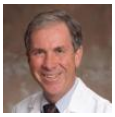
2 Tolerance to the antimicrobial peptide colistin in Pseudomonas aeruginosa biofilms is linked to metabolically active cells, and depends on the pmr and mexAB-oprM genes.

Pamp SJ, Gjermansen M, Johansen HK, Tolker-Nielsen T
Mol Microbiol. 2008 Apr; 68(1):223-40

Recommendations:

Good **15 May 2008**



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INTERESTING HYPOTHESIS | NEW FINDING

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This study demonstrates that difficulties in treating infections caused by biofilm-forming bacteria may be due to differential sensitivities of metabolically distinct subpopulations of bacterial cells in the biofilm. The authors show that combination therapy, with antibiotics targeting each distinct subpopulation, may be a successful treatment strategy for infections of biofilm-forming bacteria.

The authors used confocal laser scanning microscopy of green fluorescent protein (GFP)-expressing Pseudomonas aeruginosa strains to show two distinct physiological subpopulations in flow cell biofilms: (1) cells near the surface of the biofilm exhibiting high metabolic activity; (2) cells near the substratum with low metabolic activity. Sensitivity of each subpopulation to antimicrobial compounds was monitored by GFP (live cells) and propidium iodide staining (dead cells). In biofilms treated with the antimicrobial peptide colistin, the metabolically active subpopulation developed resistance to colistin, while the less active cells were sensitive. Development of tolerance to colistin was shown to be influenced by colistin induction of the pmr operon encoding lipopolysaccharide modification and the mexAB-oprM encoding a proton-motive force efflux pump. Ciprofloxacin and tetracycline, antibiotics that target metabolically active cells, inhibited the metabolically active subpopulation, while the less active cells were tolerant. Combined treatment with colistin and either ciprofloxacin or tetracycline eradicated nearly all cells in both populations.

Bacteria that establish biofilms often form persistent infections that are difficult to treat. Many reasons for this have been suggested but, to date, no effective means of treatment have been developed. This flow cell biofilm study indicates that combination therapy may be an effective treatment against biofilm-forming bacterial infections. Specifically, colistin plus either ciprofloxacin or tetracycline eradicated nearly all cells in a P. aeruginosa biofilm. Although there have been recent reports of successful treatment of P. aeruginosa infection in patients with cystic fibrosis with colistin and ciprofloxacin {1-3}, the data presented in this in vitro study need to be confirmed in vivo. References: {1} Valerius et al., Lancet 1991, 338:725-726 [PMID:1679870]; {2} Doring et al., J Cyst Fibros 2004, 3:67-91 [PMID:15463891]; {3} Hoiby et al., J Cyst Fibros 2005, 2:49-54 [PMID:16023416].

Disclosures
None declared

Add a comment

Good **24 Jul 2008**

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NEW FINDING | NOVEL DRUG TARGET

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Synergistic effects of antibiotics are well known, and this paper presents one interesting explanation: distinct sub-populations of cells in a biofilm that are susceptible to different classes of drugs.

Using fluorescent reporters, the authors found that ciprofloxacin and tetracycline kill active cells at the biofilm surface while colistin kills metabolically inactive cells at lower levels.

This paper highlights the importance of studying distinct and well-defined sub-populations of cells in a physiologically relevant context.

Disclosures
None declared

Add a comment

Abstract:

ABSTRACT

Bacteria living as biofilm are frequently reported to exhibit inherent tolerance to antimicrobial compounds, and might therefore contribute to the persistence of infections. Antimicrobial peptides are attracting increasing interest as new potential antimicrobial therapeutics; however, little is known about potential mechanisms, which might contribute to resistance or tolerance development towards these compounds in biofilms. Here we provide evidence that a spatially distinct subpopulation of metabolically active cells in Pseudomonas aeruginosa... more »
biofilms is able to develop tolerance to the antimicrobial peptide colistin. On the contrary, biofilm cells exhibiting low metabolic activity were killed by colistin. We demonstrate that the subpopulation of metabolically active cells is able to adapt to colistin by inducing a specific adaptation mechanism mediated by the pmr operon, as well as an unspecific adaptation mechanism mediated by the mexAB-oprM genes. Mutants defective in either pmr-mediated lipopolysaccharide modification or in mexAB-oprM-mediated antimicrobial efflux were not able to develop a tolerant subpopulation in biofilms. In contrast to the observed pattern of colistin-mediated killing in biofilms, conventional antimicrobial compounds such as ciprofloxacin and tetracycline were found to specifically kill the subpopulation of metabolically active biofilm cells, whereas the subpopulation exhibiting low metabolic activity survived the treatment. Consequently, targeting the two physiologically distinct subpopulations by combined antimicrobial treatment with either ciprofloxacin and colistin or tetracycline and colistin almost completely eradicated all biofilm cells.

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PMID: 18312276

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COMMENTS add a comment