Biofilm Exopolysaccharides Alter Sensory-Neuron-Mediated Sickness During Lung Infection

Granton, E., Brown, L., Defaye, M., Moazen, P., Almblad, H., Randall, T. E., ... & Yipp, B. G. (2024). *Cell*, 187(8), 1874-1888.

Presenter: Ni Made Teriyani **Date/Time:** 2025/03/27 15:20-16:10

Commentator: Masayuki Hashimoto, PhD **Location:** Room 601, Med College Building

Background:

Respiratory infections significantly impact vulnerable populations such as young children, the elderly, and individuals with chronic lung diseases or compromised immune systems. These infections trigger sickness behaviors—such as fever, fatigue, social withdrawal, etc—that conserve energy and activate immune defenses. While sickness behaviors are primarily driven by systemic inflammation and cytokine signaling, emerging evidence suggests that sensory neurons also play a critical role in detecting bacterial components and altering the host sickness behaviors.

Pseudomonas aeruginosa, a major opportunistic pathogen, can change between a free-living (planktonic) and biofilm-associated state. Biofilm is structured bacterial communities embedded in an exopolysaccharide (EPS) matrix, that provide protection to the bacteria community. EPS molecules not only protect bacteria but also modify host-pathogen interactions by masking bacterial surface components like lipopolysaccharides (LPS). This shielding may prevent detection by toll-like receptor 4 (TLR4) on host's sensory neurons, which potentially influencing sickness behaviors. Despite biofilms' well-documented role in immune evasion, their impact on sensory-neuron-mediated sickness remains unclear. Understanding these interactions is essential for developing strategies to manage sickness responses while maintaining effective immunity.

Objective/Hypothesis:

This study aims to elucidate the impact of biofilm EPS on sensory-neuron-mediated sickness responses during bacterial pneumonia.

Results:

The authors generated an EPS- strain (non-biofilm forming) by knocking out EPS-related genes and EPS+ strain (biofilm-forming) of *Pseudomonas aeruginosa* PAO1. These strains were then used in a lung infection model to assess their impact on host responses. Non-biofilm *P. aeruginosa* induced greater sickness severity, hypothermia, and behavioral changes compared to biofilm-producing strains. Sex-based differences were observed, with male mice exhibiting heightened sickness severity. Despite similar neutrophil recruitment and phagocytosis between infections, TLR4 deficiency reduced sickness severity in EPS-negative infections, suggesting that neuronal TLR4 plays a key role in driving sickness responses in the absence of EPS.

Further analysis revealed that lung TRPV1+ nociceptors (sensory neuron) detect LPS from non-biofilm bacterial pneumonias via TLR4, triggering vagal nociceptors that activate acute stress neurocircuits in the hypothalamus. The release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus is a key driver of sickness behavior in non-biofilm infections. Ablation of TRPV1 neurons altered sickness outcomes, demonstrating their crucial role in sensing bacterial components and modulating immune-neural interactions.

The authors then expanding the study to virulent *Escherichia coli* infections, which serve as a model for severe pneumonia, revealed that neuronal TLR4 plays a critical role in driving sickness behaviors and mortality.

Conclusion:

Biofilm EPS of pathogen alter host sickness behavior by concealing LPS from TLR4 detection on lung sensory neurons (TRPV1+), thereby modifying the lung-to-brain signaling pathway.