SARS-CoV-2 spike protein enhances MAP4K3/GLK-induced ACE2 stability in COVID-19

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The major entry receptor of SARS-CoV-2 on epithelial cells is angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 infection of airway epithelium is quite efficient; however, why ACE2 levels are generally low in airway epithelial cells of healthy individuals had puzzled scientists.

After analyzing single-cell RNA-sequencing data derived from two COVID-19 cohorts, we found that MAP4K3/GLK-positive epithelial cells were increased in patients. SARS-CoV-2-induced GLK overexpression in epithelial cells correlated with COVID-19 severity and vesicle secretion. GLK overexpression induced the epithelial cell-derived exosomes containing ACE2; the GLK-induced exosomes transported ACE2 proteins to recipient cells, facilitating pseudovirus infection. Consistently, ACE2 proteins were increased in the serum exosomes from another COVID-19 cohort. Remarkably, SARS-CoV-2 spike protein stimulated GLK, and GLK stabilized ACE2 in epithelial cells. Mechanistically, GLK phosphorylated ACE2 at two serine residues (Ser776, Ser783), leading to dissociation of ACE2 from its E3 ligase UBR4. Reduction of UBR4-induced Lys48-linked ubiquitination at three lysine residues (Lys26, Lys112, Lys114) of ACE2 prevented its degradation. Furthermore, SARS-CoV-2 pseudovirus or live virus infection in humanized ACE2 mice induced GLK and ACE2 protein levels, as well as ACE2-containing exosomes. Consistently, the GLK-phosphorylated ACE2 and ACE2-containing exosomes were also detectable in the sera of COVID-19 patients. This mechanism provides an explanation for why ACE2 levels are very low in airway epithelial cells of normal individuals, whereas SARS-CoV-2 infection of airway epithelium is quite efficient. Taken together, ACE2 stabilization by SARS-CoV-2-induced MAP4K3/GLK may contribute to the pathogenesis of COVID-19.

Keywords: MAP4K3/GLK, ACE2, UBR4, SARS-CoV-2, COVID-19