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Review

Role of Abl and Src family kinases in actin-cytoskeletal rearrangements induced by the *Helicobacter pylori* CagA protein

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ABSTRACT

The clinical outcome of infections with *Helicobacter pylori* is determined by a complex interplay of host–pathogen interactions, and persistent infection with this pathogen is the major cause of developing chronic gastritis, peptic ulcers and gastric cancer. Highly virulent strains encode a so-called type IV secretion system which translocates the CagA effector protein into gastric epithelial target cells. Injected CagA becomes tyrosine-phosphorylated on EPIYA sequence motifs by Src and Abl family kinase members. CagA then binds to and activates/inactivates various signalling proteins in a phosphorylation-dependent and phosphorylation-independent manner. In this way injected CagA can act as a master key that evolved during evolution the ability to highjack multiple downstream signalling cascades. Here we review our knowledge on the tyrosine phosphorylation motifs in CagA, the recent advances in the interaction of CagA with Src and Abl tyrosine kinases and their role in signalling events leading to changes of the phosphorylation status of actin-binding proteins cortactin, ezrin and vinculin followed by actin-cytoskeletal rearrangements, cell scattering and elongation. Detailed investigation of these pathways will help to yield novel insights and to elucidate the mechanisms of *H. pylori*-induced pathogenesis.

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Introduction

Helicobacter pylori is a human-specific microbe and one of the most successful bacterial pathogens. Genetic studies indicated that *H. pylori* spread during human migrations from east Africa around 58,000 years ago (Linz et al., 2007). Today the bacterium colonises the mucous layer of the stomach in more than half of the world's population. Persistent colonisation of the gastric epithelium and complex interactions with *H. pylori* are the major cause of chronic gastritis, peptic ulcers and gastric cancer. The pathogenesis of *H. pylori* mainly depends on the expression of several bacterial factors including the flagella, urease, catalase, neutrophil-activating protein NapA, peptidoglycan, outer inflammatory protein OipA and several adhesins such as BabA/B, SabA, AlpA/B or HopZ (Blaser and Atherton, 2004; Viala et al., 2004; Dubois and Borén, 2007; Yamaoka et al., 2008; Amieva and El-Omar, 2008; Polk and Peek, 2010). A recently discovered novel factor is the secreted protease HtrA (high temperature requirement A), which has been shown to cleave-off the ectodomain of E-cadherin, an important cellular adhesion protein and tumour suppressor, having crucial consequences for the disturbance of epithelial barrier functions (Hoy et al., 2010). However, the two best-characterised bacterial players associated with more severe disease are two extraordinary virulence factors, the *cag* (cytotoxin-associated genes) pathogenicity island (*cag*PAI) and the vacuolating cytotoxin (VacA). The *vacA* encoding gene is present in the genomes of virtually all *H. pylori* isolates worldwide, and related research has provided us with fundamental insights into the biology of this important pathogen. Secreted VacA can bind to a series of host surface molecules to trigger various effects including pore formation in the cell plasma membrane, alteration of endo-lysosomal function, cell vacuolation and apoptosis (Fig. 1) as well as T cell inhibition (Fujikawa et al., 2003; Boquet et al., 2003; Cover and Blanke, 2005; Rieder et al., 2005). The other crucial factor is the *cag*PAI, a 40 kb stretch of DNA, which is only present in the chromosomes of a subset of highly virulent isolates and was acquired by horizontal DNA transfer from a

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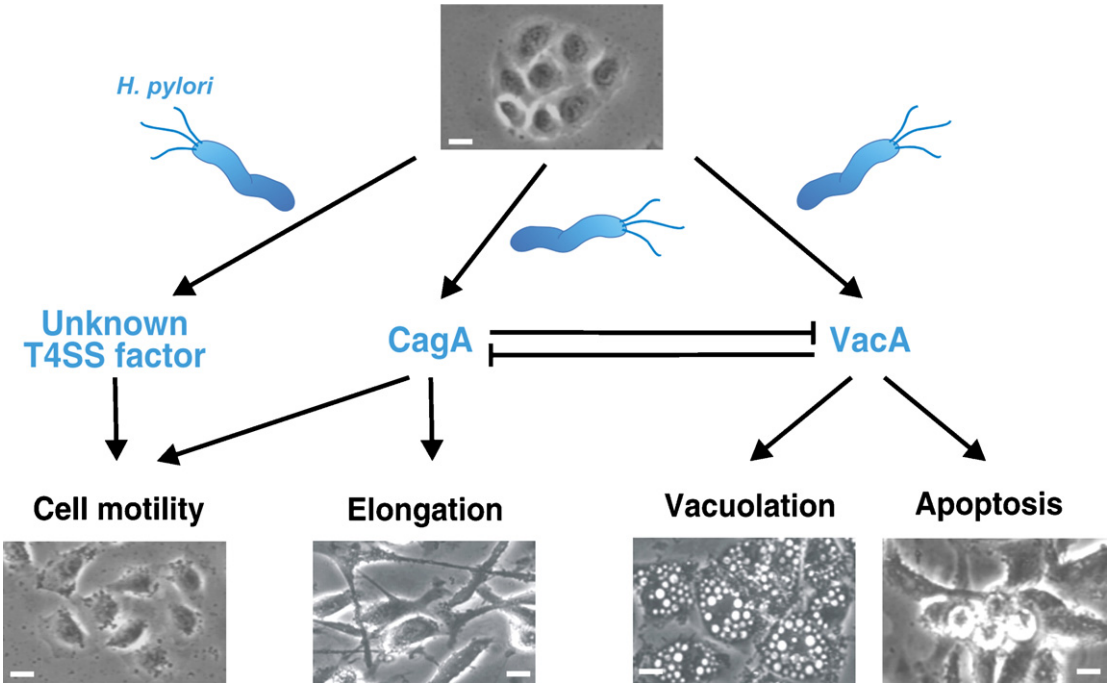

Fig. 1. Phenotypic responses of cultured AGS gastric epithelial cells during infection with *Helicobacter pylori in vitro*. Infection of cultured AGS cells with *H. pylori* wild-type isolates results in different phenotypes that can be observed in a time- and strain-dependent manner. First, AGS infected with T4SS-positive *H. pylori* exhibit a strong motility response (after 1–2 h) followed by elongation of the cells (after 3–4 h) (Selbach et al., 2002b; Moese et al., 2004). Vacuole formation can be observed during infection with VacA toxin-producing *H. pylori* (after 3–6 h). VacA is also implicated in triggering apoptosis of infected epithelial cells (after 24–48 h). However, how *H. pylori* regulates these cellular processes is still not fully clear, and it even appears that CagA and VacA have inhibitory effects on each others function (Yokoyama et al., 2005; Oldani et al., 2009; Tegtmeyer et al., 2009). For example, in infections with strains expressing highly active VacA the elongation phenotype induced by $CagA^{PY}$ can be even suppressed by a pathway involving the inhibition of EGFR (Tegtmeyer et al., 2009). Bars, 5 μm.
This figure was adapted from Backert et al. (2006) with kind permission from Elsevier.

yet unknown bacterium (Covacci and Rappuoli, 2000). Research in the last decade has shown that the *cag*PAI encodes functional components of a type IV secretion system (T4SS) (Rieder et al., 2005; Backert and Meyer, 2006), which is a syringe-like pilus protruding from the bacterial surface and is induced upon contact with target cells in order to inject virulence factors (Rohde et al., 2003; Tanaka et al., 2003; Kwok et al., 2007). Typically, transmembrane transporters of the T4SS family in various Gram-negative bacteria are composed of 11 VirB proteins (encoded by *virB1–virB11* genes) and the NTPase VirD4, a coupling factor for delivery of substrate proteins (Backert and Selbach, 2008; Fronzes et al., 2009). All VirB1–VirB11 orthologs and VirD4 as well as some accessory proteins are indeed encoded by the *cag*PAI (Fischer et al., 2001; Kutter et al., 2008; Backert et al., 2008a). Interestingly, the only known effector protein injected by the T4SS is CagA (125–145 kDa in size) having no sequence homology with any known bacterial or eukaryotic protein (Hatakeyama, 2008; Backert et al., 2010). Due to their pivotal role in *H. pylori* colonisation and pathogenesis, all these bacterial factors are currently being intensively studied to decipher how they trigger specific host cell responses.

VacA, CagA and the T4SS play a central role in the course of *H. pylori* infections as shown in the Mongolian gerbil and mouse models (Peek et al., 2000; Ogura et al., 2000; Fujikawa et al., 2003; Rieder et al., 2005) as well as *in vitro* using cultured gastric epithelial cells (Fig. 1). A hallmark of *H. pylori*-infected AGS cells is the development of the so-called "hummingbird" or "elongation" phenotype which is fully dependent on the presence of injected CagA and a yet unknown structural or injected T4SS-factor causing cell motility (Segal et al., 1999; Backert et al., 2001a; Churin et al., 2001, 2003; Stein et al., 2002; Fig. 1). This phenotype may have an important impact on pathogenesis because it could influence several processes including immune responses, wound healing, metastasis or invasive growth of cancer cells *in vivo* (Ridley et al., 2003; Schneider et al., 2008). The *H. pylori*-induced elongation phenotype is reminiscent of growth factor-induced cell scattering, which comprises several processes including (i) cell movement, driven by rearrangements in the cytoskeleton and (ii) the assembly/disassembly of cell–matrix contacts in the focal adhesions (Moese et al., 2007; Schneider et al., 2008). However, the fashion by which *H. pylori* regulates these cellular processes is little understood, and it also appears that VacA may have inhibitory effects on CagA and *vice versa* (Yokoyama et al., 2005; Oldani et al., 2009; Tegtmeyer et al., 2009; Fig. 1). Interestingly, studies on the delivery mechanism of CagA have shown that the T4SS requires a receptor on the host cell surface, the integrin member β_1 (Kwok et al., 2007; Jiménez-Soto et al., 2009). In addition, the effector protein CagA itself can also interact with β_1 integrin (Jiménez-Soto et al., 2009) as well as membrane-associated phosphatidylserine (Murata-Kamiya et al., 2010). Thus, it can be proposed that CagA is not injected into host cells in a random fashion but rather in a possibly tightly controlled way (Wessler and Backert, 2008). Experimental delivery of CagA into target cells, which can be achieved either by *H. pylori* infection or transfection of transgenes in cultured cells or expression in mice in the absence of *H. pylori*, has provided evidence that CagA evolved the ability to highjack multiple host cell signalling cascades. These signalling pathways not only include the induction of membrane dynamics, actin-cytoskeletal rearrangements and the disruption of cell-to-cell junctions as mentioned above but also proliferative, pro-inflammatory and anti-apoptotic nuclear responses (Hatakeyama, 2008; Backert et al., 2010). Currently, there are about 20 known cellular binding partners of CagA as well as some additional closely related isoforms and CagA itself, which are involved in the above signal transduction (Backert et al., 2010). A fundamental characteristic of CagA that actually led to the identification

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