FAER
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Attenuation of lung injury with an inhaled matrix metalloproteinase inhibitor

Abstract

In acute lung injury/acute respiratory distress syndrome (ALI/ARDS), pulmonary edema and poor oxygenation result from massive inflammatory damage to the lungs. Recent evidence posits a role for the proteolytic activity of matrix metalloproteases (MMPs) in the cleavage and activation of multiple chemokines regulating neutrophil migration into the inflamed lung and an increase in epithelial permeability leading to edema and hypoxemia. We hypothesize that chronic dosing of the inhaled MMP inhibitor CGS 27023A following lung injury will abrogate acute inflammation and chronic fibro-proliferative remodeling in injured mice. We also hypothesize that MMPs influence pulmonary epithelial barrier breakdown and that CGS 27023A exerts its anti-inflammatory effects by maintaining pulmonary epithelial barrier integrity thereby preventing neutrophil infiltration and edema. We will utilize a murine endotoxin model of ARDS to examine CGS 27023A effects on acute and chronic inflammatory injury. A histologic and molecular biology driven approach will be used to examine tissue injury using an ARDS scoring system, measurement of cytokines, examination of apoptotic markers, pulmonary barrier integrity and neutrophil invasion. An in vitro approach using air liquid interface cultures will examine MMPs' role in epithelial permeability and neutrophil migration. This proposal has the potential to demonstrate a novel pro-inflammatory role for MMPs in lung injury. Furthermore, we hope it establishes CGS 27023A as a potential therapeutic agent that directly treats ALI/ARDS pathophysiological dysfunction that is deliverable via ETT to ICU patients or those at high risk of intraoperative lung injury