The Blockade of IL-17 Attenuates ER Stress in LPS-induced Lung Inflammation

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Pro-inflammatory mediators modulate endoplasmic reticulum (ER) stress, defined as alterations in ER homeostasis under various stress. As a bacterial endotoxin, lipopolysaccharide (LPS) is involved in numerous inflammatory diseases, and IL-17 has been known to be implicated in LPS-induced lung inflammation. However, it is not known exactly how IL-17 interacts with ER stress in LPS-related lung inflammation. In this study, using a murine model of LPS-induced lung inflammation, effects of IL-17 inhibition using anti–IL-17 antibody on LPS-induced lung inflammation were examined, especially in relation to ER stress. Inhibition of IL-17 reduced significantly LPS-induced increases of GRP78 and CHOP protein levels in lung tissues. IL-17 inhibition also lowered LPS-induced increases of unfolded protein response (UPR)-related markers in the lung. Furthermore, increases of airway inflammatory cell infiltrations, vascular leakages, and various pro-inflammatory mediators after LPS treatment were decreased by the neutralization of IL-17. Moreover, administration of 4-phenylbutyrate (PBA), an ER stress inhibitor, attenuated pathologic features as well as increases of various ER stress markers of LPS-induced lung inflammation. And, increases in nuclear translocation of NF-κB p65, expression of Toll-like receptor4 (TLR4), and infiltration of dendritic cells (DCs) into lungs after LPS treatment were reduced after IL-17 blockade. Our results suggest that IL-17 inhibition improves LPS-induced lung inflammation partly through the modulation of ER stress.

The Presence of PI3K-γ in Alveolar Epithelial Cells Is Associated with Intracellular ROS Generation

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Overproduction of reactive oxygen species (ROS) results in oxidative stress, which is known to damage the lung and consequently lead to various lung diseases. Airway epithelium is first cell layer to contact with microbes and air pollutants. In this study, we investigated the molecular basis of ROS generation induced by lipopolysaccharide (LPS) in A549 cells, an alveolar epithelial cell line. A549 cells or NHBE cells were stimulated with LPS. The ROS generation was measured in A549 cells or NHBE cells pre-treated with a selective inhibitor of phosphatidylinositol 3-kinase γ (PI3Kγ), AS 605240 or a ROS scavenger, pyridoxamine (PM). Treatment of A549 cells with LPS caused a significant increase of intracellular ROS generation. Pretreatment with the PI3Kγ inhibitor, AS 605240 decreased the LPS–induced increase of ROS generation, phosphorylation of Akt, and production of phosphatidylinositol 3,4,5-trisphosphate in A549 cells. Treatment of A549 cells with LPS also increased the nuclear factor-κB (NF-κB) in nucleus, accompanying an increase in phosphorylation of inhibitory κB-α, degradation of the protein, and reduction of cytosolic NF-κB. Pretreatment with AS 605240 reduced the LPS–induced these changes. In addition, pretreatment with PM resulted in inhibition of nuclear NF-κB activation. Moreover, exogenous oxygen radical, hydrogen peroxide induced the activation of NF-κB in A549 cells. These results suggest that PI3Kγ plays a key role in LPS–induced ROS generation in alveolar epithelial cells therewith activating NF-κB.