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

**Project funded by own resources**

**Project title** Bacterial Type IV Secretion (T4S): Cellular, Molecular, and Evolutionary Basis of the Subversion of Host Cell Functions by Translocated Effector Proteins
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**Organisation / Research unit**
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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 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.

**Keywords** VirB T4S system, bacterial conjugation systems,
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**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

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