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Review

An Overview of Cytokine Trafficking during COVID-19 Infection

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ABSTRACT

The end of the first quarter of the 21st century will be known as when there was a deadly pandemic due to COVID-19 infection. The four subfamilies of α, β, $\triangle$, γ have a genetic variation ranging between 26 to 32 kb. Patients with COVID-19 have more than 140 inflammatory cytokines activated and this relates to the disease severity, progression, and the hyperactivation of T cells. In viral diseases, an abnormal pro-inflammatory factor release damages the lung physiology and causes oxygen deprivation. This is primed by the unregulated fabrication of a high risk of inflammatory factors like interleukin members, as well as also increasing the level of CRS and chemokines. Cytokines activate the JAK-STAT and Ras-MAPK pathways and stimulate the CRP value, the clear marker used to show infection in the body. On the other hand, for cytokines, an interleukin member is required for lymphocyte growth and development. Treatments which have been shown to effectively reestablish lymphocyte count in a variety of viral infections have been safely delivered to septic shock patients with lymphocyte abnormalities comparable to those seen in COVID-19. Many therapies have been approved and some are under trial for the effective treatment of viral infections including Tocilizumab and Siltuximab.

Key words: Alpha (α), beta (β), delta (Δ), gemma (γ), COVID-19, CRP (C reactive protein), CRS (Cytokine releasing syndrome), Tocilizumab, Siltuximab

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INTRODUCTION

Coronaviruses are enclosed, single-stranded massive RNA viruses with a positive single-stranded RNA strand in living organisms [1]. Coronaviruses are subdivided into four subfamilies; α, β, δ, and Δ. While α and β coronaviruses are assumed to have originated in mammals like bats, the δ and Δ viruses are primarily found in some mammals and aves specie. The genome size ranges from 26 to 32 kb. Among these subfamilies, more than six coronavirus subtypes are able to infect humans. Beta coronaviruses can potentially cause illness and death, while alpha coronaviruses generate asymptomatic or mildly indicative infections. SARS-CoV-2 is a beta coronavirus of the B lineage that is usually correlated to the SARS-CoV virus [1,2].

The key four viral genomes transcribe diverse N, S, SMP, and M, with HKU1 beta coronaviruses exposing a transitory membrane glycoprotein (HE) [3]. Pneumonia was an early diagnostic sign of the SARS-CoV-2-accompanying infection COVID-19, according to Chan JF and his colleagues. GI symptoms and asymptomatic infections have also been reported in modern investigations, especially in younger nurslings [4]. SARS-CoV-2, like many other viruses, infects the alveolar epithelial cells in the lungs through receptor-mediated endocytosis with the ACE2 serving as an entrance receptor [2].

COVID-19 spreads through a systemic inflammation triggered by immune system hyperactivity in reaction to the virus infection. Lung tissue loss, pulmonary-edema fluid exudation, dyspnea, and pulmonary illness can develop from this persistent inflammation [5]. When compared to healthy lungs, the coronavirus produces a significant decrease in alveolar lacunar space, enhanced immune infiltration, and cell death through apoptosis [6]. COVID-19 decreases the number of lymphocytes in the peripheral blood while elevating the provocative cytokine concentration in the serum. In extreme COVID-19 cases, cytokines, which are most presumably produced by inflammatory monocytes, may be responsible for considerable lung inflammation and pulmonary function deterioration [7].

In the case of COVID-19, these inflammatory cytokine markers help to diagnose the disease progression and sternness [8]. A cytokine storm is an immunological state marked by prompt propagation and the hyperactivation of T cells (white blood cells), macrophages, natural killer cells (NK cells), and increased production of more than 140 inflammatory markers with biochemical mediators secreted by immune and non-immune cells [9,10]. In viral diseases, an abnormal pro-inflammatory factor release damages the lung physiology and the epithelial cell barrier

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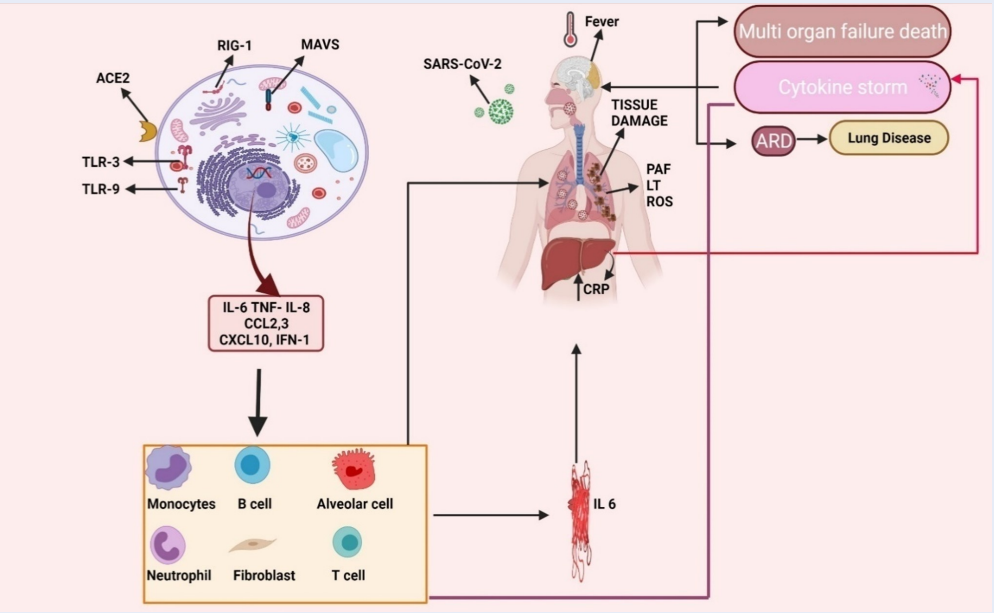

Figure 1: **Pathogenicity of COVID-19 and role of IL-6.SARS-CoV-2 mainly penetrates the nostrils, eye, and mouth when enters the host cell via an add-on to their receptors which induces an inflammatory effect**. ACE2: angiotensin-converting enzyme, LT: leukotriene, ROS: reactive oxygen spices, CRP: c-reactive protein, TNF-α: tumor necrosis factor-alpha, IFN-I: interferon type I, IL-6: interleukin6, IL-6R: interleukin-6 receptor, ARDS: acute respiratory distress syndrome.

of the alveoli resulting in vascular discharges, edema, and oxygen deprivation which leads to the irregulated fabrication of pro-inflammatory factors known as IL-6, 8, 1, GM-CSF, as well as chemokines [11]. In the current study, the role of interleukin members in COVID-19 has been evaluated.

ROLE OF INTERLEUKIN-6 (IL-6)

Multiple roles are served by IL-6 and it was initially discovered as a B-cell developmental factor involved in the maturation of immune response cells. Since then, it has been shown that IL-6 has a diverse variety of potential functions, including effects on T cells, blood vessels, and neurons [12].

During the acute phase of viral infection, there is a systemic amplification of IL-6 and it has pleiotropic protein that is generated and comes back to tissue trauma and microbial infections. Fibroblasts, keratinocytes (skin cells), mesangial cells, vascular endothelial cells, mast cells (also known as mastocytes), macrophages, dendritic cells (nerve cells), and T and B cells (WBCs) are among the cell types that produce cytokine. In COVID-19, this leads to the patient's lungs being destroyed [13–15].

Several studies have found that IL-6 is significant in the immune-pathogenesis of COVID-19, as indicated by the distinguished blood concentration of this cytokine, particularly in extreme situations [16–19]. Huang *et al.* reported higher IL-6 echelons in the case of COVID-19. It interacts through a polypeptide chain called the IL-6 receptor (IL-6R), which subsequently binds to a membrane glycoprotein called gp130 to activate intracellular signaling via the JAK-STAT and Ras-MAPK pathways [18]. In the body, like the central compartment and excretory products such as urine, a soluble derivative of IL-6R (sIL-6 R) is also present. sIL-6 R is generated from a disinterring and metalloprotease17 degradation of IL-6 R [20]. The activation of IL-6 channels promotes the liver cells to generate and secrete an acute and C-reactive protein (CRP) such as serum amyloid A, fibrinogen, and haptoglobin, which is a glycoprotein complex produced in the liver, and 1-antichymotrypsin while diminishing fibronectin, albumin, and transferrin development [21]. COVID-19 is a condition in which IL-6 plays a critical role since it is implicated in the disease etiology and is clinically correlated with prognosis [22]. Particularly, IL-6 has been shown to be a potential biological indicator in a multitude of infections, including pneumonia of various etiologies. It is frequently used in clinical practice and research [21,23,24]. Chen *et al.* reported that an enhanced baseline IL-6 was associated with physiological parameters and the finding of serum SARS-CoV-2 RNAemia which appears

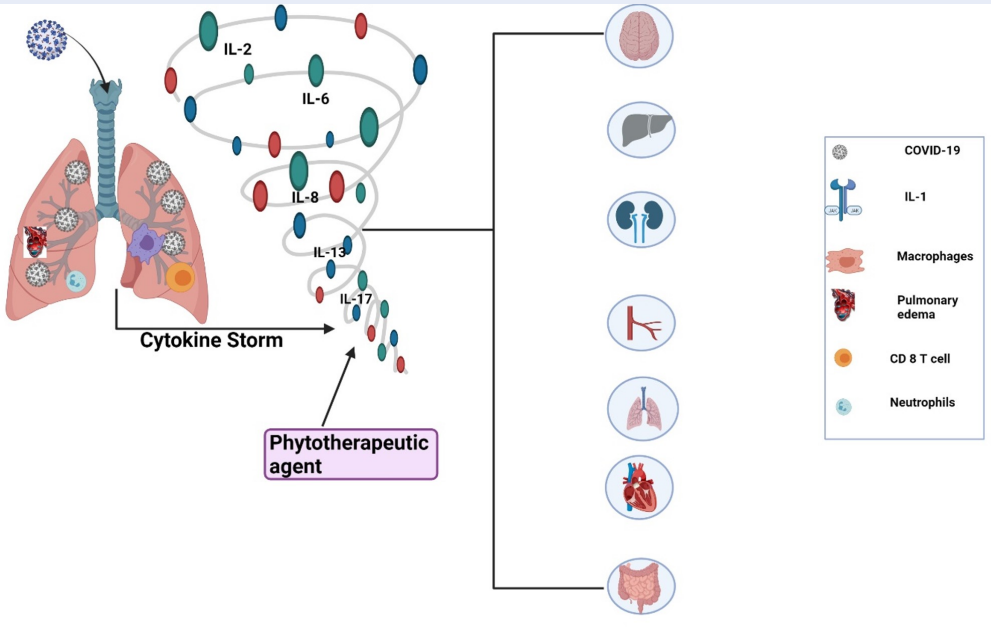

Figure 2: **The spectrum of the destruction of different body organs by cytokine storm (interleukin family) produced during COVID-19.**

to be diagnostic for critical illness. After a comparison of severe patients, it was observed that critically ill patients had about 10-fold higher IL-6 levels and all fatal cases had incredibly high IL-6 levels[25]. The increased starting point of a further provocative surrogate marker, including CRP, lactate dehydrogenase (LDH), ferritin, and D-dimer, as well as chest computed tomography (CT) abnormalities, were also determined to be favorably linked with IL-6. Patients healing from COVID-19 had lower IL-6 levels and improved lung physiology but the IL-6 levels elevated where there was an illness re-exacerbation[26]. Pandolfi et al. stated that in the case of COVID-19, the patients admitted to the ICU had higher IL-6 levels than the other admitted people in poor health[27]. In individuals with SARS-COV-2 infection, IL-6 has a potentially harmful function[28]. Additionally, certain cytokines can induce significant pulmonary destruction by aggregating neutrophils and macrophages in the respiratory tract, resulting in the formation of hyaline membranes and drawn-out concealing of the alveolar barriers, as well as tubule-interstitial destruction[29].

CRS is defined as an abnormal inflammatory reaction with clinical manifestations varying from a flu-like syndrome to an unregulated systemic inflammatory response and multi-organ disturbance, and it is connected with macrophage activation, T lymphocyte modulation, and endothelial cell amplification, as well as increased inflammatory cytokine production. IL-6 is linked to cardiomyopathy, the hastening of complement and coagulation pathways, disseminated intravascular coagulation, and vascular leakage among some of the discharged cytokines. CRS is most common in people who have received various types of immunotherapy or haploidentical allogeneic hematopoietic cell transplantation; nonetheless, COVID-19 patients may develop a CRS-like condition[30,31].

The deadly consequences of COVID-19 may be due to increased cytokine levels. Various putative therapeutics targeting the host immune system, such as inflammatory cytokine inhibition, stem cell therapy, immune cell reduction, postpartum plasma transfusion, and false extracorporeal liver sustenance, may be beneficial in the treatment of COVID-19[32]. The blocking of IL-6 is a potential therapy used for COVID-induced CRS because its level is already reported in COVID-19 cases[33]. As a result, targeting IL-6 for COVID-induced CRS could be beneficial as shown in **Table 1**.

Table 1: Table shows the IL-6 Blockers

Disorders	IL-6 Inhibitors	Results (approved indications)	
Castleman	Tocilizumab	There was upgrading in inflammatory symptoms and a reduction in steroid dose without an increase in adverse events [34]	
	Siltuximab	Development in provocative indicators increases the frequency of adverse events in patients with multicentric Castleman disease [35]	
Systemic juvenile idiopathic arthritis	Tocilizumab	In individuals with active sJIA, there was a greater improvement in signs and symptoms when compared to placebo, as well as with catch-up growth [36]	
Adult-onset Still's disease	Tocilizumab	Improvement in CR in glucocorticoid-resistant AOSD patients without attaining a statistically significant difference compared to placebo; glucocorticoid dose reduction [37]	
Rheumatoid arthritis	Tocilizumab	Recovery in symptoms and signs in active RA patients without such an increase in the incidence of disease [38]. Tocilizumab outperforms methotrexate in terms of reducing marks and indicators in people with active RA [39]	
Cytokine release syndrome	Tocilizumab	CAR T-cell treatments cause CR in CRS [40]	
Takayasu arteritis	Tocilizumab japan	Upgrading in time to deterioration in Tocilizumab group paralleled to placebo [41]	
Giant cell arteritis	Tocilizumab	Patients with a specific analysis or recurrence of large cell arthritis have a stronger CR [42] . When compared to placebo, there was a higher rate of glucocorticoid-free remission during steroid weaning [42]	
Positive results with Non-approval			
RA	Sirukumab	In individuals with active RA, there was an enhancement in warning sign severity, damage in structural progression, and quality of life [43]	
Psoriatic arthritis	Clazakizumab	Compared to placebo, there was an improvement in musculoskeletal symptoms, but not in skin disease [44]	
Systemic sclerosis	Tocilizumab	Tocilizumab reduced required energy capacity decline when compared to placebo; no alteration in skin solidifying decrease [45]	
Severe Viral Infections	Sarilumab	Sarilumab is a monoclonal antibody that targets together IL-6R and mIL-6R and is entirely human [46]	
Summary of Approved therapy for CRS related disease			
Mycophenolate mofetil	MAS and HLH	Hang-up of inosine monophosphate dehydrogenase [47]	Yes
HSC transplantation	Hemophagocytic lymphohistiocytic	Spare by hereditarily normal bone marrow [48]	Yes

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Table 1 continued

Cyclosporine A	Widely used for primary and secondary HLH	Inhibiting NF-AT migration into the nucleus to reduce the function of overactivated T cells [48,49]	Yes
Corticosteroids	Increased levels of cytokines	Additional with inherently regular bone marrow [50]	Yes
Siltuximab	"CRS"	The anti-IL-6 antibody [33]	Yes
Aspirin	Acute lung injury and ARDs	Antiplatelet effect to diminish the polymorphonuclear (PMN) leukocytes conscription [51]	Yes
Anakinra	MAS, sepsis, HIV/AIDS-associatedHLH, andCRS	IL-1 receptor antagonist blockingIL-1α andIL-1β [52]	Yes
Rilonacep	MAS	Counterbalancing of IL-1α and IL-1β [53]	Yes
Tadekinigalfa	NLRC4-associatedMAS	Human IL-18-binding protein recombinant [54]	Yes

Table 2: Level of cytokine profile and COVID-19 Patient

Sr.No	Cytokines	Alteration in COVID-19 Patient	References
1	IL-2	↑ Patients of COVID-19	[18]
2	IL-6	↑ Severity level in COVID-19	[92]
3	IL-7	↑ Values in COVID-19 patients	[18]
4	IL-8	↑with svereity in COVID-19 patient	[18]
5	IL-10	COVID-19 patients have risk to an increase the value	[77,93]
6	IL-13	↑ in COVID-19	[18]
7	PDGF	↑ in COVID-19 Patient	[18]
8	VEGF	↑ in COVID-19	[18]
9	IP10	↑ in COVID-19 patients	[18]
10	TNF-α	↑ in COVID-19 patients	[18]

INTERLEUKIN-7 (IL-7)

Interleukin-7 (IL-7) was discovered more than a decade ago[55]. The human IL-7 gene was detected on chromosome 8q12-13[56]. IL-7 is a cytokine secreted by stromal cells in the lymphoid organs which are essential for T cell growth and survival in the periphery. Exogenous stimulation has little effect on IL-7 secretion by the stromal cells, unlike most other cytokines that act on lymphocytes[57]. This pleiotropic or multiple effected interleukin-7 (IL-7) is required for lymphocytic growth and its survival[58]. Rich and Leder reported that the level of T cells increases as the IL-7 level increases[59,60].

COVID-19 is recognized as a consecutive lymphocyte destroyer since substantial long-term lymphopenia is a close universal observation in individuals with severe COVID-19, and it is linked to increased morbidity and mortality[58]. Putative cytokine interleukin 7 (IL-7) is required for the growth and development of lymphocytic cells[61,62]. Interleukin-7 (IL-7) treatments, which have been shown to effectively reestablish lymphocyte count in a variety of viral infections, has been safely delivered in septic shock patients with lymphocyte abnormalities comparable to those seen in COVID-19[63]. Francois et al. saw that IL-7 can be safely administered to critically ill COVID-19 patients without inducing inflammation or pulmonary harm, and it is the marker of immunosuppression that should be severely considered when using IL-7 alone or in combination with other treatments[58]. In addition, the plasma expression levels of IL-2, 7, and 10, granulocyte colony-stimulating factor (GCSF), IP-10, MCP-1, macrophage inflammatory protein-1a (MIP-1A), and tumor necrosis factor (TNF-alpha) are increased in critical care patients with significant illnesses compared to non-ICU patients[43].

INTERLEUKIN-8 (IL-8)

IL-8 concentration was found to be more accurate in the diagnosis of the progression of COVID-19 disease from acute to chronic than IL-7. Both mild and severe COVID-19 patients had elevated IL-8 plasma levels which increased as the disease progressed. IL-8 could therefore be cast as a biomarker for COVID-19 patients in various stages of the disease. Lili *et al.* reported that the IL-8 levels in the blood were much greater in these people which makes it an excellent indicator of the COVID-19 sickness prognosis[64]. IL-8 is a pro-inflammatory mediator that has been implicated in tissue damage and can drive neutrophils to infected areas[64]. It has been documented in the topical investigation of SARS-CoV-2 infection which could enlighten the lesser manifestation of IL-8. This is crucial for chemo-attraction and neutrophil viability[65]. IL-8 is a proinflammatory cytokine generated by blood cells and a variety of organs, and increased concentrations of IL-8 in the blood have been linked to a variety of disorders[66]. The link between IL-8 and disease duration could point to a function of IL-8 signaling in COVID-19 evolution. According to new research, the onset of polymorphonuclear-myeloid-derived suppressor cells (PMN-MDSC) curtails SARS-CoV-2 specific to the T-cell responses, and the presence of PMN-MDSC at the beginning of treatment is linked to a fatal outcome in COVID-19 patients with a higher intensity of PMN-MDSC in the patients among the non-survivor group compared with the survivor group[67].

INTERLEUKIN 10 (IL-10)

A type II cytokine is interleukin-10 (IL-10). The intron–exon genomic arrangement is analogous to that of other types of cytokines, and they fix to receptors with identical buildings in certain cases. The origin of the IL-10 gene in human chromosome 1q21–32 is made up of more than four axons divided by four introns[68]. T-helper type 2 (Th2) cells are a subgroup of regulatory white blood cell T cells called Tr1, Th1, and Th17 cells. These cells are the four key T-cell carriers of IL-10[69]. Other types of white blood cell such as human B cells and some granulocytes such as eosinophils and mast cells are possible sources of IL-10. Non-immune cell producers of IL-10 are epithelial cells, tumor cells, and keratinocytes[70–73].

In severe critically ill patients of COVID-19, the value of interleukin-10 is dramatically increased[74]. The tendency of SARS-CoV-2 infection to trigger IL-10 transcription in SARS-CoV. However, the significance of IL-10 as a potential immunological indicator when assessing the complexity of COVID-19 disease has been discovered[75,76]. Long thought to be an anti-inflammatory or immunological inhibitory mechanism generated by a vicious cycle of proinflammatory cytokines, the presence of IL-10 in COVID-19 patients means that the serum has been suspected[76,77]. Furthermore, certain researchers have advocated that recombinant IL-10 should be used as an ARDS therapy in COVID-19 patients because of its immunoregulatory and antifibrotic properties[78].

In COVID-19 patients, there is the involvement of various pro-inflammatory intermediaries and vital organ demolition[79]. The rate of mortality could be reduced by targeting IL-10. COVID-19 individuals with severe/critical illness have drastically high serum IL-10 concentrations which correspond with

disease severity[74]. In some critically ill individuals, IL-10 may worsen the viral sepsis-related hyperinflammation. COVID-19 infected patients[80].

IL-10 is mostly considered part of the down-regulation of the adaptive T cell response in the beginning[81,82]. Xiaoling *et al.* reported that the inhibition of IL-10 signaling in COVID-19 results in extreme lung inflammation, passiveness, or constructive antiviral immunity[83].

INTERLEUKIN-11

Interleukin-11 is a cytokine released by osteoblasts, fibroblasts, chondrocytes, trophoblasts, and a variety of other signaling pathways in culture[84]. IL-11 is easily noticeable during virally generated inflammation[85]. IL-11 expression can be produced by disease stimuli, implying that it can be induced by pathological stimuli as well[84].

The more restricted expression pattern of the matching receptor subunits determines IL-11. IL-11R1 is produced in low levels in the central nervous system, respiratory system, thymus, spleen, cardiovascular system, bladder, kidney, muscle, small and large gut, salivary glands, bone marrow, gonads, and uterus among the two transmembrane IL-11R sub-types[84]. IL-11 controls blood disease and bone metabolism and prevents pro-inflammatory cytokine generation[86]. It's worth noting that during the early stages of SRAS-CoV infection, thrombocytopenia and lymphopenia are frequently detected in COVID-19 patients[86].

INTERLEUKIN-13

Giancarlo et al. reported that IL-13 is involved in several activities such as (i) eosinophil, M2 macrophage mobilization to the lungs, (ii) the release of mucus in the air pathway and goblet cell metaplasia, (iii) enhancing the multiplication of smooth muscles, and (iv) the undergoing of fibrosis through fibroblast activation and subsequent collagen deposition[87]. Donlan *et al.* reported that IL-13 functions as a coordinator of pathogenic mechanisms in the lung. In COVID-19 positive individuals, the plasma altitudes of IL-13 were considerably greater than in uninfected patients[88].

Patients with acute to chronic asthma have higher amounts of IL-13 in their bronchoalveolar lavage fluid, as well as a higher gene and protein expression in their bronchial mucosal tissues[89]. IL-13 also promotes the release of periostin, a multicellular protein involved in fibroblast stimulation and collagen gel suppleness[90]. To summarize, while IL-13 plays an important part in the pathobiology of asthma, there may be several redundant processes that limit the therapeutic benefits of focusing just on IL-13[91].

CONCLUSION

In a viral infection, many cytokine mediators are stimulated to increase secretion and to cause a heightened severity and virulence in the body which leads to causing CRS and a high value of CRP. Many therapies are effective against CRS and harm cytokines which help to minimize the viral infection in the body. However, due to the notorious activity and physiology of virus activity, there is a need to engage in more trials and to study effective therapies.

ABBREVIATIONS

ARDS: Acute respiratory distress syndrome
CRP: C-reactive protein
CRS: Cytokine release syndrome
GCSF: Granulocyte colony-stimulating factor
PMN-MDSC: polymorphonuclear- 218 myeloid-derived suppressor cells
TNF-alpha: Tumor necrosis factor-alpha

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All authors significantly contributed to this work, read and approved the final manuscript.

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Not applicable.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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