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Review

Myeloid dysregulation and therapeutic intervention in COVID-19

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ABSTRACT

The dysregulation of myeloid cell responses is increasingly demonstrated to be a major mechanism of pathogenesis for COVID-19. The pathological cellular and cytokine signatures associated with this disease point to a critical role of a hyperactivated innate immune response in driving pathology. Unique immunopathological features of COVID-19 include myeloid-cell dominant inflammation and cytokine release syndrome (CRS) alongside lymphopenia and acute respiratory distress syndrome (ARDS), all of which correlate with severe disease. Studies suggest a range of causes mediating myeloid hyperactivation, such as aberrant innate sensing, asynchronized immune cellular responses, as well as direct viral protein/host interactions. These include the recent identification of new myeloid cell receptors that bind SARS-CoV-2, which drive myeloid cell hyperinflammatory responses independently of lung epithelial cell infection via the canonical receptor, angiotensin-converting enzyme 2 (ACE2). The spectrum and nature of myeloid cell dysregulation in COVID-19 also differs from, at least to some extent, what is observed in other infectious diseases involving myeloid cell activation. While much of the therapeutic effort has focused on preventative measures with vaccines or neutralizing antibodies that block viral infection, recent clinical trials have also targeted myeloid cells and the associated cytokines as a means to resolve CRS and severe disease, with promising but thus far modest effects. In this review, we critically examine potential mechanisms driving myeloid cell dysregulation, leading to immunopathology and severe disease, and discuss potential therapeutic strategies targeting myeloid cells as a new paradigm for COVID-19 treatment.

1. Introduction

Caused by infections from the SARS-CoV-2 virus, the resulting COVID-19 pandemic has now surpassed over 250 million cases and 5 million deaths globally (https://covid19.who.int/). Though most individuals experience mild symptoms, severe disease occurs in about 5–15 % of patients [1]. Compared to other respiratory viruses such as influenza, COVID-19 has a longer clinical course (9-day average, from onset of symptoms to severe disease, compared to 4-day average in influenza) [2–6]. The disease can cause more serious symptoms requiring prolonged mechanical ventilation. It can be lethal in susceptible demographics, especially older men with comorbidities such as hypertension or diabetes [7]. Postmortem pathology reveals disease features of COVID-19 that include lymphopenia and myeloid-cell dominant inflammation alongside cytokine storm syndrome (CRS) and acute respiratory distress syndrome (ARDS) [8]. Though lymphocytes, such as B and T cells, consistently show decreased numbers in patients with severe disease, their role in orchestrating antiviral cellular immunity is more complex, with studies showing both positive and negative effects on disease progression [8–10]. However, the significant increase and hyperactive nature of inflammatory myeloid cells is generally regarded as a key hallmark of disease pathogenesis (Fig. 1) [11,12], especially given that macrophage-associated cytokines and chemokines [13], as well as other molecules such as neutrophil extracellular traps (NETs) [14,15], damage-associated molecular patterns (DAMPs) [16], and S100 alarmins [17] have shown clear prognostic value.

For the initial viral infection, it has been extensively demonstrated that SARS-CoV-2, an airborne virus, primarily infects specialized epithelial cells (type II pneumocytes) in the lung alveoli, nasal goblet cells, and ciliated cells in the airway or intestine by binding the host

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receptor angiotensin-converting enzyme 2 (ACE2) via its spike (S) protein (Fig. 2) [18–20]. While infection occurs initially in the lung, other tissues, such as kidney, small intestine, brain, heart, etc., show evidence of viral infection upon autopsy [21]. In general, viral infection in epithelial cells leads to the accumulation of viral genomes and replicative intermediates that are produced during the viral life cycle, collectively termed virus-derived pathogen-associated molecular patterns (PAMPs). These PAMPs are subsequently detected by a diverse array of host-encoded endosomal and cytosolic nucleic acid sensors, known as the pattern recognition receptors (PRRs), which are key sensing mechanisms of the host immune system. Given the nature of SARS-CoV-2 as a RNA virus, multiple cytosolic PRRs, including RIG-I [22], MDA-5 [23], and LGP2 [23], mediate recognition of SARS-CoV-2 viral components in infected lung epithelial cells. Viral infection also triggers the production of DAMPs, which are endogenous host-derived molecules that are released from damaged or dying cells. DAMPs can be sensed by PRRs as well as other innate receptors, including inflammasomes, TREM receptors, and G protein-coupled receptors (GPCRs) [24,25]. After detection of viral infection through PAMP or DAMP sensing, innate sensors rapidly trigger the production of cytokines and chemokines to initiate antiviral innate and adaptive immunity [26]. While protective in moderation, elevated cytokine levels observed in CRS in patients with severe disease have functional ties to the innate immune system and reveal an immune asynchrony involving an overheated innate immune system coupled with adaptive immunosuppression [13]. The mechanisms for lymphopenia and the suppression of adaptive immunity are still under investigation. How myeloid hyperactivation is linked to initial viral infection and disease pathogenesis remains a key open question for the basic understanding of COVID-19 and the development of related therapeutic strategies. Earlier stages of the disease currently focus on antivirals, disease prevention via vaccination, or neutralizing antibodies that block viral infection. However, taming innate hyperactivation is critical towards designing effective interventions for late stage COVID-19, for which therapies are still urgently required [10]. Thus, while COVID-19 pathophysiology is still being investigated, herein we focus on myeloid cells as a critical mediator of immunopathology, delving into potential mechanisms and outlining possible myeloid-targeted immunotherapies that may influence patient outcomes (Fig. 1).

2. Features of myeloid dysregulation in COVID-19

The lung microenvironment is normally composed of a heterogenous group of cells that maintain homeostasis while serving as a frontline barrier against particulates and pathogens [27]. However, absolute numbers and ratios of these populations, particularly those involved in immunity, change upon infection by SARS-CoV-2. Single-cell profiling of broncho-alveolar lavage samples of hospitalized patients with COVID-19 across multiple studies have shown that hyperactivated myeloid cells correlate with disease progression and severity [28–30]. Along with granulocytes such as neutrophils [30,31], proinflammatory monocyte-derived macrophages (MDM) are remarkably increased in lungs with severe disease compared to normal lungs across many studies. Levels of other macrophage subsets [28], such as transitioning MDM, can also be higher in COVID-19 patients, while tissue-resident alveolar macrophages (AM) are instead enriched in control and mild disease [13,30]. Similar to the phenotype within the lung, elevated levels of dysfunctional monocytes are likewise found in the peripheral blood of severe COVID-19 patients [12,32]. These monocytes are likely poor antigen presenters, potentially myeloid-derived suppressor cells (MDSCs), given their low expression of HLA-DR, in contrast to HLA-DR^{hi} cells in patients with mild disease [12]. However, some subsets, such as transitional or nonclassical monocytes, are lower in the blood than the lung within patients with severe disease, hinting at potential trafficking and expansion from blood to the infected tissue [33]. Expansion of the inflammatory monocytic population occurs at the expense of other antiviral cell types within the myeloid lineage, such as dendritic cells (DCs) and plasmacytoid dendritic cells (pDCs), which remain at depressed levels even seven months post infection [34,35]. These two populations are critical for antigen presentation and type I interferon (IFN) production, respectively. Combined with the increased inflammatory myeloid population, their relative decrease may further escalate symptoms. However, whether the decrease is more causal or consequential in disease progression remains to be seen.

Though the exact myeloid activation program differs between studies, pathways increased in severe disease include proteases such as cathepsins [28], scavenger receptors, toll-like receptor (TLR) and signaling pathways, inflammatory transcriptional regulators [29], and cytokine and chemokine programs [36]. Cytokines, released by hyperactivated myeloid cells [28,30], are of special pathogenic importance; with no strict definition, the phenomenon of CRS is instead characterized by a large release of proinflammatory cytokines that can lead to enhanced vascular hyperpermeability, triggering ARDS [37], a major cause of COVID-19-related fatality [38–42]. The exact composition of upregulated inflammatory mediators can differ between patients and studies [43]. Cytokines such as IL-6, IL-8, IL-1, S100A8/9, GM-CSF,

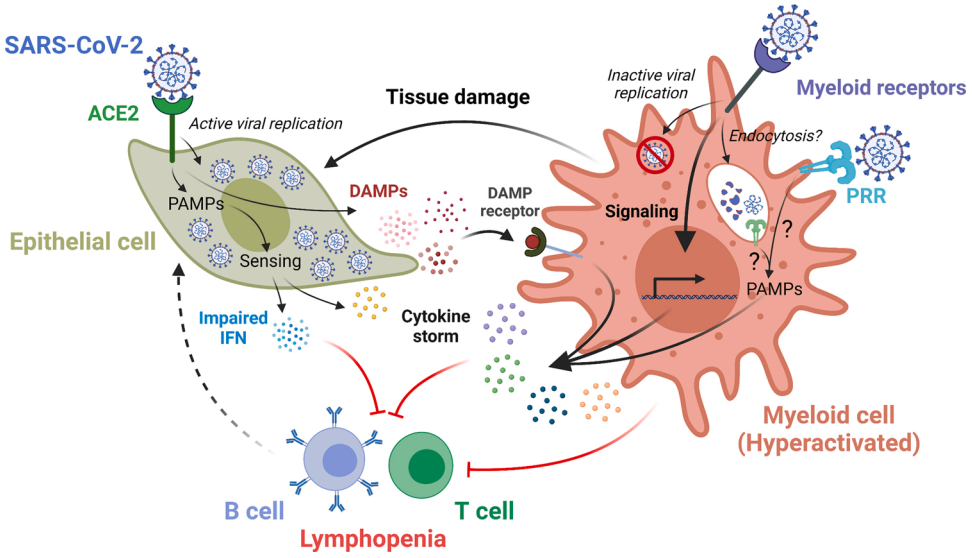
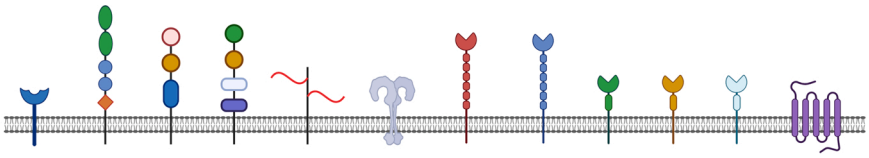


Fig. 1. Myeloid dysregulation upon SARS-CoV-2 infection. ACE2-mediated SARS-CoV-2 infection leads to active viral replication and release of DAMPs and cytokines by lung epithelial cells. Sensing DAMPs by DAMP receptors on myeloid cells, direct viral engagement with myeloid receptors, or viral interaction with PRRs on the plasma membrane and/or in the endocytic compartments may lead to the hyperactivation of myeloid cells. This triggers production and release of proinflammatory cytokines, which in turn may elicit cytokine storm and ultimately lead to lymphopenia. ACE2, angiotensin-converting enzyme 2; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; PRR, pattern recognition receptor.



Receptor or Interacting Partners	ACE2	NRP1	CD147	AXL	HS	TLR4	DC-SIGN	L-SIGN	LSECtin	ASGR1	CLEC10A	TTYH2
Dominant Expression	Epithelial cells	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Myeloid cells	Myeloid cells	Myeloid cells	Myeloid cells	Myeloid cells	Myeloid cells	Myeloid cells
Function during initial SARS-COV-2 infection	Major infection receptor	Facilitate viral binding to ACE2	Putative Infection receptor?	Putative Infection receptor?	Facilitate viral binding to ACE2	N/A	Transinfection of ACE2+ cells	Transinfection of ACE2+ cells	N/A	N/A	N/A	N/A
Function in myeloid dysregulation	N/A					Potentially induce proinflammatory cytokines						

Fig. 2. Receptor(s) or interacting partner(s) of SARS-CoV-2. ACE2, angiotensin-converting enzyme 2; NRP1, neuropilin 1; CD147, basigin; AXL, tyrosine-protein kinase receptor UFO; HS, heparan sulfate; TLR4, toll-like receptor 4; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; L-SIGN, C-type lectin domain family 4 member M; LSECtin, C-type lectin domain family 4 member G; ASGR1, asialoglycoprotein receptor 1; CLEC10A, C-type lectin domain family 10 member A; TTYH2, tweety family member 2. N/A, not applied.

TNF-α, IL-12, CXCL10, MCP-1, MIP1A, etc., have all been shown to be upregulated in patients with severe disease or associated with pulmonary inflammation or disease severity [2,12,44–50]. Though studies suggest that myeloid cells may be the dominant producers for inflammatory cytokines such as IL-6 [51] and TNF-α [52], we note that the precise cellular source of cytokines has not been determined, as other cells such as epithelial cells are likely to also be a significant producer of inflammatory cytokines.

In addition to the upregulation of inflammatory innate cytokines, a blunted IFN response is also a general immune signature for severe disease. A central paradigm of protective antiviral immunity, first informed by studying immunological responses to influenza infection, is that IFN-mediated host responses precede downstream proinflammatory ones [53]. Such multitiered and well-regulated immune responses maximize antiviral protection while avoiding collateral damage to the host. However, this does not seem to hold true for COVID-19. Through longitudinal analysis of hospitalized patients with moderate-to-severe COVID-19, it was shown that production of IFN-I and IFN-III is diminished, delayed, and induced only in a fraction of patients [54]. Meanwhile, production of proinflammatory cytokines such as TNF-α, IL-6, and IL-8 precedes IFNs in all patients and persists for a prolonged time. This is in stark contrast to cytokine responses in influenza virus-infected patients hospitalized for viral pneumonia, which are characterized by robust and early IFN production and acutely produced proinflammatory cytokines. This imbalanced response to SARS-CoV-2 infection is also recapitulated in human lung epithelium-derived cell lines and ferrets [55]. The lack of proper IFN induction could be explained by the various viral mechanisms that evade and suppress the IFN response [56,57]. Indeed, it has been extensively shown that SARS-CoV, MERS-CoV, and SARS-CoV-2 can interfere with any of the following processes in innate antiviral immunity: 1) innate sensing, 2) IFN production, 3) IFN signaling, and 4) ISG effector function [58–62]. The ability for SARS-CoV-2 to evade innate immunity is further enhanced in new variants, such as the Alpha (B.1.1.7) and Beta (B.1.351) strains [63–65]. This raises the possibility that emerging viral variants may cause more pronounced immunopathology through further dampening of IFN-I-based antiviral immunity.

3. Mechanisms of myeloid dysregulation

The immune response to SARS-CoV-2 infection defined by low levels of IFN juxtaposed to elevated proinflammatory cytokines and chemokines could explain the myeloid cell hyperactivation observed in COVID-19. With lessons learned from SARS-CoV, in a theoretical framework of immune asynchrony [13], diminished IFN levels lead to an insufficient ability to clear SARS-CoV-2, resulting in further viral replication. Chronic low IFN released in response to viral infection generates further myeloid cell accumulation and activation alongside a suppressed adaptive immune response [66]. Throughout this cycle, many innate cytokines are produced, further amplifying the innate hyperactivation [11,67]. Many innate cytokines that correlate with severe disease, such as TNF-α, IL-6, IL-8, GM-CSF, and CCL2, have diverse functional effects on myeloid cells, including generation, activation, and recruitment (Fig. 3). A classic cytokine elicited in chronic inflammation [68], TNF-α promotes hematopoietic stem cell (HSC) survival and myeloid differentiation, in addition to supporting the immunosuppressive function of myeloid derived suppressor cells [69,70]. Lung epithelial and endothelial apoptosis is also caused by TNF-α [71], contributing to the release of DAMPs and the hyperinflammatory environment. Some notable examples of DAMPs include members of the S100 protein family, in particular S100A8 and S100A9, which are alarmins that critically regulate the migration and trafficking of leukocytes and confer anti-microbial protection during bacterial infection. It has been shown that S100A8/9 becomes dramatically upregulated at mRNA and protein levels following SARS-CoV-2 infection in animal models and in patients. Inhibition of S100A8/A9 with a small-molecule inhibitor, paquinimod, has been demonstrated to alleviate COVID-19-associated inflammatory disorder in a mouse model of SARS-CoV-2 infection [72,73]. It is also worth noting that there are counter-regulatory mechanisms by the host to prevent DAMPs from triggering excessive inflammation. One such mechanism is CD24, a surface receptor that has been increasingly recognized as a negative regulator of DAMP signaling. CD24 represses DAMP-induced immunity by directly trapping DAMPs to prevent agonistic receptor binding and/or by actively suppressing downstream signaling pathways through Siglec-10/G receptor [74,75].

Outside of these DAMP-related pathways, other cytokines, such as IL-6, have been shown to induce myelopoiesis in severe infection [76]. Importantly, IL-6 plays a key role in CRS in the course of chimeric antigen-receptor T cell (CAR-T) therapy, with anti-IL-6 monoclonal antibodies being effective in ameliorating CRS symptoms [42]. Survival of myeloid cells such as neutrophils is promoted by IL-8 via inhibition of apoptosis [77]. IL-8 has been closely linked to the induction of MDSCs that potently inhibit lymphocyte activation, which can be a possible mechanism of lymphopenia. Produced by epithelial and hematopoietic cells during inflammation, GM-CSF is another important cytokine that confers a pro-inflammatory phenotype in myeloid cells characterized by the production of reactive oxygen species (ROS), cytokines, and chemokines [78]. Elevation of GM-CSF is unique to fatal COVID-19 but not influenza, suggesting GM-CSF as a disease-specific mechanism [44]. The chemoattractant cytokine CCL2 has been shown to be secreted by SARS-CoV-2 infected cardiomyocytes, promoting monocyte recruitment to the heart [79]. Although myeloid cells can limit viral replication through engulfment of infected cells upon arrival at the site of infection, an excessive production of proinflammatory cytokines, such as IL-6, TNF-α, IL-8, IL-1β, GM-CSF, IL-18, S100A8/9, etc., was observed during COVID-19. These molecular features are closely associated with dysregulated myeloid activation and can result in secondary immune recruitment, vascular leakage, and lethal respiratory dysfunction that likely underlie COVID-19 pathogenesis [42]. In the absence of appropriate regulation in normal resolution of infection, these cytokines can further activate the innate immune system, cause lymphopenia, and damage host tissue, leading to a potentially deadly feed-forward loop

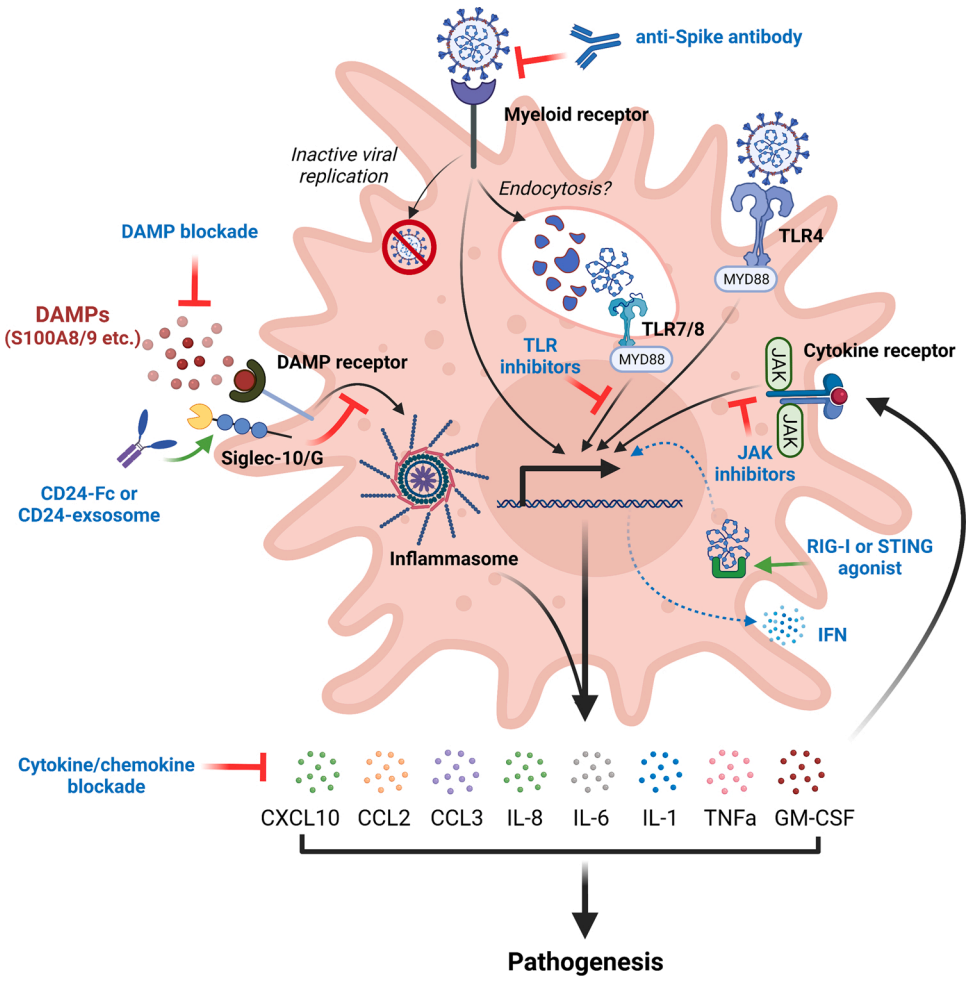


Fig. 3. Potential immunotherapies for COVID-19 by targeting various pathways in dysregulated myeloid cells to restore immune homeostasis. These immunotherapies may include: 1) blocking spike-myeloid receptor interaction; 2) inhibiting TLR signaling pathways; 3) engaging Siglec-10/G by CD24-Fc fusion protein or exosome to suppress DAMP signaling; 4) blocking JAK signaling pathway; 5) enhancing RIG-I or STING mediated production of IFNs; and 6) blocking myeloid cell-released proinflammatory cytokines, chemokines, and DAMPs.

[42]. Altogether, these data provide compelling evidence that exposure to innate cytokines is a crucial driver of myeloid recruitment and activation [12,32].

While the effect of SARS-CoV-2 induced cytokines on myeloid cells is relatively understood, few studies have examined whether proinflammatory myeloid activation occurs dependently or independently of epithelial SARS-CoV-2 infection. Single-cell transcriptomic studies of lung tissues from COVID-19 patients have revealed myeloid cells as the cellular compartment most enriched for SARS-CoV-2 RNA, with particular abundance of $CD14^{high}CD16^{high}$ inflammatory monocytes and $LDB2^{high}OSMR^{high}YAP1^{high}$ macrophages [29,36]. Notably, myeloid cells positive for SARS-CoV-2 RNA appear to have distinct transcriptional programs compared to cells that do not harbor viral RNA, including genes associated with chemokine and cytokine signaling and responses to IFN, TNF, intracellular pathogens and viruses. These results highlight the potential for viral RNA to directly trigger activation of myeloid cells. However, unlike epithelial cells, myeloid cells do not express canonical cellular receptors and proteases, such as ACE2 and TMPRSS2, that are utilized by SARS-CoV-2 for viral entry [80]. While SARS-CoV-2 viral antigens have been detected in myeloid cells [81–83], there is no evidence thus far of productive infection. Consequently, activation of myeloid cells by SARS-CoV-2 is unlikely a result of direct infection by the virus via known receptors or general viral uptake mechanisms. Here, we propose two major mechanisms linking SARS-CoV-2 infection and myeloid cells to explain how the virus can directly induce myeloid activation: 1) direct PRR stimulation in myeloid cells, and 2) modulation of myeloid activation by viral proteins.

4. Myeloid cell activation via direct innate sensing of SARS-CoV-2

The first mechanism by which myeloid cells respond to SARS-CoV-2 is through direct innate sensing. Toll-like receptor 4 (TLR4) is a cell surface PRR that is abundantly expressed on myeloid cells and responsible for detecting bacterial ligands such as lipopolysaccharides (LPS) [84]. TLR4 signaling can be activated by oxidized phospholipid (OxPL), which is produced during the respiratory virus-induced oxidative stress response, to trigger cytokine production in macrophages and acute lung injury (ALI) [85]. A recent study also found that the S protein from SARS-CoV-2 directly interacts with and activates TLR4 (Fig. 2), triggering high levels of *IL1B* and *IL6* transcription *in vitro* [86]. In addition to TLR4, myeloid cells use specialized endosomal PRR, including TLR3 (receptor for double-stranded RNA (dsRNA)), TLR7 (receptor for single-stranded RNA (ssRNA)), TLR8 (receptor for ssRNA), and TLR9 (receptor for double-stranded DNA (dsDNA)), to mediate sensing of viral genomes and replication products [87]. Upon endocytosis of viruses, endosomal TLRs sense viral genomes, presumably after the envelopes and capsids are uncoated by the degradative enzymes therein, and trigger cytokine and type I IFN production. However, SARS-CoV-2 is unlikely to directly enter the endosome in non-epithelial cells through endocytosis downstream of the spike-ACE2 interaction, as the canonical cellular receptor ACE2 is not abundantly expressed in these cells. Instead, viral products of SARS-CoV-2 may be delivered into the endosomal/lysosomal compartment through phagolysosomal fusion, a process by which the phagosome formed upon phagocytosis fuses with the lysosome and acquires lysosomal contents, such as PRRs and hydrolytic

enzymes [88]. By doing so, viral particles or PAMPs in which viral endocytosis does not normally occur can be delivered to and sampled by the endosomal PRRs to initiate an antiviral response. The phagocytic process can be further augmented by Fc-mediated phagocytosis of antibody-virion immune complexes [89]. However, we note that phagocytosis is a general viral uptake mechanism, and the specific features of SARS-CoV-2 infection, such as the hyperactivation of myeloid cells, have yet to be thoroughly explained by this theory.

In addition to initiating PRR activation *de novo*, myeloid cells can also bypass the upstream sensing and production of second messengers to directly engage downstream responses. Rather than producing second messengers from within, host cells can directly acquire these intermediate signaling molecules from the extracellular space through transport mechanisms. A salient example for this is the cGAS/STING pathway, in which cGAS detects the presence of dsDNA in the cytoplasm of infected or damaged cells [90,91]. In the context of SARS-CoV-2 infection, it was recently shown that cGAS recognizes cytoplasmic chromatin DNA derived from the nucleus due to cell-to-cell fusion caused by the infection [92]. Upon ligand recognition, cGAS then produces 2'3'-cyclic-GMP-AMP (cGAMP) to activate STING, eliciting robust IFN-I responses. Interestingly, cGAMP is not only a cell-intrinsic activator of STING, but also a paracrine mediator that orchestrates larger-scale biological responses. During viral infection, cGAMP can be exported directly to the extracellular space in a soluble, non-membrane bound form by LRRC8A:C/E heteromeric channels and imported into neighbor host cells by importers such as SLC19A1 and SLC46A2 [93–95]. In particular, SLC46A2 represents the major cGAMP importer in primary human monocytes and monocyte-derived macrophages [95]. In the context of COVID-19, uncontrolled infection with SARS-CoV-2 in epithelial cells leads to pervasive cell damage and death [96], a process that likely triggers cGAS/STING activation and cGAMP release. Extracellular cGAMP can then be transported into myeloid cells via LRRC8A and induce STING activation [94]. However, the importance of this pathway in SARS-CoV-2 infection awaits further investigation.

5. Myeloid cell activation via viral/host protein interactions

The second mechanism by which SARS-CoV-2 induces myeloid cell activation is mediated by functional interactions between viral and host proteins. Emerging evidence suggests that the SARS-CoV-2 virion contains numerous proteins capable of interacting with host receptors and modulating immune responses. The SARS-CoV-2 genome has six functional open reading frames (ORFs) that encode replicase (ORF1a/ORF1b), spike (S), envelope (E), membrane (M), and nucleocapsid (N). In addition to the genomic RNA, a nested set of subgenomic RNAs (sgRNAs) encoding accessory proteins are also produced as a part of the viral life cycle. Though the canonical receptor for viral infection, ACE2, is not expressed on myeloid cells, a myeloid cell receptor-focused ectopic expression screen recently identified five C-type lectin receptors (DC-SIGN [97], L-SIGN, LSECtin, ASGR1, and CLEC10A), in addition to Tweety family member 2 (TTYH2), as novel binding partners for the viral S protein (Fig. 2) [80]. S protein binding epitopes are distinct between ACE2 (mainly the receptor-binding domain (RBD) of S) and C-type lectins (mainly the N-terminal domain (NTD) and C-terminal domain (CTD) of S) but partially overlapping between ACE2 and TTYH2, though all of the binding occurs in an ACE2-independent manner. Although there is no active infection and replication downstream of SARS-CoV-2 engagement with these myeloid cell receptors, these glycan-dependent interactions trigger robust proinflammatory responses in myeloid cells, characterized by potent production of inflammatory cytokines such as IL-1α, IL-1β, IL-8, CXCL10, CCL2, and CCL3. Rationally engineered bispecific antibodies blocking these new interactions show significantly reduced proinflammatory responses, demonstrating the functional importance of targeting not only viral infection, but also inflammatory receptors. Outside of ACE2 and these novel myeloid receptors, other extracellular receptors have also been identified, such as neuropilin-1 (NRP1) [98,99], heparan sulfate [100], CD147 [101], sialic acids [102], and AXL [103]. Both NRP-1 and heparan sulfate binding appear to be ACE2 dependent [98,100], which may limit the benefit of combinatorial therapy targeting these interactions alongside anti-S/ACE2 blocking antibody. Of the ACE2 independent interactions, the reproducibility of the CD147/S protein interaction is currently under debate [101,104], while sialic acids show both promotion and prevention of SARS-CoV-2 binding [105]. AXL may bind to S protein and mediate infection in the lung independently of ACE2 and its other known ligands, GAS6 or protein S [103]. Moreover, some of these receptors, particularly DC-SIGN/L-SIGN, have been reported to elicit SARS-CoV-2 trans-infection of ACE2 positive cells and thus facilitate viral infection (Fig. 2) [106]. Overall, the functional relevance of many other viral/receptor interactions downstream of receptor engagement remains to be determined, along with the therapeutic utility of targeting these interactions in addition to ACE2.

Viral proteins other than S may also directly modulate myeloid cells. E protein from SARS-CoV-2 is sensed by TLR2, another PRR expressed on the cell surface or endosomal compartment [107]. The interaction is required for the release of inflammatory cytokines, such as TNF-α and IFN-γ [108], during Murine Hepatitis Virus (MHV) infection. Blocking TLR2 also protects against SARS-CoV-2-induced lethality *in vivo*. In addition, N protein has been shown to trigger NLRP3-dependent inflammasome activation, which correlates with severe COVID-19 disease [81], by directly binding to the inflammasome sensor NLRP3 [109]. This binding promotes its interaction with ASC (the adaptor molecule apoptosis-associated speck-like protein containing a CARD) and facilitates inflammasome assembly. N protein induces the production of IL-1β and IL-6, aggravates lung injury, and instigates disease in mouse models of sepsis and acute inflammation [109]. Given that inflammasomes are located in the cytoplasm, we note that inflammasome activation by N protein likely pertains to ACE2-expressing cells or cells that can be infected by SARS-CoV-2. Several accessory proteins have also been implicated in the induction of myeloid activation in COVID-19 [110]. ORF3a is the largest among all accessory proteins encoded by SARS-CoV-2, sharing 72.7 % amino acid sequence homology with SARS-CoV ORF3a. SARS-CoV ORF3a promotes inflammasome activation by inducing *IL1b* gene expression and IL-1β maturation [111]. Interestingly, infection of K18-hACE2 transgenic mice with an ORF3a-deficient SARS-CoV-2 mutant results in less pathology and improved survival compared to that of wild type virus [112]. Whether the observed attenuation of disease severity is mediated by reduced immunopathology remains to be determined. In addition, it was recently reported that SARS-CoV-2 ORF7a directly triggers the activation of $CD14^{+}$ monocytes *ex vivo*, which is characterized by a marked reduction in surface HLA expression and significantly increased production of proinflammatory cytokines, including IL-6, IL-1β, IL-8, and TNF-α [113]. ORF8, the only secreted SARS-CoV-2 viral protein, also promotes the expression of proinflammatory mediators via the IL-17 signaling pathway by interacting with host IL17RA [114]. It has also been shown to modulate cytokine expression in primary human macrophages, most notably downregulation of IL-6 and IL-8 [115]. ORF9c, which encodes a small, unstable protein with a putative transmembrane domain, has also been reported to stimulate IL-6 signaling while potently repressing IFN-I responses [116]. Whether these ORFs functionally encode for and/or structurally resemble physiological ligands of PRR and inflammasome sensors, as well as their functional receptors in the myeloid cells, remains an open question [42]. The virus also does not actively replicate in myeloid cells [80,117], resulting in fewer templates for transcription and translation - the functional relevance of viral proteins requiring host machinery in myeloid cells thus awaits further study. Recently, reversal of post-translational modifications of downstream effector pathways, such as conjugation of ubiquitin-like protein ISG15 (interferon-stimulated gene 15) [118], have also been shown to correlate with macrophage hyperpolarization [119]. Exactly which substrate(s) are responsible for this functional perturbation await future investigation.

In summary, we discuss two distinct mechanisms explaining how SARS-CoV-2 infection triggers myeloid cell activation and pathogenic inflammation. First, myeloid cells can utilize a broad array of surface and endosomal PRRs to detect the presence of viral PAMPs or viral infection associated DAMPs. Second, myeloid cells could be activated by viral proteins, including but are not limited to S, N, and various ORFs. While some of these mechanisms remain speculative and await further experimental evidence, they point to the centrality of myeloid-derived cytokines and chemokines in the pathogenesis of COVID-19. Below, we further review how these insights motivate myeloid-directed immunotherapies against COVID-19 that are currently in different stages of clinical trials.

6. Potential immunotherapies

Immunomodulatory approaches have been proposed as a promising intervention for COVID-19 management given that dysregulation of the immune response, especially hyperactivated myeloid immunity, is a major contributor of systemic and lethal COVID-19 pathogenesis [8,120]. The hypothesis was supported by the results from UK-based RECOVERY and other randomized controlled trials (RCT), which indicated that the use of anti-inflammatory agents, such as corticosteroids, was associated with reduced 28-day mortality compared with the standard of care among patients receiving oxygen support [121,122]. However, delayed viral clearance and secondary infection caused by general immunosuppression from these anti-inflammatory agents warrants concern [123,124]. In this setting, exploring more specific immunomodulators, especially those targeting the hysteric innate immune response, may emerge as a promising therapeutic strategy to prevent immune-induced injury while preserving adaptive antiviral immune function.

As aforementioned, the features of hyperactivated myeloid dysregulation triggered by SARS-CoV-2 involve aberrant sensing pathways, hypersensitive alarming mechanisms, and robust innate immune cytokine release. Molecules that target myeloid dysregulation at every stage are under investigation. Previous studies suggested that critical cytokines, such as IL-6, are key mediators of myeloid overactivation and inflammatory circuit establishment. Based on these findings, targeting cytokines in this inflammation amplification stage, especially IL-6 blockade which has shown efficacy against CRS in CAR-T therapy, received early and widespread attention (Fig. 3) [125,126]. Multiple powered trials have confirmed that IL-6 blockade (tocilizumab, sarilumab and siltuximab) were associated with modest reduction of 28-day mortality among hospitalized patients, with a 3 % decrease from IL-6 blockade to standard of care (22 % vs 25 %) [127–130]. Tocilizumab received U.S. Emergency Use Authorization for the management of hospitalized adults and children with COVID-19 in 2021. Notably, this benefit appeared more evident among patients who received non-invasive respiratory support rather than those requiring invasive mechanical ventilation, highlighting the importance of disturbing the positive-feedback cytokine network at the early stage [129]. This observation is further supported by the result from GM-CSF blockade. Intervention with lenzilumab at an early phase was shown to improve ventilation-free survival at day 28 among patients with high-risk comorbidities [131]. The successes in targeting GM-CSF may partially correlate with its critical effects on mobilizing myeloid cells and promoting the expression of IL-1, IL-6, TNF-α and other proinflammatory cytokines (Fig. 3) simultaneously [78,132,133]. However, more clinical data are required to draw conclusions regarding efficacy and safety in COVID-19 treatment. Apart from targeting cytokines themselves, inhibition of essential downstream, critical inflammatory cytokine signaling, such as the Janus kinase (JAK) pathway, has been found to strongly suppress the inflammatory cascade response [134]. Administration of orally selective JAK inhibitors, tofacitinib or baricitinib, have led to clinical improvements among hospitalized patients with COVID-19 pneumonia compared to placebo in several randomized controlled trials (RCT) [134–136]. Molecules that target other proinflammatory cytokines and signaling pathways associated with hyperactivated myeloid dysregulation also warrant attention. Agents which block IL-8 [137], TNF-α [138,139], IL-18 [140], and CCR2 [141], in addition to other pathways such as LIGHT (TNFSF14) [142], IL-1 [143–145], and IL-17 [146], have shown potential beneficial effects in preliminary data of COVID-19 management, although more evidence is still needed to identify their safety and efficacy in ongoing trials.

Correcting dysregulated myeloid activation at sensing and alarming stages also showed encouraging effects in reducing inflammatory-related injuries. In particular, targeting an impaired type I IFN response, a hallmark of severe COVID-19 and critical pathway downstream of TLR signaling [147], is becoming increasingly appreciated. In one randomized study involving 101 adults admitted to the hospital with mild-to-moderate COVID-19, patients received inhaled SNG001 for 14 days, a nebulized formulation of recombinant IFN-β. Results demonstrated a more rapid recovery and less incidence of progression to severe disease or death for those on SNG001 than placebo [148]. However, there is debate regarding optimal timing of IFN treatment for COVID-19, particularly considering that IFN treatment might exacerbate tissue destruction due to robust immune activation. Other than as monotherapy, a recent strategy to arm a RBD based vaccine fused with type I IFN offered rapid and complete protection against SARS-CoV-2 infection, which may provide a unique approach for IFN-based viral prevention [149]. Besides this, other targets, such as those involved in the PAMP signaling pathway including RIG-I agonists [150], STING agonists [151,152], and TLR inhibitors are also under investigation, which may emerge as important options for future therapeutic development. Regarding DAMP signaling, CD24, an innate immune checkpoint binding to inhibitory Siglec10/G receptor, has also been repurposed as a promising target for COVID-19 treatment (Fig. 3) [75]. In line with its encouraging results in management of graft versus host disease (GVHD), addition of CD24 fusion protein to standard of care could prevent disease progression in a pre-planned interim efficacy analysis in the SACCOVID clinical trial [153]. Unpublished data from a recent trial showed that 29 of 30 patients rapidly recovered from moderate/serious COVID-19 infections after delivering CD24-enriched exosomes to the lung, which may become a potential breakthrough for COVID-19 treatment [154]. Given the primary success of these inhaled drugs, regulating the local immune response in the lung may be a promising strategy moving forward [30,155]. Likewise, early research has found that aberrant immature neutrophils are induced during SARS-CoV-2 infection. Recent data demonstrated that alarmins S100A8/A9, which are DAMP molecules, may account for this immune disorder in severe patients. Blockade of S100A8/9 through paquinimod could rescue pneumonia with substantial reduction of SARS-CoV-2 viral loads in preclinical experiments, providing a good option for further COVID-19 treatment [72]. Collectively, these promising results provide support for the importance of correcting myeloid cell dysregulation at activation stages prior to uncontrolled, downstream cytokine storm feed forward loops (Fig. 3 and Table 1).

Strategies targeting the virus-host interaction, especially the virus-immune cell interaction, have been of great interest. A strong association between neutralization antibody levels and immune protection has been increasingly recognized [156]. Administration of neutralizing antibody, such as sotrovimab (VIR-7831), may reduce the risk of hospitalization and death in patients with mild and moderate diseases [157]. However, most of these neutralizing antibodies seem ineffective for patients with severe disease [158]. Some neutralizing antibodies may facilitate various viral functions and even worsen clinical outcomes, particularly via the antibody-dependent enhancement (ADE) effect, complicating neutralizing antibody treatment [158,159]. Of note, current antibody programs are mostly designed to block the SARS-CoV-2 S/ACE2 interaction. Given that ACE2 is minimally expressed on most human peripheral immune cells, exploring novel antibodies that target additional viral receptors are urgently required, especially those that

Table 1
Key clinical trials assessing immunotherapies in the management of COVID-19.

Drug/Targets	Trials	Study design	Primary results	Timelines of the same or similar targets
Dexamethasone (Corticosteroids)	NCT04381936 (RECOVERY) (phase 2/3, RCT) [121]	Hospitalized COVID-19	Dexamethasone resulted in a reduction in mortality of 2.8 % for usual care (22.9 % vs. 25.7 %; $p<0.001$)	Hydrocortisone (NCT02735707, phase 4); Methylprednisolone (NCT04244591, phase 2/3)
Tocilizumab (IL-6 receptor antagonist), EUA	NCT04381936 (RECOVERY) (phase 2/3, RCT) [130]	Hypoxia with systemic inflammation, receive SoC and either tocilizumab or SoC alone	Tocilizumab resulted in a reduction in mortality within 28 days as compared to SoC (31 % vs. 35 %; $p = 0.0028$)	Tocilizumab (NCT04320615, phase 3); Sarilumab (NCT04327388, phase 3); Olokizumab (NCT04380519, phase 2/3)
Clazakizumab (IL-6 antagonist)	NCT04363502 (phase 2, RCT)	Life-threatening COVID-19 infection, receive SoC and either clazakizumab or placebo	Not yet published	Clazakizumab (NCT04494724, phase 2); Siltuximab (NCT04322188, observational); Sirukumab (NCT04380961, phase 2)
Lenzilumab (GM-CSF antagonist)	NCT04351152 (phase 3, RCT) [131]	SpO2 $\leq$ 94 % or requiring supplemental oxygen, but not IMV, receive SoC and either lenzilumab or placebo	Lenzilumab improved the likelihood of SWOV by 54 % in the mITT population ($p = 0.041$) compared to placebo	Gimsilumab (NCT04351243, phase 2); Otilimab (NCT04376684, phase 2)
Mavrilimumab (GM-CSF receptor antagonist)	NCT04399980, NCT04463004, NCT04492514, (MASH-COVID) (phase 2, RCT) [133]	Severe COVID-19 pneumonia and systemic hyperinflammation, receive SoC and either mavrilimumab or placebo	No significant increase in the proportion of patients free of supplemental oxygen at day 14 in mavrilimumab group compared to placebo (57 % vs. 47 %; $p = 0.76$)	Mavrilimumab (NCT04397497, phase 2; NCT04447469, phase 2/3)
Baricitinib (JAK 1/2 inhibitor), EUA	NCT04421027, (COV-BARRIER) (phase 3, RCT) [136]	Hospitalized COVID-19, receive SoC and either baricitinib or placebo	Baricitinib resulted in a reduction in mortality by day 28 as compared to placebo (8 % vs. 13 %; $p = 0.0018$)	Tofacitinib, selective JAK1/3 inhibitor, and to lesser extent JAK2 (NCT04469114, phase 3)
CERC-002 (TNFSF14 antagonist)	NCT04412057 (phase 2, RCT) [142]	Mild to moderate ARDS, randomly receive a single dose of CERC-002 or placebo, in addition to standard of care that included high dose corticosteroids	CERC-002 increased the rate of survival and free of respiratory failure status through day 28 as compared to placebo (83.9 % vs. 64.5 %; $p = 0.044$)	Adalimumab, TNF-α antagonist, (NCT04705844, phase 3); Infliximab, TNF-α antagonist, (NCT04922827, phase 2); Etanercept, TNF-α receptor fusion protein, (pre-clinical)
Anakinra (IL-1 receptor antagonist)	NCT04341584 (CORIMUNO-ANA-1) (phase 2, RCT) [144]	Mild-to-moderate COVID-19 pneumonia, receive usual care plus anakinra or usual care alone	No significant difference in WHO-CPS score of >5 points at day 4 in anakinra group compared to placebo (36 % vs. 38 %)	Anakinra (NCT04680949, phase 3)
Canakinumab (IL-1β antagonist)	NCT04362813 (CAN-COVID) (phase 3, RCT) [145]	Patients with COVID-19 pneumonia, receive SoC and either canakinumab or placebo	No significant difference in survival rate without requiring IMV between canakinumab group and placebo group (88.8 % vs. 85.7 %, $p = 0.29$)	Canakinumab (NCT04476706, no longer available)
Secukinumab (IL-17A antagonist)	RBR-5vpyh4 (BISHOP study) (phase 2, RCT) [146]	Hospitalized COVID-19, receive SoC plus secukinumab or SoC alone	No significant difference in VFD between secukinumab group and control group (23.7 vs. 23.8 days; $p = 0.62$)	Ixekizumab (NCT04724629, phase 3)
Cenicriviroc (CCR2/CCR5 antagonist)	NCT04500418 (phase 2, RCT)	Patients with COVID-19 scoring "3" or "4" on the 7-Point Ordinal Scale, receive SoC and either cenicriviroc or placebo	Not yet published	BMS-813160 (pre-clinical)
SNG001 (Inhaled interferon β-1a)	NCT04385095 (phase 2, RCT) [148]	Adults admitted to hospital with COVID-19 symptoms, randomly receive SNG001 or placebo by inhalation for 14 days	Patients receiving SNG001 had greater odds of improvement on the OSCI scale on day 15 or 16 ($p = 0.033$)	Interferon β-1a, (NCT04350671, phase 4); Interferon β-1b (NCT04465695, phase 2); Interferon α-2b (NCT04480138, phase 2)
SACCOVID (CD24Fc)	NCT04317040 (SAC-COVID) (phase 3, RCT) [153]	Severe or critical COVID-19, receive best available treatment and either CD24Fc or placebo	SACCOVID improved the likelihood of clinical recovery by 60 % compared to placebo ($p = 0.005$). (Unpublished interim efficacy and safety analyses)	CD24-enriched exosomes (NCT04747574, phase 1; NCT04969172, phase 2)
BMS-986253 (IL-8 antagonist)	NCT04347226 (phase 2, RCT)	Hospitalized COVID-19, receive SoC plus BMS-986253 or SoC alone	Not yet published	ABX-IL8, IL-8 antagonist, (pre-clinical)
EB05 (TLR4 antagonist)	NCT04401475 (phase 2/3, RCT)	Hospitalized COVID-19, receive SoC and either EB05 or placebo	Not yet published	M5049, TLR7/8 inhibitor (NCT04448756, phase 2)

RCT, randomized controlled trial; EUA, emergency use authorization; SoC, standard-of-care; SpO2, oxygen saturation; SWOV, survival without ventilation; mITT, modified intention-to-treat analysis; JAK, Janus kinase; WHO-CPS, World Health Organization 10-point Clinical Progression Scale; OSCI, Ordinal Scale for Clinical Improvement; IMV, invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; VFD, ventilator-free days.

interfere with functional interactions between immune cells and the coronavirus. Specifically, our previous research identified that SARS-CoV-2 engages immune cells through specific extracellular proteins, C-type lectins and TTYH2, which are interactions distinct from ACE2 [80]. Engineered nanobodies (Fig. 3), which can be nebulized and delivered to the lung, potently blocked all viral immune interactions along with ACE2 and reduced proinflammatory responses. Our data reveals an important therapeutic paradigm for neutralizing not only receptors for viral infection, but also for hyperinflammation [80]. We are advancing these nanobodies towards development as a new therapeutic option for patients with COVID-19, though the clinical benefits and appropriate timing for use of these agents await further evaluation.

Although the dysregulation of the immune response was artificially separated to early and late phases, key pathogenic mechanisms in the clinic can occur in parallel and synergize with one another [160]. Consistent with the benefit of combining IL-6 blockade with

corticosteroids and baricitinib with remdesivir, the combinatorial usage of antiviruses and immunomodulators (or agents targeting different phases of immune dysregulation together) are rational and under further investigation, especially for patients with clear signs of hyper-inflammation. However, there is still limited evidence regarding the safety and efficacy of combinatorial treatment in early COVID-19. The combinational usage of immunomodulators with molnupiravir, a recent investigational oral antiviral drug primarily based on RNA mutagenesis for outpatients [161,162], might provide the possibility controlling infection early and efficiently. However, the potential risk of accelerating the emergence of variants [163] and safety concerns of its mutagenic effect on host cells must be noted. Several genetic and metabolic defects have been recently identified in patients with life-threatening COVID-19 [164]; identification of patients with high risk of immune dysregulation at initial stages provides the possibility for early combined and personalized therapy in select patients with known defects. It is also important to explore multi-specific antibodies or cocktails to prevent virus mutational escape due to new and emerging variants [165,166]. In addition, recent research suggests that dysregulated metabolic profiles and energy generation, such as upregulation of oxidative phosphorylation and downregulation of fructose and mannose metabolism [167], may be an underlying mechanism for imbalanced immune responses [168,169]. This contributes to increased mortality in COVID-19 patients with type 2 diabetes mellitus and obesity [170,171]. These new findings offer the possibility to combine agents targeting key immune-metabolic pathways for COVID-19 treatment, though disruption of normal host metabolism should be avoided. Overall, strategies targeting dysregulated myeloid responses have improved clinical outcomes of COVID-19. Earlier immunological intervention and combination of therapies with different mechanisms carry the potential to achieve greater levels of success for COVID-19 management.

7. Conclusion

Hyperactivated myeloid cells constitute a key part of COVID-19 immunopathogenesis. In this review, we summarize the major mechanisms describing how SARS-CoV-2 dysregulates myeloid cells, their functional consequences, and potential myeloid targeted immunotherapies. We outline direct innate sensing and viral/host protein interactions as potential drivers of myeloid cell hyperactivation, discussing in particular novel myeloid cell receptors for SARS-CoV-2 S protein binding that trigger subsequent myeloid overactivation. Further investigation of myeloid biology over the course of disease progression is necessary and will yield fertile ground for the development of novel immunotherapies targeting all stages of myeloid cell activation. Combinatorial strategies with early intervention will hopefully correct myeloid dysregulation while reducing viral burden, offering patients new options to manage and treat COVID-19.

Author contributions

J.W., T.T.S., T.M., and R.G. conceived the study and wrote the manuscript, Q.L. and J.W. drafted the figures.

Declaration of Competing Interest

J.W. and Q.L. are named inventors on a patent application that describes the anti-SARS-CoV-2 spike nanobodies that block both ACE2 and myeloid cell receptor interactions. J.W. is a consultant for Lilly Asia Ventures and is on the Scientific Advisory Board of *Rootpath Genomics*, which is not relevant to this work. T.M. is named an inventor on a patent entitled “Compositions and Methods for Treating, Ameliorating, and/or Preventing Viral Infections”. The other authors declare no competing interests exist.

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