Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

also enhances phosphorylation of transmembrane vascular endothelial cadherin molecules, which are then internalized and degraded. The ensuing actin cytoskeleton constriction increases pore size between endothelial cells, with consequent vascular leakage. It is known that engagement of BKB2 by bradykinin can activate BKB1, but the overall role of BKB1 in hereditary angioedema (HAE) is uncertain. Remarkably, the BKB1 receptor is rarely expressed in normal conditions, but proinflammatory cytokines can upregulate the expression of BKB1 on endothelial cells. This suggest that blockage of BKB1 in the inflammatory state should be just as important as blocking BKB2 to prevent edema in COVID-19. To support this theory, it would be interesting to analyze whether bradykinin levels and consequently des-Arg^9-bradykinin levels are increased in patients with COVID-19. Moreover, if the pathophysiology of pulmonary edema in COVID-19 corresponds with the pathophysiology of HAE, exploring therapeutic options used to treat HAE would be a logical step. Targeting the bradykinin system by either inhibiting bradykinin production or blocking bradykinin receptors may open new therapeutic options to control COVID-19–induced pulmonary edema. Further studies are required to better understand the pathophysiology of this complex disease to invent treatment options for a more adequate response in the future.

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Reply

To the Editor:

We thank Zwaveling et al[1] for appreciating our review[2] and for their insightful correspondence. They suggest that suppression of angiotensin-converting enzyme-2 (ACE-2) by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could impair the hydrolysis of des-Arg^9-bradykinin and stimulate the bradykinin receptor type 1 (BKB1) pathway to induce leakage of fluid into the lungs. In support of their hypothesis, loss of ACE-2 in an animal model aggravated acid-induced pulmonary edema, and these effects are alleviated by administration of recombinant human ACE-2.[3] In addition, a report demonstrated that SARS-CoV infection downregulates the expression of ACE-2.[4] However, other studies suggest that SARS-CoV-2 may upregulate the expression of ACE-2 in patients with coronavirus disease 2019 (COVID-19) or influenza pneumonia in alveolar epithelial cells, endothelial cells, and lymphocytes in perivascular tissue than in uninfected control autopsy lung.[5] Furthermore, single-cell RNA sequencing analysis revealed that secretory cells in the upper airway epithelium have higher ACE-2 expressions in COVID-19.[6] Thus, until the effect of SARS-CoV-2 on ACE-2 levels or functionality is thoroughly addressed in peer-reviewed publications, it is difficult to precisely determine the contributory role of ACE-2 in the bradykinin pathway during SARS-CoV-2 infection.

Zwaveling et al draw an analogy of pulmonary edema in severe COVID-19 to extravascular fluid leakage in hereditary angioedema (HAE), and hypothesized that binding of bradykinin to the bradykinin receptor type 2 (BKB2) could induce active fluid transfer through vascular pores (Fig 1, *A*). Another explanation for extravascular fluid leakage into the lungs in COVID-19 is secretion of proinflammatory cytokines such as TNF and IL-6 during the cytokine storm (Fig 1, *A*).[7] We favor a third hypothesis, where excessive and prolonged secretion of type I and type III IFNs in the airways contributes to loss of lung epithelial barrier function during COVID-19 and other RNA virus infections (Fig 1, *A*).[8,9] To test whether entry of SARS-CoV-2 through ACE-2 is sufficient to induce type III IFNs without need for viral replication, we engineered a replication-deficient SARS-CoV-2 spike-HIV-luc pseudotype virus. Infection of Caco-2 cells, which naturally express ACE-2, with this engineered virus was sufficient to increase the mRNA expression of IFN-λ2 (Fig 1, *B* and *C*), indicating that virus replication is not required for upregulating its expression. Because IFN-λ contributes to loss of lung epithelial barrier function,[8] we hypothesize that entry of SARS-CoV-2 via ACE-2 can stimulate secretion of IFN-λ and induce leakage of fluid into the lungs (Fig 1, *A*).

Zwaveling et al's hypothesis is most intriguing and certainly plausible. However, as acknowledged by the authors, there is no direct evidence showing increased levels of bradykinin or des-Arg^9-bradykinin in the patients with COVID-19 at this time. Here, we provide evidence that entry of SARS-CoV-2 through ACE-2 provides an adequate signal even without viral replication to stimulate IFN-λ2 mRNA expression, a cytokine that can cause damage to the epithelial barrier. Further investigations are required to test the hypotheses outlined in Fig 1, *A*, which may induce leakage of fluid into the lungs in COVID-19, and identify the most important pathway(s).

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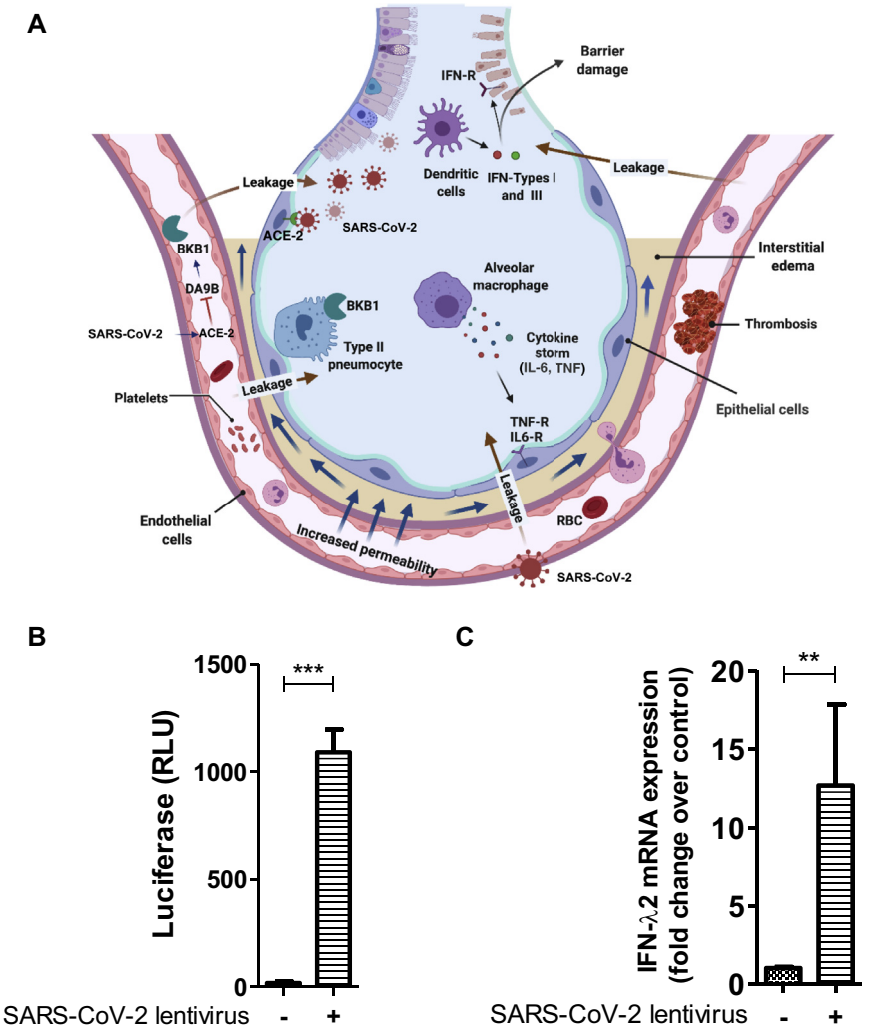

FIG 1. A, Illustration showing several postulated mechanisms of SARS-CoV-2–induced pulmonary edema. **B,** Presence of pseudotype virus detected by luciferase activity in the lysate of Caco-2 cells. Caco-2 cells were infected with SARS-CoV-2 spike-HIV-luc pseudotype virus at 5×10^3 infectious units/mL. Thus, the luciferase reporter activity serves as a measure of viral particles in the infected cells. After 24 hours of incubation, luciferase levels in the cell lysates were quantified. **C,** IFN-λ2 mRNA expression in Caco-2 cells incubated with or without SARS-CoV-2 spike-HIV-luc pseudotype virus for 24 hours. N = 3 to 6 per group were used. Data are expressed as means ± SEM. $^{**}P < .01$, $^{***}P < .001$.

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