Copper tolerance systems in *Pseudomonas aeruginosa*: role in defense against phagocytosis

Keywords

P. aeruginosa, Innate immunity, Copper tolerance, Phagocytosis, Copper enzymes

Summary

Pseudomonas aeruginosa (*Pa*) is a ubiquitous Gram-negative bacterium and a major opportunistic human pathogen. It is responsible for chronic lung infections and mortality in cystic fibrosis patients, for life threatening infections in immuno-compromised humans, and causes 10% of all nosocomial hospital-acquired infections. A diverse array of factors contributes to *Pa* virulence. Among them secretion systems are known to promote pathogenesis. One of these systems, the Tat (Twin Arginine Translocation) system allows the export of folded proteins across the cytoplasmic membrane and has been shown to be essential for virulence in a mouse model that mimics chronic lung infections by *Pa*[1]. Recent work performed by a previous PhD student in supervisor 1 team allowed to show that 34 proteins are exported by the Tat system in *Pa*[2], and that Tat is involved in many processes that are important for virulence (motility, metal tolerance, antibiotic resistance, cytotoxicity...)[3]. Now we would like to understand the role of these Tat substrates in the establishment of infection by *Pa*. In the host, copper is used as bacteriocide by macrophages during phagocytosis (innate immunity)[4]. In this project we will concentrate on the role of three Tat-dependent substrates that bind copper and for which we have evidences that they are involved in *Pa* copper tolerance. We will (i) identify their optimal condition of expression, (ii) characterize them biochemically and biophysically and (iii) evaluate their role in resistance to phagocytosis. This project has the potential to lead to the identification of new therapeutic targets against which inhibitors could be developed to render cells susceptible to macrophage-mediated killing, one of the key stages of innate immunity.

[1] Ochsner UA, Snyder A, Vasil AI, Vasil ML. (2002) *Proc Natl Acad Sci U S A.* 99(12):8312-7. [2] Gimenez MR, Chandra G, Van Overvelt P, Voulhoux R, Bleves S, Ize B. (2018) *Sci Rep*. 8:11950. doi: 10.1038/s41598-018-30393-x. [3] Gimenez MR *et al*., not published [4] Besold AN, Culbertson EM, Culotta VC. J Biol Inorg Chem. 2016 Apr;21(2):137-44. [5] Palmer T, Berks BC. (2012) *Nat Rev Microbiol*. 10(7):483-96 [6] De Buck E, Lammertyn E, Anné J. (2008) *Trends Microbiol.* (9):442-53.

The co-supervisors

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Location

BIP and LISM Laboratories, 31 chemin Joseph Aiguier, Marseille, France

Doctoral school

Life and Health Sciences (ED 62), Aix-Marseille Université

Expected profile of the candidate

Masters or engineer's degree in microbiology. The student should have good training in molecular biology, biochemistry and/or cell biology. The candidate must be able to demonstrate critical thinking, have good oral and written communication, and be able to work as part of a collaborative project.