COVID-19 cellular pathogenesis in brief

Dear Editor,

The most frequently used test for the diagnosis of COVID-19 is now reverse-transcriptase polymerase chain reaction (RT-PCR) executed by using nasopharyngeal swab specimens. The sensitivity of the severe acute respiratory syndrome (SARS)-CoV-2 RT-PCR tests has been described around 70%. The test could usually detect the virus 2 or 3 days before the onset of infectious symptoms. It should be toughly noted that the RT-PCR positivity does not mean an evidence of active and/or infectious virus. *Vice versa*, a negative result of the RT-PCR test does not exclude the SARS-CoV-2 infection.

In case the infection would be true, the SARS-CoV-2 virus simply enters the cells by attaching to the angiotensin-converting enzyme-2 (ACE2), which is expressed on pneumocytes of the lower airways. While ACE converts angiotensin I (Ang I) to Ang II, ACE2 uses Ang II as a substrate and produces Ang (1–7). The Ang II is a vasoconstrictor that causes oxidative stress, producing increased reactive oxygen species. Therefore, elevated Ang II level causes higher blood pressure, insulin resistance, proteinuria, and so on. In addition, ACE is surely correlated with asthma, chronic obstructive pulmonary disease, and acute respiratory distress syndrome. Furthermore, overactivation of ACE aggravates amyloid-β-induced apoptosis and/or neurodegeneration in Alzheimer's disease. On the other hand, the ACE2 is highly expressed in smokers and/or in patients with an underlying disease. As described below, several data have indicated the protective roles of the ACE2 pathway. Surface spike glycoprotein on the surface of SARS-CoV-2 binds to the ACE2 [Figure 1], which has been proven to be protective in pulmonary and cardiovascular diseases and so on.[1] The Ang (1–7) exerts its effects through the Mas receptor in various tissues, including kidneys, heart, brain, and vasculature, which even protects against aneurysm rupture via the Mas receptor.[2] Amazingly, upregulation of internal ACE2 could attenuate the exacerbation of nephropathy and hypertension in diabetic mice.[3] In addition, stimulation of ACE2/Ang (1–7)/Mas ameliorates Alzheimer's disease.[4] It has been reported that the ACE2/Ang (1–7)/Mas activates AKT signaling to ameliorate oxidative stress, inflammation, and hepatic steatosis.[5] In general, the PI3K/AKT activation opposes the AT1-induced apoptosis.

The PI3K/AKT pathway is thought to correlate with host protection and disease prognosis. If the SARS-CoV-2 virus destroys the ACE2/Ang (1–7)/Mas/PI3K/AKT signaling pathway, a host protection system, it would be of significance to define appropriate strategies to achieve benefits to activate the PI3K/AKT pathway. As the efficiency of pharmacological and/or vaccinal treatments against COVID-19 has been imperfect at present, dietary choices could indicate a certain role in the host protection system via the PI3K/AKT activation. For example, dietary supplementation of fish oil attenuates lipopolysaccharideinduced inflammation as shown in previous studies. Lifestyle factors such as special diets could play certain roles against the severity of COVID-19.[6]

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Conflicts of interest

There are no conflicts of interest.

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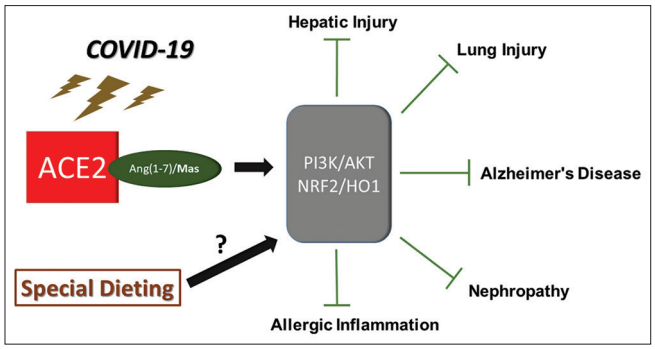

Figure 1: Schematic illustration implying that angiotensin-converting enzyme-2/angiotensin (1–7)/Mas axis protects host tissues via the PI3K/AKT/NRF2/HO1 signaling from various diseases without COVID-19. When COVID-19 infection abolishes the angiotensin-converting enzyme-2 axis, special dieting could substitute the protection by activating the PI3K/AKT signaling

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