Bacterial effector binds host cell adenylyl cyclase to potentiate Gαs-dependent cAMP production

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Subversion of host organism cAMP signaling is an efficient and widespread mechanism of microbial pathogenesis.ăBartonella effector protein A (BepA) of vasculotumorigenicăBartonella henselae protects the infected human endothelial cells against apoptotic stimuli by elevation of cellular cAMP levels by an as yet unknown mechanism. Here, adenylyl cyclase (AC) and the α-subunit of the AC-stimulating G protein (Gαs) were identified as potential cellular target proteins for BepA by gel-free proteomics. Results of the proteomics screen were evaluated for physical and functional interaction by: (i) a heterologous in vivo coexpression system, where human AC activity was reconstituted under the regulation of Gαs and BepA inăEscherichia coli; (ii) in vitro AC assays with membrane-anchored full-length human AC and recombinant BepA and Gαs; (iii) surface plasmon resonance experiments; and (iv) an in vivo fluorescence bimolecular complementation-analysis. The data demonstrate that BepA directly binds host cell AC to potentiate the Gαs-dependent cAMP production. As opposed to the known microbial mechanisms, such as ADP ribosylation of G protein α-subunits by cholera and pertussis toxins, the fundamentally different BepA-mediated elevation of host cell cAMP concentration appears subtle and is dependent on the stimulus of a G protein-coupled receptor-released Gαs. We propose that this mechanism contributes to the persistence ofăBartonella henselae in the chronically infected vascular endothelium.

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