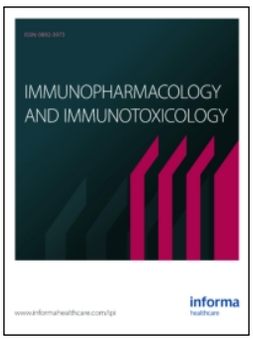

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Immunopharmacology and Immunotoxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iipi20

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To cite this article: Ratheesh M , Sheethal S , Svenia P. Jose , Sony Rajan , Sulumol Thomas , Tariq Jagmag & Jayesh Tilwani (2020): Biochemical and immunological aspects of COVID-19 infection and therapeutical intervention of oral low dose cytokine therapy: a systematic review, Immunopharmacology and Immunotoxicology, DOI: 10.1080/08923973.2020.1842444

To link to this article: https://doi.org/10.1080/08923973.2020.1842444

IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY
https://doi.org/10.1080/08923973.2020.1842444

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REVIEW

Biochemical and immunological aspects of COVID-19 infection and therapeutical intervention of oral low dose cytokine therapy: a systematic review

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ABSTRACT

The novel coronavirus (SARS-CoV-2) pandemic has now spread to all corners of the world. It causes severe respiratory syndromes which is one of the leading causes of death. Evidence shows that the novel SARS-CoV-2 has close similarities with other coronaviruses, SARS and MERS. So, SARS-CoV-2 might use the similar mechanisms of these viruses to attack the host cells. The severity of COVID-19 is associated with various factors, one of the major reasons is immune dysregulation or immune suppression. Immunity plays a significant role in maintaining the body in a healthy condition. In order to induce a timely immune response against the invaded pathogens, both innate and adaptive immunity must be in an active state. During the viral infection, there will be an excessive generation of pro-inflammatory cytokines known as cytokine storm and also, the antiviral agents in the body gets inhibited or inactivated through viral mechanisms. Thus, this might be the reason for the transition from mild symptoms to more severe medical conditions which leads to an immediate need for the invention of a new medicine.This review aims to show the host-viral interaction along with immune response, antiviral mechanism and effectiveness of oral low dose cytokines against the virus as a therapeutic approach.

ARTICLE HISTORY
Received 25 June 2020
Accepted 18 October 2020

KEYWORDS
Covid-19; Immune response; inflammation; immunomodulation; cytokine therapy

Introduction

Mankind, from the ancient times itself, has been confronted with various outbreaks and pandemics which are marked as signature events in world history. By the end of 2019, a new virus which belongs to the coronavirus family emerged in the city of Wuhan in China. The novel viral disease, hence named as COVID-19 (the virus is referred to as SARS-CoV-2) [1]. Within a limited period of time, the situation has changed drastically and the virus spread across the globe and more than 143 countries and millions of people were affected with this virus [2]. The novel coronavirus has become a matter of global health crisis due to its high infectivity and lack of any vaccines against this virus. COVID-19 patients remain either asymptomatic or show mild symptoms like high fever, severe cough, fatigue, body pain, headache and, in more severe cases, experience respiratory failure - one of the leading causes of mortality. Chances of contracting COVID-19 are not only limited to elderly people, but also in all age groups, especially those who are suffering from other diseases and even children who were initially thought to have better immunity [3]. Comparing the susceptibility of viral infection in men and women, men are more vulnerable and it was found that the plasma viral load is higher in men than in women. Studies reported that women are more immunologically protected because the genes which are responsible for the expression of immune cells are present more in the X chromosome. Thus, sexual difference might have a major role in the various aspects of COVID-19 infection [4].

The pathogenesis is still unclear and in most of the patients, the virus is found infecting the lungs, thereby causing respiratory diseases. Studies have reported that the pathophysiology of ARDS caused by COVID-19 is due to the disruption of the blood-air barrier in the alveolar sacs. As a result, the plasma enters the air sacs and causes a sudden increase in immune reaction and also attracts inflammatory cells such as monocytes and neutrophils, resulting in the excessive infiltration of inflammatory cells into the lungs and causing damage to the lungs. This damage is the result of viral attack along with the overexpression of immune cells [5]. Even though it is a protective mechanism to destroy the invading virus, it has a deleterious end-result on the body. Some other under recognized conditions of COVID-19 infections such as secondary haemophagocytic lymphohistiocytosis, hyper-inflammatory syndrome with hyper-cytokinaemia, lead to multiple organ failure associated with hyper-ferritinaemia [6]. Thus, based on the reports and studies conducted so far, the dangerous impact of this virus is due to immune dysfunction [5].

Therefore, this review will provide an overview of the SARS-CoV-2 induced immune system dysfunction and its regulation, along with the therapeutic application of oral low dose cytokines as an effective immune system booster.

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Host-viral interaction and induction of immune response

The structure of coronavirus consists of Spike (S), Membrane (M), Envelope (E) glycoproteins, Hemagglutinin esterase (HE) and nucleocapsid (N) protein (Figure 1). The viral envelope is a lipid bilayer in which the structural proteins, membrane (M), envelope (E) and spike (S) are anchored. There is also a shorter spike-like surface protein called Hemagglutinin esterase (HE) in the coronavirus subset (especially the members of betacoronavirus subgroup A) [7]. Previous studies reported that SARS-CoV-2 has close similarities with SAR-CoV. The S protein helps the virus to gain entry into the host cells and the surface unit of S protein will facilitate the binding of virus to the target receptor as well as priming of S protein by cellular protease. This permits the fusion of both viral and host cell membranes [8–10]. The similarity of SAR-CoV-2 with SARS-CoV shows that the novel coronavirus also uses the same Angiotensin converting enzyme 2 (ACE-2) receptor as its entry receptor and TMPRSS2 serine protease helps in S protein priming [11,12]. ACE 2 is a membrane protein which is present in almost all the organs but highly expressed in type 2 alveolar cells [13–15]. Likewise, it is also expressed on vascular endothelial cells and cardiac cells which may perhaps describe the cardiovascular complications that occur in some patients [5]. S protein of SARS-CoV-2 has high affinity to ACE-2 receptors and this helps the virus to be transmitted more effectively between humans [16,17].

As an anti-viral mechanism, when the SARS-CoV-2 enters the body, both innate and adaptive immune responses will be activated to control viral replication and inflammation, thereby eliminating the infected cells from the body [18,19]. In all cases of viral infections, cell mediated immunity is carried out by T cells while B cells are responsible for humoral immunity (production of antibodies). Thus, T cells and B cells play an important role in regulating immune responses [20].

The immune response against the pathogen, begins in the alveolar epithelial cells by dendritic cells (DC) and Mast cells (MC) that reside in the lungs. DC will procure the virus and get activated to present the viral antigen to circulating naive T cells in the form of antigen presenting MHC complex. Once the T cell receptor encounters the MHC complex, T cell-activation takes place [21–23]. The activated effector T cells will migrate to the site of infection and produce several cytokines (like interferons (IFN), tumor necrosis factors (TNF)), cytotoxic molecules (perforin and granzyme) and chemokines against the virus [24]. Thus, once the T cells are activated, they help to inhibit viral replication, recruit more and more cells responsible for innate and adaptive immune responses, destroy infected cells and eliminate pathogens [25–27]. There are numerous studies on the response of T cells against respiratory infections caused by viral pathogens, but only limited information on coronavirus infections.

Studies reported that in most of the patients with SARS-CoV-2 infection, there is an overactive immune response with uncontrolled activation of macrophages, increased number of neutrophils and reduced number of lymphocytes and T cells [28–30]. In the case of all the T cell variants - Helper T cells (CD 4+), Cytotoxic T cells (CD8+) and Regulatory T cells – their numbers are considerably lower in more severely affected patients than non-severe patients. The regulatory T cells perform the key role of maintaining the immune response in a state of equilibrium by inhibiting the stimulation, multiplication and pro-inflammatory function of CD4+ cells, CD8+ cells, B cells and Natural killer cells [31,32]. Virus specific CD4+ and CD8+ cells are responsible for the primary response against invading viruses and help in viral clearance. CD4+ T cells are responsible for cytokine derivation and CD8+ T cells help in cytotoxic responses, but the rapidity of viral clearance is associated with the amount of these cells [33–36]. Even though the body possesses all these mechanisms, the novel SARS-CoV-2 displays certain other mechanisms to escape from host responses and one such capability is the induction of T cell apoptosis [37]. Reduction in the number of T cells was observed and correlated to the acute phase of SARS disease along with a dramatic reduction in CD4+ and CD8+ T cells [38,39].

In the case of MC, it has both positive as well as negative impact on immune responses. MC express TLRs which will be immediately identified by the microbial pathogens and get activated in the respiratory tract and produce various inflammatory cytokines, chemokines and other chemical mediators in the lungs. Certain chemokines like CCL5 has the ability to attract CD8+ T cells for eliminating invaded pathogens and the virus activated TLR3 on MC will help in the production of antiviral IFNs as a protective mechanism but on the other hand, overexpression of these mediators will adversely affect the body through severe inflammation [40]. Altogether, these changes contribute to specific alterations in the normal and balanced immune responses and aberrant release of inflammatory cytokines to the lungs, resulting in cytokine storm and ultimately organ damage [41].

Impact of cytokine storm on respiratory problems and coagulation

One of the major features of SAR-CoV-2 infection is the induction of cytokine storm. Studies have also reported that high levels of cytokines and chemokines are observed in patients with SARS- CoV- 2 infection and these include IL-1, IL-1RA, IL-6, IL-8, IL-10, IFN-ɤ, MCP-1, FGF2, MIP-1A, GMCSF, G-CSF and TNF-α [6,42]. This hypercytokinemia dangerously impacts the body by increasing the risk of vascular hyperpermeability along with severe inflammation [43]. Among these cytokines, IL-1 is one of the most biologically active forms which are involved in inflammatory processes, hematopoiesis, immune responses etc. When this cytokine binds to its specific receptor, it will activate TLR and trigger the activation of various inflammatory pathways with the excessive production of cytokines which later induce the expression of other cytokines resulting in cytokine storm along with the activation of other molecular pathways [44]. This viral induced activation of a cascade of cytokines will result in the development of acute and chronic obstructive respiratory problems, lung inflammation, pulmonary fibrosis and other severe lung disorders. So, the inhibition of IL-1 will help to

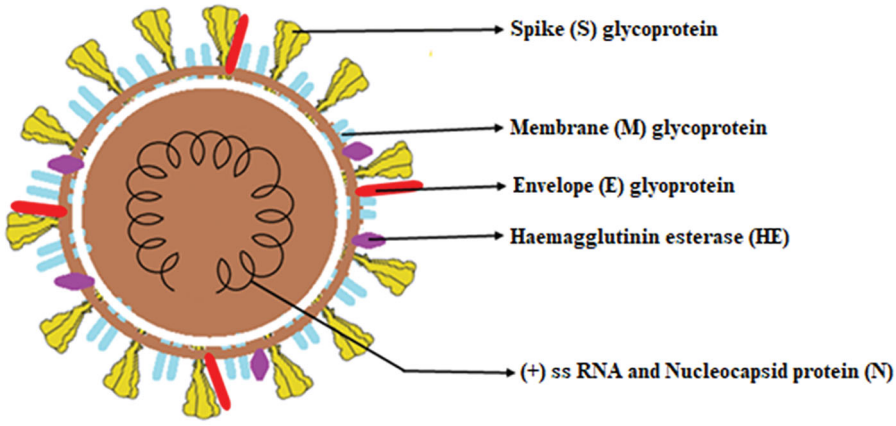

Figure 1. Structure of SARS-CoV-2 depicting the arrangement of proteins.

reduce cytokine storm and its associated respiratory problems to an extent [45].

Coagulation pathway is responsible for clot formation with the help of thrombin by the activation of platelets and conversion of fibrinogen to fibrin. Thrombin can intensify inflammatory condition through proteinase activated receptors (PARs). PAR-1 is the major thrombin receptor which facilitates platelet aggregation along with the relationships between coagulation, fibrosis and inflammation. So, thrombin is strictly controlled by a negative feedback mechanism and is assisted by physiological anticoagulants [46]. During an inflammatory condition, all these mechanisms will be compromised by an imbalanced production and consumption of anticoagulants. This will induce microthrombosis and cause intravascular coagulation which will finally lead to multiple organ failure. Evidence show that intravascular thrombosis and fibroproliferative lung disease are the common medical conditions seen in patients with severe SAR-CoV-2 infection and non survivors [13,46,47].

There are lots of studies that investigated the role of PAR-1 in host immunity against viral attacks and showed that, in-order to control the viral load, activation of PAR-1 is very important at the initial stage but if sustained, it will reduce the chance of survival due to PAR-1 mediated inflammation [48,49]. Thus, controlling PAR-1 helps to reduce the over production of proinflammatory cytokines, neutrophil induced lung inflammation and alveolar leakage [50]. Thus, thrombin and PAR-1 might be possible therapeutic targets in viral induced microthrombosis.

Major downstream Cascade activated by pathogenic invasion

SARS-CoV-2 binds with the ACE-2 receptor to enter targeted cells and it has been observed that SAR-CoV-2 can attack immune cells such as macrophages and T cells. But the fact is that, only limited ACE2 receptors are found in these immune cells [14,51].This indicates that they might be using other receptors or mechanisms to enter the host cells.

To exert an immune response, the cells have to recognize the invaded virus by pathogen associated molecular patterns (PAMPs). For RNA viruses like SARS-CoV-2, SARS-CoV and MERS-CoV, endosomal RNA pattern recognition receptors comprising Toll-like receptors (TLR-3 and 7) and RNA sensors in cytosol (like RIG-1) will detect them. This will lead to the activation of a signalling cascade which begins from NF-kB and Interferon regulatory factor 3 (IRF3) followed by its translocation into nucleus. In the nucleus, gene expression of type I Interferon (IFN) (*via* IRF3) and other pro-inflammatory cytokines (*via* NF-kB) takes place which is considered as the first line of defence against the invaded virus. Type I IFN will activate the JAK-STAT pathway by its binding with IFNAR which will in turn, activate the JAK1 and TYK2 kinases and phosphorylate STAT1 and STAT2. STAT1 and STAT2 together with IRF 9 will form a complex that initiates the transcription of IFN-stimulated genes (ISGs) with the help of IFN-stimulated response element (ISRE) containing promoters which helps to suppress viral replication [20,52]. Thus, in order to suppress the replication and spreading of the virus right from the early stages itself, IFN has to be successfully active.

In the case of severe SARS-CoV and MERS-CoV infections, IFN induced viral suppression will be blocked due to multiple strategies employed by these viruses. This inhibiting strategy exhibited by the virus is closely related to the severity of infection [53]. SARS-CoV hinders the initial ubiquitination and degradation of RNA sensors along with IRF 3 blockage. At the early stage of viral encounter, interferon synthesis will occur but, then the virus counteracts the IFN mediated signaling activation of STAT (Figure 2) [52,54]. SAR-CoV-2 shares genomic similarities with SARS-CoV and studies have revealed that the novel coronavirus also uses such strategies to modify the host immune response. Hence, they can multiply and spread without the interference of a host antiviral response.

Therapeutical intervention for SARS-CoV-2 infection

The death rate and number of victims are increasing uncontrollably. Even though some of the major impacts created by the virus such as increased viral load and associated cytokines and chemokine production are known, the treatment for the novel coronavirus is still a challenging question. As it is a novel virus and shares similarities with SARS and MERS,

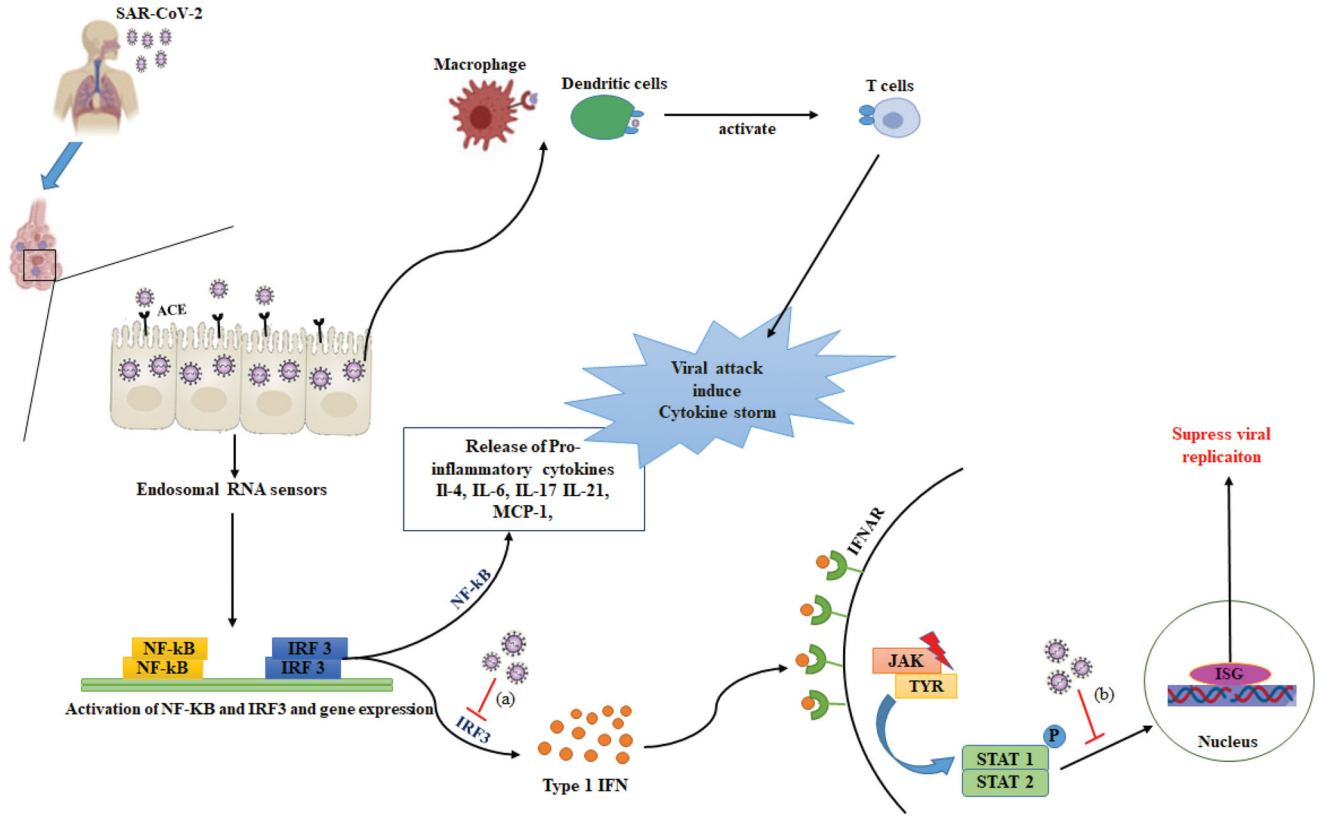

Figure 2. Downstream cascade and potential immune response activated by SARS-CoV-2. Upon infection, the SARS-CoV-2 will attack the ACE-2 expressing specific target cells mainly alveolar cells. As a result, an immune response will take place by the recruitment of various immune cells like macrophages, dendritic cells, T cells etc. and the activation of inflammatory and Type I IFN signaling pathways as a protective mechanism to supress and eliminate the virus but the persistence of this virus will lead to the overexpression of proinflammatory cytokines, called cytokine storms, and interfere with various immune responses including the production of Type 1 IFN (a) and STAT downstream signaling cascade (b).

treatment strategies employed against it are similar to those employed against SARS and MERS. Thus, the therapeutic approaches under investigation are focusing on the reduction of viral load and hyperactive cytokine induced inflammatory response using antiviral cytokines or immunomodulators, but this must be in a balanced state to maintain required inflammatory response for pathogen clearance [55–58].

Oral low dose cytokines as a potential therapy against SARS-CoV-2

Cytokines are small polypeptides which play a significant role in innate and adaptive immunity. It is produced by immune cells, endothelial cells, certain stromal cells and fibroblasts as a protective response of the host against pathogens. These cytokines are known as antiviral cytokines. In a regulated manner, antiviral cytokines would help with viral clearance [59,60]. Antiviral cytokines include interferons such as IFN-α, IFN-β, IFN-γ and IFN- λ, and Interleukins (IL) such as IL-2, IL-12, IL-15, IL-18 etc. They might coordinate the immune responses by activating cytotoxic lymphocytes, Natural killer cells and also promoting antibody mediated responses along with modifying the expression of MHC and other co-stimulatory molecules [61–66].

In the recent year, a new therapeutic approach called Low dose medicine (LDM) was developed. The concept of LDM is to treat the ailment and bring back to normal physical state by using similar biological molecules that are typically present in the body of a healthy individual. The important point to be cautious is that, the oral administration of signaling molecules, generally peptides, would have lower bioavailability. But its bioavailability can be improved by using a better drug delivery system. Studies show that the systemic administration of cytokine is not an effective way to induce at a specific site, but the oral route provides an excellent mode of administration. Previous studies have already proven that low dose cytokines are safe and effective and also maintain adequate biological activity to influence the immunomodulatory action beyond the mucosa [67–69]. In recent years, low dose cytokines are extensively used in the treatment of inflammatory diseases, allergic asthma, dermatological problems etc. and there are also, studies showing the antiviral effects of different cytokines against various types of viral infections [70–72]. So, in the current situation, promoting the use of low dose cytokine therapy might be very effective in controlling the novel coronavirus infection.

Role of interferons as an immunomodulator

Interferons are an important group of cytokines and it is mainly divided into 3 classes: classical viral induced type I interferon (IFN-α and IFN-β), Immune induced Type II interferons (IFN-γ) and recently discovered Type III interferon

(IFN- λ). Interferons are referred to as the first line of defence against a viral infection and have a major role in immunological surveillance [73–75].

Interferon-α and interferon-β

The production of Type I IFN is induced by infections caused by pathogens like bacteria or viruses or other microbial nucleic acids. IFN-α and β are the first IFN synthesized in the body through the biochemical pathways activated by pathogens. These IFNs will produce autocrine and paracrine signals to assemble other IFN response factors against the virus in the cell and promote IFN reaction in the neighboring cells to protect themselves from viral infection respectively [76–78]. The antiviral effect of Type I IFN is mediated by the STAT 1 and STAT 2 through the activation of JAK-STAT pathway [79]. There are a lot of cells that can produce IFNs like macrophages, fibroblast, leukocytes etc. They are known as interferon producing cells (IPC). At the time of antiviral immune response, IPC has the capability to stimulate NK cells, T and B cells [80,81]. Thus, Type I IFN possesses a strong antiviral activity and exhibits its action by the activation of cellular genes to inhibit viral replication along with mRNA destruction and blocks protein translation in the cells. They also help to promote more ligands for NK cell receptor expression in the infected cells and this will assist NK cells to exterminate virus infected cells [82–84].

Interferon-γ

Normally in the body IFN-γ is synthesized by the activated NK cells in response to the binding of IFN α/β and kills the infected cells as an innate immune response induction of MHC molecules [85]. The main role of type II IFN is macrophage activation and it will exert an immune response against intracellular microorganisms by promoting phagocytosis. Macrophages also produce cytokines, which in turn, activate T cells responsible for initiating the adaptive immune response. This cytokine has the ability to inhibit cell growth and trigger cell apoptosis. Therefore, IFN-γ can implement its antiviral activity for a long term and also manage the innate and adaptive immune responses [76,86,87].

Interferon-λ

IFN- λ is denoted as IL-28/29 and exhibit strong antiviral activity. When there is a viral infection, the first cytokine to be induced by the body is IFN- λ. They limit the initial infection and lower viral load and they also exhibit an anti-inflammatory effect with tissue protective properties. It has been reported that IFN- λ are essential for preventing viral transmission from the upper airways to the lungs, a process that takes place during early infection [88].

Previous studies have already stated that all these interferons possess strong anti-viral activities and hence, can be effectively used as a preventive measure against viral infections [89–92]. Thus, it might be effective against the novel SARS-CoV-2.

Role of interleukins as immunomodulator

Interleukins are another set of proteins which are closely related to the stimulation and suppression of the immune system and division of cells. CD4+ T cells, macrophages and endothelial cells are the major source of IL [93,94]. A lot of IL have been identified, based on their different properties. In this section, we are focusing only on two major ILs that can be effectively used as a low dose medicine against viral infections.

Interleukin 12

The role of IL-12 is the activation of NK cells and triggers Th0 precursor for the production of CD4+ effector cells as a result of a pathogen invasion [95]. IL-12 is very significant in that it has the ability to induce the production of IFN-γ from NK cells, T lymphocytes and also control the activity of NK cells and enhance the proliferation of T cells. Thus, its immunomodulatory action plays a pivotal role in both innate and adaptive immunity [96,97]. Studies have shown that supplementation of IL-12 protects the cells against a viral attack by stimulating the synthesis of neutralizing IgG2a antibodies [98]. Hence, it has the ability to activate the immune system and immensely support the viral clearance process and thus, IL-12 can be used against viral infections as immune boosters.

Interleukin 15

IL-15 is gaining attention due to its possible role in antiviral immune responses. Normally, as a part of the innate immune response, it is produced by activated CD 4+ cells, keratinocytes, monocytes and skeletal muscle cells. Their function is to activate the T cells and NK cells and maintain NK-T cells in an equilibrium [93]. It also promotes the survival and proliferation of CD8+ T cells, enhances its cytotoxicity and signals T cells either directly or indirectly to enter infected cells. Signaling of IL-15 supports the lymphocyte activation by promoting their effector capabilities, causing spontaneous degranulation and secretion of IFN-γ. It has the capability to maintain the antigen specific memory of CD8+ T cells for a long term [99–101]. Thus, it is clear that IL-15 is a potent antiviral cytokine which can induce an immune response effectively.

Conclusion

Immunity is a natural defence mechanism of the body, therefore it must be very strong and active in a balanced manner. For an immunocompromised individual and elderly people, the chances of being attacked by pathogens are very high and the probability of survival is very low due to their poor immunity. Both inborn and acquired immunity play a significant role in the immune response toward the invaded external factors. So, in order to boost up the immune system for its timely action, immunomodulators are really important. Many other studies have already proven that

immunomodulatory cytokines can be effectively used against various disease conditions. Hence, as a preventive measure or treatment strategy, implementation of immunomodulators like oral low dose cytokines will be very effective in tackling the severity caused by viral pathogens. Therefore, in the current scenario of COVID-19, oral low dose cytokines might be a potential therapeutic agent.

Acknowledgements

We express our sincere gratitude to Mr. Rajesh Khatri, Managing Director of Glowderma Pvt. Ltd., Mumbai for his valuable suggestion and enthusiastic support.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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