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Angiotensin-converting enzyme 2, the complement system, the kallikrein-kinin system, type-2 diabetes, interleukin-6, and their interactions regarding the complex COVID-19 pathophysiological crossroads

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Abstract

Because of the current COVID-19-pandemic, the world is currently being held hostage in various lockdowns. ACE2 facilitates SARS-CoV-2 cell-entry, and is at the very center of several pathophysiological pathways regarding the RAAS, CS, KKS, T2DM, and IL-6. Their interactions with severe COVID-19 complications (e.g. ARDS and thrombosis), and potential therapeutic targets for pharmacological intervention, will be reviewed.

Keywords

COVID-19, angiotensin-converting enzyme 2, renin angiotensin aldosterone system, complement system, kallikrein-kinin system, thrombosis, interleukin-6, diabetes

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Introduction

The aim of this review is to create a framework of different interconnected pathways that constitute the complex COVID-19 pathophysiological crossroads, as well as the interactions with common comorbidities (T2DM in particular).

First the SARS-CoV-2 virus and COVID-19 (including severe complications) will be introduced. Then, the COVID-19 relation with the RAAS will be reviewed, and a preliminary framework will be established. This framework will subsequently be expanded with the CS and the KKS. The interactions between COVID-19, T2DM, and IL-6, will be reviewed in light of this framework. Finally, some potential targets for therapeutic intervention will be discussed.

Abbreviations are listed at the end.

COVID-19

SARS-CoV-2 is a $SSRNA^{+}$, enveloped virus from the beta-coronavirus family, with a structural surface spike (S) glycoprotein that primarily binds to the N-terminal domain of ACE2, predominantly, but not exclusively, on type-II pneumocytes.[1–3] SARS-CoV-2 decreases surface ACE2 expression through directly binding to ACE2,[4–6] followed by TMPRSS2-mediated proteolytic cleavage[3,7,8] and subsequent endocytosis.[1,3,5] TMPRSS2 is essential for SARS-CoV-2 membrane fusion and subsequent cell-entry,[3,7,8] but other proteases (such as Furin) may facilitate SARS-CoV-2 cell-entry as well.[2,5,9] Surface ACE2 is further reduced via shedding, caused by Ang-II-mediated upregulation of ADAM-17[5,6,10] and androgen-mediated[8,11] upregulation of TMPRSS2.[3,7] Reduced ACE2 expression may also be modulated epigenetically via

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DNA-methylation processes,[12,13] or via crosstalk with T2DM-induced hyperglycemia.[14,15]

The SARS-CoV-2-related disease is commonly referred to as COVID-19.[1,7,16] Common COVID-19 symptoms are fever, dry cough, sore throat, dyspnea, headache, and myalgia.[1,12,17] Some atypical symptoms are anosmia (loss of smell)[18–20] and diarrhea (which may present earlier than respiratory conditions).[1,5,17] Different sex and age groups have very biased severity and mortality of COVID-19, with male, old age, and comorbidity being the most affected.[1,4,15] T2DM, hypertension, and CVD are common COVID-19 comorbidities (which are likely related to a dysregulated RAAS)[5,6,21] and are associated with ARDS[15,22,23] and high fatality.[1,23,24] Currently, there is no approved and effective medication against COVID-19.[16,22,25]

The protective mechanism during the early stages of a (viral) infection predominantly occurs through the innate immune system.[26–28] COVID-19 primarily suppresses the innate immune system, enabling the uncontrolled spread of the virus during the initial stages.[27–29] This explains a mild (sometimes even asymptomatic) presentation early on.[27,28,30] The high effectiveness of the innate immune system in children possibly explains why COVID-19 doesn't seem to affect them as much (if at all).[27,28,30] Differences in immunity[27,28,31] and gene expression[4,12,22] may contribute to COVID-19 severity. Severe COVID-19 complications are associated with excessive and dysregulated host immune responses, which may contribute to the development of lethal CRS and ARDS.[32–34]

Acute respiratory distress syndrome

ARDS, the most severe form of ALI,[35–37] is a clinical syndrome of noncardiogenic pulmonary edema.[38–40] ARDS is characterized by an excessive inflammatory response,[41–43] damage to both alveolar epithelial[38,40,41] and vascular endothelial[39,44,45] cells, the subsequent breakdown of the alveolar-capillary barrier integrity,[38,42,46] impaired AFC,[40,41,45] excessive interstitial and parenchymal neutrophil migration,[38,43,45] and activation of alveolar macrophages, platelets, and pro-coagulant processes.[42,47,48] This may result in diffuse alveolar damage,[42,49] pulmonary fibrosis,[37,50] and impaired gas exchange,[42,51] leading to (refractory) hypoxemia[35,38,42] and possibly organ dysfunction.[40,47,52]

Uncontrolled inflammation leads to excessive and prolonged activation of neutrophils,[38,43,45] which are immune cells that play an important role in the regulation of IL-6 signaling[53–55] in the pathology of pulmonary inflammatory disorders.[38,43,56] Neutrophil-mediated ROS production (via NADPH oxidase),[57,58] plays an essential part in the immune response against pathogens via NET formation and direct cellular damage.[59–61] Excessive neutrophil recruitment therefore contributes significantly to the severity of inflammatory pneumonia.[56,60,62]

In AFC, alveolar fluid is cleared via an ENaC-mediated osmotic gradient.[40,41,63] Disruption of ENaCs can lead to impaired AFC.[42,62,64]

The ECM is important for the epithelial and endothelial barrier function, since it regulates intercellular interactions and controls the migration of fluid and molecules in the interstitial space.[42,65] Changes in ECM composition affect the mechanical properties of tight-junctions in alveolar epithelial and vascular endothelial cells, modulating the alveolar-capillary barrier function.[42,66] Excess deposition of ECM proteins can lead to pulmonary fibrosis,[37,42,50] which may lead to chronic impairment of pulmonary function in ARDS survivors.[50] The amount of alveolar epithelial damage and impaired AFC capability are associated with impaired gas exchange and higher mortality.[41,42,62] Injury of the alveolar epithelium (not the vascular endothelium) determines the progression to pulmonary fibrosis.[42,67,68] Currently there is no specific treatment for post-ARDS pulmonary fibrosis other than supportive therapy.[50,69]

ARDS is one of the leading causes of death in ICU patients.[38,40,41] Current ARDS therapy mainly constitutes supportive treatments, such as mechanical ventilation.[51,70,71] This is predominantly effective in less severe cases, and may have serious side-effects.[38,70,71] High tidal volume mechanical ventilation upregulates ACE expression and Ang-II activity,[71] activates JNK and $ERK_{1/2}$,[72] and increases pulmonary parenchymal IL-6 levels via excessive alveolar distention.[70] Mechanical ventilation may promote ventilator-induced ALI, which is characterized by inflammation, increased vascular permeability, interstitial pulmonary edema, parenchymal infiltration, fibrosis, and thrombosis.[42,48,71]

The COVID-19-related ARDS may present atypically, in the sense that there is relatively well-preserved pulmonary compliance (despite the severity of hypoxemia), and systemic features of a hypercoagulable state.[73–75] To understand how and why, a trinity of interconnected systems will be discussed, starting with the RAAS.

Renin angiotensin aldosterone system

To explain why changes in ACE2 and Ang-II levels are important in COVID-19, we need to discuss their interactions with other relevant systems, as well as their relation to comorbidities and complications.

If we exclusively focus on the RAAS, it is best described as a regulatory system with two axes that control vasoconstriction and vasodilation,[3,76,77] which play an essential role in maintaining hemodynamic homeostasis.[64,78,79] The classical ACE/Ang-II/AT1R axis promotes vasoconstriction.[37,80,81] Renin increases Ang-I, which is subsequently converted to Ang-II by ACE,[35,77,82] after which Ang-II exerts its cellular effects (predominantly via the AT1R).[58,79,83] The counterregulatory ACE2/Ang-(1-7)/MasR axis promotes vasodilation.[3,76,77] ACE2 converts Ang-II to Ang-(1-7), which exerts its cellular effects predominantly via the MasR.[64,79,80]

In a perfectly balanced RAAS, neither ACE nor ACE2 should be considered good or bad, as they are both required to maintain healthy homeostasis. Since ACE is required for either axis, Ang-II and ACE2 should be considered to be the main effectors of the RAAS. This balance can go either way, meaning low ACE2/high Ang-II or high ACE2/low Ang-II. Since only low ACE2/high Ang-II is relevant regarding COVID-19, the focus will be on that type of RAAS imbalance in particular.

Ang-II will be considered first, after which ACE2 will be discussed.

Angiotensin-II

Ang-II is considered to be the major player in the ACE/Ang-II/AT1R axis.[41,83,84] A dysregulated RAAS (and associated elevated Ang-II levels) has many detrimental effects. Ang-II upregulates Aldosterone production and promotes hypertension,[83–85] CVD,[78,79,82] and fibrosis.[71,80,86] Furthermore, elevated Ang-II levels increase PKC-mediated[87–89] ROS production via NADPH oxidase[86,90,91] and $\Delta\Psi_M$ depolarization (through PKC-mediated modulation of K_{ATP} channels).[58,91,92] Ang-II-mediated ROS production stimulates $ERK_{1/2}$,[58,88,93] JNK,[91,94,95] and p38-MAPK,[83,90,96] subsequently initiating crosstalk with NF-κB[64,71,89] (Figure 1).

$ERK_{1/2}$, JNK and p38-MAPK are members of the MAPK family, and are preferentially activated by inflammation and environmental stresses (JNK and p38-MAPK in particular).[97–99] MAPK signaling plays a crucial role in regulating cell apoptosis, inflammatory responses, and cell-cell junction formation.[14,72,96] NF-κB is a transcription factor family that plays an important immunoregulatory role,[44,100,101] and modulates the production of inflammatory cytokines[44,86,89] and NADPH oxidase subunits.[102–104]

Ang-II-induced ROS production effectively induces insulin resistance,[79,86,94] and exacerbates T2DM.[64,86,89] Insulin resistance impairs the PI3K/Akt/eNOS pathway,[94,105,106] subsequently reducing glucose uptake and NO production.[86,88,89] Insulin signaling, and the role of Ang-II in insulin resistance, will be further discussed in the T2DM section. To understand the importance of Ang-II-mediated reduction of NO bioavailability in COVID-19, we will first consider the vascular endothelium.

Vascular permeability

The inner surface of the vascular tree is lined with a continuous monolayer of endothelial cells (joined together by tight-junctions), forming a protective selective permeability barrier between the circulating blood and the extravascular tissue.[39,107,108] The endothelium is a metabolically active homeostatic organ, regulating the tone, structure and permeability of the vascular system in response to different stimuli (e.g. shear stress, ACh, and insulin).[46,78,104]

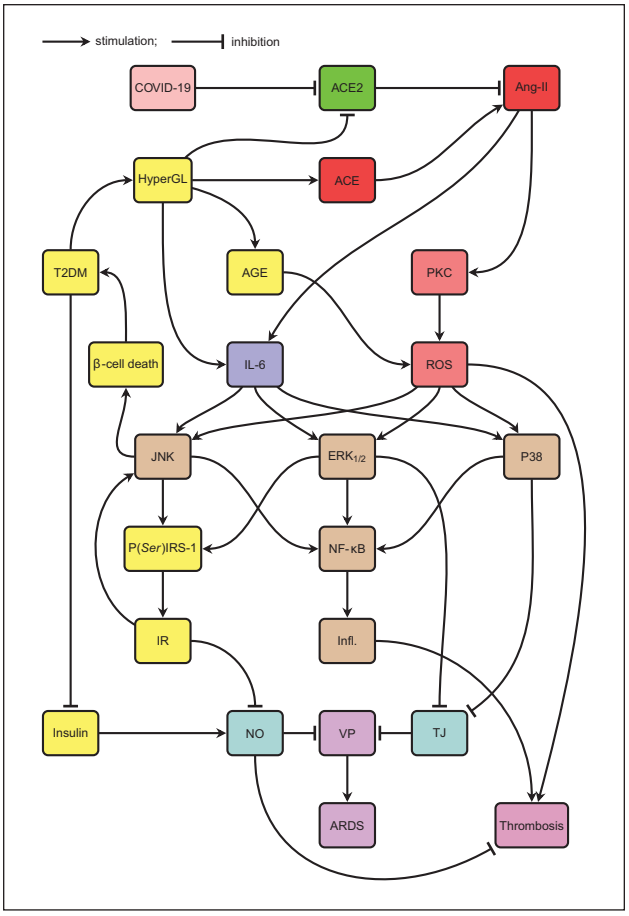

Figure 1. ROS- and IL-6-mediated MAPK signaling and their effects regarding severe COVID-19 complications, for example, ARDS and thrombosis.

Limited vascular permeability is a function of a balanced endothelial phenotype, which constitutes smooth muscle relaxation, as well as low platelet activation and low fibrin formation.[78,109,110] Endothelial dysfunction disrupts this balance and predisposes the vascular wall to inflammation, platelet activation, dysregulated coagulation, thrombosis, and increased vascular permeability.[39,48,111]

Both the disruption of endothelial tight-junctions[39,72,108] and impaired NO bioavailability[104,109,112] are two important causes of endothelial dysfunction and increased vascular permeability. ROS-mediated MAPK signaling is responsible for disruption of endothelial tight-junctions.[39,72,108] Impaired NO bioavailability occurs via eNOS uncoupling,[104,109,113] reduced eNOS activity,[74,112,114] or ROS-scavenging.[55,104,115] Prolonged and excessive vascular permeability can result in tissue damage, organ dysfunction, or even death.[116,117]

Impaired NO bioavailability plays a role in thrombosis, due to the hampering effect of NO on ROS-mediated upregulation of platelet activation, suggesting that either decreased NO bioavailability or increased ROS production is able to induce thrombosis.[114,118] Endothelial dysfunction

initiates the coagulation pathway by activating platelets and pro-coagulant cascades, while reducing anti-coagulant components and fibrinolysis.[42,114] This results in pulmonary capillary microthrombi and fibrin deposition in parenchymal and interstitial compartments,[42] which is characterized by observed high D-dimer and von Willebrand Factor in some COVID-19 patients.[21,119,120]

During an inflammatory state, endothelial cells release von Willebrand Factor,[110,120] which represents an important thrombotic risk factor.[48,121] Von Willebrand Factor is a large adhesive glycoprotein, synthesized by endothelial cells,[46,110,120] and is critical for platelet adhesion and aggregation.[48,121] ABO blood group genes affect von Willebrand Factor expression, as well as their susceptibility to proteolytic degradation via ADAMTS13.[122] This is a possible explanation why ABO blood group type may be differentially related to COVID-19 severity.[122]

Ang-II-mediated ROS production[58,90,91] and decreased NO bioavailability[79,94,123] promote vascular permeability[41,81,83] and thrombosis[6,80,82] (Figure 1). Ang-II-mediated disruption of ENaCs impairs AFC,[41,64,124] exacerbating pulmonary edema.[40,62,63] These are essential components of ARDS,[41,42,62] which is a severe COVID-19 complication.[25,76,125] Ang-II is significantly elevated in COVID-19 patients and is highly associated with viral load and lung injury.[21,76,125]

Angiotensin-converting enzyme 2

The ACE2/Ang-(1-7)/MasR axis can mitigate Ang-II-mediated negative effects.[77,79,81]

ACE2 is a homologue of ACE,[78,82,84] and a key component of the RAAS.[77,81,126] ACE2 is a two-part type-I transmembrane protein, consisting of a glycosylated extracellular N-terminal domain (containing the SARS-CoV-2-binding carboxypeptidase site), and an intracellular C-terminal cytoplasmic tail.[3,127,128] The extracellular catalytic domain of ACE2 can be cleaved and released by ADAM-17[5,6,76] or TMPRSS2.[2,3,8] ACE2 is widely expressed in the heart, kidneys, lungs, CNS, and intestines,[80,82,84] and is present in type-II pneumocytes and endothelial cells.[6,71,129] ACE2 is predominantly membrane-bound, although it does exist, with a short half-life,[52,130] in soluble form.[3,6,127]

Increased ACE2 expression, upregulating the ACE2/Ang-(1-7)/MasR axis, has multiple beneficial effects, for example, mitigation of hypertension,[80,84,131] CVD,[77,82,129] insulin resistance,[79,132,133] and T2DM.[5,25,134] ACE2 also increases NO bioavailability,[79,80,135] subsequently mitigating endothelial dysfunction,[76,82,133] vascular permeability[43,64,76] and thrombosis.[6,76,136] Furthermore, via decreased MAPK signaling,[44,71,137] ACE2 reduces inflammation,[3,43,71] ROS production,[78,138,139] and neutrophil accumulation.[56,76,95] In this manner, ACE2 protects against pulmonary edema,[35,75,76] fibrosis,[64,71,77] and ARDS.[38,43,81]

Low ACE2 expression has been associated with hypertension, CVD, T2DM, inflammation, and ARDS,[4–6] which happen to be risk factors for (severe) COVID-19 complications.[1,15,23] Since ACE2 is the SARS-CoV-2 cell-entry point,[2,3,6] there has been speculation that elevated ACE2 expression may increase susceptibility for SARS-CoV-2 infection.[140–142] ACE2 expression is higher in females than in males,[4,134] and declines with age[5,141] (in men more so than in women).[6,143] This can be explained by the upregulation of ACE2 expression by Estrogen,[4,131] and the X-chromosomal location of the ACE2 gene[3,129,144] (which is regulated epigenetically via DNA methylation).[12,13] DNA methylation is associated with biological age,[12,145,146] which suggests that biological age may be a more accurate risk factor for severe COVID-19 complications compared to chronological age.[13,147] This pattern of ACE2 expression may partly explain why elevated ACE2 levels possibly have no negative effects on COVID-19 susceptibility.[4,6,134] Also, there is a negative correlation between ACE2 expression and COVID-19 fatality.[4,5,144] SARS-CoV-2-induced downregulation of ACE2 expression may especially be detrimental in people with comorbidities, since they initially have a lower ACE2 baseline.[4,6,21] Additional COVID-19-mediated ACE2 deficiency may amplify the RAAS dysregulation,[5,6,76] resulting in upregulation of Ang-II, which is indeed significantly elevated in COVID-19 patients.[21,76,125] In the lungs, such dysregulation can induce the progression of inflammatory and thrombotic processes, because Ang-II is now unopposed by ACE2.[6,21,125] This suggests that ACE2 may not be the culprit in COVID-19, but may actually have an important protective role, despite the ACE2-mediated cell-entry mechanism of SARS-CoV-2.[5,76,134] A low ACE2 expression (or reserve) may contribute to the progression of COVID-19 to a (more) severe or fatal stage.[4,6,125] Because of the high intrinsic affinity of ACE2 with the SARS-CoV-2 spike (S1) proteins,[6] a lower ACE2 expression may not affect the susceptibility for SARS-CoV-2 infection at all.[6,127]

Although many effects of ACE2 have been attributed to the downregulation of Ang-II levels, other substrates play a major role in ACE2-related functions as well.[56,64,81]

The framework we have now established consists of the following hypothesis: *"a SARS-CoV-2-induced RAAS imbalance, comprised of reduced ACE2 expression (and a subsequent elevated Ang-II activity), plays a role in severe COVID-19 complications."*

There are still many loose ends in this narrative. In order to connect these, two more systems will be discussed, that is, the CS and the KKS. The CS and the KKS are linked.[107,148,149] The KKS and the RAAS are linked as well.[25,56,64] The RAAS, CS, and KKS, form a trinity of systems with several regulatory axes contributing to severe COVID-19 complications.

Complement system

The CS is an important component of the innate immune system, involved in host defense against micro-organisms, clearance of immune complexes and removal of apoptotic cells,[149–151] and is intrinsically linked to the coagulation pathway.[21,151,152] The CS is a key mediator of lung damage during (corona virus) infections, raising the possibility that CS activation may play a role in severe COVID-19 complications.[16,74,153]

Although most CS components are synthesized in the liver, type-II pneumocytes provide local CS proteins.[154–156] The CS components C1, $C3_a$, $C5_a$, as well as the $C5_b$-C9 MAC, all contribute to increased endothelial permeability.[107,157,158]

The CS can be activated via three pathways, that is, the classical, lectin, or alternative pathway.[154,159,160] The classical pathway entails the creation of immune complexes with IgM/IgG antibodies, binding predominantly to pathogenic antigens.[107,159,161] C1 binds to the antibody and forms C3 and C5, via initiating a series of enzymatic cascades.[107,154,162] C3 and C5 are both cleaved to $C3_a$/$C3_b$ and $C5_a$/$C5_b$ respectively.[107,154,160] $C3_a$ and $C5_a$ act as chemotactic agents for phagocytes.[107,151,154] $C3_b$ is involved in opsonization of pathogens that are subsequently destroyed by phagocytes.[107,154,159] $C5_b$-C9 forms a MAC that induces cell-lysis by punching holes through their membranes.[107,154,161] The lectin pathway involves the interaction of MBL with the pathogen (or the surface of a pathogen-infected cell), followed by the subsequent binding and activation of MASP2, directly activating similar CS cascades as in the classical pathway.[74,153,154] The alternative pathway involves a spontaneous conformation change of C3, and after a short cascade, C3 is cleaved into $C3_a$ and $C3_b$ without the use of antibodies, leading to similar cascades as the classical pathway.[151,154,163] The CS is inhibited by the SerPin $C1_{INH}$ via inhibition of C1 in the classical pathway, MASP2 in the lectin pathway, and $C3_b$ in the alternative pathway.[107,149,164]

Excessive CS activation can lead to inflammation and (excessive) neutrophil recruitment via opsonization and (via $C3_a$- and $C5_a$-mediated)[107,153,156] chemotaxis.[16,148,153] Excessive CS activation (on the endothelial surface) can lead to vascular problems, for example, endothelial damage (via MAC-induced lysis),[74,148,154] vascular permeability,[107,148,158] thrombosis,[148,151,152] (diffuse) TMA,[159,162,165] and DIC.[161,166,167] This is how excessive CS activation exacerbates ARDS,[16,74,154] pulmonary fibrosis,[50,168,169] and possibly organ dysfunction.[16,151,159]

In at least a subset of severe COVID-19 patients an excessive CS activation is found via the lectin pathway,[153,170,171] as demonstrated by elevated $C5_b$-C9 MAC components, MBL-MASP2 in the pulmonary microvasculature, and parenchymal neutrophils.[74] This is consistent with sustained and systemic CS activation and an associated pro-coagulant state.[21,74] A possible modus operandi for additional CS activation via the lectin pathway in COVID-19 is the binding of SARS-CoV-2 N-proteins to MASP2.[153] This leads to excessive CS activity,[153,171] further exacerbating CS-mediated MAC formation, inflammation, and concurrent activation of the coagulation pathway,[21,74] resulting in ARDS[16,153] and thrombosis[74,170] (Figure 2). The observed high D-dimer and von Willebrand Factor (and its associated thrombotic activity) in severe COVID-19 patients,[111,119,120] can at least be partially explained by excessive CS activation (and associated MAC-mediated endothelial dysfunction), followed by an activated coagulation pathway.[74,153,159]

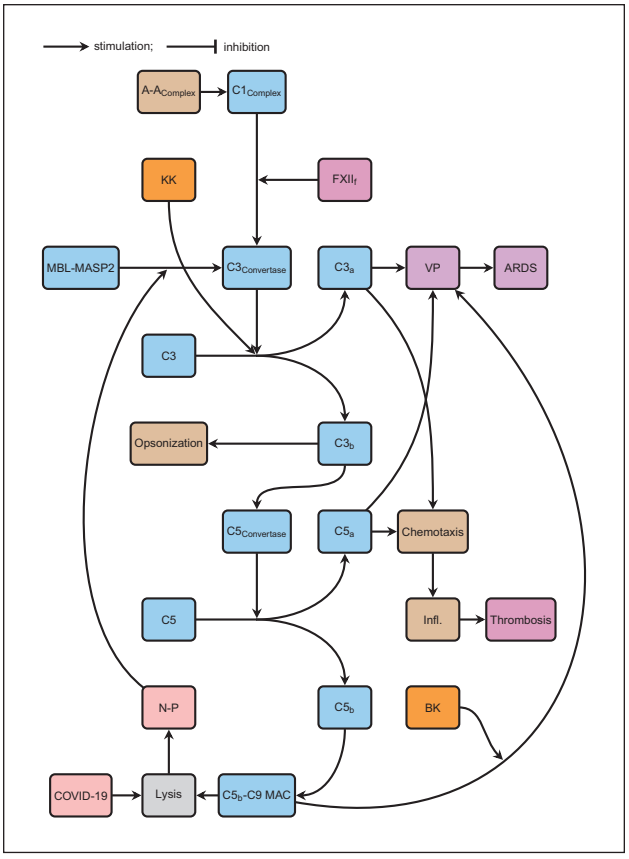

Figure 2. The CS including the COVID-19-induced lectin pathway feedback mechanism.

Our framework can now be expanded with the hypothesis: *"an excessive CS activation plays a significant role in severe COVID-19 complications."*

The CS is not only linked to the coagulation pathway,[151,161,166] but to the KKS as well,[107,148,149] which will be discussed next.

Kallikrein-kinin system

The KKS, like the CS, is an important part of the innate immune system,[149,172,173] and is activated during inflammation.[148,164,174] The KKS consists of Hageman Factor (Factor XII), PK, HK, the proteolytic KK enzymes, and

effector peptides, such as BK (and its active metabolite *des*-Arg^9-BK).[107,149,164] Factor XII gets activated via inflammatory processes and converts to Factor XII$_a$, which in turn converts PK into KK, initiating the kinin cascade[107,149,164] (cleaving HK to generate BK and other metabolites, such as *des*-Arg^9-BK).[85,148,164] Factor XII$_a$ also turns Factor XI into Factor XI$_a$, subsequently activating the coagulation pathway, linking it to the KKS.[107,149,175] KK turns Factor XII$_a$ into Factor XII$_f$, which initiates the CS via C1$_r$ cleavage, linking the KKS directly to the CS.[107,149,176] KK also turns pro-Renin into Renin, linking the KKS directly to the RAAS.[64,177,178] All these processes are inhibited by the SerPin C1$_{INH}$.[107,149,164]

The kinin BK is not very stable, and is easily degraded by ACE.[81,85,88] Another kinin, *des*-Arg^9-BK, is much more stable than BK,[148,164,179] but can be degraded by ACE2.[25,56,64] This shows another direct link between the KKS and the RAAS.[36,75,81]

KKS signaling is mediated by two receptors, B2R and B1R.[85,148,180] While the B2R is ubiquitously expressed in most healthy tissues, B1R is synthesized *de-novo* and upregulated as a consequence of tissue injury or inflammatory processes.[81,164,180] BK is the primary ligand for B2R, whereas *des*-Arg^9-BK is the primary ligand for B1R.[85,107,148]

Kinins are potent inflammatory mediators,[36,88,164] increasing vascular permeability[85,180,181] and neutrophil recruitment.[56,148,174] This may lead to inflammation,[25,148,180] edema,[75,164,180] and pain.[85,164,174] Uncontrolled and excessive KKS activation, or abnormal kinin degradation, can cause an acute accumulation of BK and/or *des*-Arg^9-BK, leading to excessive inflammation.[56,107,148] Excessive KKS activation may also promote T2DM via (MAPK-mediated)[181–183] destruction of pancreatic Langerhans islets,[85,184,185] and increase vascular permeability.[148,164,180] This results in exacerbated edema,[85,107,164] neutrophil migration,[56,148,174] thrombosis,[148,186,187] ARDS,[25,75,188] and possibly even organ dysfunction.[25,187,189]

The KKS and the CS are intrinsically linked at multiple levels, and are both activated during (vascular) inflammation (i.e. via gC1$_q$R, which binds both C1$_q$ and HK).[107,148,149] Simultaneous and uncontrolled excessive activation of both the KKS and CS (on the endothelial surface) is largely responsible for increased vascular permeability and edema.[107,148,149] KK, which cleaves HK and subsequently releases BK, also cleaves and activates C3.[148,190,191] The KKS[107,148,149] and CS[150–152] are both intrinsically linked to the coagulation pathway. The endothelial permeability-inducing effect of the C5$_b$-C9 MAC is regulated by BK.[107,192,193] The KKS and CS are both inhibited by C1$_{INH}$.[148,149,164]

ACE2 degrades the otherwise stable *des*-Arg^9-BK.[56,64,81] SARS-CoV-2 reduces ACE2 expression.[3,6,125] A reduction in pulmonary ACE2 subsequently increases Ang-II[5,125,194] and impairs the degradation of the *des*-Arg^9-BK/B1R axis of the KKS.[6,25,56] This exacerbates neutrophil migration[56,148,174] and ARDS.[25,56,75] The *des*-Arg^9-BK/B1R axis of the KKS is not affected by corticosteroids,[195–197] which means that as long as the virus is present, ACE2 will *not* be, and the kinin-induced ARDS *will* persist.[75]

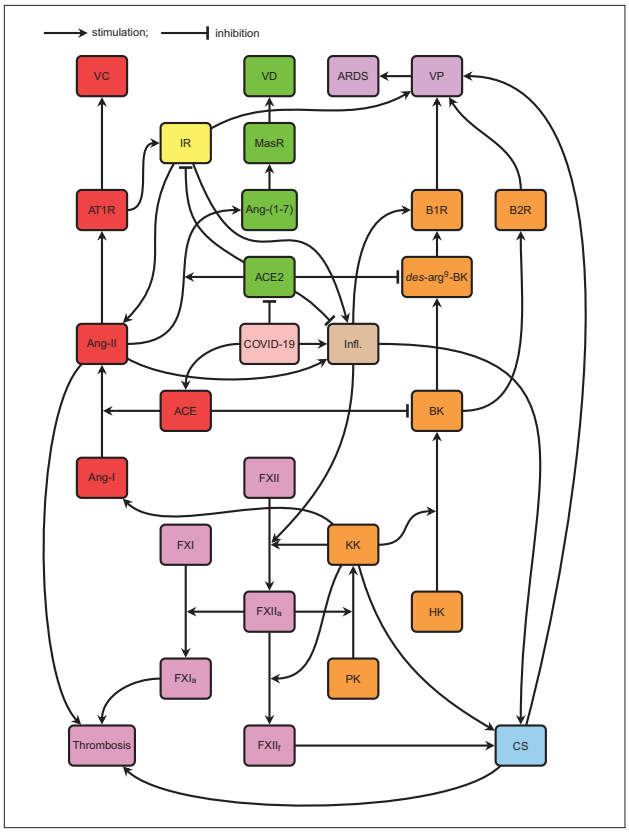

Figure 3. The trinity of systems: RAAS, CS, KKS, and their interconnections, as well as their interactions with IR, the coagulation pathway, inflammation, and COVID-19.

We now have established multiple connections between the RAAS, CS, KKS, and the coagulation pathway. In our trinity of systems, the RAAS[3,76,77] controls vasoconstriction and vasodilation, whereas the KKS[85,180,181] and the CS[107,158,198] control vascular permeability and vasodilation. ACE2 is the one ring that rules them all[75] (Figure 3). The SerPin C1$_{INH}$ effectively suppresses the KKS,[107,149,164] the coagulation pathway,[107,151,152] and all three pathways of the CS.[150,152,176]

Our framework can now be further expanded with the hypothesis: *"a SARS-CoV-2-induced reduction of ACE2 expression directly causes a disruption and excessive activation of the KKS, which is not only able to further activate an already active CS, but directly plays a significant role in the exacerbation of severe COVID-19 complications."*

Next, the T2DM interactions with our trinity of systems will be discussed.

Type-2 diabetes mellitus

T2DM is considered to be a metabolic disease, comprising insulin resistance and pancreatic β-cell dysfunction, resulting in insulin deficiency and subsequent hyperglycemia.[99,104,199] T2DM is characterized by comorbid conditions of CVD[89,104,200] and hypertension.[89,201,202] T2DM is also associated with vascular problems, for example, endothelial dysfunction, vascular permeability, platelet dysfunction, and hypercoagulation.[113,203,204] This can be partially contributed to a dysregulated RAAS[5,94,105] (low ACE2[4,5,82] and high Ang-II[79,94,106]). CVD is the main complication of T2DM.[114,204,205] However, clinical CVD can also precede the development of T2DM,[200,206,207] suggesting that T2DM and CVD may both have an underlying cause, for example, a chronic low-grade inflammatory state,[199,208,209] insulin resistance,[53,210,211] or a dysregulated RAAS.[86,89,133]

Obesity

In T2DM, macrophage infiltration into expanding adipose tissue and pancreatic islets,[212–214] as well as macrophage polarization toward the M1 phenotype[99,215,216] (as a result of IL-6 trans signaling),[53,214,217] is involved in the development of chronic low-grade inflammation in obese individuals.[199,208,218] Visceral adipose tissue in particular, is characterized by high secretion of inflammatory cytokines, and T2DM patients have more visceral adipose tissue than nondiabetics.[53,98,219] Furthermore, inflammatory cytokines in adipose tissue stimulate JNK and NF-κB,[99,214,220] which induces insulin resistance.[98,199,221] Finally, the RAAS may be disrupted in expanding visceral adipose tissue, exacerbating inflammation and insulin resistance.[6,222,223]

Insulin resistance

P(*Tyr*)IRS-1 is required for insulin-stimulated activation of the PI3K/Akt/eNOS pathway[99,206,224] and multiple downstream effectors that promote glucose uptake and NO production.[112,225,226] NO has vasoprotective effects,[79,227,228] and its bioavailability depends on the balance between the rate of its eNOS-mediated production and its ROS-mediated inactivation.[104,109,229]

Increased P(*Ser*)IRS-1 and decreased P(*Tyr*)IRS-1[98,224,230] (both induced by JNK and $ERK_{1/2}$) disrupt insulin signaling,[94,199,206] preventing activation of the PI3K/Akt/eNOS pathway.[99,115,231] Chronic P(*Ser*)IRS-1 also targets IRS-1 for degradation or migration to inaccessible subcellular compartments.[54,89,232]

Hyperinsulinemia, caused by insulin resistance, activates both JNK[230,232,233] and $ERK_{1/2}$.[88,234,235] Subsequently this further stimulates P(*Ser*)IRS-1,[97,99,230] which is how hyperinsulinemia exacerbates insulin resistance.[94,232,236] Hyperinsulinemia also upregulates Ang-II, which is how insulin resistance may disrupt the RAAS.[89,237,238]

Ang-II-mediated ROS production increases P(*Ser*)IRS-1[79,88,94] and decreases P(*Tyr*)IRS-1,[86,89,105] effectively inducing insulin resistance[87,239,240] (Figure 1). A vicious cycle between the RAAS and insulin resistance has now been created.[89,241,242]

Insulin resistance is a risk factor for T2DM,[86,206,232] obesity,[85,98,106] hypertension,[88,89,105] and CVD.[87,210,243]

β-Cell dysfunction

The progression from insulin resistance to T2DM implicates the inability of pancreatic β-cells to compensate for increased insulin demand.[53,221,244]

Sustained JNK activation causes pancreatic β-cell dysfunction,[230,232] especially in obese individuals with an exacerbated inflammatory milieu.[99,199,221]

IL-6 increases the proliferation of α-cells and apoptosis of β-cells in the pancreas,[53,245,246] suggesting a link between IL-6 and T2DM.[208,218,247] The role of IL-6 in the proliferation of α-cells may initially compensate for the impaired β-cells in T2DM and contributes to limit hyperglycemia.[53,245,248]

Hyperglycemia increases IL-6 levels, both systemically and locally in pancreatic Langerhans islets,[53,249,250] and promotes β-cell death[99,246,251] (Figure 1).

In T2DM, the KKS is activated and kinins cause damage to pancreatic Langerhans islets, suggesting a link between the KKS and T2DM.[85]

Furthermore, in T2DM, ACE2 expression is downregulated,[15,133] and increased Ang-II plays a part in reducing β-cell function via ROS-mediated apoptosis,[89,252] suggesting a link between RAAS disruption and T2DM.[64,86,89]

Hyperglycemia

Pancreatic β-cell dysfunction leading to T2DM results in insulin deficiency and subsequent hyperglycemia,[104,115,221] which has a plethora of detrimental effects.

Hyperglycemia increases the production of IL-6[53,55,250] and AGEs.[104,113,253] AGEs bind to RAGEs[99,104,254] (which are expressed on the surface of many cell types, including endothelial, epithelial, and immune cells),[62,113,255] and subsequently increases PKC-mediated[55,256,257] ROS production via NADPH oxidase.[118,203,258] Hyperglycemia-mediated ROS production stimulates $ERK_{1/2}$,[259–261] JNK,[99,262,263] and p38-MAPK,[264–266] subsequently initiating crosstalk with NF-κB[86,104,267] (Figure 1). This ROS-mediated MAPK signaling downregulates ACE2,[14,15,268] and upregulates ACE,[14,268,269] Ang-II,[89,268,270] ADAM-17,[5,271,272] and IL-6.[114,249,267] It also disrupts endothelial tight-junctions,[45,108,257] and reduces NO bioavailability (via eNOS uncoupling,[113,273,274] decreased NO production,[55,115,267] and NO scavenging[104,109,275]). Hyperglycemia-mediated ROS production effectively promotes endothelial dysfunction.[104,108,113] Therefore hyperglycemia increases vascular

permeability,[39,115,276] and subsequently promotes (pulmonary) edema.[55,203,277]

Hyperglycemia also promotes thrombosis,[24,113,118] via platelet activation, increased coagulation factors, and decreased fibrinolysis.[114,205,278]

Furthermore, hyperglycemia (even short-term) dysregulates both the innate and adaptive immune system.[24,55,265] This may affect neutrophil-IL-6 signaling, chemotaxis, phagocytosis, respiratory burst, anti-microbial activity, and production of inflammatory cytokines.[23,55,266] This creates a milieu in which SARS-CoV-2 can flourish.[15,23,24]

Finally, hyperglycemia also interferes with the CS, upregulating expression of several CS component genes, hindering $C3_b$-mediated opsonization and IG-function via glycation.[55,279,280]

Well-controlled blood-glucose levels reduce the risk of severe COVID-19 complications.[23,24,281] Therefore, our framework can now be further expanded with the hypothesis: *"T2DM-induced hyperglycemia is not only just a risk factor for severe COVID-19 complications, but is actually exacerbated (possibly even induced) by COVID-19."*

Next, the role of IL-6 signaling, and the interactions with T2DM and COVID-19 complications, will be discussed.

Interleukin 6

IL-6 has both pro- and anti-inflammatory characteristics.[53,208,282] Dysregulated or excessive IL-6 signaling is considered to be involved in insulin resistance,[104,206,247] β-cell dysfunction,[53,245,251] T2DM,[53,208,218] and CVD.[208,283,284]

Various cell types can locally produce IL-6,[284–286] which can be transported through the circulation, affecting more distant regions in the body.[53] Immune cells are simultaneously both sources and targets of IL-6.[53,283,286] Betacoronavirus infection of immune cells, for example, monocytes, macrophages, and dendritic cells, will result in their activation and subsequent secretion of IL-6.[287]

To exert its physiological effects, IL-6 utilizes both the classic and trans signaling pathway.[208,213,288] In classic signaling, IL-6 binds to mIL-6R and forms a complex with gp130, after which downstream signaling is mediated via JAK and STAT3.[283,284,286] In trans signaling, extracellular sIL-6R can bind to IL-6, forming a complex with gp130, after which downstream signaling is mediated via JAK and STAT3 in cells that do not express mIL-6R[53,284,289] (such as endothelial[53,116,284] and pancreatic α and β cells[245,246,248]). IL-6 classic signaling is mostly involved in anti-inflammatory activities, whereas IL-6 trans signaling is mostly involved in pro-inflammatory activities.[53,213,289]

Most cells express gp130, while mIL-6R is mostly found on monocytes, macrophages, neutrophils, and α- and β-cells of pancreatic Langerhans islets.[53,208,245] The widespread expression of gp130 on most cell types, including endothelial cells, dramatically expands the range of IL-6 target cells using trans signaling.[208,284,287] In order to prevent a systemic response to IL-6 trans signaling, sgp130 specifically blocks trans signaling without affecting classical signaling, and basically constitutes a physiological buffer for circulating IL-6.[53,284,288]

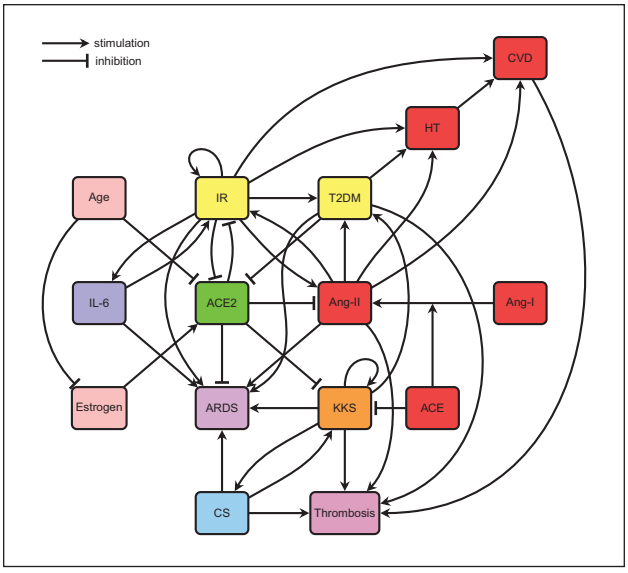

Figure 4. The RAAS, CS, KKS, IR, IL-6, and their interactions regarding severe COVID-19 complications, for example, ARDS and thrombosis, with ACE2 as master regulator.

IL-6 activates $ERK_{1/2}$,[54,206,290] JNK,[291–293] and p38-MAPK,[89,294,295] subsequently initiating crosstalk with NF-κB[44,104,249] (Figure 1). This IL-6-mediated MAPK signaling decreases P(*Tyr*)IRS-1[54,104,247] and increases P(*Ser*)IRS-1,[206,296,297] inducing insulin resistance[53,89,296] and impairing NO production.[54,206,290] IL-6-mediated MAPK signaling also disrupts endothelial tight-junctions[116,285,298] and induces endothelial cell contraction.[285,299] Therefore, IL-6 effectively increases vascular permeability[70,104,285] and exacerbates edema[116] and lung injury/ARDS.[70,300,301] The lack of mIL-6R on endothelial cells indicates trans signaling as the main mechanism involved in the detrimental effects of IL-6 on vasculature.[53,116,284]

IL-6 also induces epigenetic changes (regarding genes involved in insulin signaling) via DNMT-induced alteration of DNA methylation patterns, promoting endothelial dysfunction[54,302] and insulin resistance.[213,303,304]

IL-6 levels are significantly elevated in COVID-19 patients.[22,305,306] IL-6 plays an important role in CRS,[16,306,307] exacerbates ARDS,[70,287,305] and predicts mortality[282,305,308] (Figure 4).

Our framework can now be further expanded with the hypothesis: *"Excessive IL-6 trans signaling significantly contributes to severe COVID-19 complications."*

In the last section, we will briefly discuss some potential attractive therapeutic targets and their pharmacological interactions.

Pharmacological interactions

Due to the lack of approved targeted medication for COVID-19,[16,22,309] and developing an effective and safe vaccine may require some time, it is recommended to explore multiple potential therapeutic targets to mitigate severe COVID-19 complications.

TMPRSS2 inhibition

Since TMPRSS2 is essential for SARS-CoV-2 membrane fusion and subsequent cell-entry,[2,3,7] inhibition of TMPRSS2 activity can potentially prevent severe COVID-19 complications.[3,8,310] Nafamostat Mesylate, a clinically approved and safe medication for pancreatitis, inhibits TMPRSS2-mediated SARS-CoV-2 envelope-membrane fusion and subsequent cell-entry.[3,311,312] Nafamostat Mesylate may also protect against thrombosis and DIC via its anti-coagulant properties.[3,313]

ACE inhibition/angiotensin II receptor blockage

Both ACE-inhibitors and ARBs reduce hypertension,[85,96,129] CVD,[80,96,129] pneumonia,[314–316] insulin resistance (and T2DM).[85,86,106] They also increase ACE2 expression[1,76,80] and mitigate pulmonary edema.[71,317,318] ACE-inhibitors however, also inhibit BK degradation, subsequently increasing BK, possibly increasing vascular permeability[75,107,149] and systemic acquired angioedema.[75,149,319]

Because ACE-inhibitors and ARBs upregulate ACE2 expression,[1,76,80] and SARS-CoV-2 uses ACE2 for cell-entry,[3,6,8] it has been speculated that ACE-inhibitors and ARBs can have negative effects in COVID-19 patients.[140–142] Multiple studies however, show no association between both ACE-inhibitors and ARBs, and increased susceptibility for COVID-19 or the severity of its complications.[320–322]

Various experimental models[37,71,76] show that rhsACE2 activates the protective ACE2/Ang-(1-7)/MasR-axis of the RAAS,[71,76,80] degrades *des*-Arg^9-BK,[75] and improves ARDS symptoms.[44,71,82] Therapeutic use of rhsACE2 in COVID-19 patients may have beneficial effects, such as effectively sequestering circulating viral particles to prevent S-protein interactions with membrane-bound ACE2, while simultaneously rebalancing the RAAS into a more protective equilibrium.[6,76,323] Clinical-grade rhsACE2 can significantly inhibit SARS-CoV-2 infections in vitro (in a dose-dependent manner), reduce viral load by a factor of 1.000 – 5.000,[324] and is currently being tested in a phase-II trial in Europe.[5,127]

Complement/kinin inhibition

Inhibiting an excessively active CS may reduce severe COVID-19 complications, for example, ARDS,[153] pulmonary fibrosis,[50,154] (diffuse) TMA,[159,171] and DIC.[74,151,153] Eculizumab is a monoclonal antibody that binds to C5 and prevents cleavage into $C5_a$ and $C5_b$, as well as the formation of the $C5_b$-C9 MAC,[16,74,325] and may also reduce the risk of TMA[162,163,165] and DIC.[166,326]

Inhibiting the KKS, either by inhibiting kinin production or blocking B1R/B2R, may improve COVID-19-induced ARDS.[25,75,327] Since B1R is upregulated during inflammation,[56,107,180] and *des*-Arg^9-BK is much more stable than BK,[148,164] the *des*-Arg^9-BK/B1R axis is of major importance in vascular permeability during inflammation.[164] Unfortunately, there currently is no approved B1R-inhibitor available.[25,75,327] Icatibant is a selective B2R antagonist, traditionally used for hereditary angioedema,[25,107,164] and may improve severe COVID-19 complications.[75,327] B2R inhibition, besides reducing the KKS, also reduces the CS.[148]

$C1_{INH}$ inhibits the activation of both the CS and KKS,[148] qualifying it as an attractive potential therapeutic option for severe COVID-19 complications. Plasma-derived $C1_{INH}$, a first-line therapy for hereditary angioedema, appears to be safe.[328] Ruconest, a recombinant human C1-esterase-inhibitor, has achieved some good preliminary results in treating COVID-19 patients, according to a press release.[329]

Interleukin 6 inhibition

IL-6 inhibition mitigates vascular permeability and alveolar-capillary barrier disruption.[70,116,309]

Tocilizumab is a monoclonal antibody, mainly used for the treatment of rheumatoid arthritis.[22,308,330] It inhibits IL-6[305,306,331] via binding to both mIL-6R and sIL-6R, resulting in complete blockade of both classic and trans IL-6 signaling pathways.[287,308,330] Disruption of both pro- and anti-inflammatory activities of IL-6 may cause side-effects, for example, secondary (bacterial or fungal) infections, liver malfunction, or hypercholesterolemia.[53,208] Despite the possible side-effects, preliminary studies show that Tocilizumab appears to be effective and safe regarding severe COVID-19 complications.[22,306,309] Tocilizumab however, seems less effective in hyperglycemic patients.[332]

Sgp130Fc (a recombinant version of sgp130) specifically blocks IL-6 trans signaling, without affecting the anti-inflammatory and protective classical IL-6 signaling.[53,208,288] Therefore sgp130Fc may result in better therapeutic outcomes with fewer undesired side-effects.[53,208,333] Sgp130Fc has demonstrated robust efficacy in the treatment of several autoimmune and inflammatory conditions[53,288] with fewer side-effects than global IL-6-inhibitors.[53,208,333] Sgp130Fc may potentially have therapeutic benefits for COVID-19-induced ARDS.[333]

Summary

We have established the concluding framework regarding the COVID-19 pathophysiological crossroads: *"COVID-19 disrupts the RAAS balance via reduction of*

ACE2 expression and a subsequent elevation of Ang-II. COVID-19-induced reduction of ACE2 expression induces excessive activation of the KKS and subsequently the CS. T2DM-induced hyperglycemia is not only just a risk factor for severe COVID-19 complications, but is actually exacerbated (possibly even induced) by COVID-19. Ang-II, excessive KKS and CS activation, hyperglycemia, and IL-6 trans signaling, all contribute significantly to severe COVID-19 complications (e.g. ARDS and thrombosis/DIC)." The RAAS, CS, KKS, and the coagulation pathway, are all intrinsically connected sensitive systems, with ACE2 as master regulator. Elevated ACE2 baseline levels may protect from severe COVID-19 complications.

There are no effective approved medications against COVID-19 yet, and a vaccine may be a long way off. However, several attractive therapeutic targets in the RAAS, CS, and KKS have shown promising preliminary results against severe COVID-19 complications.

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Appendix

Abbreviations

$\Delta\Psi_M$	mitochondrial membrane potential
A-$A_{Complex}$	antigen–antibody complex
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ADAM-17	a disintegrin and metalloprotease domain 17
ADAMTS13	ADAM with a thrombospondin type 1 motif, member 13
AFC	alveolar fluid clearance
AGE	advanced glycation end product
Akt	protein kinase B
ALI	acute lung injury
Ang	angiotensin
ARB	AT1R blocker
ARDS	acute respiratory distress syndrome
AT1R	Ang-II type 1 receptor
B1/2R	bradykinin receptor 1/2
BK	bradykinin
$C1_{INH}$	C1 inhibitor
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRS	cytokine release syndrome (cytokine storm)
CS	complement system
CVD	cardiovascular disease
DIC	disseminated intravascular coagulation
DNA	desoxyribonucleic acid
DNMT	DNA methyl transferase
ECM	extra-cellular matrix
ENaC	epithelial sodium channel
eNOS	endothelial nitric oxide synthase
ERK	extracellular signal-regulated kinase
(s)gp130	(soluble) glycoprotein 130
HK	high molecular weight kininogen
HT	hypertension
ICU	intensive-care unit
IG	immunoglobulin
IL-6	interleukin 6
IR	insulin resistance
IRS-1	insulin receptor substrate 1
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
K_{ATP}	membrane potassium channels
KK	kallikrein
KKS	kallikrein-kinin system
MAC	membrane attack complex
MAPK	mitogen-activated protein kinase
MASP2	MBL serine protease 2
MasR	Mas receptor
MBL	mannose-binding lectin
(m/s)IL-6R	(membrane-bound/soluble) IL-6 receptor
NADPH	nicotinamide adenine dinucleotide phosphate
NET	neutrophil extracellular trap
NF-κB	nuclear factor κ light-chain-enhancer of activated B cells

N-P	SARS-CoV-2-produced N-proteins
NO	nitric oxide
PI3K	phosphatidyl inositol-4,5-bisphosphate 3-kinase
PK	prekallikrein
PKC	protein kinase C
P(*Ser*/*Tyr*)IRS-1	serine/tyrosine phosphorylation of IRS-1
RAAS	renin angiotensin aldosterone system
RAGE	receptor for AGE
rhsACE2	recombinant human soluble ACE2
RNA	ribonucleic acid
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SerPin	serine protease inhibitor
$SSRNA^+$	positive-sense, single-stranded RNA
STAT	signal transducer and activator of transcription
T2DM	type-2 diabetes mellitus
TJ	(endothelial) tight-junction(s)
TMA	thrombotic microangiopathy
TMPRSS2	transmembrane protease serine 2
VC	vasoconstriction
VD	vasodilation
VP	vascular permeability