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Life Sciences 258 (2020) 118166

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

The pathophysiology of SARS-CoV-2: A suggested model and therapeutic approach

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Respiratory infection
Treatment

ABSTRACT

In this paper, a model is proposed of the pathophysiological processes of COVID-19 starting from the infection of human type II alveolar epithelial cells (pneumocytes) by SARS-CoV-2 and culminating in the development of ARDS. The innate immune response to infection of type II alveolar epithelial cells leads both to their death by apoptosis and pyroptosis and to alveolar macrophage activation. Activated macrophages secrete proinflammatory cytokines and chemokines and tend to polarise into the inflammatory M1 phenotype. These changes are associated with activation of vascular endothelial cells and thence the recruitment of highly toxic neutrophils and inflammatory activated platelets into the alveolar space. Activated vascular endothelial cells become a source of proinflammatory cytokines and reactive oxygen species (ROS) and contribute to the development of coagulopathy, systemic sepsis, a cytokine storm and ARDS. Pulmonary activated platelets are also an important source of proinflammatory cytokines and ROS, as well as exacerbating pulmonary neutrophil-mediated inflammatory responses and contributing to systemic sepsis by binding to neutrophils to form platelet-neutrophil complexes (PNCs). PNC formation increases neutrophil recruitment, activation priming and extraversion of these immune cells into inflamed pulmonary tissue, thereby contributing to ARDS. Sequestered PNCs cause the development of a procoagulant and proinflammatory environment. The contribution to ARDS of increased ex-

Abbreviations: ACE, angiotensin converting enzyme; AM, alveolar macrophages; AP, activated platelets; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluids; CFR, case fatality rates; CXCL10, C-X-C motif chemokine 10; DAMPs, damage-associated molecular patterns; DIC, disseminated intravascular coagulation; EC, endothelial cell; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HMBG1, high mobility group box 1; HMG-1, high-mobility group protein 1; IL, interleukin; MAC-1, macrophage-1 antigen; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MDSC, CD11b + Gr-1+ myeloid-derived suppressor cells; MERS, middle east respiratory syndrome; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; NLRs, NOD-like receptors; NO, nitric oxide; PF4, platelet factor 4; PFA, polyenoic fatty acids; PGE2, Prostaglandin E2; PI3K, phosphoinositide 3-kinase; PICs, proinflammatory cytokines; PNC, platelet neutrophil complexes; PSGL-1, P-selectin glycoprotein ligand-1; RAGE, receptor for advanced glycation endproducts; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome CoronaVirus 2; T reg, regulatory T cell; TF, tissue factor; TGF, transforming growth factor; TLR, Toll-like receptor 9; TMPRSS2, transmembrane protease, serine 2; TNF, tumor necrosis factor; URT, upper respiratory tract; WHO, World Health Organisation; Zn, zinc

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https://doi.org/10.1016/j.lfs.2020.118166
Received 18 June 2020; Received in revised form 23 July 2020; Accepted 25 July 2020
Available online 31 July 2020
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tracellular histone levels, circulating mitochondrial DNA, the chromatin protein HMGB1, decreased neutrophil apoptosis, impaired macrophage efferocytosis, the cytokine storm, the toll-like receptor radical cycle, pyroptosis, necroinflammation, lymphopenia and a high Th17 to regulatory T lymphocyte ratio are detailed.

1. Background

The Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) is a zoonotic β-coronavirus that is closely related to SARS-CoV, which also entered the human population from an animal host [1,2]. SARS-CoV-2 is the cause of COVID-19. This is an illness that appears to lead to mild symptoms in the majority of people and indeed, many infected individuals remain asymptomatic throughout the course of the infection [3]. However, the illness often develops to severe pneumonia and acute respiratory distress syndrome (ARDS), leading to considerable morbidity and mortality. Case fatality rates (CFR) may be as high as 6.6% [4–6]. While the CFR attributed to SARS-CoV induced SARS was considerably higher and according to the World Health Organisation (WHO) may have exceeded 15% [7]. However, the absolute number of people killed by/with SARS-CoV-2, to date, is greater than both SARS and middle east respiratory syndrome (MERS) combined [8]. This is largely owing to a much higher rate of transmission, different tissue tropism and due to significant changes in its genome and protein structure compared to the other viruses (reviewed by [9]).

SARS-CoV-2 enters permissive cells as a result of S spike protein high affinity engagement with angiotensin converting enzyme (ACE)-2 receptors and subsequent cleavage by the adjacent protease TMPRSS2 in a similar manner to SARS-CoV [10,11]. However, SARS-CoV-2 initially enters and replicates in epithelial cells of the upper respiratory

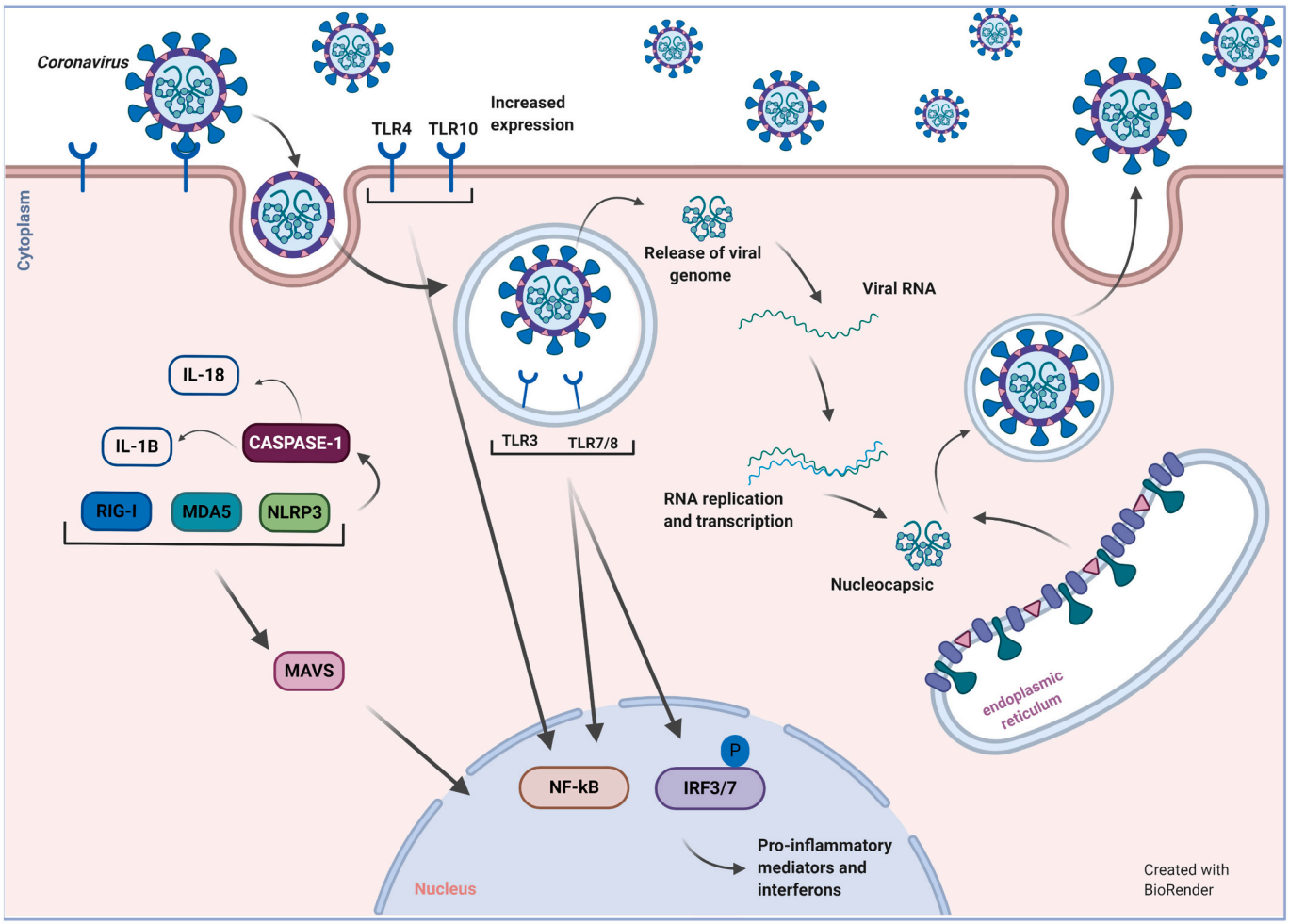

Fig. 1. Pattern Recognition receptors involved in detecting RNA viruses. Adapted from "Coronavirus Replication Cycle", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates.
The presence of invading RNA viruses is detected by a family of Toll like receptors (TLRs) RIG like receptors and NOD-like receptors. From the perspective of coronavirus recognition, the important TLRs are TLR-7 and 3 which recognise single stranded RNA and the dimers of positive and negative sense RNA formed during coronavirus replication. TLR 3 and 7 are located in late endosomes which maximises viral interaction while denying the pathogen's access to the cytoplasm and nucleus. Activation of these pattern recognition receptors results in the transcription of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and INF5 leading to the production of PICs inducible nitric oxide prostaglandins and a large number of chemokines. The presence of coronavirus RNA is also recognised by the retinoic acid-inducible gene I (RIG-)-like receptors RIG-1 and MDA5 which are located in the cytoplasm. The activation of either PPR results in the assembly of a protein complex known as MAVS which acts as a signal relay to trigger the activation of INF-3 and INF-7 leading to the production of type 1 II and III interferons. There is also evidence to suggest that coronavirus activate nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) leading to the assembly of the NLRP3 inflammasome and the resultant production of interleukin (IL)-18 and IL-1. There is evidence that SARSCoV-2 inhibits interferon via the production of the non-structural proteins ORF3a and nsp-3 leading to a muted immune response and enhanced viral replication.

tract [12,13]. This phenomenon is not observed in SARS-CoV to any significant extent [14,15]. This process likely explains the relatively high viral load in the upper respiratory tract [16], increased levels of viral shedding [13] and significantly higher transmissibility [17].

This difference in tropism may be explained in part by an increased affinity towards ACE-2 receptors, which appears to be between 10 and twenty times higher than that displayed by SARS-CoV [18,19]. This allows SARS-CoV-2 to readily replicate in the upper respiratory tract despite a relative paucity of ACE-2 bearing cells in that region [20,21].

In addition, the SARS-CoV-2 spike protein contains a Furin cleavage site in the spike protein that does not exist in SARS-CoV [22–24], allowing cleavage by cellular polyprotein convertases, such as furin and capthesin and potentially enhancing the efficiency of entry by endocytosis [12,25]. In this context, it is noteworthy that the Furin cleavage site is also seen in spike proteins of pandemic strains of influenza, including the strain responsible for the so called "Spanish flu" of the early 20th century [22,26]. The benefit to those viruses in possession of the cleavage site is increased tropism, it is conceivable that SARS-CoV-2 might be able to infect and replicate in otherwise non-permissive cells in the upper respiratory tract. There is also some evidence to suggest that cathepsin may be an alternative spike cleavage protease in cells expressing ACE-2 receptors but lacking Transmembrane protease, serine 2 (TMPRSS2) which normally plays an indispensable role in the cleavage of the spike protein thereby enabling the fusion of the viral and host membrane [25].

While changes in tissue tropism and increased cell internalisation play a role in the high transmissibility of the virus, another factor is the initially muted immune response following infection [27]. Mechanistically, this is due to significant changes in the structure of the orf3a protein in SARS-CoV-2 compared to SARS-CoV, which allows a greater capacity to inhibit the production of interferons I, II and III [28–30]. A schematic of the proposed pathways involved is presented in Fig. 1. The inhibition of the interferon response in infected cells in the upper respiratory tract allows for relatively unhindered replication of the virus, which in combination, makes an additional contribution to a high viral load in the upper respiratory tract (URT). Importantly, these factors also explain the high levels of the virus in the URT and goes some way to explaining the high transmission rates by pre and asymptomatic people which according to some studies may account for as many as half of all transmissions [31]. This may further explain why the spread of this virus has been so difficult to control [3,13,16,32].

Evidence accrued from the initial epidemic of COVID-19 in the Wuhan province of China suggests that approximately 20% of patients infected with COVID-19 develop severe disease that require hospitalisation. In addition, 20% of admitted patients develop pneumonia and ARDS thereafter, requiring protracted ventilation [33,34]. In almost 50% of cases death occurred from respiratory failure [33,34].

COVID-19 ARDS is typified by the presence of diffuse alveolar damage, fibrin-rich hyaline membranes, increased epithelial and endothelial cell permeability, fluid leakage into the pulmonary interstitium, gross disruption of gas exchange, hypoxia and respiratory failure [33,35–37] reviewed in [38]. These features are characteristic of ARDS secondary to sepsis, viral infections or many other triggers and in this respect, COVID-19 ARDS is unremarkable [39].

However, in another respect COVID-19 ARDS appears to be distinct from the ARDS associated with other respiratory viruses (e.g. H1N1 influenza Virus) due to evidence of hypercoagulation and an exhausted fibrinolytic system [38,40–42]. The importance of hypercoagulation in the pathogenesis of severe COVID-19 is further emphasised by an analysis which revealed that 70% of fatal cases satisfied a diagnosis for disseminated intravascular coagulation (DIC), while that was true in only 1% of survivors [43].

Several research teams have reported the presence of gross immune dysregulation in the lungs of patients with severe disease. For example, there is extensive evidence of activated alveolar macrophages [5,14,35,44] and a depletion in the absolute numbers of these immune cells due to excessive levels of pyroptosis [44–46]. Excessive infiltration of activated neutrophils into alveoli and lung interstitial tissue is another common finding in severe COVID-19 [36,47] review [48]. Importantly, evidence suggests that these neutrophils are a source of highly toxic neutrophil extracellular traps (NETs) [36,49]. Influx of IL-1 and tumor necrosis factor (TNF) secreting bone marrow derived monocytes is also a finding in such individuals [50]. Interestingly, these monocytes also secrete lactate dehydrogenase indicating that these immune cells are also undergoing cell death via pyroptosis [50]. The presence of excessive levels of inflammation in patients with COVID-19 ARDS is further reinforced by evidence of hypercytokinemia [44,51,52].

There is also an accumulating body of evidence suggesting excessive systemic immune activation and inflammation in patients suffering from COVID-19, with increased levels of TNF-alpha, IL-1 beta, IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1) and C-X-C motif chemokine 10 (CXCL10), being commonly reported in patients with severe symptoms and pneumonia [44,48,53–56]. Furthermore, the extent of immune activation and inflammation increases with severity of disease and is some cases ten-fold higher in critically ill patients compared to those with mild disease [57].

The importance of peripheral immune activation in the pathogenesis of severe COVID-19 is further emphasised by replicated data demonstrating that the plasma neutrophil: lymphocyte ratio is predictive of both disease severity [58] and mortality [59]. This concept is further supported by data suggesting that levels of IL-6 in the bloodstream correlate with symptom severity and morbidity, as well as being predictive of mortality [51,57,60,61].

In addition, lymphopenia is common in an environment of severe inflammation [62,63]. It is commonly observed in patients suffering severe disease [48,54,64–66]. The weight of evidence suggests that drastically reduced numbers of $CD4^+$ T cells, $CD8^+$ T cells, B cells and natural killer (NK) cells are characteristic of COVID-19 [48,54,64–66]. In addition, the degree of lymphopenia correlates with symptom severity [4,67] and inversely with inflammatory markers such as TNF-alpha and IL-6,[50]. Furthermore, remaining CD4 and CD8 T lymphocytes display signs of exhaustion and dysfunction as evidenced by increased expression of PD-1, Tim-3 and NKG2A receptors [64,68–70]. It should be noted that the extent of T cell exhaustion is predictive of greater disease severity [69].

Several research teams have also reported the presence of TH17 polarised CD4 T cells in the lungs and periphery of COVID-19 patients with severe ARDS [66,71,72]. Moreover, these T cells secrete relatively large amounts of the highly cytotoxic cytokine IL-17 [66,71,72].

The patterns and extent of immune disturbance seen in the lungs and periphery of patients suffering from severe COVID-19 are characteristic of a cytokine storm and are commonly observed in cytokine release syndromes [48,51,53,73–75]. In addition, many patients with severe disease qualify for a diagnosis of "Sepsis" under the Sepsis 3 guidelines and many authors have proposed that severe COVID-19 is a virally induced sepsis [76,77].

Thus far there are no published models of the pathophysiology of the condition from the point of viral entry and how the disease might progress. This paper aims to propose such a model We will initially focus on the engagement of the virus with type 2 alveolar cells and subsequent activation of alveolar macrophages.

2. Activation of alveolar epithelial cells and macrophages

There is ample evidence that SARS infects type 2 alveolar epithelial cells leading to their death by apoptosis and pyroptosis via the activation of NLP-3 through mechanisms described above [78,79] reviewed [80]. This is also clearly true of SARS-CoV-2 [14,36,37,46,47,81,82]. Furthermore, the weight of evidence suggests that SARS-CoV [83,84] and SARS-CoV-2 [5,14,35,44] result in the activation of alveolar macrophages (AM). This is unsurprising, given the close proximity of these

immune cells to type II pneumocytes and their expression of ACE-2 receptors [11,85,86].

The loss of type II alveolar cells and AM activation has considerable pathophysiological importance resulting in the loss of immune homeostasis in the lung [39,86–88]. This dyshomeostasis in turn is an essential element in the development of severe pneumonia and the acute respiratory distress syndrome, which occurs as a consequence of virally induced sepsis or indeed, several other inflammatory insults [39,86–88].

Pyroptosis and necroptosis of alveolar epithelial and endothelial cells are major elements in development and progression of ARDS in part by releasing high mobility group box 1 (HMBG1) and other inflammatory damage-associated molecular patterns (DAMPs) [89–91]. Hence, the pyroptotic death of type 2 alveolar cells following SARS-Cov2 infection may also be of pathophysiological significance in the development of COVID-19 and a major source of inflammation [85,86].

Activated macrophages (AMs) play a major role in maintaining immune homeostasis in the lung in the face of pathogen invasion and a myriad of inflammatory insults. The main mechanisms involved phagocytosis of dying cells, secretion of anti-inflammatory mediators such as transforming growth factor (TGF) beta, Prostaglandin E2 (PGE2) and polyenoic fatty acids (PFA), and inhibiting the activation of circulating T cells (reviewed in [85,86]). However, once activated, these AMs secrete a range of proinflammatory cytokines (PICs) and chemokines such as TNF-alpha IL-1 beta, IL-6, and IL-8 [92–94] [92–94]. In addition, AMs also secrete microvesicles, containing massive levels of TNF-alpha [95]. This increase in the secretion of inflammatory mediators is also accompanied by an increase in the number of AMs polarised into a highly inflammatory or M1 phenotype rather than the anti-inflammatory tolerogenic M2 phenotype prevalent in physiological conditions [96,97]. This is of considerable pathophysiological importance as a progressively increased population of M1 polarised alveolar macrophages over time results in excessive secretion of PICs and chemokines, and is highly predictive of mortality in ARDS patients, while an increased population of M2 polarised cells is predictive of survival [96,97]. Importantly, the subsequent release of these cytokines and chemokines into the pulmonary vasculature plays an important role in the development of ARDS by initiating a series of events which results in the activation of vascular endothelial cells (EC) [86,88,98]. This in turn leads to the recruitment of highly cytotoxic neutrophils and inflammatory activated platelets into the alveolar space, resulting in a host of pathogenic consequences, as discussed below [86,88,98].

3. Activation of vascular endothelial cells, platelets and neutrophils

3.1. Endothelial cell activation

Increased levels of PICs such as TNF-alpha and IL-1 induce endothelial cell activation via the upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [99,100], leading to a significant increase in the permeability of the pulmonary vascular endothelium [101]. The activation of pulmonary vascular endothelial cell (ECs) also promotes the recruitment of circulating neutrophils via the

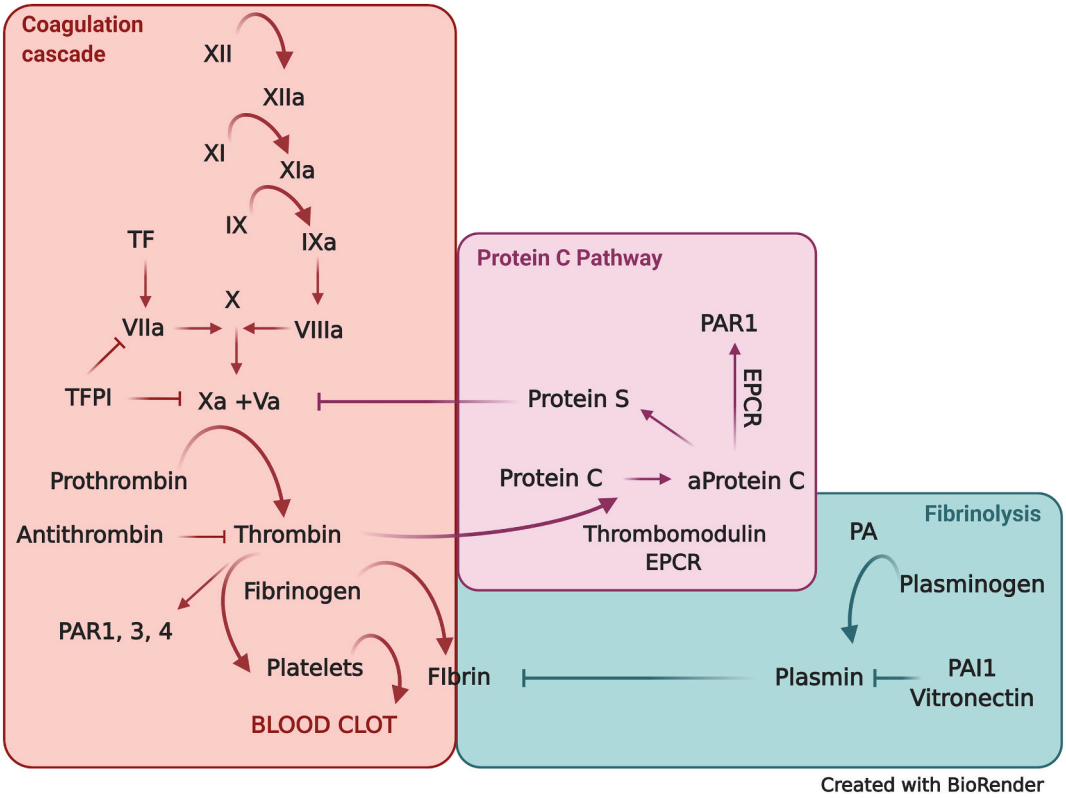

Fig. 2. The development of immunothrombosis.
Platelets activated by thrombin and or PICs initiate (PAR)–mediated signalling further increasing levels of PICs VWF and TF coupled with suppression of suppression of thrombomodulin. Platelet activation also results in increased expression of P-selectin, CD40 PF4 and a range of surface adhesion receptors ultimately recruiting neutrophils to form platelet neutrophil complexes. NET secretion by neutrophils contributes to an increased coagulation stimulate increased levels of platelet activation, aggregation and TF mediated activation of thrombin. In addition, histones play an important role in promoting thrombin generation and inhibiting protein C-mediated anticoagulant responses. PICs also play a role in the development of coagulopathy by inhibiting the protein C-protein S-thrombomodulin pathway and increasing the production of PAI-1. The combination of a hyperactivated coagulation cascade and the inhibition of anti-coagulant pathways, such as the protein C-protein S-thrombomodulin pathway and inhibition of the fibrinolytic system is characteristic of DIC. This state is also the source of micro emboli and excessive alveolar fibrin deposition in ARDS.

upregulation of surface membrane chemokines, most notably CCL5, CXCL1, MCP-1 and IL-8, the surface adherence proteins P-selectin, VCAM-1, ICAM-1 and an array of glycosaminoglycans, which play an essential role in neutrophil tethering and migration [102–104].

Once activated, vascular ECs behave in a similar manner to immune cells and become a source of PICs and reactive oxygen species (ROS) and also stimulate the activity of immune cells in the vascular environment, reviewed [105]. Activated ECs also contribute to the development of coagulopathy via several mechanisms including the recruitment of platelets, independently secreting tissue factor and VWF, decreasing the activity of thrombomodulin and protein C while stimulating the activity of PAR-1, (reviewed by [106,107]). The development of endotheliopathy is a major factor in the pathogenesis of systemic sepsis and a major player in the development and exacerbation of the underlying cytokine storm [108,109]. Crucially, the development of endotheliopathy is also a pivotal factor in the pathogenesis of ARDS [110,111] as we discuss below.

In addition, as the mechanics of the coagulation cascade play a large part in the forthcoming discussion, a diagram of the processes involved is provided in Fig. 2.

3.2. Activation of platelets

Platelets in the pulmonary vasculature are also targets for activation by the high levels of PICs and ROS secreted by alveolar macrophages and activated type II epithelial cells [112]; (reviewed by [113]). Activated platelets (AP) also become a significant source of PICs and ROS [114–116] reviewed in [117]. Importantly, APs also secrete several chemokines, most notably RANTES, and CCL4, also known as platelet factor 4 (PF4), which increase neutrophil activation, survival, recruitment to the endothelium and subsequent tethering to EC [118,119]. Finally, AP also play a crucial role in mediating and exacerbating neutrophil mediated inflammatory responses in acute lung injury and systemic sepsis by binding directly to neutrophils, resulting in the formation of platelet neutrophil complexes (PNC) [120–122].

3.3. Formation of platelet neutrophil complexes

The formation of PNCs complexes in inflammatory conditions is initiated by the binding of P-selectin expressed on the surface of APs and P-selectin glycoprotein ligand-1 (PSGL-1) expressed on neutrophils followed by the binding between platelet glycoprotein Ibα and the neutrophil beta integrin, macrophage-1 antigen (MAC-1) [121,123] (reviewed by [124]). P-selectin also plays an important role in increasing neutrophil binding to ECs, thereby increasing neutrophil rolling while increasing expression of MAC-1 in PNCs, which increases neutrophil tethering and subsequent crawling [125,126]. There are other receptors involved in the process and readers interested in a more detailed consideration of this topic are referred to excellent reviews by [127,128].

3.4. Consequences of platelet neutrophil complex formation

Evidence suggests that the formation of PNCs increases neutrophil recruitment, activation priming and the ultimate extraversion of these immune cells in an activated and primed state into inflamed lung tissue [126,129–132]. As previously discussed, this is a crucial element in the pathophysiology of ARDS [86,88,98], and understanding the mechanisms involved may identify therapeutic opportunities.

Briefly, PNCs have a reduced velocity compared to platelets and neutrophils alone and this property combined with increased endothelial adhesion increases the sequestration of neutrophils and platelets in the microvascular beds of the lung [133–135]. In addition, activated platelets and neutrophils engage in mutual amplification of PIC and ROS production, leading to an increased level of inflammation than would be achieved by either alone [126,129–132]. Sequestrated PNCs become a source of excessive PIC, ROS and chemokine production in the pulmonary vasculature in addition to the PICs, ROS and chemokines secreted by alveolar macrophages and type II epithelial cells and vascular ECs as discussed above. This facilitates neutrophil priming.

Priming may be induced by a range of cytokines, chemokines and growth factors such as TNF-alpha, IL-1 beta, IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF), or engagement with activated endothelial cells [136]. The mechanisms involved include major changes in phosphoinositide 3-kinase (PI3K) mitogen-activated protein kinases (MAPKs), phospholipase D and calcium level instigated signalling pathways [137,138]. Priming results in profound cytoskeletal reorganisation and a significant reduction in deformability and increased retention in pulmonary capillary beds [139,140]. These are resistant to apoptosis and secrete massive levels of cytotoxic products including PICs, chemokines, proteases and NETs [139,141]. The association of platelets and neutrophils has pathological consequences other than increased sequestration of neutrophils into the lung. In particular, there is ample evidence to confirm that increased sequestration of platelets and neutrophils in lung microvascular beds leads to the development of a pro-coagulant and proinflammatory environment [133–135]. The mechanisms involved are discussed below.

3.5. Platelet neutrophil complexes and the development of hypercoagulability

Platelets complexed with neutrophils enhance their phagocytic capacity and their release of ROS and other cytotoxic molecules such as myeloperoxidase (MPO) [142,143]. Platelets also stimulate neutrophil production of NETs [144,145] via a mechanism which involves inducing NETosis [125,146,147]. Mechanistically, this involves the secretion of HGMB1, which stimulates NET production via increasing receptor for advanced glycation endproducts (RAGE) mediated autophagy [147–149]. This DAMP also plays a major role in increasing NET production by increasing platelet activation via engagement with Toll-like receptor (TLR)-4, resulting in the formation of a positive feedback loop [122,150]. HMBG1 also enhances neutrophil survival, neutrophil mediated tissue damage, and contributes to the creation of a self-amplifying pattern of platelet activation and NET production [122,149,150].

In turn, NETs stimulate increased levels of platelet activation, aggregation and tissue factor (TF) mediated activation of thrombin, resulting in enhanced intravascular coagulation [124,151,152]. Several mechanisms appear to underpin the contribution of NETs to thrombus formation including TF- and FXII-mediated initiation of the coagulation cascade, increasing the recruitment and adhesion of additional platelets, inhibition of fibrinolysis and recruitment of VWF and other platelet adhesion proteins [153,154]. In addition, histones play a major role in driving thrombin generation and inhibiting protein C-mediated anticoagulant responses [155]. The importance of NETs in the development of coagulopathy is emphasised by their involvement in the pathophysiology of sepsis in numerous thrombotic diseases [156,157].

Over time, the combined effects of activated ECs, neutrophils and platelets, NETs and activated endothelial cells in the pulmonary alveocapillary vasculature lead to the development of a highly inflammatory and pro-coagulant state typified by hyperactivation of the coagulation cascade and relative exhaustion of the fibrinolytic system with excessive production of PICs, DAMPs and fibrin deposition. This is described as immuno-thrombosis [98,158,159]. This state has a major pathophysiological role in the development and exacerbation of systemic sepsis as it generates the formation of vascular microthrombi, the development of DIC and subsequent multi-organ damage or failure [109,160,161].

The sequestration of PNCs in the pulmonary vasculature and the subsequent development of immunothrombosis is also the ultimate cause of micro-thrombi and micro-emboli in the alveocapillary

circulation [162,163] and intra alveolar fibrin deposits [98,164–167]. This subsequently increases both dead-space ventilation and intra-pulmonary shunting, both characteristic features of ARDS [168] [169–171]. The development of exaggerated immunothrombosis and the failure of mechanisms required to anchor thrombi in the local environment also drive the development of DIC and readers interested in further details are referred to [172,173].

The activity of PNCs and the high levels of NET producing neutrophils resulting in immunothrombosis appears to be a plausible mechanism underpinning the development of grossly enhanced coagulation seen in COVID-19 ARDS. We now turn our attention to the development of hypercytokinemia and high rates of AM death and inflammatory lung tissue damage seen in such patients. We begin with the pathological consequences stemming from a high population of NET secreting neutrophils. These processes are depicted in Fig. 3.

4. The recruitment of activated neutrophils into alveolae and interstitial tissue

4.1. NETs and ARDS severity

As previously discussed, NETs are highly toxic to epithelial and endothelial cells and high levels in the alveolar space in patients suffering from ARDS correlate with the severity of the condition [174]. In addition, NET activity, as determined by levels of double stranded DNA, citrullinated histones, HMBG1 and MPO, is associated with almost four times the level of mortality in patients with severe pneumonia [175]. There are very high levels of NETs and neutrophils in the alveolar space of ventilated ARDS patients, with the latter secreting excessive levels of IL-6, IL-8 and CCL2, each playing a major role in increasing tissue damage either directly or via the recruitment of more neutrophils from the periphery [176]. It is, however, important to note that while the release of PICs and enzymes such as elastase and MPO from activated neutrophils makes a significant contribution to increasing inflammation and lung damage, the dominant players in this regard are the contents of NETs, most notably mtDNA, HGMB1 and histones [177,178]. Given their importance, the role of each in the pathophysiology of ARDS is briefly considered below.

4.2. Role of histones in the pathophysiology of ARDS: Increased levels of histones

Levels of extracellular histones are substantially higher in the bronchoalveolar lavage fluids (BALF) and plasma of ARDS patients,

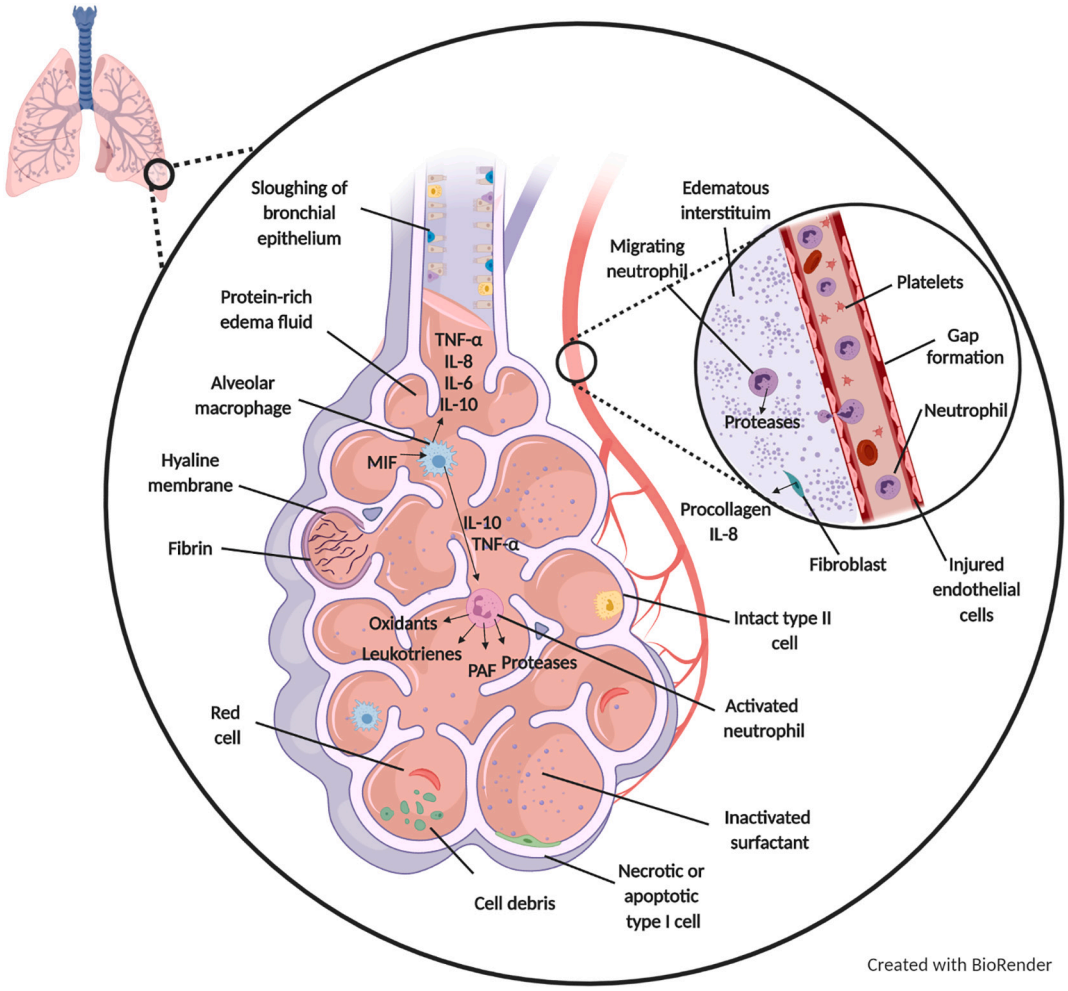

Fig. 3. The physical and immunological landscape of the lung tissue in ARDS.
Initial infection and activation of type 2 alveolar cells and alveolar macrophages results in the secretion of IL-6, PICs and a wide range of chemokines which activate vascular endothelial cells and recruit peripheral activated NET producing neutrophils. Mechanistically this is achieved via the formation of platelet neutrophil complexes which become sequestrated in the lung microcapillaries creating a hyper coagulant and highly inflammatory environment within these blood vessels and the wider pulmonary circulation. The entry of neutrophils into the lung coupled with their prolonged survival results in the development of a cytokine storm with extreme tissue damage and lung dysfunction fuelled by an interplay between PICs DAMPs ROS, NLRPs activation, macrophage pyroptosis, influx of inflammatory monocytes and necroptosis.

correlate with symptom severity and are predictive of mortality [179–181]. Histones function as a DAMP capable of activating membrane bound and cytosolic PPRs leading to the release of inflammatory mediators such as TNF-alpha, IL-1 and iNOS [182,183]. These molecules are also efficient activators of the NLP3 inflammasome and inducers of immune and epithelial cell pyroptosis [184]. This latter point is important as one mechanism underpinning the effects of histones in the development and exacerbation of ARDS involves NLRP3 activation and subsequent pyroptosis of peripheral macrophages resulting in significant increases in peripheral inflammation [179,180]. Unsurprisingly, high levels of histones in the alveoli and the interstitial tissue of the lung also increases the activation of resident immune cells, epithelial cells and endothelial cells, and induces their death by pyroptosis and necrosis. This results in further damage to the alveolar epithelium, vascular endothelium and enhances barrier dysfunction [185]. Histones released from NETs or activated but otherwise viable immune cells also contribute to the pathophysiology of ARDS other than by directly inducing severe pulmonary tissue damage and increasing levels of peripheral inflammation such as activation of the complement and coagulation cascades [185,186].

4.3. Role of mitochondrial DNA in the pathophysiology of ARDS

The presence of mtDNA in the circulation is a marker of mortality in sepsis patients in the intensive care unit [187,188]. In addition, levels of plasma mtDNA is predictive of the transition to ARDS [189] and need for ventilation in this population [190]. Mechanistically, the role of mtDNA in the pathophysiology of sepsis and ARDS also stems from its activity as a DAMP capable of activating cytosolic TLR-9 receptors, stimulating the activation of the NLRP 3 inflammasome following release from mitochondria within stressed cells or when released into the extracellular environment by apoptosis, necrosis, pyroptosis and NETosis (reviewed by [191]).

4.4. Role of HGMB1 in the pathophysiology of ARDS

HMBG-1 is another major player in the pathogenesis and pathophysiology of ARDS, and levels of this molecule in the blood are predictive of mortality in virally induced ARDS and severe pneumonia [192–195]. This heat shock protein also functions as a DAMP and plays a major role in the propagation and exacerbation of sterile inflammation and in the development of sepsis [196]. In addition, HMBG1 appears to be the dominant driver of inflammation resulting from cell necrosis and proptosis, and there is evidence to suggest that its role in the development of ARDS may be multidimensional. The association between increased HGMB1 levels and accelerated NET production by neutrophils has been discussed. This cytokine also exerts a pathological effect in the development of ARDS by aiding in delayed NET clearance, which is a distinctive element driving the development and acceleration of the condition [197,198]. Ultimately, the decreased clearance of NETs is a consequence of delayed neutrophil apoptosis [197,198] which is discussed below.

4.5. The role of decreased neutrophil apoptosis in the pathophysiology of ARDS

Several research teams have reported delayed neutrophil apoptosis and clearance of NETs in patients with sepsis related ARDS [199–202]. In addition, the percentage of the neutrophil population displaying markers of delayed apoptosis correlates with the severity of symptoms and several objective measures of tissue damage [199–202] and survival [90]. Delayed apoptosis is also accompanied by serious pathological consequences as the phenomenon may lead to neutrophil pyroptosis [203,204] or, in some instances, necroptosis [205,206] with increases in highly oxidised mtDNA, histones, HMBG1, PICs and a swathe of other inflammatory molecules [205,207,208]. Importantly, delayed neutrophil apoptosis acts as an additional source of increasing inflammation further exacerbating cell death and tissue damage [209]; review [177].

4.6. Causes of delayed neutrophil apoptosis

Spirally increasing levels of HMBG1 may contribute to decreased neutrophil clearance in ARDS patients by inhibiting neutrophil apoptosis [210–212]. In addition, increased levels of HMGB1 produced by the activity of NETs stimulates the release of NETs by other neutrophils increasing the population of neutrophils resistant to apoptosis in the lung. This results in a significant increase in inflammation and tissue damage, creating one of many feedforward loops involved in the progression of ARDS [148,150].

Another, and perhaps predominant cause of prolonged neutrophil survival and sub-optimal NET clearance in many patients suffering from ARDS would appear to be impaired alveolar macrophage phagocytic clearance of dying cells or efferocytosis [86,197,213–215]. This phenomenon has serious pathological consequences since in physiological conditions, alveolar macrophages play an indispensable role in the immunologically silent removal of neutrophils and the adoption of an anti-inflammatory profile by macrophages [216–218]. In addition, macrophage efferocytosis plays a major role in the clearance of NETs [219,220].

4.7. Causes of impaired macrophage efferocytosis

The weight of evidence suggests that high levels of HGMB1 is an important if not predominant driver of impaired alveolar macrophage efferocytosis seen in several lung disease including ARDS [210–212]. Clearly, increased NET generation is a major source of HGMB1, but it should be noted that there are also other sources of this molecule in ARDS patients which is relevant in the COVID-19 model proposed here. Such sources include alveolar macrophages, dendritic cells, alveolar epithelial cells and alveolar endothelial cells activated in response to viral activation or high levels of TNF-alpha [221–224].

High levels of TNF-alpha may also contribute to delayed neutrophil apoptosis and impaired alveolar macrophage efferocytosis in ARDS patients. Excessive levels of environmental TNF-alpha is a well-documented cause of compromised phagocytosis in these immune cells [225,226]. In addition, high levels of HMBG1 may increase the population of M1 polarised macrophages via a mechanism involving TLR-4 and RAGE activation [212,227–229]. This is of importance from the perspective of impaired efferocytosis, as macrophages polarised in such a manner display inhibited phagocytosis compared to their M2 polarised counterparts [230]. Increased polarisation of M1 polarisation is also driven by increased levels of TNF-alpha [231,232] and IL-6 [233,234].

Clearly an increasing interplay between DAMPs, cytokines and ROS secreted by epithelial cells, neutrophils and alveolar macrophages can explain high levels of inflammation and lung tissue damage seen in ARDS secondary to sepsis and COVID-19. This theme will continue to be explored in the following section which focuses on the interplay between DAMPs, TLRs, NLRs, PIC and ROS and various forms of necrotic cell death in the development of a cytokine storm. The interplay between DAMPs and pattern recognition receptors plays a pivotal role in this process.

4.8. The development of the cytokine storm and irreversible tissue damage

HMGM1, often described as the prototypical DAMP, may contribute to the development of acute or chronic lung injury by activating TLR-4, TLR-2 and RAGE receptors resulting in the activation of MAP kinases and ERK, and culminating in the nuclear translocation of NF-κB resulting in increased production of PICs and ROS [235–238]. Increased levels of PICs in turn induce the release of HMBG1 from immune and

epithelial cells and directly cause a self-amplifying cascade of inflammation, oxidative stress and lung tissue damage [239–241]; (reviewed by [242]). This process is likely central to the development of chronic, escalating inflammation and tissue damage in many illnesses such as multiple sclerosis, rheumatoid arthritis and major depression and has been described as the Toll-like Receptor Radical Cycle [243].

In the context of ARDS, the weight of evidence suggests that excessive PIC and ROS damage to cellular proteins and DNA also results in massively increased intracellular mtROS production and the subsequent activation of the NLPR 3 inflammasome [244,245]. This is an important point as inflammasome activation and the release of IL-1 and IL-18 appear to make a significant contribution to the development and progression of ARDS in the later stages of disease and high levels of the latter cytokine is associated with an extremely poor prognosis [246–248]. This is perhaps unsurprising given data highlighting the indispensable role of NLRP-3 activation in the progression of ARDS [247] and sepsis [249]. In addition information gleaned from animal studies suggests that the inhibition of this inflammasome is associated with increased rates of survival [250,251] (reviewed by [252]). There would appear to be many elements underpinning the association between increased inflammasome activity and mortality in ARDS patients. Perhaps the most important is spirally increasing cell death by pyroptosis and necrosis, most notably in macrophages and epithelial cells [244,245].

4.9. The role of pyroptosis in the pathophysiology of ARDS

As previously discussed, pyroptosis and necroptosis of alveolar epithelial and endothelial cells are major elements in the development and progression of ARDS [89–91]. There is also evidence to suggest that the pyroptotic death of neutrophils makes an independent contribution to the exacerbation of inflammation in more advanced stages of the condition [203]. However, from the perspective of ARDS related mortality, perhaps the most important element is the pyroptosis of alveolar macrophages [85,253–255]. Indeed, high levels of AM pyroptosis is another marker of mortality in patients with ARDS [256].

There is ample evidence to suggest that excessive loss of AMs as result of death via pyroptosis, or necrosis, plays an important role in the development and acceleration of lung damage by contribution to autoinflammatory pathways [257–260]. The mechanisms underpinning these observations would appear to be twofold. Firstly, the loss of resident AMs results in a repopulation of AMs derived from highly inflammatory peripheral monocytes which display grossly reduced phagocytic capacity, increased production of inflammatory mediators and susceptibility to pyroptosis and other forms of cell death [261,262] (reviewed by [263]). Secondly, accelerated pyroptosis of the AM population, results in ever increasing levels of DAMPs, PIC and ROS in turn resulting in spirally increasing tissue damage [259,264,265]; (reviewed by [85]). The weight of evidence suggests that HMBG1 may well be the dominant driver of the inflammatory responses following pyroptotic cell death, as inhibition of this molecule significantly decreases such responses [266]. Given this and the other information discussed above, it seems reasonable to conclude that interventions capable of decreasing the activity and or production of this heat shock protein may well have importance in the prevention and potentially the resolution of ARDS.

4.10. The advent of necroinflammation in the pathophysiology of ARDS

There is now accumulating evidence to suggest that the escalating increases in levels of IL-6, TNF-alpha, nitric oxide (NO) and ROS secreted by macrophages [92–94] also make a significant contributions to mortality by stimulating widespread cellular RIPK mediated necroptosis [89,94]. This form of cell death is associated with massive increases in levels of HGMB1, mtDNA, PICs, chemokines and ROS with ever amplifying levels of tissue damage, described as necroinflammation [267,268], leading to irreversible lung failure [269]. Necroptosis is predictive of non-resolving ARDS and mortality in patients on mechanical ventilation [89,94]. The pathological consequences of programmed cell death are difficult to overstate as studies have reported a causative association between the advent of widespread RIP Kinase-dependent necroptosis and the development of multiple organ failure and death in systemic inflammatory response syndrome and sepsis [270]. Elevated levels of RIP-3 in the blood is an almost invariant marker of a cytokine storm and is predictive of multiple organ failure and death. [271–273]. The mechanisms underpinning the development of necroptosis are relatively complex and readers interested in the biochemistry involved are referred to comprehensive reviews by [274,275] and the matter will not be considered further here. However of note a recent study has revealed the existence of a positive feedback loop between pyroptosis and necroptosis which leads to even higher levels of tissue damage and dysfunction [276]. This data further emphasises the importance of NLRP3 activation in the pathophysiology of ARDS and highlights the widespread inhibition of this inflammasome as a highly desirable therapeutic target.

5. The role of T cells in the pathophysiology of ARDS

An environment of severe chronic inflammation and oxidative stress seen in patients in advanced ARDS can lead to lymphopenia, compromised leucocyte function and a high Th17:regulatory T cell (T reg) ratio [277–282] contributing to the pathophysiology of the condition.

T regs play an important role in the prevention and resolution of ARDS via several routes such as promoting neutrophil clearance, inhibiting the effects of IL-6 and promoting the M2 polarisation of alveolar macrophages [283]. T regs also act as a cytokine sink and ameliorates otherwise uncontrolled inflammation via the secretion of IL-10 and TGF beta with a resultant downregulation in the production of TNF-alpha and IL-1 beta by resident and infiltrating macrophages [283,284].

TH17 polarised T cells also play a pathological role in the development and exacerbation of ARDS [284]. The main mechanism underpinning this association is increased production of IL-17 [66,71,72]. This is a highly cytotoxic molecule capable of causing significant levels of tissue damage and plays a major role in the recruitment of neutrophils from the periphery [285]. High levels of IL-17 is a marker for a poor prognosis in patients with ARDS [285]. The importance of Th17 and T regs in the pathophysiology of ARDS is emphasised by data suggesting that the TH17:T reg ratio is predictive of 28 day mortality in ventilated ARDS patients [285].

6. A suggested therapeutic approach to treatment

Many of the elements involved in the pathophysiology of ARDS are dependent on the chronic or long-term activation of NF-κB. For example there is copious evidence that activated NF-κB plays an important if not indispensable role in the initiation of platelet activation and maintaining such platelets in that state [286–290]. Activated NF-κB plays an indispensable role in the production, survival, and activation of neutrophils [291,292] and their release of NETs [293,294]. Chronically upregulated NF-κB is also an essential element enabling the activation of alveolar macrophages [295,296]. This is also true of monocyte activation and their subsequent differentiation into macrophages [297,298]. Inflammasome activation is also dependent on the upregulation of NF-κB [297,299]. Importantly there is an accumulating body of evidence implicating elevated NF-κB in the pathogenesis and progression of ARDS [300–303].

In addition there is a wealth of evidence to suggest that the maintenance and progression of ARDS also requires the presence of systemic sepsis or at the least excessive levels of systemic inflammation [85,88,304]. This is important as there is considerable evidence of sepsis in patients with severe COVID-19 and that chronic activation of

NF-κB in the development and progression of systemic sepsis (reviewed by [305]). Hence the localised suppression of NF-κB would seem to be an attractive option and [306] (reviewed by [109]).

7. Suggestions for therapeutic intervention

The weight of evidence suggests that zinc (Zn) is a highly effective NF-κB inhibitor in vivo [307–309]. This is of particular interest as several authors have reported grossly depleted Zn levels in patients with severe infections, sepsis and ARDS hence there is a case for Zn supplementation in COVID-19 [310–313]. It is also noteworthy that vitamin C levels are also commonly depleted in patients with sepsis and ARDS [314,315] and several authors have reported downregulation of NF-κB following its administration [316,317]. Vitamin D is also severely depleted in many patients with sepsis and ARDS [318,319] and dietary supplementation with this molecule also results in significant inhibition of NF-κB [320–324]. There is also growing interest in vitamin D supplementation in treating COVID-19 following the publication of a paper reporting severely depleted levels of this vitamin in patients with COVID-19 pneumonia and COVID-19 ARDS [325].

There are several other molecules with a proven pedigree as NF-κB inhibitors such as azithromycin [326,327], curcumin, melatonin and coenzyme Q_{10} [328–330].This is also true of *N*-acetyl-cysteine [331–333]. There is also evidence that aspirin is an effective NF-κB inhibitor [334–336] although it should be emphasised that doses in excess of 300 mg/day are needed to exert this effect in vivo [337,338].

8. Conclusion

A detailed and highly plausible model has been put forward in this paper demonstrating the pathophysiological steps of COVID-19 from the initial infection of type II alveolar epithelial cells by SARS-CoV-2 to the development of ARDS. There are various control points in this model at which interventions might be of therapeutic value. These include inhibition of EC platelet and neutrophil activation, inhibition of neutrophil migration and NET production, stimulation of AM phagocytosis, and inhibition of the NLRP3 inflammasome. These objectives might all be achieved via the concomitant use of one or more NF-κB inhibitors. A trial investigating the combined use of Zn, vitamin C and vitamin D would seem to be a rational option given their depleted levels in patients with sepsis and ARDS and their potential as inhibitors of NF-κB. In addition, one or more of the NF-κB inhibitors discussed above might also be considered given their benign side effect profile and the difficulty of treating ARDS once the condition has arisen.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors' contributions

GM conceptualized the work and was a major contributor in writing the manuscript. CCB created the figures. All other authors have drafted and approved the final manuscript.

Declaration of competing interest

MB is supported by a NHMRC Senior Principal Research Fellowship (1059660 and 1156072). MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. LO is supported by a NHMRC Early Career Fellowship (1158487). WM is currently funded by an Alfred Deakin Postdoctoral Research Fellowship and a Multiple Sclerosis Research Australia early-career fellowship. WM has previously received funding from the Cancer Council Queensland and university grants/fellowships from La Trobe University, Deakin University, University of Queensland, and Bond University. WM has received industry funding and has attended events funded by Cobram Estate Pty. Ltd. WM has received travel funding from Nutrition Society of Australia. WM has received consultancy funding from Nutrition Research Australia. WM has received speaker honoraria from The Cancer Council Queensland and the Princess Alexandra Research Foundation. The Food & Mood Centre has received Grant/Research support from Fernwood Foundation, Wilson Foundation, the A2 Milk Company, and Be Fit Foods. AO is supported by a Future Leader Fellowship (#101160) from the Heart Foundation Australia and Wilson Foundation. She has received research funding from National Health & Medical Research Council, Australian Research Council, University of Melbourne, Deakin University, Sanofi, Meat and Livestock Australia and Woolworths Limited and Honoraria from Novartis.

Acknowledgements

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