Immune evasion tactics and immunopathology of mixed mucoid and nonmucoid *Pseudomonas aeruginosa* populations in cystic fibrosis

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COMMITTEE MEMBERS

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**ABSTRACT**

*Pseudomonas aeruginosa* is an opportunistic pathogen that causes devastating, chronic pulmonary infections in patients with cystic fibrosis (CF). During persistent infection of the CF lung, *P. aeruginosa* acquires adaptive mutations that confer resistance to antimicrobials and host responses. Most strikingly, mutation of *mucA* results in the conversion of initially colonizing nonmucoid strains to the mucoid phenotype, which is defined by overproduction of the exopolysaccharide, alginate. Though mucoidy provides advantages to *P. aeruginosa* in withstanding environmental pressures within the airway, mucoid strains often revert back to a nonmucoid phenotype *in vitro* and *in vivo*. Importantly, mixed populations of both mucoid and nonmucoid variants are often isolated from chronically-infected CF patients, suggesting a selective advantage for the coexistence of these variants within the host.

We report that within mixed-variant communities, *P. aeruginosa* exhibits enhanced resistance to innate immune effectors, LL-37 and hydrogen peroxide (H₂O₂). Immune evasion is mediated by the production and sharing of “public goods” by both *P. aeruginosa* variants: While mucoid constituents provide protection from LL-37 via alginate production, nonmucoid revertants shield the population from H₂O₂ via catalase (KatA). We further demonstrate that *katA* expression is negatively regulated by AlgT and AlgR, two transcription factors that are essential for alginate biosynthesis. Additionally, we provide evidence that an endolysin encoded by *lys*, which is implicated in *P. aeruginosa* autolysis and extracellular DNA release, is also responsible for catalase release from nonmucoid revertants.

Given these findings, we wanted to better understand how mixed-variant *P. aeruginosa* communities interact with the host *in vivo*. Tissue damage to the CF lung is heterogeneously manifested across the organ, wherein the upper lobes of the lung are typically more damaged than the lower lobes. Existing hypotheses in the field suggested that these patterns of focal pathology in CF could
be due to unequal distribution of bacterial and host factors in different areas of the organ. As such, we sought to investigate whether mucoid and nonmucoid \textit{P. aeruginosa}, in single- or mixed-variant populations, spatially localize within certain lobes of the CF lung, and if both morphotypes differentially affect the regional, inflammatory microenvironment. Utilizing the collection of lobe-specific BAL fluid from CF patients, in combination with standard culture-based techniques, we showed that both mucoid and nonmucoid \textit{P. aeruginosa} are distributed throughout the CF lung. However, mucoid variants are specifically associated with higher regional indices of inflammation (i.e. proinflammatory cytokines) compared to nonmucoid variants.

In total, our findings contribute to a better understanding of intraspecies interactions of \textit{P. aeruginosa} that enable evasion of the host response during chronic infection. Furthermore, our data support the development of therapeutics that would target both mucoid and nonmucoid \textit{P. aeruginosa} within diversified communities \textit{in vivo}, as both variants likely contribute to the progression and pathology of CF lung disease.
Malhotra, S., Wozniak, D.J., Hayes, D, Jr. Mucoid *Pseudomonas aeruginosa* infection is associated with regional inflammation in the cystic fibrosis lung. **Oral presentation:** ACTS Annual Meeting: Translational Science; 2018 Apr 18-21; Washington, D.C.

**Malhotra, S.,** Limoli, D.H., English, A., Wozniak, D.J. Mixed communities of mucoid and non-mucoid *Pseudomonas aeruginosa* exhibit enhanced resistance to host antimicrobials. **Poster presentation:** 16th International Conference on *Pseudomonas*; 2017 Sep 5-9; Liverpool, United Kingdom.

**Malhotra, S.,** Limoli, D.H., English, A., Wozniak, D.J. Mixed communities of mucoid and non-mucoid *Pseudomonas aeruginosa* exhibit enhanced resistance to host antimicrobials. **Oral presentation:** Pediatric Medical Student Research Forum; 2017 Sep 1-2; Orlando, FL.

**Malhotra, S.,** Limoli, D.H., English, A., Wozniak, D.J. Mixed communities of mucoid and non-mucoid *Pseudomonas aeruginosa* exhibit enhanced resistance to host antimicrobials. **Poster presentation:** ACTS Annual Meeting: Translational Science; 2017 Apr 19-21; Washington, D.C.

**Malhotra, S.,** Limoli, D.H., Wozniak, D.J. Mucoid and non-mucoid isolates of *Pseudomonas aeruginosa* exhibit enhanced resistance to host antimicrobials in mixed communities. **Oral presentation:** Hayes Graduate Research Forum; 2017 Mar 3; Columbus, OH.

**Malhotra, S.,** Limoli, D.H., English, A., Wozniak, D.J. Mixed communities of mucoid and non-mucoid *Pseudomonas aeruginosa* exhibit enhanced resistance to host antimicrobials. **Oral presentation:** Mid-Atlantic Microbial Pathogenesis Meeting; 2017 Feb 12-14; Wintergreen, VA.
RECENT PUBLICATIONS


AWARDS AND HONORS

• TL1 Pre-Doctoral Fellowship- Center for Clinical and Translational Science (CCTS), The Ohio State University College of Medicine (2016-2018)
• Pediatric Medical Student Research Forum Award- Oral presentation, *Third Place* (2017)
• Department of MI&I Travel Award- For oral presentation at the Pediatric Medical Student Research Forum, Orlando, FL (2017)
• Hayes Graduate Forum Award- Oral presentation, *First Place*, Professional Biological Sciences Section (2017)
• MAMPM Trainee Travel Award- For oral presentation at the Mid-Atlantic Microbial Pathogenesis Meeting, Wintergreen, VA (2017)
• The Ohio State University College of Medicine Travel Grant- For poster presentation at the AMA Research Symposium, Dallas, TX (2014)
• Center for Microbial Interface Biology (CMIB) Symposium Travel Award- Poster presentation, *First Place*, Graduate Student Category (2014)
• Letter of commendation- Independent Study Program Year 2, The Ohio State University College of Medicine (2013)
• ID Consortium Symposium Travel Award- Outstanding oral presentation (2013)
• Biomedical Sciences Graduate Program Annual Retreat Travel Award- Oral presentation, *First Place*, and Proctor & Gamble recognition-of-excellence award (2012)
• Patient Centered Research Ethics Scholarship, *Second Place*: Essay entitled “Advocating the inclusion of pregnant women in clinical trials” (2012)
• MSTP Leadership and Academic Achievement Scholarship (2011)
FUTURE PLANS

I will be returning to medical school in the summer to complete my M.D. training. Subsequently, I hope to pursue a residency in pediatrics followed by a fellowship in pulmonology. My long-term aspiration is to impact patient care via clinical medicine and translational research.