COVID-19 Vaccines and Cytokines in Human Immunity

ABSTRACT

Background: Despite the efforts carried out to discover corona virus disease-2019 (COVID-19) vaccines, it has been found that the vaccines do not build any immunity and long-term protection from infection and protection against COVID-19 and possibly the newly worrisome virus variants of the SARS-CoV-2 coronavirus. Vaccines targeting this diverse type of infectious viral diseases may need to elicit very different types of immune responses which may require the knowledge of cytokines which play a big role in eliciting different immune responses for infectious organisms hence vital in design of vaccines. **Objective:** It is vital to educate the scientific community and the general public on the importance of cytokines and how the current COVID-19 vaccines could help trigger some dormant cytokines to help build and bolster both the adaptive and innate immune system molecularly even without recognition. **Materials and methods:** Different literature was searched from different medical and scientific indexing sites such as PubMed, Google scholar, Medline, EMBASE, Web of Science, and Science Direct. **Results:** Cytokines in the immune system can be triggered by any of the current COVID-19 vaccines within hours of vaccination and this process can help signalling molecules that can help boost the immune system to fight against infections. **Conclusion:** Pfizer-BioNTech and Moderna vaccines are very similar, both have been found to be safe and efficacious in preventing symptomatic COVID-19 disease in rigorously conducted clinical trials. Pfizer-BioNTech and Moderna vaccines are mRNA-based, while Johnson & Johnson's is an adenovirus.

Keywords: Cytokines, COVID-19, immune system, Pfizer-BioNTech, Moderna

Introduction

The immune system is regarded to be complex and pervasive with a number different cell types that either circulate throughout the body with cell playing a vital and unique role. By understanding all the details behind this network, researchers may optimize immune responses to confront specific issues, ranging from infections to cancer. All immune cells come from precursors in the bone marrow and develop into mature cells through a series of changes that can occur in different parts of the body. Immune cells for example B cells, T cells and the Natural killer (NK) are important for causing responses to specific microbes based on previous encounters (immunological memory), since they are derived from the common lymphoid progenitor and share features of both innate and adaptive immune cells, as they provide

immediate defences like innate cells but also may be retained as memory cells like adaptive cells. B, T, and NK cells also are called lymphocytes [1].

Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system capable of signalling molecules that mediate and regulate immunity, inflammation and haematopoiesis. Cytokines are also known as small soluble proteins throughout the body by cells of diverse embryological origin that confer instructions and mediate communication among immune and non-immune cells [2]. They are made up of many cell populations with T cells and macrophages as predominant producers. Current data and reports have been gained into the role of different T cell subsets for protection against infection or tumour growth. The incorporation of cytokines as molecular adjuvants in vaccines has been attempted to strengthen vaccine- induced immune responses, and as a rational approach to modulate cytokine milieu in vivo and tailor host immunity for specific situations[3].

Cytokines are known to be key regulators of the immune system that shape innate and adaptive immune responses. A portfolio of cytokines is central to the role of macrophages as sentries of the innate immune system that mediate the transition from innate to adaptive immunity. For protective immunity and less immunopathology to be achieved, there should be an appropriate equilibrium in the cytokine environment. Many laboratory and clinical research work done has broaden our understanding of the cytokine network and their conflicting roles in the development of immune responses, as well as their relevance in the establishment and maintenance of immunological memory [3].

Cytokines, including IL, IFN and TGF, are proteins, peptides or glycoproteins secreted by immune cells, which could aid cell to cell communication in immune responses. Several cytokines have also been shown to be involved in immune-mediated dormancy. The maintenance of functional dormancy in tumour cells requires the combined action of many immune factors. IFN-γ and TNF derived from T cells could directly regulate cell cycle progression of tumour cells and establish the dormant state. CD4+ T cells released antiangiogenic chemokines CXCL9 and CXCL10 leading to reduced angiogenesis and antitumor effects. Perforin-mediated cytotoxicity of NK cells also keeps tumor cells in dormant state and prevents the outgrowth of metastasis. MHC I surface expression on tumor cells could be also involved in this process. Furthermore, immunosuppressive cytokines such as TGF-β or IL-10 could lead to decreased activity of T cells. MDSCs act as potent suppressors of T cells via the production of Arginase, iNOS, ROS, and Peroxynitrite [4].

Cytokines and how they work

As part of the immune system, cytokines regulate the body's response to disease and infection, as well as mediate normal cellular processes in your body. The immune system is complex different types of immune cells and proteins do different jobs. Cytokines are among those proteins. To understand inflammation, you must understand the role cytokines play. Pro-inflammatory cytokines play a role in the development of inflammatory and neuropathic pain. Anti-inflammatory cytokines are actually inflammatory cytokine antagonists. Evidence suggests that chemokines are involved in initiating pain and the persistence of pain cells release cytokines into

your blood circulation or directly into tissues. The cytokines locate the immune cells they're designed to target and bind to the cell's receptors. This interaction triggers or stimulates specific responses by the target cells [5]

Biologic Cytokine Inhibitors

Some biologic drugs such as enbrel and Kineret (anakinra), inhibit IL-1 or TNF-α by binding to cytokine receptors hence inhibiting cytokine response. Actemra (tocilizumab) and Kevzara (sarilumab) work similarly but bind IL-6. Other biologic drugs bind cytokines, preventing them from binding to their designated receptors. For example, TNF-α inhibitors (also called TNF blockers) bind to TNF and prevent it from attaching to cell-surface receptors [6]

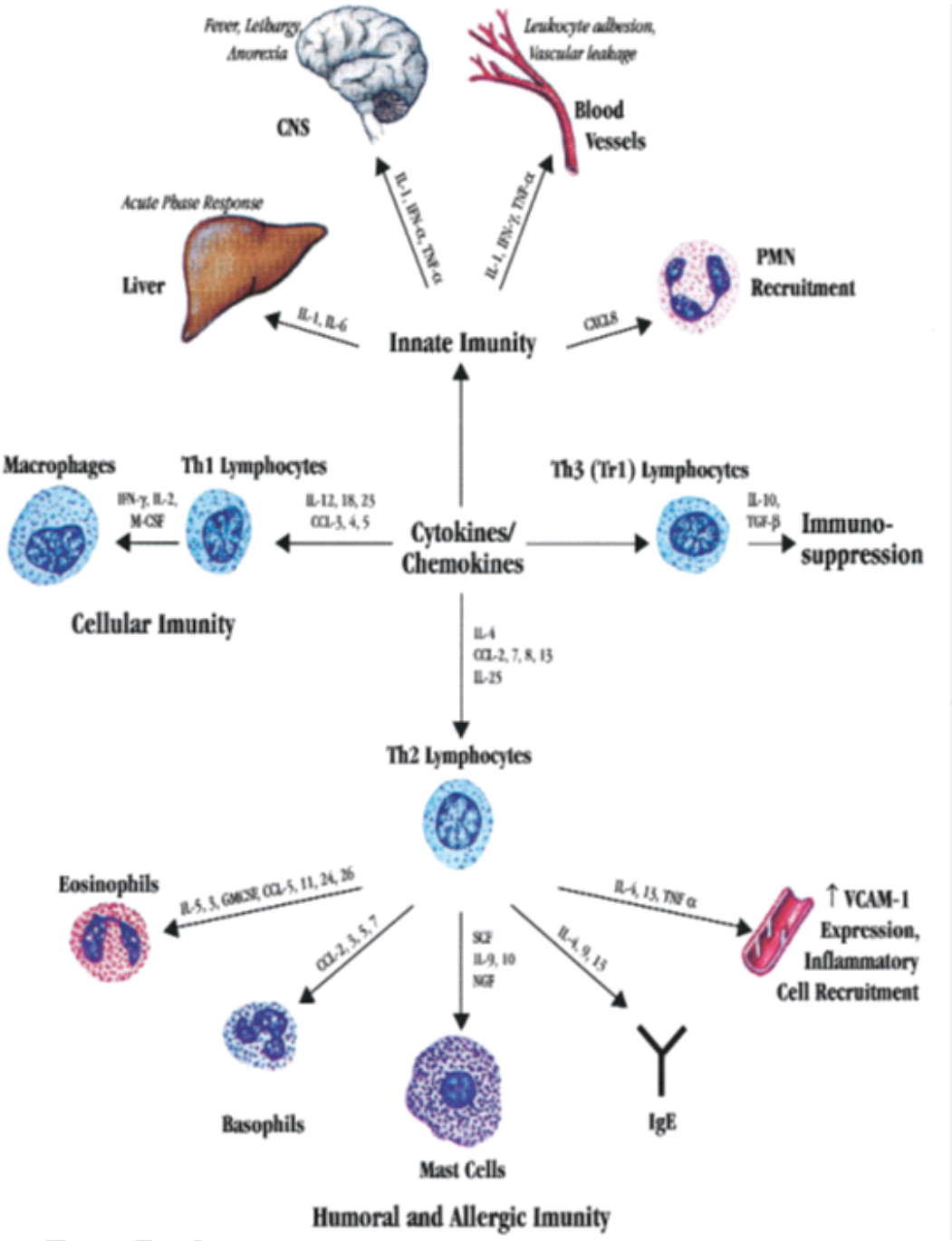

Fig. Allergic immunity

Cytokines play a vital role in controlling the cell, and hence tissue, growth, migration, development and differentiation these include a group of inflammatory cytokines such as the interleukins and interferons, growth factors such as epidermal and hepatocyte growth factor and chemokines such as the macrophage inflammatory proteins, MIP-1α and MIP-1β. They do not include the peptide and steroid hormones of the endocrine system. Cytokines have important roles in chemically induced tissue damage repair, in cancer development and progression, in the

control of cell replication and apoptosis, and in the modulation of immune reactions such as sensitization [7]

Cytokines	Action
Interferon family	Antiviral proteins
Chemokine family	Direct cell migration, adhension and activation
Tumour necrosis factor family	Regulate inflammatory and immune responses
Interleukin family	Variety of actions dependent upon interleukin and cell type
Haematopoietins	Promote cell proliferation and differentiation
Transforming growth factor beta family	Regulation of immune cells

Fig. 2. Action of cytokines

For example, cytokines made by lymphocytes can also be referred to as lymphokines. Many of the lymphokines are also known as interleukins (ILs), since they are not only secreted by leukocytes but also able to affect the cellular responses of leukocytes. Those cytokines secreted by monocytes or macrophages are termed monokines. And chemokines are cytokines with chemotactic activities. Cytokines activities could be autocrine action by binding to receptor on the membrane of the same cell that secreted it. It can also be paracrine action binding to receptors on a target cell in close proximity to the producer cell. Finally, cytokines can have endocrine activity by traveling through circulation and acting on target cells in distant parts of the body. Cytokines are a broad group of signalling proteins that are produced transiently, after

cellular activation, and act as humoral regulators which modulate the functions of individual cells, and regulate processes taking place under normal, developmental and pathological conditions). They are able to act locally, as autocrine, juxtacrine or paracrine response modifiers, and their action is initiated via specific receptors expressed primarily on the cell membranes of their target cells. Unlike hormones, cytokines are produced by cells which are not organized in special glands and which act systemically to affect biological phenomena such as inflammation, wound healing, organogenesis and oncogenesis [8]

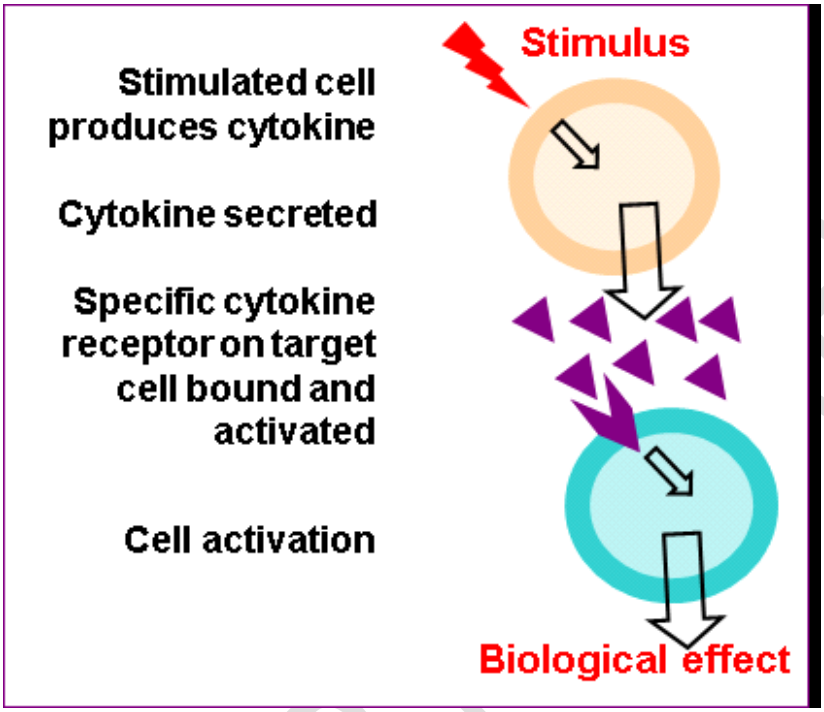

Fig. 3. cellular activation

Most cytokines show stimulatory or inhibitory activities and may synergise or antagonize the actions of other cytokines and hormones. An important feature of their action is that a single cytokine may induce one type of reaction under one circumstance and elicit entirely the opposite reaction under a different set of circumstances. This has particular relevance in their therapeutic use. The growth state of the recipient cells, the environment in terms of neighbouring cells, the cytokine concentration and the combinations of other cytokines present can all influence the type, duration and extent of reactions.

The biological activities of cytokines are mediated by specific membrane receptors which can be expressed on virtually all cell types. The mechanism by which receptor occupation by cytokines results in the generation of a signal through the receptor is not completely understood. It is likely that on binding to the extra-cellular portion of the receptor the cytokine induces a conformational change, or oligomerization of multiple receptors, resulting in an activation event in the intracellular domain itself or in receptor-associated elements such that signal transduction to elicit subsequent intracellular events occurs. Small antagonist molecules that bind to cytokine

receptors do not activate subsequent events probably because they do not deform the extra-cellular receptor sufficiently to excite subsequent events.

Cytokines as markers of cytotoxicity

In many acute and chronic inflammatory diseases in humans, such as hepatitis, rheumatoid arthritis and meningitis, plasma measurements have shown large increases in a broad range of cytokines and monitoring changes in these levels in, for example, synovial fluid in the case of arthritis can allow an indirect measure of the progression of the disease in response to therapy or in running its natural stage [7]

Vaccines in general

Vaccines contain weakened or inactive parts of a particular organism (antigen) that triggers an immune response within the body. Newer vaccines contain the blueprint for producing antigens rather than the antigen itself. Regardless of whether the vaccine is made up of the antigen itself or the blueprint so that the body will produce the antigen, this weakened version will not cause the disease in the person receiving the vaccine, but it will prompt their immune system to respond much as it would have on its first reaction to the actual pathogen. Some vaccines require multiple doses, given weeks or months apart. This is sometimes needed to allow for the production of long-lived antibodies and development of memory cells. In this way, the body is trained to fight the specific disease-causing organism, building up memory of the pathogen so as to rapidly fight it if and when exposed in the future [9]

Herd immunity

When someone is vaccinated, they are very likely to be protected against the targeted disease. But not everyone can be vaccinated. People with underlying health conditions that weaken their immune systems (such as cancer or HIV) or who have severe allergies to some vaccine components may not be able to get vaccinated with certain vaccines. These people can still be protected if they live in and amongst others who are vaccinated. When a lot of people in a community are vaccinated the pathogen has a hard time circulating because most of the people it encounters are immune. The more that others are vaccinated, the less likely people who are unable to be protected by vaccines are at risk of even being exposed to the harmful pathogens. This is called herd immunity. This is especially important for those people who not only can't be vaccinated but may be more susceptible to the diseases we vaccinate against. No single vaccine provides 100% protection, and herd immunity does not provide full protection to those who cannot safely be vaccinated. But with herd immunity, these people will have substantial protection, thanks to those around them being vaccinated. Vaccinating not only protects yourself, but also protects those in the community who are unable to be vaccinated [9]

Current and previous COVID-19 vaccines

Competent vaccines take 10 to 15 years to be fully developed and the immunity effect well known. Poliomyelitis, measles, small pox, yellow fever vaccines were all developed with much years of clinical trials and at times genetic modulations. The current COVID-19 vaccines be with Pfizer AstraZeneca, Moderna, Sputnik V, Oxford vaccine and Johnson and Johnson vaccines are

barely 2 years old and although its competency is not well documented, it has shown to reduce death rate and this is a progressive step for the human race in relation to the COVID-19 pandemic which is now been endemic.

Pfizer – BioNTech vaccine

The first COVID-19 messenger-ribonucleic acid (mRNA) vaccines currently authorized for emergent use in the United States and around the world was the Pfizer-BioNTech and the Moderna vaccines. Conventional vaccines rely on weakened and inactivated pathogens or a fragment of the pathogen to trigger an immune response. In contrast, the COVID-19 mRNA vaccines use a novel approach by which mRNA is delivered into our cells to provide the genetic instructions for our own cells to "temporarily" make a "specific" viral protein that triggers an immune response [10]. The Pfizer-BioNTech COVID-19 vaccine is composed of only one active ingredient which is the mRNA, this is protected by a group of lipids knowns as (4-hydroxybutyl) azanediyl) bis(hexane-6,1-diyl) bis (2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N, N-ditetradecylacetamide 1,2-Distearoyl-snglycero-3- phosphocholine cholesterol. The vaccine also contains salts such as Potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dehydrate which help in balancing the acidity in the body. The last ingredient in this vaccine is the sugar component known as sucrose which helps the molecules maintain their shape during freezing [11].

Moderna Vaccine

This contains mRNA just like the Pfizer BioNTech vaccine, lipids such as SM-1021,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000 [PEG2000-DMG] cholesterol 1,2-distearoyl-snglycero-3-phosphocholine which help to deliver the mRNA to the cells. Some other ingredients, include acetic acid, acid stabilizers, salt and sugar which all work together to maintain the stability of the vaccine after it's produced [12].

Mechanism of MRNA COVID 19 Vaccines (Moderna and PfizerBioNTech vaccines) in the Human system

Injections given from Pfizer and Moderna vaccines give the body genetic instruction manuals to safely learn how to fight the coronavirus. Pfizer's and Moderna's vaccines train the body to fight COVID-19 by injecting mRNA, or messenger RNA, into a person's deltoid, the rounded muscle that hugs the upper arm and shoulder. The mRNA that's injected into the muscle codes for the spike protein. The coronavirus' spike protein is what allows the virus to latch on to and invade the human cells. The mRNA vaccines train the human bodies to immunologically move in a determined pace [13]. The body sees that protein and makes an immune response against it, giving the body the protection that has been shown with both of the mRNA vaccines. [14]

Mechanism of ADENO VIRUS (cold virus) COVID 19 Vaccines (The Johnson & Johnson vaccines) in the Human system

The Johnson and Johnson vaccine injects viral DNA and not mRNA. This is a key reason why Johnson and Johnsons vaccine is much easier to manufacture and can be stored in the normal fridges in our homes and clinics. The DNA inside is not as fragile as the single-stranded mRNA

in Pfizer's and Moderna's vaccines. The DNA in the johnson and johnson vaccine is encapsulated in a harmless, non-replication-competent virus. The adenovirus is called Ad26 and is a common cold virus that has had its illness-causing genes removed, so it can't get the human system sick. Once the vaccine is injected into a person's arm, the virus injects its DNA into cells, where it's copied into messenger RNA. That mRNA then codes for coronavirus spike proteins in the same way as Pfizer's or Moderna's shots [14]

Summary

The main components in the Pfizer-BioNTech and Moderna vaccines are very similar, both vaccines have been found to be safe and efficacious in preventing symptomatic COVID-19 disease in rigorously conducted clinical trials. Pfizer - BioNTech and Moderna vaccines are mRNA-based, while Johnson & Johnson's is an adenovirus. These COVID-19 mRNA and Adenovirus vaccines are safe and have gone through the same rigorous testing process as other vaccines before being approved for emergent use in the United States and now worldwide. In clinical trials and experiments it has showed that Moderna and Pfizer Vaccines when administered were more effective overall than the Johnson and Johnson vaccine in the trials, but it was observed and noticed that all these vaccines share two very important statistics that is zero hospitalizations and zero deaths among fully vaccinated trial participants[15].

Although local and systemic side effects have been reported and shall be experienced within the population, as is the case for many other medical interventions, the risk of lacking protection against COVID-19 and developing severe disease far exceeds those posed by the vaccine itself. Either the adenovirus and mRNA COVID-19 vaccines are the same as all vaccines ultimately result in a spike protein in the right conformation that gives the body the opportunity to feel that this is the it's the protein that it is moving with. The protein prepares a vaccinated person's body to fight off a COVID-19 infection if the person comes into contact with the virus. Both the mRNA and the adenovirus vaccines appear to prevent the most severe COVID-19 infections very well [15].

Research and case reports has showed that Pfizer and Moderna two shot courses were more than 94% effective in their trials, while Johnson and Johnson (J&J) vaccine were 85% effective in preventing severe disease and death. Adenovirus vaccines like J&J's might give people a more robust form of immunity against viral variants, with antibody and T-cell responses. mRNA vaccines may provide only narrower antibody protection but that remains to be seen as more people get vaccinated and variants continue to spread [14].When taking the vaccines, the population should take note that the vaccine vial or seal is not already broken, the vaccine does not change to any colour or does not develop colours while in the vial, vaccines should be opened in the face of the receiver, syringe on the vial is new and opened in the face of the

receiver, vaccine is taken from the cold chain storage box, one should not take vaccines that are already on the table or desk of vaccine givers be it nurses, doctors or any licensed staff in charge.

Conclusion

The now incorporation of cytokines as molecular adjuvants in some vaccines has been attempted to strengthen vaccine-induced immune responses, and as a rational approach to modulate cytokine milieu in vivo and tailor host immunity for specific situations. These approaches have been tried in experimental models and veterinary species, and a few of them have entered into clinical trials. However, manipulating the cytokine network to modulate immune responses is not a simple task, because cytokine functions are complex and the final effects on the immune response will depend on timing and length of exposure, cell(s) targeted and other cytokines present in the same microenvironment [3].

Recommendation

Although most literature does no state or know the exact immunity duration or even any immunity of the COVID-19 vaccines been developed and rolled out, the population should still take the vaccines since most components of the vaccines may trigger cytokines and in the normal state and can build some undefined form of immunity so the need for the population to take the vaccines. Also, it is recommended that severe adverse reactions or even subtle adverse reactions from the vaccine that doesn't resolve or go away within 72hrs should be urgently reported to health authorities and accredited health centres for such purpose. There are rumours that mRNA vaccines will alter our DNA because the RNA molecule can convert information stored in DNA into proteins. That's simply, not true. It's critical to note that the mRNA vaccines never enter the nucleus of the cell, where our DNA is stored. After injection, the mRNA from the vaccine is released into the cytoplasm of the cells. Once the viral protein is made and on the surface of the cell, mRNA is broken down and the body permanently gets rid of it, therefore making it impossible to change our DNA. Furthermore, it is extremely important for the population to keep on masking, using the hand washing techniques regularly, using the alcohol hand sanitizers and physical or social distancing approach to help achieve a competent prevention even after taking the prescribed doses of any of the COVID- 19 vaccines [15].

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