VIRULENCE, 2017
VOL. 8, NO. 8, 1508–1510
https://doi.org/10.1080/21505594.2017.1393138

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EDITORIAL

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A glimpse into the future – new therapeutic targets could transform the way we treat staphylococcal infections

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KEYWORDS *Staphylococcus aureus*; regulatiory mutations; bacteremia; antimicrobial resistance; alternative therapeutic strategies

Staphylococcus aureus is an organism of striking versatility. Its ability to cause a wide range of diseases and to adapt to changing environments is largely due to a plethora of virulence factors controlled by intricately intertwined regulatory circuits. Acute infections such as bacteremia were suggested to be caused by planktonic cells through synthesis of secreted toxins and exoenzymes.[1] In contrast, biofilm formation and dispersal play crucial roles in the persistence and spread of *S. aureus* in chronic infections,[1,2] with biofilms conferring a considerable level of intrinsic resistance to host defenses and antimicrobial agents.[3] The rapid global emergence of antimicrobial resistance among *S. aureus* is rendering treatment of not only chronic, but also acute *S. aureus* infections increasingly difficult. The organism was therefore classified as one of the "ESKAPE" pathogens (*Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp.), which are able to escape the biocidal action of antibiotics and defy eradication by conventional therapeutic strategies.[4] Infections with resistant *S. aureus* strains are taking a heavy toll worldwide. In the United States, the Centers for Disease Control and Prevention estimate that infections due to methicillin-resistant *S. aureus* (MRSA) lead to more than 11,000 deaths per year.[5] In Europe, MRSA was reported to cause 44% of health-care associated infections (n = 171,200), 22% of attributable extra deaths (n = 5,400), and extra in-hospital costs of EUR 380 million per year.[6]

Faced with a high global burden of staphylococcal disease and the alarming prospect of a post-antibiotic era, the identification of new therapeutic targets is of paramount importance. It has been suggested that specific virulence factors and/ or master virulence regulators represent a promising therapeutic target.[7] First studies mainly focused on biofilm-associated infections provided intriguing results by protease activation.[8] or inhibition of various regulatory pathways, identifying *sarA, sigB*, and *codY* as candidate targets.[9,10] However, little is known on potential adverse effects, such as the inadvertent promotion of acute systemic infections through inhibition of biofilm formation.

In this issue of *Virulence*, Rom and colleagues demonstrate the effect of loss of regulatory elements associated with biofilm formation on virulence of USA300 strain LAC in a murine sepsis model of acute *S. aureus* infection.[11] To this end, they compared LAC wild type and *sarA, sigB, codY, rot, agr, fur*, and *mgrA* mutant strains with regard to virulence in a murine bacteremia model, total protease activity, exoprotein profiles, as well as production of alpha toxin, Spa, AgrA, and SarA. The authors were able to show that mutation of *sarA, sigB*, and *codY* led to attenuated virulence compared to the LAC wild type strain. The *sarA, sigB*, and *codY* mutant strains resulted in significantly increased murine survival in the acute sepsis model and lowered the bacterial burden in the spleen, heart, peripheral blood, and in the case of *sarA* also in the kidney. In contrast, mutation of the regulatory elements *agr, fur*, and *atl* had no impact on virulence, and mutation of *mgrA* and *rot* even increased virulence, thus shifting the focus of the search for therapeutic targets away from these regulatory elements. Hence, these results of Rom et al. call into question the widely upheld belief that *agr* represents a promising therapeutic target in the context of acute, toxin-mediated illness, with *sarA* being primarily useful in the context of chronic, biofilm-associated illness.[12–14]

The authors also showed that attenuation of virulence in *sarA, sigB*, and *codY* mutants was correlated with global changes in exoprotein profiles and with increased formation of extracellular proteases. The authors suggest that the inability of *sarA, sigB*, and *codY* mutants to repress the production of extracellular proteases is a key factor in attenuating *S. aureus*

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Comment on: Joseph S. Rom, et al. Impact of Staphylococcus aureus regulatory mutations that modulate biofilm formation in the USA300 strain LAC on virulence in a murine bacteremia model. Virulence 2017, VOL. 8, NO. 8, 1776–1790; https://doi.org/10.1080/21505594.2017.1373926

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virulence in both acute and chronic infections. Thus, these regulatory elements represent promising target candidates for new therapeutic strategies focused on de-repression of protease production. This is consistent with previous findings associating mutation of all three regulatory elements with increased susceptibility to daptomycin, and except for *codY*, also with increased susceptibility to ceftaroline.[9] In addition, while loss of *sigB* expression increased daptomycin susceptibility in an established biofilm formed by *S. aureus* strain LAC, it failed to show an effect *in vivo* in *S. aureus* strain UAMS-1, a derivative of USA200.[9] Taking the findings of this and previous studies into consideration, *sarA*, and to a lesser degree also *sigB*, seem to represent prime targets for the development of alternative therapeutic strategies.

Still, great care needs to be taken when interpreting the results generated in this study. Pronounced strain-specific variation in the effect of regulatory mutations has been comprehensively demonstrated.[15–19] The use of a single strain background (USA300 strain LAC) therefore significantly reduces the probability that extrapolation of results to *S. aureus* in general will enable a representative estimate of the effects that the loss of these regulatory elements will have in a wide variety of different strains. Further studies in other strain backgrounds are crucial to allow for conclusions on the suitability of therapeutic strategies targeting *sarA* or *sigB* to effectively treat acute and chronic infections caused by a wide range of clinical *S. aureus* isolates. Also, while the mouse model is a cornerstone of studying virulence, it is questionable whether findings would be similar in other animal hosts or the human host. Alternative animal models should be employed to corroborate the promising results generated in this study.

In spite of these limitations, the study presented by Rom et al. makes a crucial contribution towards identifying new therapeutic targets that could transform the treatment of acute and chronic staphylococcal infections. Further research is urgently needed to validate the suitability of *sarA* and other regulatory elements as targets for alternative treatment strategies and to fully exploit their potential.

Disclosure of potential conflicts of interest

The author declares that there are no commercial or financial relationships that could be construed as a potential conflict of interest.

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