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Review

Role of the renin-angiotensin system in NETosis in the coronavirus disease 2019 (COVID-19)

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ABSTRACT

Myocardial infarction and stroke are the leading causes of death in the world. Numerous evidence has confirmed that hypertension promotes thrombosis and induces myocardial infarction and stroke. Recent findings reveal that neutrophil extracellular traps (NETs) are involved in the induction of myocardial infarction and stroke. Meanwhile, patients with severe COVID-19 suffer from complications such as myocardial infarction and stroke with pathological signs of NETs. Due to the extremely low amount of virus detected in the blood and remote organs (e.g., heart, brain and kidney) in a few cases, it is difficult to explain the mechanism by which the virus triggers NETosis, and there may be a different mechanism than in the lung. A large number of studies have found that the renin-angiotensin system regulates the NETosis at multiple levels in patients with COVID-19, such as endocytosis of SARS-COV-2, abnormal angiotensin II levels, neutrophil activation and procoagulant function at multiple levels, which may contribute to the formation of reticular structure and thrombosis. The treatment of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II type 1 receptor blockers (ARBs) and neutrophil recruitment and active antagonists helps to regulate blood pressure and reduce the risk of net and thrombosis. The review will explore the possible role of the angiotensin system in the formation of NETs in severe COVID-19.

1. Introduction

Severe COVID-19 patients develop acute respiratory distress syndrome, which is a life-threatening situation. Neutrophil extracellular traps (NETs) are considered to be the core factor in the pathophysiology and clinical manifestations of thrombosis and inflammatory damage to the lung, heart, and brain tissues. Studies have revealed that SARS-CoV-2, a coronavirus, directly triggers the formation of NETs in patients with pulmonary embolism [1–5]. The process is dependent on angiotensin-converting enzyme 2 (ACE2), serine protease, viral replication and protein arginine deiminase 4 (PAD4) [1]. The levels of free DNA, myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 (Cit-H3) in sera from patients with COVID-19 are elevated [5]. All autopsy specimens showed pulmonary infiltration of neutrophils and the

Abbreviations: AAA, abdominal aortic aneurysm; ACE2, angiotensin-converting enzyme 2; ACEI, ACE inhibitors; ADAM 17, a disintegrin and metalloprotease domain 17; AGT, angiotensinogen; Ang 1–7, angiotensin 1–7; Ang II, angiotensin II; ARBs, angiotensin receptor blockers; AREs, AU-rich elements; AT1R, angiotensin II type 1 receptor; CDK4/6, cyclin-dependent kinases 4/6; Cit-H3, citrullinated histone H3; cPLA2, cytosolic phospholipase A2; dsDNA, double-stranded DNA; G-CSF, granulocyte colony stimulating factor; GSDMD, gasdermin D; HOCl, hypochlorous acid; IL-8, interleukin-8; LDGs, low-density granulocytes; LDNs, low-density neutrophils; MLKL, mixed lineage kinase domain-like; MPO-DNA, myeloperoxidase-DNA complex; NADPH oxidase, nicotinamide adenine dinucleotide phosphate-oxidase; NE, neutrophil elastase; NETosis, a program for formation of neutrophil extracellular traps; NETs, neutrophil extracellular traps; NEP, neprilysin; NF-κB, Nuclear factor kappaB; PAD4, protein arginine deiminase 4; PDE4, phosphodiesterase 4; PKC, protein kinase C; POP/ PEP, prolyl oligopeptidase/ prolyl endopeptidase; RIPK, receptor interacting protein kinase; PRCP, prolyl carboxypeptidase; RGD motif, Arg-Gly-Asp motif; TNF-α, tumor necrosis factor alpha.

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presence of NETs [1–4]. The low-density neutrophils (LDNs) that cause NETosis have been identified as the driver of lung injury, especially microvascular thrombosis and respiratory dysfunction [4]. Severe SARS-CoV-2 infection also causes microvascular thrombosis in the lung, heart, brain, pancreas, and other tissues, and induces multiorgan dysfunction, such as ST-elevation myocardial infarction [6–8], stroke [9, 10], and new-onset diabetes [11,12].

Alveolar type II epithelial cells are the main target cells after SARS-CoV-2 infection. Cell death and marked innate immune responses during infection may lead to alveolar damage [13,14], alveolar collapse [15], restricted oxygen diffusion exchange [16] and silent hypoxia [16]. SARS-CoV-2 infection also causes excessive infiltration and activation of neutrophils leading to the formation of NETs, and induces local thrombosis leading to tissue damage. In severe cases, NET components are detected in the circulation and thereby promote microthrombosis and NET-associated sequelae in remote organs [17–19].

SARS-CoV-2 uses ACE2 as a receptor to enter the cell and disrupts the balance of the angiotensin system, resulting in angiotensin II (Ang II) mediating tissue microvascular damage [20,21]. The accumulated clinical data shows that ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs) are beneficial for the treatment of COVID-19 [22,23]. However, there is a gap in understanding between the disorder of the angiotensin system and the formation of NETs triggered by SARS-CoV-2. This review will focus on the angiotensin system and discuss its coordination effect on SARS-CoV-2 on the priming and triggering of NETs.

2. Phenotypic heterogeneity of neutrophils

Neutrophils are the first cellular responders to invading pathogens and provide early immune protection. Neutrophils enter the circulation from the bone marrow and are eliminated by specialized macrophages from the circulation due to cell aging. The process exhibits different cell phenotypes and functional changes. Under inflammatory conditions, the life cycle of neutrophils will be prolonged [24]. According to the development of neutrophils, they are divided into immature neutrophils, mature neutrophils and hypersegmented neutrophils. Immature neutrophils have no distinctly divided serrated nuclei, while hypersegmented neutrophils are aged and degenerated neutrophils containing 6–10 segmental nuclei. They also can be divided into low-density granulocytes (LDGs) and normal-density granulocytes by ficoll gradient centrifugation. LDGs usually contain immature neutrophils and mature neutrophils, displaying characteristics of pro-inflammatory and immunosuppressive, and showing huge cell phenotypic heterogeneity, high oxidative burst, and functional plasticity in inflammatory conditions [25].

For the phenotypic characteristics of neutrophils in COVID-19 patients, multiple studies have confirmed the heterogeneity of neutrophils in their peripheral blood and the expansion of myeloid cells with a decrease in the proportion of basophils and eosinophils [26–28]. Even in the recovery period after 3 months of infection, the level of LDNs in the blood remained elevated [29]. The LDNs in COVID-19 patients express intermediate levels of CD16, show pro-inflammatory characteristics, spontaneously form NETs, and enhance the ability of phagocytosis and cytokine production [30]. The use of high-dimensional flow cytometry and Hierarchical clustering based on marker expression revealed a $CD16^{bright}$ population in patients with moderate COVID-19, showing higher expression levels of CD11b, CD177, and CD66b. Conversely, the immature $CD16^{dim}$ population enriched in severe COVID-19 patients shows a higher heterogeneous phenotype, such as CD66b and CD11b [26]. The conclusion of the trend of expanding to LDNs is also confirmed with another high-dimensional flow cytometry study, reflecting the characteristics of emergency myelopoiesis, neutrophil recruitment and activation [27]. Furthermore, a transcriptome analysis of single cells in whole blood has provided important information that in the severe COVID-19 patient group, neutrophil activation-related features are significantly enriched, and granulocytes show increased inflammation and inhibitory features at the same time. When comparing the severe and mild samples from the 1st to 10th days after the onset of symptoms, differential expression analysis has also identified 314-upregulated genes and 703-downregulated genes. For example, in the granulocytes of patients with severe COVID-19, the expressions of immature neutrophil-related markers CD15, NETs formation-related enzyme PAD4, pro-inflammatory MMP8, S100A8/9, and NLRC4 are elevated [31]. Similarly, another whole blood single-cell transcriptome study has also identified gene signatures that are highly correlated with neutrophils [32]. Together, these studies have demonstrated that both neutrophil characteristics of phenotypic and gene expression tend to be heterogeneous and activated.

3. Priming and triggering of NETosis by SARS-CoV-2

In patients with severe COVID-19, NETosis triggered by SARS-CoV-2 was ACE2-dependent [1]. It is reported that numerous viruses have been detected in neutrophils and even activate neutrophils to produce NETs [33]. As a single-stranded RNA virus, SARS-CoV-2 is quickly recognized by endosomal toll-like receptors (TLR) 7/8 after entering the cell, which activates the TLR-MyD88 signaling pathway, oxidative burst, NETs formation, and pro-inflammatory cytokines release [19, 34–36] (Fig. 1). Multiple reports of IgA vasculitis have been reported following SARS-CoV-2 infections [37,38]. IgA immune complexes can be recognized by FcαRI, a member of the Fc receptor immunoglobulin superfamily, and activate NETs in rheumatoid diseases [39,40]. The immune complex composed of SARS-CoV-2-IgA is used as one of the pathways to initiate NETs [41].

LDNs display a mature primed heterogeneous phenotype, and the function of β2 integrin can partly explain the heterogeneity of neutrophils. αMβ2 integrins (CD11b/CD18, complement receptor 3, or Mac-1) is an important marker of low-density neutrophils and has the ability to initiate NETs formation. There are pieces of evidence that low-density neutrophils display high expression of CD11b in both healthy and diseased individuals [42,43]. αMβ2 integrins (CD11b/CD18) has a sequence that senses the RGD motif (Arg-Gly-Asp) [44–46]. Interestingly, the spike protein of SARS-CoV-2 contains an RGD motif in its receptor binding domain, which other coronaviruses so far [47,48]. The RGD motif provides a basis for SARS-CoV-2 to invade host cells by binding to integrins. The high expression of integrins in the lung and all other important organs finally leads to systemic reactions after SARS-CoV-2 infections. αMβ2 (CD11b/CD18) activates neutrophils and regulates the plasticity and fate of neutrophils through “outside-in” signaling [49] (Fig. 1). Multiple studies have shown that αMβ2 integrins (CD11b/CD18) mediates the release of NETs induced by hantavirus, Aspergillus fumigatus, and immune complexes [48–52], which also provides indirect evidence that SARS-CoV-2 can induce the NET formation through αMβ2 integrins “outside-in” signaling. Integrins combine with their ligands to induce cell adhesion and produce "outside-in" signaling, which participates in slow rolling, enhanced adhesion, transendothelial migration and signal transduction, promotes oxidative burst, cytokine production, proliferation, survival, differentiation, degranulation, and cell polarization [53–55].

Compared with monocytes, neutrophils highly express α9β1 integrins, which upregulates neutrophil activation and promotes NETosis, thrombosis, and inflammation [56,57]. In neutrophils, β1 integrin activation promotes β2 integrin-mediated adhesion, and β2 integrin engagement induces the surface expression of β1 integrin, which identified an interaction and regulation relationship between β2 and β1 integrins [58,59]. αVβ3 integrins also contributes to the speed and linear movement of neutrophils [60], and regulates the oxidative burst in the human neutrophils adhered to fibrinogen [61]. Because of the RGD motif in the viral spike protein, cell surface integrin may act as a co-receptor for SARS-CoV-2. Studies have revealed that the cytoplasmic tail of β3 integrin mediates the endocytosis and transport of SARS-CoV-2 by binding to ACE2 in cell-free systems [62,63].

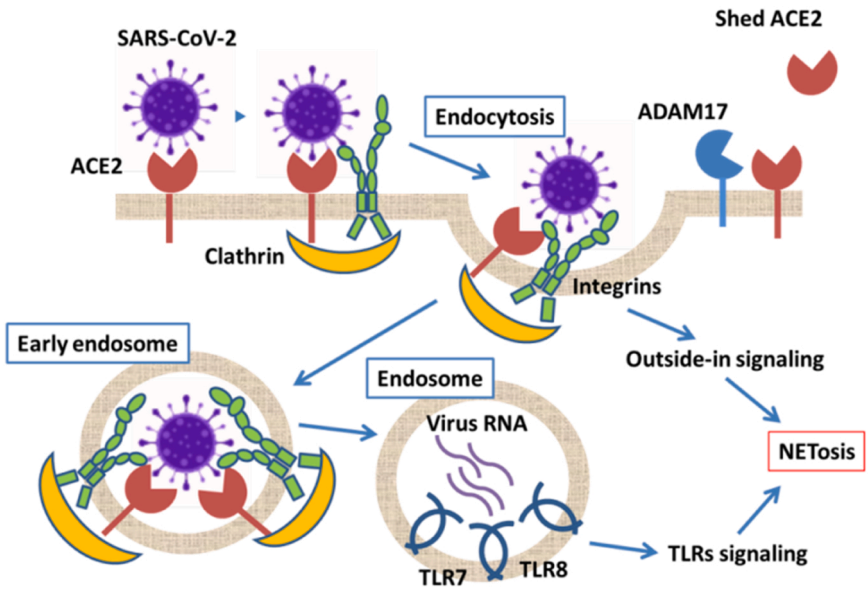

Fig. 1. In the lung, the endocytosis of SARS-CoV-2 and the activation of NETosis. The conjugation of SARS-CoV-2 with ACE2 and integrins promotes neutrophil endocytosis and intracellular virus synthesis. As a result, single-stranded RNA virus activates the TLR7/8 signaling in the endosome, while integrins trigger the outside-in signaling, which together contribute to the formation of NETs. The extramembrane motif of ACE2 can be cut off by ADAM17 to form soluble ACE2.

4. Changes of angiotensin system in COVID-19 patients

Numerous studies have confirmed a cytokine storm in COVID-19, with TNF-α, IL-1β, IL-6, IL-8, and MCP-1 rising dramatically in the lungs and circulation [17,18]. Excessive Ang-II leads to multiple deleterious cardiovascular consequences, such as increased blood pressure, cardiomyocyte apoptosis, macrophage infiltration, and secretion of proinflammatory cytokines TNF-α, IL-1β, IL-6, and MCP-1[64–68]. Activated renin-angiotensin also induces a prothrombotic state resulting from an imbalance of coagulation and fibrinolysis [69,70]. Elevated Ang II level is strongly associated with SARS-CoV-2 viral load, inflammation and lung damage in severe COVID-19 patients [71,72]. A meta-analysis showed that ACEI/ARB therapy does not increase the risk of SARS-CoV-2 infection, but instead it is associated with a reduced risk of severe COVID-19 and mortality [73].

A review pointed out that although SARS-CoV-2 genomic material was not detected in the blood of most patients with COVID-19, very low levels of the virus were found in a few cases [74]. SARS-CoV-2 RNA has also been detected in tissues and cells such as liver, kidney, and heart [74]. Another analysis of SARS-CoV-2 infection in 4103-donors of blood also showed that RNAemia was rare in plasma (0.66%) [75]. Moreover, NETosis can be triggered by the plasma of patients with COVID-19 and inhibited by the SYK inhibitor fostamatinib/R406 [76], suggesting the existence of a possible non-SARS-CoV-2-triggered mechanism of

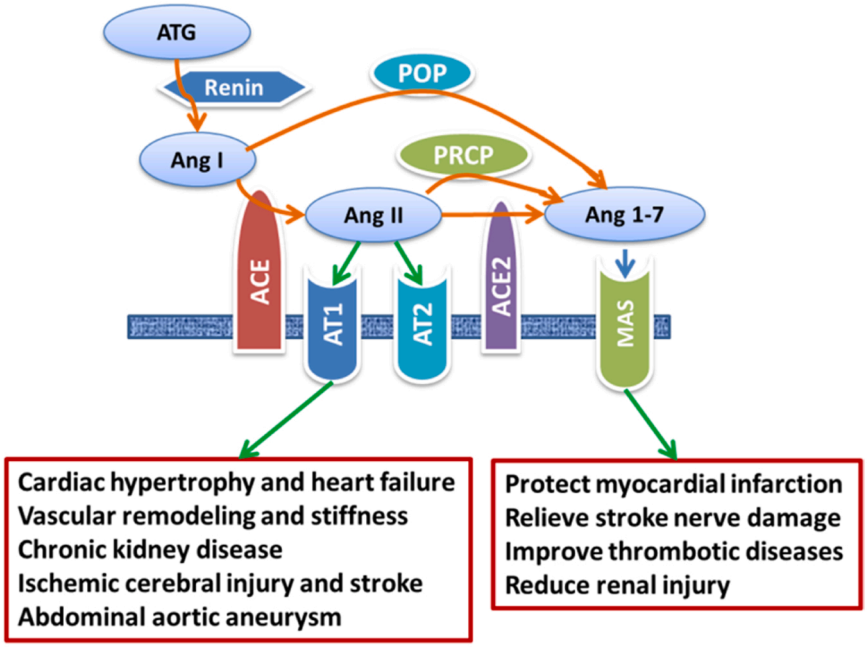

Fig. 2. The diagrammatic sketch of angiotensin system. The diagrammatic sketch shows the metabolic pathway of angiotensin. ACE: angiotensin-converting enzyme; AGT: angiotensinogen; Ang 1–7: angiotensin 1–7; Ang I/II: angiotensin I/II; AT1/2: angiotensin II type 1/2 receptor; Mas: Mas-related G protein–coupled receptor; POP: prolyl oligopeptidase; PRCP: prolyl carboxypeptidase.

NETosis. Therefore, clarifying the mechanisms of the renin-angiotensin system in the pathogenesis of COVID-19 is beneficial for improving cardiovascular comorbidities.

ACE2, which acts as a receptor for SARS-CoV-2, is highly expressed in the heart, blood vessels, and kidneys. ACE2 converts Ang II to angiotensin 1–7 (Ang 1–7) (Fig. 2). The catalytically active extracellular domain of ACE2 falls off, presenting in a soluble form in the circulation. However, there are still many factors that can affect the plasma levels of soluble ACE2 (sACE2). Several studies have revealed that patients with heart failure, lower left ventricular ejection fraction and systolic dysfunction, atrial fibrillation, aortic stenosis, obstructive coronary artery disease and cardiac remodeling have higher ACE2 plasma activity [77–80]. The plasma sACE2 levels are positively correlated with an increased risk of heart failure, myocardial infarction, stroke, and diabetes [81–83]. Severe COVID-19 patients are often accompanied by cardiovascular disease, while the high ACE2 level of cardiovascular disease patients further raises the incidence rate of severe COVID-19. Recent clinical investigations of critically ill patients with COVID-19 showed significantly heightened levels of plasma ACE2 [84–88], which is associated with an increase in the maximum severity of disease within 28 days in admitted COVID-19 patients. Similarly, the plasma ACE2 of hypertensive patients with COVID-19 is dramatically increased compared with non-hypertension patients [84]. In severe COVID-19 patients, the plasma ACE2 levels presented a parabolic increase over time with a peak value of 9–11 days after hospitalization [89]. These findings suggest that the increase in plasma sACE2 is caused by endocytosis and cleavage of ACE2 ectodomain after binding to SARS-CoV-2, so that ACE2 expression on the cell membrane is then downregulated. At the circulating cell level, this imbalance expression of ACE2 membrane protein mainly comes from the monocytes [90]. The binding of spike glycoprotein of SARS-CoV-2 to ACE2 is highly similar to that of SARS-CoV [91,92]. In vivo experimental SARS-CoV infection in wild-type mice resulted in a significant decrease in lung ACE2 expression [93]. SARS-CoV-2 infection leads to various symptoms including asymptomatic severe hypoxemia, which is also known as silent hypoxia [94,95], which promotes the expression of hypoxia-induced factor 1α (HIF-1α) [96], thereby inhibiting ACE2 expression [97,98] through a pathway that activates miRNA let-7b and LncRNA ALT1 [99,100] (Fig. 3). Furthermore, up-regulated HIF-1α expression stimulates ADAM17 expression [101,102], a cleavage enzyme in the extracellular region of ACE2, which leads to an increase in circulating ACE2 (Fig. 3).

Although individual studies have shown that the circulating Ang II concentration of COVID-19 patients is lower or unchanged than that of healthy people [103,104], most studies have demonstrated a considerable increase in circulating Ang II levels in severe COVID-19 patients. The serum concentration of Ang II was positively correlated with the severity of COVID-19 [88,105,106]. These results are derived from the induction of endocytosis due to the binding of SARS-CoV-2 to the ACE2 receptor, and the increased shedding of the extracellular domain protein of ACE2, which slows down the degradation of Ang II [107,108] (Fig. 3). It is also attributed to the fact that hypoxia promotes the ACE expression in endothelial cells [109,110], which induces Ang II production.

However, the clinical findings of Ang 1–7 blood concentration in COVID-19 patients are chaotic. This discrepancy mainly showed that the concentration decreased [105,111], remained unchanged [91,104], and elevated [86,89,112]. In the angiotensin system, another participant inhibited by HIF-1α is prolyl oligopeptidase (POP) /neprilysin on the endothelial surface [113], which converts angiotensin I to Ang 1–7 [114–116] (Fig. 3). These contradictory results on circulating Ang 1–7 levels are difficult to explain from the inhibition of ACE2 and POP by HIF-1α. Moreover, the expression or activity of the third enzyme that forms Ang 1–7, prolyl carboxypeptidase (PRCP), has not been reported to be regulated by hypoxia or SARS-CoV-2.

5. Correlation of regional high ACE expression with NETosis

Capillary endothelial cells occupy a very high proportion in the lung, heart and brain, where are the organs in which NETosis is prevalent in COVID-19 patients. Earlier studies have determined that the capillary endothelial cells of the lung make up 30% of lung cells.Furthermore, interspecies comparisons of cellular characteristics in the alveolar region of normal human, baboon, and rat lungs showed that the

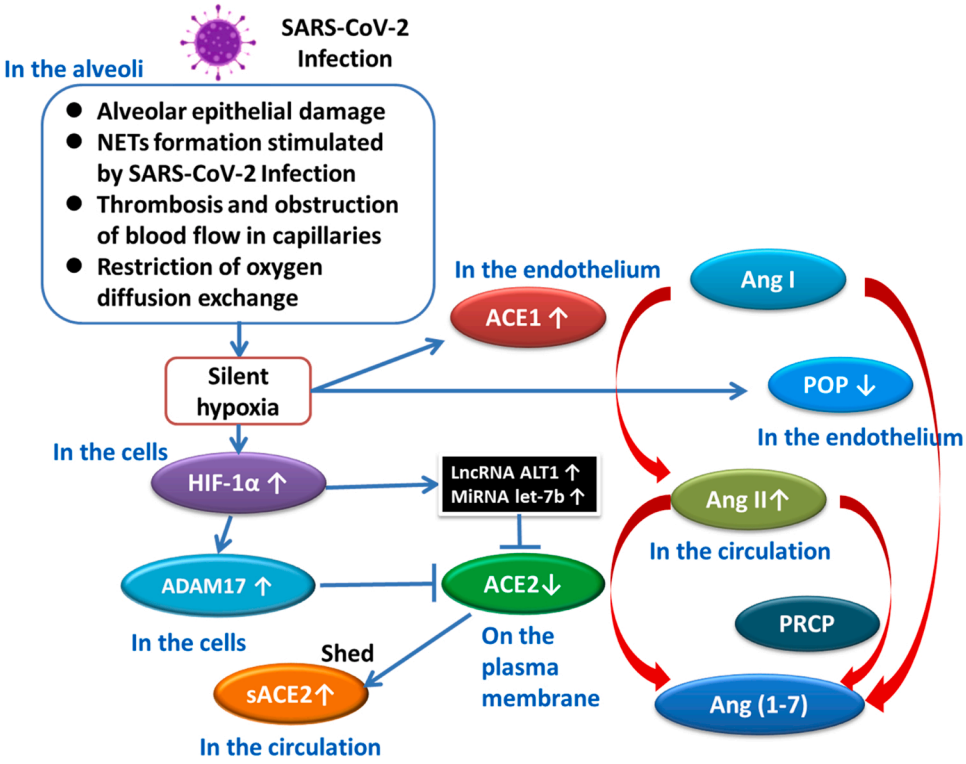

Fig. 3. The expression of angiotensin system enzymes after SARS-CoV-2 infection. In the state of acute respiratory syndrome, silent hypoxia leads to an increase in the expression of HIF-1α, which regulates the different expression of enzymes in the angiotensin system. ACE: angiotensin-converting enzyme; ADAM 17: a disintegrin and metalloprotease domain 17; Ang 1–7: angiotensin 1–7; Ang I/II: angiotensin I/II; POP: prolyl oligopeptidase; PRCP: prolyl carboxypeptidase; sACE2: soluble ACE2.

proportion, average thickness, size, and surface area of alveolar cells were relatively constant [117]. In the heart, 60% of cardiac non-cardiomyocytes are endothelial cells [118]. A more detailed analysis revealed that endothelial cells accounted for 12.2% of the atrial tissue and 7.8% of the ventricular tissue [119]. The blood-brain barrier is a unique structure dominated by capillary endothelial cells that distribute throughout the brain. The proportion of endothelial cells is 25% in the cerebral cortex and 12.2% in the spinal cord [120]. Obviously, capillary endothelial cells occupy a very high proportion in the lung, heart and brain. A study found that the lungs of Covid-19 patients exhibited a unique vascular signature of severe endothelial damage associated with intracellular virus [121], which causes capillary flow obstruction and restricts the diffusive exchange of oxygen in the lungs and other tissues causing silent hypoxia. The patients with COVID-19 had extensive thrombosis with microvascular disease, and the incidence of alveolar-capillary micro-thrombosis was 9 folds higher than that of patients with influenza, even if they both caused acute respiratory distress syndrome [121], suggesting that capillary occlusion marked by NETs is a characteristic of COVID-19.

ACE is an enzyme that catalyzes the production of Ang II and is expressed on the surface of the endothelial cells and certain cells [122]. It has been reported that the monoclonal antibody (mAb) 9B9 using ACE selectively targets the endothelium in human lung tissue with high density after systemic injection [123,124]. ACE staining in the heart was confined to endothelial cells and distributed gradients along the vascular tree around the entire arterial endothelial ring, but not in veins [125]. Using in situ hybridization detection, ACE mRNA was shown to be expressed in the choroid plexus, caudate putamen and cerebellum [126]. In the subfornix organ (SFO), the expression of ACE is found in ependymal cells, vascular endothelial cells, some glial cells, and neurons on the lumen surface [127]. However, in contrast to the cytological specificity of ACE expression, ACE2 expression is present in almost all organs and cells [128].

Therefore, the endothelial cell regional arrangements in tissues and the cell-type-specific expression of ACE are the biological basis of local Ang II high expression and high secretion after SARS-CoV-2 infection, and also the reason for high NETosis incidence in the lung, heart, and brain. Silent hypoxia induced by SARS-CoV-2 infection induces rapid local high expression of ACE, which in turn promotes the production of Ang II [96,129]. Numerous early studies have demonstrated that hypoxia promotes the plasma activities of Ang II and renin [130–132], which is consistent with the elevated plasma Ang II levels in COVID-19 patients. Long-term chronic hypoxia, such as sleep apnea syndrome and high-altitude hypoxia, leads to hypertension [133,134], heart failure [135,136], and stroke [137]. Elevated plasma Ang II also induced NETosis [138].

6. Signal pathways of NETosis induced by angiotensin II

Previous studies have suggested that the oxidative burst activity of neutrophils in patients with essential hypertension is significantly increased [139,140]. Recently, investigates have reported that patients with hypertension display heterogeneity of neutrophils, and the phenotypic activation of CD11b, CD66b, and CD63 of LDNs, which have significantly higher respiratory bursts than that of healthy individuals [141]. The up-regulation of CD63 in LDNs is consistent with the release of azurophilic granules [142], indicating that these cells have been activated and degranulated [143]. In addition, increased PD-L1 expression is a feature of LDGs. AngII increases PD-L1 mRNA stability through the binding of HuR to the AU-rich elements (AREs) in the 3'-UTR, thereby increasing the expression of PD-L1 mRNA and protein, and the percentage of $CD11b^{+}Ly6G^{+}$ granulocytes in mice [144] (Fig. 4).

In terms of initiating neutrophil heterogeneity, ACE binds β1 integrin in an RGD independent manner to trigger outside-in signaling [145, 146], while Ang II promotes the expression of β1 integrin [147,148]. Multiple studies have demonstrated that Ang II enhances the expression of αvβ3 integrins in neutrophils via the NF-κB signaling pathway [149, 150]. In a study of spontaneously hypertensive rats, the angiotensin II type 1 receptor (AT1R) antagonists improved Mac-1 (CD11b/CD18) expression of neutrophils and increased cerebral microvascular permeability [151]. Notably, the expression of CD11b in neutrophils does not increase at rest in patients with essential hypertension. However, after PMA stimulation, the neutrophils expressed CD11b faster and the primary granulosa accelerated the speed of exocytosis [152]. Hypertension and Ang II have the characteristics of inducing a low-grade chronic inflammation, which may play a priming effect on the formation of NETs as same as pro-inflammatory cytokines, such as IL-1α, IL-6, IL-8, TNF-α, G-CSF, and MIF[153–157](Fig. 4).

As is well known that malignant hypertension is the main cause of myocardial infarction, and ischemic stroke [158–161]. Naturally, as a blood pressure regulator, Ang II is the initiator of myocardial infarction

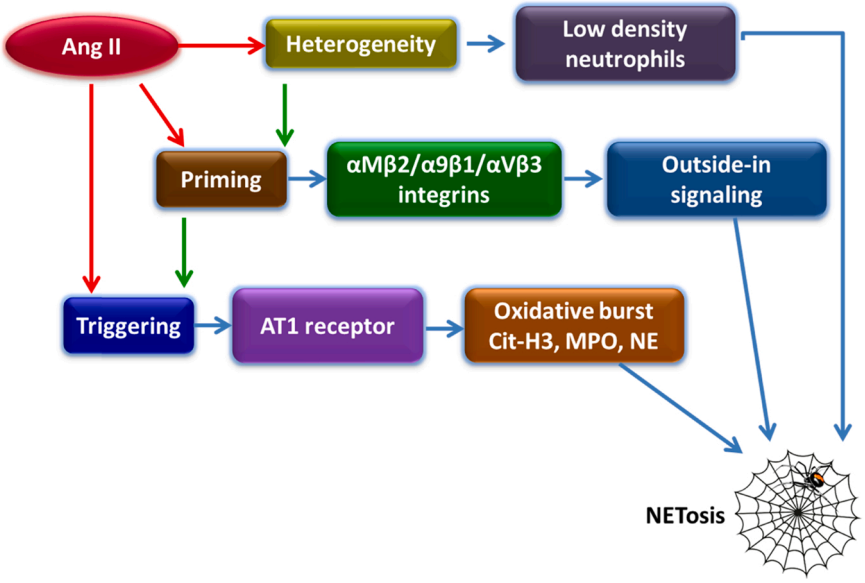

Fig. 4. In remote organs, angiotensin II initiates NETosis. Angiotensin II activates NETosis by enhancing the heterogeneity of neutrophils, eliciting cell sensitivity, and triggering signal transduction, respectively. Ang II: angiotensin II.

and ischemic stroke. In the process of inducing myocardial infarction and ischemic stroke, Ang II not only promotes the production of oxidative stress [162,163], endoplasmic reticulum stress [162], and inflammation [164,165], but also regulates necroptosis [166]. Based on these observations, ACE2 and Ang (1−7) antagonize the actions of the renin-angiotensin-system, and thereby improve acute pulmonary embolism [167,168], inhibit inflammation [169], suppress oxidative stress [170], and eliminate apoptosis caused by endoplasmic reticulum stress [171]. Accumulated data have demonstrated that NETs are also found in myocardial infarction [172,173], ischemic stroke [174,175], and pulmonary embolism [176,177].

Early studies have documented that AT1Rs are present on neutrophils [151,178]. Neutrophils produce oxidative burst when stimulated by Ang II [179,180]. In acute myocardial infarction, Ang II stimulates rapid neutrophil recruitment and infiltration by releasing CXC chemokines, such as IL-8 [181]. Past results indicate that Ang II has the potential to induce NETosis. Immunofluorescence staining showed that cit-H3 of plasma NET biomarker, myeloperoxidase (MPO) and neutrophil elastase (NE) expression increased significantly in a mouse model of abdominal aortic aneurysm (AAA) induced by Ang II infusion. Simultaneously, the circulating levels of double-stranded DNA (dsDNA) are elevated [182]. In human patients of AAA, cit-H3 in the blood and aortic tissue increased significantly compared with that of healthy controls. During the repair phase after aneurysm surgery, the blood cit-H3 of patients decreased markedly [183]. The use of PAD4 inhibitors, YW3–56 or GSK484, resulted in NETosis inhibition and further growth of aneurysms induced by Ang II [182,183]. Furthermore, at the cellular level, treatment of neutrophils with the NADPH oxidase inhibitor DPI or the PAD4 inhibitor Cl-amidine before Ang II stimulation also significantly reduced Ang II-mediated NETase [138] (Fig. 4).

The NETosis requires multiple signal transductions, including cell pyroptosis, necroptosis, mitosis, and oxidative burst to achieve the needs for protease dissociation of Azurophilic granules, cytolysis, histone cleavage, lamin B1 degradation, chromatin depolymerization, and nuclear membrane rupture. Recent findings revealed the signal transduction and cellular events required for NETosis (Fig. 5).

(1) Caspase1/4/11 and gasdermin D (GSDMD) in pyroptosis are required by NETosis and contribute to cytolysis. Presently, three research groups indicated that the pore-forming protein GSDMD cleaved by Caspase 11 is essential for NET release [184–186]. Moreover, Ang II-induced spleen tyrosine kinase (SYK) activates inflammasome activation [187–189]. Oxidative stress induced by Ang II causes the activation of JNK in human neutrophils [190,191], which is necessary for NETosis [192]. In short, it can be considered that Ang II, as a pathological susceptibility factor, can drive the NLRP3-caspase 1-GSDMD pathway to initiate NETs [184–186].

(2) A large number of studies have revealed that FAS/FASL and other receptors mediated the cytosolic apoptotic complex IIb to transduce necroptosis signals [193,194]. In necroptosis, the receptor interacting protein kinase (RIPK) 1/3 cascade phosphorylates a pseudokinase called mixed lineage kinase domain-like (MLKL), which oligomerizes on the plasma membrane, initiats the membrane rupture, and regulates the ion flow [193,194]. MLKL also plays a key role in activating the downstream PAD4 activity and NETosis [195,196]. Ang II triggers RIPK3-MLKL-mediated necroptosis through elevating Fas/FasL expression [197].

(3) A new report indicates that NETosis is accompanied by lamin B1 degradation and nuclear membrane rupture, which requires the participation of cyclin-dependent kinases 4/6 (CDK4/6). [198]. Although there are multiple pathways such as NFκB, mTOR, and STATs, the ERK1/2 pathway is fundamental for activating cyclin D1-CDK4/6 [199, 200]. It has been reported that ERK and p38 MAP kinases are involved in the activation of cPLA2 and NADPH oxidase, and that cPLA2 is required for Ang II to activate NADPH oxidase in neutrophils [190,201]. Ang II directly enhances the expression of cyclin D1 and CDK4 [202,203]. A clinical study showed elevated transcription levels of CDK4 and CDK6 in

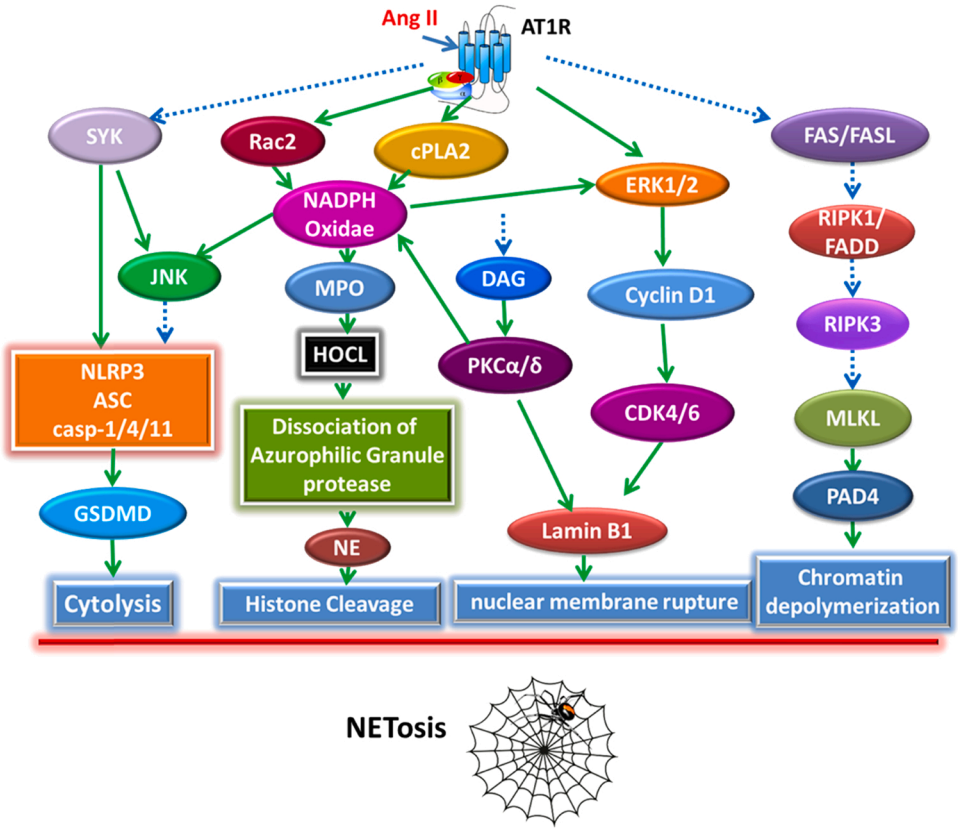

Fig. 5. Hypothesis that angiotensin II activates signaling pathways of NETosis. Parts of the signaling are based on research on non-neutrophils. Ang II: angiotensin II; ASC: apoptosis-associated speck-like protein containing a CARD; AT1R: angiotensin II type 1 receptor; Casp: caspase; CDK4/6: cyclin-dependent kinases 4 and 6; cPLA2: cytosolic phospholipase A2; DAG: diacylglycerol; ERK1/2: extracellular signal-regulated protein kinases 1 and 2; FADD: Fas associated via death domain; FAS/FASL: FAS death receptor/FAS death receptor ligand; GSDMD: gasdermin D; HOCL: hypochlorous acid; JNK: c-Jun N-terminal kinase; MLKL: mixed lineage kinase domain-like protein; MPO: myeloperoxidase; mtROS: mitochondrial reactive oxygen species; NADPH oxidase: nicotinamide adenine dinucleotide phosphate-oxidase; NE: neutrophil elastase; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; PAD4: protein arginine deiminase 4; PKC: protein kinase C; PLCγ: phospholipase Cγ; Rac2: rac family small GTPase 2; Ras: ras small GTPase; RIPK1: receptor-interacting protein 1; Src: tyrosine-protein kinase Src; SYK: spleen tyrosine kinase. Solid arrows indicate intraneutrophilic signal; dashed arrows indicate non-neutrophilic signal.

LDNs. The high ratio of LDNs in rheumatoid patients is mainly in the G2/S phase of the cell cycle [204]. Protein kinase C (PKC) α is another driving factor for the disintegration of laminin B and nuclear membrane rupture to promote NETosis [205,206].

(4) Oxidative burst is a very critical factor for NETosis [207]. PKCα is required for full assembly of NADPH oxidase and activation of the oxidative burst in neutrophils [208], while the process is stimulated by Ang II [179]. Rac2 is another key player in the NADPH oxidase assembly and activation of neutrophils. Deletion of Rac2 will lead to an impaired NADPH oxidase activity [209,210]. Moreover, its GTPase activity is closely related to NETosis [211,212]. The activation of Rac2 can also be exerted by AngII through calcineurin, mitogen activated protein kinases, and other pathways [191].

(5) In Azurophilic granules of neutrophils, MPO is activated by oxidative bursts to produce hypochlorous acid (HOCl). HOCl targets plasmalogen to generate 2-chloro fatty acids (2-ClFA). Human neutrophils treated with physiological levels of 2-ClFA initiate the NETosis process without activation and degranulation [213]. After MPO is activated, it also triggers the dissociation of neutrophil elastase (NE) from membrane-associated complexes to the cytoplasm to hydrolyze F-actin, and then transfer to the nucleus to cleavage histones [214]. Although the results of regulation of signal transduction by Ang II do not come entirely from neutrophils, an overview of signal pathways of NETosis can still be observed.

7. Inhibitors of NETosis induced by Ang II or SARS-CoV-2

A large number of clinical applications have proved that AT1R blockers and ACE inhibitors are effective and beneficial in improving severe COVID-19 symptoms, not only for serious clinical events induced by Ang II in elderly patients, such as hypertension, diabetes, or congestive heart failure [215–217], and also for NETosis and thrombosis promoted by the imbalance of the angiotensin system [218,219]. Experimental studies have revealed that AT1R receptor blockers hinder Ang II-induced AAA formation [220,221], which is one of the important comorbidities of COVID-19 [222]. NETs are important participants in the pathogenesis of AAA [182,183]. Animal experiments also confirmed that AT1R blockers impede NETosis [218]. NETosis is a PAD4-dependent phenomenon, thus, the inhibitors of the protein citrullination catalytic enzyme PAD4 have shown the effect of intercepting NETosis in the Ang II- induced AAA [182,183].

Phosphodiesterase 4 (PDE4) is a major cyclic-3',5'-adenosine monophosphate (cAMP) metabolizing enzyme. Its blockers roflumilast and rolipram can increase the level of intracellular cAMP and inhibit the formation of NETs [223,224] as well as Ang II-induced AAA [225]. In the case study, 4 patients with COVID-19 were treated with the oral PDE4 inhibitor Apremilast. Preliminary evidence proves that apremilast is safe and beneficial in the treatment of SARS-CoV-2 pneumonia. It is also suitable for patients with older age, cardiovascular comorbidities, greater extent of lung involvement, and higher IL-6 levels [226]. Many reports pointed out that PKA, a cAMP-dependent protein kinase, negatively regulates NADPH oxidase activation and prevents oxidative burst [227,228].

8. Conclusions

Unlike the NETosis triggered by SARS-CoV-2 in the lungs, the viral infection and detection rate in remote organs were extremely low, suggesting a different mechanism for the NETosis. Alveolar epithelial injury and alveolar collapse lead to severe diffusion-limited oxygen exchange and silent hypoxia, which in turn results in high ACE expression, low membrane ACE2 protein levels in endothelial-rich remote organs, and ultimately causes high local Ang II levels. Combined with the enhanced neutrophil heterogeneity of the COVID-19, NETosis is triggered by Ang II. Ang II-mediated NETs-induced thromboembolism causes severe damage to organs such as the heart and brain. The clinical efficacy and benefit of ACEIs and ARBs also partially illustrate the critical role of the renin-angiotensin system in NETosis.

CRediT authorship contribution statement

This review is based on our idea. The manuscript, or part of it, neither has been published, nor is currently under consideration for publication by any other journal. The submitting author should declare that the co-authors have read the manuscript and approved its submission to Biomedicine & Pharmacotherapy. This work was supported by grants from the Specialized Research Fund for the National Natural Science Foundation of China (81973511). The authors declare that they have no competing interests.

Conflict of interest statement

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