Universität Basel

Research Project

Molecular basis of Mycobacterium Abscessus heterogeneity during stress

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Project title Molecular basis of Mycobacterium Abscessus heterogeneity during stress
Principal Investigator(s) Boeck, Lucas ;
Project Members Wicki, Basil ;
Organisation / Research unit
Departement Biomedizin
Bereich Medizinische Fächer (Klinik) / Pneumologie
Department
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The evolutionary success of bacteria lies, to a large degree, in their adaptability; none more so than environmental mycobacteria. They have acquired multiple strategies to survive a large spectrum of stresses, and some, such as Mycobacterium tuberculosis managed to evolve from an environmental niche to become an obligate human pathogen.The focus of my proposal is Mycobacterium abscessus, a nontuberculous mycobacterium which has recently emerged as the most lethal and frequent multidrug-resistant mycobacterial infection in the developed world. M. abscessus infections are frequently impossible to treat despite prolonged combination antibiotic therapy and, at least in individuals with Cystic Fibrosis, cause accelerated lung damage and prevent safe lung transplantation. To date, the molecular strategies used by M. abscessus to resist antibiotics and escape host immune responses remain largely unknown but are likely to result from interactions between mycobacterial and non-mycobacterial virulence programmes (the latter acquired through horizontal gene transfer from other bacterial species). I have recently identified many of the critical gene networks controlling M. abscessus infection, virulence, and antimicrobial resistance through a multidimensional GWAS analysis of clinical isolates (Boeck et al in preparation). I now wish to examine how the generation of phenotypic heterogeneity by genetically identical bacteria may help M. abscessus adapt to changing environmental stresses. To do so, I will undertake three orthogonal experimental approaches (outlined below) to quantify mycobacterial heterogeneity, define the molecular basis underlying heterogeneity, and examine its functional implications during stress: Aim A: Single-cell dynamics of M. abscessus during stressOur knowledge of bacteria is almost exclusively based on the study of bulk populations. Particularly during stress (e.g. exposure to antibiotics) a large number of phenotypically different states emerge, which cannot be assessed by traditional approaches. In order to capture replication and functional dynamics I will use a custom-made microfluidic device to track millions of individual mycobacteria over time. This will allow me to characterise heterogeneity across different genetic backgrounds and during exposure to different stresses. Aim B: Genetic drivers for M. abscessus heterogeneity Phenotypic heterogeneity occurs in genetically identical individuals, mainly due to variations in transcription. The degree of phenotypic heterogeneity, however, is specified within and variable across genetic backgrounds, i.e. is a heritable genetic trait. I will combine a bacterial genome-wide association study (GWAS) approach with a forward genetic screen to identify drivers of mycobacterial heterogeneity during stress; in order to identify molecular mechanisms of involved stress pathways and heterogeneity formation. Aim C: Functional networks of stress induced M. abscessus subpopulationsThe functional properties of stress tolerant bacteria are poorly understood, and several misconceptions prevail, particularly that bacterial persistence is exclusively mediated via dormancy, a metabolically inactive state. To characterise their functional properties during stress I will

define the transcriptional networks active in specific phenotypic subpopulations of M. abscessus, and develop a functional framework for how persistence is activated and maintained.

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