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Toll-like receptor 4 mediates neutrophil sequestration and lung injury induced by endotoxin and hyperinflation*

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Objective: To address the role of Toll-like receptor 4 signaling in mediating neutrophil recruitment and lung injury induced by lipopolysaccharide challenge coupled to lung hyperinflation, using Toll-like receptor 4 knockout (*tlr4*$^{-/-}$) mice. Infiltration of polymorphonuclear neutrophils into the lung is an important feature of ventilator-induced lung injury associated with pneumonia, but the mechanisms involved in neutrophil recruitment are poorly understood.

Design: Experimental animal model.

Setting: University laboratory.

Subjects: *tlr4*$^{-/-}$ and wild-type C57BL/6 mice.

Interventions: Wild-type or *tlr4*$^{-/-}$ mice were challenged by intratracheal instillation of lipopolysaccharide (0.3 mg/kg) for 2 hrs and then subjected to normal (7 mL/kg) or high (28 mL/kg) tidal volume ventilation for another 2 hrs. In other studies, neutrophils from wild-type or *tlr4*$^{-/-}$ mice were pretreated with lipopolysaccharide for 30 mins and then infused into the isolated lung preparation for 30 mins as the lungs were ventilated with 25 cm H_2O peak inspiratory pressure.

Measurements and Main Results: Lipopolysaccharide-challenged wild-type mice ventilated with a 28 mL/kg tidal volume exhibited 12-fold increase in neutrophil sequestration, 6-fold increase in bronchoalveolar lavage albumin concentration, and 1.6-fold increase in lung water content compared with unchallenged mice exposed to normal tidal volume ventilation. However, *tlr4*$^{-/-}$ mice showed negligible neutrophil sequestration, microvascular barrier breakdown, or edema formation. Mechanical ventilation alone or combined with lipopolysaccharide caused activation of circulating neutrophils and pulmonary endothelium in wild-type mice, whereas this was prevented in *tlr4*$^{-/-}$ mice.

Conclusions: High tidal volume ventilation during pneumonia/sepsis induces lung neutrophil sequestration and injury via the Toll-like receptor 4-dependent signaling pathway. The results suggest an important role of Toll-like receptor 4 in the mechanism of lung neutrophil sequestration and acute lung injury when pneumonia/sepsis is coupled to lung hyperinflation. (Crit Care Med 2010; 38:194–201)

Key Words: inflammation; Toll-like receptor 4; lipopolysaccharide; ventilator; neutrophils; lung injury