Universität Basel

Research Project

FIC-Mediated Posttranslational Modifications at the Pathogen-Host Interface: From Studying FIC Structure, Function and Role in Pathogen-Host Interaction to the Engineering of Synthetic Activities (Akronym: FICModFun)

Third-party funded project

Project title FIC-Mediated Posttranslational Modifications at the Pathogen-Host Interface: From Studying FIC Structure, Function and Role in Pathogen-Host Interaction to the Engineering of Synthetic Activities (Akronym: FICModFun)
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Project start 01.02.2014
Probable end 31.01.2019
Status Completed

The ubiquitous FIC domain catalyzes post-translational modifications (PTMs) of target proteins; i.e. adenylylation (=AMPylation) and, more rarely, uridylylation and phosphocholination. Fic proteins are thought to play critical roles in intrinsic signaling processes of prokaryotes and eukaryotes; however, a subset encoded by bacterial pathogens is translocated via dedicated secretion systems into the cytoplasm of mammalian host cells. Some of these host-targeted Fic proteins modify small GTPases leading to collapse of the actin cytoskeleton and other drastic cellular changes. Recently, we described a large set of functionally diverse homologues in pathogens of the genus *Bartonella* that are required for their “stealth attack” strategy and persistent course of infection [1, 2]. Our preliminary functional analysis of some of these host-targeted Fic proteins of *Bartonella* demonstrated adenylylation activity towards novel host targets (e.g. tubulin and vimentin). Moreover, in addition to the canonical adenylylation activity they may also display a competing kinase activity resulting from altered ATP binding to the FIC active site. Finally, we described a conserved mechanism of FIC active site auto- inhibition that is relieved by a single amino acid exchange [1], thus facilitating functional analysis of any Fic protein of interest. Despite this recent progress only a few Fic proteins have been functionally characterized to date; our understanding of the functional plasticity of the FIC domain in mediating diverse target PTMs and their specific roles in infection thus remains limited.

In this project, we aim to study the vast repertoire of host-targeted Fic proteins of *Bartonella* to: 1) identify novel target proteins and types of PTMs; 2) study their physiological consequences and molecular mechanisms of action; and 3) analyze structure-function relationships critical for FIC-mediated PTMs and infer from these data determinants of target specificity, type of PTM and mode of regulation.

At the forefront of infection biology research, this project is ground-breaking as (i) we will identify a plethora of novel host target PTMs that are critical for a “stealth attack” infection strategy and thus will open new avenues for investigating fundamental mechanisms of persistent infection; and (ii), we will unveil the molecular basis of the remarkable functional versatility of the structurally conserved FIC domain.

Financed by
Commission of the European Union

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