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Perspective

# Inflammatory Glucose Restriction in Liver Induces Antibiotic Resistance to *Staphylococcus aureus*

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## ABSTRACT

*Staphylococcus aureus* is a major human pathogen that often causes recurrent infections. Host-pathogen interactions have been shown to have a profound effect on antibiotic sensitivity and the formation of antibiotic-resistant cells. This study investigates α toxin, an important *S. aureus* virulence factor, interacts with macrophages to alter the pathogen's microenvironment, thereby affecting its susceptibility to antibiotics. We found that atoxin-mediated activation of the NLRP3 inflammasome induces antibiotic resistance in the cytoplasm of host cells. Induction of antibiotic resistance is promoted by increased glycolysis in host cells, leading to glucose restriction and ATP depletion in *S. aureus*. In addition, inhibition of NLRP3 activation improves the efficacy of antibiotics *in vitro* and *in vivo*. Our results identify interactions between the host and *S. aureus* that result in metabolic crosstalk that can determine the outcome of antibacterial therapy.

**Keywords:** *Staphylococcus aureus*; Inflammasome; Antibiotic resistance

## DESCRIPTION

*Staphylococcus aureus* is one of the leading causes of bacterial infections worldwide. The pathogenicity and probability of *S. aureus* infection is closely associated with the ability of the host to regulate immunity. Persistent infections are often associated with mutant *Staphylococcal* strains that are less sensitive to antibiotics. However, little is known about how these mutations affect bacterial interactions with the host immune system. Here, the discovery of clinical S. *aureus* isolate activates human monocytes and the results in cell surface expression of immune stimulatory natural killer group 2D (NKG2D) ligands on the monocytes. Expression of the NKG2D ligand ULBP2 (UL16 binding protein 2) was found to be associated with bacterial degradation and phago lysosome activity. In addition, *Staphylococcus aureus* species induced ULBP2 expression was associated with changes in host cell metabolism, including elevated cytoplasmic (iso) citrate levels, decreased glycolytic flux, and mitochondrial functional activity. Interestingly, the species found the power of *Staphylococcus aureus* ULBP2 and human monocyte inflammatory cytokines are dependent on the functional ClpP protease of *S. aureus*. These findings indicate that *Staphylococcus aureus* activates ULBP2 in human monocytes an immune metabolic mechanism, indicating that inactivation of clpP may function as a potential antigenic escape mechanism. Our results provide important insights into the interaction between the host immune system and *S. aureus* evolved under the dual evolutionary pressure of host immune response and antibiotic therapy. The discovery of an immune stimulatory pathway consisting of human monocyte-based defense against *S. aureus* suggests that targeting the NKG2D pathway has the potential to treat persistent staphylococcal infections.

*Staphylococcus aureus* is an important opportunistic human pathogen distributed around the world. *Staphylococcus aureus* and humans have co-evolved to the point of symbiosis, but the bacteria are endowed with virulence factors that cause catastrophic infections. The adaption of the intracellular lifestages by *Staphylococcus aureus* is an important aspect of its etiology. By occupying the privileged intracellular compartment, the host's immune and antibiotic bactericidal effects can be avoided. However, this localization exposes *Staphylococcus aureus* to cellular processes that include autophagy, metabolic challenges, and clearance mechanisms coordinated by hosted program cell death pathways (PCDs) such as apoptosis, pyroptosis, and necroptosis. Increased evidence suggests that *S. aureus* employs a pathogenic adaptive mechanism that regulates the expression of its virulence factors to prevent elimination via the PCD pathway. This review critically analyzes the current literature on the interactions between *Staphylococcus aureus* virulence factors and the major interconnect nodes of PCD. We will discuss how *S. aureus* adaptation to human hosts plays an important role in PCD avoidance and consider future directions for studying *S. aureus* PCD interactions.

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## ANTIBIOTICS THAT TARGET CELL

### Lactamase inhibitors

They hydrolyzed important β-lactam bonds and expressed β-lactamase, which disrupts the antibacterial activity of the drug. Substitution of the native aminoadipoil chain of penicillin in larger units produced a semi-synthetic variant that was not a substrate for β-lactamase. Although methicillin was the first, it had the drawback of being unstable to acids. It was replaced by acid-stable isoxazoyl penicillin oxacillin. Immediately after the introduction of methicillin, resistance to it was confirmed, and methicillin-resistant yellow bacterium was confirmed. aureus (MRSA) has stuck even though the term methicillin is no longer used.

### Vancomycin and other glycopeptides

Vancomycin is a glycopeptide antibiotic widely used to treat severe infections caused by MRSA strains in hospitalized patients. It binds to the DAla4DAla5 dipeptide of Lipid II, prevents PBP2 and PBP2a-catalyzed glycosyl and peptide transfers, and antagonizes peptidoglycan remodeling.