Aspirin has been shown to cause a reduction in the virulence of Staphylococcus aureus–associated endocarditis. A new study reveals that salicylic acid, the major metabolite of aspirin, acts at the level of transcription to downregulate the production of fibrinogen, fibronectin, and α-hemolysin — virulence factors necessary for bacterial replication in host tissues and, now, potential therapeutic targets.
Salicylic acid: an old dog, new tricks, and staphylococcal disease

Mathias Herrmann
Department of Bacteriology and Hygiene, Institute of Medical Microbiology and Hygiene, University of Saarland, Homburg/Saar, Germany

Aspirin has been shown to cause a reduction in the virulence of Staphylococcus aureus–associated endocarditis. A new study (see the related article beginning on page 222) reveals that salicylic acid, the major metabolite of aspirin, acts at the level of transcription to downregulate the production of fibrinogen, fibronectin, and α-hemolysin—virulence factors necessary for bacterial replication in host tissues and, now, potential therapeutic targets.


One hundred and twenty years after its initial description as the pathogen that causes sepsis and abscesses (1), Staphylococcus aureus remains a dangerous organism. Staphylococcal endocarditis is on the rise (2) and still causes significant mortality (3). The methicillin-resistant S. aureus (MRSA) epidemic has entered a new era due to the spread of MRSA into the community (4) and acquisition of new resistance cassettes with the potential for genetic transfer (5). The advent of fully vancomycin-resistant, methicillin-resistant clinical isolates (6) has further weakened the available armamentarium against this pathogen.

Importance of staphylococcal attachment and invasion in endovascular disease

S. aureus is a nonmotile microorganism with a particular propensity to colonize biologic or artificial substrates using a battery of pathogenicity factors (7), allowing for specific bacterial attachment. This can be followed by cellular invasion and subsequent tissue degradation. Several lines of evidence clearly indicate that the interaction with host proteins and platelets is instrumental in the development of disease. A plethora of bacterial factors—either wall bound (8) or secreted (9,10)—mediate binding of and attachment to ECM molecules such as fibronectin, fibrinogen, collagen, and vWF. Work with deletion mutants and complemented heterologous hosts has demonstrated the particular role of adhesins that recognize fibronectin (such as fibronectin-binding protein A) and fibrinogen (such as clumping factor A, ClfA), allowing for cellular invasion and production of experimental endocarditis (11,12), and gfp reporter assays from endocarditis models clearly indicate that activation of global regulators that coordinate adhesion and toxin expression, such as aag and sar, occurs in vivo (13,14).

Distinctive effects of acetylsalicylic acid and salicylic acid on platelets and bacteria

A particular role of platelets in the pathogenesis of staphylococcal endocarditis has been suggested since the early observation by Durack of bacterial interaction with fibrin–platelet matrices at sites of nonbacterial thrombotic endocarditis (15) and the series of reports by Clawson et al. on the interaction of S. aureus with purified platelets (16). In the early 1990s, experiments with surface-activated platelets suggested to our group the importance of fibrinogen and S. aureus clumping factor in the bacteria–platelet interaction (17). These observations were subsequently confirmed and extended by use of a low-platelet-binding mutant expressing a mutated ClfA protein (18) that displays diminished virulence in an endocarditis model (19), and by identification of the secreted fibrinogen-binding proteins Coa and Efb in phage-display panning assays (20) (Figure 1).

While these observations pointed toward complex but, according to their adhesive function, rather propathogenic events at the bacteria-endocardium interface, the role of platelets had to be reevaluated after the discovery that they function as specialized inflammatory cells (21) in response to secretion of antimicrobial peptides. In fact, paradoxically, hyperexpression of α-toxin by S. aureus results in diminished virulence in experimental endocarditis, possibly because of the release of platelet microbicidal proteins (22).

The attributed role of platelets in the disease process that results in endovascular infection has prompted a number of researchers to interfere with platelet function for prevention or treatment of endocarditis. Acetylsalicylic acid (ASA, aspirin) has been used in vitro and in a number of experimental models to reduce vegetation sizes and to mitigate the course of disease (23–25). Similar effects have also been observed by Kupferwasser et al. (26). However, when they studied its metabolite, salicylic acid (SAL), in parallel to ASA, they made the interesting observation that pretreatment of bacteria with SAL reduced attachment to the valvular epithelium to an even greater extent than administration of ASA. This observation was accompanied by the in vitro finding that SAL-pretreated S. aureus cells bound to
SAL modulates key regulatory steps in pathogenesis

In this issue of the JCI, Kupferwasser and colleagues (27) extend these exciting findings. In a careful approach using a number of strains with functional gene regulator deletions and complementations in various genetic backgrounds, they demonstrated an acid stress–independent, SAL-mediated activation of the alternative staphylococcal stress response gene \( \text{sigB} \), and consequently a downregulation of the \( \text{sarA} \) and \( \text{agr} \) regulons with a concomitant decrease in the expression of \( \text{hla} \) and \( \text{fnbA} \) (Figure 2). These effects resulted in decreased bacterial adherence, and reduced toxin-mediated hemolysis and thrombolysis. Most importantly, SAL pretreatment attenuated the course of disease by decreasing the vegetation weight, the vegetation bacterial density, and the renal bacterial density.

The role of \( \text{sarA} \) and \( \text{agr} \) in the course of experimental endocarditis has already been studied previously by this group (28). What is novel in this approach is delineation of the effect of SAL on the global regulators, which induces a downregulated status of functional \( \text{sarA} \) and \( \text{agr} \). The nature of \( \text{agr} \) as a two-component signal transduction–dependent regulator may allow for autoinduction and bacterial interference (29). Another approach to the attenuation of virulence is inhibition of the electron transport (30) that drives microorganisms in a small-colony variant phenotype, as seen in a more chronic-persistent course of disease such as in cystic fibrosis (31). Yet, the establishing of a straightforward, unequivocal strategy to downregulate staphylococcal virulence using a cheap, simple, relatively nontoxic, resorbable compound such as SAL may be seen as major progress in the development of intervening strategies in addition to antimicrobial drugs.

Potential directions of future research

The study by Kupferwasser et al. (27) leaves a number of open questions.
Firstly, is there any role of SAL in established endocarditis? As downregulation of attachment factors may be of prime importance to prevent initial steps of pathogenesis, SAL may come too late for a salutary effect in treatment. In fact, the above-mentioned “paradoxic” effect due to hyperexpression of α-hemolysin may be abrogated, resulting in diminished release of platelet microbicidal proteins. Secondly, how do the findings regarding agr suppression relate to the findings of others, that in a serum milieu (32) or in established infection (33), agr expression is already largely diminished, and other regulators such as sae may play a more prominent role in the in vivo infection? Lastly, what is the mechanism of the effect of SAL on S. aureus regulation? SAL is known to exert a substantial effect on virulence in a serum milieu (27) and in established infection (33), agr suppression reduces virulence in experimental endocarditis: a host defense role for platelet microbicidal proteins. In Infect. Immun. 65:4652–4660.


