A bipartite signal mediates the transfer of type IV secretion substrates of Bartonella henselae into human cells

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Author(s) Schulein, Ralf; Guye, Patrick; Rhomberg, Thomas A; Schmid, Michael C; Schröder, Gunnar; Vergunst, Annette C; Carena, Ilaria; Dehio, Christoph
Author(s) at UniBasel Dehio, Christoph ;
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Bacterial type IV secretion (T4S) systems mediate the transfer of macromolecular substrates into various target cells, e.g., the conjugative transfer of DNA into bacteria or the transfer of virulence proteins into eukaryotic host cells. The T4S apparatus VirB of the vascular tumor-inducing pathogen Bartonella henselae causes subversion of human endothelial cell (HEC) function. Here we report the identification of multiple protein substrates of VirB, which, upon translocation into HEC, mediate all known VirB-dependent cellular changes. These Bartonella-translocated effector proteins (Beps) A-G are encoded together with the VirB system and the T4S coupling protein VirD4 on a Bartonella-specific pathogenicity island. The Beps display a modular architecture, suggesting an evolution by extensive domain duplication and reshuffling. The C terminus of each Bep harbors at least one copy of the Bep-intracellular delivery domain and a short positively charged tail sequence. This biparte C terminus constitutes a transfer signal that is sufficient to mediate VirB/VirD4-dependent intracellular delivery of reporter protein fusions. The Bep-intracellular delivery domain is also present in conjugative relaxases of bacterial conjugation systems. We exemplarily show that the C terminus of such a conjugative relaxase mediates protein transfer through the Bartonella henselae VirB/VirD4 system into HEC. Conjugative relaxases may thus represent the evolutionary origin of the here defined T4S signal for protein transfer into human cells.
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