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Review

The four horsemen of a viral Apocalypse: The pathogenesis of SARS-CoV-2 infection (COVID-19)

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SUMMARY

The pathogenesis of coronavirus disease 2019 (COVID-19) may be envisaged as the dynamic interaction between four vicious feedback loops chained or happening at once. These are the viral loop, the hyperinflammatory loop, the non-canonical renin-angiotensin system (RAS) axis loop, and the hypercoagulation loop. Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 lights the wick by infecting alveolar epithelial cells (AECs) and downregulating the angiotensin converting enzyme-2 (ACE2)/angiotensin (Ang-1−7)/Mas1R axis. The viral feedback loop includes evading the host's innate response, uncontrolled viral replication, and turning on a hyperactive adaptative immune response. The inflammatory loop is composed of the exuberant inflammatory response feeding back until exploding in an actual cytokine storm. Downregulation of the ACE2/Ang-(1−7)/Mas1R axis leaves the lung without a critical defense mechanism and turns the scale to the inflammatory side of the RAS. The coagulation loop is a hypercoagulable state caused by the interplay between inflammation and coagulation in an endless feedback loop. The result is a hyperinflammatory and hypercoagulable state producing acute immune-mediated lung injury and eventually, adult respiratory distress syndrome.

> "Effects vary with the conditions which bring them to pass, but laws do not vary. Physiological and pathological states are ruled by the same forces; they differ only because of the special conditions under which the vital laws manifest themselves"
>
> Claude Bernard
>
> (1813−1878)

1. Introduction

In December 2019, a new epidemic disease appeared in the Huanan Seafood Wholesale Market, Wuhan, Hubei Province, China. It was characterized by an upper respiratory tract infection rapidly evolving to bilateral pneumonia and eventually respiratory failure [1]. The etiologic agent was a new coronavirus which was named SARS-CoV-2, whereas the disease was called COVID-19 [2]. The disease quickly expanded from its original nucleus in Hubei and by March 11, 2020 the WHO declared it as a pandemic. As of June 23, 2020, COVID-19 has affected 188 countries around the world, with 9.131.445 confirmed cases worldwide and a death toll of 472.856 [3].

Early in the course of the pandemic, clinicians and researchers realized that full-blown COVID-19 evolved in at least three phases: the first phase with cough, fever, wheezing, fatigue, headache, diarrhea, and dyspnea, reminiscent of an upper tract respiratory infection. The second phase, with the rapid appearance of bilateral pneumonia, infiltrates with variable degrees of hypoxemia, and Omit in the third phase in which some patients developed respiratory failure leading to death [4]. Around 80% of people have SARS-COV-2 infection asymptomatic or with mild to moderate illness, mostly restricted to the upper and conducting airways. The other 20% will develop symptomatic infection needing hospital admission, and 5% will require ventilatory support in the Intensive Care Unit (ICU) [5]. The clinical phases of the infection reflect the pathogenic events starting with the virus gaining access to the lungs. The clinical manifestations and pathogenic events of any infectious disease, and COVID-19 in particular, should be viewed in the light of the damage-response framework in which several factors and forces may tip the scales to the host or pathogen side [6]. Therefore, sometimes the

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Glossary

AAK1	AP-2-associated protein kinase
ACE2	angiotensin converting enzyme 2
ACEi	ACE inhibitors
ADAM17	a disintegrin and metalloproteinase domain 17
ADE	antibody-dependent enhancement
AECs	alveolar epithelial cells
ALI	acute lung injury
Ang	angiotensin
AP-1	activator protein 1
AT1R	angiotensin II receptor type 1
AT2R	angiotensin II receptor type 2
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
COVID-19	coronavirus disease 2019
CoV	coronavirus
CCR9	C-C chemokine receptor type 9
CXCR6	C-X-C chemokine receptor type 6
DAMPs	damage-associated molecular pattens
ECs	endothelial cells
FYCO1	FYVE (Fab1-YotB-Vac1p-EEA1) coiled-coil domain autophagy adaptor 1
GPCR	G protein-coupled receptors
G-CSF	granulocyte-colony stimulating factor
ICU	intensive care unit
IFN	interferon
IL-1β	interleukin 1 beta
IL-6	interleukin-6
ISGs	interferon-stimulated genes
IP-10	interferon gamma-induced protein
IRF3	IFN regulation factor 3
JAK	janus activated kinase
kb	kilobase
LPS	lipopolysaccharide
LPV/r	lopinavir-ritonavir
LZTFL1	leucine zipper transcription factor-like 1
MIP-1A	macrophage inflammatory protein 1A
MCP-1	monocyte chemoattractant protein 1
MDY88	myeloid differentiation primary response 88
MERS	middle East respiratory syndrome
mRNA	messenger RNA
NETs	neutrophil extracellular traps
NF-*K*B	nuclear factor kappa B
NLRP3	NOD-like receptor protein 3
NO	nitric oxide
NOD	nucleotide-binding oligomerization domain
nsps	non-structural proteins
ORF	open reading frame
PAMPs	pathogen-associated molecular patterns
PBMC	peripheral blood mononuclear cells
PGI2	prostacyclin
PMN	polymorphonuclear neutrophils
PRRs	pattern recognition receptors
PAR	proteinase-activated receptor
RAS	renin-angiotensin system
rhACE2	recombinant human ACE2
RIG-I	retinoic acid-inducible gene-I
RNA	ribonucleic acid
S	spike
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLC6A20	solute carrier family 6, member 20
STAT1	signal transducer and activator of transcription 1
TACE	TNF-α converting enzyme
TBK1	TANK-binding kinase 1
TLR	toll-like receptor
TMPRSS2	type II transmembrane serine protease
TNF-α	tumor necrosis alpha
TRAF3	TNF receptor-associated factor 3
XCR1	XCL1 (Chemokine [C motif] ligand 1) and XCL3 (Chemokine [C motif] ligand 3) receptor

pathogen could be a mere initiator more than an actual perpetrator and it is the host's forces unchained by the pathogen's presence those which are to cause tissue and organ damage.

Herein, we will review the current knowledge about COVID-19 pathogenesis, and how SARS-CoV-2 infection and the host response depict the different scenarios of COVID-19. We foresee four interplaying vicious loops, namely a viral loop, a defective non-canonical RAS loop, an inflammatory loop, and a coagulation loop (Fig. 1).

With β-coronaviruses sharing most of their genome and structure, it seems quite logical that they can also share mechanisms of pathogenicity and that the host responses to these shared elements will be somewhat comparable. Therefore, in some aspects of the present review, we refer to other zoonotic coronaviruses to explain pathogenic events that can take place in COVID-19.

2. The first horseman: a sneaky virus

SARS-CoV-2 is a previously unknown β-coronavirus which shows 88% identity to the sequences of two bat-derived SARS-like coronaviruses, 79.5% identity to SARS-CoV, and about 50% identity to Middle East Respiratory Syndrome (MERS)-CoV [2]. The genome of SARS-CoV-2 is a positive-sense, single-stranded RNA with a size of 29.9 kb, containing at least ten open reading frames (ORFs) [7]. Recently, non-canonical ORFs and at least 41 RNA modifications with an unknown function, were identified [7]. The first ORFs represent two-thirds of the viral RNA. They are translated into two large polyproteins, which are later processed into 16 non-structural proteins (nsp1 to nsp16) that form the viral complex replicase-transcriptase [7]. These nsps rearrange endoplasmic reticulum into double-membrane vesicles, where viral replication and transcription take place [8,9]. The other third of the genome encodes four main structural proteins; spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins, and several accessory proteins whose functions are currently unknown but unrelated to viral replication [10].

SARS-CoV-2, like SARS-CoV, requires the ACE2 as a receptor to enter the cells [11,12]. Coronavirus S protein is a determinant of virus entry into host cells by binding the envelope spike glycoprotein to its cellular receptor ACE2 [13,14]. Although it was initially thought that SARS-CoV achieved entry by membrane fusion, a critical proteolytic cleavage at SARS-CoV S protein, mediated by type II transmembrane serine protease (TMPRSS2), brings about membrane fusion and viral infectivity [15]. After the virus entry, the RNA genome is released into the cytoplasm and translated into two polyproteins and structural proteins [16].

The survival of SARS-CoV in host cells is eased by strategies to evade the immune response. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors (PRRs) such as toll-like receptor (TLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors, nucleotide-binding oligomerization domain (NOD)-like receptors, and C-type lectin-like receptors [17]. SARS-CoV induces the

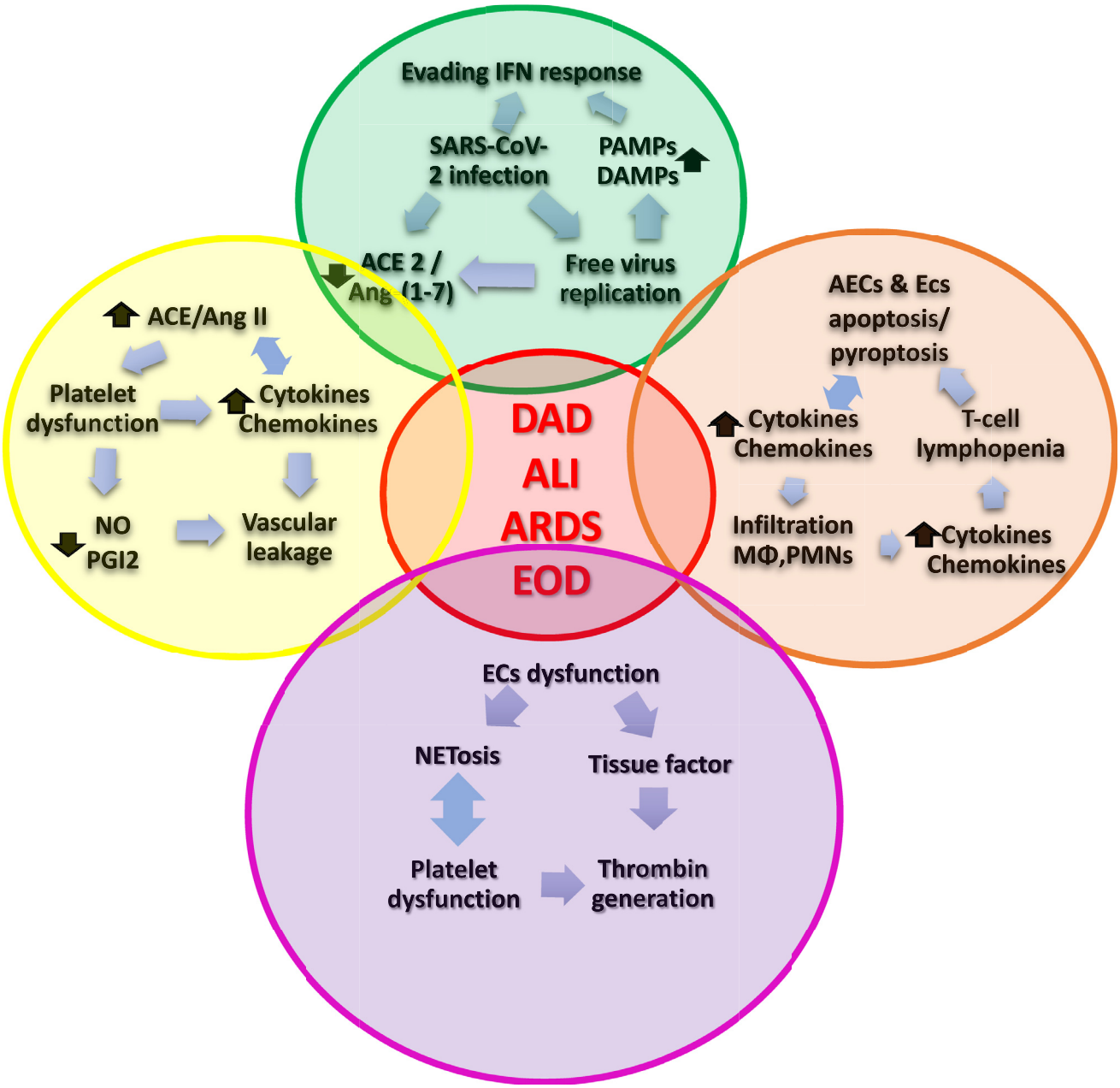

Fig. 1. *The four hurtful feedback loops in the pathophysiology of COVID-19.*

Schema representing the most remarkable pathophysiological events involved in each of the four vicious feedback loops and the complex interactions established between them. Intersections between circles represent interaction between loops. The central circle colored in red means the final events of the physiopathologic cascade. The vicious viral loop is depicted in green, the hyperinflammatory loop is colored in orange, the ACE2/Ang-(1−7) loop is colored in yellow, and the hypercoagulation loop is colored in purple.

IFN = interferon; PAMPs = Pathogen-associated molecular patterns; DAMPs = Damage-associated molecular patterns; SARS-CoV-2 = Severe acute respiratory syndrome Coronavirus 2; AECs = Alveolar epithelial cells; ECs = Endothelial cells; ACE2 = Angiotensin-converting enzyme 2; Ang-(1−7) = Angiotensin 1−7; ACE = Angiotensin-converting enzyme; Ang II = Angiotensin II; NO = Nitric oxide; PGI2 = Prostacyclin; MΦ = Macrophages; PMNs = Polymorphonuclear neutrophils; DAD = Diffuse alveolar damage; ALI = Acute lung injury; ARDS = Adult respiratory distress syndrome; EOD = End-organ disease.

production of double-membrane vesicles that lack PRRs and can then replicate in these vesicles [18]. Furthermore, several structural and nsps encoded by SARS-CoV and MERS-CoV antagonize antiviral innate immune response. Interferon (IFN) and interferon-stimulated genes (ISGs) responses are counteracted by nsp1, nsp3 macrodomain, nsps-deubiquitinase, and ORF3b, ORF6, and ORF9, thus overthrowing antiviral response [19-24]. nsp1 inhibits IFN responses by three mechanisms, inactivation of host translational machinery, degradation of host mRNAs, and inhibiting signal transducer and activator of transcription 1 (STAT1) phosphorylation [25,26]. Part of the nsp3 is a papain-like protease that antagonizes IFN and cytokine production by blocking phosphorylation of IFN regulation factor 3 (IRF3) and disrupting NF-KB signaling [24]. Nsp7 and nsp15 are also IFN antagonists by an unknown mechanism [24]. ORF3b exerts IFN antagonism through inhibition of IFNβ induction by transcription factors IRF3 and NF-KB, whereas ORF6 antagonizes IFN by inhibiting signaling through the JAK-STAT pathway [24]. M and N proteins flatten IFN signaling by inhibiting TANK-binding kinase 1 (TBK1)/IKB kinase ε (IKKE), and the negative regulation of TRAF3/6-TBK1-IRF3/NF-KB/AP1 signals [25,26].

Antagonism of IFN responses further promotes free virus replication resulting in increased viral PAMPs and DAMPs that additionally dampen IFN signaling and stimulate PRRs to induce an aberrant inflammatory response. The replicative capacity of SARS-CoV-2 is 3.20 folds more than that of SARS CoV in infected human lung tissue without significantly inducing types I, II, and III IFNs [27]. Since innate immunity is the frontline defense against SARS-CoV-2, a slow and poorly coordinated response may result in higher viral replication. This sequence of events, namely AECs infection, IFN signaling inhibition, and free viral replication depicts the viral vicious loop (Fig. 1).

3. The second horseman: a gathering storm

SARS-CoV-2 infects primarily airway and alveolar AECs, especially type II pneumocytes, the cells that produce alveolar surfactant and are predecessors of type I pneumocytes. However, it can infect any cell expressing the receptor ACE2, such as endothelial cells, pericytes, vascular smooth muscle cells, macrophages, fibroblasts, T-cells, cardiomyocytes, enterocytes, basal cell epidermal cells, and epithelial tubular distal cells [28-30]. SARS-CoV-2, in the face of unchecked replication because of dampened innate immunity, can replicate in high titres early after the infection [28,31,32].

High viral replication in AECs induces cytopathic effects, as shown by the necropsy findings of multinucleated cells (syncytia), cytoplasmic viral inclusions, and apoptosis, an ultimate cellular response to stop virus replication [33,34]. These events are followed by the production of increased levels of proinflammatory cytokines and chemokines by AECs [35,36]. Moreover, SARS-CoV nucleocapsid activates interleukin-6 (IL-6) expression in lung epithelial cells via cellular transportation of nuclear factor kappa B (NF-*K*B) [37]. Massive infiltration of inflammatory cells into the lungs is, in turn, mounted by these cytokines and chemokines [32] (Fig. 2). Although tissue-resident macrophages of the lungs localize to the airspace within alveoli, they do not seem to be the predominant subset in this response [38]. Accumulation of inflammatory monocyte-macrophages and neutrophils in the lungs following SARS-CoV-2 infection promotes the additional release of cytokines and chemokines [32] (Fig. 2). Besides, the SARS-CoV spike promotes the upregulation of IL-6 and tumor necrosis alpha (TNF-α) in macrophages[39].

Cytokines spill over from local inflammation to the systemic circulation. COVID-19 patients have high serum levels of inflammatory cytokines, including interleukin (IL)-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage

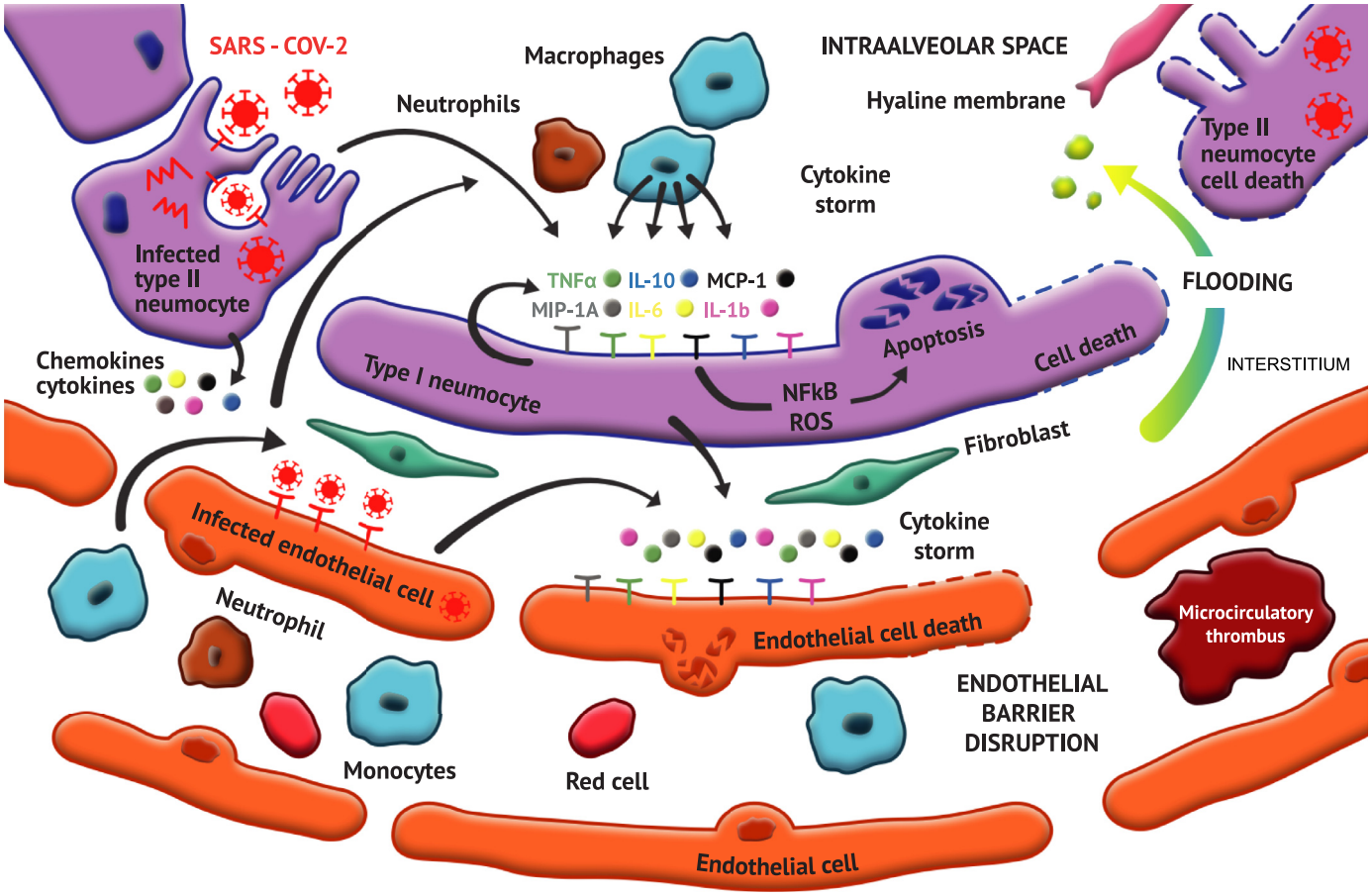

Fig. 2. *Physiopathology of acute lung injury in SARS-CoV-2 infection (COVID-19).*

SARS-CoV-2 infects primarily type II pneumocytes through binding to the ACE2 receptor. The infected and surrounding pneumocytes secret cytokine and chemokines, which attract monocyte-macrophages and neutrophils to the alveolar space, which secrete additional cytokines and chemokines. Ultimately the pneumocytes suffer apoptosis/pyroptosis releasing large amounts of proinflammatory factors. Endothelial cells are infected, overexpress adhesion molecules, and release chemokines and cytokines. Endothelial cells undergo apoptosis, which, together with alveolar cell apoptosis, increases vascular leakage and breaks the alveolar-capillary barrier. The hyperinflammatory milieu and endothelial dysfunction activate coagulation cascades through tissue factor expression, platelet activation, and NETosis all of them promoting microcirculatory thrombi formation. The break of endothelial-alveolar barrier further promotes vascular leakage resulting in interstitial and alveolar space flooding. Downregulation of the ACE2/Ang-(1−7)/Mas1R axis contributes to increasing vasoconstriction, inflammatory signals, endothelial dysfunction, vascular leakage, and prothrombotic state.

SARS-CoV-2 = Severe acute respiratory syndrome Coronavirus 2; TNF-α = Tumor necrosis factor alpha; IL-10 = Interleukin 10; MCP-1 = Macrophage chemoattractant protein 1; MIP-1A = Macrophage inhibitory protein 1A; IL-6 = Interleukin 6; IL-1β = Interleukin 1 beta; NF-*K*B = nuclear factor kappa B.

inflammatory protein (MIP)-1A, and TNF-α. These cytokine/chemokine levels correlate with disease severity [40,41]. COVID-19 patients with severe disease have increased levels of IL-6 more often than those with the mild or moderate disease [42]. Although viremia is not a prominent feature in COVID-19 and is usually short-lived, the degree and duration of SARS-CoV-2 viremia relates to the severity of disease and the serum levels of IL-6 [43].

Endothelial cells (ECs) are infected very early in the course of infection. Because of speedy viral replication and exuberant proinflammatory cytokine/chemokine response they may suffer apoptosis [32,33]. This apoptotic phenomenon takes place via Fas/FasL or TRAIL-DR-5-dependent mechanisms [44]. Besides, inflammatory monocyte-macrophages release TNF-α which also promotes apoptosis of both lung ECs and AECs [35]. ECs and AECs apoptosis compromise lung microvascular bed and alveolar cell-capillary barrier integrity, thereby resulting in vascular leakage and alveolar edema [35] (Fig. 2). Pericytes play an essential role in maintaining endothelial cell function in capillary vessels and are among the cells with the highest ACE2 expression. Their infection by SARS-CoV-2 may add to endothelial cell dysfunction leading to microcirculation disorders [29].

A striking feature of full-blown COVID-19 is severe lymphopenia. CoV-specific T-cells are decisive for viral clearance and limitation of additional damage to host tissues since they can dampen hyperreactive innate immune response [45,46]. However, when exuberant inflammatory response induced by SARS-CoV-2 takes place, T-cell response is decreased because of TNF-α-mediated cell apoptosis, thus resulting in uncontrolled inflammatory responses [35] (Fig. 1). Besides, normal T-cell activation can be suppressed by IL-6, further contributing to lymphopenia [47]. In severe COVID-19 patients with lymphocyte subsets examined, there is intense CD4 and particularly CD8 lymphopenia [42], both negatively correlating with TNF-α and IL-6 serum levels [41]. CD4 cells promote the production of virus-specific antibodies by activating T-dependent B cells, whereas CD8 cells are cytotoxic and can kill virus-infected cells. Since CD8 cells account for about 80% of the total inflammatory lung interstitial infiltrate, highly cytotoxic CD8 lymphocytes can arbitrate immune-mediated tissue damage [34]. Also, in COVID-19 patients, these cells exhibit markers of functionally exhausted T-cells such as programmed cell death protein 141.

There is upregulation of apoptosis, autophagy, and p53 pathways in PBMC of COVID-19 patients [48]. MERS-CoV can induce T-cell apoptosis through activation of the intrinsic and extrinsic apoptosis pathways [49], and SARS-CoV E protein can also promote T-cell apoptosis mediated by Cbl-XL binding [50]. Although SARS-CoV-2 can non-productively infect T lymphocytes, whether this infection induces T-cell apoptosis is not yet clear [51]. Alternatively, pyroptosis has been suggested as a cause of lymphopenia since COVID-19 patients have increased serum IL1-β levels, which is the downstream indicator of cell pyroptosis [52]. In SARS-CoV infection, viroporin 3a triggers the activation of NOD-like receptor protein 3 (NLRP3) inflammasome and the secretion of IL-1-β by macrophages [53]. Pyroptosis can release large amounts of proinflammatory factors [54]. Whatever the cause, during the late stages of infection, depletion of T-cells may promote viral survival and, consequently, may prolong the infection.

Essential to control the persistent phase of SARS-CoV-2 infection is the appearance of humoral immunity, in which antiviral neutralizing antibodies play a significant role. However, in animal models, anti-S protein-neutralizing antibodies (anti-S-IgG) may cause severe lung injury by altering inflammatory responses [55]. In SARS-CoV infection, the development of acute respiratory disease coincides with antiviral IgG seroconversion in 80% of patients [56] and patients who died developed anti-S-neutralizing antibodies faster [57]. The presence of anti-S-IgG promotes proinflammatory monocyte-macrophage lung accumulation and the production of MCP-1 and IL-8. Such proinflammatory cytokine release would be mediated through the binding of the virus-anti-S-IgG complex to the monocytes-macrophages FcγRIIA receptor since its blockade reduces the production of IFN-γ, TNF-α, IL-1, and IL-6 [55]. It would also be possible that such complexes activate the classical pathway of the complement system or induce antibody-dependent cell-mediated cytotoxicity, thus leading to cellular damage. Therefore, a possible underlying mechanism would be antibody-dependent enhancement (ADE) of viral infection that occurs in some patients with early, sub-optimal antibody activity that cannot completely clear the virus, leading to persistent viral replication and inflammation [58].

Uncontrolled viral replication, because of a delayed innate immunity response, will cause cellular damage leading to an overexuberant and dysregulated immune kickback. This hyper reaction affecting the innate and adaptative immune responses will pave the way for immune-mediated damage of tissues and organs. This sequence of events conforms the inflammatory hurtful feedback loop (Fig. 1).

4. The third horseman: a helpless lung

The RAS plays a critical role in the control of cardiovascular and renal functions by maintaining blood pressure homeostasis and hydro-electrolyte balance [59]. Initially, the RAS was conceived as a linear hormonal system in which angiotensinogen synthesized in the liver is converted into the active peptide angiotensin I (Ang I) through the action of renin [60]. Afterward, Ang I is cleaved by the ACE generating Ang II [61]. Two G protein-coupled receptors (GPCR) mediate the actions of Ang II, angiotensin II receptor type 1 (AT1R), and type 2 (AT2R) [62]. The primary role of this canonical or classical RAS pathway (ACE/Ang II/AT1R) is to increase the sympathetic nervous system tension, to cause vasoconstriction, increase blood pressure, and promote inflammation, fibrosis and myocardial hypertrophy [63].

The RAS also possesses a non-canonical, counter-regulatory branch composed of ACE2/Ang-(1−7)/Mas1R. The activity of the system will depend on the balance between the two branches. ACE2 is the main synthesizer of Ang-(1−7) by removing a single residue from Ang I to generate Ang-(1−9) and by cleaving a single residue from Ang II to generate Ang-(1−7) [64,65]. The functional receptor for Ang-(1−7) is the GPCR Mas1R [66]. The conformation of the negative or counter-regulatory axis is relevant not only because it downgrades the vasoconstrictive/ proliferative peptide Ang II to form the vasodilator heptapeptide Ang-(1−7), but also because it degrades Ang I to Ang-(1−9), thereby limiting the availability of the substrate for ACE. Ang-(1−7) binds to Mas1R, inducing vasodilation, inhibition of cell growth, anti-thrombotic, and anti-arrhythmogenic effects [67]. ACE2 activity is controlled by a disintegrin and metalloproteinase domain-containing protein 17 (ADAM-17, also called TNF-α-converting enzyme, TACE). ADAM-17 proteolytically cleaves ACE2 causing the shedding of ACE2 into the interstitium, which leads to decreased ACE2 activity in the tissue and elevates circulating ACE2 activity [68] (Fig. 3). Since blood and urine measurement of ACE2 levels is feasible, they could potentially be used as a prognostic biomarker in COVID-19[69].

RAS plays an essential role in the pathogenesis of inflammatory diseases in which most of the proinflammatory actions are caused by Ang II [67]. Ang II activates several cellular functions and molecular signaling pathways related to tissue injury, inflammation, and fibrosis. They involve calcium mobilization, free radical generation, activation of protein kinases and nuclear transcription factors, recruitment of inflammatory cells, adhesion of monocyte and neutrophils to endothelial and mesangial cells, upregulation of adhesion molecules and stimulation of expression, synthesis, and release of cytokines and chemokines [68]. AT1R mediates most of these actions [70]. The

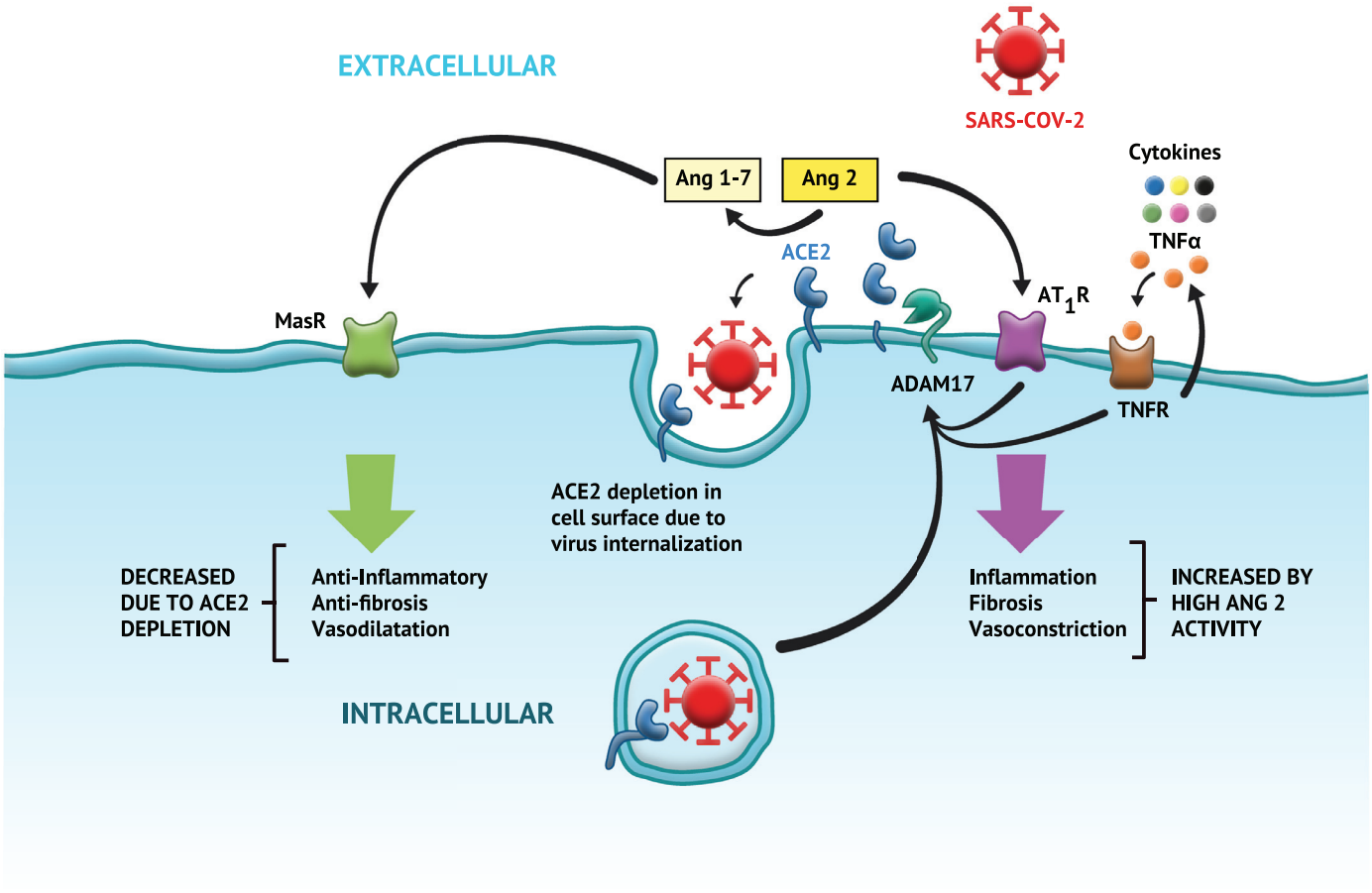

Fig. 3. *Implication of angiotensin-converting enzyme 2 (ACE2)/Angiotensin (Ang-1−7)/Mas1R in the pathogenesis of coronavirus disease 2019.*

The lung, and other organs, lose the protection of the non-canonical RAS system as a result ACE2 downregulation after SARS-CoV-2-induced endocytosis. Consequently, the canonical ACE/Ang II/AT1R becomes dominant, levels of Ang II increase with the subsequent promotion of fibrosis, myocardial hypertrophy, increased ROS, vasoconstriction, inflammation, and endothelial dysfunction. AT1R mediates most of these actions. Endocytosed SARS-CoV-2 spike proteins mediates ADAM 17-mediated proteolytic cleavage of ACE2. ADAM-17 activity is enhanced through the activated AT1R by increased levels of Ang II. TNF-α is the primary substrate of ADAM17. ADAM17 cleaves TNF-α releasing soluble TNF-α extracellularly where it has autocrine and paracrine functionalities. Activation of TNF-α receptor by TNF-α also enhances ADAM17 activity.

ACE2 = Angiotensin-converting enzyme 2; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; Ang II = Angiotensin II; ROS = Reactive oxygen species; AT1R = Angiotensin 1 receptor; ADAM17 = A disintegrin and metalloproteinase domain 17; TNF-α = Tumor necrosis factor alpha; TMPRSS2 = transmembrane protease serine 2.

counterregulatory ACE2/Ang-(1−7)/Mas1R axis negatively modulates leukocyte migration, cytokine expression and release, and fibrogenesis pathways. Hence, ACE2 deficiency increases vascular inflammation by increasing the gene expression of vascular adhesion molecules, cytokines, chemokines, and matrix metalloproteases [71]. The loss of ACE2 results in higher increases in Ang II-induced expression of inflammatory factors, enhanced vascular permeability, increased lung edema, and neutrophil accumulation [72]. The ACE2/Ang-(1−7)/Mas1R axis also plays an essential role in haemostasis, since it stimulates prostacyclin (PGI2) production and nitric oxide (NO) release by ECs and modulates platelet activity which is less adherent having, thus anti-thrombotic activity [73] (Fig. 1).

RAS exhibits high activity in lung tissue, which is the leading site of Ang II synthesis. ACE2 is a zinc metallopeptidase, type I integral membrane glycoprotein orientated with the N-terminal, and the catalytic site facing the extracellular space [74]. The union of ACE2 with SARS viral spike protein triggers enzyme internalization downregulating activity from the cell surface. Once SARS-CoV binds to its receptor, the abundance on the cell surface, mRNA expression, and the enzymatic activity of ACE2 are significantly reduced [75]. Proteolytic shedding of its extracellular domain is a second mechanism for downregulating ACE2 at the cell surface. S protein of SARS, once it binds to ACE2, induces shedding by activating ADAM17 (TACE) as do bacterial endotoxin and lipopolysaccharide (LPS) [76] (Fig. 3). Releasing ACE2 from the cell membrane is a critical step in catalyzing substrates and implies that attenuation of ACE2 activity might contribute to disease pathogenesis. The recently described induction of ACE2 expression by type I IFN in human nasal epithelial cells, thus behaving as an ISG, highlight an additional mechanism of ACE2 downregulation by SARS-CoV-2 [30]. Since IFN-induced ISGs are crucial for host antiviral response, the absence of ACE2 induction due to hampered IFN responses will further cause tissue unprotection. Therefore, in COVID-19, ACE2 plays a pivotal role because of its multifaceted task as a facilitator of entry into AECs and its potential role in the pathogenesis of acute lung injury (ALI) [75]. In the mouse model of SARS, downregulation of ACE2 protein expression resulted in worse pneumonia, increased Ang II levels, increased vascular permeability, enhanced lung edema, neutrophil infiltration, and further worsened lung function [72,77]. Catalytically active ACE2 protein alleviated the symptoms, and active protein improved the outcome of respiratory failure [72]. In COVID-19 patients, plasma concentrations of Ang II were significantly higher than in healthy individuals and Ang II levels correlated with viral load and lung injury [78].

Owing to the widespread expression of ACE2, COVID-19 is a disseminated infection. ACE2 is highly expressed in the gut and SARS-CoV-2 can productively infect enterocytes [28,79]. Despite ACE2

expression in gut being higher than in the lung, only about 10−12% of patients with COVID-19 experience gastrointestinal symptoms [79]. The contribution of the digestive system to the pathogenesis of COVID-19 through impairment of mucous membrane barrier and increased inflammatory cytokine production has not been determined yet. Similar to MERS-CoV and owing to ACE2 expression in the brush borders of the proximal tubules and in podocytes, kidney injury in COVID-19 is characterized by diffuse proximal tubule damage with virus-like particles in tubular epithelial cells and podocytes which is indicative of direct SARS-CoV-2 infection [80]. These findings translate clinically into acute kidney injury and proteinuria which affect from 0.9% to 29% of COVID-19 patients [80].

The consequence of impaired ACE2 activity in the lung because of SARS-CoV-2 infection is a reduction of Ang-(1−7) production. Ang-(1−7) binding Mas1R promotes an array of biological responses to counteract Ang II-mediated processes such as apoptosis, angiogenesis, vasoconstriction, and inflammation in the lung [81,82]. Consequently, the attenuation of ACE2 catalytic function perturbs the pulmonary RAS balance, resulting in enhanced inflammation and vascular permeability, leaving the lung defenceless in the face of the forthcoming raging cytokine storm. Besides, infection of type II pneumocytes will reduce the production of alveolar surfactant subsequently reducing pulmonary elasticity. Moreover, the loss of type II pneumocytes decreases restoration of type I pneumocytes which ultimately impacts on gas exchange and fibrosis [83]. The above event sequence depicts the RAS vicious feedback loop (Fig. 1).

5. The fourth horseman: an epidemic within the pandemic

The association between COVID-19 and coagulation disorders was beheld early during the pandemic when Chinese physicians noticed that patients treated mainly with low-molecular-weight heparin had a decreased 28-day mortality [84]. This mortality improvement was in patients with a sepsis score higher than four or a markedly elevated D-dimer[84]. COVID-19 is associated with coagulation disorders that include increases in procoagulant factors such as fibrinogen and D-Dimers, both associated with poor prognosis [85,86]. Patients admitted to the ICU had an increased incidence of venous thromboembolic events ranging from 25% to 36% [87-89]. Moreover, standard prophylaxis for venous thromboembolism failed in 7.7% of the patients [90]. Some found that most thrombotic complications were venous and primarily isolated pulmonary embolism, which suggests that it may be primary pulmonary thrombosis instead of embolic phenomena [89,91]. In line with that, microcirculatory thrombosis is a constant finding in lung pathologic studies [33,34] (Fig. 2).

Infection of ECs, together with the derangements caused by cellular infiltration and high exposure to cytokines/chemokines, eventually leads to ECs dysfunction and apoptosis [33]. All of them contribute to microvascular prothrombotic effects [92]. There is an intense interplay between haemostasis and innate immunity, called thrombo-inflammation [93]. Both the intrinsic and extrinsic coagulation pathways can activate during inflammation. ECs and macrophages activate the extrinsic pathway through expression of tissue factor [94]. The intrinsic pathway can be activated by neutrophil extracellular traps (NETs) released by polymorphonuclear neutrophils (PMN) in a process called NETosis. NETs activate ECs, platelets, and the complement system and release proteases that inactivate endogenous anticoagulants [95]. However, the role of NETs in COVID-19 is still a matter of discussion [96].

Platelets play a dual role. First, a proinflammatory role by secreting alpha granules that recruit PMN and macrophages, which are an essential source of IL-1β [97]. Besides, platelets stimulate PMN to undergo NETosis which in turn activates platelets, creating a feedback loop. The second role of platelets is to activate the coagulation pathway by assembling enzyme-cofactor-substrate complexes on their exposed surface [98] (Fig. 1).

Complement activation, which has been seen in the mouse model of SARS, contributes to immune-mediated pathology [99]. Activation of C3 and C5 promotes mast cell degranulation and recruitment of PMN and macrophages [100]. The prothrombotic effects of activated C3 and C5 include platelet and ECs activation, together with increasing tissue factor and von Willebrand factor expression [95]. To close the loop, thrombin, and other components of the coagulation cascade can, in turn, activate C3 and C5 [95].

The primary function of thrombin is to promote clot formation by activating platelets and by converting fibrinogen into fibrin [101]. However, thrombin is a pleiotropic molecule and can increase inflammation via a proteinase-activated receptor (PAR), principally PAR-1 [101] (Fig. 1). The generation of thrombin is controlled by negative feedback loops and physiological anticoagulants such as antithrombin III, tissue factor pathway inhibitor and the protein C system [101]. IL-1β, IL-6, and TNF-α promote the release of ultra-large von Willebrand multimers, and the production of tissue factor and factor VII/activated factor VII, leading to increased thrombin generation while decreasing the levels of endogenous anticoagulants [101].

The ACE2/Ang-(1−7)/Mas1R axis exerts antithrombotic effects through activation of Mas1R in platelets, which then release NO and PGI2 and by protecting from endothelial dysfunction [102,103]. Since this branch of the RAS is not working properly in COVID-19, this protective mechanism is lost (Figs. 1 and 3).

In severe COVID-19, similar to other acute viral infections, a high prevalence od antiphospholipid antibodies was found, although the role of these antibodies in the prothrombotic state of SAR-CoV-2-infected patients is still a matter of debate [104].

The progression of thrombo-inflammation may result in widespread thrombosis, which may be further enhanced by hypoxemia, hyperthermia, and hypovolemia [105]. Hypoxemia triggers increased expression of hypoxia-inducible factors, which may promote additional inflammation and may activate platelets and coagulation factors. They increase tissue factor expression, increase plasminogen activating inhibitor-1, and inhibit the endogenous anticoagulant protein S [106]. In the setting of a hyperinflammatory state and endothelial injury, activation of coagulation occurs whereas the counter-regulatory force ACE2/Ang-(1−7)/Mas1R axis is inactive, leaving the field to the full expression of a hypercoagulable state. This state may clinically translate into pulmonary thrombosis, venous thromboembolism, or other thrombotic events. If these events affect microvascular lung bed, they may further promote ALI and impair gas exchange. Whatever the location of the thrombotic event is, it worsens the patient's prognosis.

Hyperinflammatory state and defective ACE2/Ang-(1−7)/Mas1R functioning activate the fourth hurtful feedback loop. Hyperinflammation induces hypercoagulation and vice versa, while ACE2/Ang-(1−7)/Mas1R axis avoidance maximizes both (Fig. 1).

6. A broad scale of damage

The clinical spectrum of COVID-19 is broad. Not everyone who acquires SARS- CoV-2 becomes sick and the state that emerges after infection can vary among patients or within the same patient over time. Consequently, it is envisaged that virus-dependent, host-dependent, and environment-dependent factors may modify the virus-host interaction explaining not only the individual susceptibility to infection but also the broad scale of damage seen in clinical disease.

The initial viral titre in the airways could explain the different evolving patterns of COVID-19, since this will condition the intensity of cytopathic changes, which in turn will shape the strength of immune responses [35]. SARS-CoV-2 replicates in high numbers very early after infection, and in turn, the magnitude of viral replication will impact on the extent of antiviral response [27]. In humans, there

is a strong correlation between SARS-CoV and MERS-CoV titres and disease severity [35].

In animal models, the disease behaves differently if the virus infects airway epithelial cells or both airway and AECs (type I and type II pneumocytes) predominantly. The viral antigen is mainly located in airway epithelial cells in mouse models permissible to infection, but which do not develop clinical disease. In contrast, in highly susceptible mice, the antigen is detected in both airways and alveolar type I and II pneumocytes [35]. Consequently, infection of AECs seems critical for both host susceptibility and the development of lung pathology. An aspect that influences SARS-CoV-2 infection is the state of differentiation of human airway epithelia, which, in turn, correlates positively with the expression level of ACE2 in these cells [107,108]. It is noteworthy that ACE2 nasal gene expression is lower in children [109]. This fact is connected to the striking age distribution of COVID-19 in which children are often spared, affecting adults with enhanced severity and mortality as age increases [5,47]. However, the increasingly poor outcome with advancing age is influenced by the presence of common comorbidities, such as hypertension, cardiovascular disease, and diabetes, which bear a poor prognosis by themselves [47]. Besides, these comorbidities relate to a decreased activity of ACE2 in elderly patients, a deficit further exacerbated by SARS-CoV-2 infection [110]. ADE is a potentially harmful, pro-inflammatory mechanism which occurs when suboptimal titres of neutralizing antibodies against SARS-CoV-2 are present. They are unable to control infection but instead facilitate viral entry into macrophages by a Trojan horse mechanism. ADE tends to happen when the time interval between coronavirus infections is long enough for antibody fall, which could be a possible mechanism for severe COVID-19 in the aged [58].

Females with COVID-19 usually present with milder disease than males. Females exhibit higher IFN and IFN regulator factor and IL-10 production from PBMC, lower production of TNF-α, lower expression of TLR4 in PMN, lower numbers of NK cells, and lower PMN phagocytic activity than males [111]. Oestrogens downregulate Ang II and upregulate Ang-(1−7) pathways, which makes apparent gender differences in expression, activity, and tissue responsiveness of RAS components [112]. Besides, Mas1R expression was increased in female rats but not in males after the infusion of Ang II [113]. In animal models of obesity, females appear to maintain circulating Ang-(1−7) levels and are protected from hypertension and metabolic complications induced by angiotensinogen, renin, angiotensin II, and AT1R activation [114]. Stimulation of counterregulatory AT2R appears metabolically protective in female rodents, whilst there are inconsistent effects in males [115].

In the UK, 72% of COVID-19 patients in the ICU were either overweight or obese [116], and 99% of dead North Italians had obesity, hypertension, diabetes, heart disease, kidney damage, or cancer [117]. The frequent occurrence of obesity as a factor of adverse outcome is frequently shadowed by other high prevalent comorbidities in obese people making the identification of the independent role of obesity steep [118]. The association of COVID-19 with obesity has been attributed to the chronic inflammatory status, the ineffective immune response or to interaction with the RAS system.

The immune pathways are all susceptible to genetic polymorphisms with functional consequences such as variability in cytokine expression, antigen-binding affinities, receptor ligation strength, and downstream signaling [119,120]. High interconnection is a prominent feature of immune pathways and thus functional resultant polymorphisms may hamper the growth of an optimal immune response to COVID-19. Responses triggered by PAMPs recognition and its downstream molecules such as myeloid differentiation primary response 88 (MDY88) may be altered by TLR polymorphisms [121,122]. HLA genes present extreme allelic polymorphism. Since they present viral peptides to host HLA molecules to trigger an adaptative immune response, their polymorphisms may cause unevenness in antigen binding and presentation, and consequently in immune response. HLA-B*46:01 has been associated to the development and increased severity of SARS-CoV [123], and it has the fewest predicted binding affinity of SARS-Cov-2 peptides [124]. IL-6 plays a central role in the hyperactive immune response in COVID-19 patients. Since there are functional polymorphisms in the IL-6 gene that modify its protein level expression, they may affect the severity of the disease [125]. The role of RAS in the pathogenesis of COVID-19 is essential. Single nucleotide polymorphisms and haplotypes in ACE genes, such as polymorphism A/D in the ACE1 gene, have been associated with circulating and tissue concentrations of ACE levels and reduced expression of ACE2 [126,127]. Interestingly, the prevalence of COVID-19 in Europe correlates inversely with ACE D allele frequency [127]. A genetic variant of the IFN-induced transmembrane protein-3 gene is associated with COVID-19 severity. IFN-induced transmembrane protein-3 is an immune effector protein that acts restricting membrane fusion [128]. Recently, a genomewide association study in COVID-19 patients with respiratory failure identified an association signal at locus 3p21.31, which includes the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1, while there was no association signals at the HLA complex [129].

Lately, there has been a contention about the beneficial or detrimental role of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) in the outcome of patients with COVID-19. Currently, there is no evidence to support an advantageous or harmful effect of concomitant therapy with ACEi or ARB in COVID-19 patients [130].

7. Pathogenetically-based therapeutic insights

COVID-19 is a systemic infection since it may impact any tissue or organ expressing ACE2. However, the most dreadful, often life-threatening conditions, are ALI and ARDS. Therefore, the main challenge is to avoid their development to prevent ICU admission and mechanical ventilatory support. We could envisage COVID-19 as a tree in which AECs viral infection and ACE2 downregulation represent the roots. The tree trunk would be the hyperinflammatory and hypercoagulable state. The branches would be an end-organ disease, such as ALI, myocarditis, neurological disease, liver injury, gastrointestinal involvement, and skin disease.

Since the chain of events triggered by SARS-CoV-2 infection evolves quickly, any planned intervention must come as early as possible. Besides, since the pathogenesis of COVID-19 involves non-viral mechanisms, any intervention planned must also address the correction or modulation of these disbalances. Hence, any therapeutic intervention must be early and combine antiviral and adjuvant therapies. However, the moment of diagnosis and eventual hospital admission will mark the timeframe of interventions.

To tackle the roots of the disease, potential therapeutic interventions for COVID-19 should first address the viral entry into AECs. The entry of SARS-CoV-2 into AECs takes place after binding of the spike to the receptor ACE2. Specifically, the binding takes place in the receptor-binding domain of the S protein. Thus, developing neutralizing monoclonal antibodies for this domain is a rational strategy to prevent the viral union and subsequent events [131]. Another possible way of targeting the interaction between ACE2 and S protein may be the use of soluble recombinant ACE2, which may prevent the binding of the viral particle to the surface-bound, full-length ACE2 [132]. In the Vero-E6 monkey cell line, a soluble form of ACE2 blocks SARS-CoV replication and reduced SARS-CoV-2 recovery by a factor of 1000−5000 [132,133]. Besides, since SARS-CoV-2 downregulates the ACE2/Ang-(1−7)/Mas1R axis, recombinant human ACE2 (rhACE2) could prevent the development of ALI in COVID-19. rhACE2 attenuated arterial hypoxemia in a piglet model of LPS-induced ALI [134]. In phase II, open-label trial in humans with ARDS rhACE2 was well tolerated, Ang II levels decreased, whereas Ang-(1−7) and surfactant

protein D increased [135]. However, the study was not powered to detect changes in acute physiological or clinical outcomes [135]. There is a randomized controlled trial to assess rhACE2 in patients with severe COVID-19 (NCT 04287686). Apart from ACE2, SARS-CoV-2 entry involves TMPRSS2, whose inhibitor, camostat mesylate, significantly reduced lung cell line infection with SARS-CoV-2 [136].

Endocytosis is a crucial step in SARS-CoV-2 infection. AP-2-associated protein kinase (AAK1) regulates this process [137]. Baricitinib, a Janus-kinase inhibitor, has been claimed as a candidate drug for COVID-19 since it inhibits AAK1 [138]. Arbidol inhibits viral entry by inhibiting the fusion between viral and cellular membranes [139]. However, in a small retrospective study, arbidol did not meet non-inferiority versus the combination of arbidol and lopinavir/ritonavir (LPV/r) [140]. Chloroquine and its safer derivative hydroxychloroquine are effective against SARS-CoV-2 *in vitro* [141]. However, recent news from the large Recovery trial showed that there is no beneficial effect of hydroxychloroquine in patients hospitalised with COVID-19; therefore, that arm of the study was stopped [142]. Other planned large trials, such as Solidarity, stopped enrolling patients to the hydroxychloroquine arm, and the National Institutes of Health-sponsored ORCHID study was also stopped [143,144].

Numerous antivirals agents are being tested in clinical trials. LPV/r could not demonstrate enough efficacy when compared with placebo [145]. The combination of IFN, LPV/r, and ribavirin showed a shorter time to negativize nasopharyngeal swabs and superiority versus LPV/r in alleviating symptoms [146]. In two double-blind, placebo-controlled trials, remdesivir was not associated with statistically significant clinical benefits in one, whereas in the other shortened the time to recovery in hospitalized adults [147,148]. As of now, there is no antiviral drug with proven efficacy for treating patients with COVID-19.

Another strategy tries to modulate the exuberant inflammatory response in COVID-19. The use of corticosteroids is controversial and not supported by previous experience in SARS and MERS [149]. However, in the Recovery trial, dexamethasone reduced deaths by one third in patients receiving invasive mechanical ventilation and by one fifth in patients receiving oxygen without invasive mechanical ventilation [150]. Tocilizumab, a specific IL-6 receptor antagonist, is promoted to treat the hyperinflammatory state of COVID-19 because of the pathogenic role IL-6 plays. Two observational studies have shown a clinical benefit of therapy with tocilizumab in COVID-19 pneumonia with hyperinflammatory syndrome [151,152]. Anakinra, a recombinant IL-1 receptor antagonist, has proven useful in a small retrospective study of COVID-19 patients with ARDS and hyper inflammation [153]. There are additional trials in progress with tocilizumab, anakinra, and sarilumab. However, when trying to modify the cytokine response by targeting a single molecule or receptor, it should be recalled that the cytokine network is an intricate complex with a high degree of overlap, redundancy, and alternate pathways. This may explain therapy escape and eventually lack of response.

Therapeutic interventions for the consequences of hyperinflammatory and hypercoagulable states associated with COVID-19, such as ALI, ARDS or thromboembolic events, are beyond this review's scope.

8. Conclusions

Knowledge of pathophysiology is the first step to address the management of a disease appropriately. It is familiar with the mechanism that the virus uses to evade host immune defense mechanisms or those that uses to harm will permit the design of appropriate strategies to neutralize the dysfunctions or disbalances generated either by the virus or by the consequences of the infection. From the knowledge gathered, it seems that most organ damage in severe COVID-19 is done through an immune-mediated mechanism, although SARS-CoV-2 is the necessary initiator. The spectrum of disease is comprehensive, and since not all the patients will share the same evolving pattern, the search for predictive factors to promptly identify patients more prone to evolve to life-threatening disease is of the utmost importance. In severe cases, the quick evolving pattern of the disease makes early treatment imperative, at least until reliable predictive factors become widely available. The implication of viral and host-dependent mechanisms in COVID-19 pathogenesis suggests that any therapeutic strategy must combine antiviral drugs and adjuvant therapy to modulate the host's responses.

All these goals will be achieved through the broad effort of basic, translational, and clinical scientists and clinicians, and will demand a high degree of commitment from patients and their families, allied professionals, and everyone engaged in the fight against COVID-19. Among them, politicians and Health Administration Officers will play a unique role, since such a gigantic task will need the allocation of a vast amount of resources to overcome a health challenge to Mankind like none other in recent times.

9. Outstanding questions

While engrossed amid the pandemic, there was progress on the physiopathology of COVID-19. However, gaps regarding viral, environmental, and transmissibility aspects remain—the dynamic interplay between the host and the virus and how to modify it to improve disease prognosis not being the lesser.

There is a big difference in transmissibility, which is highest for SARS-CoV-2, among β-coronaviruses despite similar structure and functioning. Asymptomatic viral shedding is the main factor. However, the role of newly described ORFs and RNA modifications and their functional correlations are not evident yet. Although TMPRSS2 is involved in viral entry into the host cell, the involvement of other host proteins is still under discussion.

The role of the different epithelial cells along the bronchial tree and the alveolar space needs to be ascertained. The virus's mechanisms to invade other organs beyond the lung are already poorly known.

Clinical disease progression is somewhat unpredictable. Therefore, the identification of prognostic clinical and biological markers would optimize patients' care and resource consumption, which may be of utmost importance in pandemic times. This effort must include which role comorbidities and gender play. The definition and timing of the optimal therapeutic approach to COVID-19 will represent a colossal effort, which can be accomplished only by randomized clinical trial performance. These should include concerted actions and a combination of diverse disciplines, resources, expertise, and techniques to contribute to advances in prevention, diagnosis, and therapy. This set makes up an almost flawless meaning of translational medicine defined by the European Society for Translational Medicine (EUSTM) as "an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside, and community."

10. Search strategy and selection criteria

For this Review, our search strategy involved the review of original records, either journals or books, mainly from European and American sources, from1984 to 2020. From these sources, we hand searched reference lists of identified additional articles to retrieve additional studies. Preference was given to most relevant research, but we were also keen to highlight the breadth of the topic and hence selected some publications that showcase particular areas of interest.

We have searched PubMed and Google Scholar from database inception to May 21, 2020, for records, journals, and books for the terms “SARS-CoV-2″, “COVID-19″, “Coronavirus”, “RAAS system”, “angiotensin-converting enzyme”, “angiotensin-converting enzyme 2″, “cytokine storm”, “cytokine”, “chemokine”, “acute lung injury”, “adult respiratory distress syndrome”, “interferon”, “interleukin ”,

"Middle East respiratory syndrome", and "Severe acute respiratory syndrome". References were examined in English.

Declaration of Competing Interest

We declare no competing interests.

Contributors

The concept of the manuscript was devised by PD who also performed the overall literature searches. IM, VP, HC, and JC designed the search strategy with inputs from PD and NdB. IM, VP, HC, and JC carried out the literature searches and screening, and any discrepancies were discussed with PD and NdB. PD wrote the first draft of the review with inputs from all the authors.

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