PhD PROJECT PROPOSAL

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Fatty-acid degradation in bacterial predators and prey: to kill or to survive? A phylogenetic and metabolic modelling approach.

Supervisor (name, email, affiliated laboratory)

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Abstract

Many bacteria use fatty acids (FAs) from the environment as an energy and carbon source, degrading them by b-oxidation (1). While this process itself is well understood, there is a large number of unresolved questions on the physiological roles played by FA degradation in the lifestyle of bacteria: there is not only a large number of different FAs in the environment, but also many paralogs in bacterial genomes that could participate in the b-oxidation process. We want to shed light on the usage of FAs in different bacterial lifestyles and identify FA degradation pathways that are important for bacterial survival in different environmental conditions.
In this highly interdisciplinary project, we will combine phylogenetic analysis to classify functional families of FA degradation enzymes with developing model systems to test the different families in distinct physiological processes and metabolic modelling to estimate the contribution of FA degradation to different bacterial lifestyles.

Keywords

fatty acid metabolism, beta-oxidation, bacterial lifestyle, evolutionary analysis, metabolic modelling

Scientific question and Objectives

In this project, we want to unravel the different FA degradation pathways in bacteria and how they enable them to adapt to different physiological processes. We will first classify FA degrading enzymes and investigate their distribution across bacteria using phylogenetic analysis. We will use this classification to investigate the sequence-structure-function relationship of FA degrading enzymes. The FA enzyme classification will then be used by our experimental partners to investigate FA degradation in two physiological processes: starvation and bacterial predation, using two different bacterial models, *E. coli* and *Myxococcus xanthus*. We will use the experimental data produced by our collaboration partners to further refine the phylogenetic classification of FA degrading enzymes. At the same time, we want to investigate the metabolic changes in the different physiological conditions by performing constraint-based metabolic modelling using Flux Balance Analysis (FBA, 2) with these data.

Proposed approach (experimental / theoretical / computational) and research plan

The evolutionary analysis of FA degrading enzymes will be done using several approaches that include orthology searches using *bona fide* FA degrading enzymes as queries for reciprocal BLAST searches, combined with phylogenetic analyses (MAFFT & IQ-Tree), and complemented by structure-based modelling and analysis (Phyre, Alphafold) to estimate and predict

substrate-specificity and functionality. Synteny information will be used wherever possible. Metabolic modelling will be done using Flux Balance Analysis (FBA). Metabolic networks exist for *E. coli* and we will use the latest verified model for this species. For *M. xanthus*, we are in the process of generating a metabolic network with the help of toolboxes for model generation (e.g. DEMETER from the COBRApy toolbox, 3), together with literature, database (KEGG, EcoCyc) and synteny information, as well as information derived from the FA enzyme classification established in the first part of this project. Metabolic models will be contextualized with data from the experimental partners (RNA-seq, metabolic measurements). An important aspect of this project will be to use and develop tools for comparing results from metabolic modelling.

Interdisciplinarity and Implication of the two labs

This project is highly interdisciplinary and depends on the collaboration between the partnering labs. The student hired by the BH lab will perform all computational analysis (phylogenetic analysis, modelling, data analysis and integration). The students hired by the labs of TM and EB will perform all experimental work. The hired students should meet on a regular basis, exchange knowledge and information and participate in the lab meetings of the different labs whenever possible.

Specify with whom the person recruited will collaborate and on what aspects

The student recruited for this part of the project will be primarily affiliated with the BH team. She/he will work in close collaboration with the students from the TM and EB teams.

PhD student's expected profile

The candidate should have a sound education in computational biology and be knowledgeable in phylogenetic analysis and/or metabolic modelling. Strong willingness to acquire all required techniques to carry out this project are expected. She/he should also be able to work in a team and have excellent communication skills required for this interdisciplinary project. The working language will be English.

References related to the project

1 Pavoncello V, Barras F, Bouveret E. Degradation of Exogenous Fatty Acids in Escherichia coli. Biomolecules. 2022, 12(8):1019. doi: 10.3390/biom12081019.

2 Orth JD, Thiele I, Palsson BØ. What is flux balance analysis? Nat Biotechnol. 2010, 28(3):245-8. doi: 10.1038/nbt.1614.

3 Heinken A, Magnúsdóttir S, Fleming RMT, Thiele I. DEMETER: efficient simultaneous curation of genome-scale reconstructions guided by experimental data and refined gene annotations. Bioinformatics. 2021, 37(21):3974-3975. doi: 10.1093/bioinformatics/btab622.

Main references of the PIs related to the project (last 5 years)

Rikesh Jain, Nguyen-Hung Le, Lionel Bertaux, Jean Baudry, Jérôme Bibette, Yann Denis, Bianca H. Habermann, Tâm Mignot; bioRxiv 2023.12.11.571100; Fatty Acid Metabolism and The Oxidative Stress Response Support Bacterial Predation. doi: https://doi.org/10.1101/2023.12.11.571100 (accepted in PNAS).

Schiaffi V, Barras F, Bouveret E. Matching the β-oxidation gene repertoire with the wide diversity of fatty acids. Curr Opin Microbiol. 2024 Feb;77:102402. doi: 10.1016/j.mib.2023.102402.

Seef S, Herrou J, de Boissier P, My L, Brasseur G, Robert D, Jain R, Mercier R, Cascales E, Habermann BH, Mignot T. A Tad-like apparatus is required for contact-dependent prey killing in predatory social bacteria. Elife. 2021 Sep 10;10:e72409. doi: 10.7554/eLife.72409.

Project's illustrating image