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Effect of teicoplanin resistance on host response to *S. aureus*

Objectives *Staphylococcus (S.) aureus* is a versatile bacterium causing abscesses, infections of implants and the most feared sepsis. It adapted to humans by developing resistance to almost all known antibiotics, among them also methicillin. Methicillin-resistant *S. aureus* is treated with the glycopeptide teicoplanin. During recent years, resistance against this antibiotic of last resort has also been observed. The mechanism of teicoplanin resistance is complex; it develops stepwise due to multiple genetic changes and appears modulated by the host. In this study the contribution of the host to teicoplanin resistance was evaluated in a mouse infection model. Outcome of the infection with teicoplanin-resistant *S. aureus* and the *in vivo* changes of the bacteria were followed.

Conclusions Development of teicoplanin resistance in *S. aureus* is accompanied by a downregulation of virulence genes, which is associated with increased cell wall synthesis and a thickened cell wall. When the resistant strain is applied *in vivo* in the absence of teicoplanin, bacteria either maintain high resistance with the unfavourable properties, and this leads to bacterial clearing in the local infection model, or alternatively, the resistant bacteria can develop further into a hypersusceptible state, in which they survive. Thus, in conclusion, the changes associated with teicoplanin resistance reduce fitness of *S. aureus*. When the resistant bacteria get into the host in the absence of the drug, they can regain fitness and survive at the price of resistance.

These findings have important implications for the use of glycopeptides in clinics; they encourage the use of these antibiotics, since intermediate resistance is not stable but can evolve and give place to a hypersusceptible state after treatment stop. The findings predict that several therapy courses will be possible in clinical conditions even after initial resistance development.

Main results and findings

Glycopeptide resistance, in a set of *in vitro* step-selected teicoplanin-resistant mutants derived from susceptible *Staphylococcus aureus* SA113, was associated with slower growth, thickening of the bacterial cell wall, increased N-acetylglucosamine incorporation and decreased hemolysis. Differential transcriptome analysis showed that as resistance increased, some virulence-associated genes became downregulated. In a mouse tissue cage infection model, an inoculum of 10^4 CFU of strain SA113 rapidly produced a high-bacterial-load infection, which triggered MIP-2 release, leukocyte infiltration and reduced leukocyte viability. In contrast, with the same inoculum of the isogenic glycopeptide-resistant derivative NM67, CFU initially decreased, resulting in the elimination of the mutant in three out of seven cages. In the four cages in which NM67 survived, it partially regained wild-type characteristics, including thinning of the cell wall, reduced N-acetylglucosamine uptake and increased hemolysis; however, the survivors also became teicoplanin hypersusceptible. The elimination of the teicoplanin-resistant mutants and selection of teicoplanin-hypersusceptible survivors in the tissue cages indicated that glycopeptide resistance imposes a fitness burden on *S. aureus* and is selected against *in vivo*, with restoration of fitness incurring the price of resistance loss.

Publications of the NRP 49 project

McCallum N, Karazum H, Getzmann R, Bischoff M, Majcherczyk P, Berger-Bächi B, Landmann R.

In vivo survival of teicoplanin-resistant *Staphylococcus aureus* and fitness cost of teicoplanin resistance.

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