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Kallistatin ameliorates influenza virus pathogenesis by inhibition of kallikrein-related peptidase 1-mediated cleavage of viral hemagglutinin

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The influenza virus hemagglutinin (HA) mediates virus binding to cell receptors and promotes the release of viral RNA through membrane fusion. Proteolytic cleavage of the HA molecule by host cell trypsin-like proteases is required for viral infectivity. Kallikrein-related peptidase 1 (KLK1) is a widely distributed serine protease. Kallistatin, which is synthesized mainly in the liver and rapidly secreted into the circulation, is a naturally occurring KLK1 inhibitor. Here we investigated the roles of KLK1 and kallistatin in influenza virus infection. We show that KLK1 expression was increased whereas kallistatin expression was reduced in the lung of mice during influenza infection. Furthermore, KLK1 was capable of cleaving H1, H2 and H3 HA molecules with different efficiencies leading to enhanced viral production. By contrast, kallistatin could inhibit KLK1-mediated HA cleavage and consequently reduce viral production. Lentivirus-mediated kallistatin gene delivery protected mice against lethal influenza virus challenge and alleviated lung injury by reducing interleukin (IL)-1β levels and decreasing infiltrating inflammatory cells. Taken together, we identify that KLK1 and kallistatin contribute to the pathogenesis of influenza virus by affecting HA cleavage and inflammatory responses. This study provides a proof of principle for the potential therapeutic application of kallistatin or other KLK1 inhibitors for influenza.

Notes: