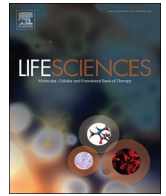ELSEVIER

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Review article

The bio-mission of interleukin-6 in the pathogenesis of COVID-19: A brief look at potential therapeutic tactics

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ABSTRACT

Interleukin-6 (IL-6), known as an inflammatory cytokine, can be involved in many innate and adaptive immune responses. The role of IL-6 in the pathogenesis of the novel coronavirus disease 2019 (COVID-19) has recently received much more attention due to the spread of the virus and its pandemic potential. Cytokine storm is among the most critical pathological events in patients affected with coronaviruses (CoVs), i.e., severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and COVID-19, causing inflammation-induced lung injury and also occurring as a result of dysregulation of immune responses to the mentioned viruses. IL-6, along with some other inflammatory cytokines, including IL-1 beta (β), IL-8, and tumor necrosis factor-alpha (TNF-α), as well as inflammatory chemokines, can significantly contribute to, fever, lymphopenia, coagulation, lung injury, and multi-organ failure (MOF). Therefore, researchers are to explore novel approaches to treat the disease through targeting of IL-6 and its receptors based on prior experience of other disorders. In this review article, the latest findings on the role of IL-6 in the pathogenesis of COVID-19, as well as therapeutic perspectives, were summarized and discussed.

1. Introduction

COVID-19 was first detected in the city of Wuhan, China, in December 2019, and the world health organization (WHO) declared a public health emergency following the spread of the virus and the possibility of a pandemic worldwide [1]. This virus was first transmitted to humans through infected animals (i.e., bats and pangolins) and then spread around the world; however, there are still many ambiguities in this regard [2]. The transmission rate of COVID-19 is reportedly very high, and each infected person can affect an average of 3.8 individuals. Mortality rates in patients with COVID-19 have also been very variable and influenced by a variety of factors such as age and the presence of underlying diseases [3].

The other two members of the coronavirus (CoV) family are SARS-CoV and MERS-CoV that can similarly cause respiratory disorders in humans in the same way as SARS-CoV-2 [4]. Moreover, SARS-CoV and SARS-CoV-2 can infect their target cells via ligation to angiotensin-converting enzyme 2 (ACE2) as the entry receptor [5]. However, more recent studies have indicated that basigin (Bsg), also called cluster of differentiation 147 (CD147) or EMMPRIN, dendritic cell (DC)-specific intercellular adhesion molecule 3 (ICAM-3)-grabbing nonintegrin (DC-SIGN, known as CD209), and CD209L (also labeled L-SIGN) can act as receptors for SARS-CoV-2 [6–8]. It should be noted that ACE2 in the human lung is highly expressed on the surface of alveolar type II epithelial cells (ECs), and it can be considered as an appropriate host for SARS-CoV-2 [9]. Besides, other types of cells, such as immune cells, including macrophages and monocytes, can express ACE2 (less than alveolar type II ECs), and as a result, they can be attacked by SARS-CoV-2 [10]. However, there is no accurate information on how other immune cells, such as T-cells, a type of lymphocytes, and DCs, are infected. Following SARS-CoV-2 infection, dysregulated inflammatory responses, infiltration of neutrophils, monocytes, and macrophages, as well as uncontrolled release of inflammatory cytokines and chemokines are taken into account as critical factors in the development of severe pneumonia, acute respiratory distress syndrome (ARDS), or MOF [11–14]. Several studies have correspondingly demonstrated a significant increase in IL-6 serum levels in patients suffering from COVID-19 [15–17]. This cytokine as an inflammatory mediator also plays an

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essential role in innate and adaptive immune responses; though, it can also have protective and anti-inflammatory properties in some pathologic states [18–20]. Furthermore, regarding the findings of recent studies, IL-6 and its receptors could be high potential diagnostic and therapeutic targets in COVID-19 patients [21]. Hence, in this review article, the latest findings on the role of IL-6 in the pathogenesis of COVID-19, as well as therapeutic perspectives, were summarized and discussed.

2. IL-6/IL-6 receptor axis, bio-structure, and signaling

To date, almost ten members of the IL-6 family have been identified including IL-6, IL-11, IL-27, IL-31, cardiotropin-1 (CT-1), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-like cytokine factor 1 (CLCF1), ciliary neurotrophic factor (CNTF), and neuropoietin (NP) [22]. The IL-6 gene is located on chromosome 7 in humans [23]. This small single-chain phosphorylated glycoprotein consists of mainly four-helix bundles, including A, B, C, and D in which A and B helices run in one direction while C and D cases run on the opposite direction [24]. There is another helix between C and D, namely E helix, located outside the A, B, C, and D bundle. Signals of IL-6 also transmit via a signal-transducing component (i.e., glycoprotein 130, also known as gp130), which is a part of the IL-6 receptor (IL-6R) (CD126, 80 kDa). Moreover, IL-6R is made up of three domains (that is, D1, D2, and D3). The D1 or immunoglobulin (Ig) domain is connected to D2 and D3 as cytokine binding domains (CBDs). The N-terminal of gp130 also consists of 6 domains (i.e., D1-D6). Besides, soluble IL-6R (sIL-6R) and membrane-bound IL-6R (mIL-6R) are two identified forms of IL-6R. As well, neutrophils, T-cells, monocytes, and hepatocytes express mIL-6R, whereas sIL-6R is produced following proteolytic cleavage of mIL-6R via a disintegrin as well as metallopeptidase domain 10 (ADAM10) and ADAM17. Additionally, alternative splicing of IL-6R messenger ribonucleic acid (mRNA) can produce sIL-6R [25], which is capable of transporting IL-6 to different parts of the body. Furthermore, a hexameric complex comprised of two IL-6/sIL-6R/gp130 heterodimers is responsible for physiological and pathological functions [24].

Both mIL-6R and sIL-6R can also transmit IL-6 signals via classical and trans-signaling pathways, respectively. Different biological consequences can even occur following ligation of IL-6 to the CBD domains of these types of receptors as well as gp130 based on the location of gp130 [26]. Moreover, leukocytes and hepatocytes can express both the mIL-6Rα and gp130 that initiate anti-inflammatory responses through the classical signaling pathway, while pro-inflammatory responses are started in all cells to express gp130 via the trans-signaling pathway [27]. Three possible signaling pathways are thus initiated due to the activation of Janus kinase (JAK) with the hexameric complex (i.e., two IL-6/IL-6R/gp130 heterodimers) including signal transducer and transcription-3 (STAT3), mitogen-activated protein kinases (MAPK), and phosphoinositol-3 kinase (PI3K), protein kinase B (PKB also known as Akt) pathways as well as nuclear factor-κB (NF-κB) [24]. In the PI3K pathway, PKB can also stimulate the mammalian target of rapamycin (mTOR), resulting in the activation of STAT3 [28]. Moreover, evidence has revealed that stimulation of PKB/Akt, MAPK, STAT3, and NF-κB prompts a wide range of inflammatory responses and pathological states in different disorders such as severe pneumonia and ARDS [29,30] (Fig. 1). Accordingly, IL-6 can act as a double-edged sword in different conditions, depending on the activated signaling pathway.

3. Bio-functions of IL-6 in immune system

IL-6 is known as a pleiotropic cytokine produced and secreted by a wide range of immune and non-immune cells such as DCs, mast cells, monocytes, macrophages, keratinocytes, mesangial cells, fibroblasts, vascular endothelial cells (ECs), as well as T and B lymphocytes following infections or tissue damage [31,32]. Evidence in this field has

established that IL-6 participates in critical cellular events such as cell proliferation, differentiation, survival, and trafficking. In this context, IL-6 acts as a double-edged sword, affecting the activation and regulation of both inflammatory and anti-inflammatory responses [33]. The biological effects of IL-6 on other cells, as well as immune responses, can be accordingly divided into two main categories: effects on innate and adaptive immunity. Concerning innate immunity, IL-6 stimulates the production of antimicrobial peptides (AMPs) and also acute phase proteins (APPs) [34,35]. For instance, IL-6 stimulates the production of c-reactive protein (CRP) in the liver through activating JAKs [36]. IL-6 can similarly enhance monocyte differentiation into macrophages via stimulating colony-stimulating factor 1 (CSF1) production [37]. Moreover, it can modulate the maturation of DCs by activating the STAT3 signaling pathway in a negative manner [38]. Once pathogens enter the body, their pathogen-associated molecular pattern molecules (PAMPs) are also detected through innate immune receptors. These cellular sensors are called pattern recognition receptors (PRRs) including nucleotide-binding oligomerization domain-like receptors (NLRs), toll-like receptors (TLR1 to TLR13), DNA sensors (absent in melanoma two also known as AIM-2 and cyclic guanosine monophosphate–adenosine monophosphate (GMP-AMP) synthase label led as cGAS), and RNA sensors (i.e. retinoic acid-inducible gene I (RIG-I) and melanoma differentiation associated gene 5 (MDA-5)) [39,40]. In viral infections, these different immune cellular pathogen recognition receptors are also able to detect and to bind to different viral PAMPs and activate transcription factor of IL-6 and other inflammatory cytokines increasing production of these cytokines [41]. In adaptive immunity, IL-6 has a wide range of activities. For example, in humoral immunity, it can augment production of IgG through regulating IL-21 expression [42]. Moreover, IL-6 plays a critical role in differentiating naive T CD4$^+$ lymphocytes. This cytokine also stimulates the production of IL-4 by T CD4$^+$ and inhibits T helper type 1 (Th1) differentiation, which can lead to Th2 stimulation. Another mechanism leading to Th2 differentiation is inhibition of interferon-gamma (IFN-γ) production by T CD4$^+$, identified as an essential cytokine in Th1 differentiation [43,44]. On the other hand, IL-6 and tumor growth factor-beta (TGF-β) can together differentiate naive T CD4$^+$ into Th17 cells to produce IL-17 in different pathological states [45]. Additionally, CD8$^+$ T-cells (namely, cytotoxic T lymphocytes or CTLs), playing a significant role in anti-tumor and anti-viral defense, can be stimulated and activated by the synergistic effect of IL-6, IL-7, and IL-15 [46]. Another essential function of IL-6 is to be involved in trafficking of leukocytes, especially neutrophils, which is most commonly seen in infections [47]. In some cases, this cytokine, along with other inflammatory cytokines, is able to trigger a cytokine storm and lead to tissue damage that occurs through dysregulation of immune responses and mechanisms [48]. One other adverse function of IL-6 disrupting the effective immune response in viral infections as well as cancers is increased expression of inhibitory molecules such as programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PDL-1) [49]. In the case of viral infections, elevated levels of IL-6 in patients have been thus positively correlated with increased replication of the virus, and persistence of the viral infection [50].

4. Biology of IL-6 in anti-viral immunity

Previous studies showed that during a viral infection, IL-6 overexpressed, and it can have potentially adverse effects on the immune responses against the virus. Evidence suggests that an imbalance in the IL-6 production can affect three main subjects in viral infection: first, virus clearance, second, virus persistence and spread, and finally, chronic viral infection. IL-6 can also stimulate the differentiation of Th0 cells to Th2 by activating the STAT3 signaling pathway, and ultimately production of the Th2 cytokines such as IL-4 and IL-13 as well as the suppressor of cytokine signaling one protein (SOCS-1). The SOCS-1, as
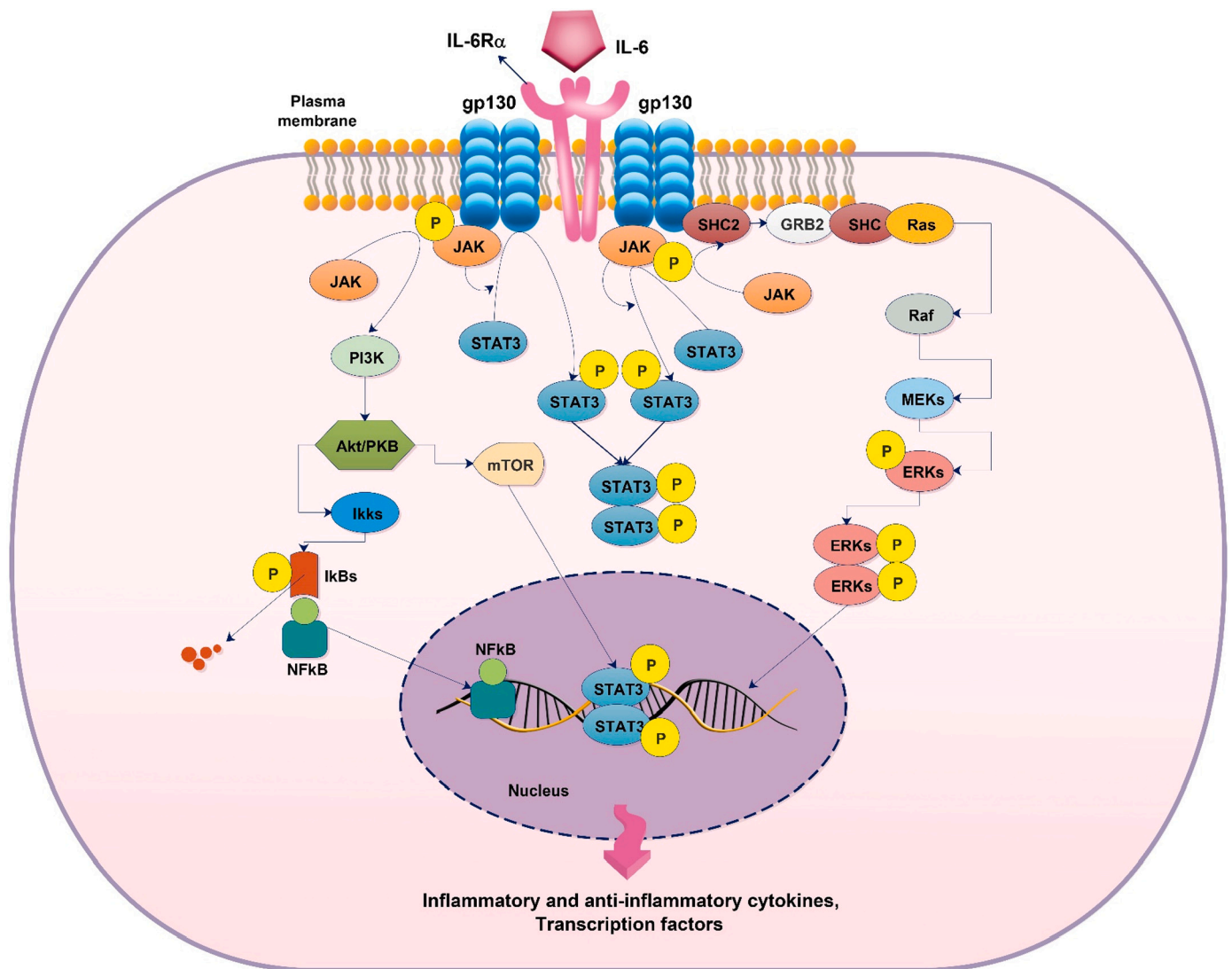
Fig. 1. IL-6 signaling pathways. Three possible signaling pathways are initiated following the activation of JAK with the hexameric complex (i.e., two IL-6/IL-6R/gp130 heterodimers), including STAT3, MAPK, and PI3K, PKB pathways as well as NF-κB. Stimulation of PKB/Akt, MAPK, STAT3, and NF-κB prompt expression of a wide range of inflammatory and anti-inflammatory cytokines as well as transcription factors.
JAK; Janus kinase, STAT3; signal transducer and transcription-3, MAPK; mitogen-activated protein kinases, PI3K; phosphoinositol-3 kinase, PKB; protein kinase B (also known as Akt), NF-κB nuclear factor-κB, P; phosphor, Ikk; IκB kinase, mTOR; mammalian target of rapamycin, GRB2; growth factor receptor-bound protein 2.

an inhibitory molecule through its impacts on STAT1 phosphorylation, is capable of impairing the production of IFN-γ and IL-2, resulting in decline levels of these cytokines by Th1 cells [51]. On the other hand, increased IL-6 and eventually SOCS-1 by interfering with the phosphorylation of STAT4 have an inhibitory effect on the IFN-II and IFN-γ production. Mentioned IFNs are involved in infected cells cytolysis via stimulation and activation of killer cells, including NK and T CD8^{+} cells. One of the main mechanisms in the removal of virally infected cells is the progression of the apoptotic pathways and their associated molecules by pro-apoptotic molecules such as granzyme B, which is produced and secreted by killer cells [52]. According to the described mechanism, the survival of infected cells could be affected by IL-6 because this multifunction cytokine can induce anti-apoptotic molecules expression via stimulation of Th17 differentiation and IL-17 production [52]. Another mechanism for developing the virus is the IL-6 and IFN-I collaboration. These cytokines increase the survival of the infected cell through an elevation of inhibitory molecules expression such as PD-L1 (CD274) on the surface of the infected cell. Ligation of PDL-1 with PD-1 (CD279) on T CD8+ cells prevents apoptosis induced by these cells [52,53].

5. Role of IL-6 in COVID-19 pathogenesis

IL-6 can be involved in modulating many host immune responses. Studies have also shown that IL-6, along with TNF-α and IL-1β, can affect many components and immune responses in viral infections, particularly the role of IL-6 in patients with COVID19 [53,54]. The contradictory roles of IL-6 in viral infections can be confusing, especially in selecting possible therapeutic targets. Experimental studies have accordingly demonstrated that anti-viral immune responses become ineffective, and infection worsens following IL-6 knock-down. The findings of the mentioned studies also revealed that IL-6 could be critical for the survival of IL-6-deficient mice and virus clearance through participating in the modulation of T and B lymphocyte-associated responses, quenching inflammation, stimulating lung tissue repair, macrophage infiltration, and phagocytosis, inhibiting apoptosis of virus-infected lung ECs, as well as regulating antibody class switching [55,56].

On the other hand, increased expression of IL-6 in some viral infections, such as COVID-19, causes multiple damages to the lung tissue and leads to infection progression. Studies on patients infected with

CoV (that is, SARS-CoV, MERS-CoV, and SARS-CoV-2) have shown that lymphopenia and cytokine storms are two significant immunopathologic findings in these patients [57–59]. Cytokine storms also occur due to impaired expression and production of inflammatory cytokines such as IL-1β, IL-4, IL-6, IL-10, IL-18 IL-33, IFN-γ, and TNF-a that can result in increased and uncontrolled inflammation and sometimes damage various tissues and organs [60–62]. This devastating immune phenomenon is typically observed in disorders such as viral infections, bacterial septic shock, ARDS, drug toxicity, autoimmune diseases, and also following chimeric antigen receptor T (CAR-T) cell therapy [63–65]. Cytokine storms, along with infiltrating immune cells (IICs) such as neutrophils and monocytes, particularly in viral respiratory infections such as influenza, SARS, and COVID-19, can additionally induce inflammation-induced lung injury. In infected cases with SARS-CoV-2, a cytokine storm can also cause MOF and ultimately lead to death. Therefore, understanding the precise role of inflammatory cytokines such as IL-6 is crucial in the immunopathogenesis of COVID-19. Produced IL-6 and macrophage colony-stimulating factor (GM-CSF) in COVID-19 by activated effector T-cells also activate inflammatory monocytes and then produce and secrete IL-6 in a positive loop [66]. In one study, impressive results had revealed that serum levels of IL-6, CRP, ferritin, and lactate dehydrogenase (LDH) had declined after treatment of patients with COVID-19 even though only IL-6 serum levels had increased significantly following the progress of the disease, which could be associated with a large number of pulmonary lesions in the findings of the computed tomography (CT) scan of the chest. Among the patients in this study, only one case had lower IL-6 serum levels following a rise in disease severity that was due to pulmonary injury caused by a bacterial infection. According to the findings of this study, IL-6 could be considered as a potential and specific biomarker in the diagnosis and monitoring of COVID-19 [54]. Immune and non-immune cells in the lung tissue such as resident alveolar macrophages, T lymphocytes, alveolar type II ECs, and lung fibroblasts are also able to produce IL-6 [67]. Following infection of alveolar type II ECs that can express ACE2 receptors with SARS-CoV-2, intracellular RNA sensors including TLR3, TLR7, RIG-I, and MDA-5 can recognize viral RNA and downstream signaling pathways initiated, leading to activation of interferon regulatory factor 3 (IRF-3) and NF-κB and eventually production of type I interferons, as well as inflammatory cytokines and chemokines which are in charge of the creation of cytokine storms and MOF [68].

Furthermore, the production of IL-8 (i.e., C-X-C motif chemokine ligand 8 (CXCL8)) and IL-6 by alveolar type II ECs and macrophages can recruit neutrophils to the lung alveoli. Subsequently, IL-6-mediated neutrophil activation can disrupt epithelial fluid transportation and surfactant production of alveolar type II ECs through producing platelet-activating factor (PAF), leukotrienes, reactive oxygen species (ROS), as well as other proteases [69].

5.1. Role of IL-6 in tissue damage

Recent studies show a positive and significant correlation between serum viral load and IL-6 levels in patients with severe COVID-19, and this viral load is associated with ARDS severity and lung tissue damage [70]. All evidence suggests a possible destructive role for IL-6 in patients with SARS-COV-2 infection [71]. Shock and organ failure in several organs, such as the kidneys, heart, lungs, and liver, are severely damaged by cytokine storms caused by an increase in inflammatory cytokines, including IL-6, IL-1β, TNF-α, IL-8, IL-2, IL-17, G-CSF, GM-CSF, CXCL10, CCL2, CCL3 in patients with COVID-19 [14]. These cytokines can also cause extensive pulmonary damage through the accumulation of neutrophils and macrophages in lung tissue, leading to the development of hyaline membranes and diffuse thickening of the alveolar barrier and ultimately diffuse alveolar damage [72]. Lymph node necrosis and spleen atrophy have also been reported in COVID-19 patients, which is discussed in the next section [73].

5.2. IL-6 and lymphopenia

One of the most important and reliable indicators in the diagnosis of patients with COVID-19 is a lymphopenia, which is characterized by a significant reduction in B and T lymphocytes, and this lymphopenia is directly related to the severity of the disease and the hospitalization of patients. Many factors and mechanisms could be involved in the development of lymphopenia, but in patients with COVID-19, damage to the spleen and lymph nodes, as well as an increase in inflammatory cytokines such as IL-6, appear to cause apoptosis of lymphocytes and a decrease in their number [74,75]. Another role of IL-6 in the occurrence of leukopenia and weakening the immune system is to reduce the number of major histocompatibility complex (MHC) class II (MHC-II) molecules on the surface of monocytes resulting in monocyte hyperactivation, uncontrolled production of IL-6, and lymphopenia [76]. It has been shown that IL-6 is able to decrease HLA-DR expression on the $CD14^+$ monocytes, and its circulatory level is inversely related to the expression of HLA-DR [76]. On the other hand, a study reported that the addition of anti-IL-6R monoclonal antibody (Tocilizumab) in the plasma-enriched medium of cells partially improved the expression of HLA-DR on the surface of monocytes and total lymphocyte counts of six COVID-19 patients elevated following treatment with Tocilizumab [77].

Besides, $CD68^+CD169^+$ macrophages that express ACE2 have been detected in the marginal zone of the spleen as well as in lymph nodes marginal sinuses. Inside these types of macrophages, the nucleoprotein antigen of SARS-COV-2 is found. Additionally, these macrophages can produce excessive IL-6 concentrations. Infected tissues with SARS-COV-2 also express FAS molecule, and it seems that mentioned macrophages can be involved in viral extension, uncontrolled inflammation and initiation of lymphocytes death in patients with COVID-19 [73].

5.3. IL-6 and coagulation

Based on the evidence, it appears that the link between inflammation and coagulation is not limited to vascular thrombotic disorders but can also occur in disorders such as vascular thrombotic disease as well as a wide range of severe infections leading to multiple organ failure and even death.

Pro-inflammatory cytokines considered as the leading players in inflammation-induced activation of coagulation. It has been shown that IL-1 and TNF-α have anti-coagulant properties, while IL-6 can stimulate coagulation cascades following inflammatory responses via interfering in the generation of tissue factor and, finally, thrombin production [78–80]. Thrombin participates in different mechanisms, including clot formation and enhances inflammation via proteinase-activated receptor-1 (PAR-1). Physiological anti-coagulants such as tissue factor pathway inhibitor, antithrombin III, and the protein C system are responsible for the regulation of thrombin production and all these regulators impaired following a hyper-inflammation condition. An imbalance between pro-coagulant molecules and anti-coagulant molecules leads to micro thrombosis, diffused intravascular coagulation, and eventually multi-organ dysfunction in patients with severe SARS-COV-2 infection [17,81].

Given the mentioned observations, it is clear that IL-6 plays an essential role in viral respiratory diseases such as CoVs or influenza and can be considered as a potential diagnostic biomarker and a suitable therapeutic target for the treatment of these types of viral infections (Fig. 2).

6. Potential therapeutic tactics for COVID-19

Regarding the best of authors' knowledge of COVID-19 and pathological functions of IL-6 in this disease, as well as lack of vaccines or drugs to prevent and treat this condition, it seems necessary to find a solution for drug design. Therefore, the available and used IL-6/IL-6R-
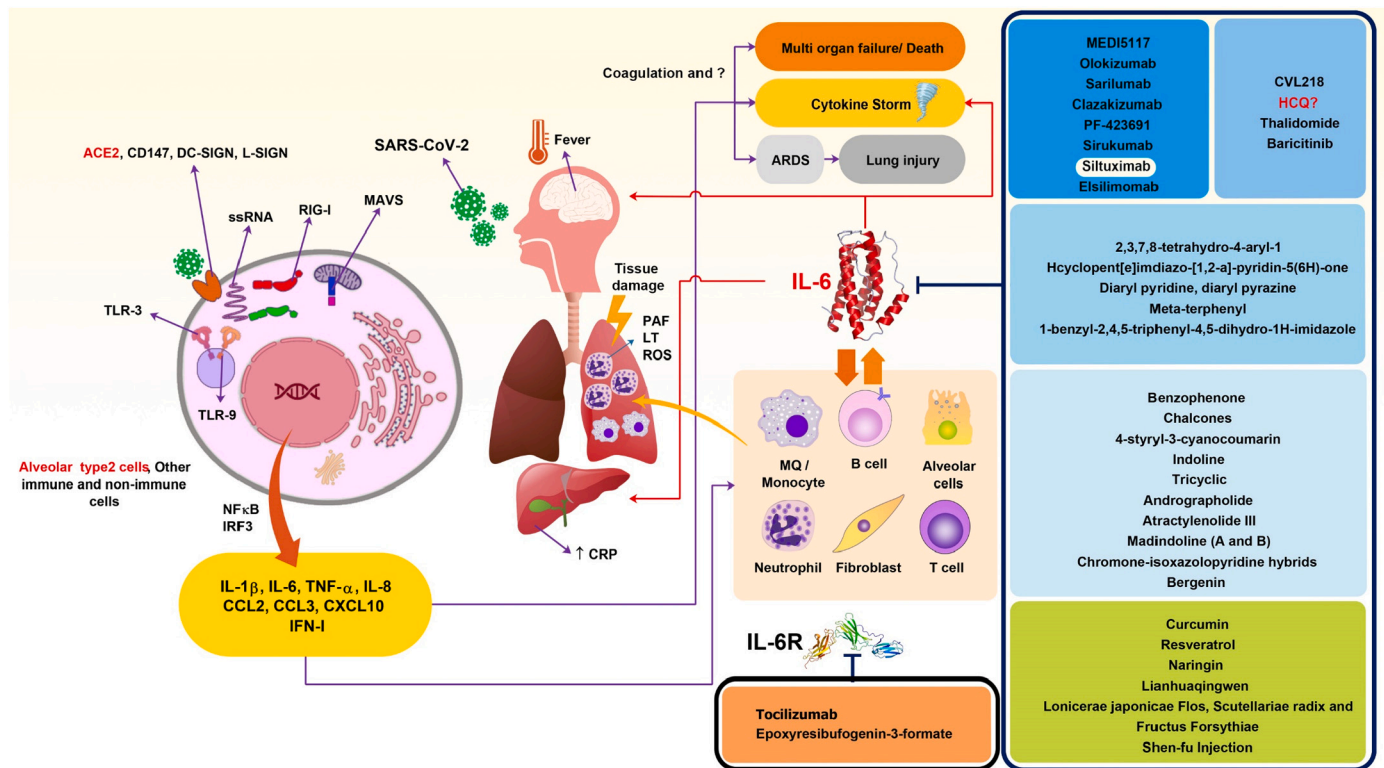
Fig. 2. Role of IL-6 in the pathogenesis of COVID-19 and possible therapeutic approaches. SARS-CoV-2 enters the human body mainly through the nose, eyes, and mouth, it enters the host cell (mainly alveolar type 2 cells) through attachment to its receptors (ACE2, CD147, DC-SIGN, L-SIGN) and stimulates inflammatory and antiviral responses through the production and secretion of cytokines and inflammatory cytokines such as IL-6. Sometimes dysregulated inflammatory responses can cause a cytokine storm, ARDS, and multi-organ failure or even death. On the other hand, it may be possible to use IL-6/IL-6R inhibitors in the treatment of patients with COVID-19.

SARS-CoV-2; severe acute respiratory syndrome coronavirus 2, ss RNA; single strain RNA, ACE2; angiotensin-converting enzyme 2, DC-SIGN; dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, TLR; toll-like receptor, RIG-I; retinoic acid-inducible gene-I, MAVS; mitochondrial anti-viral-signaling protein, MDA-5; melanoma differentiation-associated protein 5, NFκB; nuclear factor kappa-light-chain-enhancer of activated B cells, PAF; platelet-activating factor, LT; leukotriene, ROS; reactive oxygen spices, CRP; c-reactive protein, MQ; macrophage, TNF-α; tumor necrosis factor-alpha, IFN-I; interferon type I, IL-6; interleukin-6, IL-6R; interleukin-6 receptor ARDS; acute respiratory distress syndrome.

related drugs in other diseases were addressed in this review article. These medications may help treat patients with COVID-19 in the future. In this respect, IL-6, as the main cytokine that has been shown to increase in almost all patients affected with COVID-19, could be a potential and exciting target for researchers. However, this cytokine has been studied in several other inflammatory diseases such as rheumatoid arthritis (RA) and Crohn's disease (CD), and also different types of medications related to IL-6/IL-6R are currently used in clinical settings (Fig. 2).

6.1. Anti-IL-6/IL-6R monoclonal antibodies (mAbs)

Studies performed in different phases of clinical trials have reported that anti-IL-6 mAbs such as MEDI5117, Olokizumab, Sarilumab, Clazakizumab, PF-423691, Sirukumab, Siltuximab, and Elsilimomab could be useful in various inflammatory disorders [24]. However, all these mAbs have not been thus far tested in patients with COVID-19.

6.1.1. Tocilizumab

A humanized anti-IL-6 receptor mAb or Tocilizumab has been approved by the Food and Drug Administration (FDA) for the treatment of systemic juvenile idiopathic arthritis (SJIA) and RA [82]. In this line, several studies on patients affected with COVID-19 had revealed that Tocilizumab could effectively improve clinical symptoms and also prevent disease development [83–87]. Therefore, the use of Tocilizumab in COVID-19 treatment can be beneficial and more studies will probably be done on this mAb soon. However, in several case reports,

contradictory findings have been obtained as a result of Tocilizumab prescribing, some of which are mentioned in this section.

As mentioned before, Tocilizumab in patients with severe COVID-19 was related to a considerable reduction of inflammatory mediators, satisfactory alterations of CT findings, and condensed ventilatory care supplies [88,89]. Tocilizumab clinical outcomes have an optimistic effect if used in the primary phase of SARS-COV2-dependent pneumonia, along with severe respiratory syndrome [90]. The hyper-inflammatory state caused by COVID-19 may be improved by the pro-inflammatory condition of sickle cell disease and severe acute coronary syndrome. In these patients, Tocilizumab appears to be effective and safe in children as well as in adults. It has been reported that blood exchange transfusion and non-invasive ventilation as the routine treatments of the severe acute coronary syndrome could be used safe and effective [91]. Also, in mechanically ventilated SARS-CoV-2 infected patients, Tocilizumab was accompanying a decline of death despite higher super-infection incidence [92]. An interesting study on a case of multiple myeloma with SARS-CoV-2 infection showed that the patient underwent significant clinical recovery after Tocilizumab therapy. However, this finding required randomized controlled trials to confirm its findings and to evaluate the safety and effectiveness of Tocilizumab [93]. Tocilizumab therapy in an immunocompromised patient with COVID-19 and a related hemophagocytic syndrome showed that cytokine storm and multi-organ dysfunction quickly reversed, and on hospital day 30, the patient was breathing spontaneously, with protective tracheotomy [94].

Various reports indicate that, in some cases, treatment with

Tocilizumab has been problematic. Evidence showed that in patients with diabetes and non-diabetic ones, hyperglycemia could interfere with Tocilizumab therapy, and optimal management of SARS-CoV-2 infection is not achieved during this pathologic state. As a result, it could be of interest to researchers and clinicians to achieve more effective outcomes by controlling hyperglycemia following Tocilizumab therapy of patients with COVID-19 [95]. Another study reported that subsequently, Tocilizumab therapy, serum triglycine levels increased significantly peaked on day 16 (1436 mg/dL) through interfering with related metabolic pathways [96]. Although such observations in two enrolled cases cannot be generalized to all patients, the clinicians should monitor the patient for hypertriglyceridemia Tocilizumab therapy. In an investigation, two cases with COVID-19 undertreatment with Tocilizumab, it was observed that both patients progressed to secondary hemophagocytic lymphohistiocytosis (HLH) despite Tocilizumab therapy, and one patient also contracted viral myocarditis.

Regarding the clinical outcomes in these patients, Tocilizumab safety and its clinical practicality should be more considered and be used with caution in patients with COVID-19 [97]. The risk of intestinal perforation is another problem of patients with severe COVID-19, which is undertreatment with Tocilizumab. Since Tocilizumab reduces the acute phase response, intestinal perforation may not necessarily cause a remarkable rise of CRP and may primarily go unobserved in sedated and ventilated patients [98]. Recently, an investigation on patients with COVID-19 revealed that serum level of IL-6 increased initially and then reduced following Tocilizumab therapy, while in some patients, a persistent rise of IL-6 was detected, and treatment was failed. The results of this study suggest that Tocilizumab therapy may be valid only in COVID-19 patients with cytokine storms and in critically ill patients with higher levels of IL-6 in a dose and time-dependent manner [99].

Taken together, it seems that Tocilizumab therapy should be used only when the lung lesions progression confirmed by radiological and clinical manifestations. Furthermore, deciding on the timing and dose of Tocilizumab administration is also critical in increasing treatment success rate [100].

6.1.2. Siltuximab

Siltuximab, as a high affinity human/murine chimeric mAb, can bind to sIL-6 and create a stable complex. Siltuximab avoids the binding of IL-6 to both membrane and soluble forms of IL-6 receptors and is used for the treatment of adult patients with multicentric Castleman's disease, which is accompanied by dysregulated production of IL-6.

Besides, Siltuximab could provide a potential therapeutic approach in the treatment of patients with severe COVID-19 and elevated IL-6 levels. In these patients, an 11 mg/kg intravenous infusion administered every three weeks was recommended to IL-6 reduction. However, the researchers found that the effectiveness of a single dose was more significant due to the severity of SARS infection as well as the half-life of Siltuximab. It also suggested that before Siltuximab administration, it is essential to approve that total neutrophil and platelet count be higher than 1×10^9 cell/L and 75×10^9/L, respectively [101]. Another study also demonstrated that Siltuximab had a significant role in the treatment of COVID-19 patients with ARDS [102].

Regarding the presented data, inhibition of IL-6/IL-6R with Siltuximab and Tocilizumab need further assessment in handling the supposed hyper-inflammatory response mediated by severe SARS-CoV-2 infection. These primary findings are considered hypothesis-generating, and well-designed randomized clinical trials are needed to validate the outcomes [103].

6.2. IL-6 inhibitors

Previous studies aimed at treating inflammatory diseases have introduced a group of natural and synthetic compounds that are capable of inhibiting IL-6. Given the role of IL-6 in the pathogenesis of COVID-19 and the possibility of applying these inhibitory compounds in the future, some of them have been introduced here. Based on their mechanism of action, the inhibitory compounds that directly affect IL-6 or its receptors can be divided into three main categories: 1) IL-6 inhibitors, which include derivatives of 2,3,7,8-tetrahydro-4-aryl-1Hcyclopent[*e*]imdiazo-[1,2-a]-pyridin-5(6H)-one, diaryl pyridine, diaryl pyrazine, meta-terphenyl, 1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole, 2) IL-6 production inhibitors including benzophenone, chalcones, 4-styryl-3-cyanocoumarin, indoline, tricyclic, andrographolide, atractylenolide III, madindoline (A and B), chromone-isoxazolopyridine hybrids, and bergenin derivatives; and 3) IL-6 receptor inhibitors such as epoxyresibufogenin-3-formate [24].

6.3. Other anti-inflammatory drugs

6.3.1. CVL218

A phase I clinical trial study had concluded that CVL218, as a poly-ADP-ribose polymerase 1 (PARP1) inhibitor had beneficial effects through inhibition of SARS-CoV-2 replication without any noticeable cytopathic consequences. Additionally, as stated so far about COVID-19, peripheral blood mononuclear cells (PBMCs) are involved in the pathogenesis of the disease, and CVL218 can suppress the production of the CpG-induced IL-6 in these immune cells. These findings have indicated that CVL218 has anti-inflammatory properties, and it is also a potential agent in the treatment of COVID-19, particularly in patients admitted to intensive care units (ICUs) [104].

6.3.2. Hydroxychloroquine (HCQ)

The mechanism action of HCQ is to inhibit lysosomal activity via increasing intracellular pH in B cells, DCs, and macrophages as antigen-presenting cells (APCs) [105]. This process ultimately leads to a defect in the presentation of T-dependent antigens through MHC-II, enhancing the CD8$^+$ T-cell immune response and reducing the production of inflammatory cytokines such as IL-6 by T- and B-cells [106]. Prescribing HCQ in patients with COVID-19 has thus confirmed that the given drug can have beneficial effects in terms of improving patients through increasing viral clearance as well as lowering the severity of pneumonia and duration of symptoms without any severe side effects [107,108].

At the beginning of the epidemic and following the pandemic, studies have shown that HCQ can be useful in the treatment of COVID-19 patients through increasing viral clearance as well as lowering the severity of pneumonia and the duration of symptoms. In contrast, after further studies and side effects observed in these patients, the effectiveness of this drug has been questioned. For instance, recently, an observational cohort study proposed that HCQ, either alone or in combination with azithromycin, had not a survival advantage among hospitalized patients with COVID-19 [109]. Another meta-analysis also revealed that the administration of HCQ/CQ had not any considerable impacts on SARS-CoV-2 clearance and even increased hospitalized patients with COVID-19 mortality with a higher risk in COVID-19 patients with comorbidities [110]. In a randomized investigation from China, in patients with a mild to moderate SARS-CoV-2 infection recovery rates was not valuable following HCQ therapy [107]. Similarly, another study from France on 11 hospitalized COVID-19 patients also failed to approve HCQ anti-viral effects when HCQ administered combination with azithromycin [111].

A reason for the disagreement in the anti-viral effects of HCQ between these clinical trials might be due to the dosage of HCQ. This is because prescribing high doses of HCQ can increase side effects and disorders caused by the treatment, especially when these side effects are not monitored. The present prescribed dosage in COVID-19 patient may be concerning the anti-malarial dosage of HCQ; therefore, this issue should be more evaluated in the other viral infections such as SARS-CoV-2 [112].

6.3.3. Thalidomide

Known as an anti-inflammatory and immunomodulatory compound, Thalidomide is capable of stimulating T-cells, inhibit cell

proliferation, and reduce lung injury as well as pulmonary fibrosis. The effects of Thalidomide might be related to regulating immune responses and preventing the production of inflammatory cytokines such as IL-6. A case report in this line had found that Thalidomide could lead to treating pneumonia in an infected case with SARS-CoV-2 [113]. Therefore, it may be possible to use this drug to treat patients suffering from COVID-19.

6.3.4. Baricitinib

Small molecules termed JAK inhibitors are a group of anti-inflammatory drugs that can inhibit JAKs in inflammatory cytokine signaling pathways. These drugs have also been utilized to treat RA and have shown positive effects [114,115]. For instance, following treatment with Baricitinib, as a JAK1/2 inhibitor, significant improvements had been observed in the condition of RA patients due to interruption of the IL-6 signaling pathway and modulation of inflammatory immune responses [116]. Recently, a combination of Baricitinib with anti-viral drugs such as Remdesivir, lopinavir, and Ritonavir has been used in patients with COVID-19, and this novel compound has been able to reduce viral replication and infectivity and dysregulated host inflammatory responses [117].

6.4. Natural products

Natural and herbal derivatives and products, as well as traditional medicine, have been used in the treatment of pandemic and endemic diseases for hundreds of years, and they may be able to play a useful role in treating or improving patients with COVID-19. However, the safety of the use of these compounds in the treatment of SARS-CoV-2 infection should be carefully assessed. There are also other important points, such as interfering with anti-viral drugs and the toxicity of these compounds.

6.4.1. Curcumin

The roots of *Curcuma longa* L contain a biologically active dietary polyphenol ingredient called Curcumin, which has numerous therapeutic properties such as reducing inflammatory responses and helping to treat cancers as cited in previous studies [118]. The mechanism action of Curcumin as an IL-6 signaling inhibitor is interacting with several targets such as JAK2, STAT3, PI3K/Akt, and MAPK/ERK adaptor molecules, which are involved in IL-6 signaling pathways [119,120], and also reducing inflammatory cytokines such as NF-κB, IL-6, and others [121]. Studies reported that conventional poly (lactic acid) (PLA)-containing Curcumin had a remarkable anti-inflammatory effect even at 1/8 dose, i.e., 50 compared to 400 mg/kg free Curcumin (with lower bioavailability) [122]. Additionally, a meta-analysis study showed that levels of IL-6 could be reduced by curcumin supplementation through suppressing pro-inflammatory signaling pathways related to different inflammatory disorders [123]. Besides, clinical trials that used Curcumin as an anti-inflammatory compound, demonstrated that it was safe, tolerable, and nontoxic in studied patients [33]. Due to the anti-inflammatory properties of Curcumin as well as the naturalness of this substance, it may be used as an adjunct therapy in patients with COVID-19. However, this theory needs further research.

6.4.2. Resveratrol

Resveratrol (3,5,40-trans-trihydroxystibene) is considered as an anti-inflammatory polyphenol existing in peanuts, grapes, mulberries, and red wine. It has also been extensively studied as a possible therapeutic agent for the regulation of the immune system and inflammatory responses [124]. Resveratrol can also promote a powerful anti-inflammatory impact via its ability to antagonize the inflammatory cytokines of NF-κB, TNF-α, IL-6, as well as inducible nitric oxide synthase (iNOS) activity [125,126]. Although there are no data for using Resveratrol in patients with COVID-19, a study suggested that this natural polyphenol compound may be an adjunctive anti-viral agent to

consider, particularly regarding the findings of Linn et al. study that showed Resveratrol at 250 and 125 μM alleviated the monolayer destruction of the MERS-CoV infected Vero E6 cells [127]. Although the dose of Resveratrol in humans has not yet been determined, its administration in supplemental doses can be considered safe for patients [128].

6.4.3. Naringin

Naringin shows a productive anti-inflammatory activity, as reported in the present and previous studies [129–131]. This flavanone glycoside can also constrain the expression of the pro-inflammatory cytokines, including IL-1β and IL-6. Recently, the results of an investigation revealed that the application of Naringin (10, 20, 40 μg/mL) in LPS-treated macrophage cells had anti-inflammatory effects and meaningfully reduced the expression of COX-2, iNOS, IL-1β and IL-6 [132]. The mentioned study suggested that regarding the potential anti-viral and anti-inflammatory properties of flavonoids, the citrus fruit or its derived phytochemicals such as Naringin are hopeful in the use of prevention and treatment of SARS-CoV-2 infection [132]. Another experimental study showed that the administration of Naringin at different doses (25, 50 and 100 mg/kg body weight of rats) in cisplatin-induced nephrotoxicity had considerable anti-inflammatory effects [133].

6.4.4. Lianhuaqingwen

Recently, a Chinese herbal patent compound called lianhuaqingwen (LH) has been used to treat COVID-19. Considering its anti-inflammatory properties, including inhibited production of inflammatory cytokines and chemokines such as IL-6, IL-1β, TNF-α, C—C motif chemokine ligand (CCL2), as well as CXCL10, this substance has reduced the severity of symptoms in infected cases. Investigations have also shown that LH can reduce the replication of the SARS-CoV-2 in Vero E6 cells [134]. In an experimental study on influenza-infected mice undertreatment orally administered 1300 and 650 mg/kg/day of LH solution twice a day (at 12-h intervals) for five days the findings showed that in the early stages of infection, serum levels of IL-6, TNF-α, CXCL8 (IL-8), CXCL10, and CCL2 were decreased significantly [135]. Given these results, as well as the several similarities between the immunopathogenesis of influenza and SARS-CoV2, LH may be useful in the treatment of patients with COVID-19.

6.4.5. Lonicerae japonicae flos (LJF), radix scutellariae, and fructus forsythiae

Previous studies have revealed that *LJF*, *radix scutellariae*, and *fructus forsythiae* plant species in traditional Chinese medicine (TCM) has been extensively used as a drug for several inflammatory disorders. Interestingly, this herbal preparation has effectively repressed the production of inflammatory cytokines such as IL-1β, IL-6, TNF-α, IFN-γ via PBMCs, and lipopolysaccharide (LPS)-stimulated murine alveolar macrophages [136,137]. Currently, these herbal agents have been prescribed for patients with COVID-19, and findings have confirmed their beneficial effects in the treatment of the patients [136,138]. However, accurate information about patients, the dosage used, and treatment outcomes are not available.

6.4.6. Shenfu injection (SFI)

Shenfu is known as a type of TCM that contains aconite and ginseng [139]. Following an infection, systemic inflammatory response syndrome (SIRS) occurs that can lead to ARDS, MOF, or even death [140]. To explore the therapeutic impacts of SFI and its effect on NF-κB activity in PBMCs, a lipopolysaccharide (LPS)-induced SRIS model was created. It was observed that following injection of 10 mL/kg SFI, the plasma levels of IL-6 had significantly reduced in SFI treated group compared with untreated animals. Additionally, a histopathological observation had established that the lung tissue had alleviated in the SFI group [141]. Another study on sixty-eight patients with severe

sepsis undertreatment with 100 mL SFI intravenous drip once a day for seven days showed that serum level of IL-6 was remarkably decreased in the SFI treated group compared with the control group [142]. Therefore, due to the similarity of pathological immune responses in COVID-19, SIRS, sepsis, and other inflammatory-based disorders as well as the beneficial effects of SFI in decreasing the symptoms of SIRS, this compound might be considered as a potential therapeutic target for patients with COVID-19.

7. Concluding remarks

To conclude, based on the available evidence reviewed in this article, IL-6 plays a crucial role in promoting inflammatory responses after being infected with SARS-CoV-2. Most recent studies on patients with COVID-19 have also reported that IL-6 serum levels had elevated in infected cases. On the other hand, dysregulated inflammatory responses could cause lung injury, leading to ARDS, MOF, or even death. Also, a pandemic caused by SARS-CoV-2 would increase the need for medications or healing compounds for the disease. The use of drugs, mAbs, and natural or synthetic anti-IL-6/IL-6R may thus be a helpful strategy for treating or reducing the deadly side effects of COVID-19. However, extensive studies need to be fulfilled to achieve the best agent or combination.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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