Mice without a microbiome are partially protected from lung injury by hyperoxia

Kent A. Willis  
*University of Tennessee Health Science Center*

Joseph F. Pierre  
*University of Tennessee Health Science Center*

Stephania A. Cormier  
*School of Veterinary Medicine*

Ajay J. Talati  
*University of Tennessee Health Science Center*

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EDITORIAL FOCUS

Mice without a microbiome are partially protected from lung injury by hyperoxia

Kent A. Willis,† Joseph F. Pierre,‡,§ Stephania A. Cormier,¶ and Ajay J. Talati†,∥

†Division of Neonatology, Department of Pediatrics, College of Medicine, The University of Tennessee Health Science Center, Memphis, Tennessee; ‡Department of Pediatrics, College of Medicine, The University of Tennessee Health Science Center, Memphis, Tennessee; §Department of Microbiology, Immunology, and Biochemistry, College of Medicine, The University of Tennessee Health Science Center, Memphis, Tennessee; ¶Department of Biological Sciences, Louisiana State University and Department of Comparative Biomedical Sciences, Louisiana State University School of Veterinary Medicine, Baton Rouge, Louisiana; and ∥Department of Obstetrics and Gynecology, College of Medicine, The University of Tennessee Health Science Center, Memphis, Tennessee

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Historically, the lungs were considered sterile in healthy individuals, because standard bacterial culture methods failed to consistently detect microbial organisms peaceably inhabiting this niche (4). However, next-generation sequencing platforms have recently identified diverse communities of microbial organisms that reside in healthy human lungs (2). It is now generally accepted that, although at much lower density and diversity than communities in the human gut, a distinct microbiome does exist in the respiratory tract (3). Some studies further suggest the presence of a distinct lower airway microbiome with a composition that is distinct from the better characterized communities in the upper airway (4). Associations between alterations in airway microbiota and airway diseases are also becoming more apparent. It has been postulated that asthma and allergy represent interplay among consequences of abnormalities in microbial colonization and the composition of bronchial airway microbiota. Numerous studies have demonstrated that the composition of airway microbiota in asthmatic patients is different from that of healthy controls (1).

Bronchopulmonary dysplasia (BPD) is a multifactorial disease that results from the exposure of immature, preterm lungs to several noxious stimuli (8). Recent data from Lal et al. (5), our group (12), and others (9) indicate that human organs, specifically airways, harbor a commensal microbiota at the time of birth and possibly even in utero. Lal et al. (7) have previously reported that the airways of preterm infants with severe BPD are marked by distinct dysbiosis with relative increased abundance of Gammaproteobacteria and decreased Firmicutes, in particular the genus Lactobacillus (5). Multiple other studies have reported associations between airway microbial dysbiosis and BPD or severity of BPD (10). Exploring a variety of inputs connecting the airway microbiome to lung development, Lal and colleagues (6) have also shown that microbial dysbiosis may impact microRNA signaling in BPD. In subsequent microbial metagenomics analysis, Lal et al. (5) found that BPD-predisposed infants had elevated concentrations of metabolites involved in fatty acid activation, estrogen, and androgen biosynthesis, thus suggesting that the airway microbiome could alter lung development via alterations in metabolites and dysregulation of downstream signaling pathways. Taken together, these data suggest that the early airway microbiome modulates exosomal content of miRNA and induces changes in multiple metabolites. Despite these studies demonstrating association between development of BPD and microbial dysbiosis, the direction of causality between airway injury during development and respiratory colonization by organisms remained unsettled (8).

In this issue of American Journal of Physiology-Lung Cellular and Molecular Physiology, Lal and colleagues (2) developed a novel germ-free (GF) hyperoxia-exposed newborn mouse model to interrogate their hypothesis that GF mice, which are devoid of a microbiome, develop enhanced hyperoxia exposure-induced lung injury. In order to understand how the airway microbiome impacts airway development, analyzing an environment devoid of microbiome is an essential foundational step to define the pathogenic importance of the airway microbiome to the development of the mouse lung. This is the first report of the impact of the absence of a respiratory microbiome on normal and abnormal lung development in a mouse model. This study indicates that GF mice have similar lung development and function in room air to specific pathogen free (SPF) mice, which have an intact microbiome. However, contrary to their hypothesis, the authors found that neonatal hyperoxia exposure in mice with a microbiome resulted in worse alveolar hypoplasia and a greater impairment of lung mechanics as compared with GF mice. Decreased markers of pulmonary inflammation [myeloperoxidase (MPO), IFN-γ, and IL-1β] were also seen in GF animals as compared with SPF animals with hyperoxia exposure. Overall, the lung architecture of GF mice upon exposure to hyperoxia was relatively protected compared with SPF mice (Fig. 1). These findings are consistent with the group’s previous human neonatal airway microbiome study where they found increased granulocytic activity and a dysbiotic airway microbiome with a Proteobacterial preponderance in severe BPD patients (7). While some caution should be exhibited due to the intrinsic immune disruption in GF mice (11), these results make us wonder if the...
GRANTS

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

K.A.W. prepared figure; K.A.W. drafted manuscript; K.A.W., J.F.P., S.A.C., and A.J.T. edited and revised manuscript; K.A.W., J.F.P., S.A.C., and A.J.T. approved final version of manuscript.

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