

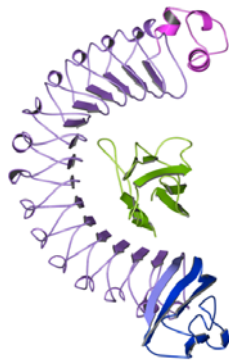
Molecular Infection: The Invasion Complex between Internalin of *Listeria monocytogenes* and human E-cadherin, Wolf-Dieter Schubert,^{a*} Thomas Wollert,^a Claus Urbanke^b and Dirk W. Heinz^a, ^a*Structural Biology, German Research Centre for Biotechnology, Mascheroder Weg 1, 38124 Braunschweig, Germany,* and ^b*Institute of Biophysical Chemistry, Hannover Medical School, Carl-Neuberg-Str. 1, D-30623 Hannover, Germany.* E-mail: wds@gbf.de

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The bacterium *Listeria monocytogenes* is a food-borne human pathogen. It infects humans by inducing its own uptake into epithelial cells of the intestine - although these are normally non-phagocytic. Recognition, adhesion and invasion of intestinal epithelial cells is mediated by a single listerial surface protein, Internalin (InlA), through specific interaction with the host cell receptor E-cadherin.

We have solved the crystal structure of the functional domain of InlA both uncomplexed and in complex with the extracellular, N-terminal domain of human E-cadherin (hEC1).

In the complex between InlA and hEC1, the superhelically twisted leucine rich repeat (LRR) domain of InlA surrounds and specifically recognizes hEC1. Site-directed mutagenesis, analytical ultracentrifugation and Biacore experiments indicate that binding affinity is remarkably weak yet highly specific: Pro16 of hEC1, a major determinant for human susceptibility to *L. monocytogenes* infection is essential for intermolecular recognition. Ca²⁺ was found to stabilize the complex. Structurally, this is corroborated by a Ca²⁺-binding site bridging the two proteins. This indicates that complex formation in the intestine is favoured by high Ca²⁺-concentrations whereas low, intracellular concentrations induce dissociation, freeing the bacterium and allowing it to move through the eukaryotic cell.



Our studies thus provide detailed insights into the molecular deception *L. monocytogenes* employs to exploit the host E-cadherin signal cascade through the expression of a single surface protein.

[1] W-D Schubert, C Urbanke, T Ziehm, V Beier, MP Machner, E Domann, J Wehland, T Chakraborty, DW Heinz (2002) Structure of internalin, a major invasion protein of *Listeria monocytogenes*, in complex with its human receptor, E-cadherin. *Cell* **111**, 825-36.