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Mechanical ventilation is a life-saving therapy that can also damage the lungs. Ventilator-induced lung injury (VILI) promotes inflammation and up-regulates matrix metalloproteinases (MMPs). Among these enzymes, MMP-8 is involved in the onset of inflammation by processing different immune mediators. To clarify the role of MMP-8 in a model of VILI and their relevance as a therapeutic target, we ventilated wild-type and MMP-8–deficient mice with low or high pressures for 2 hours. There were no significant differences after low-pressure ventilation between wild-type and knockout animals. However, lack of MMP-8 results in better gas exchange, decreased lung edema and permeability, and diminished histological injury after high-pressure ventilation. *Mmp8*$^{-/-}$ mice had a different immune response to injurious ventilation, with decreased neutrophilic infiltration, lower levels of IFN-γ and chemokines (LPS-induced CXC chemokine, macrophage inflammatory protein–2), and significant increases in anti-inflammatory cytokines (IL-4, IL-10) in lung tissue and bronchoalveolar lavage fluid. There were no differences in MMP-2, MMP-9, or tissue inhibitor of metalloproteinase–1 between

CLINICAL RELEVANCE

Matrix metalloproteinase (MMP)–8 promotes acute lung inflammation. Genetic ablation or pharmacologic inhibition of this enzyme leads to an attenuated inflammatory response that ameliorates ventilator-induced lung injury. Our results point to MMP-8 inhibition as a therapeutic target to avoid acute inflammation after high-pressure ventilation.

are currently viewed as key modulators of different cellular processes (5). Increased levels of MMPs have been documented in ventilated patients (6–8), as well as in experimental models of VILI (4), implicating MMPs in the pathophysiology of VILI (9, 10). Moreover, MMPs regulate critical processes associated with VILI,