Epigenome-driven adaptation of *Staphylococcus aureus* and regulatory control of virulence in hospital environments

Cutaneous Allergy and Host Defense, Immunology Frontier Research Center

Professor Yumi Matsuoka (Yuumi Nakamura)

Researchmap https://researchmap.jp/yuminak?lang=en

Abstract

Staphylococcus aureus is a major cause of hospital-acquired infections and is capable of long-term persistence in clinical environments. However, the molecular mechanisms underlying its adaptability and persistence remain incompletely understood. In this study, we demonstrate that hospital-associated *S.aureus* strains exhibit altered genomic DNA methylation patterns. We identify the methyltransferase MraW as a key regulator of 5-methylcytosine modification, which modulates the accessory gene regulator (Agr) quorum-sensing system. This epigenetic regulation enables flexible control of virulence factor expression, thereby promoting bacterial survival and persistence under antibiotic pressure and host immune stress.

Background & Results

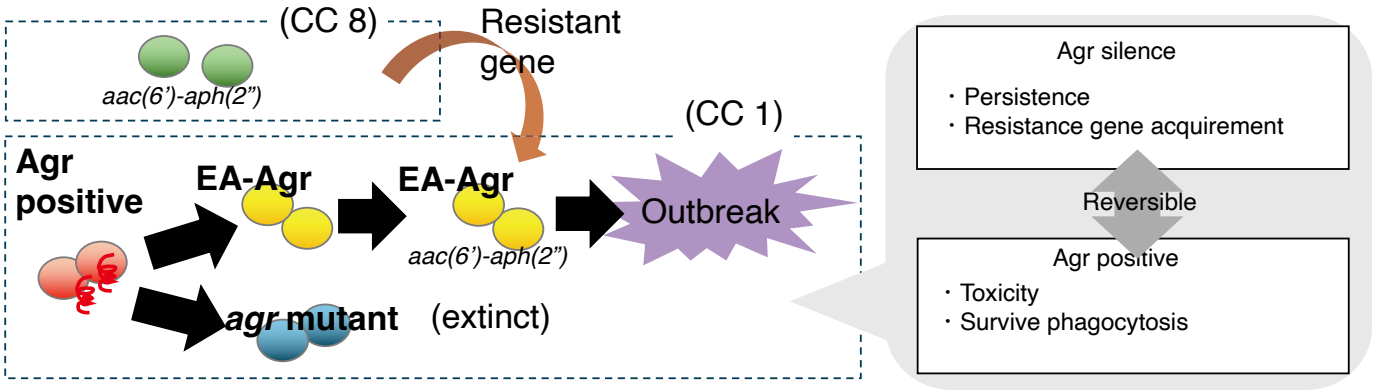
S.aureus is both a common skin commensal and an opportunistic pathogen responsible for severe infections. In hospital settings, persistent colonization by multidrug-resistant strains poses a serious clinical challenge. While genetic mutations have been considered a primary driver of bacterial adaptation, they cannot fully explain the phenotypic heterogeneity observed among genetically similar strains.

We performed integrated genomic and epigenomic analyses of hospital-derived S. aureus isolates and uncovered substantial variation in DNA methylation profiles. Notably, we found that MraW, previously characterized as a ribosomal RNA methyltransferase, also contributes to genomic DNA methylation. Altered MraW activity resulted in dynamic regulation of the Agr quorum-sensing system.

Strains with modified MraW function did not exhibit complete loss of Agr activity but instead displayed context-dependent modulation. This allowed reduced toxin production while maintaining growth and colonization capacity. In skin and infection models, these strains showed enhanced persistence, suggesting a selective advantage in environments with strong antimicrobial and immune pressures.

Significance of the research and Future perspective

This study provides a novel epigenetic perspective on *S.aureus* persistence in hospital environments. By revealing genomic methylation as a mechanism for phenotypic plasticity, our findings expand the conventional mutation-centric view of bacterial adaptation. This work offers new insights into antimicrobial strategies that target bacterial regulatory flexibility rather than viability. Such approaches may enable innovative therapies, including the control of pathogenicity without disrupting commensal balance, and offer translational potential for infection prevention and treatment.



We describe an evolutionary state, termed environmentally adapted (EA)-Agr, that gains a selective advantage in hospital environments by reversibly modulating Agr quorum sensing via genome methylation.

Patent

Treatise Yamazaki, Yuriko; Ito, Tomoka; Nakamura, Yuumi; Salcman, Barbora et al.
Altered genomic methylation promotes Staphylococcus aureus persistence in hospital environment. Nature Communications. 2024, 15.
doi: 10.1038/s41467-024-54033-3

URL https://www.ifrec.osaka-u.ac.jp/en/laboratory/yumi_matsuoka/index.htm

Keyword hospital-acquired infections, *Staphylococcus aureus*, epigenome, Agr quorum-sensing