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Mini Review

Regulation of antibiotic resistance in *Staphylococcus aureus*

Nadine McCallum, Brigitte Berger-Bächi *, Maria M. Senn

Institute of Medical Microbiology, University of Zürich, Gloriastrasse 32, CH-8006 Zürich, Switzerland

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ABSTRACT

Staphylococcus aureus has a formidable ability to adapt to varying environmental conditions and an extraordinary capacity to rapidly become resistant to virtually all antibiotics. Resistance develops either through mutations and rearrangements within the staphylococcal genome, or by the acquisition of resistance determinants. Antibiotic resistances often impose a fitness burden on the host. Such biological costs can be reduced by tight regulation and antibiotic-inducible expression of resistance genes, or by compensatory mutations. Resistance induction by antibiotics can be mediated by dedicated, antibiotic-recognizing signal transducers or by mechanisms relieving translational attenuation. Antibiotic tolerance and the expression of resistance phenotypes can also be strongly influenced by the genetic backgrounds of strains and several other factors. Modification and indirect regulation of resistance levels can occur by mutations that alter gene expression or substrate specificity of genes contributing to resistance. Insertion elements can alter resistance profiles by turning relevant genes on or off. Environmental conditions and stress response mechanisms triggered by perturbation of the cell envelope, DNA damage, or faulty intermediary metabolism can also have an impact on resistance development and expression. Clinically relevant resistance is often built up through multiple steps, each of which contributes to an increase in resistance. The driving force behind resistance formation is antibiotic stress, and under clinical conditions selection for resistance is continuously competing with selection for bacterial fitness.

Introduction

Antibiotics typically target structures and pathways that are unique and important to bacteria such as the cell wall-, DNA-, RNA- and protein synthesis machinery, but also intermediary metabolism. Bacteria can develop antibiotic resistance by altering the expression or function of their own genes or by acquiring new genes. The rate of resistance formation by mutation depends upon the number of events required for resistance to reach clinically relevant levels. The larger a bacterial population, the higher the probability that antibiotic pressure will select spontaneous or pre-existing mutants with reduced susceptibility. The exchange and acquisition of new genetic material, by transduction, transformation or conjugation, contributes to the rapid horizontal dissemination of resistance determinants. The localisation of resistance determinants on mobile elements, such as genomic islands, transposons, plasmids, or phages, greatly enhances their mobility. One of the most important opportunistic human pathogens, the Gram-positive bacterium *Staphylococcus aureus*, makes use of all known means of antibiotic resistance development.

Antibiotic resistance mechanisms can be classified into three functional categories: Inactivation of the drug, exclusion from the target by efflux or other mechanisms, and target modification. If resistance acquisition is associated with fitness costs, strains expressing resistance phenotypes will be much less viable and/or out-competed by other bacteria under non-selective conditions, unless compensatory events occur to alleviate the fitness loss. Alternatively, the expression of the resistance determinants may be tightly repressed in the absence of antibiotics. Resistance levels can also be modulated by core chromosomal genes and by the metabolic state of the bacteria. The genetic background of the strain lineage therefore plays an important role in the extent and regulation of expression of antibiotic resistances.

In this review direct regulation of resistance and its modulation by indirect factors in *S. aureus* will be discussed with a focus on cell wall-active and ribosome-targeted antibiotics.

Cell wall antibiotics

The Gram-positive bacterial cell envelope is essential for both survival and pathogenicity, forming a protective barrier against environmental stresses as well as contributing to colonisation, virulence and resistance. The main structure of the cell wall is provided by a multi-layered mesh of highly cross-linked

* Corresponding author. Tel.: +41 44 634 2650; fax: +41 44 634 4906.
E-mail address: bberger@imm.uzh.ch (B. Berger-Bächi).

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peptidoglycan surrounding the cytoplasmic membrane. The cell envelope also consists of teichoic acids, which are anionic polymers either covalently linked to the peptidoglycan (wall teichoic acids) or attached to the cytoplasmic membrane (lipoteichoic acids). Other important constituents include membrane-associated proteins, peptidoglycan-anchored surface proteins, and extracellular polysaccharide matrices. All of these components contribute to the physicochemical properties of the cell surface.

The cell envelope is the target of numerous antibiotics, most of which are involved in blocking or disrupting peptidoglycan biosynthesis (Bugg, 1999) (Fig. 1). Continual synthesis, processing and polymerisation of peptidoglycan precursor, together with cell wall degradation and turnover, is essential for maintaining cellular shape as well as allowing cell growth, septum formation and division. The last extracellular enzymatic reactions in cell wall synthesis are carried out by the penicillin-binding proteins (PBPs) and can be inhibited by the two major groups of cell wall active antibiotics, the beta-lactams and the glycopeptides. *S. aureus* possesses four PBPs, of which PBP1 and PBP2 are essential. PBP2 is responsible for de novo peptidoglycan synthesis as it is the only bifunctional PBP in *S. aureus* with both, transpeptidase and transglycosylase activity (Pinho et al., 2001). Beta-lactams, such as penicillin, oxacillin and methicillin, acylate the transpeptidase-active sites of PBPs, preventing them from acting on their natural substrate (Goffin and Ghuysen, 1998). Glycopeptide antibiotics, such as vancomycin and teicoplanin, bind with high affinity to the D-ala-D-ala terminus of extracellular precursor and nascent uncross-linked peptidoglycan, thereby sterically hindering the PBP reactions (Reynolds, 1989).

Beta-lactam resistance

S. aureus generally become resistant to beta-lactams through one of two main mechanisms. One is the production of a penicillinase, BlaZ, which hydrolytically cleaves beta-lactams of the penicillin class. Of higher relevance is the second and broader mechanism, which confers resistance to both penicillinase-sensitive and penicillinase-resistant beta-lactams, namely the production of the additional PBP, PBP2a, encoded by *mecA* (Hartman and Tomasz, 1984; Reynolds and Brown, 1985). PBP2a has a decreased affinity for beta-lactams due to its distorted active site, which significantly reduces its acylation rate (Lim and Strynadka, 2002). Therefore, in the presence of beta-lactams, PBP2a is able to maintain cell wall biosynthesis with the help of the beta-lactam-insensitive transglycosylase domain of PBP2 (Pinho et al., 2001). One particularity of methicillin-resistant *S. aureus* (MRSA) is their heterogeneous expression of resistance, whereby individual strains can generate subpopulations with different degrees of higher resistance. There is also a remarkable variability in resistance levels between different MRSA strain

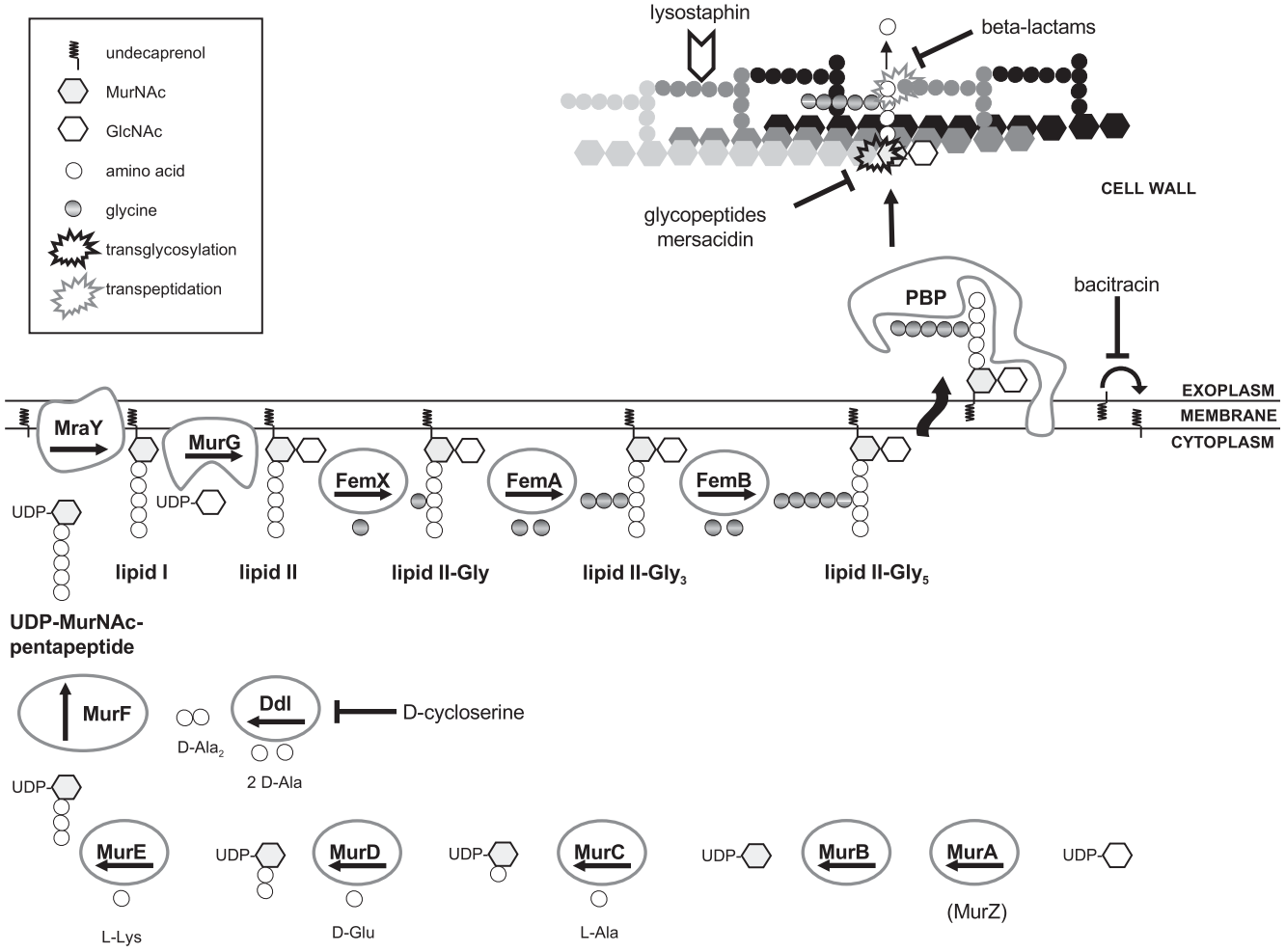

Fig. 1. Schematic representation of *S. aureus* peptidoglycan synthesis and inhibition of reactions by cell wall antibiotics. Only drugs mentioned in the text are shown. Inhibition is indicated by blocked arrows. UDP, uridine-diphosphate; MurNAc, N-acetylmuramic acid; GlcNAc, N-acetylglucosamine. Adapted from Rohrer and Berger-Bächi (2003).