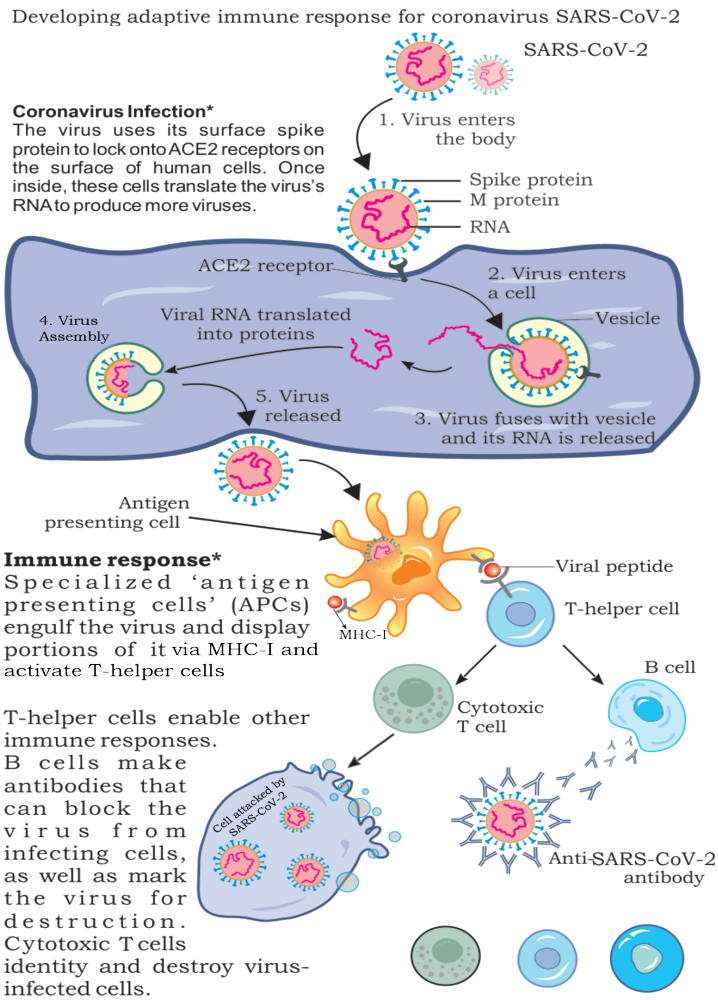

Fig. 3. Cell-Mediated Immune Response against SARS-CoV-2

The virus is transmitted through one of the following modes as described in WHO scientific brief:

- Contact and droplet transmission (including fomite transmission)
- Airborne Transmission
- Fecal Transmission

The incubation period for COVID-19 i.e., the time from exposure to SARS-CoV-2 to the time when symptoms begin to show is, on average, 5–6 days and can range from 1–14 days. Therefore people who have been exposed to the virus are advised to remain at home and stay away from others, for 14 days, in order to prevent the spread of the virus, especially where testing is not easily available.

The most common symptoms of COVID-19 are: Fever, dry cough and fatigue. Other symptoms that are less common and may affect some patients include: Loss of taste or smell, nasal congestion, conjunctivitis (also known as red eyes), sore throat, headache, muscle or joint pain, different types of skin rash, nausea or vomiting, diarrhea, chills or dizziness, irritability, confusion, reduced consciousness (sometimes associated with seizures), anxiety, depression, sleep disorders. More severe and rare neurological complications such as strokes, brain inflammation, delirium and nerve damage are also reported. Symptoms of severe COVID-19 disease include: Shortness of breath, loss of appetite, confusion, persistent pain or pressure in the chest, high temperature (above 38°C).

Among those who develop symptoms, most (about 80%) recover from the disease without needing hospital treatment. About 15 per cent become seriously ill and require oxygen, and 5 per cent become critically ill and need intensive care. Complications leading to death may include respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism and/or multiorgan failure, including injury of the heart, liver or kidneys. In rare situations, children can develop a severe inflammatory syndrome a few weeks after infection (WHO, 2021).

Passive Immunity

All the acquired immunity we have discussed so far has been active immunity. That is, the person's own body develops either antibodies or activated T cells in response to invasion of the body by a foreign antigen. However, temporary and brief immunity can be accomplished in a person without prior exposure to an antigen. This is done by administering antibodies, activated T cells, or both, obtained from the blood of someone else or from some other animal that has been actively immunized against the antigen. In such cases, antibodies last in the body of the recipient for 2 to 3 weeks, and during that time, the person can be protected against the invading agent. However, the efficacy of such treatment depends upon the invading agent. On the other hand, activated T cells last for a few weeks if transfused from another person but only for a few hours to a few days if transfused from an animal. Such transfusion of antibodies or T lymphocytes to confer immunity is called passive immunity.

Conclusion

So if the human body has evolved such a powerful system over millions of years, where do vaccines and other treatments fit into

all this? As mentioned earlier, this adaptive immunity can take many days or even weeks to establish. There is time kinetics at play. Will our immune system subdue the pathogen, or will the pathogen unleash its effect and damage our cells and make us sick to the extent that the person might die before the immune system subdues the pathogen? In the context of the SARS-CoV-2, from the day we are infected, it can take almost two weeks for the immune response to ramp up, enough time for this virus to swarm through our body wreaking havoc. In some people, this damage becomes overwhelming, and they die (WHO, 2020). This is where treatment helps and vaccination has been found to be effective to deal with several epidemics and pandemics including COVID-19. The details about vaccines and vaccination will be discussed in the second part of this article.

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