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CONTROVERSIAL ROLE OF ACE2 IN SARS-COV-2 INFECTION: A LITERATURE REVIEW

FUNÇÃO CONTROVERSA DA ACE2 NA INFECÇÃO PELO SARS-COV-2: UMA REVISÃO DE LITERATURA

EL PAPEL CONTROVERSIAL DE ACE2 EN LA INFECCIÓN POR SARS-COV-2: UNA REVISIÓN DE LA LITERATURA

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ABSTRACT

Bibliographic Review: Coronavirus-19 Disease (COVID-19) presents a clinical spectrum from oligosymptomatic to severe and multisystemic inflammation, which may be followed by death. SARS-CoV-2, the virus responsible for COVID-19, has as its main human receptor the Angiotensin-Converting Enzyme 2 (ACE2), which is also crucial in the control of the inflammatory response, through the Renin-Angiotensin-Aldosterone System (RAAS). **Objective:** Due to the controversial roles of ACE2 in SARS-CoV-2 infection, the aim of this literature review was to address its distribution in the human body, associating it with the severity of COVID-19. Thus, using the terms ACE2, SARS-CoV-2 and Coronavirus, a search was performed on the SciELO, PubMed and Scopus platforms. The research revealed that the aggressiveness of SARS-CoV-2 is related to its ability to interact with the host and, consequently, with ACE2 - widely distributed in organs and tissues. **Final Considerations:** However, since COVID-19 is an inflammatory disease, and ACE2 is critical in controlling inflammation, especially in RAAS, the data compiled in this review infers that ACE2 is more likely to act as a protective factor, against the severity of COVID-19.

Keywords: Severe Acute Respiratory Syndrome. Angiotensin Converting Enzyme 2. Coronavirus disease. Renin-Angiotensin-Aldosterone System. Coronavirus.

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RESUMO
Revisão bibliográfica: A Doença do Coronavírus-19 (COVID-19) apresenta um espectro clínico de oligossintomático a inflamação severa e multissistemica, podendo ser seguida de óbito. O SARS-CoV-2, vírus responsável pela COVID-19, tem como principal receptor humano a Enzima Conversora da Angiotensina 2 (ACE2), que também é crucial no controle da resposta inflamatória, por meio do Sistema-Renina-Angiotensina-Aldosterona (RAAS). **Objetivo:** Devido às funções controversas da ACE2 na infecção pelo SARS-CoV-2, o objetivo desta revisão de literatura foi abordar sua distribuição no corpo humano, associando-a à severidade da COVID-19. Dessa maneira, utilizando os termos ACE2, SARS-CoV-2 e Coronavírus, foi realizada uma busca nas plataformas SciELO, PubMed e Scopus. A pesquisa revelou que a agressividade do SARS-CoV-2 está relacionada à sua capacidade de interagir com o hospedeiro e, consequentemente, com a ACE2 - amplamente distribuída em órgãos e tecidos. **Considerações finais:** No entanto, uma vez que a COVID-19 é uma doença inflamatória, e que a ACE2 é fundamental no controle da inflamação, sobretudo em RAAS, os dados compilados nesta revisão inferem que a ACE2 está mais propensa a atuar como um fator de proteção, contra a severidade da COVID-19.

Palavras-chave: Síndrome Respiratória Aguda Severa. Enzima Conversora de Angiotensina 2. Doença do Coronavírus. Renin-Angiotensina-Aldosterona-Sistema. Coronavírus.

RESUMEN
La enfermedad por coronavirus-19 (COVID-19) presenta un espectro clínico que va desde la inflamación oligosintomática hasta la inflamación grave y multisistémica, que puede ir seguida de la muerte. El SARS-CoV-2, el virus responsable del COVID-19, tiene como principal receptor humano la Enzima Convertidora de Angiotensina 2 (ECA2), que también es crucial en el control de la respuesta inflamatoria, a través del Sistema Renina-Angiotensina-Aldosterona (RAAS). Debido a los controvertidos papeles de la ECA2 en la infección por SARS-CoV-2, el objetivo de esta revisión de la literatura fue abordar su distribución en el cuerpo humano, asociándola con la gravedad de COVID-19. Así, utilizando los términos ACE2, SARS-CoV-2 y Coronavirus, se realizó una búsqueda en las plataformas SciELO, PubMed y Scopus. La investigación reveló que la agresividad del SARS-CoV-2 está relacionada con su capacidad para interactuar con el huésped y, en consecuencia, con ACE2, ampliamente distribuida en órganos y tejidos. Sin embargo, dado que COVID-19 es una enfermedad inflamatoria y ACE2 es fundamental para controlar la inflamación, especialmente en RAAS, los datos recopilados en esta revisión infieren que es más probable que ACE2 actúe como un factor protector, contra la gravedad de COVID-19.

Palabras clave: Síndrome Respiratorio Agudo Severo. Enzima Convertidora de Angiotensina 2. Enfermedad por Coronavirus. Sistema Renina-Angiotensina-Aldosterona. Coronavirus.

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INTRODUCTION

Coronaviruses (CoVs) pose a serious threat to global health, as previously evidenced by Severe Acute Respiratory Syndrome (SARS), caused by SARS-CoV; Middle East Respiratory Syndrome (MERS), caused by MERS-CoV and, currently evidenced, by Coronavirus-19 disease (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (EUN 2020).

SARS-CoV-2 is an enveloped virus, which contains a positive strand Ribonucleic Acid (RNA) and twenty-one major proteins. These proteins are sixteen Non-structural proteins (NSp) (NSp1 - NSp16) and five Structural proteins (Sp) - Hemagglutinin Esterase (Sp-HE), Membrane (Sp-M), Envelope (Sp-E), Nucleocapsid (Sp-N) and the Spike (Sp-S) protein. Among the Sps, the spike protein has been highlighted due to its role in binding the SARS-CoV-2 to human Angiotensin Converting Enzyme 2 (ACE2) (FEHR & STANLEY, 2015).

Although SARS-CoV-2 is a new virus and the knowledge regarding its mechanism of infectivity remains inconclusive, it is known that SARS-CoV-2 cannot connect to human ACE2 autonomously (DALAN *et al*. 2020; HUANG *et al*. 2020). Thus, proteases such as Transmembrane Protease Serine 2 (TMPRSS2) and Furin type 1 membrane-bound (F-mb1), among others, provide proteolytic cleavage of Sp-S into two fragments (S1 and S2), hence viral connection with ACE2. These events are followed by viral entry in host cell and the establishment of the infection **(**XIAOWEI *et al*. 2020; ORTEGA *et al*. 2020).

Once the Infection is established, most individuals are clinically asymptomatic. However, a minimal amount of people, especially the most vulnerable groups (e.g. elderlies and individuals with underlying metabolic conditions such as diabetes, hypertension and hyperlipidemia), have severe and/or critical clinical manifestations of COVID-19 that can even lead to death **(**DALAN *et al*. 2020**)**.

Thus far, it's not known exactly why some individuals with COVID-19 are asymptomatic, while others develop severe illness. The literature reveals that the aggressiveness of SARS-CoV-2, possibly arises from its capacity to infect and spread easily into human cells, tissues and organs (HUSSAIN *et al*. 2020). Therefore, since the SARS-CoV-2 infection mechanism remains inconclusive, the present study aimed to review the approaches about Angiotensin Converting Enzyme 2 distribution into the human body and its interactions with SARS-CoV-2, associating these factors to the severity of COVID-19.

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SARS-CoV-2 ORIGIN AND GENOME

Coronaviruses (CoVs) are genotypically and serologically divided into four subfamilies: alpha (α), beta (β), gamma (γ) and delta (δ). Human coronavirus infections are caused by α-CoVs and β-CoVs. SARS-CoV-2, the virus responsible for COVID-19, belongs to Nidovirales order, *Coronaviridae* family, Coronavirinae subfamily and β-coronavirus genus (EUN 2020). Furthermore, although more than 38 coronaviruses (commonly disseminated in mice, bats, dromedary, pangolins, among other animals) have been identified, there is no precise answer regarding how some coronaviruses, including SARS-CoV-2, reached humans (HELMY *et al*. 2020).

Heretofore, lines of evidence suggest that SAR-CoV-2 is derived from evolutionary mechanisms, based on two hypotheses: by zoonotic transfer (animal-human) or after zoonotic transfer (human-human) (LUNDSTROM *et al.* 2020). Corroborating to these hypotheses, phylogenetic analysis demonstrated that SARS-CoV-2 shares genomic similarities among other Coronaviruses: 96% similarity with the Bat-CoV - RaTG13; 99% with the Pangolin-CoV; 79% with the SARS-CoV and 50% with the MERS-CoV genome (ZANG *et al*. 2020; WERTHEIM *et al.* 2013; ANDERSEN *et al.* 2020) **(**FIGURE 1**)**.

Figure 1: Lines of evidence about how some coronaviruses reached humans

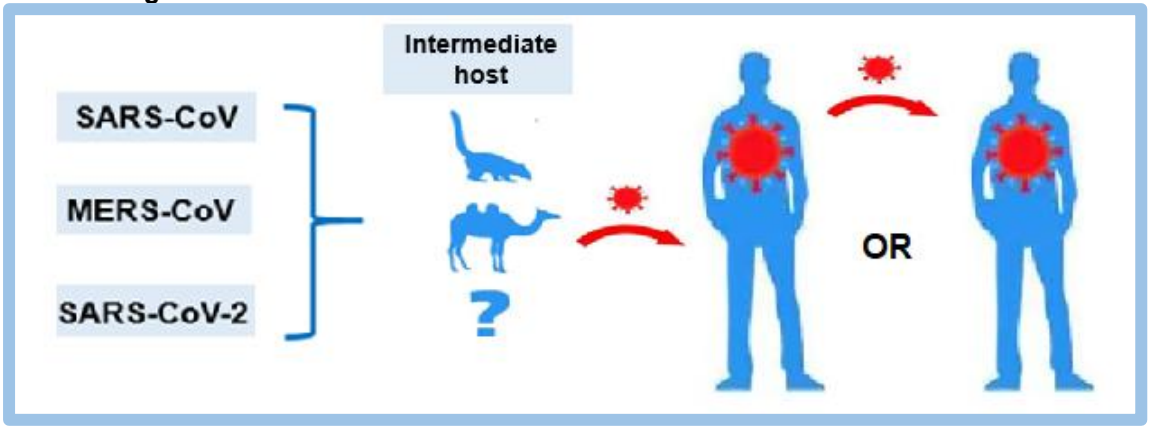

Figure: by authors. **Legend:** Lethal Human Coronaviruses: SARS, MERS and SARS-CoV-2. Possible intermediate hosts: SARS-CoV – pangolin; MERS-CoV - dromedary and SARS-CoV-2 - so far unknown (?). Possible mechanism of evolution and viral transfer: by zoonotic transfer (animal-human) or after zoonotic transfer (human-human) (WERRTHEIM *et al*. 2013; ANDERSEN *et al.* 2020).

SARS-CoV-2 is an enveloped, positive sense, single stranded ribonucleic acid (RNA) virus with a genome size of ~30 kb encoding 14 Open Reading Frames (ORFs) and 27 proteins (SANTERRE *et al*. 2021). The ORF1a and ORF1ab/b located at the 5´- end, encode the Protein Phosphatase (pp1a) and Protein Phosphatase (pp1ab), with are segregated from NSp1 to NSp16, following proteolytic cleavage by the Main Protease

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(Mpro) (MACHHI *et al.* 2020). The 3´- end of the Genome encodes five structural proteins and six accessory proteins (ORF3a, ORF6, ORF7a, ORF7b, ORF8 and ORF10) (SANTERRE *et al*. 2021).

NonStructural Proteins (NSp) play a role to create a suitable environment for RiboNucleic Acid (RNA) synthesis and Replication Transcription Complex (RTC) (YAN *et al*. 2020). Besides that, coronaviruses have enzyme domains and functions that are responsible for RNA replication and transcription of the sub-genomic RNA (WILDE *et al*. 2018). Some NSp_s are responsible for deregulating the host innate immune response - linking to prohibitin (human proteins) - hence, inducing an exacerbated expression of cytokines. Other NSp_s are responsible to set up the necessary components for virus replication, for example: forming the hexadecameric complex, also acting as primase, endoribonuclease, processivity clamp for RNA polymerase and helicase (WIT *et al*. 2016; OU *et al*. 2020). Furthermore, NonStructural proteins encode the RNA-dependent RNA polymerase domain (RdRp), which contributes to add 5′ cap (modified guanine - CAP structure) and the ExoN (part of a gene that encodes a part of the final mature RNA) to viral RNAs, and to shield viral RNA from some recognition *(*WILDE *et al*. 2018; OU *et al.* 2020).

The structural proteins of the SARS-CoV-2 - Spike protein (Sp-S), Membrane protein (Sp-M), Envelope Protein (Sp-E), Nucleocapsid protein (Sp-N) and Hemagglutinin esterase protein (Sp-HE) - play the roles of anchoring, penetration, fusion and the spread of the virus into cells. Sp-M contributes to membrane curvature, as well as binding to the nucleocapsid; Sp-E enables the assembly and release of the virus playing an important role in pathogenesis; Sp-N binds the viral genome and makes association with NSp3, which probably helps to tie the viral genome to the replicase transcriptase complex and, afterward packing the encapsulated genome into viral particles (WIT *et al.* 2016); Sp-HE, only present in β-coronavirus, acts as hemagglutinin, binding sialic acids on the surface of the glycoproteins, as well as contains acetyl esterase activity, which are believed to contribute to the action of the Sp-S, hence viral spread (OU *et al.* 2020).

In addition, among all mentioned structural proteins, it is worth highlighting the Sp-S, distinctive structure on the surface of coronaviruses, which is responsible for binding to ACE2 (main host receptor), thus mediating the fusion with the virus proteins and host cell membranes (XIAOWEI *et al.* 2020). Sp-S is composed of two subunits: subunit peripheral S1, which contains a receptor-binding domain that recognizes and binds to ACE2 (present

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on several human epithelial cell surfaces) and subunit transmembrane S2, responsible for viral fusion with the host cell (LIPPI, 2020; XIAOWEI *et al.* 2020) (FIGURE 2).

Figure 2. SARS-CoV-2 cell entry and ACE2 distribution in the human body

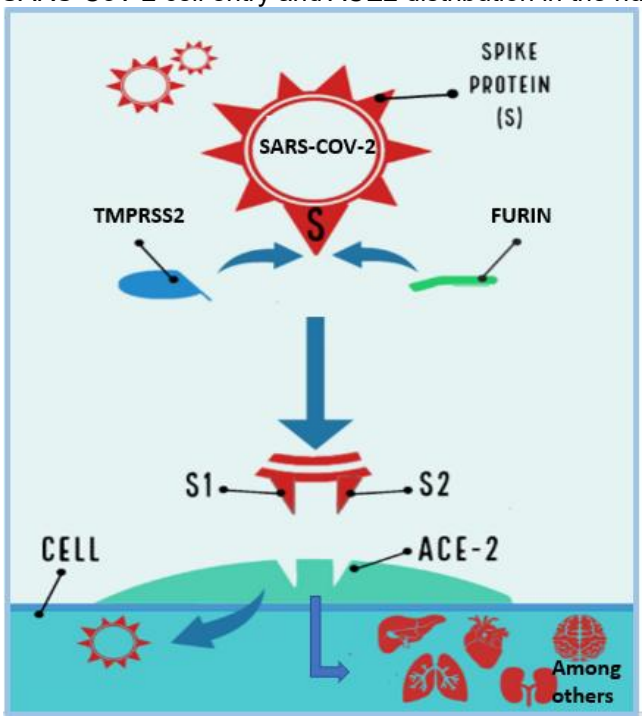

Figure: by authors**. Legend:** representation of viral entry, facilitated by Furin and transmembrane serine enzymes; S1 and S2 subunits of the spike protein; images of the liver, heart, brain, kidneys and lungs representing the organs with ACE2 abundance.

The six accessory proteins of SARS-CoV-2 participate in the viral replication, virus assembly and virus-host interactions (REDONDO *et al.* 2021). As examples, the ORF3, which is subdivided into ORF3 (a, b, c, d) presents the largest accessory proteins: ORF3a interacts with the host immune system, promoting the cytokine storms, inducing necrotic cell death, lysosomal damage, and apoptosis; ORF3b acts a potent interferon (IFN) antagonist; ORF3c or iORF1, has a mechanism that suggests it's interaction within the lipid bilayer such as membrane-disrupting or membrane-associated signaling activities; and the ORF3d, that together with Sp-N and ORF8 proteins, suggest to elicit the strongest antibody responses in COVID-19 patients (HACHIM *et al*. 2020). Besides ORF3 proteins, the ORF6 gene is a potent IFN antagonist, blocking IFN activation in the beginning of the Infection (MIORIN *et al*. 2020). ORF7b interaction with human IS suggests playing a pivotal function in the recruitment of monocytes to the lung and underling symptoms such as heart rate dysregulation in COVID-19 (FOREGON *et al*. 2021). Although the ORF8 function is still elusive, important roles such apoptosis and antagonizing the IFN signaling pathway

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have been attributed to it (WONG *et al*. 2018). The ORF9 is subdivided into ORF9 (a, b), having the ORF9a as an innate immunity suppressor limiting host interferon response, while ORF9b expression, impaired interferon signaling, antigen processing and presentation, complement signaling, as well as induces IL-6 signaling (DOMINGUEZ *et al.* 2020). Finally, the SRF10 protein, which so far does not seem to contribute to the SARS-CoV-2 infection (PANCER *et al*. 2020).

Together, structural proteins (Sp-HE, Sp-M, Sp-E, Sp-N and Sp-S) and sonstructural proteins (NSp1 to NSp16) accomplish several roles such as to connect with the host cell, viral assembly and replication (NAQVI *et al*. 2020; OU *et al*. 2020).

SARS-CoV-2 VIRAL ENTRY MECHANISM AND REPLICATION

Like other viruses, SARS-CoV-2 uses the human cellular machinery to make millions of copies of itself and establish the infection (SHANG *et al.* 2020). Viral infection begins when SARS-CoV-2 connects its Sp-S to human ACE2 and enters the host cell. However, as previously mentioned, autonomously, SARS-CoV-2 cannot connect to ACE2, being necessary that human proteases, such as cathepsins lysosomal cells (e.g. Furin type 1 membrane-bound) and Transmembrane Protease Serine 2 (TMPRSS2), cleave the SARS-CoV-2 Sp-S into S1 and S2 (SHANG *et al*. 2020; SENAPATI *et al.* 2021).

After cleavage and, consequently, changes in Sp-S conformation, S1 subunit acts by binding to human ACE2, S2 acts by promoting viral fusion with the host membrane, and the endosomal vesicle as vehicles for viral genome is generated (LIPPI, 2020). Inside the endosome, the replicase enzymes (already existing in the incoming virus) allow the SARS-CoV-2 to produce new RNA+ molecules (LIPPI, 2020). Then, the decapsulation of the virus and RNA+ molecules release occurs. After that, the two large open reading structures (ORF1a and ORF1b) are translated, hence the activation of pp1a and pp1b polyproteins, both processed into individual NSps, which form the viral transcription and replication complex (V'KOVSKI *et al*. 2021).

The formation of replication sites occurs in the membrane of the endoplasmic reticulum (ER), place where NSp_s, Sp_s and accessory proteins are translated (XIAOWEI *et al*. 2020). Thus, all the proteins needed to create a new virus come together in the middle compartment of Reticle Endoplasmic-Golgi (ERGIC) and the proteins are surrounded by a vesicle (UNDERKNOWN, 2020). Finally, the vesicle containing the virion merges from the

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host cell plasma membrane to release the new virus, which will bind to a new ACE2 and initiate a new cycle (HUSSIN & SIDDAPPA, 2020) (Figure 3).

Figure 3. SARS-CoV-2 viral entry mechanism and replication

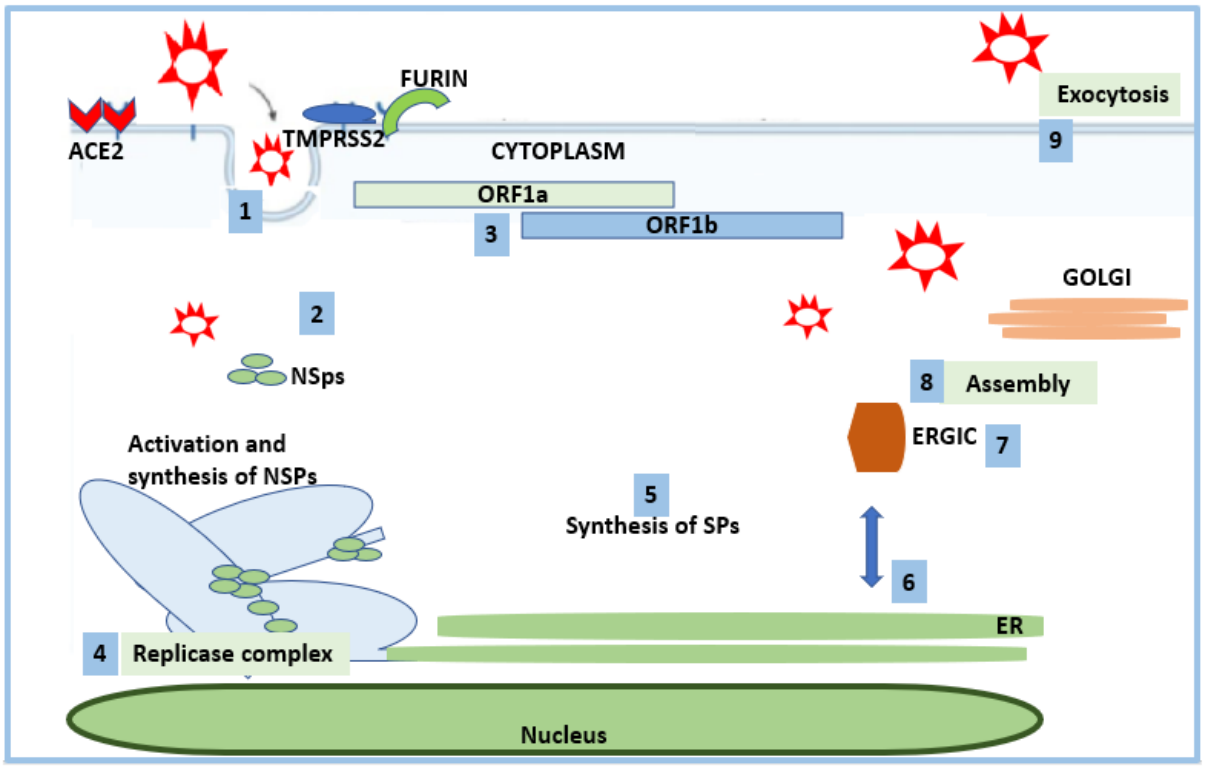

Figure: by authors**. Legend:** 1) Viral Sp-S to human angiotensin-2 converting enzyme (ACE-2) binding and viral fusion; 2) Release and uncoating of genomic RNA; 3) Immediate translation of ORF1a and ORF1b; 4) Cleavage and activation of NSps and viral replication complex formation; 5) Transcription and translation of NSps, Sps and accessories proteins; 6 and 7) Transiting of translated proteins by ER and ERGIC; 8) Combination of proteins, assembly and virion formation; 9) Virion Fusion with the membrane and exocytosis. Source: adapted from V'Kovski *et al.* (2021).

SARS-CoV-2 PATHOGENESIS AND CLINICAL SYMPTOMS

Viral replication of SARS-CoV-2 is followed by an exacerbated inflammatory response by the host's immune system (HI-S) (HUI *et al.* 2020). The presence of SARS-CoV-2 in human cells, activates viral proteases Papain-like protease (Plpro), 3C-Like protease (3CLpro) and SARS Unique Domain (SUD) (CANRONG *et al.* 2020). These proteases interfere, respectively, in the mechanisms of the human interferon system (component of the first line of defence to the HIS), in the expression of human ubiquitin (an important marker of foreign protein destruction) and, in the activity of human RNA-G4 (highly stable RNA structure, essential for the regulation of cell cycle and HI-S) (CANRONG *et al.* 2020; HUI *et al.* 2020; BÁEZ-SANTOS *et al.* 2015).

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Once the HI-S is impaired, due to the activity of Plpro, 3CLpro and SUD, the infected host's cells disorderly recruit pro-inflammatory cytokines, such as Interleukins (ILs) and Tumor Necrosis Factor (TNF), which trigger an exacerbated immune response against the invading virus (HUI *et al*. 2020). This exacerbated response generates an inflammatory exudate (plasma proteins and leukocytes) that accumulates, inordinately, in the inflamed cells and tissues, and may expand throughout the body. The inflammatory exudate compromises multiple organs (e.g. lungs, heart, kidneys, liver, brain) and in Renin Angiotensin Aldosterone System (RAAS). In RAAS, ACE2 plays a cardinal renal and cardiovascular pathophysiology role, acting as a vasodilator, anti-fibrotic, anti-coagulant and anti-apoptotic (HAMMING *et al*. 2007; OLIVEIRA *et al*. 2020).

The aggressiveness of SARS-CoV-2 infection is mainly presented in elderlies, and individuals with underlying metabolic conditions such as diabetes and obesity (TANAKA *et al*. 2020). In cases of diabetes, once ACE2 is expressed in the endocrine pancreas, SARS-CoV-2 direct binds ACE2 on β-cells, and this might contribute to insulin deficiency and hyperglycemia. In addition, apart from the usual endocrinologic disorders mechanisms (impaired neutrophil chemotaxis and phagocytosis) by which diabetes predisposes in general, is noteworthy that, in SARS-CoV-2 infection, the patients also can have lymphocytopenia and an increase in Interleukin-6 (IL-6) and cytokines levels, which may play a more deleterious role in COVID-19 symptoms (SINGH *et al.* 2020). Likewise to diabetes, the cases of obesity related to the severity of the COVID-19 suggest being due to accelerated fat breakdown in these patients (TANAKA *et al*. 2020). Moreover, increased adiposity has been associated with alterations in multiple cytokines, chemokines and adipokines - increased pro-inflammatory cytokines such as tumour necrosis factor-α (TNFα) and interleukin-6 (IL-6). These alterations can lead to platelet coagulation and therefore to thrombosis, as well as interleukin-8 (IL-8), leptin and adiponectin release. All these alterations contribute for the exacerbated inflammatory response presented in severe COVID-19 (GUPTA *et al*. 2020).

In addition, comorbidities associated with COVID-19 severity revealed a broad set of ACE2 expression (PINTO *et al*. 2020). Independently of the organ affected by SARS-CoV-2, the inflammatory chemicals can expand towards to multiple organs and the lymphatic system, triggering a systemic inflammatory response, leading the individual to death (HAMMING *et al.* 2004).

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RENIN–ANGIOTENSIN–ALDOSTERONE-SYSTEM (RAAS) AND ACE-2

As previously mentioned, the human angiotensin converting enzyme 2 plays a cardinal role, regulating RAAS. For instance, as renal and cardiovascular pathophysiology - fluid and electrolyte balance, blood-pressure regulation, vascular permeability and inflammatory response (HAMMING *et al*. 2007; DALAN *et al.* 2020).

For activation of the RAAS, the renin protease is released by the juxtaglomerular cells of the kidney, due a series of physiological stimuli by the individual. Renin protease, which acts on the circulating precursor angiotensinogen to generate angiotensin-I (Ang-I), in RAAS, can follow four pathways: one vasoconstrictor and three vasodilator routes (two of them, due to ACE2) (SHI *et al*. 2021; GUPTA *et al*. 2020).

In vasoconstrictor pathway, Ang-I is converted by ACE to Angiotensin-II (Ang-II) and Ang-II binds to its Ang-II-receptor-type1 (AT1), hence, AT1 causes pro-inflammatory, pro-fibrotic and pro-apoptotic effects. The three vasodilator pathways result in the formation of Angiotensin 1-7 (Ang 1-7), which is responsible for binding to its Mas-receptor (Mas-R), hence, promoting anti-inflammatory, anti-fibrotic and anti-apoptotic effects (KUBA *et al*. 2013; GUPTA *et al.* 2020).

The three vasodilator pathways of RAAS are classified as: a) on the first vasodilator route, Ang-I is converted by ACE2 into Angiotensin 1-9 (Ang 1-9), which is converted to (Ang 1-7), via angiotensin-converting enzymes (ACE) and neutral endopeptidase (NEP); b) on the second vasodilator route, Ang-I is converted into (Ang 1-7) via prolyl-endopeptidase (PEP) and prolyl-carboxypeptidase (PCP); c) on the third vasodilator route, Ang-II is converted into (Ang 1-7) by the action of ACE2 (SHI X, et al., 2021; KUBA *et al*. 2013; GUPTA *et al*. 2020). Furthermore, the action of ACE2 in degrading Ang-II to (Ang 1–7) suggests that ACE2 is a counter-regulatory to ACE by shifting the balance between Ang-II and (Ang 1–7), thus acting as a functional clearance mechanism for Ang-II (HAMMING *et al*. 2007; SHI et al. 2021).

However, once SARS-CoV-2 binds to ACE2, this enzyme is internalized to endosomes, leading ACE2 to a subcellular location shift, that could alter its capacity to act in RAAS (HAMMING *et al*. 2007; OLIVEIRA *et al*. 2020). In other words, unbalance of ACE2 may trigger maladaptive functions of RAAS, including as a result of tissue damage (KUBA *et al*. 2013; GUPTA *et al.* 2020) (Figure 4).

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Figure 4. ACE2 in RAAS system

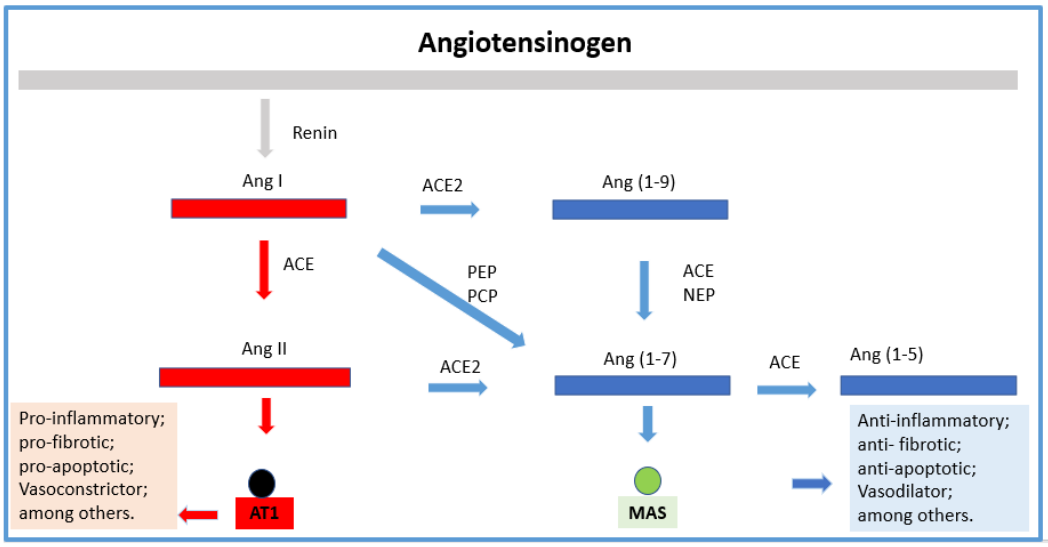

Figure: by authors**. Legend:** In red: vasoconstrictor pathway; in blue: three vasodilator pathways. Source: Kuba *et al.* (2013); Gupta *et al.* (2020).

4.1 ANGIOTENSIN-CONVERTING ENZYME2 HUMAN BODY DISTRIBUTION

Despite the ACE2 being more abundant on the surface of the well-differentiated and ciliated airway epithelium of the lungs, this enzyme also is distributed in various human tissues and cells (e.g. oral and nasal mucosa, nasopharynx, stomach, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, brain, arterial and venous endothelial, enterocytes of the small intestine, among others) (HAMMING *et al*. 2007; OLIVEIRA *et al.* 2020).

In lungs, the abundance of ACE2 expression, especially in individuals infected with SARS-CoV-2, may suggest that the imbalance of ACE2 expression in the lungs benefits the pathogenesis of SARS-CoV-2, leading an exacerbated host immune response (HUI *et al*. 2020). As the viral cycle occurs, the alveoli cells release unregulated pro-inflammatory chemicals such as cytokines, interleukins and tumor necrosis factor, which trigger two important events: 1) High permeability in blood vessels, which allows the blood and fluids from inside the vessels to pass through the pulmonary alveoli, resulting in a threat on the blood vessel gas exchange - between oxygen (O2) and carbon dioxide (CO2) (SINGER *et al*. 2016; HUI *et al.* 2020); 2) High extension of blood vessels, which allows the vessels to support more and more blood and fluids, that hence, also threatening gas exchange (HUI *et al*. 2020).

Thus, the individual may develop lobar pneumonia (one or more lobes of the lungs are affected) or bronchopneumonia (many areas of both lungs are affected). Pneumonia

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causes difficulty in breathing, chest pain, cough, fever, chills, mental confusion, headache, muscle pain and fatigue, which might lead to respiratory failure and death (MACHHI *et al.* 2020).

However, as previously mentioned, ACE2 is distributed not only in the lungs, but also in various organs and tissues of the human body. The following table is a brief description of the ACE2-rich cells and tissues, hence the possible targets for SARS-CoV-2 infection (TABLE 5).

Table 5. Human cells and tissues with greater abundance of ACE2 and the result of the interaction between SARS-CoV-2 and ACE2

Cells and tissues with higher expression of ACE2	Results of the interaction between SARS-CoV-2 and ACE2
Arterial and venous endothelium (GUPTA *et al.* 2020)	Produces excess thrombin, inhibits fibrinolysis and activates complement pathways, initiating a thrombus inflammatory response, which leads to microthrombi deposition and microvascular dysfunction.
Heart (SHI *et al.* 2021)	Myocardial injury, acute coronary syndromes, cardiomyopathy, acute cor pulmonale, arrhythmias, cardiogenic shock, as well as thrombotic complications. Downregulation of ACE2, which inhibits cardioprotective role of (Ang 1-7), leading to increased levels of TNFα production, hence inflammation.
Kidney (GUPTA *et al.* 2020)	Acute kidney injury, which is demonstrated by haematuria, proteinuria, hyperkalemia and acidosis associated with the high cell turnover.
Intestine (GUPTA *et al.* 2020)	SARS-CoV-2 may mediate direct tissue damage, given the abundant presence of ACE2 in intestinal glandular cells.
Liver (GUPTA *et al.* 2020)	Hepatocellular injury followed by an elevated aminotransferases and bilirubin. Demonstrated by Kupffer cell proliferation, chronic hepatic congestion, steatosis, portal fibrosis, lymphocytic infiltration and ductular proliferation, lobular cholestasis, liver cell necrosis, and thrombosis.
Brain (ORTEGA *et al.* 2020)	SARS-CoV-2 neural parenchyma invasion may occur via nasal epithelial cells or via retrograde axonal transport. Demonstrated by: a) mild complications - headache, dizziness, myalgia, fatigue, anorexia, anosmia, ageusia; b) severe complications - acute stroke, confusion or impaired consciousness, meningoencephalitis, haemorrhagic reversible encephalopathy syndrome, acute necrotizing encephalopathy, and most rarely Guillain-Barré Syndrome.

Figure: by authors.

The association of worsening clinical pulmonary manifestation and/or multiple organ failure, plus declining of virus load and the onset of the cytokine storm, suggest that severe cell and tissue damage is largely immunopathological in nature (HAIBO *et al.* 2020).

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ACE2 AND SARS-CoV-2 CONNECTION AND THE SEVERITY OF COVID-19

SARS-CoV-2 and ACE2 connection may cause ACE2 an unbalance in the human cells, hence, affect the prognosis of the COVID-19 (DALAN *et al.* 2020; ZOU *et al.* 2020). However, recent literature offers contradictory findings whether this unbalance and different prognosis, make ACE2 acts as risk or protective factor in SARS-CoV-2 infection (GUPTA *et al.* 2020; OLIVEIRA *et al.* 2020).

Related to the ACE2 as a risk factor, Gupta *et al.* (2020) and Dalan *et al.* (2020) suggest that once ACE2 is the primary SARS-CoV-2 receptor, the abundance of ACE2 may facilitate not only the infection, but also the severity of COVID-19. In addition, Hrvoje *et al.* (2020) refers to ACE2 expression as the main doorway for viral entry. Therefore, to mitigate the risk of SARS-CoV-2 infection, ACE2 inhibition suggests promoting the decline in SARS-CoV-2 entry into the cell (GUPTA *et al.* 2020; DALAN *et al.* 2020).

Related to the ACE2 as a protective factor, Abassi *et al.* (2020) emphasizes that the depletion of ACE2 by SARS-CoV-2 binding may be responsible for the more severe clinical presentation of COVID-19, especially, in the group of high-risk patients (HRVOJE *et al.* 2020; ABASSI *et al*. 2020). Considering COVID-19 as an inflammatory disease, and considering ACE2 as crucial in RAAS - promoting anti-inflammatory, anti-fibrotic and anti-apoptotic effects (HAMMING *et al.* 2007), ACE2 abundance may prevent the aggressiveness of SARS-CoV-2 infection (OLIVEIRA *et al.* 2020). Corroborating with Oliveira *et al.* (2020), Ferrario *et al*. (2005) highlight that downregulation of ACE2 in organs, after virus infection, disturbs the local balance between the RAAS and ACE2/angiotensin-(1–7)/MAS axis, which may be associated with organ injuries. In addition, Wentão *et al*. (2020) defends that besides to acting as a receptor for SARS-CoV-2, ACE2 hydrolyzes Ang-II to angiotensin-(1–7), and the ACE2/angiotensin-(1–7)/MAS counteracts the negative effects of the RAAS and exerts anti-inflammatory effects. Thus, once SARS-CoV-2 uses ACE2 as its receptor, the downregulation of ACE2 expression, hence the disrupting of physiological balance between ACE/ACE2 and Ang-II/angiotensin-(1–7) may be involved in multiple organ injury in COVID-19 (ZOU *et al*. 2020). Moreover, ACE2 inhibition suggests to cause a failure in biological activity of RAAS, consequently, an augment in cell injury, primarily in patients with comorbidities such as diabetes and hypertension (DALAN *et al.* 2020; TANAKA *et al*. 2020; HAMMING *et al.* 2004).

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FINAL CONSIDERATIONS

This review approached ACE2 distribution in the human body and its interactions with SARS-CoV-2, associating these factors to the severity of COVID-19. Although ACE2 plays a cardinal role as main receptor for SARS-CoV-2 (a risk factor for viral infection), this enzyme is essential in RAAS - acting as anti-inflammatory, anti-fibrotic, anti-apoptotic and vasodilator (protective factors for COVID-19 severity). Thus far, even further evidence is needed to affirm the exact role of ACE2 in SARS-CoV-2 infection, this literature suggests that ACE2 is more likely to act a protective role against the severity of COVID-19 than to act as susceptibility factor.

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CONFLICT OF INTERESTS

None.

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