Universität Basel

Research Project

The Role of Toxin-Antitoxin Modules in Pseudomonas aeruginosa Phenotypic Heterogeneity and Antibiotic Tolerance

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Project title The Role of Toxin-Antitoxin Modules in Pseudomonas aeruginosa Phenotypic Heterogeneity and Antibiotic Tolerance
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Stochastic binary decisions generate phenotypic heterogeneity in bacterial populations, thereby contributing to bet-hedging processes and to division-of-labor. While specific bimodal programs were implicated in bacterial virulence 1 and antibiotic tolerance 2, the mechanisms leading to bi-nary cellular responses and the resulting consequences for population fitness and resilience are often unclear. Here, we aim at dissecting the role of two novel toxin-antitoxin (TA) modules in Pseudomonas aeruginosa, one of three human pathogens recently listed as critical-priority by the WHO. One of the hallmarks of bacterial TA systems is the binary expression of toxins or toxin-like factors, leading to the generation of functional heterogeneity in bacterial populations. We hypoth-esize that the TA modules PA1029-PA1030 and PA2780-PA2781 contribute to behavioral heteroge-neity and antibiotic tolerance of cultures of *P. aeruginosa* and by that contribute to the establish-ment of successful infections. To strengthen this idea, we propose to embark on a thorough func-tional examination of both modules.In the first part of the project, we plan to dissect the regulation and function of the toxin PA1030 and its antitoxin PA1029. Activating mutations in the PA1030 gene were originally identified in isolates of chronically infected CF patients and were shown to confer strongly increased tolerance against different classes of antibiotics. Our preliminary data suggest that stochastic expression of PA1030 generates persisters by modulating the cellular NAD pool. We propose a combination of biochemical, structural and cell biology experiments to determine the mechanisms of toxin action on the cells' metabolism and its stochastic control. These experiments will test the central hypoth-esis that the PA1029-PA1030 TA module generates persisters upon sensing the depletion of a cen-tral metabolite. We will investigate the role of this TA module in chronic infections by characterizing TA variants from clinical isolates and by quantifying the expression of the TA components in pa-tient samples.ăIn the second part of the project, we will dissect the TA-like module PA2780-PA2781, which through its stochastic expression generates behavioral diversity in P. aeruginosa cells colonizing surfaces to form biofilms. Biofilms are multicellular communities that strongly promote chronic infections by protecting pathogens from phagocytic clearance and safeguarding bacteria from an-tibiotic killing. Based on preliminary results, we hypothesize that PA2780-PA2781 converts regu-latory input from the global Gac/Rsm cascade into a binary cellular response, generating pheno-typic heterogeneity through the control of c-di-GMP-dependent processes like virulence, biofilm formation and persistence. We postulate that this system provides *P. aeruginosa* with a bet-hedging strategy to functionally diversify during infection and colonization of host tissues. Our studies will uncover the mechanisms of stochastic expression and downstream processes of this TA-like mod-ule and will investigate its role in *P. aeruginosa* virulence and persistence.ă

Keywords Antibiotic tolerance, Toxin-antitoxin module, Pseudomonas aeruginosa, Biofilm formation, Phenotypic heterogeneity, stochastic binary gene expression, chronic infection
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