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

Gerwyn Morris[a], Chiara C. Bortolasci[a,b,*], Basant K. Puri[c], Lisa Olive[a,d], Wolfgang Marx[a], Adrienne O'Neil[a,e], Eugene Athan[a,f], Andre F. Carvalho[a,g,k], Michael Maes[a,h,i], Ken Walder[a,b], Michael Berk[a,j]

[a] Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia
[b] Deakin University, Centre for Molecular and Medical Research, School of Medicine, Geelong, Australia
[c] C.A.R., Cambridge, UK
[d] School of Psychology, Deakin University, Geelong, Australia
[e] Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia
[f] Barwon Health, Geelong, Australia
[g] Department of Psychiatry, University of Toronto, Toronto, Canada
[h] Department of Psychiatry, King Chulalongkorn University Hospital, Bangkok, Thailand
[i] Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria.
[j] Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Florey Institute for Neuroscience and Mental Health and the Department of Psychiatry, The University of Melbourne, Melbourne, Australia
[k] Centre for Addiction and Mental Health (CAMH), Toronto, Canada

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

* Corresponding author at: IMPACT – the Institute for Mental and Physical Health and Clinical Translation, Deakin University, 75 Pigdons Road, Waurn Ponds, Victoria 3218, Australia.
E-mail address: chiara.b@deakin.edu.au (C.C. Bortolasci).

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

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

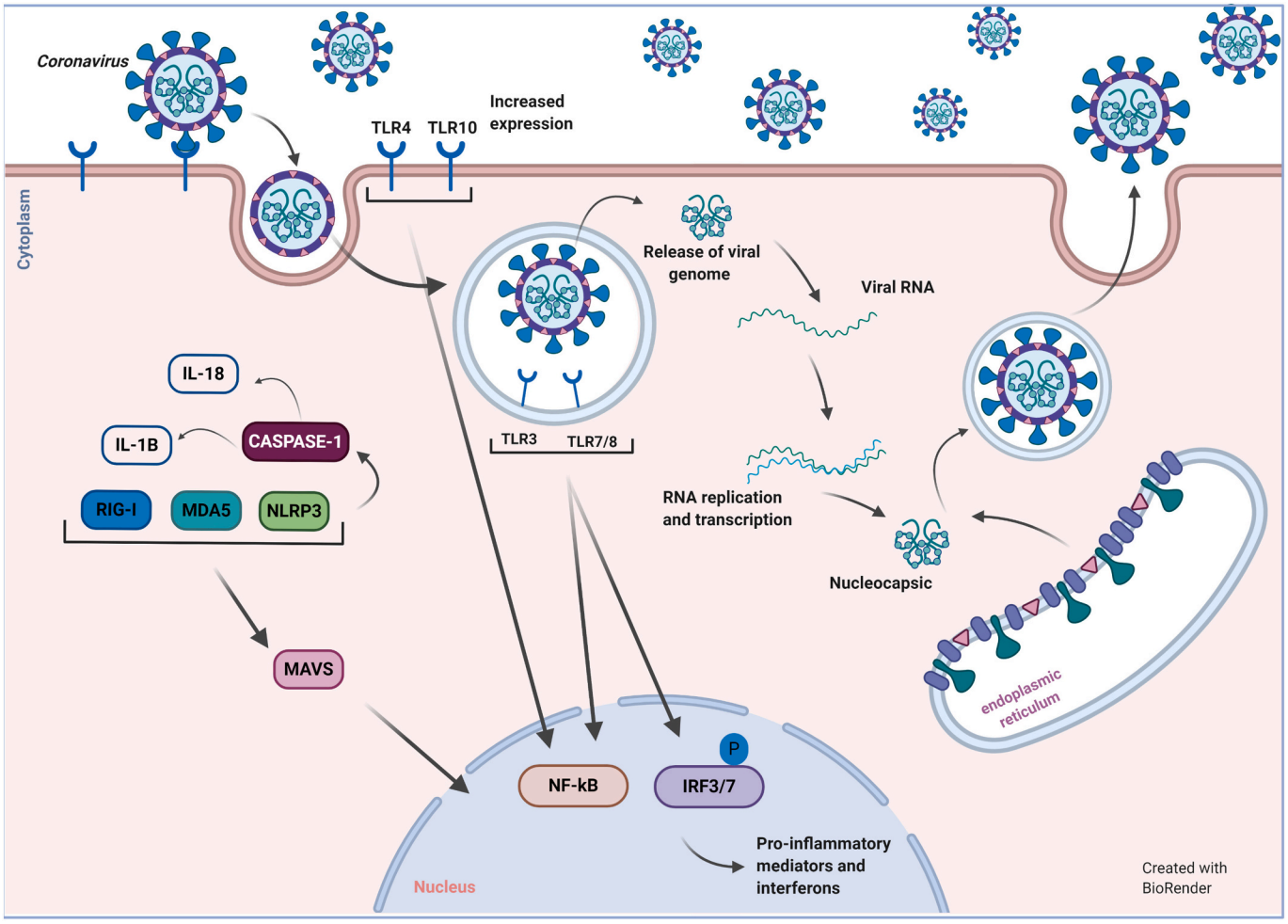

Fig. 1. Pattern Recognition receptors involved in detecting RNA viruses. Adapted from "Coronavirus Replication Cycle", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates.
The presence of invading RNA viruses is detected by a family of Toll like receptors (TLRs) RIG 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

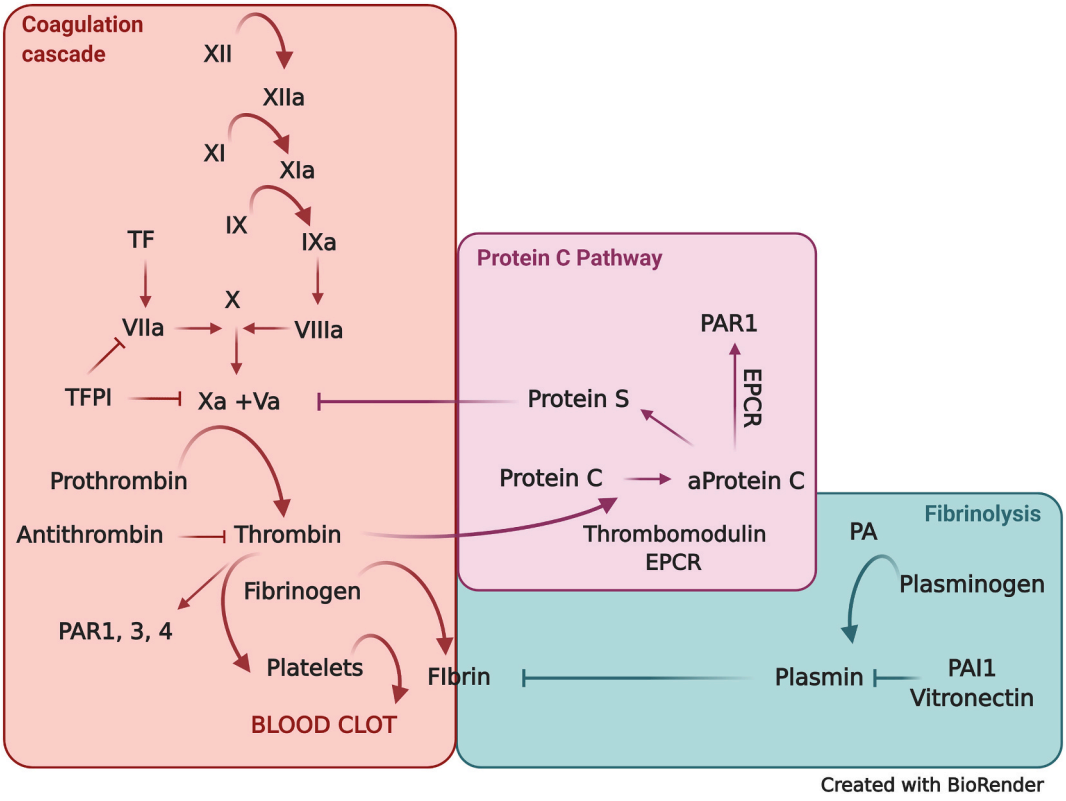

Fig. 2. The development of immunothrombosis.
Platelets activated by thrombin and or PICs initiate (PAR)–mediated signalling further increasing levels of PICs VWF and TF coupled with suppression of suppression of thrombomodulin. Platelet activation also results in increased expression of P-selectin, CD40 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,

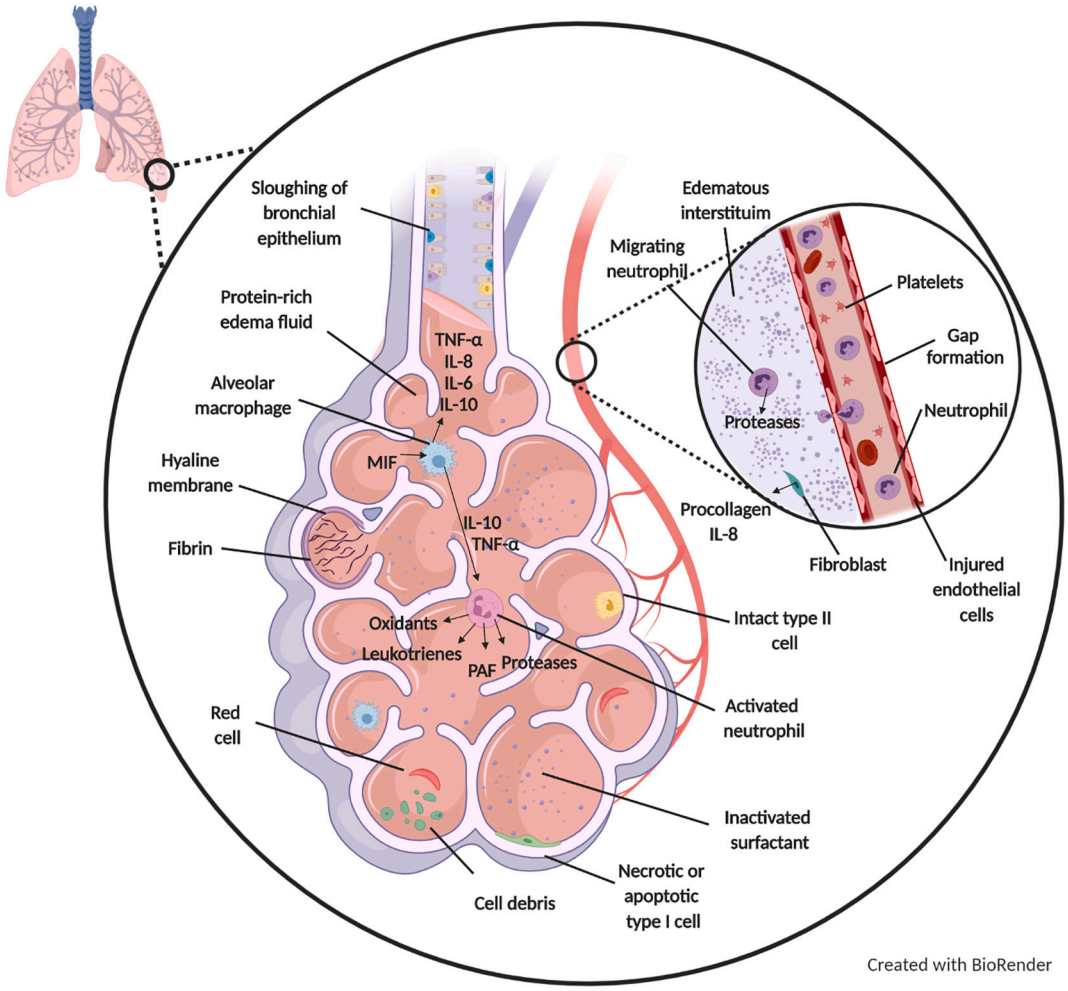

Fig. 3. The physical and immunological landscape of the lung tissue in ARDS.
Initial infection and activation of type 2 alveolar cells and alveolar macrophages results in the secretion of IL-6, PICs and a wide range of chemokines which activate vascular endothelial cells and recruit peripheral activated 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

....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....
....

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

References

[1] E. de Wit, N. van Doremalen, D. Falzarano, V.J. Munster, SARS and MERS: recent insights into emerging coronaviruses, Nat. Rev. Microbiol. 14 (2016) 523–534.
[2] J. Liu, X. Zheng, Q. Tong, W. Li, B. Wang, K. Sutter, et al., Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV, J. Med. Virol. 92 (2020) 491–494.
[3] X. He, E.H.Y. Lau, P. Wu, X. Deng, J. Wang, X. Hao, et al., Temporal dynamics in viral shedding and transmissibility of COVID-19, Nat. Med. 26 (2020) 672–675.
[4] H. Li, L. Liu, D. Zhang, J. Xu, H. Dai, N. Tang, et al., SARS-CoV-2 and viral sepsis: observations and hypotheses, Lancet 395 (10235) (2020) 1517–1520.
[5] Y. Wang, Y. Wang, Y. Chen, Q. Qin, Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures, J. Med. Virol. 92 (2020) 568–576.
[6] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727–733.
[7] C.A. Donnelly, A.C. Ghani, G.M. Leung, A.J. Hedley, C. Fraser, S. Riley, et al., Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong, Lancet (London, England) 361 (2003) 1761–1766.
[8] E. Mahase, Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate, Bmj 368 (2020) m641.
[9] N. Petrosillo, G. Viceconte, O. Ergonul, G. Ippolito, E. Petersen, COVID-19, SARS and MERS: are they closely related? Clin. Microbiol. Infect. 26 (6) (2020) 729–734 (S1198-743X(20)30171-3).
[10] M. Vaduganathan, O. Vardeny, T. Michel, J.J.V. McMurray, M.A. Pfeffer, S.D. Solomon, Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19, N. Engl. J. Med. 382 (2020) 1653–1659.
[11] P. Verdecchia, C. Cavallini, A. Spanevello, F. Angeli, The pivotal link between ACE2 deficiency and SARS-CoV-2 infection, Eur J Intern Med 76 (2020) 14–20 (S0953-6205(20)30151-5).
[12] W. Sungnak, N. Huang, C. Bécavin, M. Berg, R. Queen, M. Litvinukova, et al., SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes, Nat. Med. 26 (5) (2020) 681–687.
[13] L. Zou, F. Ruan, M. Huang, L. Liang, H. Huang, Z. Hong, et al., SARS-CoV-2 viral load in upper respiratory specimens of infected patients, N. Engl. J. Med. 382 (2020) 1177–1179.
[14] R.J. Mason, Pathogenesis of COVID-19 from a cell biologic perspective, Eur. Respir. J. (2020) 2000607.
[15] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, JAMA. 323 (2020) 1239–1242.
[16] K.K.-W. To, O.T.-Y. Tsang, W.-S. Leung, A.R. Tam, T.-C. Wu, D.C. Lung, et al., Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study, Lancet Infect. Dis. 20 (5) (2020) P565–574.
[17] Y. Liu, A.A. Gayle, A. Wilder-Smith, J. Rocklöv, The reproductive number of COVID-19 is higher compared to SARS coronavirus, Journal of Travel Medicine 27 (2020).
[18] W. Tai, L. He, X. Zhang, J. Pu, D. Voronin, S. Jiang, et al., Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine, Cell. Mol. Immunol. 17 (6) (2020) 613–620.
[19] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.-L. Hsieh, O. Abiona, et al., Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (2020) 1260–1263.
[20] S. Bertram, A. Heurich, H. Lavender, S. Gierer, S. Danisch, P. Perin, et al., Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts, PLoS One 7 (2012) e35876.
[21] I. Hamming, W. Timens, M. Bulthuis, A. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2004) 631–637.
[22] B. Coutard, C. Valle, X. de Lamballerie, B. Canard, N.G. Seidah, E. Decroly, The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade, Antivir. Res. 176 (2020) 104742.
[23] X. Ou, Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, et al., Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV, Nat. Commun. 11 (2020) 1620.
[24] A.C. Walls, Y.-J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell 181 (e6) (2020) 281–292.
[25] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (e8) (2020) 271–280.
[26] H. Kido, Y. Okumura, E. Takahashi, H.-Y. Pan, S. Wang, D. Yao, et al., Role of host cellular proteases in the pathogenesis of influenza and influenza-induced multiple organ failure, Biochim. Biophys. Acta Protein Proteomics 1824 (2012) 186–194.
[27] T.R. O'Brien, D.L. Thomas, S.S. Jackson, L. Prokunina-Olsson, R.P. Donnelly, R. Hartmann, Weak induction of interferon expression by SARS-CoV-2 supports clinical trials of interferon lambda to treat early COVID-19, Clin. Infect. Dis. (2020) ciaa453.
[28] D. Blanco-Melo, B.E. Nilsson-Payant, W.-C. Liu, S. Uhl, D. Hoagland, R. Møller, et al., Imbalanced host response to SARS-CoV-2 drives development of COVID-19, Cell 181 (5) (2020) 1036–1045.e9.
[29] Y. Konno, I. Kimura, K. Uriu, M. Fukushi, T. Irie, Y. Koyanagi, et al., SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist whose Activity Is further Increased by a Naturally Occurring Elongation Variant, bioRxiv (2020) (2020.05.11.088179).
[30] E. Sallard, F.-X. Lescure, Y. Yazdanpanah, F. Mentre, N. Peiffer-Smadja, Type 1 interferons as a potential treatment against COVID-19, Antivir. Res. 178 (2020) 104791.
[31] L. Liu, X. Lei, X. Xiao, et al., Epidemiological and clinical characteristics of patients with coronavirus Disease-2019 in Shiyan City, China, Front. Cell. Infect. Microbiol. 10 (2020) 284.
[32] C. Rothe, M. Schunk, P. Sothmann, G. Bretzel, G. Froeschl, C. Wallrauch, et al., Transmission of 2019-nCoV infection from an asymptomatic contact in Germany, N. Engl. J. Med. 382 (2020) 970–971.
[33] S. Shi, M. Qin, B. Shen, Y. Cai, T. Liu, F. Yang, et al., Association of cardiac injury with Mortality in hospitalized patients with COVID-19 in Wuhan, China, JAMA Cardiol. (2020).
[34] P. Wu, F. Duan, C. Luo, Q. Liu, X. Qu, L. Liang, et al., Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China, JAMA Ophthalmol (2020).
[35] L. Carsana, A. Sonzogni, A. Nasr, R. Rossi, A. Pellegrinelli, P. Zerbi, et al., Pulmonary Post-mortem Findings in a Large Series of COVID-19 Cases from Northern Italy, medRxiv (2020) (2020.04.19.20054262).
[36] S.E. Fox, A. Akmatbekov, J.L. Harbert, G. Li, J.Q. Brown, R.S. Vander Heide, Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans, medRxiv (2020) (2020.04.06.20050575).
[37] S. Tian, W. Hu, L. Niu, H. Liu, H. Xu, S.-Y. Xiao, Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer, J. Thorac. Oncol. 15 (2020) 700–704.
[38] M. Ranucci, A. Ballotta, U. Di Dedda, E. Bayshnikova, M. Dei Poli, M. Resta, et al., The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome, J. Thromb. Haemost. (2020).
[39] J.N. Gonzales, R. Lucas, A.D. Verin, The acute respiratory distress syndrome: mechanisms and perspective therapeutic approaches, Austin J Vasc Med. 2 (2015) 1009.
[40] L. Gattinoni, D. Chiumello, P. Caironi, M. Busana, F. Romitti, L. Brazzi, et al., COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. (2020).
[41] L. Gattinoni, S. Coppola, M. Cressoni, M. Busana, S. Rossi, D. Chiumello, Covid-19 does not Lead to a "typical" acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. (2020).
[42] X. Tang, R. Du, R. Wang, T. Cao, L. Guan, C. Yang, et al., Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1, Chest (2020).
[43] F. Wang, H. Hou, Y. Luo, G. Tang, S. Wu, M. Huang, et al., The laboratory tests and host immunity of COVID-19 patients with different severity of illness, JCI Insight (2020).
[44] M. Liao, Y. Liu, J. Yuan, Y. Wen, G. Xu, J. Zhao, et al., The Landscape of Lung Bronchoalveolar Immune Cells in COVID-19 Revealed by Single-Cell RNA Sequencing, medRxiv (2020) (2020.02.23.20026690).
[45] B. Salomé, A. Magen, Dysregulation of lung myeloid cells in COVID-19, Nat. Rev. Immunol. (2020) Apr 6 : 1.
[46] M. Yang, Cell pyroptosis, a potential pathogenic mechanism of 2019-nCoV infection, SSRN Electron. J. (2020) January 29, 2020.
[47] X.H. Yao, T.Y. Li, Z.C. He, Y.F. Ping, H.W. Liu, S.C. Yu, et al., A pathological report of three COVID-19 cases by minimally invasive autopsies, Zhonghua Bing Li Xue Za Zhi 49 (2020) E009.
[48] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, et al., Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect. Dis. 71 (15) (2020) 762–768.
[49] Y. Zuo, S. Yalavarthi, H. Shi, K. Gockman, M. Zuo, J.A. Madison, et al., Neutrophil extracellular traps in COVID-19, JCI Insight 5 (11) (2020) e138999.
[50] W. Wen, W. Su, H. Tang, W. Le, X. Zhang, Y. Zheng, et al., Immune Cell Profiling of COVID-19 Patients in the Recovery Stage by Single-Cell Sequencing, medRxiv (2020) (2020.03.23.20039362).
[51] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson,

COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (2020) 1033–1034.
[52] D. Zhang, R. Guo, L. Lei, H. Liu, Y. Wang, Y. Wang, et al., COVID-19 Infection Induces Readily Detectable Morphological and Inflammation-Related Phenotypic Changes in Peripheral Blood Monocytes, the Severity of which Correlate with Patient Outcome, medRxiv (2020) (2020.03.24.20042655).
[53] B. Liu, M. Li, Z. Zhou, X. Guan, Y. Xiang, Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J. Autoimmun. 111 (2020) 102452.
[54] Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, et al., COVID-19 infection: the perspectives on immune responses, Cell Death Differ. 27 (5) (2020) 1451–1454.
[55] C. Wang, J. Cai, R. Chen, Z. Shi, X. Bian, J. Xie, et al., Aveolar macrophage activation and cytokine storm in the pathogenesis of severe COVID-19, Research Square 57 (2020) 102833.
[56] R. Zhang, X. Wang, L. Ni, X. Di, B. Ma, S. Niu, et al., COVID-19: melatonin as a potential adjuvant treatment, Life Sci. 250 (2020) 117583.
[57] X. Chen, B. Zhao, Y. Qu, Y. Chen, J. Xiong, Y. Feng, et al., Detectable Serum SARS-CoV-2 Viral Load (RNAaemia) Is Closely Associated with Drastically Elevated Interleukin 6 (IL-6) Level in Critically Ill COVID-19 Patients, medRxiv (2020) (2020.02.29.20029520).
[58] A.-P. Yang, J. Liu, W. Tao, H.-m. Li, The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients, Int. Immunopharmacol. (2020) 106504.
[59] Y. Liu, X. Du, J. Chen, Y. Jin, L. Peng, H.H.X. Wang, et al., Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19, The Journal of infection 81 (1) (2020) e6–e12.
[60] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (7) (2020) 1–8.
[61] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intensive Care Med. 46 (5) (2020) 846–848.
[62] J.-M. Cavaillon, M. Adib-Conquy, Immune status in sepsis: the bug, the site of infection and the severity can make the difference, Crit. Care 14 (2010) 167.
[63] T. Girardot, T. Rimmele, F. Venet, G. Monneret, Apoptosis-induced lymphopenia in sepsis and other severe injuries, Apoptosis 22 (2017) 295–305.
[64] B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, et al., Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19), medRxiv (2020) (2020.02.18.20024364).
[65] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England) 395 (2020) 497–506.
[66] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (2020) 420–422.
[67] X. Cao, COVID-19: immunopathology and its implications for therapy, Nat. Rev. Immunol. 20 (2020) 269–270.
[68] C. Moon, Fighting COVID-19 exhausts T cells, Nat. Rev. Immunol. 20 (2020) 277.
[69] H.-Y. Zheng, M. Zhang, C.-X. Yang, N. Zhang, X.-C. Wang, X.-P. Yang, et al., Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients, Cell. Mol. Immunol. 17 (2020) 541–543.
[70] M. Zheng, Y. Gao, G. Wang, G. Song, S. Liu, D. Sun, et al., Functional exhaustion of antiviral lymphocytes in COVID-19 patients, Cell. Mol. Immunol. 17 (2020) 533–535.
[71] E.J. Giamarellos-Bourboulis, M.G. Netea, N. Rovina, K. Akinosoglou, A. Antoniadou, N. Antonakos, et al., Complex immune dysregulation in COVID-19 patients with severe respiratory failure, Cell Host Microbe 27 (6) (2020) 921–1000.e3.
[72] S.F. Pedersen, Y.C. Ho, SARS-CoV-2: a storm is raging, J. Clin. Invest. 130 (2020) 2202–2205.
[73] B.J.B. Moore, C.H. June, Cytokine release syndrome in severe COVID-19, Science (2020) eabb8925.
[74] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the `cytokine Storm' in COVID-19, The Journal of infection 80 (6) (2020) 607–613.
[75] C. Zhang, Z. Wu, J.-W. Li, H. Zhao, G.-Q. Wang, The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality, Int. J. Antimicrob. Agents 55 (5) (2020) (105954-).
[76] J.T. Poston, B.K. Patel, A.M. Davis, Management of critically ill adults with COVID-19, JAMA 323 (18) (2020) 1839–1841.
[77] M. Wujtewicz, A. Dylczyk-Sommer, A. Aszkiełowicz, S. Zdanowski, S. Piwowarczyk, R. Owczuk, COVID-19 – what should anaethesiologists and intensivists know about it? Anaesthesiology intensive therapy 52 (2020) 34–41.
[78] E.C. Mossel, J. Wang, S. Jeffers, K.E. Edeen, S. Wang, G.P. Cosgrove, et al., SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells, Virology 372 (2008) 127–135.
[79] Z. Qian, E.A. Travanty, L. Oko, K. Edeen, A. Berglund, J. Wang, et al., Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus, Am. J. Respir. Cell Mol. Biol. 48 (2013) 742–748.
[80] Q. Liu, Y.-h. Zhou, Z.-Q. Yang, The cytokine storm of severe influenza and development of immunomodulatory therapy, Cell. Mol. Immunol. 13 (2016) 3–10.
[81] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (2020) 1061–1069.
[82] X.-H. Yao, Z.-C. He, T.-Y. Li, H.-R. Zhang, Y. Wang, H. Mou, et al., Pathological evidence for residual SARS-CoV-2 in pulmonary tissues of a ready-for-discharge patient, Cell Res. 30 (6) (2020) 541–543.
[83] N.L. La Gruta, K. Kedzierska, J. Stambas, P.C. Doherty, A question of self-preservation: immunopathology in influenza virus infection, Immunol. Cell Biol. 85 (2007) 85–92.
[84] K. Shinya, Y. Gao, C. Cilloniz, Y. Suzuki, M. Fujie, G. Deng, et al., Integrated clinical, pathologic, virologic, and transcriptomic analysis of H5N1 influenza virus-induced viral pneumonia in the rhesus macaque, J. Virol. 86 (2012) 6055–6066.
[85] E.K.Y. Fan, J. Fan, Regulation of alveolar macrophage death in acute lung inflammation, Respir. Res. 19 (2018) 50.
[86] X. Huang, H. Xiu, S. Zhang, G. Zhang, The role of macrophages in the pathogenesis of ALI/ARDS, Mediat. Inflamm. 2018 (2018) (1264913-).
[87] D. Chakraborty, S. Zenker, J. Rossaint, A. Hölscher, M. Pohlen, A. Zarbock, et al., Alarmin S100A8 activates alveolar epithelial cells in the context of acute lung injury in a TLR4-dependent manner, Front. Immunol. 8 (2017).
[88] S. Han, R.K. Mallampalli, The acute respiratory distress syndrome: from mechanism to translation, Journal of immunology (Baltimore, Md: 1950) 194 (2015) 855–860.
[89] H. Faust, N.S. Mangalmurti, Collateral damage: necroptosis in the development of lung injury, Am. J. Phys. Lung Cell. Mol. Phys. 318 (2020) L215-L25.
[90] M. Sauler, I.S. Bazan, P.J. Lee, Cell death in the Lung: the apoptosis-necroptosis axis, Annu. Rev. Physiol. 81 (2019) 375–402.
[91] H. Ueno, T. Matsuda, S. Hashimoto, F. Amaya, Y. Kitamura, M. Tanaka, et al., Contributions of high mobility group box protein in experimental and clinical acute lung injury, Am. J. Respir. Crit. Care Med. 170 (2004) 1310–1316.
[92] J.D. Aberdein, J. Cole, M.A. Bewley, H.M. Marriott, D.H. Dockrell, Alveolar macrophages in pulmonary host defence the unrecognized role of apoptosis as a mechanism of intracellular bacterial killing, Clin. Exp. Immunol. 174 (2013) 193–202.
[93] J.E. Losa García, F.M. Rodríguez, M.R. Martín de Cabo, M.J. García Salgado, J.P. Losada, L.G. Villarón, et al., Evaluation of inflammatory cytokine secretion by human alveolar macrophages, Mediat. Inflamm. 8 (1999) 43–51.
[94] C.-Y. Yang, C.-S. Chen, G.-T. Yiang, Y.-L. Cheng, S.-B. Yong, M.-Y. Wu, et al., New insights into the immune molecular regulation of the pathogenesis of acute respiratory distress syndrome, Int. J. Mol. Sci. 19 (2018) 588.
[95] S. Soni, M.R. Wilson, K.P. O'Dea, M. Yoshida, U. Katbeh, S.J. Woods, et al., Alveolar macrophage-derived microvesicles mediate acute lung injury, Thorax 71 (2016) 1020–1029.
[96] E.D. Morrell, P.K. Bhatraju, C.R. Mikacenic, F. Radella 2nd, A.M. Manicone, R.D. Stapleton, et al., Alveolar macrophage transcriptional programs are associated with outcomes in acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 200 (2019) 732–741.
[97] C. Song, H. Li, Y. Li, M. Dai, L. Zhang, S. Liu, et al., NETs promote ALI/ARDS inflammation by regulating alveolar macrophage polarization, Exp. Cell Res. 382 (2019) 111486.
[98] F. Frantzeskaki, A. Armaganidis, S.E. Orfanos, Immunothrombosis in acute respiratory distress syndrome: cross talks between inflammation and coagulation, Respiration 93 (2017) 212–225.
[99] J.S. Pober, W.C. Sessa, Evolving functions of endothelial cells in inflammation, Nat. Rev. Immunol. 7 (2007) 803–815.
[100] P.E. Szmitko, C.-H. Wang, R.D. Weisel, Jrd Almeida, T.J. Anderson, S. Verma, New markers of inflammation and endothelial cell activation, Circulation 108 (2003) 1917–1923.
[101] S. Sukriti, M. Tauseef, P. Yazbeck, D. Mehta, Mechanisms regulating endothelial permeability, Pulm Circ 4 (2014) 535–551.
[102] P. Cejkova, I. Nemeckova, J. Broz, M. Cerna, TLR2 and TLR4 Expression on CD14(++) and CD14(+) Monocyte Subtypes in Adult-Onset Autoimmune Diabetes, 160 Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia, 2016, pp. 76–83.
[103] I. Mitroulis, V.I. Alexaki, I. Kourtzelis, A. Ziogas, G. Hajishengallis, T. Chavakis, Leukocyte integrins: role in leukocyte recruitment and as therapeutic targets in inflammatory disease, Pharmacol. Ther. 147 (2015) 123–135.
[104] D.P. Ramji, T.S. Davies, Cytokines in atherosclerosis: Key players in all stages of disease and promising therapeutic targets, Cytokine Growth Factor Rev. 26 (2015) 673–685.
[105] J. Mai, A. Virtue, J. Shen, H. Wang, X.-F. Yang, An evolving new paradigm: endothelial cells – conditional innate immune cells, J. Hematol. Oncol. 6 (2013) 61.
[106] V.W.M. van Hinsbergh, Endothelium–role in regulation of coagulation and inflammation, Semin. Immunopathol. 34 (2012) 93–106.
[107] J.W. Yau, H. Teoh, S. Verma, Endothelial cell control of thrombosis, BMC Cardiovasc. Disord. 15 (2015) (130-).
[108] J.C. Chang, Sepsis and septic shock: endothelial molecular pathogenesis associated with vascular microthrombotic disease, Thromb. J. 17 (2019) (10-).
[109] C. Nedeva, J. Menassa, H. Puthalakath, Sepsis: inflammation is a necessary evil, Frontiers in cell and developmental biology 7 (2019).
[110] C.M. Hendrickson, M.A. Matthay, Endothelial biomarkers in human sepsis: pathogenesis and prognosis for ARDS, Pulm Circ 8 (2018) (2045894018769876-).
[111] F.R. Millar, C. Summers, M.J. Griffiths, M.R. Toshner, A.G. Proudfoot, The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities, Thorax 71 (2016) 462–473.
[112] P. Pignatelli, L. De Biase, L. Lenti, G. Tocci, A. Brunelli, R. Cangemi, et al., Tumor necrosis factor-alpha as trigger of platelet activation in patients with heart failure, Blood 106 (2005) 1992–1994.
[113] M. Qiao, G.G. Ying, A.C. Singer, Y.G. Zhu, Review of antibiotic resistance in China and its environment, Environ. Int. 110 (2018) 160–172.

[114] M. El Haouari, Platelet oxidative stress and its relationship with cardiovascular diseases in type 2 diabetes mellitus patients, Curr. Med. Chem. 26 (2019) 4145–4165.
[115] J.E. Freedman, Oxidative stress and platelets, Arterioscler. Thromb. Vasc. Biol. 28 (2008) s11–s16.
[116] F. Violi, P. Pignatelli, S. Basili, Nutrition, supplements, and vitamins in platelet function and bleeding, Circulation 121 (2010) 1033–1044.
[117] M. Hamilos, S. Petousis, F. Parthenakis, Interaction between platelets and endothelium: from pathophysiology to new therapeutic options, Cardiovascular diagnosis and therapy 8 (2018) 568–580.
[118] I. Øynebråten, N. Barois, T. Bergeland, A.M. Küchler, O. Bakke, G. Haraldsen, Oligomerized, filamentous surface presentation of RANTES/CCL5 on vascular endothelial cells, Sci. Rep. 5 (2015) 9261.
[119] O. Sonmez, M. Sonmez, Role of platelets in immune system and inflammation, Porto biomedical journal 2 (2017) 311–314.
[120] M. Finsterbusch, W.C. Schrottmaier, J.B. Kral-Pointner, M. Salzmann, A. Assinger, Measuring and interpreting platelet-leukocyte aggregates, Platelets 29 (2018) 677–685.
[121] V. Sreeramkumar, J.M. Adrover, I. Ballesteros, M.I. Cuartero, J. Rossaint, I. Bilbao, et al., Neutrophils scan for activated platelets to initiate inflammation, Science 346 (2014) 1234–1238.
[122] K. Stark, Platelet-neutrophil crosstalk and netosis, HemaSphere 3 (2019) 89–91.
[123] Y. Wang, H. Gao, C. Shi, P.W. Erhardt, A. Pavlovsky, D. A Soloviev, et al., Leukocyte integrin Mac-1 regulates thrombosis via interaction with platelet GPIbα, Nat. Commun. 8 (2017) (15559-).
[124] A.Z. Zucoloto, C.N. Jenne, Platelet-neutrophil interplay: insights into neutrophil Extracellular trap (NET)-driven coagulation in infection, Frontiers in Cardiovascular Medicine 6 (2019).
[125] J. Etulain, K. Martinod, S.L. Wong, S.M. Cifuni, M. Schattner, D.D. Wagner, P-selectin promotes neutrophil extracellular trap formation in mice, Blood 126 (2015) 242–246.
[126] K.N. Kornerup, G.P. Salmon, S.C. Pitchford, W.L. Liu, C.P. Page, Circulating platelet-neutrophil complexes are important for subsequent neutrophil activation and migration, J. Appl. Physiol. 109 (2010) 758–767.
[127] T. Iba, E. Watanabe, Y. Umemura, T. Wada, K. Hayashida, S. Kushimoto, et al., Sepsis-associated disseminated intravascular coagulation and its differential diagnoses, J. Intensive Care 7 (2019) 32.
[128] J. Rayes, J.H. Bourne, A. Brill, S.P. Watson, The dual role of platelet-innate immune cell interactions in thrombo-inflammation, Research and Practice in Thrombosis and Haemostasis 4 (2020) 23–35.
[129] D. Duerschmied, G.L. Suidan, M. Demers, N. Herr, C. Carbo, A. Brill, et al., Platelet serotonin promotes the recruitment of neutrophils to sites of acute inflammation in mice, Blood 121 (2013) 1008–1015.
[130] M. Ghasemzadeh, E. Hosseini, Intravascular leukocyte migration through platelet thrombi: directing leukocytes to sites of vascular injury, Thromb. Haemost. 113 (2015) 1224–1235.
[131] N. Maugeri, P. Rovere-Querini, V. Evangelista, C. Godino, M. Demetrio, M. Baldini, et al., An intense and short-lasting burst of neutrophil activation differentiates early acute myocardial infarction from systemic inflammatory syndromes, PLoS One 7 (2012) e39484.
[132] C. Page, S. Pitchford, Neutrophil and platelet complexes and their relevance to neutrophil recruitment and activation, Int. Immunopharmacol. 17 (2013) 1176–1184.
[133] G.J. Graham, T.M. Handel, A.E.I. Proudfoot, Leukocyte adhesion: reconceptualizing chemokine presentation by glycosaminoglycans, Trends Immunol. 40 (2019) 472–481.
[134] E.A. Middleton, A.S. Weyrich, G.A. Zimmerman, Platelets in pulmonary immune responses and inflammatory lung diseases, Physiol. Rev. 96 (2016) 1211–1259.
[135] G. Ortiz-Muñoz, B. Mallavia, A. Bins, M. Headley, M.F. Krummel, M.R. Looney, Aspirin-triggered 15-epi-lipoxin A4 regulates neutrophil-platelet aggregation and attenuates acute lung injury in mice, Blood 124 (2014) 2625–2634.
[136] Y. Yao, H. Matsushima, J.A. Ohtola, S. Geng, R. Lu, A. Takashima, Neutrophil priming occurs in a sequential manner and can be visualized in living animals by monitoring IL-1β promoter activation, Journal of immunology (Baltimore, Md: 1950) 194 (2015) 1211–1224.
[137] J. Hao, L.Q. Meng, P.C. Xu, M. Chen, M.H. Zhao, p38MAPK, ERK and PI3K signaling pathways are involved in C5a-primed neutrophils for ANCA-mediated activation, PLoS One 7 (2012) e38317.
[138] K.L. Vogt, C. Summers, E.R. Chilvers, A.M. Condliffe, Priming and de-priming of neutrophil responses in vitro and in vivo, Eur. J. Clin. Investig. 48 (Suppl. 2) (2018) e12967.
[139] C. Summers, N.R. Singh, J.F. White, I.M. Mackenzie, A. Johnston, C. Solanki, et al., Pulmonary retention of primed neutrophils: a novel protective host response, which is impaired in the acute respiratory distress syndrome, Thorax 69 (2014) 623–629.
[140] R.L. Zemans, M.A. Matthay, What drives neutrophils to the alveoli in ARDS? Thorax 72 (2017) 1–3.
[141] J.K. Juss, D. House, A. Amour, M. Begg, J. Herre, D.M.L. Storisteanu, et al., Acute respiratory distress syndrome neutrophils have a distinct phenotype and are resistant to phosphoinositide 3-kinase inhibition, Am. J. Respir. Crit. Care Med. 194 (2016) 961–973.
[142] A. Assinger, E. Buchberger, M. Laky, A. Esfandeyari, C. Brostjan, I. Volf, Periodontopathogens induce soluble P-selectin release by endothelial cells and platelets, Thromb. Res. 127 (2011) e20–e26.
[143] A. Gros, V. Ollivier, B. Ho-Tin-Noé, Platelets in inflammation: regulation of leukocyte activities and vascular repair, Front. Immunol. 5 (2014) 678.
[144] S.R. Clark, A.C. Ma, S.A. Tavener, B. McDonald, Z. Goodarzi, M.M. Kelly, et al., Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood, Nat. Med. 13 (2007) 463–469.
[145] J.N. Katz, K.P. Kolappa, R.C. Becker, Beyond thrombosis: the versatile platelet in critical illness, Chest 139 (2011) 658–668.
[146] A. Carestia, T. Kaufman, L. Rivadeneyra, V.I. Landoni, R.G. Pozner, S. Negrotto, et al., Mediators and molecular pathways involved in the regulation of neutrophil extracellular trap formation mediated by activated platelets, J. Leukoc. Biol. 99 (2015) 153–162.
[147] N. Maugeri, L. Campana, M. Gavina, C. Covino, M. De Metrio, C. Panciroli, et al., Activated platelets present high mobility group box 1 to neutrophils, inducing autophagy and promoting the extrusion of neutrophil extracellular traps, J. Thromb. Haemost. 12 (2014) 2074–2088.
[148] S.-W. Kim, H. Lee, H.-K. Lee, I.-D. Kim, J.-K. Lee, Neutrophil extracellular trap induced by HMGB1 exacerbates damages in the ischemic brain, Acta neuropathologica communications 7 (2019) 94.
[149] G.A. Ramirez, A.A. Manfredi, N. Maugeri, Misunderstandings between platelets and neutrophils build in chronic inflammation, Front. Immunol. 10 (2019).
[150] P. Huebener, J.P. Pradere, C. Hernandez, G.Y. Gwak, J.M. Caviglia, X. Mu, et al., The HMGB1/RAGE axis triggers neutrophil-mediated injury amplification following necrosis, J. Clin. Invest. 125 (2015) 539–550.
[151] O. Elaskalani, N.B. Abdol Razak, P. Metharom, Neutrophil extracellular traps induce aggregation of washed human platelets independently of extracellular DNA and histones, Cell Communication and Signaling 16 (2018) 24.
[152] T.A. Fuchs, A. Brill, D. Duerschmied, D. Schatzberg, M. Monestier, D.D. Myers, et al., Extracellular DNA traps promote thrombosis, Proc. Natl. Acad. Sci. 107 (2010) 15880–15885.
[153] T.J. Gould, Z. Lysov, P.C. Liaw, Extracellular DNA, Histones: double-edged swords in immunothrombosis, J. Thromb. Haemost. 13 (Suppl. 1) (2015) S82–S91.
[154] K. Martinod, D.D. Wagner, Thrombosis: tangled up in NETs, Blood 123 (2014) 2768–2776.
[155] C.T. Ammollo, F. Semeraro, J. Xu, N.L. Esmon, C.T. Esmon, Extracellular histones increase plasma thrombin generation by impairing thrombomodulin-dependent protein C activation, J. Thromb. Haemost. 9 (2011) 1795–1803.
[156] M. Jiménez-Alcázar, N. Kim, T.A. Fuchs, Circulating extracellular DNA: cause or consequence of thrombosis? Semin. Thromb. Hemost. 43 (2017) 553–561.
[157] M.L. van Montfoort, F. Stephan, M.N. Lauw, B.A. Hutten, G.J. Van Mierlo, S. Solati, et al., Circulating nucleosomes and neutrophil activation as risk factors for deep vein thrombosis, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 147–151.
[158] B. Engelmann, S. Massberg, Thrombosis as an intravascular effector of innate immunity, Nat. Rev. Immunol. 13 (2013) 34–45.
[159] A.S. Kimball, A.T. Obi, J.A. Diaz, P.K. Henke, The emerging role of NETs in venous thrombosis and immunothrombosis, Front. Immunol. 7 (2016).
[160] A. Assinger, W.C. Schrottmaier, M. Salzmann, J. Rayes, Platelets in sepsis: an update on experimental models and clinical data, Front. Immunol. 10 (2019) 1687.
[161] A. Dewitte, S. Lepreux, J. Villeneuve, C. Rigothier, C. Combe, A. Ouattara, et al., Blood platelets and sepsis pathophysiology: a new therapeutic prospect in critically [corrected] ill patients? Ann. Intensive Care 7 (2017) (115-).
[162] M.Y. Lim, K.I. Ataga, N.S. Key, Hemostatic abnormalities in sickle cell disease, Curr. Opin. Hematol. 20 (2013) 472–477.
[163] S. Pfeiler, S. Massberg, B. Engelmann, Biological basis and pathological relevance of microvascular thrombosis, Thromb. Res. 133 (2014) S35-S7.
[164] P. Prabhakaran, L.B. Ware, K.E. White, M.T. Cross, M.A. Matthay, M.A. Olman, Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury, Am. J. Phys. Lung Cell. Mol. Phys. 285 (2003) L20-L8.
[165] A. Sapru, M.A.Q. Curley, S. Brady, M.A. Matthay, H. Flori, Elevated PAI-1 is associated with poor clinical outcomes in pediatric patients with acute lung injury, Intensive Care Med. 36 (2010) 157–163.
[166] M. Xue, Z. Sun, M. Shao, J. Yin, Z. Deng, J. Zhang, et al., Diagnostic and prognostic utility of tissue factor for severe sepsis and sepsis-induced acute lung injury, J. Transl. Med. 13 (2015) 172.
[167] H. Yadav, D.J. Kor, Platelets in the pathogenesis of acute respiratory distress syndrome, Am. J. Physiol. Lung Cell. Mol. Physiol. 309 (2015) L915-L23.
[168] C. Brun-Buisson, C. Minelli, G. Bertolini, L. Brazzi, J. Pimentel, K. Lewandowski, et al., Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study, Intensive Care Med. 30 (2004) 51–61.
[169] J. Doorduin, J.L. Nollet, M.P.A.J. Vugts, L.H. Roesthuis, F. Akankan, J.G. van der Hoeven, et al., Assessment of dead-space ventilation in patients with acute respiratory distress syndrome: a prospective observational study, Critical care (London, England) 20 (2016) (121-).
[170] A. Ozolina, M. Sarkele, O. Sabelnikovs, A. Skesters, I. Jaunalksne, J. Serova, et al., Activation of coagulation and fibrinolysis in acute respiratory distress syndrome: A prospective pilot study, Front Med (Lausanne). 3 (2016) (64-).
[171] M. Sarkar, N. Niranjan, P.K. Banyal, Mechanisms of hypoxemia, Lung India 34 (2017) 47–60.
[172] S. Gando, Y. Otomo, Local hemostasis, immunothrombosis, and systemic disseminated intravascular coagulation in trauma and traumatic shock, Critical care (London, England) 19 (2015) (72-).
[173] T. Ito, PAMPs and DAMPs as triggers for DIC, J. Intensive Care 2 (2014) (67-).
[174] I. Bendib, L. de Chaisemartin, V. Granger, F. Schlemmer, B. Maitre, S. Hue, et al., Neutrophil extracellular traps are elevated in patients with pneumonia-related acute respiratory distress syndrome, Anesthesiology 130 (2019) 581–591.
[175] F. Ebrahimi, S. Giaglis, S. Hahn, C.A. Blum, C. Baumgartner, A. Kutz, et al., Markers of neutrophil extracellular traps predict adverse outcome in community-

acquired pneumonia: secondary analysis of a randomised controlled trial, Eur. Respir. J. 51 (2018) 1701389.
[176] C. Mikacenic, R. Moore, V. Dmyterko, T.E. West, W.A. Altemeier, W.C. Liles, et al., Neutrophil extracellular traps (NETs) are increased in the alveolar spaces of patients with ventilator-associated pneumonia, Critical care (London, England) 22 (2018) 358.
[177] C. Brostjan, R. Oehler, The role of neutrophil death in chronic inflammation and cancer, Cell Death Dis. 6 (2020) (26-).
[178] H.-H. Peng, Y.-J. Liu, D.M. Ojcius, C.-M. Lee, R.-H. Chen, P.-R. Huang, et al., Mineral particles stimulate innate immunity through neutrophil extracellular traps containing HMGB1, Sci. Rep. 7 (2017) 16628.
[179] Y. Jin, M. Sun, X. Jiang, Q. Zhang, D. Feng, Z. Wen, Extracellular histones aggravate acute respiratory distress syndrome by inducing peripheral blood mononuclear cells pyroptosis, Zhonghua wei zhong bing ji jiu yi xue 31 (2019) 1357–1362.
[180] X. Lv, T. Wen, J. Song, D. Xie, L. Wu, X. Jiang, et al., Extracellular histones are clinically relevant mediators in the pathogenesis of acute respiratory distress syndrome, Respir. Res. 18 (2017) 165.
[181] H. Zhang, J. Villar, A.S. Slutsky, Circulating histones: a novel target in acute respiratory distress syndrome? Am. J. Respir. Crit. Care Med. 187 (2013) 118–120.
[182] R. Allam, C.R. Scherbaum, M.N. Darisipudi, S.R. Mulay, H. Hagele, J. Lichtnekert, et al., Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4, J Am Soc Nephrol 23 (2012) 1375–1388.
[183] P. Szatmary, W. Huang, D. Criddle, A. Tepikin, R. Sutton, Biology, role and therapeutic potential of circulating histones in acute inflammatory disorders, J. Cell. Mol. Med. 22 (2018) 4617–4629.
[184] R. Allam, M.N. Darisipudi, J. Tschopp, H.J. Anders, Histones trigger sterile inflammation by activating the NLRP3 inflammasome, Eur. J. Immunol. 43 (2013) 3336–3342.
[185] Z. Xu, Y. Huang, P. Mao, J. Zhang, Y. Li, Sepsis and ARDS: the dark side of histones, Mediat. Inflamm. 2015 (2015) (205054-).
[186] T.J. Standiford, P.A. Ward, Therapeutic targeting of acute lung injury and acute respiratory distress syndrome, Transl. Res. 167 (2016) 183–191.
[187] K. Nakahira, S.-Y. Kyung, A.J. Rogers, L. Gazourian, S. Youn, A.F. Massaro, et al., Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation, PLoS Med. 10 (2013) (e1001577-e).
[188] H.P. Yan, M. Li, X.L. Lu, Y.M. Zhu, W.-X. Ou-yang, Zh. Xiao, et al., Use of plasma mitochondrial DNA levels for determining disease severity and prognosis in pediatric sepsis: a case control study, BMC Pediatr. 18 (2018) 267.
[189] H.E. Faust, J.P. Reilly, B.J. Anderson, C.A.G. Ittner, C.M. Forker, P. Zhang, et al., Plasma mitochondrial DNA levels are associated with ARDS in trauma and Sepsis patients, Chest 157 (2020) 67–76.
[190] J.D. Simmons, D.R. Freno, C.A. Muscat, B. Obiako, Y.-L.L. Lee, V.M. Pastukh, et al., Mitochondrial DNA damage associated molecular patterns in ventilator-associated pneumonia: prevention and reversal by intratracheal DNase I, J. Trauma Acute Care Surg. 82 (2017) 120–125.
[191] S. Grazioli, J. Pugin, Mitochondrial damage-associated molecular patterns: from inflammatory signaling to human diseases, Front. Immunol. 9 (2018) (832-).
[192] U. Andersson, K.J. Tracey, HMGB1 is a therapeutic target for sterile inflammation and infection, Annu. Rev. Immunol. 29 (2011) 139–162.
[193] C.C. Tseng, W.F. Fang, S.Y. Leung, H.C. Chen, Y.C. Chang, C.C. Wang, et al., Impact of serum biomarkers and clinical factors on intensive care unit mortality and 6-month outcome in relatively healthy patients with severe pneumonia and acute respiratory distress syndrome, Dis. Markers 2014 (2014) 804654.
[194] H. Wang, M.F. Ward, A.E. Sama, Targeting HMGB1 in the treatment of sepsis, Expert Opin. Ther. Targets 18 (2014) 257–268.
[195] S. Zhu, W. Li, M.F. Ward, A.E. Sama, H. Wang, High mobility group box 1 protein as a potential drug target for infection- and injury-elicited inflammation, Inflamm. Allergy Drug Targets 9 (2010) 60–72.
[196] D.S. Pisetsky, The translocation of nuclear molecules during inflammation and cell death, Antioxid. Redox Signal. 20 (2014) 1117–1125.
[197] M. Grégoire, F. Uhel, M. Lesouhaitier, A. Gacouin, M. Guirriec, F. Mourcin, et al., Impaired efferocytosis and neutrophil extracellular trap clearance by macrophages in ARDS, Eur. Respir. J. 52 (2018) 1702590.
[198] B.N.V. Scott, P. Kubes, Death to the neutrophil! A resolution for acute respiratory distress syndrome? Eur. Respir. J. 52 (2018) 1801274.
[199] R. Duffin, A.E. Leitch, S. Fox, C. Haslett, A.G. Rossi, Targeting granulocyte apoptosis: mechanisms, models, and therapies, Immunol. Rev. 236 (2010) 28–40.
[200] L. Fialkow, L. Fochesatto Filho, M.C. Bozzetti, A.R. Milani, E.M. Rodrigues Filho, R.M. Ladniuk, et al., Neutrophil apoptosis: a marker of disease severity in sepsis and sepsis-induced acute respiratory distress syndrome, Critical care (London, England) 10 (2006) R155.
[201] L. Galluzzi, I. Vitale, S.A. Aaronson, J.M. Abrams, D. Adam, P. Agostinis, et al., Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018, Cell Death Differ. 25 (2018) 486–541.
[202] G. Matute-Bello, W.C. Liles, F. Radella 2nd, K.P. Steinberg, J.T. Ruzinski, L.D. Hudson, et al., Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome, Crit. Care Med. 28 (2000) 1–7.
[203] L. Liu, B. Sun, Neutrophil pyroptosis: new perspectives on sepsis, Cell. Mol. Life Sci. 76 (2019) 2031–2042.
[204] J.C. Ryu, M.J. Kim, Y. Kwon, J.H. Oh, S.S. Yoon, S.J. Shin, et al., Neutrophil pyroptosis mediates pathology of P. aeruginosa lung infection in the absence of the NADPH oxidase NOX2, Mucosal Immunol. 10 (2017) 757–774.
[205] N. Germic, Z. Frangez, S. Yousefi, H.-U. Simon, Regulation of the innate immune system by autophagy: neutrophils, eosinophils, mast cells, NK cells, Cell Death Differ. 26 (2019) 703–714.
[206] X. Wang, Z. He, H. Liu, S. Yousefi, H.-U. Simon, Neutrophil necroptosis is triggered by ligation of adhesion molecules following GM-CSF priming, J. Immunol. 197 (2016) 4090–4100.
[207] H. Wang, T. Li, S. Chen, Y. Gu, S. Ye, Neutrophil extracellular trap mitochondrial DNA and its autoantibody in systemic lupus erythematosus and a proof-of-concept trial of metformin, Arthritis Rheum. 67 (2015) 3190–3200.
[208] S. Yousefi, C. Mihalache, E. Kozlowski, I. Schmid, H.U. Simon, Viable neutrophils release mitochondrial DNA to form neutrophil extracellular traps, Cell Death Differ. 16 (2009) 1438–1444.
[209] R. Grecian, M.K.B. Whyte, S.R. Walmsley, The role of neutrophils in cancer, Br. Med. Bull. 128 (2018) 5–14.
[210] A. Friggeri, Y. Yang, S. Banerjee, Y.J. Park, G. Liu, E. Abraham, HMGB1 inhibits macrophage activity in efferocytosis through binding to the alphavbeta3-integrin, Am. J. Physiol. Cell Physiol. 299 (2010) C1267–C1276.
[211] G. Liu, J. Wang, Y.-J. Park, Y. Tsuruta, E.F. Lorne, X. Zhao, et al., High mobility group protein-1 inhibits phagocytosis of apoptotic neutrophils through binding to phosphatidylserine, Journal of immunology (Baltimore, Md: 1950) 181 (2008) 4240–4246.
[212] F. Schaper, K. de Leeuw, G. Horst, H. Bootsma, P.C. Limburg, P. Heeringa, et al., High mobility group box 1 skews macrophage polarization and negatively influences phagocytosis of apoptotic cells, Rheumatology (Oxford) 55 (2016) 2260–2270.
[213] R. Mahida, D. Thickett, Differential effect of ARDS on alveolar macrophage efferocytosis compared to bacterial phagocytosis, Eur. Respir. J. 52 (2018) (LSC-1043).
[214] R. Mahida, D. Thickett, Impaired alveolar macrophage efferocytosis in ARDS causes accumulation of apoptotic neutrophils & prolonged inflammation, Eur. Respir. J. 52 (2018) PA4283.
[215] P.M. Potey, A.G. Rossi, C.D. Lucas, D.A. Dorward, Neutrophils in the initiation and resolution of acute pulmonary inflammation: understanding biological function and therapeutic potential, J. Pathol. 247 (2019) 672–685.
[216] M.R. Elliott, K.M. Koster, P.S. Murphy, Efferocytosis signaling in the regulation of macrophage inflammatory responses, J. Immunol. 198 (2017) 1387–1394.
[217] M.C. Greenlee-Wacker, Clearance of apoptotic neutrophils and resolution of inflammation, Immunol. Rev. 273 (2016) 357–370.
[218] M.T. Silva, Macrophage phagocytosis of neutrophils at inflammatory/infectious foci: a cooperative mechanism in the control of infection and infectious inflammation, J. Leukoc. Biol. 89 (2011) 675–683.
[219] D.M. Boe, B.J. Curtis, M.M. Chen, J.A. Ippolito, E.J. Kovacs, Extracellular traps and macrophages: new roles for the versatile phagocyte, J. Leukoc. Biol. 97 (2015) 1023–1035.
[220] C. Farrera, B. Fadeel, Macrophage clearance of neutrophil extracellular traps is a silent process, J. Immunol. 191 (2013) 2647–2656.
[221] J. Ding, X. Cui, Q. Liu, Emerging role of HMGB1 in lung diseases: friend or foe, J. Cell. Mol. Med. 21 (2017) 1046–1057.
[222] J. Kim, J. Song, M. Lee, Combinational delivery of HMGB1 A box and heparin for acute lung injury, J. Control. Release 213 (2015) e57.
[223] Y.-H. Ma, T.-T. Ma, C. Wang, H. Wang, D.-Y. Chang, M. Chen, et al., High-mobility group box 1 potentiates antineutrophil cytoplasmic antibody-inducing neutrophil extracellular traps formation, Arthritis research & therapy 18 (2016) (2-).
[224] Smit PJ, Guo WA, Davidson BA, Mullan BA, Helinski JD, Knight PR, 3rd. Dietary advanced glycation end-products, its pulmonary receptor, and high mobility group box 1 in aspiration lung injury. J. Surg. Res. 2014;191:214–23.
[225] K. McPhillips, W.J. Janssen, M. Ghosh, A. Byrne, S. Gardai, L. Remigio, et al., TNF-alpha inhibits macrophage clearance of apoptotic cells via cytosolic phospholipase A2 and oxidant-dependent mechanisms, J. Immunol. 178 (2007) 8117–8126.
[226] S. Michlewska, I. Dransfield, I.L. Megson, A.G. Rossi, Macrophage phagocytosis of apoptotic neutrophils is critically regulated by the opposing actions of pro-inflammatory and anti-inflammatory agents: key role for TNF-alpha, FASEB J. 23 (2009) 844–854.
[227] R. Li, Y. Shang, Y. Yu, T. Zhou, W. Xiong, X. Zou, High-mobility group box 1 protein participates in acute lung injury by activating protein kinase R and inducing M1 polarization, Life Sci. 246 (2020) 117415.
[228] Z. Su, P. Zhang, Y. Yu, H. Lu, Y. Liu, P. Ni, et al., HMGB1 facilitated macrophage reprogramming towards a proinflammatory M1-like phenotype in experimental autoimmune myocarditis development, Sci. Rep. 6 (2016) 21884.
[229] J. Wang, R. Li, Z. Peng, B. Hu, X. Rao, J. Li, HMGB1 participates in LPS-induced acute lung injury by activating the AIM2 inflammasome in macrophages and inducing polarization of M1 macrophages via TLR2, TLR4, and RAGE/NF-κB signaling pathways, Int. J. Mol. Med. 45 (2020) 61–80.
[230] Y. Yao, X.-H. Xu, L. Jin, Macrophage polarization in physiological and pathological pregnancy, Front. Immunol. 10 (2019) (792-).
[231] A. Ait-Lounis, F. Laraba-Djebari, TNF-alpha modulates adipose macrophage polarization to M1 phenotype in response to scorpion venom, Inflamm. Res. 64 (2015) 929–936.
[232] Y. Degboé, B. Rauwel, M. Baron, J.-F. Boyer, A. Ruyssen-Witrand, A. Constantin, et al., Polarization of rheumatoid macrophages by TNF targeting through an IL-10/STAT3 mechanism, Front. Immunol. 10 (2019).
[233] J. Braune, U. Weyer, C. Hobusch, J. Mauer, J.C. Brüning, I. Bechmann, et al., IL-6 regulates M2 polarization and local proliferation of adipose tissue macrophages in obesity, J. Immunol. 198 (2017) 2927–2934.
[234] L. Luckett-Chastain, K. Calhoun, T. Schartz, R.M. Gallucci, IL-6 influences the balance between M1 and M2 macrophages in a mouse model of irritant contact dermatitis, J. Immunol. 196 (196) (2016) (17-.17).
[235] I. Guijarro-Muñoz, M. Compte, A. Álvarez-Cienfuegos, L. Álvarez-Vallina, L. Sanz,

Lipopolysaccharide activates toll-like receptor 4 (TLR4)-mediated NF-κB signaling pathway and proinflammatory response in human pericytes, J. Biol. Chem. 289 (2013) 2457–2468.
[236] Z.-W. He, Y.-H. Qin, Z.-W. Wang, Y. Chen, Q. Shen, S.-M. Dai, HMGB1 acts in synergy with lipopolysaccharide in activating rheumatoid synovial fibroblasts via p38 MAPK and NF-κB signaling pathways, Mediat. Inflamm. 2013 (2013) 1–10.
[237] S. Mulrennan, S. Baltic, S. Aggarwal, J. Wood, A. Miranda, F. Frost, et al., The role of receptor for advanced glycation end products in airway inflammation in CF and CF related diabetes, Sci. Rep. 5 (2015).
[238] T. Pusterla, J. Nèmeth, I. Stein, L. Wiechert, D. Knigin, S. Marhenke, et al., Receptor for advanced glycation endproducts (RAGE) is a key regulator of oval cell activation and inflammation-associated liver carcinogenesis in mice, Hepatology 58 (2013) 363–373.
[239] M. Entezari, M. Javdan, D.J. Antoine, D.M.P. Morrow, R.A. Sitapara, V. Patel, et al., Inhibition of extracellular HMGB1 attenuates hyperoxia-induced inflammatory acute lung injury, Redox Biol. 2 (2014) 314–322.
[240] S. Lee, C. Piao, G. Kim, J.Y. Kim, E. Choi, M. Lee, Production and application of HMGB1 derived recombinant RAGE-antagonist peptide for anti-inflammatory therapy in acute lung injury, Eur. J. Pharm. Sci. 114 (2018) 275–284.
[241] Z. Luan, B. Hu, L. Wu, S. Jin, X. Ma, J. Zhang, et al., Unfractionated heparin alleviates human lung endothelial barrier dysfunction induced by high mobility group box 1 through regulation of P38–GSK3β–snail signaling pathway, Cell. Physiol. Biochem. 46 (2018) 1907–1918.
[242] L. Qu, C. Chen, Y. Chen, Y. Li, F. Tang, H. Huang, et al., High-mobility group box 1 (HMGB1) and autophagy in acute Lung injury (ALI): A review, Med. Sci. Monit. 25 (2019) 1828–1837.
[243] K. Lucas, G. Morris, G. Anderson, M. Maes, The toll-like receptor radical cycle pathway: a new drug target in immune-related chronic fatigue, CNS & Neurological Disorders - Drug Targets (Formerly Current Drug Targets) 14 (2015) 838–854.
[244] Y. Long, X. Liu, X.-Z. Tan, C.-X. Jiang, S.-W. Chen, G.-N. Liang, et al., ROS-induced NLRP3 inflammasome priming and activation mediate PCB 118- induced pyroptosis in endothelial cells, Ecotoxicol. Environ. Saf. 189 (2020) 109937.
[245] Y. Wang, P. Shi, Q. Chen, Z. Huang, D. Zou, J. Zhang, et al., Mitochondrial ROS promote macrophage pyroptosis by inducing GSDMD oxidation, J. Mol. Cell Biol. 11 (2019) 1069–1082.
[246] T. Dolinay, Y.S. Kim, J. Howrylak, G.M. Hunninghake, C.H. An, L. Fredenburgh, et al., Inflammasome-regulated cytokines are critical mediators of acute lung injury, Am. J. Respir. Crit. Care Med. 185 (2012) 1225–1234.
[247] J.J. Grailer, B.A. Canning, M. Kalbitz, M.D. Haggadone, R.M. Dhond, A.V. Andjelkovic, et al., Critical role for the NLRP3 inflammasome during acute lung injury, J. Immunol. 192 (2014) 5974–5983.
[248] H. Makabe, M. Kojika, G. Takahashi, N. Matsumoto, S. Shibata, Y. Suzuki, et al., Interleukin-18 levels reflect the long-term prognosis of acute lung injury and acute respiratory distress syndrome, J. Anesth. 26 (2012) 658–663.
[249] V. Kumar, Inflammasomes: Pandora's box for sepsis, J. Inflamm. Res. 11 (2018) 477–502.
[250] L. Jin, S. Batra, S. Jeyaseelan, Deletion of Nlrp3 augments survival during polymicrobial sepsis by decreasing autophagy and enhancing phagocytosis, J. Immunol. 198 (2017) 1253–1262.
[251] M.J. Kim, S.H. Bae, J.C. Ryu, Y. Kwon, J.H. Oh, J. Kwon, et al., SESN2/sestrin2 suppresses sepsis by inducing mitophagy and inhibiting NLRP3 activation in macrophages, Autophagy 12 (2016) 1272–1291.
[252] L.G. Danielski, A.D. Giustina, S. Bonfante, T. Barichello, F. Petronilho, The NLRP3 inflammasome and its role in sepsis development, Inflammation 43 (2020) 24–31.
[253] L. Hou, Z. Yang, Z. Wang, X. Zhang, Y. Zhao, H. Yang, et al., NLRP3/ASC-mediated alveolar macrophage pyroptosis enhances HMGB1 secretion in acute lung injury induced by cardiopulmonary bypass, Lab. Investig. 98 (2018) 1052–1064.
[254] T. Traeger, W. Kessler, A. Hilpert, M. Mikulcak, M. Entleutner, P. Koerner, et al., Selective depletion of alveolar macrophages in polymicrobial sepsis increases lung injury, bacterial load and mortality but does not affect cytokine release, Respiration 77 (2009) 203–213.
[255] D.-D. Wu, P.-H. Pan, B. Liu, X.-L. Su, L.-M. Zhang, H.-Y. Tan, et al., Inhibition of alveolar macrophage pyroptosis reduces lipopolysaccharide-induced acute lung injury in mice, Chin. Med. J. 128 (2015) 2638–2645.
[256] W. Zhang, C.M. Coopersmith, Dying as a pathway to death in sepsis, Anesthesiology 129 (2018) 238–240.
[257] Z. Li, M.J. Scott, E.K. Fan, Y. Li, J. Liu, G. Xiao, et al., Tissue damage negatively regulates LPS-induced macrophage necroptosis, Cell Death Differ. 23 (2016) 1428–1447.
[258] A. Linkermann, B.R. Stockwell, S. Krautwald, H.-J. Anders, Regulated cell death and inflammation: an auto-amplification loop causes organ failure, Nat. Rev. Immunol. 14 (2014) 759–767.
[259] J. Xu, Y. Jiang, J. Wang, X. Shi, Q. Liu, Z. Liu, et al., Macrophage endocytosis of high-mobility group box 1 triggers pyroptosis, Cell Death Differ. 21 (2014) 1229–1239.
[260] J. Yang, Y. Zhao, P. Zhang, Y. Li, Y. Yang, Y. Yang, et al., Hemorrhagic shock primes for lung vascular endothelial cell pyroptosis: role in pulmonary inflammation following LPS, Cell Death Dis. 7 (2016) (e2363-e).
[261] A.C. McQuattie-Pimentel, G.R.S. Budinger, M.N. Ballinger, Monocyte-derived alveolar macrophages: the dark side of Lung repair? Am. J. Respir. Cell Mol. Biol. 58 (2018) 5–6.
[262] D. Schulz, Y. Severin, V.R.T. Zanotelli, B. Bodenmiller, In-depth characterization of monocyte-derived macrophages using a mass cytometry-based phagocytosis assay, Sci. Rep. 9 (2019) (1925-).
[263] G. Hu, J.W. Christman, Editorial: alveolar macrophages in Lung inflammation and resolution, Front. Immunol. 10 (2019).
[264] H. Wang, H. Yang, C.J. Czura, A.E. Sama, K.J. Tracey, HMGB1 as a late mediator of lethal systemic inflammation, Am. J. Respir. Crit. Care Med. 164 (2001) 1768–1773.
[265] H. Yang, H. Wang, C.J. Czura, K.J. Tracey, The cytokine activity of HMGB1, J. Leukoc. Biol. 78 (2005) 1–8.
[266] L. Vande Walle, T.-D. Kanneganti, M. Lamkanfi, HMGB1 release by inflammasomes, Virulence 2 (2011) 162–165.
[267] K. Newton, G. Manning, Necroptosis and inflammation, Annu. Rev. Biochem. 85 (2016) 743–763.
[268] K. Zhu, W. Liang, Z. Ma, D. Xu, S. Cao, X. Lu, et al., Necroptosis promotes cell-autonomous activation of proinflammatory cytokine gene expression, Cell Death Dis. 9 (2018) 500.
[269] B. Wang, J. Li, H.-M. Gao, Y.-H. Xing, Z. Lin, H.-J. Li, et al., Necroptosis regulated proteins expression is an early prognostic biomarker in patient with sepsis: a prospective observational study, Oncotarget 8 (2017) 84066–84073.
[270] J. Reilly, M. Shashaty, B. Anderson, J. Palakshappa, M. Hotz, J. Christie, et al., 1344: plasma RIP3, A regulator of necroptosis, is associated with mortality & organ dysfunction in sepsis, Crit. Care Med. 44 (2016) 411.
[271] L. Duprez, N. Takahashi, F. Van Hauwermeiren, B. Vandendriessche, V. Goossens, T. Vanden Berghe, et al., RIP kinase-dependent necrosis drives lethal systemic inflammatory response syndrome, Immunity 35 (2011) 908–918.
[272] K.C. Ma, E.J. Schenck, I.I. Siempos, S.M. Cloonan, E.J. Finkelsztein, M.A. Pabon, et al., Circulating RIPK3 levels are associated with mortality and organ failure during critical illness, JCI Insight 3 (2018).
[273] E.J. Schenck, K.C. Ma, D.R. Price, T. Nicholson, C. Oromendia, E.R. Gentzler, et al., Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis, JCI Insight 4 (2019) e127143.
[274] G. Morris, A.J. Walker, M. Berk, M. Maes, B.K. Puri, Cell death pathways: a novel therapeutic approach for neuroscientists, Mol. Neurobiol. 55 (2018) 5767–5786.
[275] M. Sarhan, W.G. Land, W. Tonnus, C.P. Hugo, A. Linkermann, Origin and consequences of necroinflammation, Physiol. Rev. 98 (2018) 727–780.
[276] H. Chen, Y. Li, J. Wu, G. Li, X. Tao, K. Lai, et al., RIPK3 collaborates with GSDMD to drive tissue injury in lethal polymicrobial sepsis, Cell Death Differ. (2020) (Online ahead of print).
[277] T. Maj, W. Wang, J. Crespo, H. Zhang, W. Wang, S. Wei, et al., Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor, Nat. Immunol. 18 (2017) 1332–1341.
[278] M.A. Moro-García, J.C. Mayo, R.M. Sainz, R. Alonso-Arias, Influence of inflammation in the process of T lymphocyte differentiation: proliferative, metabolic, and oxidative changes, Front. Immunol. 9 (2018).
[279] G. Morris, G. Anderson, P. Galecki, M. Berk, M. Maes, A narrative review on the similarities and dissimilarities between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and sickness behavior, BMC Med. 11 (2013) (64-).
[280] G. Morris, M. Berk, P. Galecki, M. Maes, The emerging role of autoimmunity in myalgic encephalomyelitis/chronic fatigue syndrome (ME/cfs), Mol. Neurobiol. 49 (2014) 741–756.
[281] G. Morris, E.M.V. Reiche, A. Murru, A.F. Carvalho, M. Maes, M. Berk, et al., Multiple immune-inflammatory and oxidative and nitrosative stress pathways explain the frequent presence of depression in multiple sclerosis, Mol. Neurobiol. 55 (2018) 6282–6306.
[282] A. Saeidi, K. Zandi, Y.Y. Cheok, H. Saeidi, W.F. Wong, C.Y.Q. Lee, et al., T-cell exhaustion in chronic infections: reversing the state of exhaustion and reinvigorating optimal protective immune responses, Front. Immunol. 9 (2018).
[283] S. Lin, H. Wu, C. Wang, Z. Xiao, F. Xu, Regulatory T cells and acute Lung injury: cytokines, uncontrolled inflammation, and therapeutic implications, Front. Immunol. 9 (2018) (1545-).
[284] J.J.M. Wong, J.Y. Leong, J.H. Lee, S. Albani, J.G. Yeo, Insights into the immunopathogenesis of acute respiratory distress syndrome, Ann Transl Med 7 (2019) 4.
[285] C. Mikacenic, E.E. Hansen, F. Radella, S.A. Gharib, R.D. Stapleton, M.M. Wurfel, Interleukin-17A is associated with alveolar inflammation and poor outcomes in acute respiratory distress syndrome, Crit. Care Med. 44 (2016) 496–502.
[286] C.-C. Chang, W.-J. Lu, E.-T. Ong, C.-W. Chiang, S.-C. Lin, S.-Y. Huang, et al., A novel role of sesamol in inhibiting NF-κB-mediated signaling in platelet activation, J. Biomed. Sci. 18 (2011) 93.
[287] W.-J. Lu, J.-J. Lee, D.-S. Chou, T. Jayakumar, T.-H. Fong, G. Hsiao, et al., A novel role of andrographolide, an NF-kappa B inhibitor, on inhibition of platelet activation: the pivotal mechanisms of endothelial nitric oxide synthase/cyclic GMP, J. Mol. Med. 89 (2011) 1261–1273.
[288] W.J. Lu, K.H. Lin, M.J. Hsu, D.S. Chou, G. Hsiao, J.R. Sheu, Suppression of NF-κB signaling by andrographolide with a novel mechanism in human platelets: regulatory roles of the p38 MAPK-hydroxyl radical-ERK2 cascade, Biochem. Pharmacol. 84 (2012) 914–924.
[289] E. Malaver, M.A. Romaniuk, L.P. D'Atri, R.G. Pozner, S. Negrotto, R. BenzadÓN, et al., NF-κB inhibitors impair platelet activation responses, J. Thromb. Haemost. 7 (2009) 1333–1343.
[290] S.L. Spinelli, A.E. Casey, S.J. Pollock, J.M. Gertz, D.H. McMillan, S.D. Narasipura, et al., Platelets and megakaryocytes contain functional nuclear factor-kappaB, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 591–598.
[291] S. von Vietinghoff, M. Asagiri, D. Azar, A. Hoffmann, K. Ley, Defective regulation of CXCR2 facilitates neutrophil release from bone marrow causing spontaneous inflammation in severely NF-κB–deficient mice, J. Immunol. 185 (2010) 670–678.
[292] D. Wang, I. Paz-Priel, A.D. Friedman, NF-κB p50 regulates C/EBPα expression and inflammatory cytokine-induced neutrophil production, J. Immunol. 182 (2009) 5757–5762.
[293] M.J. Lapponi, A. Carestia, V.I. Landoni, L. Rivadeneyra, J. Etulain, S. Negrotto,

et al., Regulation of neutrophil extracellular trap formation by anti-inflammatory drugs, J. Pharmacol. Exp. Ther. 345 (2013) 430–437.
[294] B.M. Mohammed, B.J. Fisher, D. Kraskauskas, D. Farkas, D.F. Brophy, A.A. Fowler 3rdet al., Vitamin C: a novel regulator of neutrophil extracellular trap formation, Nutrients 5 (2013) 3131–3151.
[295] P. Moine, R. McIntyre, M.D. Schwartz, D. Kaneko, R. Shenkar, Y. Le Tulzo, et al., NF-kappaB regulatory mechanisms in alveolar macrophages from patients with acute respiratory distress syndrome, Shock (Augusta, Ga) 13 (2000) 85–91.
[296] M.D. Schwartz, E.E. Moore, F.A. Moore, R. Shenkar, P. Moine, J.B. Haenel, et al., Nuclear factor-kappa B is activated in alveolar macrophages from patients with acute respiratory distress syndrome, Crit. Care Med. 24 (1996) 1285–1292.
[297] T. Liu, L. Zhang, D. Joo, S.-C. Sun, NF-κB signaling in inflammation, Signal Transduction and Targeted Therapy 2 (2017) 17023.
[298] S. Takashiba, T.E. Van Dyke, S. Amar, Y. Murayama, A.W. Soskolne, L. Shapira, Differentiation of monocytes to macrophages primes cells for lipopolysaccharide stimulation via accumulation of cytoplasmic nuclear factor kappaB, Infect. Immun. 67 (1999) 5573–5578.
[299] Y. He, H. Hara, G. Nunez, Mechanism and regulation of NLRP3 inflammasome activation, Trends Biochem. Sci. 41 (2016) 1012–1021.
[300] Y. Gao, H. Zhang, L. Luo, J. Lin, D. Li, S. Zheng, et al., Resolvin D1 improves the resolution of inflammation via activating NF-κB p50/p50–mediated cyclooxygenase-2 expression in acute respiratory distress syndrome, J. Immunol. 199 (2017) 2043–2054.
[301] R.K. Mishra, H.R. Potteti, C.R. Tamatam, I. Elangovan, S.P. Reddy, C-Jun is required for nuclear factor-kappaB-dependent, LPS-stimulated Fos-related Antigen-1 transcription in alveolar macrophages, Am. J. Respir. Cell Mol. Biol. 55 (2016) 667–674.
[302] V. Pooladanda, S. Thatikonda, S. Bale, B. Pattnaik, D.K. Sigalapalli, N.B. Bathini, et al., Nimbolide protects against endotoxin-induced acute respiratory distress syndrome by inhibiting TNF-α mediated NF-κB and HDAC-3 nuclear translocation, Cell Death Dis. 10 (2019) 81.
[303] G. Umberto Meduri, W. Bell, S. Sinclair, D. Annane, Pathophysiology of acute respiratory distress syndrome. Glucocorticoid receptor-mediated regulation of inflammation and response to prolonged glucocorticoid treatment, Presse medicale (Paris, France: 1983) 40 (2011) e543–e560.
[304] G.U. Meduri, D. Annane, G.P. Chrousos, P.E. Marik, S.E. Sinclair, Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy, Chest 136 (2009) 1631–1643.
[305] S.F. Liu, A.B. Malik, NF-kappa B activation as a pathological mechanism of septic shock and inflammation, Am. J. Physiol. Lung Cell. Mol. Physiol. 290 (2006) L622–l45.
[306] F. Steinhagen, S.V. Schmidt, J.-C. Schewe, K. Peukert, D.M. Klinman, C. Bode, Immunotherapy in sepsis - brake or accelerate? Pharmacol. Ther. 208 (2020) 107476.
[307] S. Bao, M.J. Liu, B. Lee, B. Besecker, J.P. Lai, D.C. Guttridge, et al., Zinc modulates the innate immune response in vivo to polymicrobial sepsis through regulation of NF-kappaB, Am. J. Physiol. Lung Cell. Mol. Physiol. 298 (2010) L744–L754.
[308] D.L. Knoell, M.-J. Liu, Impact of zinc metabolism on innate immune function in the setting of sepsis, International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung Journal international de vitaminologie et de nutrition 80 (2010) 271–277.
[309] M.J. Liu, S. Bao, J.R. Napolitano, D.L. Burris, L. Yu, S. Tridandapani, et al., Zinc regulates the acute phase response and serum amyloid A production in response to sepsis through JAK-STAT3 signaling, PLoS One 9 (2014) e94934.
[310] B.Y. Besecker, M.C. Exline, J. Hollyfield, G. Phillips, R.A. Disilvestro, M.D. Wewers, et al., A comparison of zinc metabolism, inflammation, and disease severity in critically ill infected and noninfected adults early after intensive care unit admission, Am. J. Clin. Nutr. 93 (2011) 1356–1364.
[311] M.A. Cirino Ruocco, E.D. Pacheco Cechinatti, F. Barbosa Jr., A.M. Navarro, Zinc and selenium status in critically ill patients according to severity stratification, Nutrition (Burbank, Los Angeles County, Calif) 45 (2018) 85–89.
[312] T.P. Shanley, N. Cvijanovich, R. Lin, G.L. Allen, N.J. Thomas, A. Doctor, et al., Genome-level longitudinal expression of signaling pathways and gene networks in pediatric septic shock, Molecular medicine (Cambridge, Mass) 13 (2007) 495–508.
[313] H.R. Wong, T.P. Shanley, B. Sakthivel, N. Cvijanovich, R. Lin, G.L. Allen, et al., Genome-level expression profiles in pediatric septic shock indicate a role for altered zinc homeostasis in poor outcome, Physiol. Genomics 30 (2007) 146–155.
[314] A. Ang, J.M. Pullar, M.J. Currie, M.C.M. Vissers, Vitamin C and immune cell function in inflammation and cancer, Biochem. Soc. Trans. 46 (2018) 1147–1159.
[315] S.-O. Kuhn, K. Meissner, L.M. Mayes, K. Bartels, Vitamin C in sepsis, Curr. Opin. Anaesthesiol. 31 (2018) 55–60.
[316] J.M. Cárcamo, A. Pedraza, O. Bórquez-Ojeda, D.W. Golde, Vitamin C suppresses TNF alpha-induced NF kappa B activation by inhibiting I kappa B alpha phosphorylation, Biochemistry 41 (2002) 12995–13002.
[317] T.E. Ichim, B. Minev, T. Braciak, B. Luna, R. Hunninghake, N.A. Mikirova, et al., Intravenous ascorbic acid to prevent and treat cancer-associated sepsis? J. Transl. Med. 9 (2011) 25.
[318] J.A. Kempker, J.E. Han, V. Tangpricha, T.R. Ziegler, G.S. Martin, Vitamin D and sepsis: an emerging relationship, Dermatoendocrinol 4 (2012) 101–108.
[319] P. Nair, B. Venkatesh, D.J. Hoechter, H. Buscher, S. Kerr, J.R. Center, et al., Vitamin D status and supplementation in adult patients receiving extracorporeal membrane oxygenation, Anaesth. Intensive Care 46 (2018) 589–595.
[320] R. Bergholm, M. Leirisalo-Repo, S. Vehkavaara, S. Mäkimattila, M.-R. Taskinen, H. Yki-Järvinen, Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 1637–1641.
[321] A. Csiszar, M. Wang, E.G. Lakatta, Z. Ungvari, Inflammation and endothelial dysfunction during aging: role of NF-kappaB, J Appl Physiol (1985) 105 (2008) 1333–1341.
[322] N. Goncalves-Mendes, J. Talvas, C. Dualé, A. Guttmann, V. Corbin, G. Marceau, et al., Impact of vitamin D supplementation on influenza vaccine response and immune functions in deficient elderly persons: A randomized placebo-controlled trial, Front. Immunol. 10 (2019).
[323] T. Ishii, K. Itoh, S. Takahashi, H. Sato, T. Yanagawa, Y. Katoh, et al., Transcription factor Nrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages, J. Biol. Chem. 275 (2000) 16023–16029.
[324] W. Ni, S.W. Watts, M. Ng, S. Chen, D.J. Glenn, D.G. Gardner, Elimination of vitamin D receptor in vascular endothelial cells alters vascular function, Hypertension (Dallas, Tex: 1979) 64 (2014) 1290–1298.
[325] P.C. Ilie, S. Stefanescu, L. Smith, The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality, Aging Clin. Exp. Res. (2020) 1–4.
[326] Z.H. Aghai, A. Kode, J.G. Saslow, T. Nakhla, S. Farhath, G.E. Stahl, et al., Azithromycin suppresses activation of nuclear factor-kappa B and synthesis of pro-inflammatory cytokines in tracheal aspirate cells from premature infants, Pediatr. Res. 62 (2007) 483–488.
[327] F.F. Stellari, A. Sala, G. Donofrio, F. Ruscitti, P. Caruso, T.M. Topini, et al., Azithromycin inhibits nuclear factor-κB activation during lung inflammation: an in vivo imaging study, Pharmacol. Res. Perspect. 2 (2014) (e00058-e).
[328] G. Morris, G. Anderson, M. Berk, M. Maes, Coenzyme Q10 depletion in medical and neuropsychiatric disorders: potential repercussions and therapeutic implications, Mol. Neurobiol. 48 (2013) 883–903.
[329] G. Morris, B.K. Puri, A.J. Walker, M. Maes, A.F. Carvalho, K. Walder, et al., Myalgic encephalomyelitis/chronic fatigue syndrome: from pathophysiological insights to novel therapeutic opportunities, Pharmacol. Res. 148 (2019) 104450.
[330] G. Morris, B. Stubbs, C.A. Kohler, K. Walder, A. Slyepchenko, M. Berk, et al., The putative role of oxidative stress and inflammation in the pathophysiology of sleep dysfunction across neuropsychiatric disorders: focus on chronic fatigue syndrome, bipolar disorder and multiple sclerosis, Sleep Med. Rev. 41 (2018) 255–265.
[331] M. Farid, M.B. Reid, Y.-P. Li, E. Gerken, W.J. Durham, Effects of dietary curcumin or N-acetylcysteine on NF-κB activity and contractile performance in ambulatory and unloaded murine soleus, Nutrition & Metabolism 2 (2005) 20.
[332] R.L. Paterson, H.F. Galley, N.R. Webster, The effect of N-acetylcysteine on nuclear factor-κB activation, interleukin-6, interleukin-8, and intercellular adhesion molecule-1 expression in patients with sepsis*, Crit. Care Med. 31 (2003) 2574–2578.
[333] X.-Y. Wu, A.-Y. Luo, Y.-R. Zhou, J.-H. Ren, N-acetylcysteine reduces oxidative stress, nuclear factor-κB activity and cardiomyocyte apoptosis in heart failure, Mol. Med. Rep. 10 (2014) 615–624.
[334] X. Liu, X. Wang, X. Duan, D. Poorun, J. Xu, S. Zhang, et al., Lipoxin A4 and its analog suppress inflammation by modulating HMGB1 translocation and expression in psoriasis, Sci. Rep. 7 (2017) (7100-).
[335] H.P. Sham, K.H. Walker, R.-E.E. Abdulnour, N. Krishnamoorthy, D.N. Douda, P.C. Norris, et al., 15-epi-Lipoxin A(4), resolvin D2, and resolvin D3 induce NF-κB regulators in bacterial pneumonia, Journal of immunology (Baltimore, Md: 1950) 200 (2018) 2757–2766.
[336] L.-C. Wang, R.-L. Jiang, W. Zhang, L.-L. Wei, R.-H. Yang, Effects of aspirin on the expression of nuclear factor-κB in a rat model of acute pulmonary embolism, World J Emerg Med 5 (2014) 229–233.
[337] D. Liao, L. Zhong, T. Duan, R.H. Zhang, X. Wang, G. Wang, et al., Aspirin suppresses the growth and metastasis of osteosarcoma through the NF-κB pathway, Clin. Cancer Res. 21 (2015) 5349–5359.
[338] A. Ornelas, N. Zacharias-Millward, D.G. Menter, J.S. Davis, L. Lichtenberger, D. Hawke, et al., Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention, Cancer Metastasis Rev. 36 (2017) 289–303.