A bacterial toxin-antitoxin module is the origin of inter-bacterial and inter-kingdom effectors of Bartonella

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4062206
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Year 2017
Title A bacterial toxin-antitoxin module is the origin of inter-bacterial and inter-kingdom effectors of Bartonella
Journal PLoS Genetics
Volume 13
Number 10
Pages / **Article-Number** e1007077
Host-targeting type IV secretion systems (T4SS) evolved from conjugative T4SS machineries that mediate interbacterial plasmid transfer. However, the origins of effectors secreted by these virulence devices have remained largely elusive. Previous work showed that some effectors exhibit homology to toxins of bacterial toxin-antitoxin modules, but the evolutionary trajectories underlying these ties had not been resolved. We previously reported that FicT toxins of FicTA toxin-antitoxin modules disrupt cellular DNA topology via their enzymatic FIC (filamentation induced by cAMP) domain. Intriguingly, the FIC domain of the FicT toxin VbhT of Bartonella schoenbuchensis is fused to a type IV secretion signal-the BID (Bep intracellular delivery) domain-similar to the Bartonella effector proteins (Beps) that are secreted into eukaryotic host cells via the host-targeting VirB T4SS. In this study, we show that the VbhT toxin is an interbacterial effector protein secreted via the conjugative Vbh T4SS that is closely related to the VirB T4SS and encoded by plasmid pVbh of B. schoenbuchensis. We therefore propose that the Vbh T4SS together with its effector VbhT represent an evolutionary missing link on a path that leads from a regular conjugation system and FicTA toxin-antitoxin modules to the VirB T4SS and the Beps. Intriguingly, phylogenetic analyses revealed that the fusion of FIC and BID domains has probably occurred independently in VbhT and the common ancestor of the Beps, suggesting parallel evolutionary paths. Moreover, several other examples of TA module toxins that are bona fide substrates of conjugative T4SS indicate that their recruitment as interbacterial effectors is prevalent and serves yet unknown biological functions in the context of bacterial conjugation. We propose that the adaptation for interbacterial transfer favors the exaptation of FicT and other TA module toxins as inter-kingdom effectors and may thus constitute an important stepping stone in the evolution of host-targeted effector proteins.
Publisher Public Library of Science
ISSN/ISBN 1553-7390 ; 1553-7404
URL https://www.ncbi.nlm.nih.gov/pubmed/29073136
edoc-URL https://edoc.unibas.ch/59169/
Full Text on edoc Available;
Digital Object Identifier DOI 10.1371/journal.pgen.1007077
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/29073136
ISI-Number WOS:000414161300036
Document type (ISI) Article