Interferon response

Project Lab Members | Agent based model | Experimental Model | Techniques / Methodology | Literature

Project Lab Members

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Agent based model

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Experimental Model

We use in vitro PAO1, C elegans model and mouse model of surgical stress.

Techniques / Methodology

More details here.

Literature

[PubMed: oprf pseudomonas](pubmed: oprf pseudomonas)
[NCBI: db=pubmed; Term=oprf pseudomonas](NCBI: db=pubmed; Term=oprf pseudomonas)

*Killing from the inside: Intracellular role of T3SS in the fate of Pseudomonas aeruginosa within macrophages revealed by mgtC and oprF mutants.*

Related Articles

*Killing from the inside: Intracellular role of T3SS in the fate of Pseudomonas aeruginosa within macrophages revealed by mgtC and oprF mutants.*


Authors: Garai P, Berry L, Moussouni M, Bleves S, Blanc-Potard AB

Abstract

While considered solely an extracellular pathogen, increasing evidence indicates that Pseudomonas aeruginosa encounters intracellular environment in diverse mammalian cell types, including macrophages. In the present study, we have deciphered the intramacrophage fate of wild-type P. aeruginosa PAO1 strain by live and electron microscopy. P. aeruginosa first resided in phagosomal vacuoles and subsequently could be detected in the cytoplasm, indicating phagosomal escape of the pathogen, a finding also supported by vacuolar rupture assay. The intracellular bacteria could eventually induce cell lysis, both in a macrophage cell line and primary human macrophages. Two bacterial factors, MgtC and OprF, recently identified to be important for survival of P. aeruginosa in macrophages, were found to be involved in bacterial escape from the phagosome as well as in cell lysis caused by intracellular bacteria. Strikingly, type III secretion system (T3SS) genes of P. aeruginosa were down-regulated within macrophages in both mgtC and oprF mutants. Concordantly, cyclic di-GMP (c-di-GMP) level was increased in both mutants, providing a clue for negative regulation of T3SS inside macrophages. Consistent with the phenotypes and gene expression pattern of mgtC and oprF mutants, a T3SS mutant (pscN) exhibited defect in phagosomal escape and macrophage lysis driven by internalized bacteria. Importantly, these effects appeared to be largely dependent on the ExoS effector, in contrast with the known T3SS-dependent, but ExoS independent, cytotoxicity caused by extracellular P. aeruginosa towards macrophages. Moreover, this macrophage damage caused by intracellular P. aeruginosa was found to be dependent on GTPase Activating Protein (GAP) domain of ExoS. Hence, our work highlights T3SS and ExoS, whose expression is modulated by MgtC and OprF, as key players in the intramacrophage life of P. aeruginosa which allow internalized bacteria to lyse macrophages.

PMID: 31220187 [PubMed - in process]
Potentiation of -lactam antibiotics and -lactam/-lactamase inhibitor combinations against MDR and XDR Pseudomonas aeruginosa using non-ribosomal tobramycin-cyclam conjugates.

Related Articles

J Antimicrob Chemother. 2019 May 28;:

Authors: Idowu T, Ammeter D, Arthur G, Zhanel GG, Schweizer F

Abstract

OBJECTIVES: To develop a multifunctional adjuvant molecule that can rescue -lactam antibiotics and -lactam/-lactamase inhibitor combinations from resistance in carbapenem-resistant Pseudomonas aeruginosa clinical isolates.

METHODS: Preparation of adjuvant was guided by structure-activity relationships, following standard protocols. Susceptibility and checkerboard studies were assessed using serial 2-fold dilution assays. Toxicity was evaluated against porcine erythrocytes, human embryonic kidney (HEK293) cells and liver carcinoma (HepG2) cells via MTS assay. Preliminary in vivo efficacy was evaluated using a Galleria mellonella infection model.

RESULTS: Conjugation of tobramycin and cyclam abrogates the ribosomal effects of tobramycin but confers a potent adjuvant property that restores full antibiotic activity of meropenem and aztreonam against carbapenem-resistant P. aeruginosa. Therapeutic levels of susceptibility, as determined by CLSI susceptibility breakpoints, were attained in several MDR clinical isolates, and time-kill assays revealed a synergistic dose-dependent pharmacodynamic relationship. A triple combination of the adjuvant with ceftazidime/avibactam (approved), aztreonam/avibactam (Phase III) and meropenem/avibactam enhances the efficacies of -lactam/-lactamase inhibitors against recalcitrant strains, suggesting rapid access of the combination to their periplasmic targets. The newly developed adjuvants, and their combinations, were non-haemolytic and non-cytotoxic, and preliminary in vivo evaluation in G. mellonella suggests therapeutic potential for the double and triple combinations.

CONCLUSIONS: Non-ribosomal tobramycin-cyclam conjugate mitigates the effect of OprD/OprF porin loss in P. aeruginosa and potentiates -lactam/-lactamase inhibitors against carbapenem-resistant clinical isolates, highlighting the complexity of resistance to -lactam antibiotics. Our strategy presents an avenue to further preserve the therapeutic utility of -lactam antibiotics.

PMID: 31139830 [PubMed - as supplied by publisher]

Improving the autotransporter-based surface display of enzymes in Pseudomonas putida KT2440.

Related Articles

Microb Biotechnol. 2019 May 02;:

Authors: Tozakidis IEP, Lüken LM, Üffing A, Meyers A, Jose J

Abstract

Pseudomonas putida can be used as a host for the autotransporter-mediated surface display of enzymes (autodisplay), resulting in whole-cell biocatalysts with recombinant functionalities on their cell envelope. The efficiency of autotransporter-mediated secretion depends on the N-terminal signal peptide as well as on the C-terminal translocator domain of autotransporter fusion proteins. We set out to optimize autodisplay for P. putida outer membrane protein OprF, the activity was more than 12-fold enhanced to 638 mU ml⁻¹ OD-1 compared with the signal peptide of V. cholerae CtxB (52 mU ml⁻¹ OD-1 ). This positive effect was confirmed with -glucosidase as a second example enzyme. Here, cells expressing the protein with N-terminal OprF signal peptide showed more than fourfold higher -glucosidase activity (181 mU ml⁻¹ OD-1 ) than with the CtxB signal peptide (42 mU ml⁻¹ OD-1 ). SDS-PAGE and flow cytometry analyses indicated that the increased activities correlated with an increased amount of recombinant protein in the outer membrane and a higher number of enzymes detectable on the cell surface.

PMID: 31044490 [PubMed - as supplied by publisher]