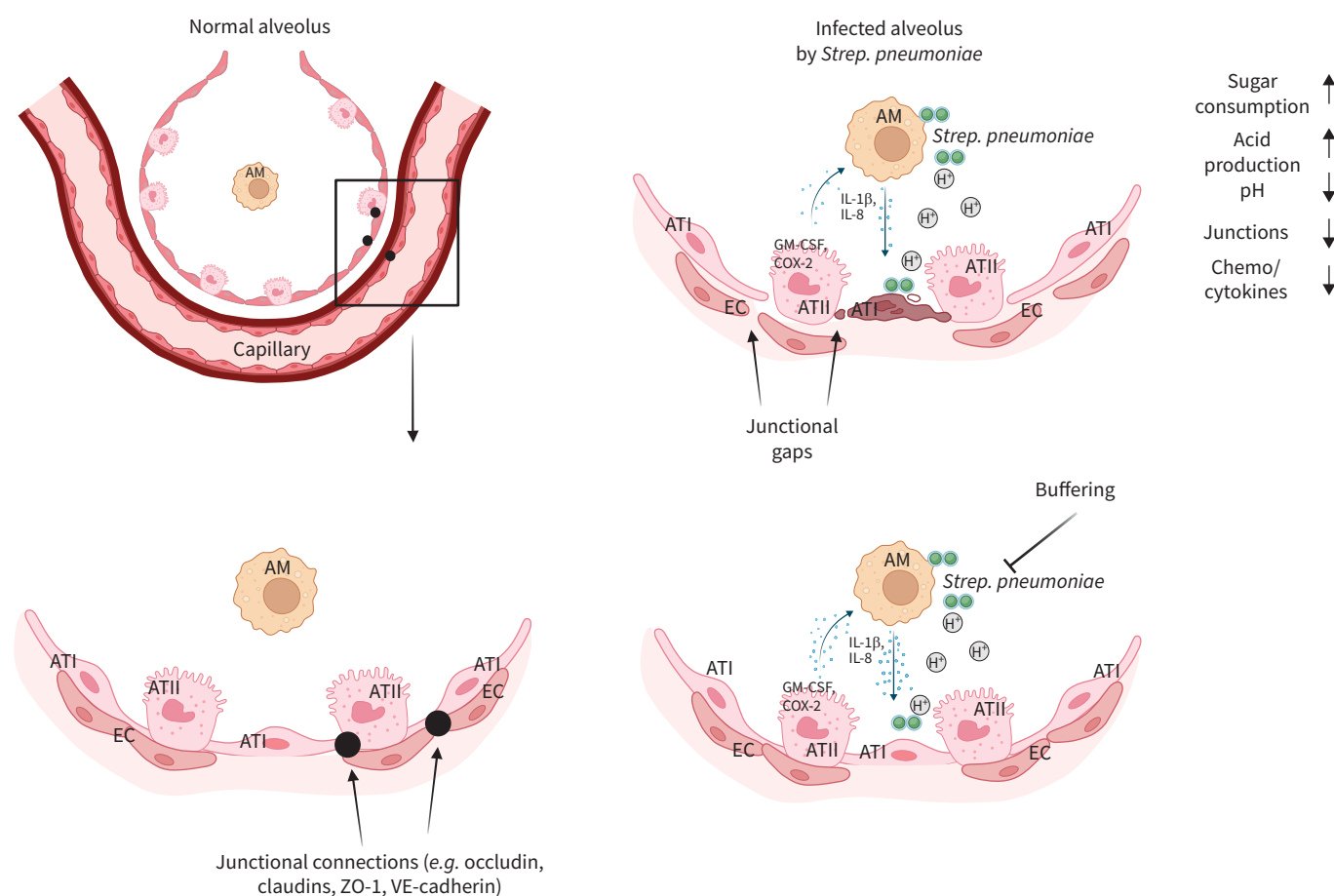


Microenvironmental acidification by pneumococcal sugar consumption fosters barrier disruption and immune suppression in the human alveolus

Diana Fatykhova, Verena N. Fritsch , Keerthana Siebert, Karen Methling, Michael Lalk, Tobias Busche, Jörn Kalinowski, January Weiner, Dieter Beule, Wilhelm Bertrams, Thomas P. Kohler, Sven Hammerschmidt, Anna Löwa, Mara Fischer , Maren Mieth, Katharina Hellwig, Doris Frey, Jens Neudecker, Jens C. Rueckert, Mario Toennies, Torsten T. Bauer, Mareike Graff, Hong-Linh Tran, Stephan Eggeling, Achim D. Gruber, Haike Antelmann, Stefan Hippenstiel and Andreas C. Hocke



GRAPHICAL ABSTRACT Microenvironmental acidification by pneumococcal sugar consumption fosters barrier disruption and immune suppression in the human alveolus. AM: alveolar macrophage; ATI/II: alveolar type I/II cells; EC: endothelial cells; ZO: zonula occludens protein; VE: vascular endothelial; *Strep. pneumoniae*: *Streptococcus pneumoniae*; IL: interleukin; H⁺: hydrogen; GM-CSF: granulocyte-macrophage colony-stimulating factor; COX: cyclo-oxygenase.



SHAREABLE PDF

Microenvironmental acidification by pneumococcal sugar consumption fosters barrier disruption and immune suppression in the human alveolus

Diana Fatykhova¹, Verena N. Fritsch^{1,2}, Keerthana Siebert¹, Karen Methling³, Michael Lalk³, Tobias Busche^{4,5}, Jörn Kalinowski⁴, January Weiner⁶, Dieter Beule^{6,7}, Wilhelm Bertrams⁸, Thomas P. Kohler⁹, Sven Hammerschmidt⁹, Anna Löwa¹, Mara Fischer¹, Maren Mieth¹, Katharina Hellwig¹, Doris Frey¹, Jens Neudecker¹⁰, Jens C. Rueckert¹⁰, Mario Toennies¹¹, Torsten T. Bauer¹¹, Mareike Graff¹², Hong-Linh Tran¹³, Stephan Eggeling¹³, Achim D. Gruber¹⁴, Haike Antelmann², Stefan Hippenstiel^{1,15} and Andreas C. Hocke^{1,15}

¹Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Infectious Diseases, Respiratory Medicine and Critical Care, Berlin, Germany. ²Institute of Biology-Microbiology, Freie Universität Berlin, Berlin, Germany. ³University of Greifswald, Institute of Biochemistry, Metabolomics, Greifswald, Germany. ⁴Center for Biotechnology, University Bielefeld, Bielefeld, Germany. ⁵NGS Core Facility, Medical School OWL, Bielefeld University, Bielefeld, Germany. ⁶Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Core Unit Bioinformatics, Berlin, Germany. ⁷Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany. ⁸Institute for Lung Research, Universities of Giessen and Marburg Lung Center, German Center for Lung Research (DZL), Philipps University Marburg, Marburg, Germany. ⁹Department of Molecular Genetics and Infection Biology, Interfaculty Institute for Genetics and Functional Genomics, Center for Functional Genomics of Microbes, University of Greifswald, Greifswald, Germany. ¹⁰Department of General, Visceral, Vascular and Thoracic Surgery, Charité – Universitätsmedizin Berlin, Berlin, Germany. ¹¹HELIOS Clinic Emil von Behring, Department of Pneumology and Department of Thoracic Surgery, Chest Hospital Heckeshorn, Berlin, Germany. ¹²Department of Thoracic Surgery, DRK Clinics, Berlin, Germany. ¹³Department of Thoracic Surgery, Vivantes Clinics Neukölln, Berlin, Germany. ¹⁴Department of Veterinary Pathology, Freie Universität Berlin, Berlin, Germany. ¹⁵Contributed equally.

Corresponding author: Andreas C. Hocke (andreas.hocke@charite.de)



Shareable abstract (@ERSpublications)

Sugar catabolism and subsequent lactate production by fermentative bacteria such as *Streptococcus pneumoniae* may serve as an independent virulence mechanism causing alveolar barrier disruption and inflammatory impairment in human lung tissue. <https://bit.ly/3Xd8SWN>

Cite this article as: Fatykhova D, Fritsch VN, Siebert K, *et al.* Microenvironmental acidification by pneumococcal sugar consumption fosters barrier disruption and immune suppression in the human alveolus. *Eur Respir J* 2024; 64: 2301983 [DOI: 10.1183/13993003.01983-2023].

This extracted version can be shared freely online.

Copyright ©The authors 2024.

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

This article has an editorial commentary:
<https://doi.org/10.1183/13993003.01841-2024>

Received: 8 Nov 2023
Accepted: 14 Aug 2024



Abstract

Streptococcus pneumoniae is the most common causative agent of community-acquired pneumonia worldwide. A key pathogenic mechanism that exacerbates severity of disease is the disruption of the alveolar–capillary barrier. However, the specific virulence mechanisms responsible for this in the human lung are not yet fully understood. In this study, we infected living human lung tissue with *Strep. pneumoniae* and observed a significant degradation of the central junctional proteins occludin and vascular endothelial cadherin, indicating barrier disruption. Surprisingly, neither pneumolysin, bacterial hydrogen peroxide nor pro-inflammatory activation were sufficient to cause this junctional degradation. Instead, pneumococcal infection led to a significant decrease of pH (~6), resulting in the acidification of the alveolar microenvironment, which was linked to junctional degradation. Stabilising the pH at physiological levels during infection reversed this effect, even in a therapeutic-like approach. Further analysis of bacterial metabolites and RNA sequencing revealed that sugar consumption and subsequent lactate production were the major factors contributing to bacterially induced alveolar acidification, which also hindered the release of critical immune factors. Our findings highlight bacterial metabolite-induced acidification as an independent virulence mechanism for barrier disruption and inflammatory dysregulation in pneumonia. Thus, our data suggest that strictly monitoring and buffering alveolar pH during infections caused by fermentative bacteria could serve as an adjunctive therapeutic strategy for sustaining barrier integrity and immune response.