Corynebacterium pseudodiphtheriticum exploits Staphylococcus aureus virulence components to compete for the human nasal colonization niche.

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Commensal bacteria in the human nose suppress pathogen colonization by competing for nutrients, and commensal bacteria produce toxic compounds that inhibit incoming competitors. Microbial species-specific interactions affect human nasal colonization by *Staphylococcus aureus*. However, the complex interactions that mediate these effects on *S. aureus* nasal colonization are difficult to study. We show that *Corynebacterium pseudodiphtheriticum*, a member of the nasal microbiota, mediates contact-independent bactericidal activity against *S. aureus*. Resistant *S. aureus* isolates are recovered at a low frequency. To understand the pathways associated with killing and resistance, a *S. aureus* transposon mutant library was utilized to identify mutant strains that were resistant to killing. Inactivation of agrC, which encodes for the sensor kinase of the Agr Quorum Sensing System (Agr QS) that regulates expression of many virulence factors in *S. aureus*, conferred resistance to killing. Analysis of the spontaneously resistant *S. aureus* isolates revealed that each showed decreased expression of the Agr QS components. *S. aureus* strains N315 and Mu50, which have low levels of Agr QS activity were resistant to killing. Analysis of pathways regulated by Agr QS revealed that loss of the Phenol Soluble Modulins, which are effectors of Agr QS, also conferred resistance to bactericidal activity. These data suggest that *C. pseudodiphtheriticum* kills *S. aureus* by targeting virulence components. *S. aureus* overcomes targeted killing, but only at the cost of attenuated virulence. Commensal manipulation of virulence components as a mechanism to compete for a colonization niche may represent an unexplored possibility for development of novel antimicrobial compounds.