Letter to Editor

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Des-Arg9 Bradykinin and Bradykinin Potentially Trigger Cytokine Storm in Patients with COVID-19

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DEAR EDITOR

Cytokine storm and acute immune response in the lungs of patients with COVID-19 caused by a novel SARS-CoV-2 is obvious with clinical and pathological manifestations including cough, pain, vasodilation, inflammation, and acute respiratory distress syndrome (1-4). SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) for entry to the alveolar type II (AT2) cells in the lungs. (5) Of note, ACE2 is a member of the renin-angiotensin system cleaving peptides such as angiotensin II, and des-Arg^9 bradykinin (DABK); thereby inactivating DABK and inhibiting inflammation. Through *in vitro* and *in vivo* experiments, ACE2 contribution to pulmonary inflammation and consequent vascular permeability has been unveiled. Upon infection, ACE2 is downregulated resulting in activation of DABK/B1 receptor signaling axis locally in the lungs, which in turn promotes the expression of chemokine C-X-C motif chemokine 5 (CXCL5) in pulmonary epithelial cells. (6-9) When CXCL5 binds CXC receptor 2 (CXCR2), mainly on neutrophils, they are recruited and infiltrate the lungs, leading to the acute lung inflammation seemingly as a result of NF-kB signaling activation. (10) DABK by binding bradykinin B1 receptor (BKB1R), may act as a potential candidate for suppression of lung hyperinflammatory reactions during COVID-19. In addition, bradykinin B2 receptor (BKB2R) may also be a target whose ligand, bradykinin (BK), is one of the underlying factors in the angioedema with clinical manifestations similar to COVID-19 (Figure 1). In hereditary angioedema, life-threatening attacks were rare in the pediatric age group, just like what was observed in COVID-19 (11).

Increased proinflammatory cytokines and chemokines participating in the cytokine storm observed in severe pulmonary injuries probably resulted from increased levels of DABK and BK locally in the lungs of the COVID-19 patients. Therefore, inhibition of

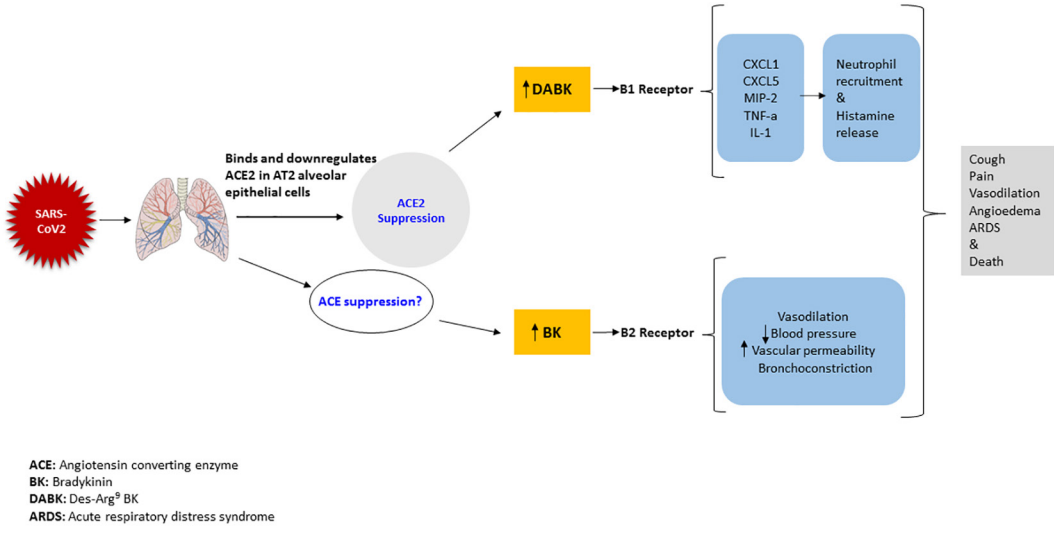

Figure 1. Des-Arg bradykinin and bradykinin pathway and manifestations resulted from SARS-CoV-2 infection.

BKB1R and BKB2R receptors of DABK/BK axis may decrease the severity of the cytokine storm and reduce the fatality of COVID-19.

Conflicts of Interest: None declared.

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