Inflammatory Mechanisms in COVID-19, Atherosclerosis

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Clinical studies have demonstrated that COVID-19 mortality is predominantly related to thromboembolic disease and coagulation abnormalities, in which the so-called “cytokine storm” and systemic inflammation play an orchestrating role. Inflammation plays an important pathogenic role in atherosclerotic cardiovascular disease in general and in ischemic heart disease in particular. Endothelial dysfunction, hyperinflammation, and coagulopathy contribute to disease severity and death in patients infected with SARS-CoV-2, while also being prevalent features of atherosclerosis. The presence of a cytokine storm in patients with COVID-19 causes ARDS or multiorgan dysfunction, including an increased risk of plaque rupture and direct myocardial injury (i.e., myocarditis), leading to high mortality rates. An optimal regulation of the cytokine storm in the early stages of the disease can contribute to treatment effectiveness and reduce the risk of cardiovascular complications, which are the leading cause of death in these patients.

Keywords: COVID-19 ; SARS-CoV-2 ; atherosclerosis ; inflammation

1. Inflammation in COVID-19

Coronaviruses (CoVs) are single-stranded RNA viruses that belong to the Coronaviridae family. The International Committee on Taxonomy of Viruses (ICTV) classifies the CoVs into four categories: α, β, γ, and δ. SARS-CoV-2 is the most recent coronavirus to infect humans. SARS-CoV, MERS-CoV, and SARS-CoV-2 are all viruses that cause extreme pneumonia. The SARS-CoV-2 genome is less than 30 kb in length and contains 14 open reading frames (ORFs) that encode non-structural proteins (NSPs) for viral replication and assembly processes; structural proteins such as spike (S), envelope (E), membrane/matrix (M), and nucleocapsid (N); and accessory proteins. COVID-19 is defined as an illness caused by the novel coronavirus. SARS-COV-2’s higher transmissibility, diverse clinical manifestations, and lower pathogenicity may be attributed to differences in biology and genome structure as compared to SARS-CoV and MERS-CoV.

SARS-CoV-2 enters human cells mainly by binding the angiotensin-converting enzyme 2 (ACE2), which is highly expressed by alveolar lung cells, vascular endothelium, cardiac myocytes, and other cells [1]. Patients suffering from cardiovascular or cerebrovascular comorbidities have a higher risk of infection and worse outcomes [2][3][4]. The virus spreads not only by inhalation of viral particles but also through contaminated surfaces, where it can live for 24–72 h depending on the type of surface. In most cases, the incubation time is shorter than 14 days, with the patient being contagious even though asymptomatic [1]. Commonly identified symptoms include fever, dry cough, dyspnea, chest pain, fatigue, and myalgia. Other less frequent symptoms are headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting [5]. The virus decreases the Type-I Interferon (IFN) response and increases T cell apoptosis, as well as natural killers (NK) cell abnormalities. The direct attack and resulting immune system weakness may explain some of the extreme complications seen in COVID-19 patients, such as hypoxemia, ARDS, arrhythmias, trauma, acute myocardial injury, and acute kidney injury [6][1][7]. In the vast majority of COVID-19 patients, the typical chest computed tomography scan presents bilateral pulmonary parenchymal ground-glass and consolidative opacities, which is even worse in ICU-admitted patients with bilateral multiple lobular and subsegmental areas of consolidation [2][3][8][9]. Laboratory findings are not pathognomonic, with lymphopenia, prolonged prothrombin time, and elevated lactate dehydrogenase being the most prominent. Some patients with extreme bilateral pneumonia have elevated levels of aspartate aminotransferase, creatine kinase, creatinine, C-reactive protein (CRP), D-dimers, and ferritin [10].

2. The Cytokine Storm in COVID-19

The spectrum of symptoms ranges from asymptomatic infections to mild respiratory symptoms to the lethal form of COVID-19, which is associated with severe pneumonia, acute respiratory distress, and fatality. In the early stages of the disease, initial symptoms such as fever, cough, diarrhea, myalgia, or fatigue are present. COVID-19 patients may develop profound hypoxemia early in their disease course. However, overt respiratory failure at these early stages is unusual. Rarely, a minority of patients develop aggravating symptoms leading to multiorgan dysfunction and serious ARDS due to an intense inflammatory response and cytokine overproduction—the cytokine storm. Cytokines are small cell-signaling protein molecules, which may have autocrine or paracrine actions, facilitating intracellular crosstalk [11][12]. The cytokine family consists of more than 100 members, sub-categorized into several smaller clusters such as interleukins (ILs), INFs, colony-stimulating factors (CSFs), tumor necrosis factors (TNFs), and chemokines [13]. A cytokine storm resembling the hyperinflammatory state of COVID-19 has previously been recognized in several critically ill adults, namely those suffering from macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH). MAS/sHLH has historically been classified based on the cause of the disease and is categorized into primary (genetic) and secondary (non-genetic) types, and further subdivided into viral, autoimmune, or neoplasia-related [14]. The classic MAS/sHLH is characterized by fever, adenopathy, hepatosplenomegaly, anemia, other cytopenias, liver function abnormalities, and triggered hypercoagulation secondary to inflammation, followed by pronounced hypercytokinemia [7].

In immunodeficient patients with severe COVID-19 pneumonia, primary HLH may be the potential underlying cause. After entering respiratory epithelial cells, SARS-CoV-2 provokes the activation of Th1 cells to secrete pro-inflammatory cytokines. It is pictured by the failure of perforin, NK, and CD8+ cytotoxic T cells, which lead to cell lysis initiating apoptosis of virally infected cells. Additionally, IFN-γ, which is produced by a large number of widespread T cells, causes excessive macrophage activation [15]. In COVID-19 patients, the incidence of cardiovascular symptoms is high due to the systemic inflammatory response and immune system disorders during disease progression [16]. The exact mechanism of cardiac involvement in COVID-19 remains unclear. One potential mechanism is a direct myocardial involvement mediated via ACE2 or a direct viral effect on the heart muscle called myocarditis. Other proposed mechanisms of myocardial injury include cytokine activity and respiratory insufficiency, all of which may result in myocardial cell apoptosis through a gradual decrease in oxygen provided to the heart muscle [16]. In most immunocompetent patients with severe COVID-19 pneumonia, MAS/sHLH is suspected as the triggering cause of hyper-inflammation. The potential association between SARS-CoV-2 and sHLH relies on its key feature to bind Toll-like receptors (TLRs) and activate inflammasomes (caspases) releasing IL-1β [17]. In vitro cell studies indicate that in the early stages of SARS-CoV infection, respiratory epithelial cells, dendritic cells (DCs), and macrophages exhibit a delayed release of cytokines and chemokines [18]. The induction of low levels of antiviral factor IFNs and high levels of pro-inflammatory cytokines (IL-1β, IL-6, and TNF) as well as specific chemokines (C-C motif chemokine ligand (CCL)-2, CCL-3, and CCL-5) describe this hyperinflammatory state [19][20]. Therefore, the severity of COVID-19 has been strongly associated with the volume of hypercytokinemia, referring to interleukins IL-1β, IL-2, IL-6, IL-7, IL-10, TNF-alpha, granulocyte colony-stimulating factor (G-CSF), IFN-γ-induced protein 10 kDa/CXCL10, monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 1-α, both in serum and affected tissues [7][15]. After the secretion of the pro-inflammatory cytokines IL-1, IL-6, and G-CSF, low levels of IFN-αβ and IFN-γ induce inflammatory cell infiltration through mechanisms involving the Fas–Fas ligand (FasL) or the TRAIL–death receptor 5 (DR5) and trigger the apoptosis of airway and alveolar epithelial cells. Endothelial and epithelial cell apoptosis damages the pulmonary microvascular and alveolar epithelial cell barriers, resulting in vascular leakage, alveolar edema, and gradually, hypoxia [21][22]. Finally, the accumulated mononuclear macrophages engage in phagocytic activity on the debris of dead cells and tissues, secreting more pro-inflammatory cytokines (TNF, IL-6, IL-1β, and inducible nitric oxide synthase (NOS)) and chemoattractants (such as CCL-2, CCL-3, CCL-5, CCL-7, and IFN-γ-induced protein 10) [21]. The pro-inflammatory feed-forward loop of cytokines on innate immune cells results in a cytokine storm, coagulopathy, and acute respiratory distress syndrome [23] (**Table 1**).

Table 1. Cytokines involved in COVID-19 and their prognostic data.

IL-/TNF- and IFN-Family Cytokines	
Factor	**Prognostic Value**
IL-1β	**Elevated levels IL-1β have been associated with hypercoagulation, disseminated intravascular coagulation, and severe symptoms [24].**
IL-2	**Increases in IL-2 or its receptor IL-2R are directly proportional to the severity of the disease [8].**
IL-4	**IL-4 has negative effects on CD8+ memory T cells; elevated IL-4 levels are associated with cytokine storm and severe respiratory symptoms [25].**

IL-/TNF- and IFN-Family Cytokines	
Factor	**Prognostic Value**
IL-6	**Higher levels of IL-6 accelerates the inflammatory process, contributing to the cytokine storm and worsening the prognosis [14].**
IL-12	**NA**
IL-17	**Elevated IL-17 levels have been reported in patients with SARS-CoV-2 as part of the cytokine storm, and they are associated with viral load and disease severity [26].**
IL-18	**NA**
IL-21	**NA**
IL-33	**Higher IL-33 levels have been associated with lung fibrosis and skeletal muscle wasting [27].**
TNF-alpha	**TNF-alpha was one of the cytokines whose overproduction was related to a poor prognosis in patients with SARS-CoV-2, finding an inverse relationship between TNF-alpha levels and T cell counts [28].**
TGF-β	**NA**
IFN-α	**NA**
IFN-γ	**IFN-γ levels are associated with greater viral load and lung damage [29].**
	Chemokines
CCL2/MCP-1	**CCL2 levels were higher in patients with COVID-19 and even higher among those admitted to the Intensive Care Unit [3].**
CCL3/MIP-1A	**NA**
CCL5	**NA**
CXCL9	**NA**
CXCL10/IP-10	**IP-10 levels were found to be elevated in patients with COVID-19 and even higher in those who required Intensive Care Unit admission, suggesting their relationship with lung damage and disease severity [3].**

IL- = Interleukin, TNF-alpha = Tumor Necrosis Factor-alpha, TGF-β = Transforming Growth Factor-β, IFN- = Interferon, CCL = C-C Motif Chemokine Ligand, CXCL = C-X-C Motif Chemokine Ligand, MCP-1 = Monocyte chemoattractant protein-1, MIP-1A = Macrophage inflammatory protein-1A, IP-10 = Interferon gamma-induced protein 10.

3. Inflammation and Pro-Inflammatory Cytokines in Atherosclerosis

Atherosclerosis is characterized by the formation of plaques in the vessel wall. These develop through complex pathophysiological pathways that involve pro- and anti-inflammatory cytokines, secreted by vascular endothelial cells, leukocytes, platelets, and mast cells [13][11]. Endothelial injury, impaired lipid metabolism, and hemodynamic disruption, followed by flow-mediated inflammatory changes in the endothelium, are the main steps in plaque formation and atherosclerosis progression [2]. Inflammation begins when the endothelial cells become activated and secrete adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), E-selectin, and P-selectin) and other inflammatory factors while the smooth muscle cells secrete chemokines and chemoattractants (monocyte chemoattractant protein-1 (MCP-1)), which jointly draw monocytes, lymphocytes, mast cells, and neutrophils into the arterial wall, followed by their migration to the sub-endothelial space [13][30]. The effect of two pro-inflammatory cytokines, TNF-alpha and IL-1, which promote the expression of cytokines, adhesion molecules as well as the migration and mitogenesis of vascular smooth muscle and endothelial cells, is of particular interest [31]. TNF-alpha and IFN-γ have also been associated with the disruption of endothelial cell junctions, leading to leukocyte transmigration, vascular permeability, and matrix degradation, all of which facilitate atherosclerosis development [13][30][31][32].

With regards to human monocytes, three subsets exist owing to differences in functions [33]. $CD14^{+}CD16^{++}$ monocytes, similar to murine lymphocyte antigen 6 complex (Ly6C) low monocytes, patrol the vasculature and are involved in the early inflammatory response, while $CD14^{+}CD16^{+}$ monocytes exert both phagocytic and anti-inflammatory actions. Classical $CD14^{++}CD16^{-}$ monocytes, which are similar to murine Ly6C high monocytes, differentiate to macrophages and engulf a large number of chemically modified (by reactive oxygen species) low-density lipoprotein (LDL) particles known as oxidized LDL (oxLDL), which are prone to phagocytosis [13][34]. The accumulation of oxLDL in the macrophages

transforms them into foam cells, contributing in this way to atherosclerotic plaques [35]. T cells, B cells, neutrophils, dendritic cells, and myeloid cell proliferation are types of resistant chemoattracted cells found in atherosclerotic lesions [36].

Selectins and platelet endothelial cell adhesion molecule (PECAM-1) assist the accumulation of leukocytes into the sub-endothelial space, inducing the inflammation and volume of the lipid core [37]. Fibrous tissue is added to form a fibrous cap over the lipid-rich necrotic cores and just under the endothelium at the blood interface. With aging, the persistent unregulated action of proteolytic enzymes dissolves the fibrous tissue; the fibrous cap becomes thinner and weakens. This thin cap is prone to rupture, exposing the thrombogenic material of the internal arterial wall leading to thrombus formation. As far as the vulnerability of plaque is concerned, studies have focused on the collagenolytic action of matrix metalloproteinases and cysteine proteases in the plaque [38]. The expression of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) increases the risk of plaque rupture, bleeding, and thrombosis [39][40]. Recent studies have shown that IL-1, as well as TNF-alpha and its superfamily of CD40/CD40L ligand, disrupt the fibrinolytic and anti-thrombotic actions triggering thrombotic events [41]. It has also been described that in later stages of atherosclerosis, cytokines such as TNF-alpha, INF-γ, IL-1, and IL-6 act differently, inducing smooth muscle cell apoptosis and matrix degradation, leading to plaque destabilization [42][43]. Similar effects have been noted following the increase of acute-phase proteins, the proliferation of foam cells, and the reduced secretion of NO. CRP has also been linked to a pro-thrombotic function, as it is associated with TF upregulation, decreased levels of prostaglandins (PGI2) and endothelial NOS, and the impairment of coagulation balance, as measured by the thromboxane A2/PGI2 ratio [44][45][46][47]. Finally, the triple activity of INF-γ has been found to destabilize the plaque (as it prevents smooth muscle differentiation), the procollagen-I gene expression, and the collagen crosslinking enzyme, lysyl oxidase [48][49][50].

4. Similarities in the Inflammatory Processes Operating in COVID-19 and Atherosclerosis

COVID-19 presents not only complications in the venous and arterial circulations, but also multiorgan dysfunction [18]. This excessive response has a lot in common with the systemic low-grade inflammation in atherosclerosis. Initially, the impaired vessel endothelium following exposure to cytokines leads to decreased vasodilation in both atherosclerosis and COVID-19, as there is a reduction in the secretion of NO in both situations. Moreover, an improper activation of the coagulation cascade has been observed in COVID-19 patients [51]. Coagulation activation and endothelial dysfunction could be the expression of the sustained inflammatory response associated with vascular inflammation. Interestingly, this endothelium-related prothrombotic state is more prevalent in the lungs than in the lower limbs, even lacking particular risk factors and a history of thromboembolism [51]. The American Heart Association (AHA) suggests that viral infection reduces the cohesion of atherosclerotic plaque and encourages the progression of atherosclerosis and coronary heart disease [51]. IL-1β and IL-6 have major roles in both diseases. IL-6 may be significantly elevated in patients with ARDS from SARS-CoV-2, inducing the secretion of acute phase reactants, although the magnitude of cytokine level is not specific for the disease [52]. Studies showed that the higher circulating cytokine levels are, the more severe manifestations of COVID-19 pneumonia are seen [52]. In the same way, IL-18 and IL-12 in combination with IL-1β induce IFN-γ secretion and promote Th cell and NK activity in both atherosclerosis and COVID-19 [53][54]. Additionally, there are similarities in the secretion of IFN-α, IFN-γ, and TGF-β, as well that of TNF-alpha [7]. It is hypothesized that the atherogenic cytokines found in the plasma of COVID-19 patients are regulated by the shedding of ACE2, the portal allowing SARS-CoV-2 cell entry, or after virus incursion intracellularly [7]. Finally, in COVID-19, the apoptosis of endothelial and epithelial cells in the pulmonary microvasculature and tissues causes the release of chemokines, mainly from the CXC family CXCL9 and CXCL10, MCP-1 (CCL2), CCL2, and CCL3, which can be found in atherosclerotic plaque formation, leading to monocyte/lymphocyte recruitment and infiltration into the subendothelium [19][55][56].

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