Interestingly, tyrosine-phosphorylation of CagA (CagA p-Tyr) of the actin cytoskeleton and disruption of matrix adhesion. This destabilizes the E-cadherin-β-catenin complex and causes the dephosphorylation of focal adhesion kinase (FAK) and as a consequence of FAK substrates like Paxillin [20]. In gastric epithelial cells reduced FAK activity leads to a reduction of focal adhesion sites and contributes to cell detachment and increased cell motility.

While dephosphorylation of proteins on tyrosine residues appears important for promoting detachment of epithelial cells from the extracellular matrix, CagA-mediated inhibition of the cellular serine-threonine kinase Par1b/MARK2 was shown to be crucial for disruption of apical-basolateral cell polarity [21,22]. Par1b/MARK2 inhibition was independent of CagA activation via tyrosine phosphorylation and required the carboxyterminal CagA multimerization motif (CM - PFLKRHDVDDLSK). This CagA motif was shown to act as a structural analogue of Par1b/MARK2 substrates and it binds to the substrate binding pocket of the kinase, thereby inhibiting its activity [23]. Par1b/MARK2 inhibition leads to reorganization of microtubules and breakdown of tight junctions. Furthermore, Par1b/MARK2 inhibition also affected cortical actin and stress fiber formation and cell motility by preventing the inactivation of the RhoA specific guanosine exchange factor GEF-H1, thus synergizing with CagA p-Tyr-dependent functions [24].

The CM motif is also involved in direct binding to E-cadherin thereby preventing the association of E-cadherin with β-catenin. This destabilizes the E-cadherin-β-catenin complex and causes redistribution of β-catenin to the nucleus where it initiates the transcription of cancer-related genes [25]. Since serine-phosphorylation of β-catenin targets the molecule for degradation via the proteasome and prevents nuclear localization, CagA seems to synergize with other host signaling pathways to prevent β-catenin phosphorylation and degradation. Additionally, CagA was shown to induce the β-catenin pathway by interacting with c-Met and activation of the c-Met associated PI3K-AKT signaling pathway [8].

In conclusion, CagA perturbs host phosphatase- and kinase-
signaling pathways that regulate processes that have been shown to be important in epithelial-to-mesenchymal transition and tumor formation by disrupting cellular adhesion to the extracellular matrix, cadherin-mediated cell adhesion and tight junction formation. Together these processes may lead to an increased risk for developing gastric cancer and strengthen the hypothesis of CagA as the only bacterial oncogene to date.

However, many questions concerning CagA function in *H. pylori* associated gastric diseases remain unanswered. One daunting question is why some strains of *Helicobacter* have acquired the type IV secretion system during evolution and translocate the CagA effector. Cancer development and host mortality is clearly an undesired outcome from the bacterial perspective and a result not only of CagA activity; but also of other mechanisms, most notably chronic bacterial inflammation. For this reason, a possible physiologic advantage of CagA-translocating strains remains somewhat elusive, despite intense research and much progress in the field. Interestingly, *H. pylori* strains lacking the type IV secretion system and CagA are perfectly able to colonize the human stomach and cause chronic infection, albeit inflammatory responses are significantly reduced during infection with such strains. Therefore, suggesting a role for CagA as a colonization factor is also not undisputed. Nevertheless, the hypothesis that *H. pylori* uses CagA to gain more efficient access to nutrients from host tissue exudates, rather than from food content in the gastric lumen remains attractive. In agreement with this hypothesis, cancer is likely an accidental event, which is the long-term result of CagA activity, chronic gastric inflammation, and additional contributing factors. It should be stated that only a minority of those infected develop gastric disease and even fewer develop gastric cancer, indicating a role for host genetic factors. Clearly, the presence of strains expressing the type IV secretion system and efficiently translocating CagA into the host is an important factor, but not sufficient per se to trigger severe disease in every infected individual. Without doubt many interesting questions concerning *H. pylori* virulence and CagA function remain to be answered.

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**References**


