TITLE: ACTIVITY OF COMPOUNDS SECRETED BY COMMENSAL *Staphylococcus epidermidis* ON BIOFILM FORMATION BY *S. aureus*

AUTHORS: GLATTHARDT, T.[1]; CAMPOS, J.C.M.[1]; COIMBRA, T.F.S.[1]; CHAMON, R.C.[1]; ANTUNES, L.C.M.[2]; DOS SANTOS, K.R.N.[1]; FERREIRA, R.B.R.[1]

INSTITUTION: [1]INSTITUTO DE MICROBIOLOGIA PAULO DE GÓES, UNIVERSIDADE FEDERAL DO RIO DE JANEIRO (AV. CARLOS CHAGAS FILHO, 373, CCS, SALA I2-010, CEP 21941-902, RIO DE JANEIRO – RJ, BRAZIL). [2]CENTRO DE REFERÊNCIA PROF. HÉLIO FRAGA, FUNDAÇÃO OSWALDO CRUZ, RIO DE JANEIRO, BRASIL (ESTRADA DA CURICICA, 2000, CEP:22780-194, RIO DE JANEIRO – RJ, BRASIL).

ABSTRACT:

The skin is colonized by a wide range of microorganisms, collectively known as microbiota. *S. epidermidis* is one of the most frequently found species in this microbial community. *S. epidermidis* can limit the growth of some pathogens by producing proteases and bacteriocins, and this includes skin pathogens such as *S. aureus*. *S. aureus* causes diverse types of infections, ranging from skin abscesses to life-threatening bloodstream infections. Resistance to several antibiotics is a common virulence trait of *S. aureus*, 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 production of secreted molecules by *S. epidermidis* isolated from human skin microbiota that present activity against the virulence of clinical strains of *S. aureus*. *S. epidermidis* isolated from skin microbiota was grown to stationary phase and the bacterial supernatant was collected, filtered and concentrated. The impact of these extracts on biofilm production of *S. aureus* clinical isolates was analyzed, since biofilm production is an important virulence factor of these strains. By using a microtiter dish biofilm formation assay, we showed that the molecules present in the supernatant of *S. epidermidis* caused a reduction in biofilm production in 19 out of 29 (65.5%) *S. aureus* strains. Ten (52.6%) of these strains showed a stronger decrease in biofilm formation, and we showed that their biofilms were mainly protein-based. These results were also confirmed by confocal microscopy. The activity on biofilm formation was independent from bacterial growth, since the molecules had no effect on the growth of *S. aureus*. Analysis of the effect of *S. epidermidis* supernatant on *S. aureus* gene expression indicated a reduction on *icaA* expression, a gene associated with polysaccharidic biofilm production. Preliminary data also indicated that the supernatant has an impact on preformed biofilms. Biofilm formation is one of the main virulence factors of *S. aureus* and has been related to chronic and recurrent infections and antimicrobial resistance. Therefore, molecules that can counteract this virulence factor could lead to the discovery of new therapeutic agents for the control of *S. aureus* infections.

KEYWORDS: Microbiota, anti-virulence, *S. epidermidis*, *S. aureus*, biofilm

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