A translocated bacterial protein protects vascular endothelial cells from apoptosis

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The modulation of host cell apoptosis by bacterial pathogens is of critical importance for the outcome of the infection process. The capacity of Bartonella henselae and B. quintana to cause vascular tumor formation in immunocompromised patients is linked to the inhibition of vascular endothelial cell (EC) apoptosis. Here, we show that translocation of BepA, a type IV secretion (T4S) substrate, is necessary and sufficient to inhibit EC apoptosis. Ectopic expression in ECs allowed mapping of the anti-apoptotic activity of BepA to the Bep intracellular delivery domain, which, as part of the signal for T4S, is conserved in other T4S substrates. The anti-apoptotic activity appeared to be limited to BepA orthologs of B. henselae and B. quintana and correlated with (i) protein localization to the host cell plasma membrane, (ii) elevated levels of intracellular cyclic adenosine monophosphate (cAMP), and (iii) increased expression of cAMP-responsive genes. The pharmacological elevation of cAMP levels protected ECs from apoptosis, indicating that BepA mediates anti-apoptosis by heightening cAMP levels by a plasma membrane-associated mechanism. Finally, we demonstrate that BepA mediates protection of ECs against apoptosis triggered by cytotoxic T lymphocytes, suggesting a physiological context in which the anti-apoptotic activity of BepA contributes to tumor formation in the chronically infected vascular endothelium.
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