



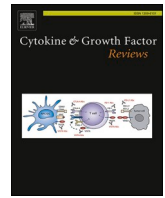
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Before the “cytokine storm”: Boosting efferocytosis as an effective strategy against SARS-CoV-2 infection and associated complications

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ABSTRACT

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is responsible for the ongoing COVID-19 pandemic, and causes many health complications, including major lung diseases. Besides investigations into the virology of SARS-CoV-2, understanding the immunological routes underlying the clinical manifestations of COVID-19 is important for developing effective therapeutic interventions. The clearance of SARS-CoV-2-infected apoptotic cells by professional efferocytes, through a process termed as ‘efferocytosis’, is essential for maintaining tissue homeostasis, and reducing the chances of health complications caused by SARS-CoV-2 infection. In this review, we focus on the cellular events leading to engagement of the SARS-CoV-2 with type 2 alveolar cells, and how SARS-COV-2 infection impairs the macrophage anti-inflammatory programming. We also discuss accounts of impaired efferocytosis, and the “cytokine storm” which occur concomitantly with the SARS-CoV-2 infection. Finally, we propose how targeting impaired efferocytosis, due to the SARS-CoV-2 infection, may be a beneficial therapeutic strategy to combat COVID-19, and its complications.

1. Introduction

The Corona Virus Disease 2019 (COVID-19) has quickly emerged as one of the leading causes of death. The WHO has elevated the novel coronavirus (COVID-19) outbreak to the rank of a global pandemic [1]. The severe acute respiratory Corona Virus 2 (SARS-COV-2) is the cause of COVID-19 [2]. However, the pathologies associated with COVID-19 are still poorly defined. Patients affected by COVID-19 can develop different kinds of clinical manifestations, including pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and multi-organ dysfunction [3]. The signs and symptoms of COVID-19 have been

attributed to uncontrolled host immune response, and compromised functions of myeloid cells, which include dendritic cells, monocytes, tissue macrophages, and granulocytes, suggesting that both hyper-inflammation and unresolved tissue damages may contribute to the pathogenesis of severe COVID-19 infection [4–6].

The SARS-CoV-2 virus infects alveolar cells of the lungs, and other cells in various tissues, and triggers cell death along a variety of modes, such as apoptosis, necrosis, pyroptosis, autophagy-induced cell death, and ferroptosis [7]. The body, in turn, by a process known as efferocytosis, maintains tissue homeostasis by phagocytosis of the apoptotic bodies of dying cells. The efficient clearance of damaged or dead cells,

Abbreviations: ACE2, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; AMP, adenosine monophosphate; ATP, adenosine triphosphate; BAI1, brain angiogenesis inhibitor 1; cAMP, cyclic adenosine monophosphate; COPD, Chronic obstructive pulmonary disease; COVID-19, coronavirus disease of 2019; COX2, cyclooxygenase 2; CXCL, chemokine (C-X-C motif) ligand; DAMP, damage associated molecular pattern; DC, dendritic cell; FDA, food and drug administration; GAS-6, Growth arrest specific gene 6; HCoV229E, human coronavirus 229E; HIV, human immunodeficiency virus; HMGB1, High mobility group box 1 protein; IL, interleukin; LC3, microtubule-associated protein 1 A/1B-light chain 3; LPC, lysophosphatidylcholines; Macrophage, Macrophages; MARS-CoV, middle east respiratory syndrome-related coronavirus; MERTK, proto-oncogene tyrosine-protein kinase MER; MFG-E8, milk fat globule-EGF factor 8 protein; PS, Phosphatidyl serine; Rac-GEF, Rac guanine nucleotide exchange factor; RAGE, receptor for advanced glycation end products; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2-AC, Severe acute respiratory syndrome coronavirus 2 infected apoptotic cell; SOCS, Suppressor Of Cytokine Signalling; S1P, sphingosine-1-phosphate; TGF- β , transforming growth factor beta; TIM, T cell immunoglobulin mucin receptor; TMPRSS2, transmembrane serine protease 2; TNF- α , tumour necrosis factor α ; TLR, toll like receptor; TUNNEL, Terminal deoxynucleotidyl transferase dUTP nick end labelling; WHO, World health organization.

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through the process of efferocytosis, prevents further tissue dysfunction caused by the release of damage-associated molecular patterns (DAMP). The efferocytes, cells such as macrophages and monocytes, promote disease tolerance to maintain host fitness, without affecting the pathogen burden; they do so, upon recognising pathogenic signals, by resolving inflammation, by releasing anti-inflammatory cytokines, reducing pro-inflammatory cytokine production, and reorienting towards an anti-inflammatory phenotype [8]. Moreover, efferocytosis not only prevents the deleterious effect of secondary necrosis, and but also helps in and promotes the repair of damaged tissue to sustain physiological function [9–11]. On the contrary, impaired efferocytosis causes chronic inflammation, resulting in severe lung diseases and autoimmune disorders [12].

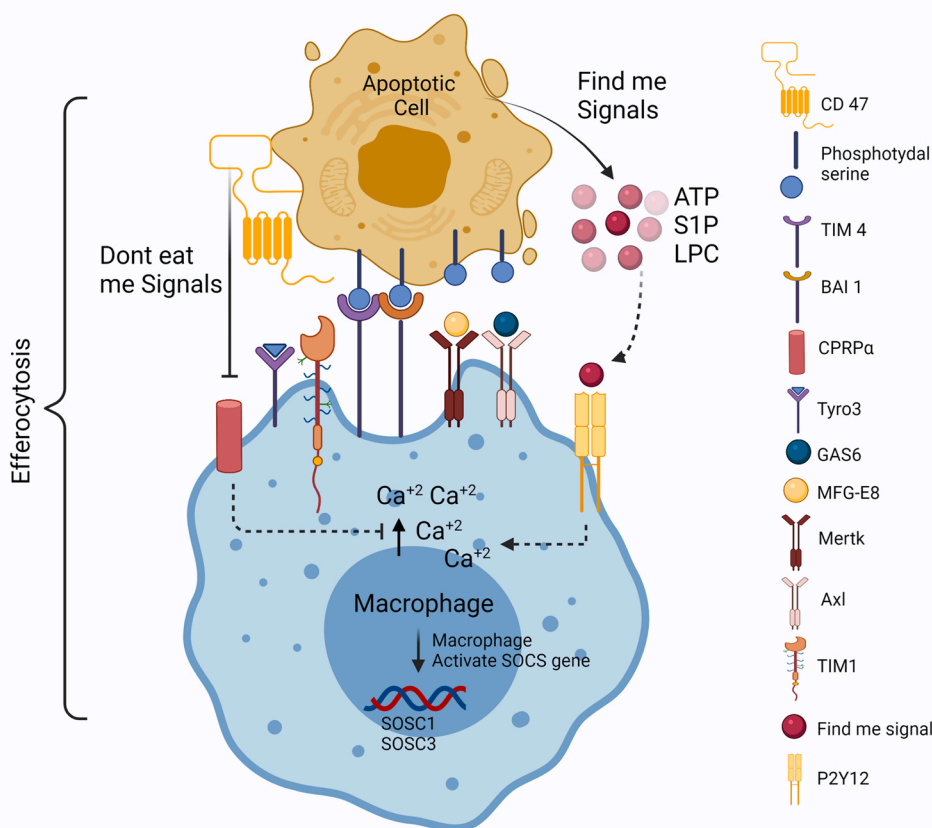
COVID-19 infection has been shown to hamper the proper function of alveolar macrophages, although the mechanism remains vague. The inadequate clearance of apoptotic cells generated due to the SARS-CoV-2 infection contributes to COVID-19-associated autoimmune disorders [13]. Thus, the clearance of apoptotic bodies by boosting efferocytosis in SARS-CoV-2-infected tissues can play an important role in the management of COVID-19 pathology by preventing inflammatory responses, such as a ‘cytokine storm’ [14]. Because of the consistent spread of the COVID-19 disease all over the world, it is of great significance to gain more in-depth knowledge of how to combat its possible side-effects. This review article aims to discuss the engagement of the SARS-CoV-2 with type 2 alveolar cells, and how SARS-CoV-2 infection impairs macrophage anti-inflammatory programming. Besides this, we will discuss and hypothesise the probable link between impaired efferocytosis and COVID-19 disease, and attempt to propose possible treatment options to combat COVID-19 side-effects.

2. The process of efferocytosis, and the role played by the macrophages

Efferocytosis is the process of phagocytosis of apoptotic and necrotic cells, in any damaged tissue, by professional efferocytes, such as macrophages and dendritic cells (DCs). Sometimes, non-professional efferocytes, such as epithelial cells, astrocytes, Sertoli cells, and neural progenitor cells, also participate in this process of phagocytosis [15,16]. Apoptotic cells contain autoantigens, such as adenosine, heat-shock proteins, and high-mobility group box-1 proteins (HMGB1), and the release of these necrotic factors, during secondary necrosis, causes chronic inflammation, sepsis, and autoimmunity [17]. In healthy individuals, the uptake of apoptotic and necrotic cells by macrophages is so efficient that very few apoptotic cells escape efferocytosis. Efferocytosis, a highly orchestrated process, actively induces the macrophage phenotype that favours damaged tissue repair, and helps to suppress chronic inflammation [18]. Impaired efferocytosis is the common thread between a plethora of chronic health conditions, including cystic fibrosis, chronic obstructive pulmonary disease (COPD), asthma, and ARDS [19]. It has been proposed that providing a pharmacological fillip to the efferocytosis process might arrest lung disease progression [20].

The process of efferocytosis is systematically different from many other types of phagocytosis, and involves several phases, including apoptotic cell finding, apoptotic cell binding, apoptotic cell internalisation, and apoptotic cell digestion [21]. Apoptotic cells actively release soluble factors to attract the mononuclear phagocytic cells (macrophages and DCs). Key ‘find-me’ signals involved in this process are: chemokines, such as C-X-C motif chemokine ligand 1 (CX3CL1) [22], lysophosphatidylcholine (LPC) [23], sphingosine-1-phosphate (S1P) [24–27], and triphosphate nucleotides [28,29], such as ATP [30]. Apoptotic cells release these ‘find-me’ signals through caspase 3/7-activated hexameric pannexin-1 channels [31] (Fig. 1). Apart from such

Fig. 1. Schematic representation of efferocytosis mechanism performed by professional macrophage efferocyte. Phosphatidylserine, which is generally present on the inner layer of the plasma membrane, is exposed to the outside after receiving the apoptotic signals and release find-me signals in the form of nucleotides (ATP), sphingosine-1-phosphate (S1P), and lipophosphatidyl choline (LPC). TIM-4 and BAI-1 directly bind with phosphatidylserine (PS), and all the TAM receptors such as Mertk, Axl, TIM-1–3, and Tyro-3 bind with PS through the bridging molecules like MFG-E8 and GAS-6 proteins. Find-me signals bind with the P2Y12 receptor present on the plasma membrane of macrophages and help to create a Ca^{2+} gradient, which promotes the movement of macrophages towards the apoptotic cells. Suppressors of cytokine signalling 1 and 3 genes (SOCS1 and SOCS3) are activated for the maintenance of inflammatory programming. Apoptotic cells also express the don't eat me signal through the binding of CD-47 with $\text{CPRP}\alpha$ present on the macrophage cell membrane.



secreted molecules, apoptotic cells also display phosphatidylserine (PS) on the outer surface of the plasma membrane, to bind with the “find-you” signals [32]. Thus, the “find-me” and “find-you” signals both help in the binding of the professional efferocytes with apoptotic cells. Professional efferocytes digest apoptotic bodies through the activation of autophagy-related gene product, Microtubule-associated protein 1A/1B light chain 3 (LC3) [33], and induce specific signal transduction pathways that up-regulate efferocytotic receptors and opsonins [18].

There are 12 types of PS efferocytotic receptors found to date, which form a heterogeneous group of surface proteins that bind to PS directly, or via soluble PS-binding opsonins [34–36]. Four major families of PS efferocytosis receptors have been studied so far, which include (1) Brain-specific angiogenesis inhibitor (BAI), (2) T-cell immunoglobulin and mucin domain-containing (TIM), (3) Stablin, and (4) CD300. Macrophages and DCs bind PS directly through the receptors: BAI1 and TIM-4 [37]. The adhesion G-protein coupled receptor BAI1 directly binds to the PS with the activation of the Elmo-Dock bipartite Rac-GEF [38]. BAI1 expression is restricted to gastric and intestinal phagocytes, and important for the process of efferocytosis [39]. Lee et al. first demonstrated that *BAI1*-deficient mice display increased colonic inflammation and tissue damages [40]. It has also been reported that *BAI1* deletion in macrophage and colonic epithelial cells leads to an increase in the level of pro-inflammatory cytokines, such as IL-1 α , IL-6, and TNF- α [40]. These findings suggest that inflammatory gene expression is regulated and influenced by the activation of Elmo-Dock signalling [41].

Whereas BAI1 is directly involved in juxtacrine signalling, the TIMs: TIM-1, TIM-3, and TIM-4; and the receptor tyrosine kinases TYRO3, AXL, and MERTK, collectively known as TAMs, are involved in the process of efferocytosis, mediated by mononuclear efferocytes, through bridging molecules, serum proteins such as GAS6 and ProS1 [37] (Fig. 1). The TIM family receptors, such as TIM1 and TIM3, are required to bind with PS to suppress NF- κ B activation, and the production of pro-inflammatory regulators, such as TNF, IL-6, and CCL5, in proximal tubular cells [42,43]. It has recently been reported that TIM-4-mediated corpse engulfment can trigger LC3-associated autophagy [44]. The activation of TIM and TAM receptors inhibits pro-inflammatory cytokine signalling through the induction of Suppressor of cytokine signalling 1 and 3 (SOCS1 and SOCS3) [45,46]. Moreover, recent reports have suggested that A2A and A2B receptors, present on macrophages, mediate the suppression of pro-inflammatory chemokines, such as CXCL1 and CXCL2, and up-regulate the pro-resolution factors, such as Nuclear Receptor 4A1 (NR4A1) and Thrombospondin 1 (THBS1), during the process of efferocytosis [47,48]. Moreover, TAM deficiency disrupts apoptotic cell clearance by the macrophages, without disturbing other phagocytic properties [49,50]. TAM receptor MERTK binds with PS through bridging molecules that inhibit NF- κ B signalling, thus reducing the release of pro-inflammatory cytokines [51,52].

Some bridging molecules, including complement components, Milk fat globule-epidermal growth factor 8 (MFG-E8), Cellular communication network factor 1 (CCN1), Growth arrest-specific 6 (GAS6), and Protein S (PROS), are also involved in the process of recognition and binding of apoptotic cells with efferocytes [35,36] (Fig. 1). Binding of these bridging molecules to the PS, through α v β 3/5 integrin/vitronectin receptors on phagocytes, promotes Rac activation and corpse internalisation [53,54]. Thus, α v integrin plays a key role in macrophage adhesion and performs an important role in the process of efferocytosis.

Direct interaction of stabilin surface receptors (Stab1 and Stab2), present on macrophage, with PS improves the efficacy of efferocytosis or apoptotic cell clearance [55–57]. *In vitro* analyses have revealed that the expression of the Stab2 receptor induces the production of anti-inflammatory cytokine TGF- β [56]. On the other hand, *Stab1/Stab2* double knock-out mice have a shorter life span, and increased with tissue inflammation [58,59].

Another “find-me” signalling molecule, S1P also provokes anti-apoptotic and anti-inflammatory gene expression in macrophages.

These gene expressions are increased characterised by the suppression of TNF- α and IL-2, along with the increased production of IL-10, vascular endothelial growth factor (VEGF), and prostaglandin E2 (PGE2). The S1P receptor (S1PR), present on the plasma membrane of macrophage, prompts the conversion to an M2-like anti-inflammatory phenotype inducing the production of cAMP and cyclooxygenase-2, and the suppression of NF- κ B signalling [60]. S1P binding with also increases intra-macrophage Ca²⁺ concentration, which promotes the movement of macrophage towards the apoptotic cells [61].

Macrophages, involved in the innate immune system, play a crucial role in the antiviral response, tissue repair, and fibrosis. They can phagocytose virus, bacteria, as well as apoptotic cells to trigger an immune response, maintain tissue homeostasis, and promote regeneration [62]. Monocyte-derived macrophages co-exist as one of two sub-types, first, the classically activated or M1-like, and another, the alternatively activated or M2-like; cytokine signalling causes their phenotypic programming, and recruitment to the inflamed tissue [62–64]. Cytokine secretion profile sometimes varies between M1- and M2-like macrophages. M1-like macrophages are associated with microbial activity, pro-inflammatory cytokine production, and immune responses, while M2-like macrophages are recruited to heal the damaged tissue after viral infection. Therefore, the recruitment of macrophages into the damaged tissue is crucial for a balanced and controlled antiviral immune response, and for the clearance of dead cells caused by viral infection.

In the lungs, efferocytosis is predominantly orchestrated by not only the epithelial cells, but also the alveolar macrophages, the professional efferocytes that are well-distributed in the alveolar space, interspersed throughout the mucus layer and the interstitial space [65]. There are a few notable differences between alveolar macrophages and their counterparts in other tissues. The weaker efferocytotic capacity of alveolar macrophages, compared to other macrophages in different tissues, is compensated by a higher capacity for self-renewal and repair, which, thus, allows them to maintain homeostasis in the respiratory tract [66–68]. Moreover, alveolar macrophages require lower activation energy to activate inflammatory genes, against bacteria or viruses, than their counterparts in other tissues [69,70]. Alveolar macrophages undertake the release of anti-inflammatory cytokines, transforming growth factor- β (TGF- β), and interleukin 10 (IL-10), while inhibiting the secretion of pro-inflammatory cytokines, including Tumour necrosis factor- α (TNF- α), IL-1, IL-8, and leukotriene C4 (LTC4) [71,72] (Fig. 2). Interestingly, impaired efferocytosis has been detected in the airways of patients suffering from lung diseases due to the increased burden of apoptotic cells, which culminates in chronic inflammation. In fact, the impaired clearance of apoptotic cells by professional efferocytes is the upstream event to sustained chronic lung inflammation [73].

3. The impact of SARS-CoV-2 infection on the respiratory system and its associated immune milieu

In a healthy individual, the airway epithelium acts as a barrier against the routine onslaught of viruses, bacteria, and different particles, to prevent infection and tissue injury. SARS-CoV-2 generally enters the human body through the respiratory tract, and compromises the airway epithelium, alveolar epithelium, and vascular endothelium [74,75] (Fig. 3). According to *in vitro* analyses, it has been observed that ciliated airway epithelial cells are the primary site of SARS-CoV-2 infection [76]. Like with other types of coronaviruses, the SARS-CoV-2 infection occurs through, initially, the binding of the viral S (spike) protein to the Angiotensin-converting enzyme 2 receptors (ACE2), abundantly present on the surface of lung alveolar epithelial cells, followed by the cleavage of the spike protein by Transmembrane serine protease 2 (TMPRSS2) [77–81]. SARS-CoV-2, after infiltrating the nasal mucosa, replicates and triggers the repertoire of immune and inflammatory responses that constitute the signs and symptoms of COVID-19 infection [82].

The upper respiratory tract epithelium, upon being affected by SARS-CoV-2, suffers from impaired gas exchange and respiratory failure.

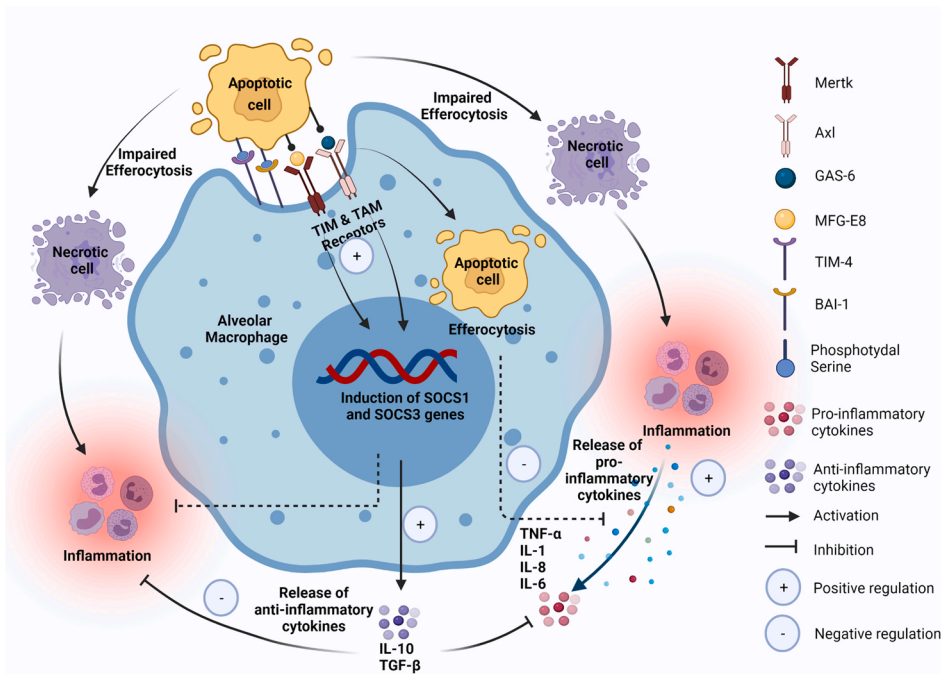


Fig. 2. Alveolar macrophages maintain lung tissue homeostasis through the process of efferocytosis. First alveolar macrophages find the apoptotic cells and bind with the help of TIM and TAM receptors. In the process of efferocytosis, apoptotic cell finding, apoptotic cell binding, and apoptosis of cells are internalised done by professional efferocytes such as macrophages. This process helps to maintain tissue homeostasis by the inhibition of pro-inflammatory cytokines release. Apoptotic cells convert into necrotic cells due to impaired efferocytosis and cause inflammation. The main reason for inflammation is the release of pro-inflammatory cytokines such as $TNF-\alpha$, IL-8, IL-1, and IL-6. TAM receptors, after binding with the ligands present on apoptotic cells, get activated and induced SOCS genes. Induction of SOCS1 and SOCS 3 genes helps to release anti-inflammatory cytokines and inhibit the release of pro-inflammatory cytokines. Anti-inflammatory cytokines such as $TGF-\beta$ and IL-10 inhibit inflammation caused by necrotic cells and help to maintain lung tissue homeostasis.

Triggering a chain reaction, the virions produced by the infected epithelial cells also infect other adjacent cells, such as neighbouring epithelial cells, endothelial cells, and macrophages, which are, in fact, the active participants in the process of efferocytosis [83]. Interestingly, macrophages frequently interact with ACE2-expressing cells present in the lung tissue, dialogues which could help them in sensing, and orienting towards defensive and destructive functions. [84]. Chan et al. have reported that the viral proteins expressed in the hamster model upon SARS-CoV-2 infection can cause widespread cell apoptosis [85]. The vascular endothelium is also an important site for COVID-19 infection [86]. Infection of endothelial cells occurs in the luminal or interstitial site, and this infection triggers the release of cytokines and chemokines. The 'cytokine storm', caused due to the infection with SARS-CoV-2, impairs macrophage function, and hinders the process of efferocytosis or apoptotic cell clearance [87].

The epithelial cells which are infected by SARS-CoV-2 express inflammatory mediators, such as CXCL10, and interferon [88,89]. *In vitro* analyses have shown that type II alveolar cells, upon infection with influenza virus or coronavirus, secrete pro-inflammatory cytokine mediators, such as IL-6, IL-8, IL-29, CCL5, CXCL9, CXCL10, and CXCL1152 [90].

The brutality of SARS-CoV-2 infection can be stratified based on the chemokine level present in the SARS-CoV-2 infected patients. Higher levels of CCL7, CCL3, and CXCL9 have been found in severe cases of COVID-19, compared with mild and moderate cases [91]. According to Huang et al., the plasma levels of CXCL10, CCL2, and CCL3 are reported to be higher in ICU patients than non-ICU patients, affected by SARS-CoV-2 [92]. Another study has revealed that the plasma levels of homeostatic chemokines, such as CXCL12, neutrophil-targeted CXCL1, eosinophil-targeted CCL11, and the memory T-cell-homing chemokine CCL27, stayed high during infection [93]. COVID-19 patients suffering from pneumonia and hypoxia show a higher level of CCL3 and CXCL10 [94]. Higher levels of chemokine secretion due to SARS-CoV-2 infection in lung tissue cause the release of higher levels of pro-inflammatory cytokines, and may hinder the process of apoptotic cell clearance, which may lead to different kinds of lung-related disorders and several complications.

4. Impaired efferocytosis and the consequent pro-inflammatory programming linked with SARS-CoV-2 infection

Given that viruses can take over and down-regulate antiviral immune responses prompted by macrophages to enhance their own replication and pathogenesis, it has been postulated that there is a similarity between HCoV-229E, SARS-CoV, MARS-CoV, and SARS-CoV-2 in their ability to cause respiratory tissue damage and several types of respiratory disorders associated with high morbidity and mortality. Development of these respiratory disorders may be linked to imbalanced macrophage populations during SARS-CoV-2 infection and, consequently, impaired efferocytosis [13,95,96]. Like other SARS-CoV, SARS-CoV-2 impairs the function of the macrophages, the professional efferocytes involved in the process of efferocytosis. Non-classical macrophages, such as monocyte, M1-like macrophage, and M2-like macrophage, have also been detected in the peripheral blood of COVID-19 patients [97]. The infection of the ACE2+ macrophage by SARS-CoV-2 enhances the secretion of IL-6 from the macrophage [98]. The massive secretion of IL-6 from the macrophage induces the apoptosis of lymphocytes through Fas signalling [98]. A disproportionately large ratio of apoptotic cells to macrophages, engendered due to SARS-CoV-2 infection, may be the reason for impaired efferocytosis.

Associated with macrophage activation and the development of respiratory distress syndrome, is the release of inflammatory cytokines, such as IL-6, $TNF-\alpha$, IL-1 β , and IFN- γ , directly [99]. Macrophage activation syndrome and dysregulated immune response have been found in COVID-19 patients suffering from severe respiratory failure [100]. Wang et al., have shown, in two severe cases of COVID-19, that the lung cavities were filled with macrophages and neutrophils, along with increased IL-6, $TNF-\alpha$, and PD-L1; these might be responsible for 'cytokine storm' and pulmonary fibrosis [101]. Besides pulmonary fibrosis and failure, other complications such as hyper-coagulation or clot formation have been found in COVID-19 patients [102–104]. A recent finding has suggested that the spleen macrophages are responsible for the viral spread, and exacerbate the subsequent 'cytokine storm' [105]. Multiple research groups have proposed that patients suffering from SARS-CoV-2 infection have increased plasma levels of fibrinogen and D-dimer [102–104]; in fact, correlation studies have revealed that 71%

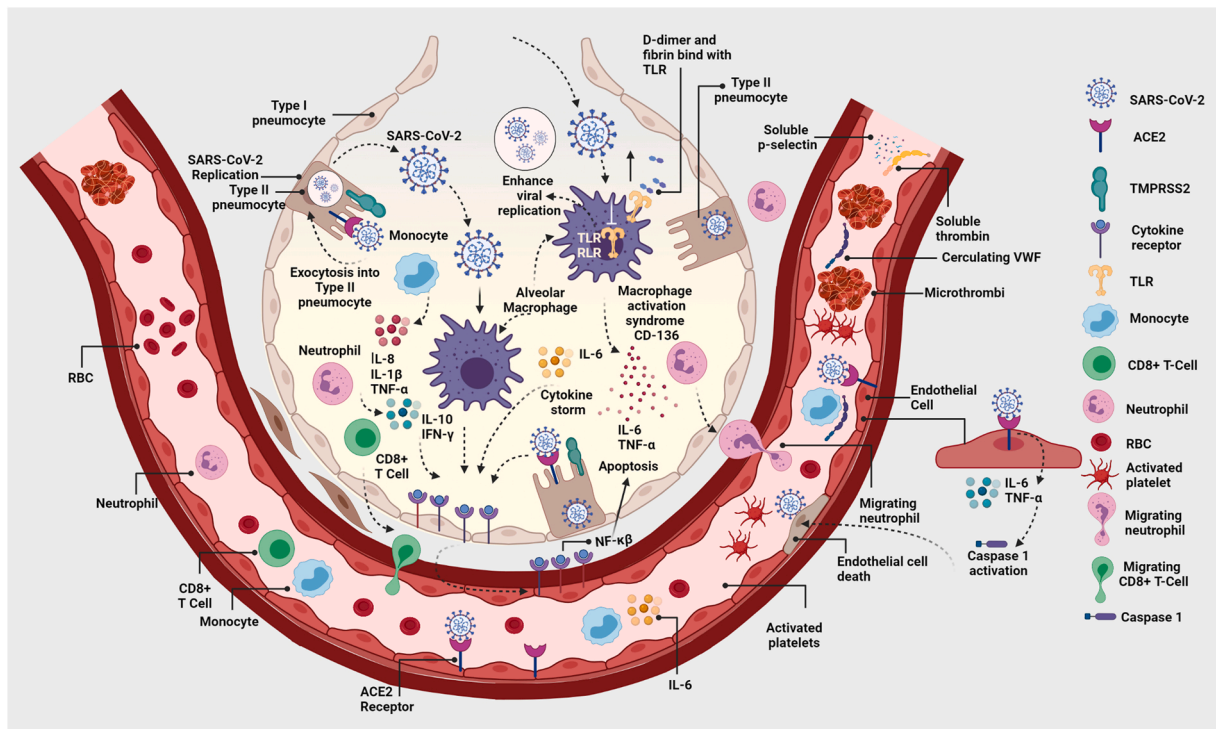


Fig. 3. Macrophage activation syndrome due to SARS-CoV-2 infection. After the infection, SARS-CoV-2 enters through the respiratory tract and binds to the ACE2 receptor present on type II pneumocytes. Spike protein (S-protein) present on SARS-CoV-2 is cleaved by transmembrane protease TMPRSS2. This cleavage helps SARS-CoV-2 to bind with ACE2 receptor and exocytosis into pneumocyte cell. After exocytosis, SARS-CoV-2 enhances their replication and targets to attack alveolar macrophage present in the alveolar space. Subsequently, infected with SARS-CoV-2, alveolar macrophages, neutrophils, and other immune cells release inflammatory cytokines like IL-6, IL-8, IL-1 β , TNF- α , IFN- γ , IL-10 as well as several chemokines. The incidence of rapid release of different inflammatory cytokines is called 'cytokine storm', which attacks own cells and tissue rather than fighting off the virus. Inflammatory cytokines released from different immune cells bind to their specific receptor present on type I pneumocyte cells and the endothelial cells. After binding inflammatory cytokines to their specific receptors, it activates NF- κ B signalling, which rapidly promotes apoptosis of type I epithelial and endothelial cells. 'Cytokine storm', which is generated by the infection with SARS-CoV-2, causes endothelial cell activation, and damage associated with cytokine storm is triggered through multiple pathways, including the release of pro-inflammatory cytokines and complement activation. As a result of this activation, endothelial cells release ultra-large VWF (von Willebrand factor) and p-selectin, which binds to platelets, monocyte, and neutrophil to develop microvascular thrombosis. D-dimer and fibrin are released in the alveolar space by the infection with SARS-CoV-2, bind to TLR and RLR present on alveolar macrophages and hinders the function of macrophages in the process of efferocytosis by enhancing SARS-CoV-2 replication. SARS-CoV-2 binds to ACE2 receptors present on endothelial cells, stimulates the release of pro-inflammatory cytokines such as IL-6 and TNF- α , and causes activation of caspase-1. Activated caspase-1 is responsible for endothelial cell death or apoptosis.

of non-survivors had a higher level of D-dimer and fibrin degradation products [106]. Interestingly, increased levels of fibrin and fibrinogen may modulate the function of macrophages by triggering the release of the pro-inflammatory cytokine TNF- α [107], and also engage with Toll-like receptors (TLRs), which boosts the release of pro-inflammatory cytokines, such as IFN- γ , TNF- α , IL-6, and IL-1 β [108] (Fig. 4). These reports suggest that there may be a strong relationship between disrupted macrophage function and the hypercoagulability found in COVID-19 patients.

Recently, it has been reported that epithelial cell lines (both human lung epithelial Calu-3 and simian kidney epithelial Vero CCL-81), infected with SARS-CoV-2, show apoptotic features [109,110]. Moreover, Habib et al. have already linked COVID-19 infections with ferroptosis-mediated cell death [7]. Exposure of phosphatidylserine (PS) on the outer surface of SARS-CoV-2 infected cells leads to induction of programmed cell death, or apoptosis, through annexin V binding [111, 112]. Other groups, through extensive imaging and staining of the spike protein of the virus, have shown that macrophages efficiently engulf SARS-CoV-2-infected dying cells [13,113]. It has also been proposed that the engulfment of SARS-CoV-2-AC (SARS-CoV-2 infected apoptotic cell) by macrophage significantly increases the production of IL-6 and IL-1 β , and switches the latter from an anti-inflammatory, resolutive programming to an inflammatory phenotype [13] (Fig. 4).

It has also been reported that efferocytosis of SARS-CoV-2 infected

dying cells might hamper the routine clearance of apoptotic cells. Since the primary aspect of efferocytosis is the engulfment of multiple apoptotic cells within a short period of time, this capability of professional efferocytes, such as macrophages, is essential when the ratio of apoptotic cells to efferocytes is higher after events which trigger acute inflammatory responses [114–116]. Therefore, continual efferocytosis is important, after an infection, to maintain tissue homeostasis and controlled inflammation [117].

5. Therapeutic strategies to combat SARS-CoV-2 infection: targeting impaired efferocytosis concomitant with the cytokine storm-induced complications

Impaired efferocytosis and huge production of pro-inflammatory cytokines due to SARS-CoV-2 infection have been observed in COVID-19-positive patients. The rapid surge of pro-inflammatory cytokines may be linked with the reduced expression of efferocytotic receptors. This 'cytokine storm' is one of the major causes of post-COVID-19 complications. Therefore, targeting 'cytokine storms' with potent antibodies or drugs could be a treatment option (Table 1). In view of the present situation, the need of the hour is to find a therapeutic strategy to combat SARS-CoV-2 infection and SARS-CoV-2 infection-related complications. The 'Big five' lung diseases have seen a resurgence during the COVID-19 pandemic: according to Google Trends analyses, the

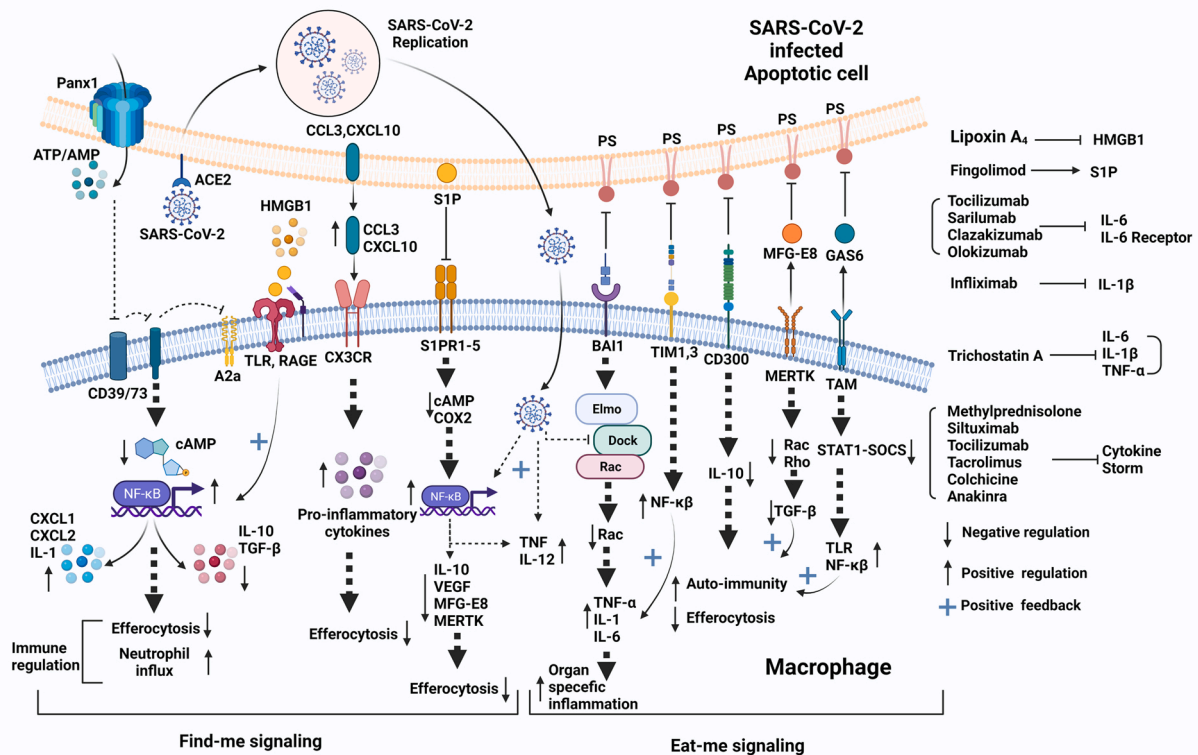


Fig. 4. Impaired efferocytosis signals concomitant with cytokine storm due to SARS-CoV-2 infection. SARS-CoV-2 infection alters two main signalling pathways (Find-me and Eat-me signalling) involved in the process of efferocytosis. SARS-CoV-2 infection hampers the binding of find-me signalling molecules such as ATP/AMP to their receptor-like A2a and down-regulates cyclic AMP production. Down-regulation of cAMP induces NF- κ B signalling. Stimulation of NF- κ B signalling up-regulates the production of chemokines and pro-inflammatory cytokines like CXCL1, CXCL2, and IL-1 and again down-regulates the synthesis of anti-inflammatory cytokines such as IL-10 and TGF- β . This up and downregulation of inflammatory cytokines troubles immune regulation by impaired efferocytosis. SARS-CoV-2 infection also helps to release HMGB1, which binds to TLR2, TLR4, and Receptor for advanced glycation endproducts (RAGE), thus shows a positive regulation towards NF- κ B signalling. Increased chemokines such as CCL3 and CXCL10 are directly correlated with impaired efferocytosis by the production of pro-inflammatory cytokines. Mutation or downregulation of S1P signalling also down-regulates the production of cAMP and COX2 and stimulates NF- κ B signalling. Stimulation of NF- κ B signalling inhibits the expression of TAM receptor protein MERTK and bridging molecule MFG-E8, causes impaired efferocytosis. SARS-CoV-2 infection also down-regulates the expression of TIM and TAM receptors associated with Eat-me signalling such as BAI1, TIM1–3, MERTK and produces cytokine storm, which is connected with inflammation and impaired efferocytosis. Some proposed drugs are mentioned for targeting impaired efferocytosis concomitant with cytokine storm.

incidence of the ‘Big five’ lung diseases, except for lung cancer, including Asthma, COPD, pneumonia, and ARDS has increased during the COVID-19 pandemic [118]. In the case of lung diseases, SARS-CoV-2 infection causes inflammation and bronchial cell apoptosis. The conversion of these massive numbers of apoptotic cells into necrotic ones, due to impaired efferocytosis, may result in the production and release pro-inflammatory cytokines in a large quantity, which could be the main reason behind COVID-19 complications. Therefore, targeting impaired efferocytosis could be a novel therapeutic strategy against COVID-19 infection.

Recent studies have revealed that the engulfment of SARS-CoV-2-AC reduces the transcription of PS receptors, including that of the scavenger receptors CD36 and SRA-I, α V β 5 integrin (ITGB5), and T cell immunoglobulin mucin receptor 4 (TIM4), but not that of MER proto-oncogene tyrosine kinase (MERTK) [13]. Hence, it is clear that efferocytosis of SARS-CoV-2-infected dying cells depresses the expression of efferocytotic receptors, and impairs the continual elimination of apoptotic cells by macrophages. Since it has been found that activation of MERTK regulates immunosuppressive profiles, characterised by high IL-10 and TGF- β levels [119], Dexamethasone, a potent activator of the MERTK receptor, has been permitted, and is being broadly used, for the treatment of seriously ill COVID-19 patients [120].

It is assumed that the release of S1P, involved in the process of efferocytosis, is impaired by SARS-CoV-2 infection, and this can slow down the process of SARS-CoV-2-infected apoptotic cell clearance

[121]. The immunomodulatory action of the orally available drug Fingolimod (FTY720), a modulator of S1PR, is being harnessed for the treatment of multiple sclerosis (MS) [122]. Several studies have reported that Fingolimod can potentially also be utilised for the treatment of the human immunodeficiency virus (HIV) disease [123,124]. It has been reported that the case of a 57-year-old female, who was affected with SARS-CoV-2, upon a regime of Fingolimod treatment, had a positive outcome, thus, indicating that the immunomodulatory effect of Fingolimod might indeed prove to be beneficial to reduce the mortality caused due to the SARS-CoV-2 infection [125]. A clinical trial of Fingolimod (FTY720) in COVID-19 patients is already underway (NCT04280588). Moreover, thymoquinone, an anti-inflammatory agent, has also been shown to be effective against impaired S1P signalling system [126]. Therefore, both Thymoquinone and Fingolimod can be co-opted as therapeutic options to improve impaired efferocytosis through the modulation of S1P signalling.

Interestingly, the SARS-CoV-2 particle mimics apoptotic cells, by exposing PS on the viral envelope, which interacts with the phagocytic machinery of target cells, inducing its internalisation [127]. Morizono et al. were the first to report that TAM receptors are involved in viral molecular mimicry. Here, the GAS6 protein acts as a bridging molecule, connecting TAM receptors with the exposed PS, and prompts efficient entry and replication of the virus. Sustained TAM signalling is important for potent viral infection, thus TAM inhibitors may reduce viral infectivity [128,129]. This study predicted that TAM receptors and bridging

Table 1

Potential alternative approaches to treat cytokine storm induced complications in COVID-19 patients.

Target	Drug	Mechanism	References
IL-6 or IL-6 receptor	Tocilizumab (NCT04322773) Sarilumab (NCT04359901; NCT04357808) Clazakizumab (NCT04348500; NCT04381052; NCT04343989; NCT04381052) Olokizumab (NCT04380519)	Neutralizing IL-6 or its receptor.	Ascierto et al. [136]; Buonaguro et al. [137]; Luo et al. [138]; Michot et al. [139]; Xu et al. [140]; Zhao [141]; Zhang et al. [142].
IL-1 β	Canakinumab (NCT04362813; NCT04348448)	Targeting IL-1 β by decreasing C-reactive protein through Anti-IL-1 β antibodies	Ucciferri et al. [143].
TNF- α	Infliximab (NCT04425538; NCT04344249)	evaluation of XPro1595, which prevents TNFs from binding to their receptors by forming heterotrimers with soluble TNF	Steed et al. [144].
Expression of pro-inflammatory cytokines like IL-6, IL-1 β , and TNF- α	Trichostatin A	Decreases IL-6 production by modulating mRNA stability Decrease IL-1 β , and TNF- α Decrease systemic inflammation	DrugDrugMechaniGrabiec et al. [145]; Han and Lee [146]; Cui et al. [147].
Cytokine storm	Methylprednisolone (NCT04244591, NCT04273321) Siltuximab (NCT04329650) Tocilizumab (NCT04377503, NCT04345445) Tacrolimus (NCT04341038) Colchicine (NCT04350320; NCT04375202) Anakinra (NCT04324021; NCT04443881)	Immunosuppressive drugs targets NO (nitric oxide) and TNF- α , inhibits T cell activation, and decreases the extravasation of immune cells.	Sloka and Stefanelli [148].

molecules, part of the process of efferocytosis, may be involved in COVID-19 viral entry. Moreover, the interaction of AXL, a TAM receptor, with SARS-CoV-2 has been shown to promote infection in epithelial cells [130]. Recently, the FDA has approved the use of Gilteritinib, an inhibitor of AXL, since it shows antiviral efficacy against SARS-CoV-2 infection in Vero E6 cells [131]. Another AXL inhibitor Bemicentinib (BGB324), has been fast-tracked towards phase II clinical trials by ACCORD (Accelerating COVID-19 Research and Development Platform) [131]. Therefore, GAS6/AXL targeting through Gilteritinib, Bemicentinib, and others AXL inhibitors could be a promising avenue for anti-COVID-19 treatment.

Lipoxin A4, belonging to a unique class of lipid mediators, possesses a wide spectrum of anti-inflammatory properties [132]. First reported by Wang et al., Lipoxin A4 stimulates the efferocytosis activity of alveolar macrophage [132]. Lipoxin A4 upregulates efferocytosis by blocking High mobility group box protein 1 (HMGB1), a well-known DAMP protein that acts as an "alarmin", *i.e.*, promotes inflammation along with impaired phagocytosis. HMGB1 binds to TLR2, TLR4, and RAGE to activate or upregulate the NF- κ B signalling pathway, which enhances the expression of leucocyte adhesion molecules, along with the production of pro-inflammatory cytokines [133]. Interestingly, HMGB1 expression has been shown, in the rat model, to be negatively correlated to that of the ACE2 receptor [134]. Moreover, Kuba et al. have reported that, in the mouse model, SARS-CoV infection downregulates ACE2 expression [135]. Therefore, it can be hypothesised that reduced ACE2 expression due to SARS-CoV-2 infection can increase HMGB1, thus contributing to the "cytokine storm", which is a hallmark of the worst COVID-19 infection scenarios. In fact, the elevated level of HMGB1 suppresses efferocytosis in patients suffering from ARDS, a major lung disease that has emerged as a post-COVID-19 complication. Thus, Lipoxin 4 could indeed be a novel therapeutic option against COVID-19 complications [132].

6. Conclusions

This review presents various mechanisms of defective efferocytosis linked with pandemic COVID-19. We discuss how efferocytosis clears and digests apoptotic cells, maintains tissue homeostasis, and plays a pivotal role in rendering key immune functions. The entry of SARS-CoV-

2 through the airway respiratory tract, and their binding to ACE2 receptors present on lung epithelial cells, allows them to exploit the host cells for their replication. Consequently, a huge number of cells suffer apoptosis due to SARS-CoV-2 infection. Macrophages, the professional efferocytes, are recruited to the infection or damaged site to clear SARS-CoV-2-AC. Although an efficient efferocytosis process is supposed clear the apoptotic load, as discussed above, the replicated SARS-CoV-2 enter the macrophages by hijacking the apoptotic process, and hamper the efferocytosis machinery. SARS-CoV-2 infection alters the expression level of efferocytotic receptors, which are involved in clearing SARS-CoV-2-AC, and is also responsible for triggering a 'cytokine storm' by causing the release of pro-inflammatory cytokines on a large scale. Thus, the 'cytokine storm' production, due to impaired efferocytosis, may be the reason for COVID-19 complications. Major lung diseases, caused by SARS-CoV-2 infection, are observed in COVID-19 patients as complications. Hence, it is critical to understand that the gravity of COVID-19 complications is no less than that of the SARS-CoV-2 infection itself. It is concerning that recent studies have shown that the SARS-CoV-2 virus may keep mutating frequently, and possibly into more virulent strains. In the foreseeable future, drug treatment holds promise of being a more effective option. However, research studies will continue to unearth new information, given that the pathophysiology of COVID-19 disease, and its relation to different diseases remain to be fully deciphered. This review underlines that targeting efferocytosis concomitant with the 'cytokine storm' can be an effective strategy against SARS-CoV-2 infection and its complications.

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Declaration of Competing Interest

The authors declare that they have no known competing financial

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Author contributions

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