Acta virologica **65**: 3 – 9, 2021 doi: 10.4149/av_2021_102

REVIEW

Mechanisms and potential therapeutic targets of hyperinflammatory responses in SARS-CoV-2

Ifeoma Felicia Chukwuma[1], Victor Onukwube Apeh[1,2], Okwesili Fred Chiletugo Nwodo[3]

[1]Department of Biochemistry, Faculty of Biological Sciences, University of Nigeria, Nsukka, Nigeria; [2] Federal College of Dental Technology and Therapy, Enugu, Nigeria; [3]University of Mka, Mka, Benue State, Nigeria

Received July 1, 2020; accepted September 20, 2020

Summary. – Coronavirus infection is now the leading cause of death globally. Despite the several bedsides-to- bench investigations carried out by researchers all over the world to identify the best prophylactic and therapeutic options for this deadly virus, no novel vaccine or treatment drug has been developed. Accumulating evidence suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with hyper inflammation characterized by excessive release of pro-inflammatory cytokines known as a cytokine storm. The hallmark of this unregulated inflammatory response includes viral sepsis, pneumonitis shock, coagulopathy, and acute respiratory distress syndrome (ARDS) which is the major cause of death in COVID-19 patients. In the midst of cytokine storm and coagulopathy, anti-viral agents alone will not provide the much-needed therapeutic effect. Hence, the need to combine anti-inflammatory agents such as interferons, angiotensinogen converting enzyme 2 (ACE-2) inhibitors, interleukin 6 (IL-6), and Janus kinase (JAK) family inhibitors, anticoagulants and other agents involved in inflammation resolution. This review critically presented a comprehensive overview of SAR-CoV-2, unveiled the mechanisms of the inflammatory response in SARS-CoV-2 and also highlighted possible specific prophylactic and therapeutic interventions that will circumvent inflammatory induced deaths in COVID-19 patients.

Keywords: COVID-19; SARS-CoV-2; cytokine storm; coagulopathy and anti-inflammatory

E-mail: chukwuma.ifeoma@unn.edu.ng; odoifeoma1@gmail.com; phone: +234-7064614452.

Abbreviations: ACE-2 = angiotensinogen converting enzyme 2; ARDS = acute respiratory distress syndrome; COVID-19 = Coronavirus disease-19; DAMP = danger-associated molecular patterns; D-dimer = dimerized plasmin fragment D; DIC = disseminated intravascular coagulation; ICU = intensive care unit; IFN = interferon; IL = interleukin; IRF3 = interferon regulatory factor 3; JAK = Janus kinase; MERS-CoV = middle-east respiratory syndrome coronavirus; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B; PAMPs = pathogen-associated molecular pattern; PRR = pattern-recognition receptor; SARS-CoV 2 = severe acute respiratory syndrome coronavirus 2; SPM = specialized pro-resolving mediator; TLR = Toll-like receptors; TNF-α = tumor necrosis factor alpha

Overview of SARS-CoV-2

Coronaviruses are a group of enveloped viruses belonging to the Coronaviridae family, with non-segmented, single-stranded, and positive-sense RNA genomes (Fung *et al*., 2019; Kaul, 2020). The virus contains structural spike (S) proteins (outer glycoprotein), nucleocapsid (N) protein (which is within the phospholipid bilayer), and membrane (M) protein (a type 111 transmembrane glycoprotein) and non-structural proteins, which are encoded by the various genetic loci on the RNA of the viruses (Kaul, 2020; Kumar *et al*., 2020). Novel coronavirus-induced pneumonia was named as coronavirus disease 2019 (COVID-19) by the WHO on February 11, 2020 (Li *et al*.,

2020). Genomic studies carried out on SARS-CoV-2 have shown that the isolated novel β-CoV shows 88% identity to the sequence of SARS-like coronavirus and about 50% identity in the sequence of middle-east respiratory syndrome coronavirus (MERS-CoV). Based on its similarity with SARS-CoV, it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Viral Classification Commission (Li *et al*., 2020).

COVID-19 infected patients exhibit mostly symptoms like fever, fatigue, headache, cough, difficulty in breathing, and sore throat (Kumar *et al*., 2020). COVID-19 patients may be classified according to disease progression into two groups: asymptomatic or mild cases that usually recover and severe cases (approximately 15%) that develop multi-organ failure, primarily respiratory failure, requiring intensive care unit (ICU) (Tufan *et al*., 2020).

Recently, SARS-COV-2 is the leading major cause of morbidity and mortality with approximately 300,000 deaths globally (Mortus and Manek, 2020). Available data show that people with underlying health challenges such as cardiovascular diseases, cancer, hypertension, chronic respiratory disease, and diabetes are at higher risk of dying from the disease (Kumar *et al*., 2020). In other studies, obesity and smoking were associated with increased risks as well as age and sex. A research carried out in China and Italy shows that approximately 64–71% of deceased COVID-19 patients are male (Henry *et al*., 2020). This is attributed to the decrease in the receptor for angiotensinogen converting enzymes 2 (ACE2) associated with binding of the virus to the host cells in children and females while the higher death rate in the aged could be due to decrease in the immune system with age. Hence, the overall susceptibility and rate of recovery is dependent on the person's immune system (Lin *et al*., 2020; Tufan *et al*., 2020).

Studies have shown that hyper inflammation characterized by cytokine storm, immunothrombosis, and coagulopathy are the major cause of mortality in patients with COVID-19 (Levi *et al*. 2020; Mehta *et al*., 2020; Merad and Martin, 2020). Hence, there is a need to look inward on the inflammatory mechanisms in COVID-19 patients. This review critically analyzed the mechanisms of the inflammatory response in COVID-19 patients and also highlighted potential therapeutic intervention which will invariably serve as a therapeutic target for drug design.

Mechanisms of inflammatory response in SARS-CoV-2

Recognition and response against viral infections

Inflammation response in viral infection involves four major components. They are inducers, sensors, responding mediators, and the effects of the mediators on the surrounding tissue (Huang and Glass, 2010). The first step of an inflammatory cascade is recognition of infection or damage by germ-line encoded receptors, called pattern-recognition receptors (PRRs). PRRs recognize structures conserved in microbes, called pathogen-associated molecular patterns (PAMPs) (Chen *et al*., 2018), as well as endogenous molecules derived from internal injuries called danger-associated molecular patterns (DAMPs) (Huang and Glass, 2010). Several PRRs, have selective ability to detect PAMPs, DAMPs, or both and these include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-1-like receptors (RLRs) and NOD-like receptors (NLRs) (Ahmed, 2011). RNA viruses (like SARS-CoV-2) can be recognized by endosomal and cytoplasmic PRRs (including TLR3, TLR7, RIG-I, and MDA-5) (Henry *et al*., 2020). TLRs together with myeloid differentiation factor-88 (MyD88) meditate the transmission of PAMP and DAMP (Chen *et al*., 2018). This will activate TLRs intracellular signaling leading to recruitment of adaptor proteins (including interferon regulatory factor 3 (IRF3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and activator protein 1 (AP-1), that promote the production of type I interferons (IFN-I) via both transcriptional and post-transcriptional mechanisms (Ahmed, 2011). IFN-1 acts as key player in the host response against viral infections, as they block viral replication and augment anti-viral effectors mechanisms at the entry site (Henry *et al.,* 2020). This is initiated when the JAK-STAT pathway is activated by type I IFN via interferon αβ receptor (IFNAR), followed by JAK1 and TYK2 kinases phosphorylation of STAT1 and STAT2 (Prompetchara *et al*., 2020). STAT1/2 forms a complex with IRF9 and together they are transported into the nucleus to initiate the transcription of IFN-stimulated genes (ISGs) under the control of IFN-stimulated response element (ISRE) containing promoters (Chen *et al*., 2018; Prompetchara *et al*., 2020). When this response is mounted successfully, viral replication and dissemination are inhibited.

Evasion of inflammatory defense by SARS-CoV-2

To avert the host immune system, SARS-CoV-2 just like SARS-CoV and MERS-CoV can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their dsRNA (Li *et al*., 2020). Once inside the host, SARS-CoV-2 represses the transcription of adaptor proteins (IRF3, NF-κB, and AP-1), and acts as an antagonist to the interferon pathway by regulating the signaling and synthesis of type I interferon (IFN) (Tufan *et al*., 2020) SARS-CoV-2 interferes with IFN production through inhibition of IRF3 nuclear translocation and interferon (IFN)

signaling using viral structural (M, N) and non-structural proteins (Prompetchara *et al.*, 2020). Downregulation of interferon pathway will in turn delay antiviral host response thereby enhancing viral replication and extensive virus-induced direct cytopathic effects in early stages of disease (Henry *et al.*, 2020). The SARS-CoV-2 achieves this by upregulating the translation process in favor of viral protein synthesis and also amplifies the replication of the virus in the patients (Wu *et al.*, 2020). In conjunction with cytokines, chemokines, and DAMPs released from infected pneumocytes it facilitates the recruitment of effector cells such as monocytes and neutrophils to the infected site (Tay *et al.*, 2020). In most individuals, recruited cells clear the infection in the lungs, the immune response recedes and patients recover. However, in some COVID-19 patients, a dysfunctional immune response occurs and activates the release of monocyte-derived FCN^{+} macrophages in the bronchoalveolar lavage fluid (BALF) of patients (Tay *et al.*, 2020). Merad and Martin (2020) reported that BALF from patients with severe COVID-19 is enriched in CCL2 and CCL7, two chemokines that are most potent in the recruitment of CC-chemokine receptor 2-positive ($CCR2^{+}$) monocytes. These macrophages and polymorphonuclear cells can, in turn, produce high levels of pro-inflammatory cytokines (including interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α)) and chemokines, which further amplify the recruitment of innate immune cells, potentially culminating in hyper inflammation and the observed cytokine storm that characterizes the most severe cases of COVID-19 (Henry *et al.*, 2020).

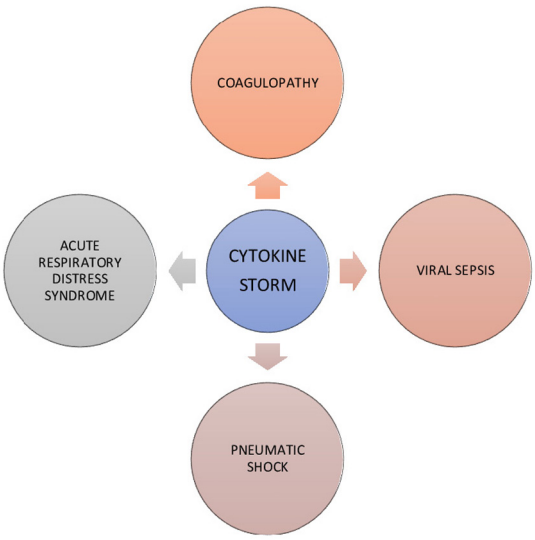

Fig. 1

Cytokine storm

Cytokine storm in coronavirus infection leads to viral sepsis, pneumatic shock, coagulopathy and severe respiratory distress syndrome.

Cytokine storm

Cytokine storm termed as a macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH) is the major cause of organ damage in COVID-19 patients (Tufan *et al.*, 2020). The most common cytokines present in non-intensive care unit patients are IL-1b, IFN-c, IP-10, MCP-1, IL-4, and IL-10 (Fu *et al.*, 2020), while COVID-19 patients needing ICU mainly have elevated serum levels of innate cytokines, IP-10, MCP-1, MIP-1A, and TNF-α which are involved in the disease progression and severity (Prompetchara *et al.*, 2020). Cytokine storms will trigger a violent attack by the immune system to the body triggering viral sepsis, pneumonitis shock, and acute respiratory distress syndrome (ARDS) (Fig. 1) which may lead directly to respiratory failure and organ failure (Panigrahy *et al.*, 2020; Prompetchara *et al.*, 2020). Multiple organ failure, especially of the cardiac, hepatic, and renal systems finally leads to death in severe cases of SARS-CoV-2 infection (Li *et al.*, 2020; Tay *et al.*, 2020). In a multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 ng/ml in non-survivors against 614.0 ng/ml in survivors; $p < 0.001$) and IL-6 ($p < 0.0001$), suggesting that mortality might be due to virally driven hyper inflammation (Levi *et al.*, 2020).

Coagulation pathway in COVID-19

Coagulation (thrombosis) during inflammatory response is usually targeted at inhibiting the spread of pathogens, protecting the endothelium, and also to enhance activation of innate immune cells (Han *et al.*, 2020). Paradoxically, SARS-CoV-2 impairs innate and adaptive antiviral responses, triggers hyper inflammation, and deranges the renin-angiotensin-aldosterone system (RAAS), all culminating to promote detrimental hypercoagulability, disseminated intravascular coagulation (DIC) and immunothrombosis which normally progress to COVID-19 induced ARDS, a major cause of mortality among COVID-19 patients (Tang *et al.*, 2020). Hypercoagulation in COVID-19 patients is associated with increased angiotensin 11 expression which increases plasminogen activator inhibitor C-1 expression, which is consistent with the observation of reduced fibrinolysis in patients (Henry *et al.*, 2020; Mortus and Manek, 2020). Similarly, angiotensin II-mediated pulmonary vasoconstriction can lead to stasis and hypercoagulability, as can COVID-19 induction of anti-phospholipid antibodies and complement during cytokine storms, causing vasculitis and microthromboses (Mortus and Manek, 2020).

Remarkably, available evidence suggests that the coagulopathy associated with COVID-19 is a combination of low-grade DIC and localized pulmonary thrombotic microangiopathy, which could have a substantial impact on organ dysfunction in the most severely affected patients. Han *et al.* (2020) who studied coagulation homeostasis in 94 SARS-CoV-2 patients reported significant increase in dimerized plasmin fragment D (D-dimer) (10.36 ± 25.31 in COVID-19 patients vs. 0.26 ± 0.18 found in normal patients), fibrin/fibrinogen degradation product (FDP) (33.83 ± 82.28 vs. 1.55 ± 1.09) and fibrinogen (FIB) (5.02 ± 1.53 vs. 2.90 ± 0.53) whereas antithrombin (AT) (85.46 ± 14.43 vs. 98.82 ± 12.91) and prothrombin time activity (PT-act) (80.59 ± 12.77 vs. 96.86 ± 26.92) were found to be lower in patients with COVID-19. In another study carried out on 41 admitted hospital patients who had been identified as having laboratory-confirmed SARS-CoV-2 infection in China, prothrombin time and D-dimer level on admission were higher in ICU patients (median prothrombin time 12.2 s (IQR 11.2–13.4); median D-dimer level 2.4 mg/l (0.6–14.4) than non-ICU patients (median prothrombin time 10.7 s (9.8–12.1), p 0.012; median D-dimer level 0.5 mg/l (0.3–0.8), p 0.0042) (Kumar *et al*., 2020). More strikingly, increased D-dimer concentrations greater than 1 μg/ml at the time of admission could help clinicians identify patients who are likely to have a poor prognosis (Kaul, 2020). Other clinical abnormalities seen in COVID-19 which might be associated with coagulopathy are increased lactate dehydrogenase and high ferritin concentrations and post mortem microvascular platelet-rich thrombotic deposition in small vessels of the lungs and other organs (Levi *et al*., 2020).

Anti-inflammatory drug targets

The following anti-inflammatory targets together with antiviral agents will help to circumvent the high mortality rate associated with COVID-19.

Angiotensin-converting enzymes 2 (ACE-2) inhibitors

SARS-CoV-2 has a transmembrane S glycoprotein on its outer shell which binds to the ACE-2 receptors. However, the binding affinity for ACE-2 of the S surface glycoprotein of SARS-CoV-2 is considerably higher than that of the homologous protein on SARS-CoV, thus potentially magnifying virulence and pathogenicity *in vivo* of the more recent SARS-CoV-2 coronavirus (Henry *et al*., 2020). Once the virus is attached to the ACE-2 receptors of the host cell the cellular proteases start priming the S protein and allow the virus fusion with cellular membrane of the host cell which results in the entry of the virus into the cell cytoplasm, where it releases its RNA genome and replicates, forming new viral particles. The host cell disintegrates and the virus spreads to other cells (Pandey *et al*., 2020; Soy *et al*., 2020). Undoubtedly, treating COVID-19 patients with ACE-2 inhibitor is of utmost importance as it will block entry of SARS-CoV-2 virus in to the host cell which will "nip in the bud" SARS-CoV-2 infection. Based on published data, many COVID-19 patients with other health comorbidities such as hypertension and diabetes are currently under medications with ACE-2 inhibitors or angiotensinogen receptor blockers such as losartan, lisinopril, or olmesartan (Wu *et al*., 2020).

Interferons (IFNs)

Interferons are the first cytokines released during viral infections to inhibit viral replication. Unfortunately, patients with SARS-CoV-2 have low levels of interferons. Similar upregulation of pro-inflammatory cytokines together with downregulation of antiviral cytokine was observed in MERS-CoV infection (Soy *et al*., 2020). Impaired production of IFN led to the Food and Drug Administration's (FDA) approval of INFs for the treatment of various conditions like multiple sclerosis, hepatitis B and C viral infection, hairy cell leukemia and acquired immune-deficiency syndrome (AIDS). This shows that INF could be very useful in the prophylactic treatment of SARS-CoV-2. Among the subtypes of IFNs, INF-β1b and INF-β1 are the most potent inhibitors of SARS-CoV and MERS-CoV) (Pandey *et al.,* 2020). Trial testing administration of type 1 and type 111 interferons have been initiated in COVID-19 patients (Merad and Martin, 2020). IFN can be administered alone or in combination with nucleoside analog ribavirin in the clearance of viral infection. Also, open-label, controlled, randomized Phase II clinical trial to estimate the antiviral efficacy and safety of pegylated IFN lamda (NCT04343976) and pegylated IFN lamda-1A (NCT04388708) in patients with COVID-19 infection has been initiated (Pandey *et al*., 2020).

Janus kinase (JAK) family inhibitors

The JAK-STAT pathway is a signaling mechanism through which extracellular factors can control gene expression (Chen *et al*., 2018). This pathway mediates the effects of many ILs, IFN, and growth factors involved in the hyper inflammatory response in COVID-19 patients (Tufan *et al*., 2020). JAK inhibitors work by interfering with the JAK-STAT signaling pathway which could affect both inflammation and cellular viral entry in SARS-CoV-2 infection (Mehta *et al*., 2020). Currently, many clinical trials are ongoing for testing the effects of JAK inhibitors such as baricitinab, tofacitinib, and ruxolitinib (Tufan

et al., 2020), but the most commonly used is baricitinab due to its high affinity, once-daily oral dosing of 2 or 4 mg and less side effects (Zhao, 2020). Baricitinab is a numb-associated kinase (NAK) inhibitor, which regulates viral entry into cells. It regulates the JAK-STAT pathway, which is used for suppressing pro-inflammatory cytokine production and systemic inflammation (Soy *et al*., 2020). Besides, baricitinib may block AP-2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK) which are host kinases that regulate viral endocytosis (Tufan *et al*., 2020). However, caution should be applied in patients administered with JAK inhibitors to prevent inhibition of other cytokines such as TNF-α which has anti-viral activity (Zhao, 2020).

Interleukin 1 (IL-1) receptor antagonist

Studies have shown that SARS-CoV-2 provokes significant elevation of pro-inflammatory cytokines, in particular IL-1β, IL-6, and TNF-α leading to activation of thrombin generation, decrease in the levels of endogenous anticoagulants, antithrombin and activated protein C (Henry *et al*., 2020). The use of IL-1 receptor antagonist (IL-Ra) which binds the same IL-1 receptor like IL-1β without inducing signal transduction which amplifies inflammatory response is a good therapeutic target in a cytokine storm. One such antagonist currently registered for a clinical trial of COVID-19 is ankinra with daily subcutaneous administration of 100 mg doses (Tufan *et al*., 2020). Ankinra is a recombinant non-glycosylated form of IL-Ra which competes with IL-1β for receptor binding. It is mostly recommended when other biologics like anti-IL-6 and anti-TNF therapies which are preferable, are refractory or contraindicated (Rider *et al*., 2016). However, ankinra is forbidden in patients receiving TNF blockers or live vaccine. Also, a combination of ankinra with corticosteroids or other immunosuppressive drugs increases the risk of infection (Rider *et al*., 2016). Hence, there is a need to balance the risk and its beneficial ratio. Canakinumab, is another humanized monoclonal anti-IL-1β drug with high affinity used as IL-blocker. However, the use of canakinumab for severe COVID-19 infections has not been reported yet (Soy *et al*., 2020).

Interleukin 6 (IL-6) inhibitors

High levels of IL-6 in COVID-19 patients usually provoke vascular permeability, plasma leakage, and disseminated intravascular coagulation (DIC) causing the observed pulmonary damage, ARDS, and multi-organ failure observed in patients (Levi *et al*., 2020). Several therapeutic agents have been developed to inhibit IL-6 signaling via the IL-6 receptor or its post-receptor downstream signaling pathways (JAK/STAT) (Tufan *et al*., 2020). The use of IL-6 inhibitors could help in early phase of respiratory involvement to prevent permanent damage to the alveolar pneumocytes in patients with respiratory failure**.** A study from China reported a clear benefit in 15 of 20 (75%) patients treated with IL-6 blocker, leading to FDA approval of IL-6 blocker in patients with COVID-19 (Merad and Martin, 2020). Tocilizumab has been recommended for treatment of severely and critically ill COVID-19 patients with elevated IL-6 (Xu *et al*., 2020; Zhao, 2020). Tocilizumab is an IL-6 antibody that binds to the IL-6 receptor preventing binding of IL-6 and inhibits the uncontrolled secretion of ILs thereby reducing the inflammation and other related conditions with IL-6 (Pandey *et al*., 2020; Tufan et *al*., 2020). Trials to block IL-6 signaling using tocilizumab have been launched across the world and some clinical benefits have been seen in a subset of patients. A study conducted on 24 COVID-19 patients receiving 8 mg/kg of intravenous tocilizumab showed that IL-6 was significantly higher in non-survivors than in survivors (2398.5 (430.5–9372) pg/ml against 290.5 (58.5–1305.5) pg/ml, p = 0.022) Hence, it was concluded that blocking IL-6 using tocilizumab preliminarily resulted in the improvement of this hyper inflammatory state (Quartuccio *et al*., 2020). Also, in another study from China in 20 diagnosed as severe or critically ill patients using tocilizumab decreased the level of lymphocytes in 85% of the patients (17/20) while abnormal C-reactive protein returned to normal in 84.2% (16/20) of the patients (Xu *et al*., 2020). Thus, blocking IL-6 would potentially reduce the detrimental immune response caused by SARS-CoV-2. Numerous studies are also ongoing in other countries to determine the efficacy of other IL-6 inhibitors like sarilumab and siltuximab. However, IL-6 inhibitors should not be given to older people or people with past medical histories inhibiting the immune system which may result in severe health issues (Kumar *et al*., 2020).

Tumor necrosis factor alpha (TNF-α) inhibitors

TNF-α is a central alarm cytokine, which is mainly secreted from activated macrophages or dendritic cells in response to association with PRRs (Rider *et al*., 2016). Clinical studies have shown that although serum TNF-α levels were moderately elevated in patients with SARS, much higher serum levels were observed in patients with COVID-19 infection, which positively correlates with disease severity (Soy *et al*., 2020). Thus, the use of TNF-α inhibitors could be effective in blocking the entry and the resultant cytokine storm (Tufan *et al*., 2020). TNF-α inhibitors were shown to be effective for the treatment of skin and joint inflammation, but they carry the risk of several adverse effects, mainly concerning infections. TNF-α is

a fundamental factor for fighting intracellular bacteria and is therefore not surprising that TNF-α inhibition was shown to increase the risk for reactivation of tuberculosis (Rider *et al*., 2016).

Anticoagulant

As evidence, occlusion and micro thrombosis formation in pulmonary small vessels of a critical patient with COVID-19 have been reported from a recent lung organ dissection (Tang *et al*., 2020). Research carried out by Klok *et al*. (2020), in 2 Dutch hospitals on 184 ICU patients shows that 31% had a thrombotic complication, so, they recommended thrombosis prophylaxis in all COVID-19 patients admitted to ICU. Anticoagulation therapy is recommended for COVID-19 patients when the D-Dimer value is 4 times higher than the normal upper limit, except for patients with anticoagulant contraindications (Thachil, 2020). Low molecular weight heparin (LMWH) or unfractionated heparin is the most commonly used anticoagulant in hospitals for preventing DIC and venous thromboembolism (VTE) in patients, (Levi *et al*., 2020; Lin *et al*., 2020). The recommended dose of LMWH is 100U per kg weight per 12 h by subcutaneous injection for at least 3–5 days (Lin *et al*., 2020). Heparin has anti-inflammatory properties and may also inhibit viral attachment via conformational changes to the SARS-CoV-2 surface receptor S1 (Wu *et al*., 2020). Also, heparin can antagonize histone and thus protect the endothelium through its effects on histone methylation and the mitogen-activated protein kinase (MAPK) and NF-κB signal pathways (Thachil, 2020). In study carried out on 449 patients with severe COVID-19, 99 of them received heparin (mainly with low molecular weight heparin) for 7 days or longer. D-dimer, prothrombin time, and age positively, and platelet count negatively, correlated with 28-day mortality in multivariate analysis (Tang *et al*., 2020). However, anticoagulants should be used with great caution because the activation of coagulation reduces pathogens compartmentalization and invasion. Hence, anticoagulant treatment in patients without significant coagulopathy has potential risk. This may explain the relatively higher mortality of heparin users compared with non-users in patients with D-dimer ≤ 1 ULN (Tang *et al*., 2020). Thus, excessive use of anticoagulants on patients with low thrombosis risk may lead to the development of DIC which affects prognosis (Han *et al*., 2020). It is recommended that clinicians should closely monitor the indicators of laboratory examination of patients to be alert for side effects after anticoagulant treatment.

Resolution of inflammation

Resolution of inflammation is aimed at restoring tissue homeostasis by counter-regulation of cytokines and chemokines, reduction of neutrophil infiltration, the transformation of macrophages, and initiation of healing (Chen *et al*., 2018). Inflammation resolution in COVID-19 patients is targeted at inhibiting the release of inflammatory cytokines and mediators such as prostaglandin and leukotrienes that trigger local inflammation. Resolution to avert inflammatory associated mortality in COVID-19 can be mediated through anti-inflammatory substances secreted by macrophages such as cytokines (like IL-10), growth factors (transforming growth factor β) or by harnessing endogenous specialized pro-resolving mediators (SPM) like resolvin, lipoxins and protectins (Huang and Glass, 2010). It can also be achieved by stimulating arachidonic acid-derived eicosatrienoic acids (EETs) pathway by administering soluble epoxide hydrolase (sEH) inhibitors to stabilize EET levels (Panigrahy *et al*., 2020). This will promote the clearance of cellular debris and also activate anti-inflammatory programs that inhibit cytokine storm. Besides, both SPM and EETs have been reported to attenuate thrombosis and also promote clot removal. Reports have shown that n-3 polyunsaturated fatty acid such as eicosapentaenoic acid and docosahexaenoic acid obtained from a diet high in fish oil or through dietary supplementation with fish oils or purified oils exert antiviral effects by serving as precursors for biosynthesis of endogenous SPM (resolvin and protectins) involved in inflammatory resolution (Reimers and Ljung, 2019).

Conclusion

The understanding of the cellular and molecular mechanisms involved in the inflammatory process in SARS-CoV-2 infection will provide scientific basis for the discovery of promising targets for the development of new drugs to treat SARS-CoV-2. Undoubtedly, proper targeting of the inflammatory mechanism by balancing benefits with side effects will subvert the high rate of mortality in COVID-19 patients.

References

Ahmed AU., Front. Biol. 6 (4), 274–281, 2011. https://doi.org/10.1007/s11515-011-1123-9

Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L., Oncotarget 9, 7204–7218, 2018. https://doi.org/10.18632/oncotarget.23208

Fu Y, Cheng Y, Wu Y., Virol. Sin. 35, 266–271, 2020. https://doi.org/10.1007/s12250-020-00207-4

Fung S, Liu DX., Microbiology 73, 529–557, 2019. https://doi.org/10.1146/annurev-micro-020518-115759

Han H, Yanga L, Liu R, Liu F, Wu K-L, Li J, Liu X-H, Zhu C-L., Clin. Chem. Lab. Med. 58, 1116–1120, 2020. https://doi.org/10.1515/cclm-2020-0188

Henry BM, Vikse J, Benoit S, Favaloro EJ, Lipp G., Clin. Chim. Acta 507, 167–173, 2020. https://doi.org/10.1016/j.cca.2020.04.027

Huang W, Glass CK., Arterioscler. Thromb. Vasc. Biol. 30, 1542–1549, 2010.

Kaul D., Curr. Med. Res. Pract. 10, 54–64, 2020. https://doi.org/10.1016/j.cmrp.2020.05.012

Klok, FA, Kruip, MJHA, NJM van der Meer, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, Paassen JV, Stals, MAM, Huisman MV, Endeman H., Thromb. Res. 191, 145–147, 2020. https://doi.org/10.1016/j.thromres.2020.04.013

Kumar M, Taki K, Gahlot R, Sharma A, Dhangar K., Sci. Total Environ. 734, 139278, 2020. https://doi.org/10.1016/j.scitotenv.2020.139278

Levi M, Thachil J, Iba T, Levy JH., Lancet Haematol. 7 (8), E438–E440, 2020. https://doi.org/10.1016/S2352-3026(20)30145-9

Li X, Geng M, Peng Y, Meng L, Lu S., J. Pharm. Anal. 10, 102–108, 2020. https://doi.org/10.1016/j.jpha.2020.03.001

Lin L, Lu L, Cao W, Li T., Emerg. Microbes Infect. 9, 727–732, 2020. https://doi.org/10.1080/22221751.2020.1746199

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ., Lancet 395(10229), 1033–1034, 2020. https://doi.org/10.1016/S0140-6736(20)30628-0

Merad M, Martin JC., Nat. Rev. Immunol. 20, 355–362, 2020. https://doi.org/10.1038/s41577-020-0331-4

Mortus JR, Manek SE., JAMA Network Open. (6), e2011192, 2020. https://doi.org/10.1001/jamanetworkopen.2020.11192

Pandey A, Nikam AN, Shreya AB, Mutalik SP, Gopalan D, Kuikarni S, Padya BS, Fernandes G, Mutalik S, Prassel R., Life Sci. 256, 117883, 2020. https://doi.org/10.1016/j.lfs.2020.117883

Panigrahy DK, Gilligan MM, Huang S, Gartung A, Cortes-Puch I, Sime P, Phipps RP, Serhan CN, Hammock BD., Cancer Metastasis Rev. 39, 337–340, 2020. https://doi.org/10.1007/s10555-020-09889-4

Prompetchara E, Ketloy C, Palaga T., Asian Pac. J. Allergy Immunol. 38, 1–9, 2020.

Quartuccio L, Sonaglia A, Pecori D, Peghin M, Fabris M, Tascini C, Vita SD., J. Med. Virol. 92 (11), 2852–2856, 2020. https://doi.org/10.1002/jmv.26149

Reimers A, Ljung H., Ther. Adv. Psychopharmacol. 9, 1–18, 2019.

Rider P, Carmi Y, Cohen I., Int. J. Cell Biol. 11, 9259646, 2016. https://doi.org/10.1155/2016/9259646

Soy M, Keser G, Atagunduz P, Tabak F, Atagunduz I, Kayhan S., Clin. Rheumatol. 39, 2085–2094, 2020. https://doi.org/10.1007/s10067-020-05190-5

Tang N, Bai H, Chen X, Gong J, Li D, Sun Z., J. Thromb. Haemost. 18, 1094–1099, 2020. https://doi.org/10.1111/jth.14817

Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP., Nat. Rev. Immunol. 20, 363–374, 2020. https://doi.org/10.1038/s41577-020-0311-8

Thachil J., J. Thromb. Haemost. 18, 1020–1022, 2020. https://doi.org/10.1111/jth.14821

Tufan A, Guler AA, Matucci-Cerinic., Turk. J. Med. Sci. 50, 620–632, 2020. https://doi.org/10.3906/sag-2004-168

Wu R, Wang L, Kuo HD, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z, Poiani GJ, Amorosa L, Brunetti L, Kong A-N., Curr. Pharmacol. Rep. 2020, 1–15, 2020.

Xu X, Han M, Li T, Sun W. Wang D. Fu B. Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wie H., Proc. Natl. Acad. Sci. USA 117(20), 10970–10975, 2020. https://doi.org/10.1073/pnas.2005615117

Zhao M., Int. J. Antimicrob. Agents 55(6), 105982, 2020. https://doi.org/10.1016/j.ijantimicag.2020.105982