

TITLE: Antibiofilm compounds secreted by commensal *Staphylococcus epidermidis* against *Staphylococcus aureus*

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ABSTRACT:

S. epidermidis is one of the most frequently found species in the skin human microbiome and is known to produce molecules, as proteases and bacteriocins, that can inhibit growth and establishment of some pathogens, as *S. aureus*. *S. aureus* cause a number of infections, ranging from skin abscesses to life-threatening bloodstream infections, and methicillin-resistant isolates have been a major public health concern due to the limited treatment options. Given the increasing prevalence of resistant strains, it is imperative to search for new strategies against this pathogen and the use of anti-virulence compounds has been raised as an innovative approach. Thus, this study aimed to investigate the impact of the molecules secreted by commensal *S. epidermidis* on virulence traits of clinical *S. aureus* strains. Our results showed that a skin commensal isolate of *S. epidermidis*, RF1, produce molecules that reduced biofilm formation by *S. aureus* clinical isolates without affecting growth. We then tested additional *S. epidermidis* strains, two skin commensal, three clinical isolates and two type-strains. This time, the two commensal strains inhibited growth of *S. aureus* clinical isolates, different from the results obtained with the RF1 strain. All isolates were able to reduce biofilm production by *S. aureus* at different levels, but RF1 showed a greater activity. In order to investigate the mechanisms involved on biofilm reduction, we analyzed the global transcription of *S. aureus* biofilm cells grown in the presence of RF1 molecules by RNAseq. Not only a significant regulation of genes associated with biofilm formation was observed but also regulation of *agr* operon, one of the major *S. aureus* virulence gene regulation systems. Besides the effect on biofilm formation, RF1 molecules showed a significative effect of dispersion of *S. aureus* biofilms, and when associated with oxacillin, an antibiotic commonly used for treatment of *S. aureus* infections, a lower concentration of antibiotic was required to obtain non-viable biofilms cells. Treatment with proteinase K, trypsin, sodium metaperiodate, boiling and protease inhibitors showed no effect on the activity of anti-biofilm molecules. Biofilm formation has been associated with chronic and recurrent infections and antimicrobial resistance by *S. aureus*. So, molecules that can counteract this virulence factor could lead to the discovery of new therapeutic agents for the control of *S. aureus* infections.

KEYWORDS: antivirulence, antibiofilm, microbiota, *Staphylococcus epidermidis*, *Staphylococcus aureus*

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