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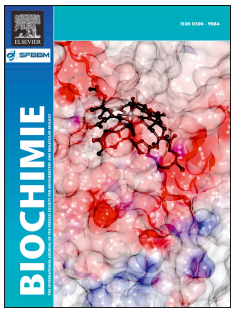

The *Staphylococcus aureus* FASII bypass escape route from FASII inhibitors

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Abstract

Antimicrobials targeting the fatty acid synthesis (FASII) pathway are being developed as alternative treatments for bacterial infections. Emergence of resistance to FASII inhibitors was mainly considered as a consequence of mutations in the FASII target genes. However, an alternative and efficient anti-FASII resistance strategy, called here FASII bypass, was uncovered. Bacteria that bypass FASII make use of exogenous fatty acids to build their membranes, and thus dispense with the need for FASII. This strategy is used by numerous Gram-positive low GC% bacteria, including streptococci, enterococci, and staphylococci. Some bacteria repress FASII genes once fatty acids are available, and "constitutively" shift to FASII bypass. Others, such as the major pathogen *Staphylococcus aureus*, may undergo high frequency mutations that favor FASII bypass. This capacity is particularly relevant during infection, as the host supplies the fatty acids needed for bacteria to bypass FASII and thus become resistant to FASII inhibitors. Screenings for anti-FASII resistance in the presence of exogenous fatty acids confirmed that FASII bypass, anti-FASII-resistant strains exist among clinical and veterinary isolates. Polymorphisms in *S. aureus* FASII initiation enzymes favor FASII bypass, possibly by increasing availability of acyl-carrier protein, a required intermediate. Here we review FASII bypass and consequences in light of proposed uses of anti-FASII to treat infections, with a focus on FASII bypass in *S. aureus*.