

## Understanding Mechanism of Infection and Outlining Definitive Therapy for Corona Virus (COVID-19)

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**Abstract:** During several months of 2003, severe acute respiratory syndrome (SARS) spread rapidly through the world. A new coronavirus (SARS-CoV) was identified as the SARS pathogen which triggered severe pneumonia and acute, often lethal, lung failure. Moreover, among infected individuals influenza such as the Spanish flu and the emergence of new respiratory disease viruses have caused high lethality resulting from acute lung failure. Study conducted by [12][ab Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al] showed that, in cell lines, angiotensin-converting enzyme 2 (ACE2) has been identified as a potential SARS-CoV receptor. The high lethality of SARS-CoV infections, its enormous economic and social impact, fears of renewed outbreaks as well as the potential misuse of such viruses as biologic weapons make it paramount to understand the pathogenesis of SARS-CoV. It was established, well beyond doubt that ACE2 is a crucial COVID-19/SARS-CoV receptor in vivo. COVID-19 infections and the Spike protein of the SARS-CoV reduce ACE2 expression. Notably, injection of SARS-CoV Spike into mice worsens acute lung failure in vivo that can be attenuated by blocking the renin-angiotensin pathway. These results provide a molecular explanation why COVID-19 infections cause severe and often lethal lung failure and suggest Angiotensin II receptor blocker such as **losartan** a rational therapy for Corona (COVID-19) and possibly other respiratory disease viruses.

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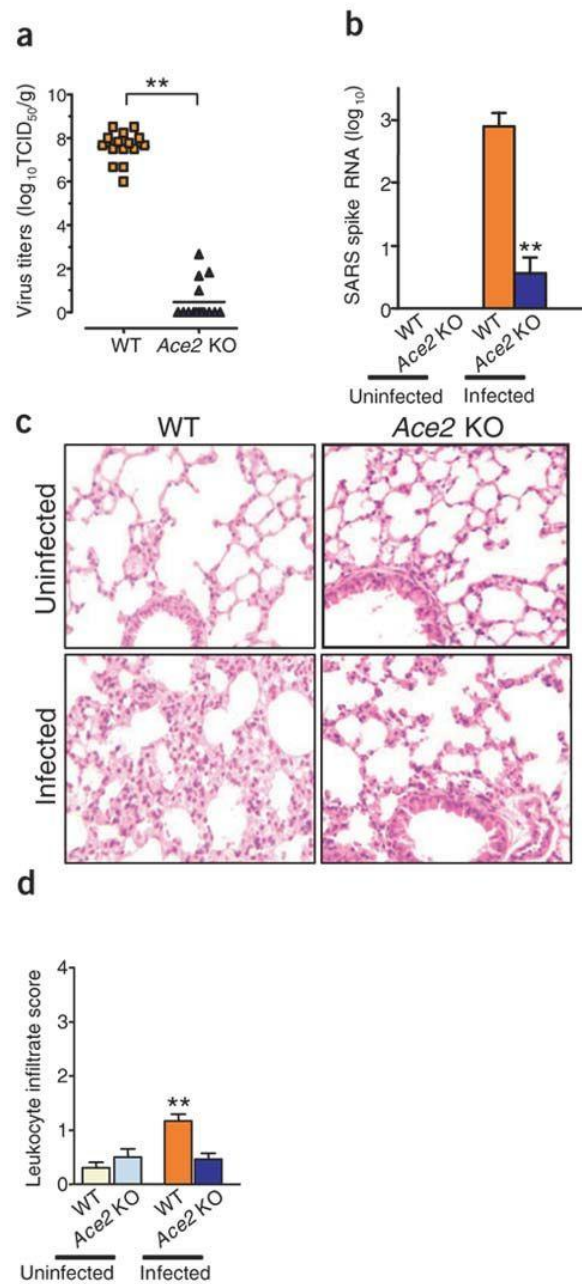
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### I. Main

ACE2 has been shown to be the entry point into human cells coronaviruses, including SARS-CoV, the virus that causes SARS.[11] [12] A number of studies have identified that the entry point is the same for SARS-CoV-2,[13] the virus that causes COVID-19.[14][15][16][17]

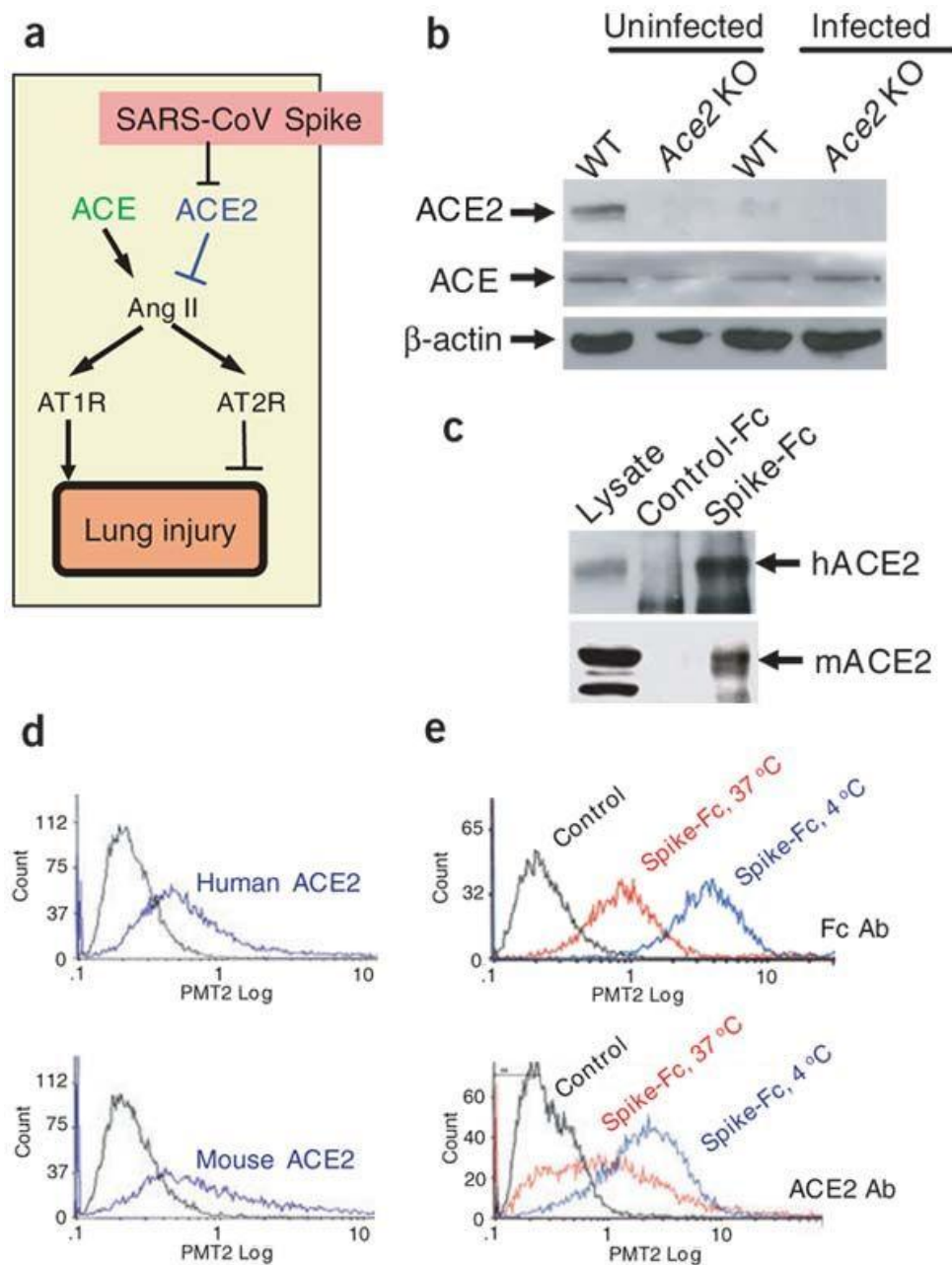
**Figure 1: ACE2 is a crucial receptor for SARS-CoV infections in vivo.**[12][*ab* Kuba K, Imai Y, Rao S,



Gao H, Guo F, Guan B, et al]

a,b) SARS-CoV replication (a) and detection of SARS-CoV Spike RNA (b) in wild-type (WT) and Ace2 knockout mice. Viral replication was determined from lung tissue at day 2 of infection. Virus titers (mean log<sub>10</sub>TCID<sub>50</sub> per gram lung tissue) are shown for individual mice. n = 15 per group. SARS-CoV Spike RNA expression was assayed using real-time RT-PCR and normalized to mouse Actb. Data are shown as mean + s.e.m. n = 15 per group. \*\*P < 0.01. (c) Lung histopathology (original magnification ×200) and (d) lung injury scores as defined by leukocyte infiltration of control and SARS-CoV-infected wild-type and Ace2 knockout mice. Lung samples were taken on day 6 after SARS-CoV infection.

Figure 2: Down regulation of ACE2 expression by SARS-CoV infection and SARS-CoV Spike protein.

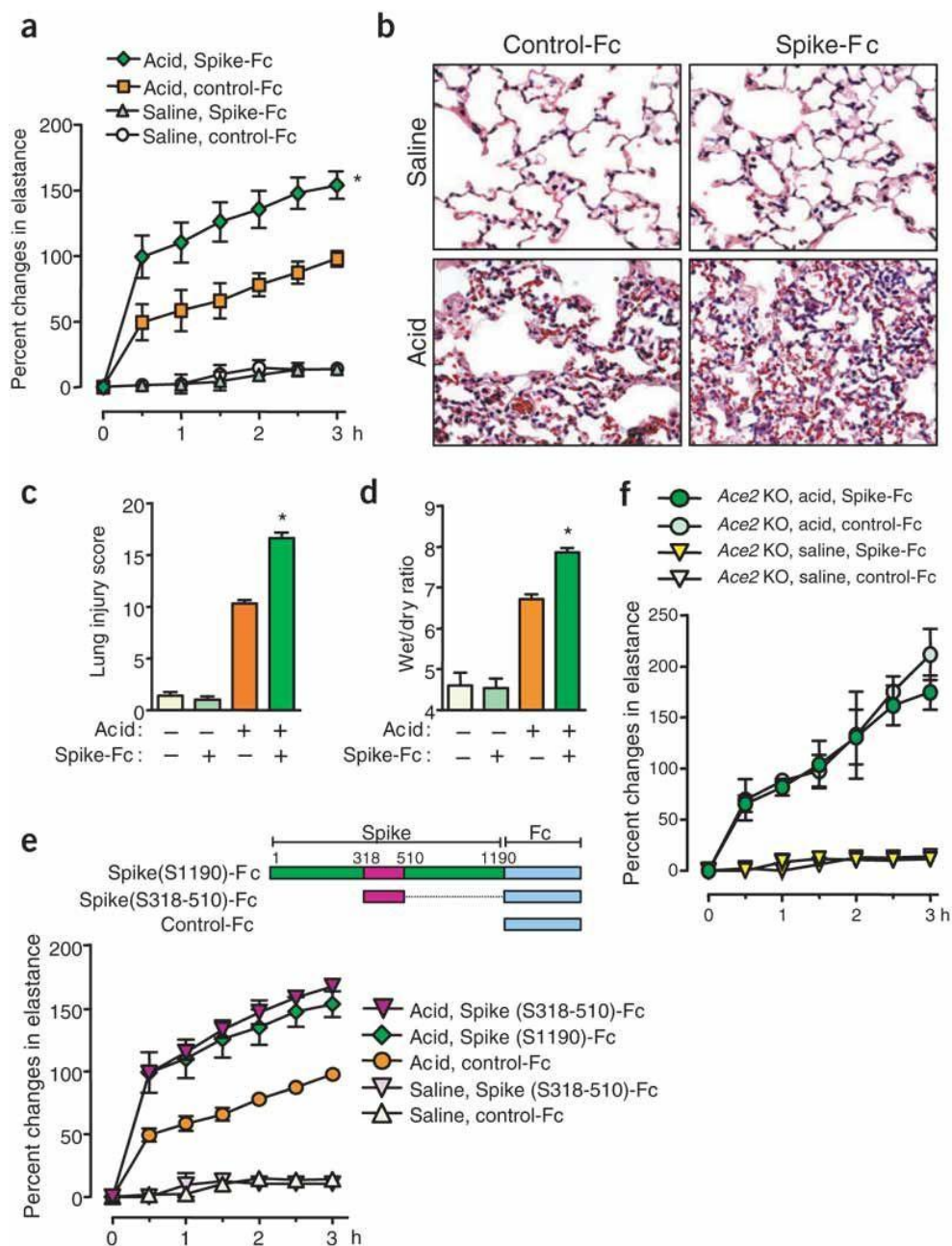


[12][*ab* Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al]

(a) Schematic diagram of the renin-angiotensin system in acute lung failure and proposed SARS-CoV action. (b) Decreased ACE2 protein, but normal ACE levels, in the lungs of SARS-CoV-infected mice. Lung homogenates were prepared from control and SARS-CoV-infected wild-type or Ace2 knockout (KO) mice on day 2 and analysed by western blot. (c) Binding of recombinant Spike(S-1190)-Fc protein to human ACE2 (hACE2) and mouse ACE2 (mACE2) in pull-down assays. Spike-Fc but not control-Fc protein pulled down hACE2 and mACE2 from total-cell extracts of A549 human alveolar epithelial cells and IMCD mouse kidney epithelial cells, respectively. Total lysates are shown as controls. (d) Binding of Spike-Fc protein to human and mouse ACE2 in cell culture. 293 cells transfected with hACE2 or mACE2 were incubated with Spike-Fc and the binding was detected by FACS (blue lines). Nontransfected 293 cells incubated with Spike-Fc followed by Fc-specific antibodies are shown as controls (black line). (e) Decreased cell-surface expression of ACE2 after binding to Spike-Fc protein at 37 °C compared to 4 °C in Vero E6 cells. ACE2 surface expression was detected at 3 h of incubation with Spike-Fc using an ACE2-

specific monoclonal antibody. Similar data were obtained using Fc-specific antibody to directly detect surface-bound Spike-Fc and to avoid masking of the ACE2 epitope. Representative FACS histograms are shown including a background control with an isotope-matched antibody.

Figure 3: The SARS-CoV Spike protein enhances the severity of acute lung injury.[12][ab Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al]



a) Lung elastance measurements after saline or acid instillation in Spike-Fc protein–(5.5 nmol/kg) or control-Fc– (5.5 nmol/kg) treated wild-type mice. n = 5–7 per group. \*P < 0.05 for the whole time course comparing Spike-Fc–treated and control-Fc–treated wild-type mice after acid injury. (b) Lung histopathology. Representative images are shown. Original magnification, ×200. (c) Lung injury score . \*\*P < 0.01 versus control-Fc–treated wild-type. (d) Wet to dry weight ratios of lungs as readout for pulmonary edema in control and Spike-Fc–treated mice in the presence or absence of acid-induced lung injury. \*P < 0.05 between control and Spike-Fc–treated mice with acid challenge. (e) Severe acute lung failure by Spike(S318-510)-Fc (5.5 nmol/kg) treatment in acid-challenged mice. The scheme (upper panel)

shows the ACE2-binding domain of Spike (S318-510). Lung elastance measurements (lower panel) showed that Spike(S318-510)-Fc induced severe acute lung failure in acid-challenged wild-type mice, comparable to Spike(S1190)-Fc. n = 5–7 per group. P < 0.05 for the whole time course comparing Spike(S318-510)-Fc or Spike(S1190)-Fc-treated and control-Fc-treated wild-type mice after acid injury. (f) Lung elastance measurements after acid instillation in Spike-Fc protein–(S1190; 5.5 nmol/kg) or control-Fc–(5.5 nmol/kg) treated Ace2 knockout (KO) mice. n = 5–7 for each group

## II. Conclusion:

This can be conclusively inferred that decreasing the levels of ACE2, in cells, might help in fighting the infection. On the other hand, ACE2 has been shown to have a protective effect against virus-induced lung injury by increasing the production of the vasodilator angiotensin 1–7.[18] In fact, the interaction of the spike protein of the virus with the ACE2 induces a drop in the levels of ACE2 in cells,[12] possibly inducing lung damage. Therefore, the available (AT1R) blockers (Angiotensin II receptor blocker) such as **losartan**, can help in curing COVID-19 need to be tested by data-mining of clinical patient records.[19] Besides, high dosage of **Vitamin D**, be considered because it has been shown to increase expression of ACE2 in cells,[20]. A possible way of combating the infection could be the injection of **soluble ACE2** into the blood stream which will have the twofold effect of competing with cellular ACE2, preventing the attachment of the virus to non-infected cells and replenishing ACE2 in infected cells.[21]

Studies have suggested a close co-morbidity link between hypertension and heart disease and COVID-19 which may be related to these patients normally being prescribed ACE inhibitors.[22]

Treatment with angiotensin-converting enzyme (ACE) inhibitors results in an up-regulation of ACE2 in some organs.[23] ACE2 is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. This increased expression of ACE2 may facilitate infection with SARS-CoV or SARS-CoV-2. Hence, patients with diabetes or hypertension being treated with ACE inhibitors may be at increased risk of COVID-19 infection.[22]

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