Covid-19 infection and mortality – A physiologist's perspective enlightening clinical features and plausible interventional strategies

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Editorial

Coronavirus 2019 (SARS-CoV-2) binds to converting enzyme 2 receptors (ACE2) in host cells, as was also reported for its recent preceding epidemic causing viral family member, SARS-CoV-1, responsible for the 2003-2004 outbreak in southeastern China (1). ACE2 is abundant in the lungs, heart, blood vessels, tests, brain and intestine(2, 3), and is responsible for the production of Angiotensin 1-7, which exerts vasodilatory, natriuretic/diuretic, anti-inflammatory and antifibrotic effects via the Mas receptor (2, 4). In the lung, the organ most vulnerable to SARS-CoV-2 infection in the ongoing current pandemic, ACE2 is localized to type II (AT2), and to a lesser extent to type I (AT1) alveolar cells (4). Remarkably, AT2 express many genes that are profoundly involved in the reproduction and transmission of the virus (5). The kidney and testis, two additional organs susceptible to SARS-CoV-2 also express high immunoreactivity to ACE2(2, 3), which therefore can be reasonably hypothesized as a candidate for possible involvement in the clinical manifestations of SARS-CoV-2, which also encompass acute kidney injury and impaired fertility (6-8) (Fig 1). Furthermore, preliminary available data from infected patients illustrate that patients treated with angiotensin-II inhibitors (ACE-I)/angiotensin receptor blockers (ARBs) or non-steroidal anti-inflammatory drugs (NSAIDs) exhibit severe symptoms with a higher mortality rate as compared to non-user counterparts (6-8). Of notable relevance is the demonstration that that ACE-I, ARBS and even mineralocorticoid receptor (MR) blockers remarkably augment the expression of ACE-2 both in diabetic patients (6, 9) and animals with experimental heart failure (10). Similarly, NSAIDs, non-selectively block cyclooxygenase (COX)-1 and COX-2, both enzymes being abundant in kidney tissue and well-established for the role in beneficial vasodilatory and natriuretic responses, as the case with ACE2. Thus, inhibition of

COX1/2 by NSAIDs or blockade of RAAS by ACE-I or ARBs along with concomitant elimination of ACE2 by SARS-CoV-2, may underly the exaggerated vulnerability of hypertensive, diabetic and cardiovascular disease subjects (6-8). Therefore, it is appealing to propose and test the implementable hypothesis that activation of Mas receptor by selective compound such as AVE0091 or the administration of ACE2 blockers such as targeted antibodies or chemical blockers (MLN-4760) will attenuate SARS-CoV-2 associated morbidity/mortality by preventing viral entry into ACE2 expressing cells (see Figure 1).

Furin is an additional potential pathway that could be targeted to minimize the infectious and lethal capability of SARS-CoV-2. Furin, also termed paired basic amino acid cleaving enzyme (PACE), has a substrate specificity for the consensus amino-acid sequence Arg-X-Lys/Arg-Arg at the cleavage site (11). Besides its key role in the regulation of blood clotting, growth signaling and tumor progression (12), furin is also involved in the pathogenesis of several viral infections, including HIV and other coronaviruses, where it cleaves viral enveloping proteins, permeating viral functionality (12, 13). The action of furin on the SARS-CoV-2 spike envelope trimeric transmembrane glycoprotein (S) has already been studied in depth(14, 15). This S- glycoprotein, essential for the entry of the virus into the cell, contains two functional domains: an ACE2 binding domain (also called receptor binding domain-RBD), and a second domain essential for fusion of the viral and cell membranes (1, 4, 5). Furin activity exposes the binding and fusion domains, essential steps for the entry of the virus into the cell(15) (see Figure 1). Since the S- glycoprotein of all coronaviruses contains a similar furin cleavage site, it is plausible that the activity of this enzyme is essential for the zoonotic transmission of many coronaviruses, including Covid-19 enveloped by a MERS-CoV and Sars-CoV S glycoprotein

containing a furin cleavage site (14, 15). Furin conceivably exerts its action intracellularly, as well as extracellularly, as it presents also as a circulating enzyme (16). Notably, heart failure specifically is associated with cardiac furin upregulation, perhaps explaining the vulnerability of such patients to Covid-19 infection(17). Moreover, furin is detected in T-cells which are activated during infections and circulate through the body (18). This may form a feed-forward loop of furin-facilitated coronavirus replication that may be responsible for hypersensitive immunological response (cytokine storm) in some patients, leading to fulminant myocarditis, ravaged lung tissue and lethal multi-organ failure. In these perspectives, likely, targeting furin might be an option for the prevention or treatment of Sars-CoV2 infection. Available approaches are using furin Inhibitor I, Furin Convertase Inhibitor (Chloromethylketone) or peptidyl-chloromethyl ketones, already used for HIV infection (19).

To conclude, cleavage of the S-glycoprotein by furin and its binding to ACE2-expressing cells in the lung, kidney, heart, intestine and testis are key steps in the zoonotic SARS-CoV-2 transmission. Upregulation of ACE2 and furin in cardiovascular and metabolic disease states, especially in the presence of ACE-i/ARBS/MR blockers or NSAIDs may sensitize these patients to the deleterious impact of SARS-CoV-2. Furthermore, it is appealing to assume that inhibition of furin, essential for viral intracellular translocation, or blocking the viral anchoring capability of ACE2, might be potential treatment options in combating this new formidable threat to the health and well-being of the human civilization.

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Figure legend:

Figure 1: The initial step after the invasion of SARS-CoV-2 is binding to membranal ACE2 widely expressed in various organs including, lungs, heart, kidney, intestinal, vascular endothelium and testis. This step is preceded by furin mediated exposure of the viral receptor binding protein (RBP) localized to S-glycoprotein (S1 domain of the viral spike). Furin is expressed in various target organs including the heart, but is also present in the circulation as a free enzyme, making it a key factor in the uncovering of RBP and eventually in SARS-CoV-2 transmission. Moreover, circulating and intracellular furin enhance the affinity of the virus to ACE2, not only by exposing the viral binding site on S1 domain but also by revealing the effusion site on the S2 domain in the viral spike. Consequently, the virus undergoes endocytosis and massive replication accompanied by profound activation by the abundant intracellular furin and probably Cathepsin. The activated intracellular SARS-CoV-2 undergo exocytosis where it binds again to ACE2 elsewhere, thus creating a vicious feed-forward devastating cycle. This may explain the non-remitting clinical presentation in critically ill SARS-CoV-2 infected patients. Importantly, drugs that upregulate ACE2 such as ACE-I, ARBs, MR antagonists, sensitize ACE2 expressing target organs to SARS-CoV-2.