Universität Basel

Research Project

Tolerance as a potential reservoir for the development of drug resistance

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Principal Investigator(s) Jenal, Urs ;
Organisation / **Research unit**
Departement Biozentrum / Growth & Development
Departement Biozentrum / Infection Biology
Departement Biozentrum / Molecular Microbiology (Jenal)
Department
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Abstract

The widespread use of antibiotics promotes the spread of existing resistance mechanisms and the evolution of novel resistance traits. While resistant microorganisms are able to grow in the presence of the antibiotic, drug tolerance and drug persistence allow survival during transient antibiotic treatment windows. The mechanisms responsible for drug tolerance and persistence are currently unknown, representing a major obstacle for the development of anti-persistence drugs and other intervention strategies to cure persistent bacterial infection and interfere with resistance development. The often rare and transient nature of the multi-drug tolerant phenotype represents a particular challenge for the experimental and clinical exploration of persisting bacteria calling for a concerted and multi-pronged research approach to uncover their specific properties, clinical significance, and possible eradication strategies. While drug persistence mechanisms have been pioneered primarily in *E. coli*, it remains unclear how universal these features are. Importantly, it is also unclear if tolerance or persistence relates to the emergence of resistance traits and what their relevance is in the human patient.

To uncover the different mechanisms of antibiotic survival and their implications for resistance development, we use *Pseudomonas aeruginosa*, an important human pathogen causing both acute and chronic infections. Preliminary experiments demonstrated that 1) high levels of tolerance and persistence rapidly evolve in *P. aeruginosa*populations challenged with different classes of antibiotics; 2) evolution of high-level persistence always precedes resistance development; and 3) increased persistence is transient in a situation where resistance development is possible (single drug treatment) but is sustained in situations where resistance development is not possible (multi-drug treatment). These studies indicated that i) rapid evolution of high level persistence facilitates the emergence of drug resistance; and that ii) persistence alone (without resistance) can promote prolonged survival during drug treatment regimes. This is highly relevant as it suggests that populations of pathogens in human patients treated with antibiotics can rapidly evolve high levels of persistence to survive, thereby representing a reservoir for the selection of drug resistance traits.

To reach a better understanding of the molecular and physiological basis of drug tolerance and of the stochastic emergence of persister cells we propose to address the following three key questions: 1) Does increased tolerance facilitate the fixation of drug resistance? 2) What are the mechanisms of drug tolerance and persistence in the model pathogen *P. aeruginosa*? 3) How relevant is drug tolerance in the human patient? Our goals are to identify mechanisms of drug tolerance employed by *P. aeruginosa*and to outline the dynamic relationship between acquisition of tolerance and resistance both *in vitro*and in the

patient. Results from this proposal will fill fundamental knowledge gaps about the core and accessory characteristics of persisters, develop improved biomarkers for persistence and illuminate new avenues for therapeutic intervention through anti-persister antibiotic administration protocols. For these purposes, we will combine experimental evolution of laboratory and clinical *P. aeruginosa*strains with global analysis tools to investigate which strategies the bacterium employs to gradually overcome the challenge by different classes of antibiotics. Deep-genome sequencing of evolved lineages will be performed in order to follow the mutation acquired by the bacterial population and the dynamics of the clonal diversification over time. Fluorescence-activated cell sorting coupled to proteome analysis will be used to characterized discrete sub-populations displaying distinct phenotypes while single cell behaviours will be visualized by real-time microfluidic microscopy. The utilisation of descriptive and predictive quantitative models integrating the covariance between proteomic profiles and quantifiable microbial antibiotic parameters such as MICs, persistence and tolerance scores will shed light on the physiological basis of the bacterial response to drug treatment. We will extend these analyses to clincal *P. aeruginosa*isolates with the aim of defining general signatures and a comprehensive physiological model for persistence.

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