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並說明其內容

A

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Quantitative Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry for Rapid Resistance Detection

Christoph Lange,[a] Sören Schubert,[b] Jette Jung,[b] Markus Kostrzewa,[a] Katrin Sparbier[a]
Bruker Daltonik GmbH, Bremen, Germany[a]; Max von Pettenkofer-Institut, Munich, Germany[b]

Antibiotic resistance in Gram-negative microorganisms is an increasing health care problem. The rapid detection of such resistance is crucial for starting an early specific therapy and to enable initiation of the required hygiene measures. With continued emphasis on reducing the cost of laboratory testing, only economical/low-cost approaches have a chance of being implemented. During recent years, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has been developed to be a standard method in microbiology laboratories for the rapid and cost-efficient identification of microorganisms. Extending the usage of MALDI-TOF MS in the clinical microbiology laboratory to the area of resistance testing is an attractive option. Quantitative MALDI-TOF MS using an internal standard facilitates the measurement of the quantity of peptides and small proteins within a spectrum. These quantities correlate to the number of microorganisms and therefore to the growth of a microorganism. The comparison of growth in the presence or absence of an antibiotic allows for analysis of the susceptibility behavior of a strain. Here, we describe a novel method and its application in the analysis of 108 *Klebsiella* sp. isolates. After 1 h of incubation at a meropenem concentration of 8 μg/ml, a sensitivity of 97.3% and a specificity of 93.5% were achieved (compared to Etest results).

B

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Biological Cost of Different Mechanisms of Colistin Resistance and Their Impact on Virulence in *Acinetobacter baumannii*

Alejandro Beceiro,[a] Antonio Moreno,[a,b] Nathalie Fernández,[a] Juán A. Vallejo,[a] Jesús Aranda,[a,b,c] Ben Adler,[d,e] Marina Harper,[d,e] John D. Boyce,[d] Germán Bou[a]

Servicio de Microbiología-INIBIC, Complejo Hospitalario Universitario A Coruña (CHUAC), A Coruña, Spain[a]; Servicio de Microbiología, Complejo Hospitalario Pontevedra, Pontevedra, Spain[b]; Departament de Genètica i Microbiologia, Facultat de Biociències, Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallès, Barcelona, Spain[c]; Department of Microbiology, Monash University, Melbourne, Victoria, Australia[d]; Australian Research Council Centre of Excellence in Structural and Functional Microbial Genomics, Monash University, Melbourne, Victoria, Australia[e]

Two mechanisms of resistance to colistin have been described in *Acinetobacter baumannii*. One involves complete loss of lipopolysaccharide (LPS), resulting from mutations in *lpxA*, *lpxC*, or *lpxD*, and the second is associated with phosphoethanolamine addition to LPS, mediated through mutations in *pmrAB*. In order to assess the clinical impacts of both resistance mechanisms, *A. baumannii* ATCC 19606 and its isogenic derivatives, AL1851 Δ*lpxA*, AL1852 Δ*lpxD*, AL1842 Δ*lpxC*, and ATCC 19606 *pmrB*, were analyzed for *in vitro* growth rate, *in vitro* and *in vivo* competitive growth, infection of A549 respiratory alveolar epithelial cells, virulence in the *Caenorhabditis elegans* model, and virulence in a systemic mouse infection model. The *in vitro* growth rate of the *lpx* mutants was clearly diminished; furthermore, *in vitro* and *in vivo* competitive-growth experiments revealed a reduction in fitness for both mutant types. Infection of A549 cells with ATCC 19606 or the *pmrB* mutant resulted in greater loss of viability than with *lpx* mutants. Finally, the *lpx* mutants were highly attenuated in both the *C. elegans* and mouse infection models, while the *pmrB* mutant was attenuated only in the *C. elegans* model. In summary, while colistin resistance in *A. baumannii* confers a clear selective advantage in the presence of colistin treatment, it causes a noticeable cost in terms of overall fitness and virulence, with a more striking reduction associated with LPS loss than with phosphoethanolamine addition. Therefore, we hypothesize that colistin resistance mediated by changes in *pmrAB* will be more likely to arise in clinical settings in patients treated with colistin.

C

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RESEARCH ARTICLE Open Access

Role of the BaeSR two-component system in the regulation of *Acinetobacter baumannii adeAB* genes and its correlation with tigecycline susceptibility

Ming-Feng Lin[1,2], Yun-You Lin[1], Hui-Wen Yeh[3] and Chung-Yu Lan[2,4*]

Abstract

Background: Tigecycline resistance in *Acinetobacter baumannii* is primarily acquired through overexpression of the AdeABC efflux pump. Besides AdeRS, other two-component regulatory systems (TCSs) involving the regulation of this transporter have not been clarified.

Results: In this study, we found that the TCS genes *baeR* and *baeS* are co-transcribed and function as stress responders under high osmotic conditions. The *baeSR* and *adeAB* genes showed increased transcription in both the laboratory-induced and clinical tigecycline-resistant strains compared with the wild-type strain. The deletion of *baeR* in the ATCC 17978 strain led to 67–73% and 68% reduction in *adeA* and *adeB* expression, respectively, with a resultant 2-fold decrease in the tigecycline minimal inhibition concentration (MIC). In contrast, the overexpression of *baeR* resulted in a doubled tigecycline MIC, with a more than 2-fold increase in *adeA* and *adeB* expression. The influence of *baeR* knockout on *adeAB* gene expression can also be observed in the laboratory-induced tigecycline-resistant strain. A time-kill assay showed that the *baeR* deletion mutant showed an approximate 1-$\log_{10}$ reduction in colony forming units (CFUs) relative to the wild-type strain when the tigecycline concentration was 0.25 μg/mL throughout the assay period. The wild-type phenotype could be restored by trans-complementation with pWH1266-*kan*^{r}-*baeR*. Increasing the tigecycline concentration to 0.5 μg/mL produced an even more marked 4.7-$\log_{10}$ reduction in CFUs of the *baeR* deletion mutant at 8 h, while only a 2.1-$\log_{10}$ reduction was observed for the wild-type strain.

Conclusions: Taken together, these data show for the first time that the BaeSR TCS influences the tigecycline susceptibility of *A. baumannii* through the positive regulation of the resistance-nodulation-division efflux pump genes *adeA* and *adeB*.

Keywords: *Acinetobacter baumannii*, Tigecycline, Two-component regulatory system, Efflux pumps

D

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PLOS ONE

A Thermostable *Salmonella* Phage Endolysin, Lys68, with Broad Bactericidal Properties against Gram-Negative Pathogens in Presence of Weak Acids

C

Hugo Oliveira[1], Viruthachalam Thiagarajan[2], Maarten Walmagh[3], Sanna Sillankorva[1], Rob Lavigne[3], Maria Teresa Neves-Petersen[4,5], Leon D. Kluskens[1], Joana Azeredo[1]*

1 Centre of Biological Engineering, University of Minho, Braga, Portugal, **2** School of Chemistry, Bharathidasan University, Tiruchirappalli, India, **3** Laboratory of Gene Technology, Katholieke Universiteit Leuven, Leuven, Belgium, **4** Nanomedicine Department, International Iberian Nanotechnology Laboratory, Braga, Portugal, **5** Medical Faculty, Aalborg University, Aalborg, Denmark

Abstract

Resistance rates are increasing among several problematic Gram-negative pathogens, a fact that has encouraged the development of new antimicrobial agents. This paper characterizes a *Salmonella* phage endolysin (Lys68) and demonstrates its potential antimicrobial effectiveness when combined with organic acids towards Gram-negative pathogens. Biochemical characterization reveals that Lys68 is more active at pH 7.0, maintaining 76.7% of its activity when stored at 4°C for two months. Thermostability tests showed that Lys68 is only completely inactivated upon exposure to 100°C for 30 min, and circular dichroism analysis demonstrated the ability to refold into its original conformation upon thermal denaturation. It was shown that Lys68 is able to lyse a wide panel of Gram-negative bacteria (13 different species) in combination with the outer membrane permeabilizers EDTA, citric and malic acid. While the EDTA/Lys68 combination only inactivated *Pseudomonas* strains, the use of citric or malic acid broadened Lys68 antibacterial effect to other Gram-negative pathogens (lytic activity against 9 and 11 species, respectively). Particularly against *Salmonella* Typhimurium LT2, the combinatory effect of malic or citric acid with Lys68 led to approximately 3 to 5 log reductions in bacterial load/CFUs after 2 hours, respectively, and was also able to reduce stationary-phase cells and bacterial biofilms by approximately 1 log. The broad killing capacity of malic/citric acid-Lys68 is explained by the destabilization and major disruptions of the cell outer membrane integrity due to the acidity caused by the organic acids and a relatively high muralytic activity of Lys68 at low pH. Lys68 demonstrates good (thermo)stability properties that combined with different outer membrane permeabilizers, could become useful to combat Gram-negative pathogens in agricultural, food and medical industry.