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COMMENTARY

Endotoxin-induced acute lung injury in old C57BL/6J mice is a translationally relevant geroscience model

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Abstract

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are clinically important inflammatory lung conditions that contribute to substantial morbidity and mortality in humans, notably in the elderly population. Direct lung infection is a common cause of ALI and can be modeled by experimental administration of lipopolysaccharide (LPS) bacterial endotoxin. Acute pulmonary pathology observations are presented using an intratracheal LPS-induced ALI experimental model in aged C57BL/6J mice. Collectively the histopathologic findings in LPS treated mice demonstrate several key characteristic features of ALI, supporting the translational relevance of this model for investigating the pathogenesis of lung injury in older adults.

Keywords: Acute lung injury, bacterial endotoxin, LPS, aging, mouse model, lung pathology, C57BL/6J, geroscience

The geroscience approach to aging assumes that all diseases that affect primarily older adults have a common and major underlying cause of declining function and resilience that is part of the aging process. This has been established for chronic diseases, but is now a reality for acute infections since increasing age is associated with decreased resilience to pathologic effects of infectious disease agents. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are considered to occur along a continuum, where initial lung injury results from direct (*e.g.* pneumonia, aspiration of acid) or indirect (*e.g.* pancreatitis, sepsis) conditions, and ARDS represents a manifestation of severe ALI [1]. The incidence of severe ALI appears to be increasing, especially with the recent pandemic of COVID-19, with an increasing mortality rate. Lipopolysaccharide (LPS) bacterial endotoxin exposure is one of several approaches to induce experimental ALI [2]. LPS can be administered to the lungs either intranasally or intratracheally resulting in direct lung injury. In support of the use of LPS for modeling human ALI, it has been shown that marmosets, a small nonhuman primate species, develop ALI in response to aerosol administration of LPS [3]. The underlying pathophysiology of ALI/ARDS involves injury to both the alveolar epithelium and vascular endothelium. Histologically, characteristic features that may be present in various degrees of acute disease include neutrophilic alveolitis, deposition of hyaline membranes, vascular congestion, hemorrhage and formation of microthrombi [4].

An issue in many of the LPS animal model studies is that younger animals are used [5], thus raising the concern of whether observations and conclusions are translationally relevant. Therefore, more studies need to be done in older aged animals to validate whether the pulmonary pathology simulates the pathology seen in the lungs of older patients, especially since older individuals experience greater disease severity.

To address this gap, we conducted a preliminary study in male and female C57BL/6J mice, 24 months of age, obtained from the National Institute on Aging Aged Rodent Colony and housed in a specific pathogen free facility at the University of Washington. Mice were acclimated for three weeks, then given intratracheal LPS (*E. coli* 055:B5; Sigma) at a concentration of 800 µg in 50 µL of saline, or 50 µL of saline (control). After 48 hours, mice were euthanized by cervical dislocation, and lungs perfused with 10% neutral buffered formalin, fixed for 48 hours, followed by processing into paraffin blocks and staining of slides with hematoxylin and eosin. Slides were read by a board-certified veterinary pathologist (J Klug).

Mice given LPS developed moderate to severe lung pathology, characterized by a predominance of intra-alveolar inflammatory cell infiltrates composed of neutrophils and lesser mononuclear cells, as well as interstitial inflammation, vascular congestion and hemorrhage as shown by

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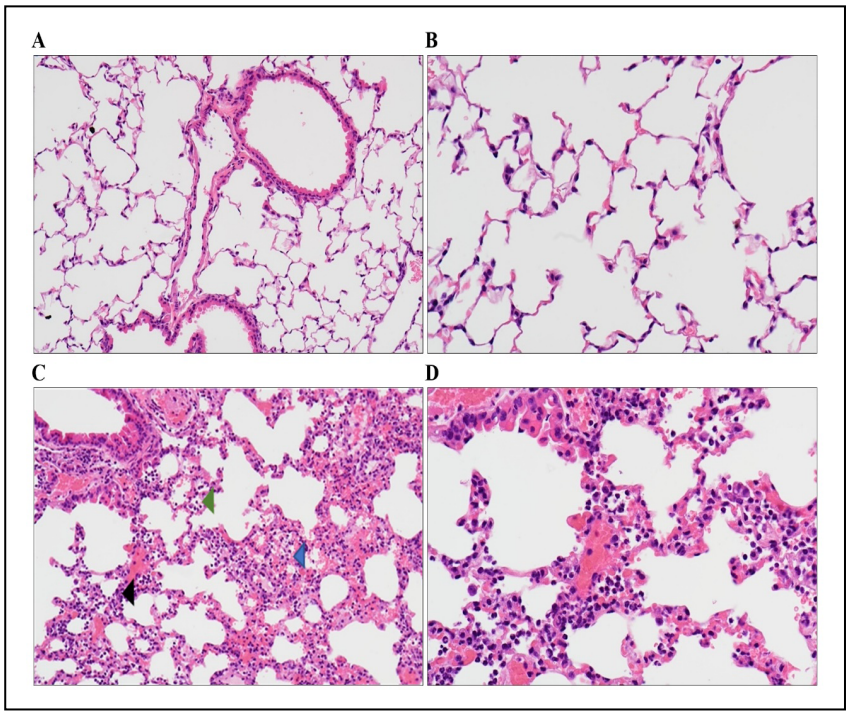

Figure 1. Representative images of H&E-stained lung sections from saline (**A**, **B**) and LPS (**C**, **D**) treated mice. The mice treated with LPS (**C, D**) show inflammation within alveoli (green arrow), interstitium (black arrow), as well as hemorrhage (blue arrow). Magnification-200x (**A** and **C**), 400x (**B** and **D**).

representative images in Figure 1. Our preliminary observations in old (24 months) C57BL/6 mice are similar to that reported in younger (18 months) C57BL/6 mice [6]. Therefore, intratracheal instillation of LPS into the lungs of old mice induces characteristic pulmonary pathology features of ALI including neutrophilic alveolitis, vascular congestion, and hemorrhage. The advantage of using old C57BL/6 mice is that they have significant comorbidities, thus providing a more translationally relevant model to study pathology of acute injury conditions of the lungs seen in older people. Further geroscience studies are warranted to explore age-related differences in disease progression, immune responses, and potential therapeutic interventions.

Declarations

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Conflicts of interest: Warren Ladiges is a member of the editorial board of *Aging Pathobiology and Therapeutics*. The authors declare that they have no conflicts and were not involved in the journal's review or decision regarding this manuscript.

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