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Cytokines: The Game Changer in Pathogenesis of Covid-19

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Abstract

A small particle of the size about 100 micrometers (SARS-V2) has shaken the world. In some Covid-19 patients a severe immune reaction was found in which cells release too many cytokines into the blood too quickly. Cytokines are regulators of host responses to infection, immune responses, inflammation, and trauma. In addition, cytokines activate those cells, stimulating them to produce more cytokines. Normally, this feedback loop is kept in check by the body. Some cytokines act to make disease worse. Cytokine storms might explain why some people have a severe reaction to corona viruses while others only experience mild symptoms. They could also be the reason why younger people are less affected, as their immune systems are less developed and so produce lower levels of inflammation-driving cytokines.

Since, in early 2020, Covid -19 became pandemic, globally multi-pronged research started to get rid of corona virus 2 (SARS-CoV-2) [1, 2]. For such a task, it was necessary to understand the pathogenesis of covid-19, due to the fact that SARS-CoV-2, is new and its mechanism of action and its interrelationship with the human body organs is not fully known yet. Nevertheless, it is known that all viruses and bacteria when invade the body interact with the immune system, inflammation starts and if the immune system cannot get rid of the invaders, pathogenesis starts.

Cytokines

The name 'cytokine' is derived from the Greek words for cell (cyto) and movement (kinos). Cytokine is a general term used for all signalling molecules. These chemicals will have vital role in immuno-pathology. Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are released by many different cells in the body including those of the immune system during activation where they coordinate the body's response against infection and trigger inflammation. Cytokines mediate and regulate immunity, inflammation and haematopoiesis [3, 4]. Cytokines cannot cross the lipid bilayer of cells to enter the cytoplasm. Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as immuno- modulating agents [5]. In some viral infections cytokines are flooded and because of this flooding instead of protecting the body this protein becomes the cause of death [6].

There are two other molecules come under this category but with the specific function: the one is chemokines these are specific cytokines that functions by attracting cells to sites of infection/inflammation; and the other are Interleukins a group of cytokines that were first seen to be expressed by white blood cells. Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene [7].

Viruses- host cell interaction

Although details of the cellular responses to this virus SARS-CoV2 are not known, a probable course of events can be postulated based on past studies with SARS-CoV. When the immune system is fighting pathogens, cytokines signal immune cells such as T-cells and macrophages to travel to the site of infection on primary viral infection, the host cells respond by production of a range of cytokines [4]. Cytokines are regulators of host responses to infection, immune responses, inflammation, and trauma in addition; cytokines activate those cells, stimulating them to produce more cytokines. Normally, this feedback loop is kept in check by the body. Some cytokines act to make disease worse (proinflammatory cytokines), whereas others serve to reduce inflammation and promote healing (anti-inflammatory cytokines; these include interleukin-1β (IL-1β), IL-2, IL-6, IL-10, IL-12, IL-13, tumour necrosis factor alpha (TNF-α), IFN-α/β, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [6, 7]. In addition to these, they also regulate a number of physiological and pathological role including innate immunity, acquired immunity and a plethora of inflammatory responses. The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells.

Cytokine Storm

A severe immune reaction in which is the body releases too many cytokines into the blood too quickly. Cytokines play an important role in normal immune responses, but having a large amount of them released in the body all at once can be harmful. A cytokine storm can occur as a result of an infection, autoimmune condition, or other disease. It may also occur after treatment with some types of immunotherapy. Signs and symptoms include high fever, inflammation (redness and swelling), and severe fatigue and nausea. Sometimes, a cytokine storm may be severe or life threatening and lead to multiple organ failure. Also called as hypercytokinemia [8].

The phenomenon became more widely known after the 2005 outbreak of the avian H5N1 influenza virus, also known as "bird flu", when the high fatality rate was linked to an out-of-control cytokine response. In 2006, six healthy young men were left in intensive care with multiple organ failure as a result of an out-of-control cytokine immune response during a preclinical trial of a new kind of drug. This reaction happened just 90 minutes after receiving a dose of the drug sometimes the body's response to infection can go into overdrive.

For example, when SARS -CoV-2 – the virus behind the covid-19 pandemic – enters the lungs, it triggers an immune response, attracting immune cells to the region to attack the virus, resulting in localised inflammation. But in some patients, excessive or uncontrolled levels of cytokines are released which then activate more immune cells, resulting in hyper inflammation. This can seriously harm or even kill the patient. Diseases such as covid-19 and influenza can be fatal due to an overreaction of the body's immune system called a cytokine storm. Cytokine storms are a common complication not only of covid-19 and flu but of other respiratory diseases caused by coronaviruses such as SARS and MERS. They are also associated with non-infectious diseases such as multiple sclerosis and pancreatitis.

Cytokine storms might explain why some people have a severe reaction to corona viruses while others only experience mild symptoms. They could also be the reason why younger people are less affected, as their immune systems are less developed and so produce lower levels of inflammation-driving cytokines. Some pilot studies have shown promising results. Corticosteroids could be used to suppress the cytokine storm and have been used in some patients [9].

Cytokines in response to COVID-19

There are still many unresolved questions regarding the pathogenesis of this disease. However, some of the clinical features are shared between COVID-19 and previously identified beta-coronavirus infections. High levels of some cytokines associated with COVID-19 could prevent long-term antibody responses to the SARS-CoV-2 virus immunity to COVID-19 is not durable because the antibodies decline over time [10, 11]. When the researchers studied the lymph nodes of patients who had died of the disease, they found high levels of TNF-α -- one of the most abundant cytokines present in cases of COVID-19 -- in these organs. This finding led them to conclude that TNF may be preventing the germinal centres from forming in people with COVID-19 as well. Without the formation of germinal centres, there is unlikely to be long-term memory to this virus developing from natural infections, meaning that while antibodies may protect people for a relatively short time, a single person who recovers from the disease could get infected again, perhaps six months later, or even multiple times with SARS-CoV-2. This suggests that developing herd immunity may be difficult. However, as vaccines do not induce cytokine storms, a vaccine-induced immune response would likely include the development of a germinal centre, thus ensuing the creation and immortalization of high-quality antibodies that would provide long-lasting protecting against COVID-19.

"However, we have to set appropriate expectations. Just because a vaccine comes out doesn't mean you can go back to life as it was before the pandemic. It is important to remember that a vaccine is like many other products - what matters is not just that a product is available, but also how effective it is" said the authors [12, 13].

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