Universität Basel

Research Project

Bacterial Type IV Secretion (T4S): Cellular, Molecular and Evolutionary Basis of the Subversion of Host Cell Functions by Translocated Effector Proteins

Third-party funded project

Project title Bacterial Type IV Secretion (T4S): Cellular, Molecular and Evolutionary Basis of the Subversion of Host Cell Functions by Translocated Effector Proteins
Principal Investigator(s) Dehio, Christoph ;
Co-Investigator(s) Stahlberg, Henning ; Hiller, Sebastian ; Schirmer, Tilman ;
Organisation / Research unit
Faculty of Science
Departement Biozentrum
Departement Biozentrum / Infection Biology
Departement Biozentrum / Molecular Microbiology (Dehio)
Department
Project Website http://p3.snf.ch/Project-173119
Project start 01.04.2017
Probable end 31.03.2021
Status Completed

The type IV secretion (T4S) systems of Gram-negative bacteria are versatile nanomachines ancestrally related to bacterial conjugation systems. Numerous bacterial pathogens targeting eukaryotic host cells have adopted these supramolecular protein assemblies for the intracellular delivery of bacterial effector proteins from the bacterial cytoplasm directly into the host cell cytoplasm. We are using zoonotic pathogens belonging to the closely related genus Bartonella (causing bartonellosis) and Brucella (causing brucellosis) to address fundamental questions related to the roles of T4S systems and their effector proteins in the establishment of chronic bacterial infection.Over the past 16 years we have - with support from the SNSF (grants 61777, 109925, 132979, and 149886) - established Bartonella as a powerful model for studying the cellular, molecular and evolutionary basis of T4S in bacterial pathogenesis. In early studies we have shown that the VirB T4S system represents an essential virulence device that translocates a cocktail of Bartonella effector proteins (Beps) into mammalian host cells, which subverts multiple cellular functions that facilitate chronic infection. We have then functionally characterized the bipartite secretion signal of Beps composed of a C-terminal BID domain and a charged tail. In recent years, we have assigned physiological functions to several Beps, identified some of their host cellular targets and performed corresponding structure-function analysis. We have also shown that all Beps are derived from a single ancestral effector that resulted from the fusion of a FIC domain derived from a bacterial toxin-antitoxin system that mediates AMPylation of target proteins and a BID domain derived from the secreted substrate (relaxase) of a conjugation system. We have further shown that independent Bep arsenals evolved in parallel in three Bartonella sublineages by gene duplication and diversification events, eventually resulting in Bep arsenals that facilitated adaptation of the host-restricted bartonellae to novel mammalian hosts. In the frame of the proposed project (subproject A), we want to deepen our understanding of the molecular functions of representatives of the growing repertoire of Beps by identifying their host targets and performing molecular and structure-function analysis. A major goal will be to understand the functional versatility of the limited set of Bep effector domains - FIC, BID and phosphorylated tyrosine arrays - to subvert a wide spectrum of host functions. Moreover, we want to characterize the physiological functions of representative Beps during infection using cell culture and animal infection

models, with a focus of understanding how they facilitate evasion of innate immune responses by the pathogen and support bacterial spreading from the dermal infection site towards the replicative niches in deep tissues and blood.The Brucella project - funded by SNSF grants 132979 and 149886 - was initiated six years ago as a new research line. We are studying the role of the T4S system and its effectors in trafficking of the Brucella containing vacuole (BCV) and the establishment of an intracellular replication niche in the endoplasmic reticulum (ER). We have shown that the T4S system-dependent escape of the early BCV from the degradative endocytic network and its trafficking towards the ER depends on retrograde endosome-to-Golgi trafficking pathways. Moreover, using yeast as surrogate model we have been able to map the wiring of T4S effectors to conserved eukaryotic signaling and trafficking pathways and we identified candidates of some of their mammalian target proteins by yeast two-hybrid screens. In the frame of the proposed project (subproject B) we intend to (i) refine our understanding of the T4S-dependent intracellular trafficking route of the BCV towards the replicative niche in the ER and (ii) study the molecular functions of individual T4S effectors in this process. Due to the small size of the biosafety 3 (BSL3) laboratory presently used by us at the nearby Swiss TPH Institute this project will remain a rather small activity and limited to cell culture infection models until 2018 when we will move into the new Biozentrum building with its state-of-the-art BSL3 facility that will allow us to significantly expand our activities in this project, including animal experimentation.

Keywords bacterial pathogenesis; immune response; type IV secretion ; bacterial effector protein; chronic infection; Bartonella; Brucella; animal infection model; Stat3

Financed by

Swiss National Science Foundation (SNSF)

Follow-up project of 2190067 Bacterial Type IV Secretion (T4S): Cellular, Molecular, and Evolutionary Basis of the Subversion of Host Cell Functions by Translocated Effector Proteins

Add publication

Published results

4106892, Dehio, Christoph; Bumann, Dirk, Editorial overview: Bacterial systems biology, 1879-0364, Current Opinion in Microbiology, JournalItem (Kommentare, Editorials, Rezensionen, Urteilsanmerk., etc. in einer wissensch. Zeitschr.

4062191, Harms, Alexander; Segers, Francisca H. I. D.; Quebatte, Maxime; Mistl, Claudia; Manfredi, Pablo; Körner, Jonas; Chomel, Bruno B.; Kosoy, Michael; Maruyama, Soichi; Engel, Philipp; Dehio, Christoph, Evolutionary Dynamics of Pathoadaptation Revealed by Three Independent Acquisitions of the VirB/D4 Type IV Secretion System in Bartonella, 1759-6653, Genome biology and evolution, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4062206, Harms, Alexander; Liesch, Marius; Körner, Jonas; Québatte, Maxime; Engel, Philipp; Dehio, Christoph, A bacterial toxin-antitoxin module is the origin of inter-bacterial and inter-kingdom effectors of Bartonella, 1553-7390 ; 1553-7404, PLoS Genetics, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4398935, Sedzicki, Jaroslaw; Tschon, Therese; Low, Shyan Huey; Willemart, Kevin; Goldie, Kenneth N.; Letesson, Jean-Jacques; Stahlberg, Henning; Dehio, Christoph, 3D correlative electron microscopy reveals continuity of Brucella -containing vacuoles with the endoplasmic reticulum, 0021-9533 ; 1477-9137, Journal of cell science, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4487708, Lobet, Elodie; Willemart, Kevin; Ninane, Noëlle; Demazy, Catherine; Sedzicki, Jaroslaw; Lelubre, Christophe; De Bolle, Xavier; Renard, Patricia; Raes, Martine; Dehio, Christoph; Letesson, Jean-Jacques; Arnould, Thierry, Mitochondrial fragmentation affects neither the sensitivity to TNFα-induced

apoptosis of Brucella-infected cells nor the intracellular replication of the bacteria, 2045-2322, Scientific reports, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4062208, Omasits, Ulrich; Varadarajan, Adithi R.; Schmid, Michael; Goetze, Sandra; Melidis, Damianos; Bourqui, Marc; Nikolayeva, Olga; Québatte, Maxime; Patrignani, Andrea; Dehio, Christoph; Frey, Juerg E.; Robinson, Mark D.; Wollscheid, Bernd; Ahrens, Christian H., An integrative strategy to identify the entire protein coding potential of prokaryotic genomes by proteogenomics, 1088-9051 ; 1549-5469, Genome Research, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4062202, Québatte, Maxime; Dehio, Christoph, Systems-level interference strategies to decipher host factors involved in bacterial pathogen interaction: from RNAi to CRISPRi, 1369-5274 ; 1879-0364, Current Opinion in Microbiology, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4062199, Québatte, Maxime; Christen, Matthias; Harms, Alexander; Körner, Jonas; Christen, Beat; Dehio, Christoph, Gene Transfer Agent Promotes Evolvability within the Fittest Subpopulation of a Bacterial Pathogen, 2405-4712 ; 2405-4720, Cell Systems, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4062195, González-Prieto, Coral; Gabriel, Richard; Dehio, Christoph; Schmidt, Manfred; Llosa, Matxalen, The Conjugative Relaxase TrwC Promotes Integration of Foreign DNA in the Human Genome, 0099-2240 ; 1098-5336, Applied and Environmental Microbiology, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

3681269, Stanger, Frédéric V.; de Beer, Tjaart A. P.; Dranow, David M.; Schirmer, Tilman; Phan, Isabelle; Dehio, Christoph, The BID Domain of Type IV Secretion Substrates Forms a Conserved Four-Helix Bundle Topped with a Hook., 0969-2126 ; 1878-4186, Structure, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

Add documents

Specify cooperation partners