Chapter

Renin Angiotensin System, Gut-Lung Cross Talk and Microbiota. Lessons from SARS-CoV Infections

Andreia Matos, Alda Pereira da Silva, Joana Ferreira, Ana Carolina Santos, Maria Clara Bicho and Manuel Bicho

Abstract

The two antagonistic systems of angiotensin converting enzyme (ACE)-1 and ACE-2 are in the "eye of the hurricane" of severe acute respiratory syndrome coronavirus (SARS-CoV-2). The receptor of the SARS-CoV-2 is the same as ACE-2, which causes its under-expression after binding it, followed by the internalization of the complex virus-ACE-2. ACE-2 have multiple functions with specially relevance in cardiovascular diseases. Furthermore, the non-enzymatic role of ACE-2 gives rise to a Hartnup disease, a phenocopy involving microbiota. With this chapter, we intent to explore the key pathways involved in SARS-CoV-2 infection, from the host perspective, considering our hypothesis related to transporter of neutral amino acids, which includes tryptophan precursor of serotonin and kynurenine.

Keywords: severe acute respiratory syndrome coronavirus (SARS-CoV-2), renin-angiotensin system, tryptophan precursors, microbiome, genetic susceptibility

1. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initiated in Wuhan in China, revisited 17 years later an outbreak that started in 2002 in China caused by a virus very similar to SARS-CoV-2 [1]. Identification and sequencing of the virus responsible for COVID-19 determined that it was a novel coronavirus that shared 88% sequence identity with two bat-derived SARS-like CoV, suggesting it's origin in bats [2]. Additionally, it was shown that this coronavirus, which was termed 2019-nCoV or SARS-CoV-2, shared 79.5% sequence identity with SARS-CoV [2].

After inhalation of SARS-CoV-2, it invades nasal epithelial cells (superior respiratory tract) and type II pneumocytes through binding the SARS spike protein to angiotensin-converting enzyme 2 (ACE-2) receptors [3]. This complex is proteolytically processed by transmembrane protease serine 2 (TMPRSS2), leading to cleavage of ACE-2 and activation of the spike protein, thereby facilitating viral entry into the target cell. For SARS-CoV-2 entry into a host cell, its spike protein needs to be cleaved by cellular proteases at 2 sites, termed S protein priming by the

serine protease TMPRSS2, then the viral and cellular membranes can fuse [4]. It has been suggested that cells in which both ACE-2 and TMPRSS2 are expressed are most susceptible to entry by coronaviruses from the SARS family, among which is the virus described to cause SARS and, also SARS-CoV-2 [4, 5].

In relation to the mechanism of infection, the infected cells trigger the host's immune response, and the inflammatory cascade is initiated by innate immune cells, being the host environment extremely important for internalization and multiplication of the virus [6]. Possible mechanisms of receptor and signaling mechanisms responsible for induction of inflammatory mediators, such as cytokines or chemokines, may be related to the release of danger signal molecules, like certain cytokines, or may be involve a different recognition pathway mediated by immune cells throughout known pattern recognition receptors, such as toll-like receptors (TLRs) [7].

The heterologous protection against infections through epigenetic, transcriptional, and functional reprogramming of innate immune cells may contribute to different susceptibility to severity of SARS-CoV-2 [7, 8]. Furthermore, the changes in metabolic and endocrine pathways associated with SARS-CoV-2 infection may untangle a more profound understanding of this disease and contribute to a more adequate response.

2. Host systemic reactions of SARS-CoV-2 infection

Although the SARS-CoV-2 infection is highly associated to respiratory infection, it is also true, that this infection reflects a systemic involvement with multiple symptoms, including fever, persistent dry cough, shortness of breath, chills, muscle pain, headache, loss of taste or smell, and gastrointestinal symptoms [9]. Interestingly, according to the clinical features of individuals affected with SARCoV-2, a significant proportion of patients initially present some atypical gastrointestinal symptoms such as diarrhea, nausea, and vomiting [10].

Coronaviruses are one of many pathogens known to cause postinfectious olfactory dysfunction, nasal epithelial cells and mainly goblet cells in a high expression patterns of the ACE-2 receptor, which is required for SARS-CoV-2 entry. Olfactory dysfunction and anosmia are highly implicated in SARS-CoV-2 infection. The inclusion of loss of smell or taste among these symptoms follows the emergence of evidence suggesting that SARS-CoV-2 frequently impairs the sense of smell. Olfactory disfunction, defined as reduced or distorted ability to smell during sniffing (orthonasal olfaction) or eating (retronasal olfaction), is often reported in mild or even asymptomatic cases [11]. There have also been reports of acute-onset (sudden) anosmia, sometimes in the absence of other symptoms, as a marker of SARS-CoV-2 [12].

Disruption of cells in the olfactory neuroepithelium may result in inflammatory changes that impair olfactory receptor neuron function, cause subsequent olfactory receptor neuron damage, and/or impair subsequent neurogenesis [13]. Such changes may cause temporary or longer-lasting olfactory disease.

Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes, and neutrophils. Subsequently the integrity of the alveolar-capillary membrane is compromised by the inflammatory response triggered by SARS-CoV-2 [14]. In the late stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early-phase acute respiratory distress syndrome [14], bradykinin may contribute to this pulmonary edema [15].

Another contribution for systemic reaction of SARS-CoV-2 infection is the nasal gene expression of ACE-2. Indeed, the lower rates of SARS-CoV-2 infection

were found in children. From nasal epithelial samples collected as part of a study involving patients with asthma from 2015 to 2018, a comprehending a cohort of 305 patients aged 4 to 60 years, evidenced that the lower expression of ACE-2 in the nasal epithelium were found in younger children and ACE-2 expression was higher with each subsequent age group after adjusting for sex and asthma [16]. Yet, a recent study bring some data that children may be a potential source of contagion in the SARS-CoV-2 in spite of milder disease or lack of symptoms, and immune dysregulation is implicated in severe post-infectious multisystem inflammatory syndrome in children [17].

3. Implications of angiotensin-converting enzymes and renin-angiotensin system in SARS-CoV-2

Overexpression of human ACE-2 enhanced disease severity of SAR-CoV-2 infection, being the lung injury aggravated by the presence of SARS-CoV spike. Interestingly, in mice model, the lung injury was attenuated by blocking the renin-angiotensin pathway and depended on ACE-2 expression [18].

In contrast to other coronaviruses, SARS-CoV-2 became highly lethal because the virus deregulates a lung protective pathway. About 83% of cells that express ACE-2 were alveolar epithelial type II cells (AECII), suggesting that those cells can serve as a reservoir for viral invasion [19]. In addition, gene ontology enrichment analysis showed that the expression ACE-2 by AECII have high levels of multiple viral process-related genes, including regulatory genes for viral processes, viral life cycle, viral assembly, and viral genome replication, suggesting that the ACE2-expressing AECII facilitate viral replication in the lung [20].

Expression of the ACE-2 receptor is also found in many extrapulmonary tissues including heart, kidney, and intestine [21]. In human lung, the ACE-2 is expressed in endothelial and smooth muscle cells of large and small blood vessels, and in alveolar and bronchial epithelial cells.

Contrarily to ACE-1, the ACE-2 is barely present in the circulation, but widely expressed in mentioned organs. Although ACE-2 is more related to the physiopathology of SARS-CoV, ACE-1 converts angiotensin I into angiotensin Ang II, then ACE-2 break down angiotensin II into molecules that counteract angiotensin II, but if the virus occupies the ACE-2 'receptor' on the surface of cells, then its role is blunted [22]. Angiotensin I, can cause vasoconstriction, inflammation, and fibrosis by signaling through angiotensin II type 1 receptors. ACE-2 cleave angiotensin II to angiotensin 1–7, which can suppress inflammation and fibrosis and generate vasodilation by binding to the *mas* receptor (**Figure 1a**) [23–26].

Moreover, ACE-2 is a negative regulator of the renin-angiotensin system (RAS), and functions as the key SARS coronavirus receptor and stabilizer of neutral amino acid transporters [27]. As previously mentioned, the ACE-2 catalyzes the conversion of angiotensin II to angiotensin 1–7, thereby counterbalancing ACE activity, and converts angiotensin I to generate angiotensin 1–9 [3]. The RAS is an acute phase pathway involved in the multisystemic response of cardiovascular and hematopoietic systems, maintenance of blood pressure homeostasis, as well as fluid and salt balance in mammals [28]. Abnormal activation of RAS has been associated with the pathogenesis of cardiovascular and renal diseases such as hypertension, myocardial infarction and heart failure. Therefore, these disorders share underlying pathophysiology related to the RAS and COVID19 that may be clinically insightful [29].

Cardiovascular disease and pharmacologic RAS inhibition both increase ACE-2 levels, which may increase the virulence of SARS-CoV-2 within the lung and

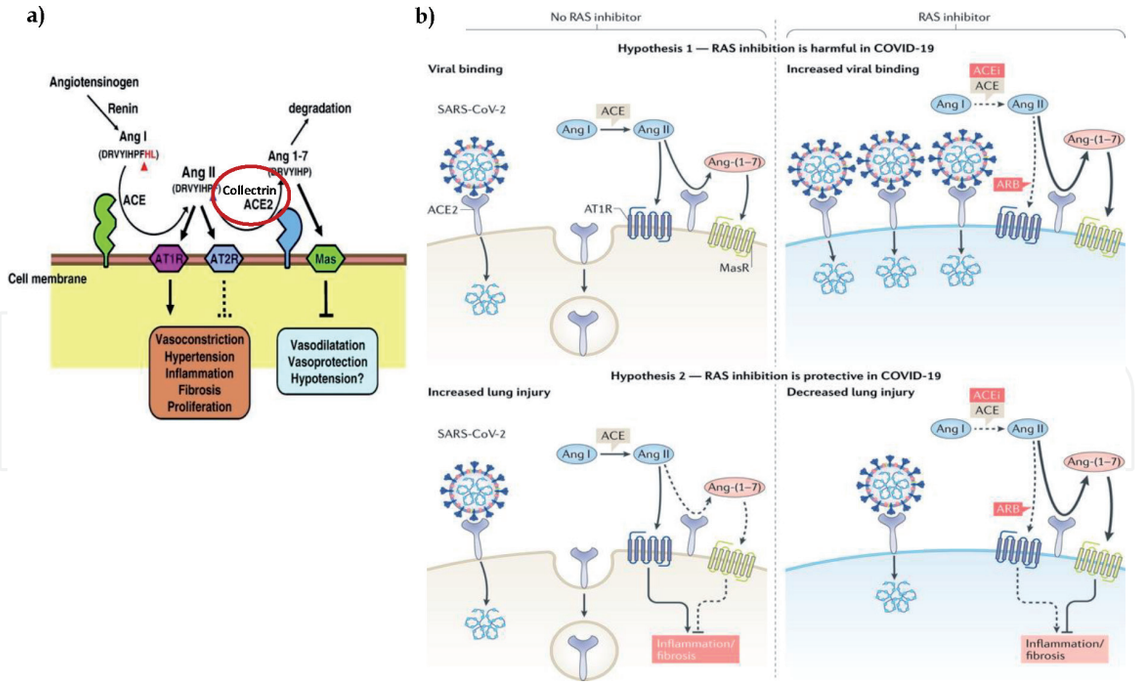

Figure 1.
Integrative schematic diagram of the role of ACE (ACE-1), ACE-2 and collectrin in the renin–angiotensin system (a) (adapted from [30]) and the impact of RAS inhibition in SARS-CoV-2 infection (b) [31].

heart, since the receptor of the two viruses is the same enzyme protein of the cell membrane [32]. Conversely, mechanistic evidence from related coronaviruses suggests that SARS-CoV-2 infection may downregulate ACE-2, leading to toxic over accumulation of angiotensin II that induces acute respiratory distress syndrome and fulminant myocarditis [33]. Therefore, RAS inhibition could mitigate this effect [34]. ACE-2 genetic variants may determine the circulating angiotensin 1–7 levels only in hypertensive females that probably had dose effects related to the localization in the X Chromosome of ACE-2 gene [35].

The bradykinin-kallikrein system can further contribute to local vascular leakage leading to angioedema, due to a local vascular problem because of activation of bradykinin 1 receptor (B1R) and B2R on endothelial cells in the lungs. The RAS is needed to inactivate des-Arg9 bradykinin, which is a potent ligand of the B1R [15]. In the late stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early-phase acute respiratory distress syndrome.

Other aspect to be pointed out is collectrin (**Figure 1a**), an homolog of ACE-2, that have been identified as essential molecules required for expression of neutral amino acid transporters on the cell surface of epithelial cells. Collectrin (Tmem27) is a transmembrane glycoprotein that is highly expressed in the kidney and vascular endothelium [36]. Furthermore, concordant with metabolic and endocrine changes associated with SARS-CoV-2 infection, collectrin might also have a role in insulin secretion in pancreatic β-cells and/or growth of islet cells [37].

Detailing the mechanism of ACE-1 and its possible role in SARS-CoV-2, ACE-1 has pleiotropic actions involving the cardiovascular and hematopoietic systems [23–25]. The two catalytic domains of ACE-1 has different affinities for its promiscuous substrates respectively in the N domain for goralitide or N-acetyl-seryl-aspartyl-lysyl-proline (NacSDKP), an inhibitor of hematopoiesis and fibrogenesis and that have influence on blood pressure predominantly the C-domain for Angiotensin I or for both domains as is the case of Bradykinin [25, 27].

Unpublished results from our group reflected an inverse correlations of ACE activity with antioxidant erythrocyte and plasma activity enzymes, and direct correlation with lower relative concentrations of glutathione associated to proinflammatory conditions like obesity and several autoimmune diseases (**Figure 2**).

In terms of detection of SARS-CoV-2, the RT-PCR is a cheaper, easier and short turn-around time method for detection of RNA component of SARS-CoV-2, in upper respiratory samples, comparing with sequencing technology. Considering the

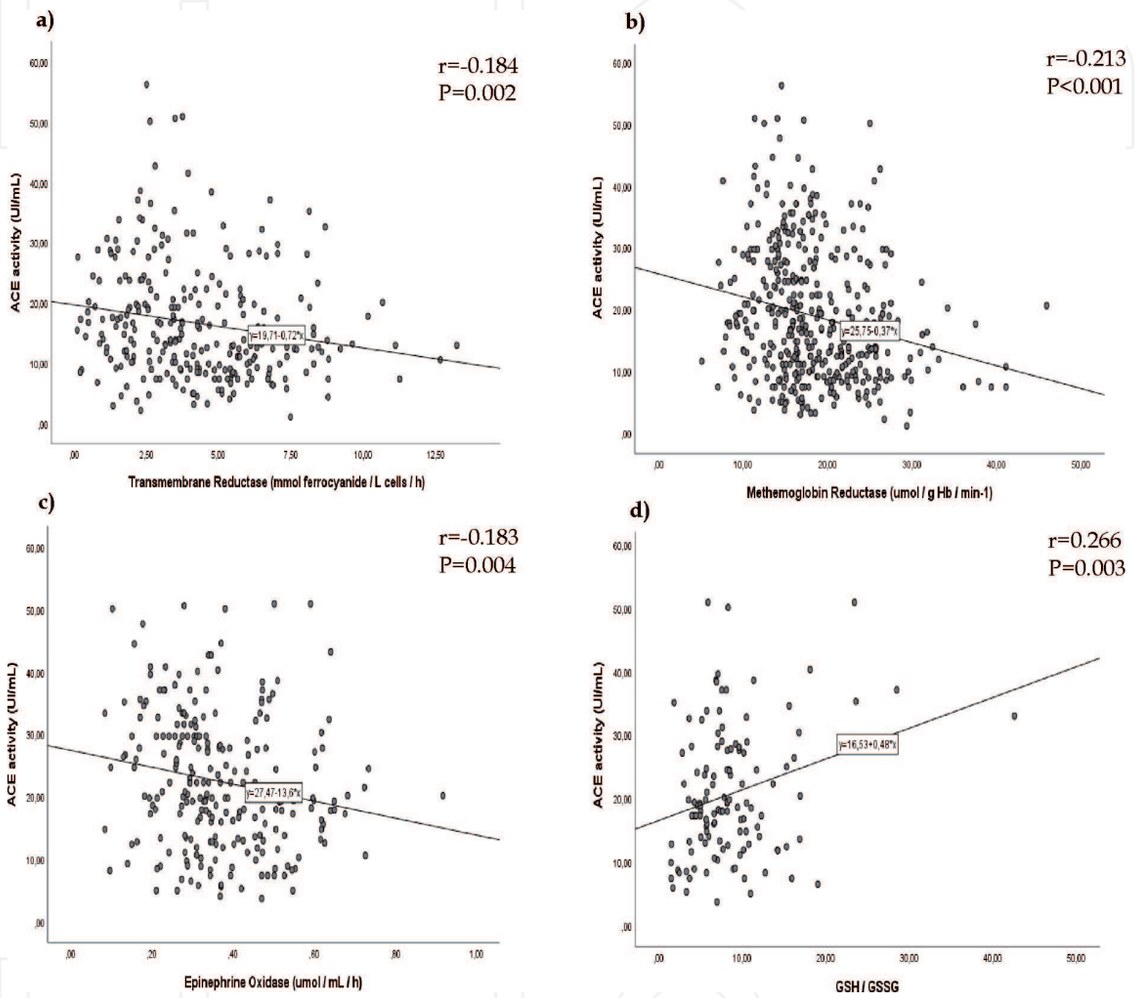

Figure 2.
Correlation between ACE and transmembrane redox system (a), erythrocyte methaemoglobin reductase (b), plasma epinephrine oxidase (c) and with plasma ratio of oxidized glutathione to reduced glutathione (d).

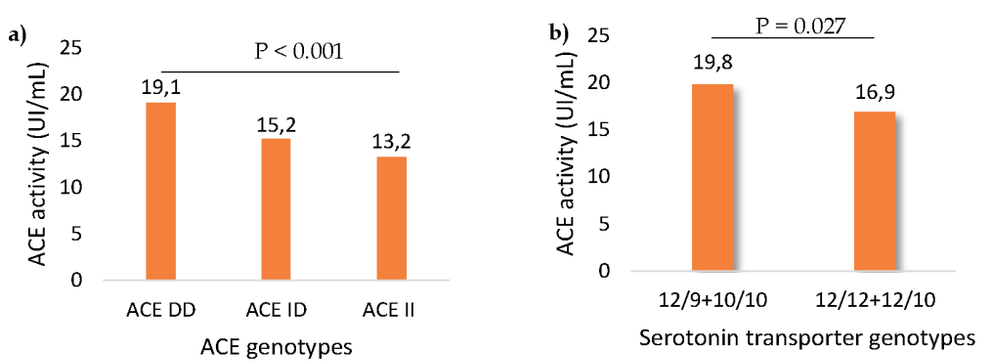

Figure 3.
Distribution of ACE activity according to ACE (a) and SERT (serotonin transporter) (b) genotypes.

genetic variability, the ACE-1 Insertion/Deletion (I/D) functional polymorphism influence its activity in plasma as it was reported by us and other authors (**Figure 3a**) [23, 38]. However, the ACE I/D polymorphism is not associated with increased susceptibility or poor outcome after SARS-CoV-1 infection [39]. Paradoxically, in studies on longevity from our and other groups, individuals with DD genotype, with higher activities of ACE, are more represented in centenarians [40, 41].

The response to this pathway when exaggerated, as is the case of the SARS-CoVs infections, causes intense inflammatory and fibrogenic processes. On the contrary, the system initiated by ACE-2 also has pleiotropic antagonistic actions of the classic system and it has an anti-inflammatory and anti-fibrogenic system [42]. Furthermore, both systems have functional polymorphic genetic variations [23, 38, 39, 43–45].

Genetic polymorphisms in the RAS are putative markers prone to affect the clinical course of SARS-CoV-2 infection. Cao et al. in 2020 suggested that ACE-2 and SARS-CoV-2 associated frequencies among populations can be justified by allele sequences distributions. The greatest are in East Asians populations with higher expressions in tissues that suggest different susceptibilities or response to SARS-CoV-2 in different ecosystems [44].

4. Correlations of immune response, acute phase proteins and tryptophan precursors in SARS-CoV-2 infection

As previously mentioned, the major clinical complication in patients with SARS-CoV-2 is respiratory failure due to local hyperinflammation and acute respiratory distress syndrome. The pathophysiology of these complications has strong similarities to other severe viral lung infections, such as influenza, and other infections caused by coronaviruses (SARS and Middle East respiratory syndrome). An important mechanism mediating lung pathology in these infections is a cytokine storm leading to the so-called "macrophage activation syndrome" with crucial role for monocytes and macrophages [46, 47].

Accordingly with the major clinic complications of this infection, this extreme inflammation compromises the respiratory performance, which often requires ventilator support or, even, extracorporeal membrane oxygenation [48]. However, in approximately 80% of cases, the latter did not prevent mortality, owing to insufficient lung perfusion, which could be explained by developing thromboembolic complications. In this context, clinical trials are underway to determine whether anticoagulants (e.g., heparin) or profibrinolytic drugs (e.g., tissue plasminogen activator) ameliorate severe infection with thromboembolic complications [30, 49].

From the inflammatory perspective, these infection leads to changes in circulating concentrations of proinflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP1A), and interferon gamma-induced protein 10 (IP10), comparing patients in intensive care unit (ICU) and to those who do not need treatment in the ICU, although the concentrations of some of these cytokines are only moderately increased [50]. This strong increase in systemic inflammation is associated with endothelial dysfunction, increased coagulation activity reflected by elevated d-dimers [50] and hyperactive CCR6 + Th17+ T cells locally in the lung [9]. The increase in systemic concentrations of proinflammatory cytokines was minimal, even during days 7–9, when the patient was symptomatic. This suggests that a mild course of infection is associated with few systemic inflammatory effects. Still, the hyper-inflammation occurs in SARS-CoV-2 and is associated with worse outcomes [48].

Gender differences have been widely discussed in different pathologies, indeed these differences may reflect sex chromosome genes and sex hormones, including estrogens, progesterone, and androgens, with implications to the differential regulation of immune responses between the genders [51]. In studies of hypertension, there is a clear difference between genders taking on account the distribution of ACE-2 genetic polymorphisms associated levels of angiotensin 1-7 [52].

Concerning SARS-CoV-2 infection, a male bias in mortality has emerged in the COVID-19 pandemic, which is consistent with the pathogenesis of other viral infections. Biological gender differences may manifest themselves in susceptibility to infection, early pathogenesis, innate viral control, adaptive immune responses or the balance of inflammation and tissue repair in the resolution of infection [53]. The differences in immune response according with gender, suggest less robust T cell-mediated immunity in male patients with worsening outcome and higher innate cytokine activity, compared to female patients [54].

Evidence reflected the gender as an important driver of risk of mortality and response to the SARS-CoV-2 pandemic. The sex differences in SARS-CoV-2 mortality, severity and recovery, may underly implications of cardiovascular disease (CVD) risk factors, reflecting a plausible biological reasons for this sex difference in SARS-CoV-2 infection [55]. This disproportionate death ratio in men may partly be explained by their relatively higher contribution of pre-existing diseases (i.e., CVD, hypertension, diabetes, and chronic lung disease), higher risk behaviors (i.e., smoking and alcohol use), and occupational exposure [55]. There may be other behavioral and social differences that favor women, with prior studies suggesting women are more likely than men to follow hand hygiene practices and seek preventive care [55].

The host metabolism supports viral pathogenesis by fueling viral proliferation, by providing free amino acids and fatty acids as building blocks. Alterations in tryptophan metabolism and kynurenine pathway regulates inflammation and immunity [56]. The indolamine-2, 3-dioxygenase (IDO) is an intracellular, non-secreted enzyme, which catabolizes kynurenine from tryptophan with interesting role in viral and bacterial infections [57]. Since many microbial organisms rely on the essential amino acid tryptophan, its degradation by IDO-expressing cells of the innate immune system was favored as the major IDO-mediated mechanism against infections [58]. In infectious disease states, IDO has been shown to exert pleiotropic effects, even with opposing outcomes. IDO prevents viral spread and from host perspective also acts to suppress immune reactions thereby promoting infectious diseases [56, 59].

Tryptophan metabolism was the top pathway affected by SARS-CoV-2. As such, focused analysis of this pathway highlighted significant decreases (inversely proportional to IL-6 concentration) in tryptophan, serotonin, and indolepyruvate levels. In contrast, increases in kynurenine, kynurenic acid, picolinic acid, and nicotinic acid suggested hyperactivation of the kynurenine pathway [58]. Furthermore, the levels of IL-6 in serum were significantly different from SARS-Cov-2 patients and controls and they were correlated with changes in tryptophan metabolism [58]. From this study, targeted metabolomics analyses were performed on sera using ultra-high-pressure liquid chromatography-mass spectrometry (UHPLC–MS), highlighting significant associations of COVID-19 and IL-6 levels with amino acid metabolism, purines, acylcarnitines, and fatty acids [58]. Dysregulation of nitrogen metabolism was also seen in infected patients, with altered levels of most amino acids, along with increased markers of oxidant stress (e.g., methionine sulfoxide, cystine), proteolysis, and renal dysfunction (e.g., creatine, creatinine, polyamines). Increased circulating levels of glucose and free fatty acids were also observed, consistent with altered carbon homeostasis. Interestingly, metabolite levels in these

pathways correlated with clinical laboratory markers of inflammation (i.e., IL-6 and C-reactive protein) and renal function (i.e., blood urea nitrogen). This initial observational study identified amino acid and fatty acid metabolism as correlates of SARS-CoV-2 [58].

In our group, we also demonstrated that a functional variable number of tandem repeats (VNTR) genetic polymorphism of serotonin transporter, whose expression is activated by IL-1, has some relation with the ACE serum levels that can be associated with unbalanced ACE-ACE-2 system (**Figure 3b**) [38].

Polymorphisms in genes coding for IL-10, TNF-alpha and IL-6 influence circulating levels, and behave as promoters of severe systemic inflammatory response that can probably has an interindividual and gender dependent impact [53].

At the other end of the iceberg, the immunocompromised patients could be protected against SARS-CoV-2, since unlike other common viruses, coronaviruses have not shown to cause more severe disease in immunosuppressed patients, at least statistically significant [60]. Our own immune response appears to be the main driver of lung tissue damage during infection. Starting around the 2nd week of symptoms, patients experience a "storm of cytokines" – autoimmune reaction, where your body over-reacts and in attacking coronavirus, your lungs get caught in the body immunologic response [47, 61]. In the first week of the illness it's the virus itself that's triggering most of your symptoms, but then in severe cases, it's our own inflammatory responses that takes over in causing the most of the damage. So this "storm of cytokines" is killing our immune cells, therefore, could patients with immunosuppressive profile be protected from this reciprocal attack?

The children account for less than 2% of identified cases of SARS-CoV-2 [62]. Interestingly, young children, including infants who are more susceptible to other infections, have milder symptoms and less severe SARS-CoV-2. Nevertheless, children seem to have similar rates of becoming infected compared with middle-aged adults following close contact with a person infected with SARS-CoV-2 [33].

Long-term boosting of innate immune responses, also termed "trained immunity," by certain live vaccines (Bacillus Calmette–Guérin - BCG, oral polio vaccine, measles) induces heterologous protection against infections through epigenetic, transcriptional, and functional reprogramming of innate immune cells [63].

5. Endocrine and metabolic contributions in SARS-CoV-2 infection: ACE-2 downregulation in SARS-CoV-2 as phenocopy of Hartnup disease

Epidemiological data showed that the elderly and those with co-morbidities (diabetes, obesity, and cardiovascular, respiratory, renal, and lung diseases) are most susceptible to COVID-19 and more likely to suffer from the most severe disease complications [64]. Viral infections mobilize free fatty acids to support capsid-associated membrane formation, which was described for other coronaviruses and is explained, in part, by activating phospholipase A2, a target amenable to pharmacological intervention [65].

Hartnup disease is a condition caused by the body's inability to absorb certain protein building blocks (amino acids) from the diet. As a result, affected individuals are not able to use these amino acids to produce other substances, such as vitamins and proteins. Most people with Hartnup disease are able to get the vitamins and other substances they need with a well-balanced diet [27, 66].

Individuals with Hartnup disease have high levels of various amino acids in their urine (aminoaciduria). For most affected individuals, this is the only sign of the condition. However, in other cases, individuals have episodes exhibiting other

signs, which can include skin rashes, difficulty of coordination of movements (cerebellar ataxia), and psychiatric symptoms, such as depression or psychosis. These episodes are typically temporary and are often triggered by intercurrent infection, stress, nutrient-poor diet, or fever. These features tend to go away once the trigger is changed, although the aminoaciduria remains. In affected individuals, signs and symptoms most commonly occur in childhood [67, 68].

As previously mentioned, the two antagonistic systems ACE, ANG II, AT1R and ACE2, ANII 1–7 are in the "hurricane eye" of SARS-CovV-2 and the non-enzymatic role of ACE-2 give rise to Hartnup disease phenocopy. ACE-2 is also a stabilizing protein (very similar to collectrin in kidney) of the neutral amino acid transporter mutated in the Hartnup disease [27].

In mice with ACE-2 deletion in the small intestine, there was also a decrease in tryptophan absorption secondary to the lower expression of the neutral amino acid transporter accompanied by a phenotype very similar to that of Hartnup's disease phenotypes [69]. This situation can be caused by SARS-COVs and probably explains the gastro intestinal symptoms sometimes associated with those viral infections. In this case, it may be the result of the accumulation of nephrotoxic and pro-inflammatory pulmonary products (indole derivatives) or lack of anti-inflammatory kynurenines (IDO derivatives), as a consequence of dysbiosis at large intestine resulting from the lack of absorption of several neutral and aromatic amino acids namely tryptophan [70, 71].

6. New highlights of possible microbioma association to SARS-CoV-2 infection

Concordantly to exposed in this chapter, the SARS-CoV-2 is more than a severe respiratory infection and actually integrate a multisystemic coordination. Metabolic syndrome and microbiome had been associated in intervention from ACE-2. This relation has an explanation that is now much more clarified and that goes through the IDO derivatives (Kynurenines) associated with aryl hydrocarbon receptor (AhR) and anti-inflammatory response Th22 [56].

The rationale of the non-enzymatic role of ACE-2 to serotonin and IDO derivatives to kynurenines has an explanation based in the activation of AhR functions by these tryptophan metabolites as they activates anti-inflammatory cytokines that may counteract the SARS-CoV-2 gastrointestinal and pulmonary symptoms characterized by a "cytokine storm" [72]. This can have their origin in the dysbiosis related to the tryptophan catabolism in indol derivatives by unbalanced *Lacobacillus spp* (decreased) specially in high salt microenvironment characteristic of western pattern diets [71, 73, 74].

Importantly, ACE-2 is highly expressed on the luminal surface of intestinal epithelial cells, functioning as a co-receptor for nutrient uptake, in particular for amino acid resorption from food [75]. Therefore the intestine might also be a major entry site for SARS-CoV-2 and the infection might have been initiated by eating food from the Wuhan market, the putative site of the outbreak. Whether SARS-CoV-2 can indeed infect the human gut epithelium has important implications for fecal–oral transmission and containment of viral spread. Moreover, the ACE-2 tissue distribution in other organs could explain the multi-organ dysfunction observed in patients [66, 71, 76, 77]. Any perturbation in host-microbiota crosstalk can be an initiating or re-enforcing factor in SARS-CoV-2 pathogenesis.

Some bacteria produce bioactive neurotransmitters that have previously been proposed to modulate nervous system activity and behaviors of their host. A large

array of metabolites drives the crosstalk between the host and its microbiome. The three currently most studied categories of metabolites involved in host-microbiota interactions are short-chain fatty acids produced by bacteria from the fermentation of fibbers, bile acids produced in the liver and transformed by the gut microbiota before re-affecting the host, and tryptophan metabolites, which are the topic of this review [72].

Tryptophan is an essential aromatic amino acid composed of a b carbon connected to the 3 position of an indole group and it is a biosynthetic precursor of a large number of microbial and host metabolites [78]. It's metabolism follows three major pathways in the gastrointestinal tract: the direct transformation of Tryptophan into several molecules, including ligands of the (AhR) by the gut microbiota [78]; the kynurenine pathway in both immune and epithelial cells via IDO-1 [79]; and the serotonin (5-hydroxytryptamine [5-HT]) production pathway in enterochromaffin cells via Tryptophan hydroxylase 1 (TpH1) [72]. The AhR is implicated in lung inflammation [80].

The gut microbiota influences the health of the host, especially with regard to gut immune homeostasis and the intestinal immune response. In addition to serving as a nutrient enhancer, L-tryptophan plays crucial roles in the balance between intestinal immune tolerance and gut microbiota maintenance.

7. Final marks

These lessons derived of SARS-CoVs infections outbreaks (2003 and 2019) can explain the role of the two antagonistic RASs pathways on the hypoxic pulmonary vasoconstriction an homeostatic mechanism in response to alveolar hypoxia secondary to acute lung injury in SARS, optimizing ventilation, perfusion and systemic oxygen delivery. Moreover, the new knowledge about the role of RAS proteins, namely, ACE-2 in gut with pleiotropic actions on the metabolism of tryptophan in the crosstalk microbiota–intestine, intestine-kidney and probably intestine-lung can help in designing new, based on probiotics and prebiotics or repurposing ancient therapies for disorders involving those organ crosstalk resultant physio pathologies.

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Conflict of interest

The authors declare that they have no competing interests.

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