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Title: Kallistatin protects against LPS-induced mouse lung injury

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Body: Acute lung injury (ALI) is caused by overwhelming lung inflammation, resulting in diffuse alveolar damage, edema, and subsequently respiratory dysfunction. The mortality remains high, and the treatments are exclusively supportive because of lacking selective and efficacious pharmaceutical agents targeting on the pathogenesis of ALI. Kallistatin is a serine proteinase inhibitor that exhibits pleiotropic functions in vasodilation, anti-angiogenesis, anti-inflammation, and anti-apoptosis, which may contribute to its therapeutic effects in a variety of human diseases. Kallistatin is also found in the lungs, implicating its involvement in the regulation of lung functions. However, the role of kallistatin in the pathophysiology of ALI is still unclear. Herein, we hypothesized that kallistatin plays a role in protection against lung injury. Using kallistatin gene-transferred mice by delivering plasmid DNA encoding human kallistatin into the lungs, we examined the protective effect of kallistatin against LPS-induced lung injury. We found that the severity of lung injury was attenuated in kallistatin gene-transferred mice compared with untreated mice, indicated by decreasing cell counts, LDH and protein levels of bronchoalveolar lavage fluids (BALF). BALF levels of TNF-α, IL-1β, MIP-2, and IL-6 were also lower in human kallistatin gene-transferred mice than untreated mice, suggesting a decline in inflammatory response after LPS treatment. In addition, the kallistatin gene-transferred mice showed less extent of epithelial cell apoptosis shown by TUNEL staining. Our data demonstrate for the first time that kallistatin protects against LPS-induced lung injury through attenuation of inflammation and epithelial cell apoptosis.