NecroX-5 Inhibits the LPS-induced Lung Inflammation through the Regulation of NLRP3 Inflammasome

Oxidative stress caused by ROS and RNS has been implicated in various airway pathological conditions. The NLRP3 inflammasome is an intracellular complex that regulates release of proinflammatory cytokines such as IL-1β, in response to exogenous pathogen-associated molecular patterns and endogenous danger signals. NecroX-5, a novel compound is one of the derivatives of NecroX series compounds, which shows the mitochondrial ROS scavenging activity. In this study, we aimed to define the effects of NecroX-5 on LPS-induced lung inflammation in a murine model of acute lung injury, focusing on the interaction between mitochondrial ROS generation and NLRP3 inflammasome activation. The administration of NecroX-5 restored the levels of GSH, decreased the LPS-induced mitochondrial ROS generation, the levels of NLRP3 expression and IL-1β in lungs, the numbers of airway inflammatory cells in BAL fluids, the histologic changes in lung tissues, and the increase in the levels of inflammatory cytokines in LPS-inhaled mice. Blockade of IL-1β using neutralizing antibody resulted in the substantial improvement of the pulmonary inflammatory features. These findings suggest that NecroX-5 improves lung inflammation and plasma exudation by regulating mitochondrial ROS generation and provide the potential of NecroX-5 as a therapeutic agent for acute lung injury. Additionally, NLRP3 inflammasome plays a crucial role in the pathogenesis of LPS-induced lung inflammation and its activation is closed related to mitochondrial ROS production.

IL-17 Enhances ER Stress in LPS-induced Lung Inflammation

IL-17 appears to act rapidly as an innate immune responder during infection, before the onset of a classic role of IL-17 through adaptive T cell response. In addition, IL-17 is implicated in lipopolysaccharide (LPS)-induced lung inflammation, in which ER stress has been known to play a pivotal role pathophysiological. In this study, to elucidate the role of IL-17A in LPS-induced lung inflammation focusing on the link with ER stress in a mouse model of LPS-induced lung injury, we treated the mice with IL-17A neutralizing antibodies and 4-PBA, a representative ER stress regulator. In addition, we evaluated the effects of IL-17A on ER stress induced in LPS-stimulated bronchial epithelial cells. Our result showed that inhibition of IL-17A diminished the typical features of lung injury including pulmonary neutrophilia and vascular leakage and the increased ER stress and improves LPS-induced lung inflammation. Moreover, 4-PBA also attenuates the LPS-induced lung inflammation and the expression of IL-17A. Intriguingly, the expression of IL-17A was observed in LPS-stimulated airway epithelial cells and IL-17A can induce the enhancement of ER stress and NF-κB activation in airway epithelial cells. Lastly, our results also showed that increases in nuclear translocation of NF-κB, infiltration of DCs into lungs, and TLR4 expression after LPS treatment were significantly reduced by the inhibition of IL-17A in the lung. This study indicates that the relationship between IL-17 and ER stress plays an important role in the pathogenesis of LPS-induced inflammation.