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COVID-19: The significance of platelets, mitochondria, vitamin D, serotonin, and the gut microbiota

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Abstract

We provide a brief review of the significance of platelets, mitochondria, vitamin D, serotonin, and the gut microbiome in COVID-19. We hypothesize that hyperactive platelets and mitochondrial dysfunction, as well as low vitamin D level, gut dysbiosis, and increased serum serotonin produced by enterochromaffin cells, may all represent important aspects in the pathophysiology of COVID-19.

Keywords: Platelets, mitochondria, vitamin D, serotonin, gut-brain axis, COVID-19, SARS-CoV-2.

1 Introduction

In December 2019, coronavirus disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China. COVID-19 was declared a global pandemic in early 2020. Although COVID-19 is considered to be a respiratory disease, the latest results provided evidence that SARS-CoV-2 can also infect organs, like the kidneys, liver, heart, gut, skin, endocrine organs, blood vessels, and brain [1-3]. While our current understanding of COVID-19's pathogenesis remains limited, a better understanding of COVID-19 pathomechanisms would be essential to develop effective management and prevention strategies. There are several known factors in the pathogenesis representing potential therapeutic targets for COVID-19, including the angiotensin-converting enzyme 2 (ACE2 or SARS-CoV-2 receptor), cytokine storm, renin-angiotensin system (RAS)-mediated bradykinin storm, dysregulated immune response, hyperactive platelets, mitochondrial dysfunction, microvascular thrombosis, and microbiota dysbiosis, among others [4-13].

In the next sections of this article, we first give a short overview of COVID-19 and the significance of the ACE2 receptors as well as the cytokine storm in this disease. This is followed by sections on the importance of platelets, mitochondrial dysfunction, decreased vitamin D levels, microbiome (intestinal dysbiosis), and serotonin. Each of these sections is divided into a general part and a part specifically addressing the relationship with the SARS-CoV-2 infection. Subsequently, pathophysiological hypotheses are formulated and possible therapeutic interventions are discussed.

2 COVID-19

Although the vast majority of COVID-19 patients experience only mild to moderate symptoms, the disease remains fatal in a small but significant percentage of those infected. Symptoms include fever, fatigue, dyspnea, dry cough, severe hypoxia, gastrointestinal disease, including diarrhea and nausea, headache, altered mental status, anosmia, and confusion [14]. Early reports from China also indicated that neurologic symptoms are found in about 36% of patients hospitalized with COVID-19 [15]. Patients with severe COVID-19 complications may also develop acute respiratory distress syndrome (ARDS) presenting with dyspnea, acute respiratory failure, myocardial injury, arrhythmias, cardiomyopathy with heart failure, acute kidney injury, encephalopathy, acute ischemic stroke, and systemic coagulopathy [16-19]. Poor outcomes of COVID-19 have been associated with cardiovascular risk factors such as hypertension, coronary artery disease, diabetes mellitus, ambient (outdoor) air pollution particularly high nitrogen dioxide (NO₂) concentration, and smoking [20, 21]. Older age with comorbidities is also strongly associated with poor prognosis, likely as a result of a weakened immune response [22, 23]. Despite the diversity in the initial presentation, most COVID-19 patients proceed to develop fever and respiratory symptoms [23].

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. The viral envelope of SARS-CoV-2 consists of a lipid bilayer, where the viral membrane (M), envelope (E), and spike (S) structural glycoproteins are anchored. SARS-CoV-2 uses ACE2 as a host cell receptor. During viral infection, the S protein binds to the host ACE2 receptor on the cell surface then the S protein is cleaved into S1 and S2 subunits by the cellular transmembrane serine protease 2 (TM-PRSS2). S1 contains the receptor-binding domain (RB-D) that binds to the peptidase domain (PD) of ACE2, while S2 is responsible for membrane fusion [24].

SARS-CoV-2 can enter the host cells through binding to cellular receptors and receptor-mediated endocytosis. After entering the host cell the viral RNA is released to the cytosol where the S protein induces fusion between the envelope of the virus and an endosome [25]. Next, viral RNA (which serves as an mRNA) is translated into viral proteins that shape a replication complex to make additional RNA, which will further assemble with the viral proteins into a new virus. Finally, the newly synthesized virus is released (see details in V'kovski et al. 2020) [26].

3 ACE2

ACE2 is present in various cell types and tissues, including the lungs, heart, blood vessels, kidneys, liver, testis, and the gastrointestinal tract (GIT) [25]. The renin-angiotensin system (RAS) is a hormone system within the body that is essential in the regulation of blood pressure and fluid balance, vasoconstriction, sodium intake, potassium excretion, inflammation, autoimmunity, and aging [27, 28]. ACE2 is a membrane-associated and

membrane-secreted enzyme that cleaves Ang I into Ang 1-9 and Ang II into Ang 1-7 peptides that are able to modulate the actions of AngII, the major effector of RAS, and lead to activating the anti-inflammatory and vasodilation-promoting receptor MAS (MASR) [29, 30]. Under normal circumstances, ACE2 counteracts the harmful effect of the ACE/RAS pathway through its downstream ACE2-Angiotensin (1-7)-MAS proto-oncogene receptor axis [31]. Ang II is also a multifunctional pro-fibrogenic cytokine that has several deleterious effects e.g., increasing blood pressure, promoting inflammation, and causing damage to both blood vessels and various types of tissues via the RAS pathways.

When SARS-CoV-2 binds to ACE2, it reduces ACE2 expression so that it cannot perform its normal role in the regulation of Ang II [32]. However, currently, there is still a controversy regarding the role of the loss of ACE2 expression in the development of severe acute respiratory failure and the exact processes of SARS-CoV-2 binding to ACE2 and how it could modulate the ACE2 enzymatic activity is still being investigated [33, 34].

3 Cytokine storm

Although the exact mechanism of COVID-19-induced lung injury is still not completely known, the term cytokine storm, i.e. an over-production of soluble markers of inflammation, has become the most commonly described pathogenic factor in its development [35-37]. According to Sinha et al. [35], patients with the hyperinflammatory phenotype of ARDS have 10 to 200 fold higher mean IL-6 levels than patients with severe COVID-19. Thus, increased circulating mediators of the proposed cytokine storm are probably due to both endothelial dysfunction and systemic inflammation [38]. The term "cytokine storm" indicates a hyperactive immune response through the release of interleukins, interferons, TNF, chemokines, and various other mediators [35].

5 Platelets

5.1 Summary of Key Physiological Functions

There are almost one trillion platelets (anucleated blood cells) in the blood. Platelets are not only mediators of homeostasis and thrombin generation but are also key players in homeostasis, inflammation, and immune response, and first guards in detecting and responding to diverse pathogens and damage signals in the vasculature and the extravascular space [39-43]. Platelets have various granules and lysosomes. The α -granules contain more than 300 soluble proteins including P-selectin as membrane-associated receptors and soluble cargo proteins, such as platelet factor 4 (PF4) and fibrinogen [44]. The α -granules also contain chemokines, including CXCL1 and interleukin-8, cytokines, and growth factors, including fibroblast growth factor (FGF). Dense δ -granules contain glutamate, serotonin, histamine, ADP, polyphosphates, pyrophosphates, and high concentrations of cations, particularly calcium. Platelet lysosomes contain glycohydrolases, enzymes that degrade glycoproteins, glycolipids, and glycosaminoglycans [45]. Platelets are a major source of microparticles (also termed microvesicles) in circulation [46]. These microparticles also contain an abundant amount of messenger RNA and non-coding micro RNA (miRNA) that function in the post-transcriptional regulation of gene expression [47].

Platelets act as major pro-inflammatory cells under inflammatory conditions [48]. Platelets express pathogen recognition receptors (PRRs), such as toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and RIG-I-like

receptors (RLRs) that can recognize bacterial or viral moieties and respond to these diverse infecting pathogens [49].

Viral infections often result in platelet activation [50]. Viruses can directly interact with platelets or megakaryocytes. In addition, platelets can also be activated by viral antigen-antibody complexes and can generate anti-platelet antibodies [51]. These processes can produce increased platelet consumption and removal often resulting in thrombocytopenia that is commonly observed during viral infection.

The coagulation cascade can be activated by various viruses, such as HIV, CVB3, Dengue virus, and Ebola virus, as a host defense mechanism to limit the spread of the virus [52]. In addition, uncontrolled coagulation due to dysfunction of either the cellular component consisting of endothelial cells and platelets or proteins, including coagulation factors, anticoagulants, and fibrinolysis protease, has an important role in the pathogenesis of influenza by augmenting viral replication and immune pathogenesis [53]. The influenza virus can provoke extreme activation of endothelial cells and platelets that in turn leads to the activation of the coagulation cascade with concurrently impaired anti-coagulation and fibrinolytic signaling. Such a pro-coagulant state can cause hemorrhagic fever and is often associated with ARDS in severe influenza infection [53]. However, the aggressive immune response during severe influenza also initiates perturbed coagulation processes that cause endothelial activation and vascular leakage in the lung with disseminated intravascular coagulation and pulmonary microembolism [54, 55].

During inflammatory processes, activated platelets perform through very complex interactions with various circulating cells as well as the endothelium where the released platelet granules and microparticles have essential functions. Activated platelets can bind to the endothelium and release various inflammatory and angiogenic molecules from their α -granules [56]. The interaction between platelets and the intact endothelium is mainly achieved by glycoproteins and glycans. P-selectin glycoprotein works as a cell adhesion molecule (CAM) stored in membranes of α -granules of platelets and Weibel-Palade bodies of endothelial cells. P-selectin is translocated to the surface upon cell activation [57]. Activated platelets also release microparticles that contain diverse proteins including adhesion molecules, like P-selectin, chemokines, like RANTES, cytokines, like IL-1 β , and many others. Various forms of RNA such as mitochondrial RNA (mtRNA, a highly potent inflammatory trigger) and non-coding micro RNA (miRNA, involved in post-transcriptional regulation) are also released [42, 58-61]. Activated platelets may also release some of their mitochondria that interact with neutrophils and trigger neutrophil adhesion to the endothelial wall [59]. Extracellular mitochondria can also induce paracrine or endocrine responses in the host organism [62].

Platelets contain only about five mitochondria. Thus, the health of platelets is essentially determined by the health of their mitochondria [63]. Apoptosis of platelets is achieved via two main pathways: the intrinsic (or mitochondrial) or the extrinsic pathway. The intrinsic mitochondrial apoptosis pathway determines the lifespan of platelets by the action of the mitochondrial Bcl-xl protein [64]. Major steps of platelet apoptosis in response to multiple external chemical stimuli by mitochondrial pathway include (a) mitochondrial membrane potential depolarization, (b) opening of the mitochondrial permeability transition pore (MPTP), (c) activation and translocation of pro-apoptotic BAX, BAK, and BID, (d) release of cytochrome c from the mitochondrial matrix to the cytosol, and (e) activation of caspase-9 [65]. Interestingly, HIV-infected subjects exhibited increased platelet activation, increased mitochondrial dysfunction, and activation of the intrinsic pathway of apoptosis in platelets as compared to healthy controls [66].

As platelet function changes during aging, it is associated with numerous age-related pathological processes and diseases [67-69]. Increased platelet hyperactivity in diseases

is associated with aging, such as cardiovascular disease and sepsis, exaggerated inflammation, and thrombosis [68]. In older subjects, platelets are more easily activated and are less sensitive to inhibition, and the platelet count is low [70]. The platelet transcriptome is altered in the aged human resulting in altered platelet function and excessive inflammation.

In aged individuals, platelet signaling to monocytes produces more cytokines because of increased platelet-derived granzyme A [68]. Spontaneous platelet aggregation also increases with age [71]. Irregular morphological changes occur in platelets with age [72]. Furthermore, oxidative stress-related processes also increase in platelets with aging [73]. Endothelial dysfunction can also increase the tendency for platelet aggregation with aging [68, 74, 75]. Nitric oxide (NO) is a powerful vasodilator and important protective molecule for the vasculature. Endothelial NO synthase (eNOS) produces most of the vascular NO. NO inhibits platelet activation, adhesion, and aggregation. However, reduced NO bioactivity is associated with arterial thrombosis and endothelial dysfunction [76, 77].

5.1 Platelet Hyper-Reactivity May Play a Key Role in the Pathophysiology of COVID-19

Manne et al. [78] found altered platelet gene expression and functional responses associated with protein ubiquitination, antigen presentation, and mitochondrial dysfunction in COVID-19 patients. The authors also concluded that platelets and megakaryocytes do not express ACE2 mRNA or protein. Manne et al. also detected COVID-19 N1 gene-derived mRNA in platelets from 2 out of 25 COVID-19 patients [78]. This suggests that platelets may be able to take up SARS-CoV-2 mRNA independent of the ACE2 receptor. In addition, circulating platelets, neutrophils, monocytes, and T-cell aggregates are significantly increased in COVID-19 patients compared to controls. The P-selectin expression also increases in platelets of COVID-19 patients in both the resting and activated state. Zhang et al. [4] found that platelets are hyperactive in patients with COVID-19 and demonstrated that platelets express ACE2 and TMPRSS2, a serine protease for spike protein priming. Authors revealed that COVID-19 patients present with increased mean platelet volume (MPV) and platelet hyperactivity, which correlated with a decrease in the overall platelet count. Furthermore, Zhang et al. [4] also demonstrated that SARS-CoV-2 and its spike protein directly stimulate platelets and induce coagulation factor release, inflammatory cytokine secretion, and leukocyte-platelet aggregates (LPAs) formation. Manne et al. [78] proposed that platelet hyper-reactivity may play a key role in the pathophysiology of COVID-19 via increased platelet-platelet and platelet-leukocyte interactions. At the moment, if platelets are expressing ACE2 or not, and how SARS-CoV-2 can enter into platelets is an ongoing discussion with controversial empirical findings [4, 78].

6 Mitochondria

6.1 Summary of Key Physiological Functions

Mitochondria are best known for their role in the generation of ATP by aerobic respiration. Mitochondria generate almost 90% of the total number of cellular ROS by oxidative phosphorylation (OXPHOS) [79]. However, mitochondria are signaling organelles that regulate countless cellular functions. Mitochondria perform fundamental functions as metabolic and redox hubs and act as key integration centers for cellular signaling pathways in eukaryotic cells [80-86]. Mitochondria have their own genome (mtDNA) which

is replicated independently of the host genome. Mitochondrial DNA is more susceptible to damage than nuclear DNA. Mitochondria frequently fuse and divide and their morphology and intracellular distribution are changed according to the energy demand of cells [87]. Mitochondria, including mtDNA, can be transferred between cells, spreading the inflammatory signal across a population of cells [88]. Mitochondria are involved in the regulation of complex processes, like synaptic plasticity and transmission [89], and play essential roles in the synthesis and secretion of neurotransmitters [90].

Mitochondrial dysfunctions and oxidative stress have been associated with multiple human diseases, such as cancer, atherosclerosis, Parkinson's disease, Alzheimer's disease, other neurodegenerative diseases, heart and lung diseases, diabetes, obesity, and autoimmune diseases, among others [88, 91, 92].

Mitochondrial dysfunction has been increasingly recognized as an important aspect of the aging process [93, 94]. In aged individuals, mitochondria exhibit decreased oxidative capacity, reduced oxidative phosphorylation, decreased ATP production, increased ROS generation, decreased antioxidant defense, and enhanced mitochondria-mediated apoptosis [95, 96]. The mitochondrial antiviral-signaling protein (MAVS) is essential for antiviral innate immunity, inducing apoptosis when viral infection of a cell is detected [83]. Since mtDNA has about a 10-fold greater mutation rate than nuclear DNA and less repair capacity, damage to the mtDNA has an important role in various diseases [97].

6.2 Mitochondrial Dysfunctions as an Effect of SARS-CoV-2 Infection

Recent studies have suggested that mitochondrial dysfunction may have a key role in the development of COVID-19 and may be partially responsible for the dysregulated immune response [4, 6, 7]. Saleh et al. [6] suggested that SARS-CoV-2 may have an essential impact on both intra- and extracellular mitochondrial function, a mechanism that may influence the severity of the disease. There is increasing concern that coagulation abnormalities in COVID-19 may be associated with mortality [98, 99]. Saleh et al. [6] also hypothesized that both intracellular mitochondrial dysfunction produced by SARS-CoV-2 infection and extracellular mitochondria released by platelets may affect coagulation leading to clot formation and disseminated systemic thrombosis.

Wu et al. [100] compared hundreds of SARS-CoV-2 genomes with other coronavirus genomes and the human transcriptome. This study suggested that SARS-CoV-2 genomic and subgenomic RNA (sgRNA) transcripts could be enriched in the host mitochondrial matrix and nucleolus. According to Singh et al. [7], when SARS-CoV-2 enters the host cell, it may perturb mitochondrial function both indirectly by ACE2-dependent regulation of mitochondrial mechanisms and directly by altering mitochondrial function to escape regulatory processes operating during host cell immune response and help virus replication during SARS-CoV-2 infection. In addition, Gordon et al. [101] revealed that a significant number of host mitochondrial proteins can interact with the SARS-CoV-2 proteins. It seems that the distinct localization of viral RNA and mitochondrial proteins have an important role in COVID-19 pathogenesis.

7 Vitamin D

Vitamin D is a secosteroid hormone present in two typical forms: 25(OH)D₂ or ergocalciferol. It is usually obtained from dietary vegetable sources and oral supplements, and 25(OH)D₃ or cholecalciferol is formed during skin exposure to ultraviolet B (UVB) radiation. Both D₂ and D₃ are biologically inactive. The biologically active form of vitamin D is 1,25(OH)₂D₃ (calcitriol or 1,25-dihydroxycholecalciferol) that is produced in the liver

and the kidney [102]. Vitamin D has an essential role in calcium homeostasis and bone mineralization, cell proliferation and differentiation, immunity, anticoagulation, and anti-inflammation, and works as a transcription factor by regulating the expression of numerous genes [102-105]. The sun's UVB radiation is the best natural source of vitamin D. Vitamin D insufficiency is a major public health problem worldwide due to inadequate exposure to sunlight, inefficient production in the skin, greater sun protection, increased body mass index in the population, inadequate dietary intake, and diseases, like gastrointestinal disorders, renal and liver diseases [106, 107].

The serum 25-hydroxyvitamin D [$25(\text{OH})\text{D}_3$] concentration is the best indicator of vitamin D deficiency since it reflects both dietary intake of vitamin D and skin-related synthesis [108]. Vitamin D deficiency is associated with musculoskeletal and cardiovascular disorders, arterial diseases, venous thromboembolism, autoimmune diseases, dermatological and cancer diseases, metabolic syndrome, obesity, hypertension, and diabetes, among others [109-113]. Low levels of vitamin D are also associated with mental disorders like depression, seasonal affective disorder, and schizophrenia [113-115]. The vitamin D receptor (VDR) has been demonstrated in most human tissues and has more than 1000 target genes [116]. The activity of vitamin D is mediated in a genomic manner via the nuclear VDR and in a non-genomic more rapid manner via cell membrane and/or cytoplasm VDR [117].

Tryptophan hydroxylase is the rate-limiting enzyme of serotonin biosynthesis. Patrick and Ames found [118] that vitamin D activates the Tryptophan Hydroxylase 2 (TPH2) gene that converts tryptophan to serotonin in the brain. This suggests that proper concentrations of vitamin D may be needed to produce serotonin in the brain. However, there are two different tryptophan hydroxylase (TPH) genes for serotonin synthesis. Vitamin D induces transcriptional activation of TPH2 in the brain, but in the peripheral tissues, vitamin D produces a repression of tryptophan hydroxylase 1 (TPH1). Patrick and Ames [118] also demonstrated that the gene that encodes TPH1 could be inhibited by vitamin D, which subsequently inhibits serotonin production in the gut and other tissues. Serotonin, when produced in excess, promotes inflammation. Furthermore, deficiency in peripheral TPH1 and serotonin presents a reduced risk for thrombosis and thromboembolism in mice [119]. In addition, the induction of cytokine storm can be reduced by vitamin D [120].

Studies found that most DNA or RNA viruses induce cell death through ROS stress in infected cells [120-125]. Recently, the mitochondrial vitamin D receptor has been identified in human platelets and differentiated megakaryocytes [126, 127]. Consiglio et al. [128] revealed that activated VDR can control mitochondrial respiratory activity. In addition, Ricca et al. [129] demonstrated that local effects of the VDR not only regulate mitochondrial respiratory activity but also protect it from ROS damage. Thus, VDR helps preserve mitochondrial integrity and cell survival in certain cell types including both tumor and host cells.

In all cell types, VDR can regulate mitochondrial (COX2 and MT-ATP6) and nuclear transcription (COX4 and ATP5B) of proteins that take part in the mitochondrial respiratory processes as well as ATP synthesis [129]. It may be possible that SARS-CoV-2 induces intracellular mitochondrial dysfunction and unregulated overproduction of ROS [6]. These processes damage cellular membranes and change mitochondrial membrane permeability, inducing cytochrome C release and apoptotic death. However, the vitamin D-VDR complex can impede the apoptosis triggered by ROS [129, 130].

Cell autonomy involves programmed cell death (PCD) of the infected cells, preventing the propagation of the virus through apoptosis, autophagy, and non-apoptotic necroptosis [85, 131]. It has been observed that different kinds of PCD are very complex processes and

are deeply intertwined [131]. For instance, apoptosis plays essential functions in homeostasis, development, and human disease by facilitating the removal of unwanted, damaged, or infected cells. In contrast, apoptosis may also have a pathogenic role by contributing to cell death and tissue injury, and can also be beneficial to viruses as it allows them to increase their production and propagation [131]. Viruses can directly induce apoptosis without the involvement of immune cells. Furthermore, the intrinsic (or mitochondrial) apoptotic signaling pathway is involved in virus-induced disease [131].

7.1 Vitamin D May Improve the Outcome of SARS-CoV-2 Infection

There is a close connection between inflammation and thrombosis [132]. Several studies have found that vitamin D has anti-thrombotic effects [133-135]. In endothelial cells, vitamin D regulates vasodilator NO synthesis by regulating the activity of the endothelial NO synthase (eNOS) [136]. In addition, suppression of the rennin-angiotensin-aldosterone system (RAAS) by activated VDR has also been demonstrated [137]. Thus, vitamin D in the form of 1,25(OH)₂D₃ can be regarded as a novel negative endocrine regulator of the renin-angiotensin system. Furthermore, vitamin D reverses AngII-induced injury by ROS via the peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway [138].

Numerous studies have suggested that vitamin D may improve the outcome of COVID-19 infection [120, 139-142]. It is possible that vitamin D may repress cytokine production and simultaneously enhance the innate immune system and reduce the overactivation of the adaptive immune system [143, 144]. Marik et al. [145] suggested that the vitamin D status may influence the risk of dying from SARS-CoV-2. Zheng et al. [146] found that vitamin D attenuated lung injury through stimulating Alveolar Type II (ATII) cell proliferation and migration. In addition, they found that vitamin D reduced epithelial cell apoptosis and inhibited TGF-β- induced epithelial to mesenchymal transition (EMT). A very recent study by Meltzer et al. [141] suggested that vitamin D can reduce the risk for developing COVID 19 and may reduce the severity of COVID-19. Padhi et al. [140] found an inverse correlation between 25(OH)₂D₃ levels and SARS CoV-2 infection and mortality in the Indian population.

Since vitamin D also has therapeutic potential for the resolution of ARDS, it would be important to conduct randomized clinical trials and large population studies in an attempt to assess the potential beneficial effects of vitamin D administration on COVID-19 outcomes and to determine the appropriate dose [120].

8 Mitochondria and the gut-brain axis

8.1 Summary of key physiological functions

The microbiome (i.e. the genomic content of the gut microbiota) and the microbiota (gut microbes) play essential roles in healthy human immune function and metabolism [147-149]. Microorganisms produce a large number of metabolites that can affect the host's energy metabolism, cell-to-cell communication, immunity, development of individual phenotype, appetite control, and neurodevelopment processes [149, 150].

The gut microbiota can significantly regulate the development and function of the innate and adaptive immune system [151] and interact with host cells, affecting the host's mitochondrial function [152, 153]. Furthermore, there is a cross-talk between the microbiota and the mitochondria involving redox signal processes mediated by ROS, nitric oxide (NO), short-chain fatty acids (SCFAs), and H₂S [153-155]. Thus, the microbiota can influence cell homeostasis and metabolism via host cell mitochondrial regulation. Any

disruption or imbalance of the microbiota in the intestinal bacterial ecosystem is termed dysbiosis that can have a serious negative impact on human development and health.

There is bi-directional communication between gut microbes and vital human organs [13]. For instance, there is continuous bi-directional signaling between the brain and the gut through a system that is referred to as the gut-brain axis [156]. In addition, perturbations of the lung microbiota inside airways can also affect the composition of intestinal microbiota [157]. Ahlawat et al. [157] proposed that there is a gut–lung axis, a bi-directional communication system where respiratory infections are frequently accompanied by GIT symptoms. In addition, inflammatory bowel disease (IBD) patients with perturbed intestinal microbiota also have reduced lung function [158]. Thus, it seems that dysbiosis could be linked to respiratory disorders and infections.

8.2 COVID-19, Neurological Diseases and Gut Dysbiosis

Various studies have found high rates of various central and peripheral neurologic signs and symptoms and altered mental functions (mostly delirium) in COVID-19 patients [2, 159-164]. Neurological and psychiatric effects caused by infection, include anosmia and ageusia, ischaemic stroke, brain haemorrhage and memory loss, encephalopathy, altered mental states (e.g. delirium), confusion, or prolonged unconsciousness [2, 164]. These symptoms in COVID-19 tend to be non-specific. Some acute mental symptoms (similar to positive symptoms of psychoses), such as temporary hallucinations and delusions are typical in patients with ARDS or other critical illnesses [165].

Suggested mechanisms include direct viral invasion via systemic blood circulation, distribution of infected immune cells, or perturbed gut microbial systems [166,167].

Although central nervous system (CNS) symptoms and syndromes are associated with SARS-CoV-2, the underlying neuropathologic mechanisms are still not well understood. In a comprehensive post-mortem study conducted by Matschke et al. [168], SARS-CoV-2 RNA or its proteins were commonly detected in brain tissue samples, but the presence of the virus was not proportional to the mild cytotoxic T lymphocyte (CTL) infiltration, astrogliosis, and microgliosis, suggesting that immune-mediated processes and indirect virus effects could be in the background of the pathogenesis of CNS symptoms. It was observed that CTL infiltration and associated microglial activation were most pronounced in the brainstem and meninges, and the olfactory bulbs showed usually a high degree of astrogliosis and microgliosis [168]. This more severe neuropathologic involvement of the olfactory bulbs correlates with the findings that 82% of the asymptomatic COVID-19 patients (SARS-CoV-2 carriers) were identified with olfactory deficits [169]. The extensive inflammation, especially in the olfactory bulbs and medulla oblongata, found in a prospective autopsy cohort study as well, might cause anosmia and dampening of the respiratory system [170]. Sporadic SARS-CoV-2 infected cells present at late stages of COVID-19, together with a generalized sustained activation of the immune system with the formation of neutrophil extracellular traps (NETs) frequently form aggregates with platelets [170]. It suggests that systemic coagulopathy in combination with an autonomous maladaptive immune response could be the primary driver of lethal COVID-19. The fact, that in different studies SARS-CoV-2 was not detectable in the spinal fluid (CSF), but there was a high prevalence of autoantibodies (mainly against unknown auto-antigens in the brain) in CSF from patients with COVID-19 and neurological complications [171]. It suggests that neurological manifestations of COVID-19 may also be caused by indirect immune-mediated mechanisms targeting various unknown processes of the nervous system.

Numerous experimental and clinical observations have revealed that SARS-CoV-2 infection is frequently accompanied by symptoms in the GIT and that the gut microbiota plays a key role in the pathogenesis of sepsis and ARDS [172-175]. There are several ideas regarding the role of ACE2 in dysbiosis in COVID-19 patients. For example, Ahlawat et al. [157] suggested that the host immune system releases inflammatory mediators that induce a cytokine storm and produce lung hyperpermeability. The virus travels to the intestine and binds to intestinally-expressed ACE2 receptors on the enterocytes [157]. The entry of SARS-CoV-2 into the cell through membrane fusion markedly down-regulates ACE2 receptors, resulting in a loss of the catalytic effect of these receptors at the external site of the membrane. In addition, the microbial composition is perturbed, altering the host immune response. At the same time, the intestinal permeability is damaged by inflammatory mediators so that gut microbes and their metabolites can enter the circulation and travel to other organs, like the lungs producing further abnormalities.

The RAS (including ACE2) is in fact present throughout the GIT [176]. The RAS has an important role in the regulation of glucose, amino acid, fluid and electrolyte absorption and secretion, intestinal blood flow, intestinal motility, and inflammation [177]. Researchers are currently looking for possible solutions like RAS-blocking agents, ACE inhibitors, and angiotensin receptor blockers (ARBs) in patients with COVID-19 that may influence COVID 19-related intestinal effect [174, 178].

SARS-CoV-2 can directly infect neurons and the gut [2]. The proinflammatory state, produced by a viral infection, maybe the general mechanism involved in the induction of blood-brain barrier (BBB) damage. Alquisiras-Burgos et al. [179] proposed that SARS-CoV-2 could infect cells in the central nervous system, mainly via the brain microvascular endothelial cells of the BBB.

Gut microbial systems can affect brain development, function, and behavior via endocrine, neural, metabolic, and immunological pathways [180]. As mentioned above in the previous section regarding gut dysbiosis, there is growing evidence that SARS-CoV-2 infection can affect the digestive system and produce intestinal disorders in about 30% of the infected patients [181, 182]. SARS-CoV-2 could perturb gut microbial systems that may be involved in the pathogenesis of neuropsychiatric symptoms via the gut-brain axis [183]. Bostancıoğlu [184] proposed that SARS-CoV-2 invasion of the gastrointestinal system starts with oral invasion and probably exists before the brain invasion. In addition, when the GI tract is invaded, the virus may enter the central nervous system through vascular and lymphatic systems or the vagus nerve. Moreover, Villapol [167] suggested that COVID-19 infection can be associated with the lung-gut-brain axis and microbiome dysbiosis.

9 Mitochondria and the gut-brain axis

9.1 Summary of key physiological functions

About 95% of the body's serotonin (5-hydroxytryptamine, 5-HT) is produced by enterochromaffin cells (ECs) in the GIT. Serotonin is an active metabolite and is released from ECs and can modulate peristaltic, secretory, vasodilatory, vagal, and nociceptive reflexes [185]. 5-HT produced by ECs is taken up by circulating platelets [186]. Serotonin works as a neurotransmitter in the CNS, whereas in the periphery, it acts as a ubiquitous hormone involved in vasoconstriction and platelet function [187]. Serotonin has essential endocrine, autocrine, paracrine actions and may also function as a growth factor [188, 189]. Serotonin has a strong antioxidant and free radical scavenging ability [190, 191]. Moreover, studies have suggested that unregulated ROS can also be important mediators

of BBB breakdown [192, 193]. In addition, increased serotonin levels in the circulation can induce a transient breakdown of the BBB mediated by 5-HT₂ receptors [194, 195].

Serotonin is a weak platelet agonist that helps platelet activation [196]. Platelets present 5-HT_{2A} receptors for serotonin on their surface [197, 198]. Platelet serotonin transporters (SERT) can quickly reuptake 5-HT, transport it into platelet dense bodies, and take part in 5-HT release during platelet activation [197]. Serotonin is secreted by the platelets in dense granules during platelet activation that plays a role in local platelet aggregation and vasoconstriction in the surrounding blood vessels (**Fig. 2**) [186, 199]. Plasma serotonin concentration can quickly increase when platelets become activated [186]. The increase in circulating serotonin could induce a transient breakdown of the BBB, which may be mediated by 5-HT₂ receptors [200-203]. In autoimmune arthritis, Cloutier et al. [204] found that serotonin as a platelet-derived mediator can initiate the formation of gaps between endothelial cells in the joint microvasculature.

Several studies have indicated that serotonin and 5-HT_{2A} receptors may play a crucial role in the contraction of vascular smooth muscle, platelet activation and aggregation, and thrombus formation [205-208]. The increased plasma concentration of serotonin is a general feature of cardiovascular diseases frequently associated with enhanced platelet activation and thrombosis [209]. Abnormal serotonin concentrations in the blood plasma or increased platelet serotonin uptake or abnormal release contribute to the development of various diseases in the vasculature [189]. Increased extracellular serotonin facilitates platelet aggregation through receptor-independent and receptor-dependent signal mechanisms. In the receptor-dependent pathway, 5-HT binds to 5-HT surface membrane receptors that initiate a G-protein signaling pathway that induces calcium release from intracellular stores to activate the vesicular release of pro-coagulant molecules from α -granules [210]. In the receptor-independent signalling mechanism, during activation and aggregation of platelets, serotonin attaches to small GTPases through transamidation, a process commonly referred to as serotonylation. As a result of this binding, GTPases become constitutively active and induce α -granule exocytosis from platelets [187].

9.2 Serotonin, COVID-19, and the Role of Antidepressants

Various studies have found that perturbed coagulation processes, increased platelet activity, and blood 5-HT levels are associated with anxiety and depression, and that depression is a significant risk factor for ischemic heart and cerebrovascular disease and/or mortality after myocardial infarction [211-214]. In addition, the administration of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), like fluoxetine or norfluoxetine, can reduce platelet activation and plasma 5-HT concentrations [211, 215, 216]. For example, antidepressants could hinder a procoagulant effect in patients with anxiety and/or depression [215]. Plasma serotonin concentration can quickly increase when platelets become activated. However, SSRIs have anticoagulant properties, reducing chemokine and cytokine expression in the infected cells. They are effective in chronic obstructive pulmonary disease and may help prevent excessive cytokine release that is responsible for aggravating sickness progression and subsequent increasing TNF α in COVID-19 patients [217, 218].

Recently, Lenze et al. [219] performed double-blind, randomized research to reveal whether antidepressant fluvoxamine could have a protective effect on COVID-19 patients. The authors proposed that this antidepressant could help prevent the immune system overreaction produced by SARS-CoV-2. They found that COVID-19 patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over

15 days. This research has raised questions about whether cytokines are really playing important roles in COVID-19 deaths. If not, fluvoxamine may have beneficial effects by some other mechanism that is not yet understood.

10 Conclusion

In human circulation, platelets are essential mediators of hemostasis and thrombin generation and are key players of homeostasis, inflammation, and immune responses, as well. In addition, platelet health is essentially determined by the health of their mitochondria [63]. Recent studies have proposed that mitochondrial dysfunction may play a key role in the development of COVID-19 and may be responsible for the dysregulated immune response during COVID-19 infection [5-7].

When SARS-CoV-2 enters the host cells (or platelets), the virus may also perturb mitochondrial processes. Several host mitochondrial proteins can interact with the SARS-CoV-2 proteins, suggesting that viral RNA and proteins in mitochondria take fundamental roles in COVID-19 pathogenesis [101]. When SARS-CoV-2 breaks down mitochondrial and cellular defenses, it may produce unregulated and increased ROS generation that damage the membrane, and other cellular structures and processes. This changes mitochondrial membrane permeability and induces cytochrome C release and apoptotic cell death via the intrinsic, i.e., mitochondrial pathway.

The intrinsic mitochondrial apoptosis pathway determines the lifespan of platelets by the action of the mitochondrial Bcl-xl protein [64]. In addition, intrinsic apoptosis may also be favorable to viruses as it allows them to increase their production and propagation. Interestingly, HIV-infected subjects exhibited increased platelet activation, mitochondrial dysfunction, and activation of the intrinsic pathway of apoptosis in platelets when compared to healthy controls [66].

Vitamin D, as mentioned above, is a hormone with countless essential functions in homeostasis, cellular, immunological, and genetic regulation processes, among others [103-105, 133, 134]. Vitamin D may improve the outcome of SARS-CoV-2 infection in patients [120, 139-142]. Activated VDRs in mitochondria in human cells and platelets control mitochondrial respiratory activity to protect mitochondria from ROS damage induced by COVID-19. Through this mechanism, they may help preserve mitochondrial integrity and thus cell survival [128-130]. In addition, the vitamin D–VDR complex may be able to block the apoptosis triggered by ROS [129, 130]. It is probable that vitamin D is able to hamper viral spread through mitochondrial processes and could impede the virus-induced apoptosis triggered by ROS in various cells and platelets. This may explain the potential beneficial effects of vitamin D administration on COVID-19 outcomes [120, 139-141].

During SARS-CoV-2 infection, activated platelets release serotonin resulting in an increase of plasma serotonin concentration that could increase platelet aggregation and vascular permeability and could further induce platelet activation via 5-HT_{2A} receptors on circulating platelets. SERT molecules on the platelet membrane clear plasma 5HT in an attempt to stabilize the concentration of plasma 5HT [197, 220]. Here, it should be mentioned that SSRIs have anticoagulant properties. They reduce chemokine and cytokine expression in the infected cells and are effective in severe chronic obstructive pulmonary disease. Furthermore, they may help in hindering excessive cytokine release that is responsible for the subsequent increase in TNF α and aggravating sickness progression in COVID-19 patients [217, 218].

Gut microorganisms produce a large number of metabolites that can affect the host's energy metabolism, cell-to-cell communication, the innate and adaptive immune system,

and neurodevelopment processes [149, 150]. The microbiota can influence cell homeostasis and metabolism via host cell mitochondrial regulation [152-155]. Any disruption of the microbiota, termed dysbiosis, can have a serious negative impact on human development and health [154, 221]. SARS-CoV-2 infection is frequently associated with gastrointestinal symptoms [172-174]. SARS-CoV-2 could produce dysbiosis and perturb the microbial bacterial composition. This produces increased inflammatory mediators and changes intestinal permeability so that gut microbes and inflammatory mediators can go into circulation and travel to other organs, including the lungs and brain, causing abnormalities in their physiological function [167].

Ahlawat et al. [13, 157] proposed that the gut-lung axis, as bi-directional immunological co-ordination between gut and lungs, facilitates SARS-CoV-2 infection. Ahlawat et al. [13, 157] also suggested that during SARS-CoV-2 infection, the host immune system releases inflammatory mediators that induce a cytokine storm and produce lung hyper-permeability. This response may be partially mediated by the virus through intestinal alterations. The SARS-CoV-2 along with the inflammatory mediators travel to the intestine through circulation where it reduces the expression of ACE2 receptors on the enterocytes as a result, ACE2 cannot execute its normal role in the regulation of ANG II.

Several studies have found a high rate of neurologic diseases (especially encephalopathy) and altered mental function in COVID-19 patients [159-162]. Even though SARS-CoV-2 could directly infect neurons [2], neurological symptoms usually are non-specific and not all symptoms are associated with direct infection of cells in the nervous system. SARS-CoV-2 caused neurological diseases may result from disturbances of the gut microbiota that perturb bi-directional signaling systems such as the gut-brain axis or the lung-gut-brain axis, in addition to the more explored mechanisms including coagulation dysfunction, cardio-vascular comorbidities, and others [156, 167, 183, 222]. We agree with the assumption introduced by others that platelet hyper-reactivity via increased platelet-platelet and platelet-leukocyte interactions may have a key role in the pathophysiology of COVID-19 and that the supposed cytokine storm is probable due to endothelial dysfunction and related systemic inflammation [4, 38, 78]. The platelet hyper-reactivity mechanism seems to provide a reasonable explanation for COVID-19 being more dangerous for older individuals since the dysfunction of platelets and mitochondria, as well as endothelial cells, increases with age.

Under inflammation, activated platelets can bind to the endothelium and release inflammatory and angiogenic molecules including serotonin from their dense granules [56]. We recently presented a hypothesis [223] that peripheral serotonin, produced by enterochromaffin cells and picked up and stored by circulating platelets, may act as a general membrane permeability regulator [224] in host organs and tissues including the brain. Our hypothesis [223] is consistent with the idea, that platelet hyper-reactivity may have a central role in the pathophysiology of COVID-19. Specifically, increased extracellular serotonin from activated platelets during COVID-19 infection may facilitate platelet aggregation and perturb cellular and microvascular permeability in host organs (for example, in lung and gut systems) and tissues, and could also produce a transient breakdown of the BBB mediated by 5-HT₂ receptors [194, 195, 200-203]. This may facilitate either a direct entry of the SARS-CoV-2 into the nervous system causing local inflammation or inflammatory mediators may also enter the brain resulting in an indirect, systemic effect of the virus.

Our hypothesis [223] may also give a possible explanation of how antidepressants could help prevent the immune system overreactions produced by SARS-CoV-2. Lenze et al. [219] showed that fluoxetine may reduce anxiety and/or depression in COVID-19 patients

as well as reduce platelet activity and blood 5-HT levels, which finally could inhibit platelet aggregation and perturbation of microvascular permeability.

Furthermore, since about 95% of the body's serotonin is produced by ECs in the GIT that is taken up by circulating platelets [186], it may also support how antidepressants may have a beneficial effect on the outcome of COVID-19 in patients via the gut-brain axis [183].

In addition to the proposed key role of platelet hyper-reactivity during COVID-19 [4, 38, 78], our hypothesis also incorporates the following additional pathophysiological aspects (**Fig. 1**):

- (1) Since platelets are small anucleate blood cells that contain few (5-8) mitochondria, platelet mitochondria and the intrinsic mitochondrial apoptosis pathway can determine the platelet lifespan [64, 225]. Mitochondria from SARS-CoV-2 infected cells are highly vulnerable, and vulnerability increases with age [226]. While apoptosis plays an essential role in homeostasis, it can also be beneficial to viruses since it can allow them to increase their production and propagation [131]. Viruses can directly induce intrinsic mitochondrial apoptotic signaling pathways without the involvement of immune cells [66, 131]. Thus, perturbed mitochondrial processes by SARS-CoV-2 may easily cause platelet dysfunction and intrinsic mitochondrial apoptosis.
- (2) Serotonin secreted by enterochromaffin cells, which are taken up by circulating platelets and then released from activated platelets into the circulation, can facilitate platelet aggregation and increase microvascular permeability in host organs and tissues and can produce impaired BBB during SARS-CoV-2 infection.
- (3) Our hypothesis [223] also provides a possible explanation of how antidepressants [219] could decrease the immune system overreaction - produced by SARS-CoV-2 - via reduced platelet activity and blood 5-HT levels.
- (4) Since vitamin D and VDR could regulate the mitochondrial respiratory activity, and protect platelet mitochondria (and mitochondria of various cells) from ROS damage, it suggests that vitamin D may hamper SARS-CoV-2 spread through mitochondrial processes and could impede the virus-induced apoptosis triggered by ROS in various cells and platelets.
- (5) Since the functions of platelets, mitochondria, and endothelial cells deteriorate with aging, it may give an explanation why COVID-19 is so dangerous for older adults.
- (6) It is also emphasized that SARS-CoV-2 infection-produced dysbiosis could also be associated with a high frequency of gut, lung, and neurologic symptoms via the gut-brain axis or the lung-gut-brain axis. 5-HT produced and released from the ECs is an important GIT signalling molecule that regulates GIT motility and inflammation. It seems that increased 5-HT may contribute to diarrhea and the severity of COVID-19 [227].

We hope that our hypothesis (**Fig. 2**) about some possible signal pathways of platelet hyperactivation by SARS-CoV-2) will contribute to a better understanding of the pathogenesis of SARS-CoV-2 infection at the molecular level, and may be helpful for prevention, as well as for pharmacological and neuropharmacological investigations.

Fig. (1). Visualization of the key aspects of our summary and hypothesis. SARS-CoV-2 enters into cells and platelets of the host by ACE2 and TMPRSS2, and the viral RNA is released to the cytosol where the S protein induces fusion between the envelope of virus and endosome. It must be noted that the ACE2 dependent endocytic pathway is still contested because it is questionable that the platelets could express ACE2 [4, 78, 228]. SARS-CoV-2 RNA binds to proteins such as Toll-like receptors that trigger innate immune responses. SARS-CoV-2 proteins may perturb mitochondrial functions. SARS-CoV-2 activates VDR in mitochondria in human cells and platelets that try to control mitochondrial respiratory activity via protection from ROS damage, and try to preserve mitochondrial integrity and cell survival. In addition, vitamin D can reverse AngII-induced injury

by ROS via the peroxisome proliferator-activated receptor- γ (PPAR- γ) pathway. If SARS-CoV-2 overcomes mitochondrial and cellular defenses, an infection may produce unregulated and increased ROS generation that damage membrane and cellular processes and as a result change mitochondrial membrane permeability that induces cytochrome C release and apoptotic death via an intrinsic pathway that is favorable to virus propagation. Activated platelets bind to the endothelium and release inflammatory and angiogenic molecules (like serotonin) from their granules that perturb (micro)vascular permeability in circulation. The increased plasma concentration of serotonin is associated with enhanced platelet activation and thrombosis. SERT molecules on the platelet membrane clear plasma 5HT and try to stabilize the concentration of plasma 5HT. The SARS-CoV-2 infection causes dysbiosis and perturbs the microbial composition and host immune system. Next, the intestinal permeability is damaged by inflammatory mediators and consequently, gut microbes and their metabolites can go into circulation and travel to organs, like the lungs, and produce abnormalities. There may be a gut–lung axis (bi-directional immunological coordination) between the gut and lung that facilitates SARS-CoV-2 infection. Furthermore, many respiratory infections are often accompanied by GI symptoms. SARS-CoV-2 infection is also frequently associated with neurologic diseases. The increased extracellular serotonin facilitates platelet aggregation that disturbs vascular permeability and induces a transient breakdown of the BBB mediated by 5-HT₂ receptors. The breakdown of the BBB helps SARS-CoV-2 to enter directly into the brain. Or as a consequence of SARS-CoV-2 infection, inflammatory mediators from the infected gut, organs, tissues, and circulation may also get into the brain. Antidepressants may decrease the immune system overreaction via reduced platelet activity and blood 5-HT levels.

Fig. (2). Visualization of our proposed mechanisms of how SARS-CoV-2 may induce platelet hyperactivation. Apoptosis can be triggered by various extrinsic and intrinsic signals such as ROS, RNS, DNA-damaging agents, heat shock, serum deprivation, viral infection, and hypoxia. The extrinsic pathway to apoptosis is regulated by certain ligands binding to “death” receptors, and the intrinsic pathway is controlled by mitochondria. It is possible that SARS-CoV-2 is able to initiate mitochondrial apoptosis through various pathways: (1) ACE2 dependent endocytic pathway [34]. It must be noted that the ACE2 dependent endocytic pathway is still controversial because it is questionable that the platelets could express ACE2 [4, 78, 228]; (2) Uptake of SARS-CoV-2 mRNA (or protein) independent of ACE2 by platelets [7] via, for example, CD147, CD26, or extracellular vesicles (3) Via the autoantibody pathway by IgG fractions from severe COVID-19 patients [229]. The intrinsic mitochondrial apoptosis pathway determines the lifespan of platelets. Since platelets contain few mitochondria, this means that the proper function of platelets is inherently dependent on mitochondrial processes. When platelets cannot undergo mitophagy (the selective degradation of mitochondria by autophagy), they undergo apoptosis, which produces increased thrombus formation. It seems that SARS-CoV-2 could particularly manipulate complex mitochondrial mechanisms (for example SARS-CoV-2 RNA and proteins localized to mitochondria [7] that perturb the electron transport chain, which creates unregulated overproduction of ROS. Unregulated overproduction of ROS triggers complex processes, which directly or indirectly force an excessive initiation of mitochondrial apoptosis. In addition, since mitochondria act as metabolic and redox hub of cells and platelets, mitochondrial dysfunction induces excessive initiation of mitochondrial apoptosis which also triggers platelet hyperactivation, which increases the secretion of α-granules and dense granules, P-selectin expression, complement activation, etc. All these processes can

promote platelet aggregation and enhance (or perturb) microvascular permeability. Numerous studies have suggested that vitamin D improves the outcome of COVID-19 infection [139-142]. In addition, the vitamin D receptor in mitochondria in human cells and platelets could regulate mitochondrial respiratory activity and protect it from ROS damage induced by SARS-CoV-2 [128, 129]. Furthermore, serotonins secreted by enterochromaffin cells that are taken up by means of circulating platelets and then released from activated platelets into the circulation can promote platelet aggregation and enhance microvascular permeability in host organs and tissues during SARS-CoV-2 infection. Thus, over-activated platelets release serotonin, leading to an increased plasma serotonin level that could trigger platelet aggregation and vascular permeability, and stimulate further platelet activation via 5-HT_{2A} receptors on circulating platelets in SARS-CoV-2 infection. Legend: FcγRIIA (CD32a): a low-affinity Fc receptor (FcR) for the constant region of IgG that recognizes immune complexes (ICs). p38-MAPK: p38 mitogen-activated protein kinases are a class of mitogen-activated protein kinases. 5-HT_{2A}: 5-hydroxytryptamine receptor 2A. Bcl-2: B-cell lymphoma 2 family of regulator proteins that regulate apoptosis. TLR7: Toll-Like Receptor 7 is an endosomal sensor that recognizes single-stranded RNA viruses.

List of abbreviations

1,25(OH)₂D₃ = 1,25-dihydroxyvitamin D₃
 25(OH)D₂ = 25-hydroxyvitamin D₂
 25(OH)D₃ = 25-hydroxyvitamin D₃
 5-HT = 5-hydroxytryptamine
 5-HT_{2A} = 5-hydroxytryptamine receptor 2A
 ACE2 = Angiotensin-Converting Enzyme 2
 ADP = Adenosine Diphosphate
 ADP = Adenosine Diphosphate
 Ang 1-7 = Angiotensin-(1-7)
 Ang 1-9 = Angiotensin-(1-9)
 Ang I = Angiotensin I
 Ang II = Angiotensin II
 ARB = Angiotensin Receptor Blocker
 ARDS = Acute Respiratory Distress Syndrome
 ATII = Alveolar Type II
 ATP0 = Adenosine Triphosphate
 ATP5B = Mitochondrial ATP Synthase β-subunit
 BAK and BAX = Bcl-2 Family Members
 BAX = Bcl-2-Associated X Protein
 BBB = Blood-Brain Barrier
 Bcl-2 = B-cell Lymphoma 2 Family of Regulator Protein
 Bcl-xl = B-cell Lymphoma-Extra Large
 BID = Bcl2 Interacting Protein
 CAM = Cell Adhesion Molecule
 CLR = C-type Lectin Receptor
 CNS = Central Nervous System
 COVID-19 = Coronavirus Disease-2019
 COX2 = Cytochrome c Oxidase Subunit 2
 COX4 = Cytochrome c Oxidase Subunit 4
 CTL = Cytotoxic T Lymphocyte
 CVB3 = Coxsackievirus B3
 CXCL1 = Chemokine (C-X-C Motif) Ligand1
 CSF = Cerebrospinal Fluid
 DNA = Deoxyribonucleic Acid
 EC = Enterochromaffin Cell
 EMT = Epithelial-to-mesenchymal Transition
 eNOS = Endothelial NO Synthase
 FcγRIIA = (CD32a) Lowyaffinity Fc Receptor (FcR)
 FGF = Fibroblast Growth Factor
 GIT = Gastrointestinal Tract
 GTPase = GTP Hydrolase
 H₂S = Hydrogen Sulfide
 HIV = Human Immunodeficiency Virus

IBD = Inflammatory Bowel Disease
IC = Immune Complex
IL-6 = Interleukin 6
LPAs = Leukocyte–Platelet Aggregates
MAS = Proto-Oncogene
MASR = Vasodilation-Promoting Receptor
MAVS = Mitochondrial Antiviral-Signaling Protein
miRNA = Non-Coding Micro RNA
MPTP = Mitochondrial Permeability Transition Pore
MPV = Mean Platelet Volume
MT-ATP6 = Mitochondrial ATP Synthase Subunit 6
mtRNA = Mitochondrial RNA
NET = Neutrophil Extracellular Trap
NO = Nitric Oxide
NLR = NOD-like Receptor
NO₂ = Nitrogen Dioxide
OXPHOS = Oxidative Phosphorylation
p38-MAPK = p38 Mitogen-activated Protein Kinase
PCD = Programmed Cell Death
PF4 = Platelet Factor 4
PPAR- γ = Peroxisome Proliferator-activated Receptor- γ
PRR = Pathogen Recognition Receptor
RAS = Renin Angiotensin System
RBD = Receptor Binding Domain
RLR = RIG-I-like Receptor
RNA = Ribonucleic Acid
ROS = Reactive Oxygen Species
SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2
SCFAs = Short-chain Fatty Acids
SERT = Platelet Serotonin Transporter
sgRNA = Subgenomic RNA
SSRI = Selective Serotonin Reuptake Inhibitor
TGF- β = Transforming Growth Factor-beta
TLR = Toll-like Receptor
TMPRSS2 = Cellular Transmembrane Serine Protease 2
TNF = Tumor Necrosis Factor
TPH = Tryptophan Hydroxylase
UVB = Ultraviolet B
VDR = Vitamin D Receptor

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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