




# Role of Monocytes/Macrophages in Covid-19 Pathogenesis: Implications for Therapy

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**cov-Abstract:** Emerging studies from SARS-CoV-2-infected patients indicate a preponderant role of monocytes/macrophages in the pathogenesis of this viral infection, in a similar way to that previously observed in other coronavirus outbreaks (SARS and MERS). The clinical presentation of severe patients resembles viral-associated hemophagocytic syndrome, a rare condition previously seen during lethal influenza pandemics and during previous SARS and MERS coronavirus outbreaks. SARS-CoV-2 infection triggers an over-exuberant inflammatory response due to the development of a cytokine storm and the depletion of the adaptative immune compartment, which may prelude sepsis in many cases. The present review summarizes past evidence on the role of monocytes/macrophages in previous coronavirus outbreaks and the emerging knowledge on their role in COVID-19 pathogenesis. Treatment strategies incorporating the blockade of migration and differentiation of monocyte-macrophage, such as granulocyte macrophage-colony stimulating factor inhibitors, might enhance the promising results seen so far with selective cytokine blockade.

**Keywords:** monocyte/macrophage, COVID-19 infection, anti-GM-CSF, coronavirus

## Introduction

Novel coronavirus infection (SARS-Cov-2) produces a severe respiratory syndrome, similar to the severe acute respiratory syndrome (SARS) observed in previous coronavirus outbreaks. This syndrome is associated to intensive care unit (ICU) admission and high lethality rates.<sup>1</sup> Emerging studies on SARS-CoV-2 pathogenesis point to infiltration of pro-inflammatory monocytes as key mediators of the hyper-inflammatory response produced during viral shedding in the infectious phase, and mainly involved in the cytokine storm observed during the inflammatory phase in severe cases. Zhang et al observed that during SARS-CoV-2 infection, there are morphological and inflammation-related phenotypic changes in peripheral blood monocytes that correlate with the patient's outcome, suggesting that an excessive monocyte-macrophage activation may lead to the subsequent respiratory failure in severe patients.<sup>2</sup> Characterization of lung immune microenvironment through bronchoalveolar lavage fluid in first SARS-CoV-2 patients also showed a predominant monocyte-derived macrophage infiltration in the severely damaged lungs and a highly expanded clonal CD8+T cell in mild patients; suggesting that a robust adaptive immune response is connected to a successful control of SARS-CoV-2 infection.<sup>3</sup>

Dysregulation of the immune response is one of the hallmarks of severe SARS-CoV-2 infection, with lower lymphocytes counts and an increased neutrophil-lymphocyte ratio. Acute phase reactants levels (C-reactive protein (CRP) and ferritin) are

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highly increased along with inflammatory cytokines such as IL-6.<sup>4</sup> This stimulates the production of an excessive, non-effective host immune response by innate cells, which is associated with severe lung injury. Hyperinflammation observed in severe infection results in an immunosuppression status with a clinical course that resembles hemophagocytic syndrome, triggering the production of fatal hypercytokinaemia and consequently multiorgan failure.<sup>5</sup>

## Lessons Learned from SARS and MERS Coronavirus Outbreaks

Other coronaviruses have caused major outbreaks of severe respiratory infections in the 21<sup>st</sup> century. In 2002, SARS-Cov-1 was identified as the cause of severe acute respiratory syndrome (SARS) in the Guangdong province of China, which subsequently spread to more than 30 countries with more than 8000 cases reported worldwide and a 10% case fatality rate.<sup>6</sup> Ten years later, an outbreak of another coronavirus in the Arabian Peninsula was identified, called Middle East respiratory syndrome (MERS), provoking a severe, acute respiratory illness similar to SARS with nearly of 2500 cases in at least 27 countries.<sup>7</sup>

These previous highly pathogenic human respiratory coronaviruses showed close similitudes with the current SARS-CoV-2 outbreak, triggering an exuberant inflammatory response leading to respiratory failure and lung damage. Studies of these previous coronavirus outbreaks showed that a robust viral replication was accompanied by a delayed type I interferon (IFN-I) signalling and a lung immunopathology with very low survival.<sup>8,9</sup> This delayed activation of the IFN-I pathway and promoted the accumulation of inflammatory monocytes infiltrating from peripheral blood, resulting in a cytokine storm and the absence of a virus-specific T cell response. A characteristic of patients who developed severe SARS was an increased number of macrophages in the lungs<sup>10,11</sup> signalling this cell as the key mediator to lung destruction.

Furthermore, human coronaviruses have showed their ability to infect human leukocytic cell lines and peripheral blood mononuclear cells.<sup>12</sup> Moreover, coronavirus infection of a primary monocytic cell line leads to cell activation and an aberrant production of pro-inflammatory mediators with increased chemoattraction. This observation suggests that, for some human coronavirus, monocytes/macrophages could serve as a reservoir which, consequently, would work as vectors for viral dissemination to other tissues.<sup>13,14</sup> This fact has so far not been

proven for SARS-CoV-2. Infection of macrophages might be enhanced by an antibody-dependent effect, where previous non-neutralizing antibodies against coronavirus facilitate binding to Fc receptors in monocytes and macrophages.<sup>15</sup> In vitro infection of human macrophages by SARS-CoV-1 induced high expression of chemokines such as CXCL10 and CCL2 and a poor induction of Interferon- $\beta$ .<sup>16</sup> In another study, strong up-regulation of several inflammatory chemokines (MIP-1 $\alpha$ , RANTES, IP-10 and MCP-1) linked to a low expression of the antiviral cytokines interferon- $\alpha/\beta/\gamma$  and IL-12 in SARS-infected monocytes was interpreted as a escape mechanism for coronavirus.<sup>17</sup>

Differences in the transcriptional profile of monocytic cells infected with different coronaviruses were also observed. SARS-CoV-1 induced down-regulation of interferon- $\alpha/\beta$  and cathepsin/proteasome genes, while hypoxia/hyperoxia related genes were up-regulated. However, coronavirus 229E (Cov-229E), causing common cold, does not induce these changes, showing that regulation of immune-related genes in monocyte/macrophage might be important for differences in pathogenesis between coronavirus strains.<sup>18</sup> Modulation of intrinsic functions of monocyte-derived macrophages and dendritic cells by coronavirus-induced lung epithelial cytokines (IL-6 and IL-8) was responsible for the exacerbated pathogenesis during SARS-CoV-1 infection of human lung epithelial cells in culture.<sup>19</sup> Given the importance of monocyte/macrophage cells during the immune response, it is possible that infection by coronaviruses and alteration of their function may be an important clue to unravel the course of infection in humans.

SARS-CoV-1 also demonstrated potential neurotropism, as several patients experienced central nervous symptoms during the course of the illness. Moreover, the brain tissue revealed the presence of high amounts of the monokine-induced by interferon- $\gamma$  (MIG) produced by monocytic cells, and infiltration of CD68+ monocytes/macrophages and CD3+ T lymphocytes in the brain mesenchyme<sup>20</sup> during pathologic examination.

## Cytokine Storm and Immunopathology

A large number of clinical data collected from SARS-CoV-2 patients suggest the presence of a mild-to-severe cytokine storm in patients requiring admission, which has also been argued as an important cause of death.<sup>5,21</sup> Cytokine

storm or cytokine release syndrome (CRS) is a form of systemic inflammatory response usually triggered by a variety of factors such as infections and drugs.<sup>22</sup> CRS occurs when large numbers of leucocytes are activated and release pro-inflammatory cytokines, which recruits and activates more leucocytes in a positive feedback loop of hyperinflammation.<sup>23</sup> Recently, a key role for macrophages in driving CRS was revealed by analysing CRS produced following chimeric antigen receptor-modified T (CAR T) therapy.<sup>24,25</sup> These studies identified human monocytes as the major source of IL-1, IL-6 and nitric oxide – the main hallmarks of CRS. Monocyte depletion or therapeutic depletion of IL-6 and IL-1 prevented CRS in this model. Similarly, in two clinically relevant animal models, depletion of macrophages at disease onset was shown to decrease lethality and limit the cytokine storm, pointing to macrophage-based therapies for CRS.<sup>26</sup>

CRS is closely linked to the macrophage activation syndrome (MAS), a life-threatening complication of several autoimmune diseases related to hemophagocytic lymphohistiocytosis (HLH). MAS is characterized by pancytopenia, liver insufficiency, hyperferritinemia, coagulopathy and neurologic symptoms due to uncontrolled proliferation of well-differentiated macrophages; leading to widespread hemophagocytosis and cytokine overproduction.<sup>27,28</sup>

Severe COVID-19 patients developing pneumonia exhibit features of the systemic hyper-inflammation that is characteristic of MAS.<sup>29,30</sup> This overexuberant immune response associated with MAS may be driving SARS-CoV-2 related adult respiratory distress syndrome (ARDS), as typical of severe SARS pathogenesis.

At the same time, viral infection can trigger MAS and HLH, in what is known as virus-associated hemophagocytic syndrome (VAHS), a severe complication of various viral infections often resulting in multiorgan failure and death.<sup>31</sup> These phenomena have been observed during lethal influenza pandemics, such as 2009 influenza A H1N1, 1998 avian influenza H5N1, and 1918 Spanish flu H1N1.<sup>32,33</sup> VAHS clinical course presented as an aggressive, life-threatening condition, analogous to HLH, and associated with massive pro-inflammatory cytokine release, elevated plasma levels of acute phase reactants, and the accumulation of activated T-lymphocytes and macrophages in various organs. Further, VAHS has been linked to the high fatality rate in MERS-Cov outbreak and SARS-CoV,<sup>34</sup> and is now linked to the current SARS-CoV-2.<sup>5,35</sup>

Also, MAS and VAHS are linked to thrombotic events and coagulopathy<sup>36,37</sup> highlighting the key role of monocyte-

macrophages in the regulation of coagulation events.<sup>38</sup> Monocytes and macrophages can act as procoagulant factors, and interact with blood coagulation mechanisms resulting in thrombus formation and extravascular fibrin accumulation.<sup>39</sup> COVID-19 is linked to a microvascular vessel obstructive thrombo-inflammatory syndrome in lung and other vital organs, leading to multiple organ failure and death.<sup>40,41</sup>

## Action of IL-6 and GM-CSF on Monocyte-Macrophage Differentiation

IL-6 and granulocyte macrophage-colony stimulating factor (GM-CSF) are cytokines closely linked to regulation of monocyte activation and differentiation to macrophages. Both cytokines increased during the cytokine storm in SARS-CoV-2 patients requiring ICU<sup>29</sup> and are involved in the immunopathology of autoimmunity and the inflammatory condition; they were identified as therapeutic blockade targets of the cytokine storm during systemic inflammatory responses, as observed in MAS and HLH.<sup>42,43</sup> In this sense, emerging reports indicate that SARS-CoV-2 infection precedes the onset of various autoimmune and autoinflammatory diseases, including the newly described paediatric inflammatory multisystemic syndrome.<sup>44</sup> This new evidence reinforces the link between infectious diseases and the triggering of autoimmune and autoinflammatory sequelae.<sup>45</sup>

IL-6 is an essential factor in the molecular control of monocyte activation and differentiation. It is secreted by a variety of cellular types, including macrophages, fibroblasts, T-cells and endothelial cells<sup>46</sup> in response to infection, and it sends out an early warning signal to the entire body, activating inflammatory events and immunity. IL-6 regulates the differentiation of monocytes to macrophages, up-regulating expression of functional GM-CSF receptors on monocytes, and switching the differentiation of monocytes from dendritic cells with antigen-presenting functions to inflammatory macrophages.<sup>47</sup> IL-6 is the chief stimulator of the production of most acute phase proteins, and critical for the febrile response. During systemic inflammation such as in MAS, IL-6 is pyrogenic by binding to IL-6 receptors on brain endothelial cells to induce prostaglandin synthesis and aggravate inflammation;<sup>48</sup> furthermore, it dictates the transition from acute to chronic inflammation by changing the nature of the leucocyte infiltrate from polymorphonuclear neutrophils to monocyte/macrophages.<sup>49</sup>

Obesity and diabetes, both risk factors for greater severity in COVID-19 patients, are closely related to perturbation of the monocyte compartment, with a marked shift toward a pro-inflammatory phenotype which might contribute to the development of low-grade inflammation observed in obesity.<sup>50</sup> IL-6 has been highlighted as a driver of this metabolic inflammation<sup>51</sup> and therefore increased risk for severe COVID-19 condition.

Moreover, during CRS, IL-6 is an important member of the cytokine network and plays a key role in acute inflammation. In SARS-CoV-2 infection, blockade of IL-6 signal transduction with Tocilizumab has become an important therapeutic weapon in a small series of severe cases with early reports of success; this evidence demonstrates that blockade of cytokine storm is an effective therapeutic option.<sup>21</sup>

GM-CSF, another monocyte/macrophage-related cytokine, has an important effect under inflammatory conditions, promoting neutrophil and monocyte migration, proliferation and maturation. GM-CSF stimulates stem cells to produce granulocytes and monocytes, and promotes migration of monocytes to the inflammatory tissues and differentiation to inflammatory macrophages.<sup>52</sup> In autoimmune inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis, GM-CSF has a pathogenic role; several inhibitory drugs are currently undergoing clinical trials.<sup>53</sup> Both autoimmune conditions are frequently associated with viral infections, suggesting a key role for viruses in the dysregulation of tolerance immune mechanisms and the triggering of autoimmune diseases.<sup>54</sup>

In a similar way, GM-CSF blockade has been demonstrated to inhibit the cytokine release syndrome and neuroinflammation in the management of CART cell therapy-associated toxicities,<sup>55</sup> thus arising as a promising drug for SARS-CoV-2 patients.

## Monocytes, ACE2 and RAAS

It has been reported that ACE2 is the main host cell receptor for human pathogenic coronaviruses (SARS-CoV-1, MERS and SARS-CoV-2) and that it plays a key role in the entry of the virus into the cell and viral spreading and pathogenesis, interfering in the renin-angiotensin-aldosterone system (RAAS).<sup>56</sup> ACE2 is widely distributed in various human tissues and may be a determinant factor of activity in severe disease pathogenesis.<sup>57</sup> Several immune cells are involved in the RAAS, playing a pivotal role in the regulation of vascular inflammation and hypertension.<sup>58</sup> Human monocyte subsets exhibit different expression on angiotensin-

converting enzyme type 1 and 2 (ACE1 and ACE2) and may be directly involved in the regulation of vascular homeostasis via the RAAS mechanisms<sup>59</sup> Therefore, SARS-CoV-2 activated-monocytes could also be critically involved in the pathogenic effect on the vascular homeostasis, through perturbation of ACE2 function.

RAAS activation in monocytes through its physiological effectors plays a key role in promoting and maintaining inflammation. Monocytes have been demonstrated to be actively involved in all key stages of acute coronary syndromes and constitute an important part of the coagulation system<sup>60</sup> Therefore, SARS-CoV-2 activation of monocytes and perturbation of RAAS through ACE2-monocyte activation may trigger acute coronary syndromes in predisposed patients, as shown in COVID-19 infection.<sup>61</sup>

## Antibody-Dependent Enhancement of Macrophages

Antibody-dependent enhancement (ADE) of virus infection is a phenomenon whereby virus-specific non-neutralizing antibodies enhance the entry of the virus, and in some cases the replication, into monocytes/macrophages through interaction with Fc receptors;<sup>62</sup> the result is that a normally mild viral infection becomes life-threatening. This phenomenon has been described as mediator of acute lung injury in both SARS and MERS outbreaks<sup>63,64</sup> and demonstrated in animal models. This evidence suggests that people exposed to MERS-CoV who failed to develop a neutralizing antibody response may be at risk of severe lung disease on re-exposure to MERS-CoV.<sup>65</sup> Similarly, evaluation of SARS vaccines in mice induced protection against infection but challenged animals exhibited an exacerbated immunopathologic-type lung disease.<sup>66</sup> Anti-spike viral protein antibodies were identified as mediators of the infection of immune cells<sup>15,67</sup> causing severe acute lung injury by skewing macrophage responses during acute SARS-CoV-1 infection.<sup>34</sup> Recent studies have revealed complex roles for antibodies in viral entry, describing an ADE effect with neutralizing antibody to the surface spike protein of coronaviruses, and molecular mechanisms for ADE in coronavirus entry.<sup>68</sup> Binding of these antibodies to the viral spike triggers a conformational change that mediates viral entry into Fc receptor-expressing cells. This evidence reveals the impact of antibody dosages on viral entry and serves as a guide for future vaccine design and antibody-based

drug therapies<sup>69</sup> The potential danger of these suboptimal antibody responses has been also noted for COVID-19 highlighting the importance of safety evaluation of candidate vaccines.<sup>70</sup>

ADE effect on monocytes is also currently proposed as an explanation for the geographic discrepancy in the pathogenesis of the current SARS-CoV-2 epidemic around the world. Prior exposure to similar antigenic epitopes from local circulating coronaviruses might be a possible explanation for the geographic differences of lethality rates; it may also provide an explanation to the high death rates among elderly people, more exposed to previous coronaviruses.<sup>71</sup>

This ADE mechanism is not exclusive to coronaviruses and was also observed during influenza pandemics,<sup>72</sup> in dengue<sup>73</sup> and VIH<sup>74</sup> viral infections, leading to enhanced pathology.

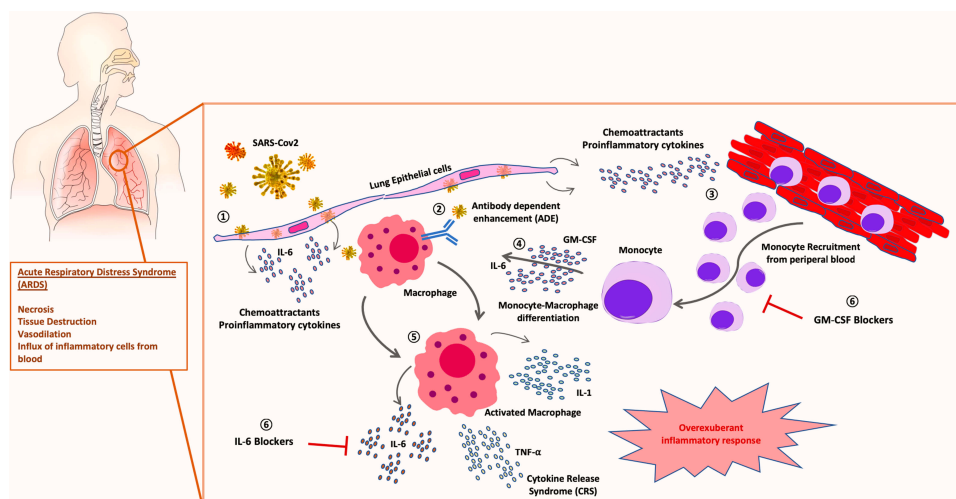
## Targeting IL-6 and GM-CSF as a Therapeutic Approach in SARS-CoV-2 Patients

Several biological agents targeting pro-inflammatory cytokines have demonstrated effectiveness in SARS-CoV-2 severe pathology<sup>75</sup> Tocilizumab is a recombinant human IL-6 monoclonal antibody, which binds to soluble and membrane-bound IL-6 receptors (IL-6R). Blocking IL-6 signalling is highly effective in the attenuation of

inflammatory responses<sup>76</sup> according to the experience gained in rheumatic and other inflammatory diseases, and the prevention of CRS caused by CART immunotherapy.

Other drugs proposed for avoiding harmful CRS syndrome in SARS-CoV-2 patients are JAK inhibitors drugs, which inhibit signalling cascades for a variety of inflammatory cytokines.<sup>77</sup> However, one of the most significant concerns about JAK inhibitors is the inhibition of IFN- $\alpha$ , with anti-viral properties and theoretically useful against SARS-Cov2; further, JAK inhibitors also inhibit IL-10, which is the main regulator cytokine of the immune system.

An interesting alternative, in combination with cytokine blocking drugs, could be the use of GM-CSF inhibitors to inhibit monocyte/macrophage differentiation and migration to pulmonary tissues. Several GM-CSF inhibitor drugs are currently undergoing clinical trials for rheumatic arthritis (RA) and other inflammatory conditions. Otilimab (GSK3196165) is a fully human antibody against GM-CSF, currently in Phase III in patients with RA, and it has shown promising results in initial developmental phases. Namilumab (MT203) is currently being tested for application in RA and psoriatic arthritis. Lenzilumab (KB003), is a humanized monoclonal antibody that targets GM-CSF originally designed for the treatment of chronic myelomonocytic leukaemia; it is currently under clinical trial for refractory large B-cell lymphoma and has demonstrated to be effective in vitro to avoid CRS in CART-associated toxicities.<sup>55</sup> Very recently, GM-CSF neutralization with lenzilumab showed positive results related to improved



**Figure 1** Role of monocyte-macrophage in SARS-CoV-2 pathogenesis: 1) SARS-CoV-2 infection of lung tissue induces release of chemoattractant proinflammatory cytokines by epithelial cells and fibroblasts. 2) Viral antibody-dependent enhancement (ADE) of macrophages could trigger SARS-CoV-2 infection of leucocytes. 3) Chemoattractant gradient induces massive recruitment of inflammatory monocytes from peripheral blood. 4) Monocyte-macrophage activation and differentiation is triggered by GM-CSF and IL-6. 5) An overexuberant activation of macrophages produces the cytokine release syndrome (CRS) responsible for the acute respiratory distress syndrome (ARDS) typical of severe patients. 6) Therapeutic blockade of IL-6 and GM-CSF combination could avoid severe lung immunopathology in COVID-19 patients.

clinical outcomes, oxygen requirement and ameliorated cytokine storm in a single-centre study<sup>78</sup> Mavrilimumab is a human monoclonal antibody that inhibits human GM-CSF receptor (GM-CSF-R) and is also an investigational drug for the treatment of rheumatic diseases<sup>79</sup> Also, very recently, mavrilimumab treatment has shown improved clinical outcomes in non-mechanically ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation in a single-centre study<sup>80</sup> The use of this monocyte-macrophage differentiation inhibitor drugs could be employed at initial phases of CRS to avoid massive migration of inflammatory monocytes to pulmonary tissues, preventing the cytokine storm and immunopathology associated to SARS-CoV-2 infection. A combination of GM-CSF inhibitor drugs and selective cytokine blockers could act synergistically to ameliorate lung injury (Figure 1) in patients at high risk of ICU admission and mechanical ventilation support. Monitorization of pro-inflammatory cytokines and acute phase reactants levels would help identify patients who can benefit from this therapy. Results from ongoing clinical trials will provide more extensive knowledge about indications and potential limitations of this therapy.

## Future Directions

Undoubtedly, monocyte-macrophage cells have a preponderant role in the immunopathology associated to severe outcome in SARS-CoV-2 infection. Given that these cells are considered drivers of CRS, future studies should focus on monitoring them, aiming to early detect individuals initiating uncontrolled and ineffective immune responses and developing targeted therapeutic approaches. This could shed light on strategies to prevent or at least decrease lung injury and the high lethal rates associated to SARS-CoV-2. Treatment strategies that encompass blocking migration and differentiation of these cells, such as GM-CSF inhibitors, might enhance the promising results seen with selective cytokine blockade.

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## Disclosure

Jose Gomez-Rial reports personal fees from and being a speaker in scientific meetings and advisor for Merck Sharp and Dohme, GlaxoSmithkline, and Pfizer, outside the submitted work. Irene Rivero-Calle reports trials fees paid to the institution from Ablynx, Jansen, and Mediumimmune, grants, personal fees, other from GSK, grants and personal fees (research grants and honoraria as an advisor and speaker, and for attending conferences and practical courses; trials fees paid to the institution) from Pfizer, MSD, Sanofi Pasteur, outside the submitted work. Federico Martín-Torres has received honoraria from GSK, Pfizer, Sanofi Pasteur, MSD, Seqirus, and Janssen for taking part in advisory boards and expert meetings, and for acting as speaker in congresses outside the scope of the submitted work. FM-T has also acted as principal investigator in RCTs of the above-mentioned companies as well as Ablynx, Regeneron, Roche, Abbott, Novavax, and MedImmune, with honoraria paid to his institution. The authors report no other possible conflicts of interest in this work.

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