FEBS Letters 587 (2013) 259–265

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Adherens junctions as targets of microorganisms: A focus on *Helicobacter pylori*

Angela Margarida Costa [a,b], Marina Leite [a], Raquel Seruca [a], Ceu Figueiredo [a,b,*]

[a] IPATIMUP - Institute of Molecular Pathology and Immunology of the University of Porto,Portugal
[b] Faculty of Medicine of the University of Porto, Porto, Portugal

ARTICLE INFO

Article history:
Received 4 October 2012
Revised 7 December 2012
Accepted 10 December 2012
Available online 19 December 2012

Edited by Wilhelm Just

Keywords:
Adherens junction
E-cadherin
Pathogenesis
Helicobacter pylori

ABSTRACT

Mucosal epithelia are targeted by several microorganisms as a way of adhesion, internalization, and/or exploitation of the host properties to induce disease. *Helicobacter pylori* are worldwide prevalent bacteria that colonize the human stomach. Persistent infection of the gastric mucosa with *H. pylori* and concurrent chronic gastritis are risk factors for ulcer disease and gastric carcinoma. Therefore, interactions at the *H. pylori*–epithelial interface are important to understand the pathogenesis of these bacteria and the host responses that contribute to disease development. Here, we provide an overview of the interactions between microorganisms and the adherens junctions with an emphasis on *H. pylori*.

1. Epithelial cell–cell junctions

Mucosal epithelia establish an interface between the external environment and the internal organs. They are physical and functional barriers that prevent external elements, like microorganisms, to reach the interstitial space and the bloodstream. This is mainly accomplished by the existence of cell–cell junctions – tight junctions, adherens junctions, desmosomes, and gap junctions – which are essential components of epithelial integrity [1,2].

The tight junctions are the most apical set of cell–cell junctions that separate the apical and basolateral domains of the plasma membrane, and selectively regulate the paracellular flux of ions and small molecules [3]. They are composed of transmembrane proteins occludin, claudins, and junctional adhesion molecules (JAMs), and cytosolic proteins zonula occludens (ZO)-1, -2, and -3, that bridge transmembrane proteins with the cytoskeleton [4].

Adherens junctions are localized immediately below tight junctions and their main function is to maintain cell–cell adhesion. The major component of the adherens junctions is the transmembrane protein E-cadherin. The extracellular part of E-cadherin establishes homophilic interactions with E-cadherin molecules of neighboring cells, promoting cohesion of the epithelium. E-cadherin may also establish heterophilic interactions, namely with the receptor tyrosine kinases EGFR and c-Met, modulating their signaling properties [5,6]. The cytoplasmic domain of E-cadherin is associated with β-, p120-, and α-catenins, and this complex establishes a connection to the actin cytoskeleton via Eplin. These protein–protein interactions, as well as the phosphorylation status of the catenins, are important in junction stabilization [7,8].

Desmosomes provide mechanical stability and intercellular communication to neighboring cells. They are composed of transmembrane desmoglein and desmocollin cadherins that bind cytoplasmatic plakoglobin and plakophilin, which in turn interact with desmoplakin. The latter anchors intermediate filaments and establishes a mechanical continuum across cells [9]. Gap junctions are plaques of many small channels constituted by connexins that allow intercellular passage of ions and small molecules. In addition, gap junctions have a role in regulating cell morphology, establishing polarity, and rearrangement of the cytoskeleton [10].

2. Adherens junctions as targets of microorganisms

Disruption of the intercellular junctions is a strategy used by several microorganisms as a means of adhering to cells, entering cells, and/or exploiting host signaling to their advantage. Although in mucosal epithelia the tight junctions prevent most microorganisms from penetrating into deeper tissues, some can breach this barrier and reach cell–cell junctions at levels below the tight junctions, namely the adherens junctions.

* Corresponding author. Address: IPATIMUP, Rua Dr. Roberto Frias S/N 4200-465 Porto, Portugal. Fax: +351 22 5570799.
E-mail address: cfigueiredo@ipatimup.pt (C. Figueiredo).

0014-5793/$36.00
http://dx.doi.org/10.1016/j.febslet.2012.12.008

2.1. Adherens junctions as receptors for microorganisms

At the adherens junctions, E-cadherin is used as a receptor for adhesion and/or internalization by several microorganisms, allowing microbial persistence in the host, avoidance of mechanical clearance, and increased pathogenesis (Table 1).

The best studied pathogen that uses E-cadherin for adhesion and internalization into the host cells is *Listeria monocytogenes*. *L. monocytogenes* is a Gram-positive foodborne pathogen that can cause diseases such as gastroenteritis, meningoencephalitis, and sepsis [11]. To adhere to and to promote its internalization into host cells, *L. monocytogenes* utilizes cell wall surface internalins A (InlA) and B (InlB) [12]. InlA specifically binds to E-cadherin [12] and recruits α-, β- and p120-catenins to the site of bacterial entry, triggering dynamic events of actin polymerization and membrane extensions, culminating in bacterial uptake [13,14].

Candida albicans is an opportunistic fungus that can cause hematogenously disseminated and mucosal candidiasis. Fungal invasion of the host cells is an important pathogenic feature of *C. albicans*-related diseases. One of the mechanisms that underlies *C. albicans* invasion is the adhesion to N-cadherin on endothelial cells and to E-cadherin on oral epithelial cells. Adhesion followed by endocytosis occurs via the agglutinin-like sequence (Als3) adhesin expressed by *C. albicans* hyphae [15].

Streptococcus pneumonia is a Gram-positive bacterium that frequently colonizes the upper respiratory tract of humans. This asymptomatic colonization can however progress to invasive diseases, including pneumonia, sepsis and meningitis. It has been shown that *S. pneumoniae* adheres to the epithelial cell surface in the first steps of nasopharyngeal carriage and colonization, and E-cadherin has been identified as a receptor for the pneumococcal surface adhesin A (PsaA) [16].

Clostridium botulinum is a Gram-positive bacterium that can cause food-borne botulism in humans. *C. botulinum* produces a potent neurotoxin, the botulinum neurotoxin (BoNT), which is the etiological agent of botulism. BoNT forms large protein complexes through association with non-toxic components, such as hemagglutinin (HA). HA directly binds E-cadherin and disrupts E-cadherin-mediated cell–cell adhesion and the epithelial barrier [17], providing a putative explanation for the passage of the orally-ingested BoNT from the gut lumen to the systemic circulation through the intestinal epithelial barrier.

2.2. Adherens junctions disruption by microorganisms

E-cadherin has also been reported as a target of bacterial proteases. E-cadherin cleavage leads to weaker cell–cell adhesion which may allow access of the microorganisms to the intercellular epithelial spaces and underlying tissues.

Enterotoxigenic *Bacteroides fragilis* (ETBF) are Gram-negative pathogens associated with diarrheal disease. ETBF produce a toxin named fragilysin or BFT which specifically cleaves the extracellular domain of E-cadherin on intestinal and on other polarized epithelial cells, resulting in junction disassembly [18]. E-cadherin cleavage by BFT releases β-catenin to the cytoplasm, resulting in β-catenin nuclear localization and stimulation of β-catenin–TCF-dependent cell proliferation [19]. This BFT-mediated extracellular domain cleavage of E-cadherin also induces proteolysis of intracellular E-cadherin, in a process dependent on γ-secretase [20].

Porphyromonas gingivalis is a Gram-negative and highly invasive intracellular pathogen and an etiological agent of human adult periodontitis. *P. gingivalis* produces cysteine proteases termed gingipains, namely HRgpA, RgpB, and Kgp, which are able to degrade E-cadherin. This process of disruption of the adherens junctions suggests that *P. gingivalis* can invade the underlying connective tissues via the paracellular pathway [21].

Enterococcus faecalis are Gram-positive commensal bacteria of the mammalian gastrointestinal tract, which can cause opportunistic infections when they penetrate the gut barrier. The GelE metalloprotease from *E. faecalis* cleaves the extracellular domain of E-cadherin, and is implicated in the development of chronic intestinal inflammation by impairment of the epithelial barrier integrity. Mice that are susceptible to intestinal inflammation show reduced levels of the extracellular domain of E-cadherin, which result from GelE-mediated proteolytic cleavage [22].

The contact of *C. albicans* with oral and with intestinal epithelial cells induces E-cadherin cleavage, both in the extracellular and in the intracellular domains, and γ-secretase is implicated in the latter cleavage event [23,24]. Interestingly, during the interaction of *C. albicans* with oral epithelial cells, E-cadherin is degraded only in localized areas of tissue invasion by the Sap5p secreted aspartyl-protease of the fungus [24].

Staphylococcus aureus are Gram-positive bacteria that are responsible for a considerable number of clinically relevant infections, including those of the skin and of the lower respiratory tract. One of the most important virulence factors of *S. aureus* which contributes to the pathogenesis of pneumonia is α-hemolysin (Hla). Hla induces injury in epithelial cells by interacting with its receptor, the zinc-dependent metalloprotease ADAM10. Hla upregulates ADAM10 metalloprotease activity in alveolar epithelial cells, and the upregulation of ADAM10 results in cleavage of E-cadherin. E-cadherin cleavage leads to disruption of the epithelial barrier function, thus contributing to the pathogenesis of lethal acute lung injury [25].

Table 1
Infectious agents and proposed mechanisms of targeting of the adherens junctions.

Species	Virulence factor	Host target/proposed mechanism	Reference
Listeria monocytogenes	InlA	Adhesion to E-cadherin and host cell invasion	[12, 13, 14]
Streptococcus pneumoniae	PsaA	Adhesion to E-cadherin and host colonization	[16]
Clostridium botulinum	BoNT HA	Adhesion to E-cadherin and disruption of host cell–cell adhesion	[17]
Candida albicans	Als3	Adhesion to E-cadherin and host cell invasion	[15]
	Sap5p	Extracellular and intracellular E-cadherin cleavage	[24]
Bacteroides fragilis	BFT	Extracellular and intracellular E-cadherin cleavage	[18,19,20]
Porphyromonas gingivalis	HRgpA, RgpB, Kgp	Extracellular E-cadherin cleavage	[21]
Enterococcus faecalis	GelE	Extracellular E-cadherin cleavage	[22]
Escherichia coli	HtrA	Extracellular E-cadherin cleavage	[64]
Shigella flexneri	HtrA	Extracellular E-cadherin cleavage	[64]
Campylobacter jejuni	HtrA	Extracellular E-cadherin cleavage	[64]
Helicobacter pylori	HtrA	Extracellular E-cadherin cleavage	[63]
	?	Extracellular E-cadherin cleavage via ADAM-10	[60]
Staphylococcus aureus	Hla	Extracellular E-cadherin cleavage via ADAM-10	[25]
Pseudomonas aeruginosa	?	Alteration of phosphorylation and localization of adherens junctions proteins	[26]