Is targeting Akt a viable option to treat advanced-stage COVID-19 patients?

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One of the primary reasons for high mortality in the advanced-stage coronavirus disease-2019 (COVID-19) patients is the uncontrolled inflammation in the lungs leading to acute respiratory distress syndrome (ARDS). Controlling the pathological inflammation in the ARDS lungs without compromising the immune system’s fight against the virus is indeed a daunting task. In this situation, an appropriate therapeutic target would be the one that will not only reverse the damaging inflammation and promote resolution but also helps to check the root cause of the virus infection. Akt is a potential therapeutic target for the advanced-stage COVID-19 patients; its inhibition will potentially suppress the pathological inflammation, cytokine storm, fibroproliferation, and platelet activation associated with COVID-19, and at the same time prevent scarring and promote resolution in injured lungs. As pharmacological inhibition of Akt has also been reported to inhibit angiotensin-converting enzyme 2 (ACE2) expression, a receptor for the virus entry into the lung cells, targeting Akt for COVID-19 looks a viable option.

Severe acute respiratory syndrome (SARS), an acute respiratory distress syndrome (ARDS) caused by the coronavirus-2 (SARS-CoV-2), is the primary reason for high mortality associated with coronavirus disease-2019 (COVID-19) (25). The prolonged asymptomatic incubation period in COVID-19 patients ranging between 1 and 14 days (5.1 days median) is a major bottleneck in its early detection and preventing it from infecting the lungs of some patients (12). Additionally, comorbidities such as diabetes and hypertension (10, 24) and a history of medications such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors (9) further worsens the COVID-19 associated ARDS. The effect of comorbidities (14) and the use of cardiovascular medications (19) are believed to be due to the increased expression of ACE2, a putative receptor for SARS-CoV-2 (23). As current treatment options for ARDS are very limited (21, 22), treating advanced COVID-19 patients is a bigger challenge due to the reasons above. Early detection and preventing a lung infection would be the most desirable approach to treat COVID-19 patients. Although some COVID-19 patients present early symptoms, many patients harboring SARS-CoV-2 remain on a long asymptomatic period and are undetected until complications arise (10, 12). Having a large population suffering from metabolic diseases and hypertension in Western countries (17), the potential risk of COVID-19 associated ARDS is also higher. Hence, it is not always possible to cure COVID-19 patients before severe lung infection takes hold. The next obvious question is, how do we treat advanced-stage COVID-19 patients with lung infections? One potential option would be to target ACE2 or pathways promoting ACE2 expression or activation. Alternately, COVID-19 patients can also be treated by engineered peptides, antibodies, or compounds to disrupt or prevent the interaction between SARS-CoV-2 spike protein and ACE2 (23) that will prevent reinfections and limit the lung damage. A better option to manage advanced-stage COVID-19 patients would be a drug that can not only suppress inflammation but also promote the resolution of lung injury and prevent scarring (Fig. 1).

The phosphoinositide 3 (PI3)-kinase/Akt pathway promotes inflammation in several disease states (8). Whereas genetic deletion of Akt1 gene reduced inflammation and improved cardiac function in mice following myocardial ischemia (13, 16), pharmacological Akt inhibition suppressed inflammation.
in mice, myofibroblast differentiation, and prevented vascular rarefaction to halt pulmonary fibrosis progression (1, 2). Furthermore, whereas Akt1 deficiency in macrophages resulted in reduced foam cell formation (13), inhibition of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) leading to Akt activation in the regulatory T cells (Tregs) promoted inflammation (18). Adoptive transfer of Tregs has demonstrated to suppress fibroproliferation and improve injury resolution in an animal model of experimental lung injury (6, 15), suggesting that increasing the number of Tregs in ARDS lungs would be an ideal strategy to treat COVID-19 patients in the advanced stages. However, the pharmacological means to increase the number of Tregs in ARDS lung was not available until we recently demonstrated that the number of the effector (activated) Tregs in the advanced stages of bacterial endotoxin-induced experimental lung injury in mouse lungs can be increased by Akt inhibition with compounds such as triciribine and MK2206, promoting injury resolution and recovery (3). Whereas ACE2 has been implicated in pulmonary arterial hypertension (7) and lung inflammation (11), Akt inhibition with MK2206 and triciribine has been reported to ameliorate the pathological effects of ACE2 in hepatic steatosis (4). However, a link between the Akt pathway and ACE2 activation in COVID-19 patients needs to be investigated.

Although the host PI3-kinase/Akt pathway is utilized by the viruses in general for its survival and replication (5, 20), this has not been demonstrated in the case of the SARS-CoV-2 virus replication in the lung epithelial cells. On the contrary, an adverse effect of Akt suppression by promoting the SARS-CoV-2 virus replication in the patient lung epithelial cells also cannot be ruled out. Nevertheless, pharmacological inhibition of the Akt pathway using inhibitors such as triciribine and MK2206, alone or in combination with the currently evolving standard of care, provides potential treatment options for COVID-19 patients with ARDS. Based on the preclinical observations from non-COVID-19 lung disease research, Akt suppression is expected to increase Tregs in the lungs of COVID-19 patients, in turn, suppressing inflammation and fibroproliferation, promoting the resolution of injury, and preventing vascular rarefaction in the lungs as a result of SARS-CoV-2 infection. This, however, needs further experimental validation in a suitable preclinical COVID-19 model such as the non-human primates before clinical trials are conducted in COVID-19 patients.

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AUTHOR CONTRIBUTIONS
P.R.S prepared figure; drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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