CELL
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SIGNALING

REVIEW   **Open Access**

"Targeted disruption of the epithelial-barrier by *Helicobacter pylori*"

Lydia E Wroblewski[1*] and Richard M Peek Jr[1,2,3*]

Abstract

Helicobacter pylori colonizes the human gastric epithelium and induces chronic gastritis, which can lead to gastric cancer. Through cell-cell contacts the gastric epithelium forms a barrier to protect underlying tissue from pathogenic bacteria; however, *H. pylori* have evolved numerous strategies to perturb the integrity of the gastric barrier. In this review, we summarize recent research into the mechanisms through which *H. pylori* disrupts intercellular junctions and disrupts the gastric epithelial barrier.

Review

The gastric epithelium and *Helicobacter pylori*

The gastric epithelium is comprised of a single layer of cells that invaginate to form highly organized gastric glands, populated by a distinct variety of cell types. The gastric epithelium can mediate digestive processes; however, an essential function of the gastric mucosal epithelium is to maintain a protective barrier that separates luminal contents containing pathogenic microorganisms such as *Helicobacter pylori*, from the underlying tissue compartments. *H. pylori* is a Gram-negative bacterial pathogen that selectively colonizes the gastric epithelium of approximately half of the world's population [1]. The most common outcome of *H. pylori* infection is chronic asymptomatic gastritis [2]; however, long-term colonization with *H. pylori* significantly increases the risk of developing gastro-duodenal diseases. Among infected individuals, approximately 10% develop peptic ulcer disease, 1-3% develop gastric adenocarcinoma, and less than 0.1% develop mucosa associated lymphoid tissue (MALT) lymphoma [3]. Accordingly, *H. pylori* is classified as a Type I carcinogen, and is considered to be the most common etiologic agent of infection-related cancers, which represent 5.5% of the global cancer burden [4].

H. pylori strains are extremely diverse and have evolved sophisticated virulence strategies that affect host cell signaling pathways and play an important role in

determining the outcome of infection [1]. Disease-associated *H. pylori* strains possess the *cag* pathogenicity island (*cag* PAI), which encodes components of a bacterial type IV secretion apparatus, and functions to export the terminal product of the *cag* PAI, CagA, across the bacterial membrane and into host gastric epithelial cells [5-7]. There are two mechanisms reported through which *H. pylori* may translocate CagA into host cells. One mechanism requires the interaction of CagL, a pilus localized component of the type IV secretion apparatus, with integrin $\alpha_5\beta_1$ on host epithelial cells [8]. An alternative mechanism is the type IV secretion apparatus induces externalization of phosphatidylserine, which resides on the inner leaflet of the cell membrane under resting conditions. CagA is then able to interact with phosphatidylserine and gain entry to host epithelial cells [9]. Although all *H. pylori* strains induce gastritis, strains that contain the *cag* PAI (*cag*⁺) augment the risk for severe gastritis, atrophic gastritis, and distal gastric cancer compared to those strains that lack the *cag* island (*cag*⁻) [10-21]. Following injection into host epithelial cells, CagA becomes tyrosine phosphorylated at glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs, which induces cell morphological changes, initially termed the 'hummingbird phenotype'. These alterations are linked to cellular migration and, importantly, may compromise the integrity of the gastric barrier [22-26]. Non-phosphorylated CagA also exerts effects within gastric epithelial cells that contribute to pathogenesis; including, but not limited to, activation of β-catenin, disruption of apical-junctional complexes, and loss of cellular-polarity [27-32]. Non-phosphorylated CagA interacts

* Correspondence: Lydia.Wroblewski@vanderbilt.edu; Richard.
Peek@vanderbilt.edu
[1]Division of Gastroenterology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA
Full list of author information is available at the end of the article

with the cell adhesion protein E-cadherin, the hepatocyte growth factor receptor c-Met, phospholipase PLC-g, the adaptor protein Grb2, and the kinase PAR1b/MARK2 [30,32-34], which culminate in pro-inflammatory and mitogenic responses, disruption of cell-cell junctions, and loss of cell polarity. These events will be discussed in more detail in subsequent sections (see sections: Disruption of the tight junction by *H. pylori* and Disruption of the adherens junction by *H. pylori*).
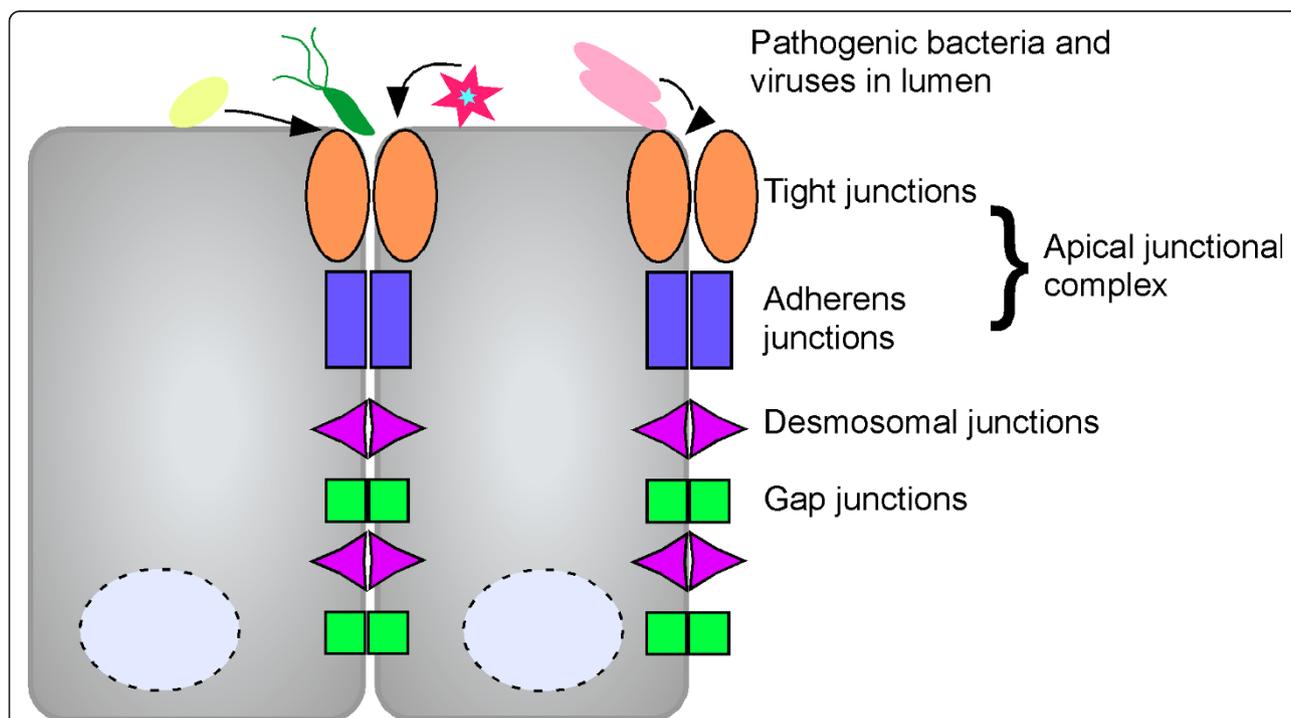
Intercellular junctions

Intercellular contacts are required to maintain the molecular architecture and selective barrier function of epithelial tissue. Within the gastric mucosa, barrier function is essential for preventing potentially harmful elements present in the gastric lumen from gaining access to the gastric mucosa. Intercellular junctions include the tight-junction which is juxtaposed at the most apical region of polarized cells, and the adherens junction which is located immediately below; collectively, these comprise the apical junctional complex which plays a pivotal role in regulating paracellular flux of ions and small molecules. The apical junctional complex also maintains cell polarity and regulates cell proliferative processes through relatively undefined signaling pathways. In addition to the apical junctional complex, gap junctions and desmosomes are also constituents which contribute to cell-cell contacts (Figure 1). In contrast to the apical junctional complex, which forms a tight seal between epithelial cells, gap junctions link the cytosol of adjacent cells to permit ions and small molecules to shuttle between cells [35]. Little is known in regard to how *H. pylori* may alter gap junctions, although there are data to suggest that CagA-positive strains may down-regulate gap junctions [36]. Desmosomes tightly tether adjacent cells through attachment to intermediate filaments [37], and loss of desmosomes has recently been linked to tumor development and early invasion [38,39]. To our knowledge, there are no reports of *H. pylori* interacting with desmosomes, making this an attractive area of study. What is clear, however, is that *H. pylori* preferentially adhere to gastric epithelial cells in close proximity to the apical junctional complex [27,40], and can alter localization of component proteins that constitute apical-junctional complexes [27,41-43]. Furthermore, barrier function is compromised in *H. pylori*-induced gastritis [44], and disruption of the apical junctional complex is associated with gastric cancer [45].

Overview of tight junctions

Tight junctions are located at the most apical region of the cell; they mediate adhesion between epithelial cells, and form tight seals between cells to create the major barrier in the paracellular pathway. Tight junctions are highly dynamic structures consisting of integral


Figure 1 Intercellular junctions form the epithelial barrier. Several bacteria, including *H. pylori*, and viruses interact with and disrupt cell-cell junctions of polarized epithelia. Intercellular junctions include tight junctions, adherens junctions, desmosomal junctions, and gap junctions.

membrane proteins and membrane-associated proteins, which collectively form a complex protein network. Scaffolding proteins link transmembrane proteins to the actin cytoskeleton. Integral membrane proteins, such as occludin, claudins, and junctional adhesion molecules (JAMs) are important components of the tight junction that span junctions and connect membranes on adjacent

cells to form a seal (Figure 2). Collectively, these components play critical roles in maintenance of barrier function, cell polarity, and intercellular adhesion.

Occludin was the first transmembrane tight junction protein to be identified [46], and it contains four transmembrane domains, two extracellular loops, and two intracellular loops. The C-terminus physically associates
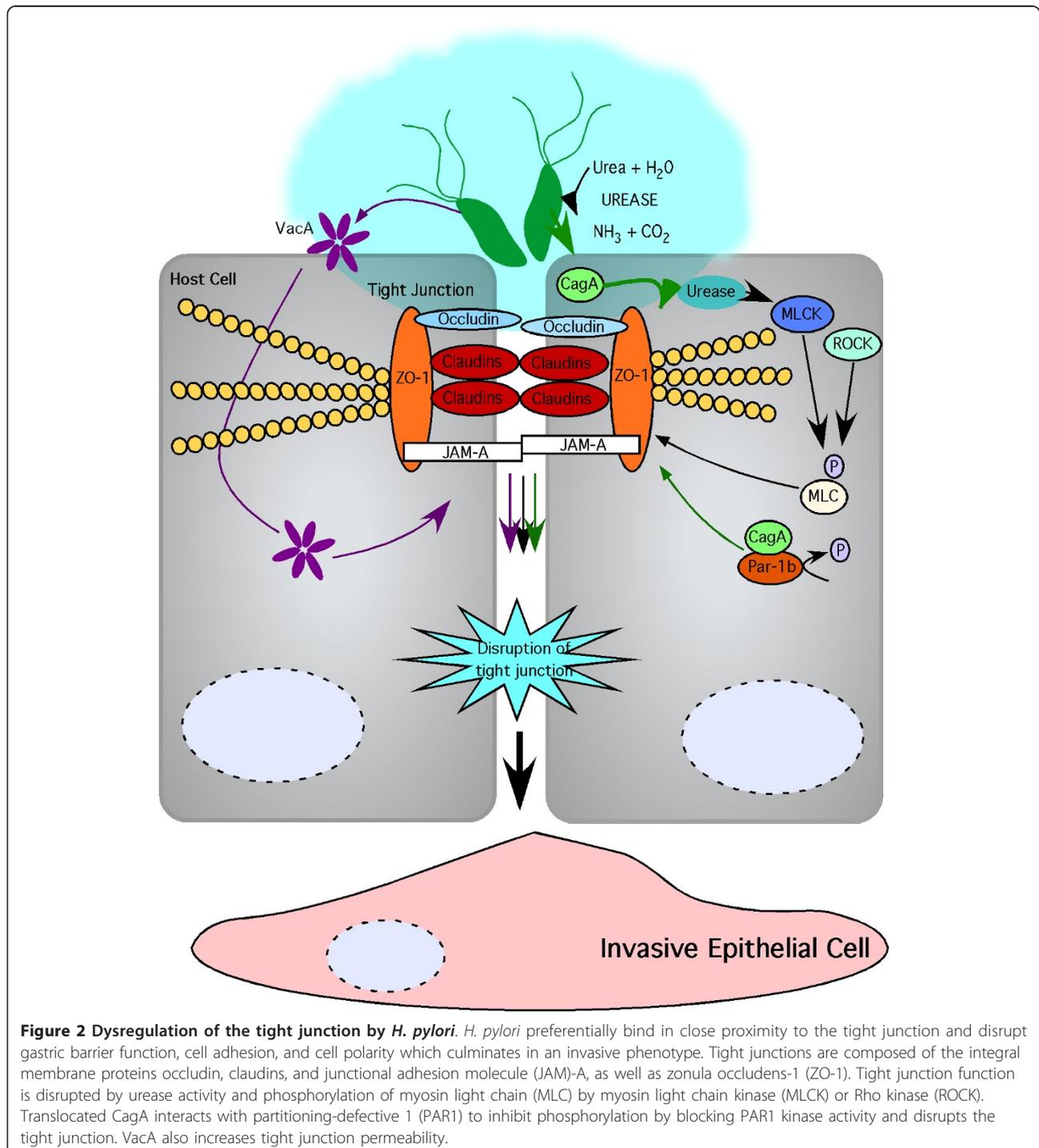
Figure 2 Dysregulation of the tight junction by *H. pylori*. *H. pylori* preferentially bind in close proximity to the tight junction and disrupt gastric barrier function, cell adhesion, and cell polarity which culminates in an invasive phenotype. Tight junctions are composed of the integral membrane proteins occludin, claudins, and junctional adhesion molecule (JAM)-A, as well as zonula occludens-1 (ZO-1). Tight junction function is disrupted by urease activity and phosphorylation of myosin light chain (MLC) by myosin light chain kinase (MLCK) or Rho kinase (ROCK). Translocated CagA interacts with partitioning-defective 1 (PAR1) to inhibit phosphorylation by blocking PAR1 kinase activity and disrupts the tight junction. VacA also increases tight junction permeability.

with ZO-1 and this interaction is essential for tight junction assembly [47]. Occludin deficient mice exhibit a complex phenotype, and initial studies indicated that occludin was not required for tight junction assembly or maintenance of barrier function [48]. However, subsequent characterization of occludin deficient mice suggests that occludin is essential for regulation of epithelial tight junctions. Occludin is highly phosphorylated on serine and threonine residues and phosphorylated occludin is the form that is associated with the tight junction [49]. Recent work suggests PKCη and PKCζ phosphorylation of occludin is required for complete assembly of the tight junction [50,51].

Claudins represent a family of 24 transmembrane proteins and are the main constituents of the tight junction intercellular strands [45]. Claudins, like occludin, are tetraspanning proteins with two extracellular loops and two intracellular loops; however, they do not posses sequence homology to occludin. Claudins mediate calcium-independent cell-cell adhesion and form either homodimers or heterodimers. Different combinations of claudin isoforms can mediate cell-type-specific differences in tight junctions [45].

JAM-A is a member of the immunoglobulin superfamily of proteins and contains an extracellular domain comprised of two Ig-like domains, a single transmembrane domain, and a short cytoplasmic C-terminal domain with a PDZ binding motif that is important for the interaction with tight junction scaffolding proteins. The extracellular domain of JAM-A contains dimerization motifs and forms homophilic contacts. The detailed role of JAM-A in regulating tight junction function is not fully understood; however, since it is known to interact with many other proteins, JAM-A may regulate tight junction formation by targeting proteins to the tight junction and may regulate epithelial permeability, inflammation, proliferation and migration [52,53]. Dimerization of JAM-A is required for the assembly of a protein complex with the PDZ domain-containing molecules Afadin and PDZ-guanine nucleotide exchange factor (GEF). This activates Rap1A, which stabilizes β1 integrin protein levels and increases cell migration [53]. JAM-A also acts as a receptor for viruses and is required for hematogenous dissemination of reovirus [54]. Whether JAM-A is utilized as a receptor by bacteria is currently unknown.

In addition to integral membrane proteins, tight junction proteins also include membrane-associated proteins such as zonula occludens-1 (ZO-1). ZO-1 is a member of the MAGUK (membrane-associated guanylate kinase homologs) family, characterized by a PDZ domain, SH3 domain and guanylate kinase domain. ZO-1 interacts with the C-terminus of occludin [55] and with claudins [56], and can also interact with proteins found in the adherens junction [57] and attach to the actin cytoskeleton [58].

Disruption of the tight junction by *H. pylori*

Disruption of the tight junction complex is associated with a variety of human diseases and cancers, including cancers of the gastrointestinal tract [45]. *H. pylori* are commonly found adhering to gastric epithelial cells, preferentially in close proximity to the apical junctional complex [27,40,59], possibly to gain maximal access to essential nutrients released by gastric epithelial cells [60]. Viable *H. pylori* have also been identified within the lamina propria, gastric lymph nodes, and within the intracellular canaliculi of parietal cells [61-63]; thus, an alternative hypothesis is that *H. pylori* may utilize the tight junction as a means to gain entry to the lamina propria [64].

Numerous studies have demonstrated that *H. pylori* modulates the tight junction [27,29,41-43,65-68]; however, what is less clear are the specific *H. pylori* constituents that mediate these changes in barrier function. In studies using polarized MDCK cells infected with a variant of *H. pylori* that was cell-adapted for increased adhesion, translocated CagA was shown to recruit ZO-1 and JAM-A to the site of bacterial attachment [27]. In MDCK cells, ectopic expression of GFP-CagA was also shown to disrupt the tight junction by inducing mislocalization of ZO-1 to the basolateral membrane, and inducing loss of apicobasal polarity characterized by a redistribution of the apical glycoprotein gp135 to the basolateral membrane and adoption of an invasive cellular phenotype [29]. Concordant with studies using MDCK cells, co-culture of primary human gastric epithelial cells results in membrane disruption of ZO-1 and redistribution of ZO-1 to small vesicles in the cytoplasm. However, the precise role of CagA in this cascade remains to be fully determined as total levels of ZO-1 protein remain unchanged between uninfected cells and those infected with CagA-positive or CagA-negative strains [42].

CagA has also been shown to dysregulate the tight junction through an interaction with partitioning-defective 1b (PAR1b)/microtubule affinity-regulating kinase 2 (MARK2). PAR1b is one of four structurally related members of the PAR1 family of kinases, and has an essential role in maintaining epithelial cell polarity by phosphorylating microtubule-associated proteins (MAPs), and destabilizing microtubules to permit the asymmetric distribution of molecules required for cells to maintain polarity [32,69-71]. CagA binds all four PAR1 isoforms with varying affinity [72], and the PAR1b-binding region of CagA has been identified as the 16-amino-acid CagA sequence also termed the CagA-multimerization (CM) sequence, which is involved

in CagA dimerization [73]. The initial 14 amino acids of the CM motif bind to the MARK2 kinase substrate binding site, thereby mimicking a host cell substrate [74] to inactivate the kinase activity of PAR1, leading to defects in epithelial cell polarity and disruption of tight junctions [32] (Figure 2). Interestingly, the number of CM repeats correlates with the virulence potential of CagA. Within Western *H. pylori* strains, the number of CagA CM repeats is directly proportional to the ability of CagA to bind PAR1b, while the CM sequence of CagA isolated from East-Asian *H. pylori* strains binds PAR1b more strongly than the CM sequence isolated from Western strains of *H. pylori* [75]. There is also a direct correlation between the level of PAR1b-binding-activity of CagA and the extent of cellular morphologic aberrations or disruption of the tight junction [75].

In other studies, CagA-independent alterations in tight junction structure and function have been demonstrated. The addition of purified VacA to MDCK cells lowers transepithelial electrical resistance (TER) and increases tight junction permeability to low-molecular weight molecules and ions. However, purified VacA-induced changes in tight junction function were not associated with alterations in ZO-1, occludin, or the adherens junction protein E-cadherin [76]. This was confirmed using live bacterial infection of MDCK cells with an isogenic *vacA* mutant strain. In this system, no alterations were seen in TER over a 20 hour infection [68]. In contrast, co-culture of MKN28 gastric epithelial cells with an isogenic *vacA* mutant strain decreased TER to the same extent as wild-type *H. pylori* [43]. We speculate that these reported differences in the role of VacA on modulating TER may be due to using different cell models and/or different strains of *H. pylori*. It would be interesting to determine *in vivo* if VacA is required for gastric barrier disruption.

In two independent studies, *H. pylori* strain SS1 was reported to disrupt barrier function in the gastric mucosa [41,66]. These findings also suggest that CagA is not important for *H. pylori* disruption of the tight junction, because although *H. pylori* strain SS1 is CagA positive, it lacks a functional type IV secretion system and cannot inject CagA into epithelial cells [77]. Another research group used canine intestinal epithelial cells, and found that co-culture of these cells with *H. pylori* stain SS1 induces redistribution of claudin-4 and claudin-5 and decreases membrane expression of these two tight junction proteins. Interestingly, the distribution and expression of ZO-1 and JAM-A were not changed [41]. More recently, the *H. pylori* Cag$^+$ strain 60190 was found to disrupt claudin-4 localization, and decrease cellular expression of claudin-4 in a CagA- and VacA-independent manner [78]. Further dissection of the signaling pathways involved suggested that *H. pylori*

phosphorylates IL-1 receptor type I, and in a Rho kinase-dependent manner disrupts claudin-4 at the tight junction [78].

The influence of *H. pylori* generated ammonium on tight junctions has also been investigated. Ammonium produced by *H. pylori* reduces TER in Caco-2 human colonic epithelial cells, which is associated with increased levels of a 42 kDa truncated form of occludin [67]. Urease catalyzes the hydrolysis of urea into carbon dioxide and ammonia, and functional urease activity was found to be required for *H. pylori*-induced disruption of TER in gastric epithelial cells [43] (Figure 2).

Paracellular permeability controlled by the tight junction can be regulated by myosin light chain kinase (MLCK)-mediated phosphorylation of myosin light chain (MLC), which increases the tension placed on the tight junction [79]. In SCBN canine intestinal cells it was determined using a selective inhibitor of MLCK, that activation of MLCK by *H. pylori* strain SS1 leads to decreased barrier function and increased expression of claudin-4 and claudin-5 [41]. Collectively these data suggest that in a CagA-independent manner, *H. pylori* decreases expression of claudin-4 and claudin-5, activates MLCK and subsequently disrupts barrier function [41]. In another study using a membrane-permeable inhibitor of MLCK (PIK) [80], activation of MLCK by *H. pylori* and the subsequent phosphorylation of MLC were also shown to disrupt barrier function by decreasing TER in human gastric epithelial cells, and *ureB* was required for maximal phosphorylation of MLC [43]. PKC activation may also be important for *H. pylori*-regulation of the tight junction [65] as activation of PKC increases TER by reducing phosphorylation of MLC [81] and decreased TER in T84 colonic epithelial cells induced by *H. pylori* was prevented by concurrent activation of PKC using the phorbol ester phorbol 12-myristate 13-acetate (PMA) [65].

Several studies have shown that *H. pylori* disrupts occludin localization at the tight junction [41,43,66]. This has been observed in two different cell line models [41,43], as well as in two different mouse models of *H. pylori* infection [43,66]. Despite the consistency in results between models, the *H. pylori* virulence factor required for disruption of occludin remains to be determined. The precise role of occludin in regulating barrier function is currently unclear, although, occludin is implicated in regulation of gastric barrier function [82], and emerging evidence suggests an important role for occludin in mediating barrier permeability.

Alterations in tight junction proteins induced by *H. pylori* and the virulence factors that are important for this disruption appear to be strain specific and discrepancies between different research groups are likely confounded by the use of different model systems. Another

factor that may contribute to discrepancies as to the role of CagA in disrupting the tight junction may be the polarization state of the cells under study [60,83]. Recent work examining the role of CagA for replication of *H. pylori* on MDCK cells has shown CagA-dependent as well as CagA-independent effects, depending on the polarization state of the host cell. CagA is required for *H. pylori* to disrupt MDCK cell polarity, and CagA-deficient *H. pylori* are not able to replicate on polarized cells when they are unable to access nutrients from the basolateral surface [60].

Adherens junction

Adherens junctions are required for maintenance of adhesive cell-cell contacts, cell polarity, and for signal transduction to the nucleus to regulate transcription. Adherens junctions are dynamic structures and are formed on a foundation of calcium-dependent homophilic contacts between E-cadherin on the surface of adjacent epithelial cells [84]. Other key components of the adherens junction are the armadillo protein family members p120-catenin (p120) and β-catenin, and the actin-binding protein α-catenin. E-cadherin has long extracellular and cytoplasmic domains; the extracellular domains of E-cadherin form homophilic interactions [85], while the cytoplasmic tail interacts directly with several intracellular proteins including p120 and β-catenin, which in turn bind α-catenin [86-88]. Previous data suggested that α-catenin interacts directly with the actin cytoskeleton; however this has been called into question as the interactions between β-α-catenin and α-catenin-actin were not found to occur simultaneously *in vitro* [89,90]. More recently EPLIN (epithelial protein lost in neoplasm) was identified as an α-catenin binding partner, and EPLIN was determined to mediate the interaction of the cadherin-catenin complex with actin [91] (Figure 3). There are currently no published reports as to whether *H. pylori* may disrupt the adherens junction through interactions with EPLIN, making this a potentially fruitful area of study.
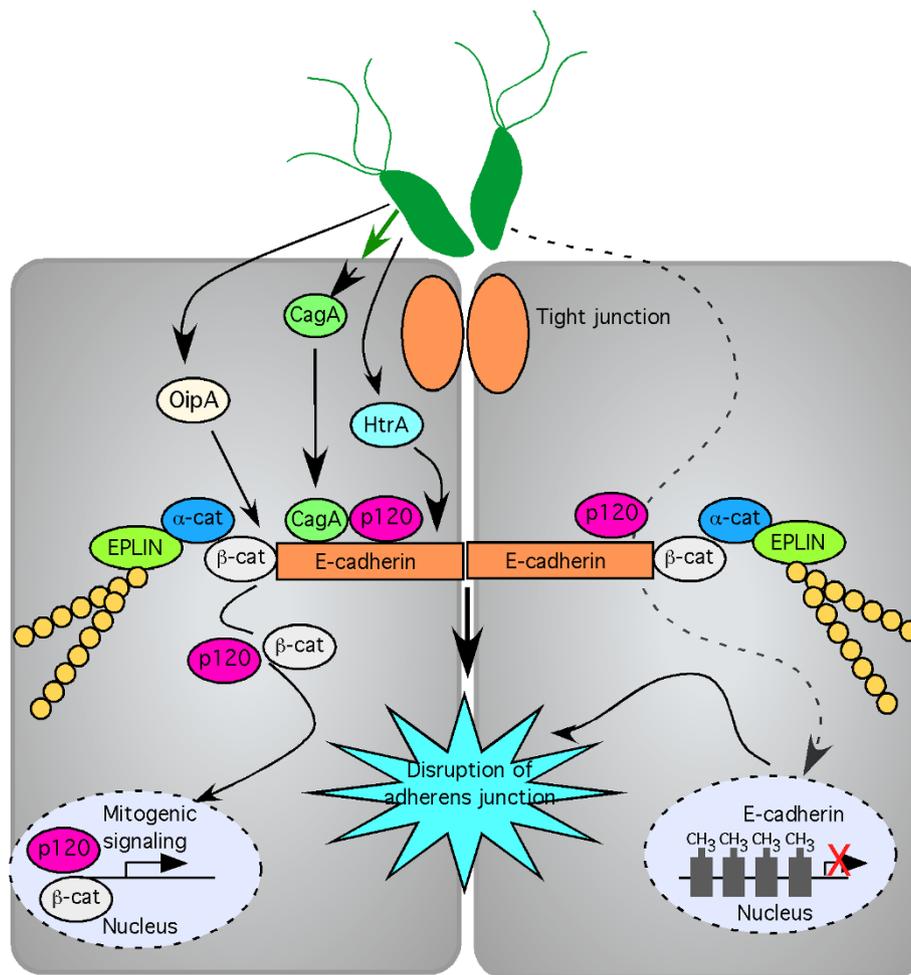
Disruption of the adherens junction by *H. pylori*

In numerous studies, *H. pylori* infection has been shown to induce E-cadherin gene promoter methylation, which ultimately leads to a reduction in E-cadherin expression [92-94]. Loss of E-cadherin function is associated with gastric cancer [92-94], and hypermethylation of the E-cadherin promoter can be reversed by eradication of *H. pylori* [93-95]. Decreasing the stability of the adherens junction by altering E-cadherin expression may be one mechanism through which *H. pylori* disrupts gastric barrier function and promotes disease progression (Figure 3).

H. pylori infection disrupts the adherens junction and initiates translocation of E-cadherin, β-catenin, and

p120 from the membrane into the cytoplasm of epithelial cells [31,96-98]. Specifically, transfected CagA physically interacts with E-cadherin in a manner that does not require CagA tyrosine phosphorylation [30]. The interaction of CagA with E-cadherin results in destabilization of the E-cadherin/β-catenin complex, and accumulation of cytoplasmic and nuclear β-catenin, which subsequently transactivates β-catenin-dependent genes that may promote carcinogenesis [30,99] (Figure 3). It is now thought that CagA not only interacts with E-cadherin, but also interacts with p120, and forms a multi-protein complex composed of c-Met, E-cadherin, and p120. This prevents tyrosine phosphorylation of c-Met and p120, and attenuates the invasive phenotype induced by CagA [99]. Through activation of PI3-K/Akt signaling by non-phosphorylated CagA, *H. pylori* also activates β-catenin and downstream pathways associated with disease development [100]

Under normal physiological conditions, cytoplasmic β-catenin is regulated by glycogen synthase kinase-3β (GSK-3β), which phosphorylates β-catenin within a multi-protein inhibitory complex that includes the adenomatous polyposis coli (APC) tumor suppressor protein. This complex constitutively targets β-catenin for degradation by the ubiquitin-proteasome pathway [101]. However, in gastric adenocarcinoma along with other cancers, increased expression of β-catenin, mutations within APC, and/or inhibition of GSK-3β are frequently observed, all of which function to stabilize β-catenin in the cytoplasm [102]. Other mechanisms through which *H. pylori* induces increased cytoplasmic expression of β-catenin are via PI3K-dependent inactivation of GSK-3β [100,103], and direct interaction with membrane associated β-catenin via CagA [30,104]. Cytoplasmic β-catenin subsequently translocates to the nucleus where it interacts with T-cell factor/lymphoid enhancer factor-1 (Tcf/LEF-1) transcription factors to regulate transcription of genes that can influence carcinogenesis [30,104]. In a gerbil model of infection, nuclear accumulation of β-catenin occurs following infection with carcinogenic Cag+ *H. pylori* strains [28]. Concordantly, in human gastric biopsies there is an increase in levels of nuclear β-catenin in gastric epithelium harvested from patients infected with *H. pylori* cag+ strains when compared to persons infected with *H. pylori* cag- strains, or uninfected persons [28]. Recent work has shed new light on the role of CagA in disrupting the adherens junction with the discovery of an inhibitory domain within the N-terminus of CagA [105]. The first 200 amino acids of the CagA N-terminus counteract host responses evoked by the C-terminus of CagA and reduce host-cell responses by strengthening cell-cell contacts and decreasing CagA-induced β-catenin activity [105]. Thus it appears that

Figure 3 Dysregulation of the adherens junction by *H. pylori*. *H. pylori*-translocated CagA interacts with E-cadherin and p120. This destabilizes the adherens junction and results in nuclear translocation of β-catenin and p120 and alterations in transcriptional activity. The *H. pylori* outer membrane protein OipA disrupts adherens junctions through redistribution of β-catenin, and *H. pylori*-secreted high-temperature requirement A (HtrA) cleaves E-cadherin, disrupting the adherens junction. Hypermethylation of the E-cadherin promoter also occurs in response to *H. pylori* infection and epithelial protein lost in neoplasm (EPLIN) binds α-catenin and links the cadherin-catenin complex with actin.

CagA has evolved domains to tightly regulate β-catenin activation within host cells.

Although important, CagA is not the only bacterial factor that disrupts adherens junction proteins [97,106-108]. In a Mongolian gerbil model of gastric cancer, inactivation of the *H. pylori* outer membrane protein OipA decreased nuclear localization of β-catenin and reduced the incidence of gastric cancer, suggesting OipA may be associated with the redistribution of β-catenin and promotion of the carcinogenic process [106]. Proteolytic cleavage of E-cadherin is independent of CagA in studies that utilized a human breast cancer cell (MCF-7) model [97], and in human gastric NCI-N87 cells [109]. Recent work has identified *H. pylori* high-temperature requirement A (HtrA) as a novel secreted virulence factor that cleaves E-cadherin

and disrupts the adherens junction [107], (Figure 3). Loss of E-cadherin from the adherens junction is also associated with dissociation of β-catenin and p120 from the adherens junction into the cytosol. Similar to findings by Bebb *et al.* [108], β-catenin did not translocate to the nucleus, and as such, did not modulate transcription [97].

Under normal physiological conditions, nuclear expression of p120 is low; however, in tumor cells, expression of p120 is elevated [110-112]. *H. pylori* has recently been associated with mislocalization of p120 to the nucleus in human gastric epithelia, and in infected murine primary gastric epithelial cells [42,98]. Further analysis of downstream signaling pathways determined that p120 mis-localized to the nucleus in response to *H. pylori* acts to relieve transcriptional

repression of *mmp-7*, a matrix metalloproteinase implicated in gastric tumorogenesis, by an interaction with Kaiso [98]. Nagy *et al.* have also recently reported that a p120- and β-catenin target gene, PPARδ, regulates gastric epithelial proliferation via activation of cyclin E. These are potentially important mechanisms through which *H. pylori* may lower the threshold for developing gastric cancer [98].

Conclusions

The gastric epithelium is primed to secrete effector molecules that control gastric function, and the highly organized nature of gastric glands is essential for regulating gastric integrity and maintaining a protective barrier between harmful luminal contents and the underlying tissue compartments. *H. pylori* has developed numerous strategies to penetrate the gastric epithelial barrier by altering the structure and function of the apical junctional complex. The role of CagA in disrupting the apical junction complex is divisive; however, the actions of CagA are critical in a number of contexts. In addition to CagA, *H. pylori* also utilizes other factors to modify the gastric barrier. These include VacA, OipA, urease, and the newly identified HtrA, in addition to disrupting the gastric barrier through altering cell polarity. Future studies will provide further insight into understanding how *H. pylori* factors and signaling pathways culminate in loss of barrier function. These studies are of utmost importance as many gastric diseases including gastric cancer may develop as a result of compromised barrier function.

Author details
[1]Division of Gastroenterology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA. [2]Department of Cancer Biology, Vanderbilt University Medical Center, Nashville, TN 37232, USA. [3]Department of Veterans Affairs Medical Center, Nashville, TN 37212, USA.

Authors' contributions
LEW and RMP drafted and wrote the manuscript. LW prepared the figures. Both authors read and approved the final manuscript

Competing interests
The authors declare that they have no competing interests.

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