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Editorial

# From ACE2 to COVID-19: A multiorgan endothelial disease

To date, three coronaviruses have caused major human outbreaks in the 21st century. In 2002–2003, SARS-CoV (the severe acute respiratory syndrome-associated coronavirus) caused 8447 reported SARS cases and 813 deaths, with a case fatality rate of ~10% (Park, 2020; Cleri et al., 2010; Lin et al., 2006; Satija and Lal, 2007). MERS-CoV (the Middle East respiratory syndrome coronavirus) was first reported in 2012 in Saudi Arabia, caused several outbreaks in Middle Eastern countries and South Korea (Cui et al., 2019; da Costa et al., 2020; Majumder et al., 2017; Kim et al., 2017; Ramadan and Shaib, 2019; Killerby et al., 2020), and had a case fatality rate of 25–40% (Majumder et al., 2014; Al Awaidy and Khamis, 2019; Mobaraki and Ahmadzadeh, 2019). Recently, SARS-CoV-2, the etiologic agent of COVID-19, which was declared a pandemic on March 11, 2020 (Park, 2020), was reported in late 2019 (Yang et al., 2020a). As of August 27, 2020, COVID-19 caused >24,300,000 cases and >830,000 deaths worldwide (Medicine JHUSo, 2020). SARS-CoV-2 and SARS-Co-V share 79% identity at the genomic level (Lu et al., 2020), and the surface glycoprotein S, which mediates cellular entry, is 76% identical at the amino acid level between the two (Ou et al., 2020; Walls et al., 2020).

SARS-CoV and SARS-CoV-2 bind ACE2 (Walls et al., 2020; Hoffmann et al., 2020), which is also the cellular receptor for a third human respiratory coronavirus, HCoV-NL63 (Jia et al., 2005; Hofmann et al., 2005). HCoV-NL63 was first identified in a 7-month-old baby with bronchiolitis and conjunctivitis in early 2004 (van der Hoek et al., 2004) and linked to common colds in children, the elderly, and immunocompromised individuals (Fielding, 2011). HCoV-NL63 is distributed worldwide (Abdul-Rasool and Fielding, 2010), occurs seasonally (Milewska et al., 2018), and usually causes mild upper or lower respiratory infections (Abdul-Rasool and Fielding, 2010; Wang et al., 2020), but was occasionally linked to severe infection or death (Konca et al., 2017; Mayer et al., 2016; Oosterhof et al., 2010).

Biophysical assays indicate that SARS-CoV-2 binds ACE2 with a 10−20-fold higher affinity than SARS-CoV (Wrapp et al., 2020). X-ray crystallography showed that while the SARS-CoV receptor-binding motif has a sharp turn three-residue Pro-Pro-Ala motif, the receptor-binding region of SARS-CoV-2 has a four-residue Gly-Val-Glu-Gly motif that forms additional hydrogen bonds and establishes closer contact with ACE2 (Shang et al., 2020; Lanza et al., 2020).

ACE2 is differentiated from other viral receptors in that it interfaces with a major endocrine vasoactive signaling pathway, the renin-angiotensin-aldosterone system (RAAS). RAAS is a vital hormonal mechanism that controls sodium-potassium balance, hemodynamic stability, and blood pressure (Muñoz-Durango et al., 2016; Chamsi-Pasha et al., 2014), regulates neural, cardiovascular, and renal function (Li et al., 2017a), and is involved in tissue remodeling (Kaparianos and Argyropoulou, 2011; Ames et al., 2019) and immune homeostasis (Crowley and Rudemiller, 2017; Rudemiller and Crowley, 2016).

Angiotensinogen, produced primarily by the liver, is cleaved by renin, which is generated by the renal juxtaglomerular apparatus to form the inactive decapeptide angiotensin I (Ang I) (Dalan et al., 2020). Angiotensin-converting enzyme (ACE), mostly synthesized in the lungs (Xiao et al., 2020), cleaves Ang I to form the octapeptide angiotensin II (Ang II) (Perlot and Penninger, 2013; Oudit et al., 2003). Angiotensin II acts via two G-protein-coupled receptors, Ang II receptor type 1 receptor (AT1R) and Ang II receptor type 2 receptor (AT2R) (Kuba et al., 2010). Ang II binds with a high and equal affinity to AT1R and AT2R (Chow and Allen, 2016). The two receptors differ in tissue distribution, the signaling pathways they activate, and their effects (Chow and Allen, 2016; Juillerat-Jeanneret, 2020; Abadir, 2011). Most of the Ang II cardiovascular effects occur through AT1R; AT2R is less well understood (Abadir, 2011; Ichiki, 2013). Ang II mediates aldosterone release from the adrenal gland, which results in sodium retention and increased blood pressure through AT1R (Dalan et al., 2020). Ang II has additional effects that include vasoconstriction (Vukelic and Griendling, 2014; Benigni et al., 2010; Hubloue et al., 2004), fibrosis (Chamsi-Pasha et al., 2014; Hamming et al., 2007; Marshall et al., 2004; Williams, 2001), endothelial dysfunction (Gomolak and Didion, 2014), inflammation (Gomolak and Didion, 2014), and increased coagulation (Senchenkova et al., 2010; Verdecchia et al., 2020).

The discovery of human ACE2 in 2000 by two independent genomics-based approaches (Tipnis et al., 2000; Donoghue et al., 2000) unveiled the existence of a counter-regulatory arm of the RAAS (Wang et al., 2012). Even though both ACE and ACE2 are members of the RAAS (Danilczyk et al., 2003; Simoes and Teixeira, 2016), they have distinct substrate specificities (Mendoza-Torres et al., 2015; Kuba et al., 2006). Evolutionarily, ACE2 is a chimeric protein (Perlot and Penninger, 2013). Its amino-terminal region harbors a metalloprotease catalytic domain that has a 42% identity with the metalloprotease catalytic domain of ACE (Donoghue et al., 2000). Its carboxy-terminal region has a nearly 48% identity with

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human collectrin (Zhang et al., 2001). While *ACE* is located on human chromosome 17, *ACE2* is on the X chromosome, possibly explaining some of the gender differences in the physiology of the RAAS (Oudit et al., 2003).

A key role for ACE2 is to convert the octapeptide Ang II into the heptapeptide angiotensin-(1-7) ((Ang-(1-7)) (Turner et al., 2004). ACE2 also cleaves a single residue from Ang I to generate angiotensin-(1-9) ((Ang-(1-9)) (Tipnis et al., 2000; Donoghue et al., 2000), but its affinity for Ang II is 400-fold higher (Lazartigues et al., 2007). Ang-(1-7) binds to the Mas receptor (Santos et al., 2003) and negatively regulates the RAAS (Kuba et al., 2010) causing vasodilation, cell growth inhibition (Lazartigues et al., 2007), and exerting anti-proliferative (Wang et al., 2012), anti-thrombotic (Fraga-Silva et al., 2008; Fraga-Silva et al., 2010), and anti-arrhythmogenic effects (Simões e Silva et al., 2013). Thus, the ACE2/Ang-(1-7)/Mas axis, as a negative regulator of the RAAS, opposes the ACE/Ang II/AT1R axis (Perlot and Penninger, 2013).

After its discovery, ACE2 was thought to have a narrow tissue distribution (Lazartigues et al., 2007), but subsequent studies documented its wide presence across many cell types (Borriello and Ianniello, 2020). This is another characteristic that makes ACE2 unique among viral receptors. ACE2 is present in type II alveolar cells (Xu et al., 2020) and alveolar macrophages (Magrone et al., 2020; Kai and Kai, 2020), salivary glands (Song et al., 2020), the conjunctiva (Zhang et al., 2020), the gastrointestinal tract (Wong et al., 2020), neurons, glial cells (Zhou et al., 2020; Bostancikliogl, 2020), adipose tissue (Gheblawi et al., 2020), arterial and venous endothelial cells (Hamming et al., 2004), arterial smooth muscle cells (Hamming et al., 2004), cells in the heart, kidney, liver, (Patel et al., 2014), uterus, vagina (Jing et al., 2020), and the mucosa of the oral cavity (Xu et al., 2020). In addition, several endocrine organs express ACE2, including cells of the pancreas (Liu et al., 2020), thyroid (Li et al., 2020a), testis (Pal and Banerjee, 2020; Leal et al., 2009), ovary (Reis et al., 2011; Pan et al., 2013), adrenal glands (Li et al., 2020a), pituitary (Wang et al., 2017; Alenina and Bader, 2019), and the human placenta (Valdés et al., 2006).

ACE2 levels change in obesity, diabetes, heart disease, hypertension, and kidney and lung disease, which is another differentiating characteristic of this viral receptor (Hamming et al., 2007; Gheblawi et al., 2020; Sriramula et al., 2011; Úri et al., 2016; Moon, 2011). It has been debated whether this relationship is causative or compensatory (Ingraham et al., 2020; Chu and Leung, 2009; Koka et al., 2008; Shi et al., 2010). ACE2 is upregulated in the adipocytes of individuals with type 2 diabetes mellitus and obesity (Kruglikov and Scherer, 2020) and in several animal models of obesity (Patel et al., 2016a; Patel et al., 2016b; Gupte et al., 2008). Acute hyperglycemia upregulates, and chronic hyperglycemia downregulates ACE2 (Bornstein et al., 2020). ACE2 expression also changes in malignancies (Fu et al., 2020; Yang et al., 2020b), a finding that has implications for assessing the risk of severe COVID-19 in cancer patients (Dai et al., 2020; Chai et al., 2020; Yamaguchi et al., 2017). Obesity, diabetes, and hypertension were recognized early during the COVID-19 pandemic among the conditions that increase the risk of severe disease and complications (Pan et al., 2020; Huang et al., 2020; Lippi et al., 2020; Singh et al., 2020; Caussy et al., 2020; Dietz and Santos-Burgoa, 2020; Kassir, 2020). For example, in a retrospective cohort study of obese patients admitted to intensive care, COVID-19 severity increased with BMI (Simonnet et al., 2020). Other conditions that increase COVID-19 severity include chronic respiratory diseases and cancer (Puig-Domingo et al., 2020; Ofori-Asenso et al., 2020). Some of the same comorbidities were identified during the MERS (Hajjar et al., 2013; Kulcsar et al., 2019; Alqahtani et al., 2018; Assiri et al., 2013) and SARS (Chan-Yeung and Xu, 2003; Yang et al., 2006; Chan et al., 2003; Gu and Korteweg, 2007) outbreaks as risk factors for more severe coronavirus disease.

By increasing viral internalization, ACE2 upregulation may enhance the viral load and increase disease severity. At the same time, ACE2 is protective in experimental models of lung failure (Kuba et al., 2006), and its downregulation accelerates tissue-specific pathologies. In a mouse model of acute respiratory distress syndrome, *Ace2* deficiency worsened acute lung injury, increased vascular permeability, caused edema and inflammatory infiltrates, and impaired lung function. ACE deficiency on this genetic background, or treatment with exogenous ACE2 protein, markedly protected from acute lung injury (Imai et al., 2005). SARS-CoV and the SARS-CoV spike protein downregulated ACE2 lung expression without changing ACE levels, indicating that the infected wild-type mice resemble ace2 knockout mice (Kuba et al., 2005). It appears that during SARS-CoV or SARS-CoV-2 infection, ACE2 down-regulation decreases signaling through the ACE2-angiotensin-(1-7)-Mas receptor (Verdecchia et al., 2020; Kai and Kai, 2020; Li et al., 2020b) and amplifies signaling through the ACE-angiotensin II-AT1R receptor axis (Kai and Kai, 2020; Deshotels et al., 2014). Ang II is known to increase IL-6 expression in a dose-dependent manner (Funakoshi et al., 1999; Senchenkova et al., 2019; Skurk et al., 2004). The other two axes activated by ACE2 downregulation are the ACE2/DABK/bradykinin/B1R axis and the complement signaling pathways (Mahmudpour et al., 2020). ACE2 cleaves a terminal residue in des-Arg$^9$ bradykinin (DABK) (Sodhi et al., 2018), an inflammatory factor in the lung, leading to its inactivation. Reduced ACE2 activity would, therefore, cause increased DABK activity and inflammation (Mahmudpour et al., 2020).

A feature that is shared by several medical conditions that increase COVID-19 severity is the presence of low-grade systemic inflammation (Chiappetta et al., 2020; Zabetakis et al., 2020; Ciornei, 2020). In several studies, elevated IL-6 was associated with increased COVID-19 severity or case fatality rate (Chen et al., 2020; Ulhaq and Soraya, 2020; Aziz et al., 2020). Obesity is an established cause of low-grade systemic inflammation (Ellulu et al., 2017; Xu, 2013; O'Rourke, 2009; Calder et al., 2011), which contributes to a heightened risk of several chronic degenerative diseases, including hypertension (Chamarthi et al., 2011), cardiovascular disease (Lopez-Candales et al., 2017; Guarner and Rubio-Ruiz, 2015; Moore, 2019), and diabetes (Qu et al., 2014; Akbari and Hassan-Zadeh, 2018; Pitsavos et al., 2007).

Another observation about patient groups at risk for severe COVID-19 is the presence of underlying medical conditions characterized by endothelial dysfunction. A consequence of inflammation (Castellon and Bogdanova, 2016; Steyers and Miller, 2014; Huang and Vita, 2006; Daiber et al., 2017), endothelial dysfunction also promotes and maintains inflammation (Hadi et al., 2005; Sun et al., 2019) and was described in aging (Higashi et al., 2012) and chronic degenerative conditions such as diabetes mellitus (Shi and Vanhoutte, 2017; Kaur et al., 2018), hypertension (Higashi et al., 2012; Ghiadoni et al., 2012; Bernatova, 2014), and obesity (Engin, 2017; Virdis et al., 2019; Bhatta et al., 2017). Other viruses that cause endothelial activation include Ebola and Marburg viruses, dengue virus, hantaviruses, and influenza A virus (Spiropoulou and Srikiatkhachorn, 2013; Armstrong et al., 2013). ACE2 protects endothelial function (Li et al., 2017b; Li et al., 2013; Paz Ocaranza et al., 2020) and exerts anti-inflammatory effects (Zhang et al., 2015; Rodrigues Prestes et al., 2017), and ACE2/ACE imbalances accelerate endothelial dysfunction and worsen the progression of vascular disease (Tikellis and Thomas, 2012; Olkowicz et al., 2015). With a surface comparable to that of six tennis courts, and a total length of ~100,000 km, or ~2.5 times the Earth circumference (Higashi et al., 2012; Higashi et al., 2009), the human vascular endothelium is a large (Higashi et al., 2012; Anggård, 1990; Talman and Kivelä, 2018), diffuse (Anggård, 1990; Henderson and Henderson, 1995; Krüger-Genge et al., 2019), and very active (Baumgartner-Parzer and Waldhäusl, 2001) endocrine organ. Vascular endothelium activation and

damage occur as part of COVID-19 (Varga et al., 2020; De Lorenzo et al., 2020; Escher et al., 2020; Huertas et al., 2020), resulting in a microvascular injury syndrome that may create a procoagulant state (Magro et al., 2020; O'Sullivan et al., 2020) and explain the systemic nature of the disease.

ACE2-Ang-(1-7)-Mas signaling induces antithrombotic effects (Verdecchia et al., 2020; Fraga-Silva et al., 2010) as a result of the Mas-mediated nitric oxide release from platelets (Fraga-Silva et al., 2008; Fang et al., 2013). ACE2 down-regulation in COVID-19 (Kai and Kai, 2020; Kuba et al., 2005; Vaduganathan et al., 2020), induced by internalization of the virus-receptor complex, could be particularly detrimental in individuals with already existing ACE2 deficiency and further dysregulate the balance between the ACE-Ang II-AT1R and the ACE2-Ang-(1-7)-Mas axes (Verdecchia et al., 2020). It was proposed that two hits to the RAAS could drive COVID-19 progression. The first one is the chronic inflammation that activates the ACE-Ang II axis, and the second one is the viral infection, which inactivates the ACE2-Ang-(1,7) axis (Tseng et al., 2020). This imbalance may explain the systemic coagulation and thrombotic events reported in COVID-19 patients (Middeldorp et al., 2020). The cumulative incidence of thrombotic complications in patients with COVID-19 in intensive care units reached 31–49% in one study, even among those who received pharmacological thromboprophylaxis (Klok et al., 2020a; Klok et al., 2020b). In another study that examined consecutive patients who died of COVID-19, 58% had deep venous thrombosis (Wichmann et al., 2020). Studies of pregnant women with COVID-19 documented an increased prevalence of decidual arteriopathy (Shanes et al., 2020) and fetal vascular thrombosis (Baergen and Heller, 2020).

SARS-CoV-2 binding to a cellular receptor that belongs to an endocrine signaling pathway, and the subsequent dysregulation in inflammation (Henry et al., 2020; Mehta et al., 2020; Kadkhoda, 2020), endothelial function (Bermejo-Martin et al., 2020), and coagulation (Henry et al., 2020), define the framework that underlies COVID-19 pathogenesis. Not only does SARS-CoV-2 affect all three of these domains by inducing an inflammatory cytokine storm (Mehta et al., 2020; Ye et al., 2020; Sun et al., 2020), multiorgan endothelial dysfunction (Varga et al., 2020), and thrombotic complications (Giannis et al., 2020; Frydman et al., 2020; Vivas et al., 2020), but perturbations in these three major axes are also intimately interconnected. For example, chronic inflammation may result in endothelial dysfunction (Castellon and Bogdanova, 2016) and thrombotic events (Aksu et al., 2012; Branchford and Carpenter, 2018; Prasad et al., 2016), endothelial dysfunction promotes thrombosis (Yau et al., 2015), and acute thrombosis can accelerate endothelial dysfunction (Kashyap et al., 2001). An acute need in the wake of the current pandemic is to better understand the physiological interconnectedness among these three major pathways, interrogate their relative contribution to pathogenesis, and unveil the manner and the extent to which SARS-CoV-2 individually modulates each of them. This will provide a valuable set of tools indispensable for understanding a novel viral infection that is fundamentally different, and markedly more complex, than all the infectious diseases that we have studied to date.

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