Editorial

ACE2 the Janus-faced protein – from cardiovascular protection to severe acute respiratory syndrome-coronavirus and COVID-19

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Angiotensin converting enzyme 2 (ACE2) is the major enzyme responsible for conversion of Ang II into Ang-(1-7). It also acts as the receptor for severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2, which causes Coronavirus Disease (COVID)-19. In recognition of the importance of ACE2 and to celebrate 20 years since its discovery, the journal will publish a focused issue on the basic science and (patho)physiological role of this multifunctional protein.

Angiotensin converting enzyme 2 (ACE2) is a key element in the protective arm of the renin–angiotensin system (RAS) [1,2]. It was discovered 20 years ago when it was found to possess over 60% similarity to ACE [3,4]. However, the active sites of ACE and ACE2 differ and accordingly, ACE inhibitors do not inhibit activity of ACE2 [5]. ACE2 is a glycoprotein metalloprotease that exists in two forms: membrane-bound and soluble [3,4,6]. The membrane-bound form contains a transmembrane domain that anchors its extracellular domain to the plasma membrane. In its soluble form, it is cleaved and secreted as the N-terminal ectodomain and is found in very low concentrations in the circulation. The significance of circulating ACE2 is unclear, although levels may be increased in disease (diabetes, CKD, hypertension) [4,5]. ACE2 has multiple substrates including kinins, apelin, neurotensin, dynorphin, ghrelin, amyloid and angiotensins [1–4]. The best known function of ACE2 is to act as the physiological counterbalance of ACE providing homeostatic regulation of angiotensin II (Ang II) by converting Ang I into Ang-(1-9), and by converting Ang II into Ang-(1-7), which is tissue-protective [7] (Figure 1). ACE2 is expressed in organs important in blood pressure regulation (vessels, heart, kidneys) as well as in the ovaries, testes, small intestine and lungs [1–4,7].

Besides its enzymatic function, ACE2 has non-catalytic actions including the regulation of renal amino acid transport, intestinal neutral amino acid transport and pancreatic insulin secretion [1,2] (Figure 1). Some of these effects are mediated through collectrin, a homolog of ACE2 [8–10]. Moreover, it acts as a receptor for some coronaviruses (CoVs) [11,12]. In 2003, severe acute respiratory syndrome (SARS) CoV (SARS-CoV) was identified as a novel respiratory pathogen leading to a global outbreak of SARS, and in 2012 a new CoV was shown to cause Middle-East respiratory syndrome (MERS) [13]. In 2019, SARS-CoV-2 was discovered as the cause of Coronavirus Disease-19 (COVID-19) [13,14]. SARS-CoV-2 infection is initiated through inoculation of the respiratory tract mucosa using ACE2 acting as the functional receptor for cell entry, a process involving the serine protease TMPRSS2 [15–20]. Viremia and replication in the lung, and possibly the gastrointestinal tract, follows.

The global impact of COVID-19 has been massive, touching everybody in some way or another. Following the first cases in Wuhan, reported in December 2019 [21], the infection spread rapidly until in March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [22]. To date (23 March 2020) WHO statistics indicate that more than 14500 people in 190 countries/areas/territories have...
Figure 1. ACE2 is a multifunctional protein

ACE2 has enzymatic (catalytic) and non-enzymatic (non-catalytic) functions. As a key element of the protective axis of the RAS, it is responsible for production of Ang-(1-7) and Ang-(1-9). The major non-catalytic functions include renal amino acid transport, intestinal neutral amino acid transport, and pancreatic insulin secretion.

died from SARS-CoV-2. These numbers are increasing daily and will continue to multiply over the next weeks and months. The exact source of COVID-19 is still unknown, although the natural host of the virus is thought to be bats (based on virus genome sequencing) and/or turtles, snakes, and pangolins [23–25]. There has been great progress in delineating the global epidemiology of the disease, tracking of infected individuals and defining the clinical features that characterize the acute respiratory disease [26,27]. However there is still a paucity of information on the molecular mechanisms whereby SARS-CoV-2 causes the disease and how host–pathogen interactions and host immune responses occur. While ACE2 and TMPRSS2 have been identified as part of the molecular machinery linked to SARS-CoV-2 effects, and have been suggested as putative therapeutic targets [15–20], there are still many unknowns about the underlying biology of the system. There is an urgent need to better understand the basic science of SARS-Cov-2-ACE2, so that disease-specific antiviral therapies can be developed.

Considering the important role of the RAS in the pathophysiology of hypertension and cardiovascular and renal diseases [28], it has been suggested that ACE inhibitors and Ang II-receptor blockers (ARBs) may increase the risk of COVID-19 infection by up-regulating ACE2 [29,30]. On the other hand, it has been proposed that inhibitors of the RAS, particularly ARBs, may actually have therapeutic benefit in COVID-19 by targeting the host response to the virus [31]. This is based on the fact that (i) ARBs increase ACE2 expression/activity leading to increased production of Ang-(1-7), which is tissue-protective and (ii) ARBs inhibit Ang II-induced inflammation and acute injury in the lungs [31,32]. However, to date there is no convincing clinical evidence linking ACE inhibitors and/or ARBs to COVID-19 severity and mortality and further clinical research is needed [33].

In only two decades, ACE2 has emerged as an important Janus-faced multifunctional protein: while it promotes cardiovascular health (through its tissue-protective actions) it also facilitates the devastations of SARS-CoV-2 infectivity responsible for the COVID-19 pandemic. It has also been suggested as a potential therapeutic target for SARS-CoV-2 [34–36]. To celebrate the 20-year discovery of ACE2, Clinical Science will publish a focused issue on ‘ACE2—a multifunctional protein’, guest edited by Prof M. Bader, Prof A. Turner and Dr N. Alenina. This issue will include state of the art review articles and research papers addressing the molecular and cellular biology, regulation and (patho)physiological functions of ACE2 in health and disease. This is perfectly aligned with the mission of the journal, which is to translate molecular bioscience and experimental research into medical insights to advance human health.
Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations
ACE2, angiotensin converting enzyme 2; ARB, Ang II-receptor blocker; CoV, coronavirus; COVID-19, Coronavirus Disease-19; RAS, renin–angiotensin system; SARS, severe acute respiratory syndrome; WHO, World Health Organization.

References