Clinical Presentations and Pathogenicity Mechanisms of Bacterial Foodborne Infections

Nicole Tegtmeyer, Manfred Rohde, and Steffen Backert

1 Introduction

The gastrointestinal (GI) tract is one of the largest and most important organs in humans. In a normal male, the GI tract is approximately 6.5 m (20 ft) long and is covered by the intestinal epithelium, which has a surface of about 400–500 m^2. This epithelium not only exhibits crucial absorptive and digestive properties, it also represents an efficient barrier against commensal microbial flora as well as foodborne pathogens. The gut flora consists of more than 1,000 microbial species, which shape a highly complex and dynamic community (Hooper and Gordon 2001; Eckburg et al. 2005). The exclusion of these microbes is not only a result of the continuous physical barrier formed by the tightly bound epithelial cells; the intestinal epithelium also exhibits crucial host immune functions to recognize commensals and eliminate pathogens (Sansonetti 2004; Tsolis et al. 2008). The immune system controls the resident microflora and defends against infections by foodborne pathogens through two functional arms: the innate immunity and the adaptive immunity. Interestingly, commensal bacteria that colonize the gut also protect the host from intruding pathogens by imposing a colonization barrier, also called the barrier effect (Stecher and Hardt 2008). The recognition of these microbes is commonly based on the identification of pathogen-associated molecular patterns (PAMPs) by defined pattern recognition receptors (PRRs) expressed in a variety of host cells. Typical PAMPs are lipopolysaccharides (LPSs), flagellins, or peptidoglycans that are either present on the bacterial cell surface or spontaneously released from the bacteria upon contact with the target cell. Such factors are commonly recognized at the plasma membrane by PRRs. A classical PRR is the family of Toll-like receptors (TLRs), which consists of 10–15 members in most mammalian species (Beutler et al. 2006; Palm and Medzhitov 2009). The pattern recognition by TLRs is subsequently transduced into proinflammatory signaling pathways that activate numerous transcription factors, including nuclear factor kappa B (NF-κB) and AP-1 (Tato and Hunter 2002; Chen and Greene 2004; Backert and Koenig 2005; Ghosh and Hayden 2008). Most of these signals are transported through dendritic cells (DCs), which deliver pathogen-derived antigens from the tissues to the secondary lymphoid organs and prime T cells by providing costimulation as well as appropriate

N. Tegtmeyer • S. Backert (✉)
University College Dublin, School of Biomolecular and Biomedical Sciences,
Science Center West, Belfield Campus, Dublin 4, Ireland
e-mail: steffen.backert@ucd.ie

M. Rohde
Helmholtz Centre for Infection Research, Braunschweig, Germany

O.A. Oyarzabal and S. Backert (eds.), *Microbial Food Safety: An Introduction*, Food Science Text Series,
DOI 10.1007/978-1-4614-1177-2_2,

cytokines and other mediators. These mediator molecules also activate macrophages, neutrophils, and mast cells, which are recruited to the site of infection and then eliminate a given pathogen. The functions of the above-mentioned immune and epithelial cells have been reviewed thoroughly (Hornef et al. 2002; Boquet and Lemichez 2003; Liston and McColl 2003; Monack et al. 2004; Backert and Koenig 2005; Pédron and Sansonetti 2008; Tsolis et al. 2008).

Despite the sophisticated immune system, some foodborne pathogens have coevolved with their hosts to overcome protective cell barriers and to establish short- or long-term infections. *Escherichia coli, Campylobacter, Salmonella, Listeria, Shigella,* and other bacterial species as well as some enteric viruses and parasites represent the most common foodborne pathogens (Fang et al. 1991; Salyers and Whitt 1994; Sougioultzis and Pothoulakis 2003; Eckmann and Kagnoff 2005; Lamps 2007). Importantly, infections with these microbes are one of the leading causes of morbidity and death of humans worldwide. Estimations by the World Health Organization (WHO) indicate that the human world population suffered from 4.5 billion incidences of diarrhea, causing 1.8 million deaths, in the year 2002 (WHO 2004). These infections are especially problematic among infants, young children, and immunocompromised persons, whereas the majority of enteric infections in healthy adults seem to be self-limiting. Those patients who undergo endoscopic biopsy often have chronic or debilitating diarrhea, systemic symptoms, or other significant clinical scenarios. Foodborne infections are estimated to affect one in four Americans each year. Most of these infections (67%) are caused by the noroviruses, but *Campylobacter* and nontyphoidal *Salmonellae* together account for about one fourth of the cases of illness in which a pathogen can be detected (Mao et al. 2003). Less common bacterial infections, such as with Shiga toxin-producing *E. coli*, *Shigella,* or *Listeria* species, cause fewer infections but are also important because of their severe complications or high mortality rate or both (Sougioultzis and Pothoulakis 2003). Upon ingestion, such pathogens commonly pass through the stomach in sufficient numbers to infect the small intestine or colon. To establish and maintain a successful infection in this compartment, microbial pathogens have evolved a variety of strategies to invade the host, avoid or resist the innate immune response, damage the cells, displace the normal flora, and multiply in specific and normally sterile regions. During evolution, several bacterial pathogens developed well-known weapons, such as protein toxins or effector proteins of a specialized type III secretion system (T3SS), which play major roles in these processes (Thanassi and Hultgren 2000; Burns et al. 2003; Alouf and Popoff 2005). Most, but not all, bacterial foodborne pathogens can be classified as so-called "invasive bacteria," which are able to induce their own uptake into gastric epithelial cells that are normally nonphagocytic. According to specific characteristics of the entry process, we distinguish between the "zipper" and "trigger" mechanisms, respectively (Cossart and Sansonetti 2004). The "zipper"mechanism is initiated by a bacterial surface protein (adhesin), which binds to a specific host cell receptor followed by internalization of the bacterium, whereas the "trigger" mechanism involves injected bacterial factors by T3SSs, which often mimic or hijack specific host cell factors to trigger the uptake process (Fig. 1). Typical examples and morphologic features are shown in respective scanning electron micrographs (Fig. 2, top). The invasion process commonly involves rearrangements of the cytoskeleton and/or the microtubule network, which facilitate bacterial uptake at the host cell membrane (Rottner et al. 2005). Other cross-talks alter the trafficking of cellular vesicles and induce changes in the intracellular compartment in which they reside, thus creating niches favorable to bacterial survival and growth. Finally, a variety of strategies also exist to deal with other components of the epithelial barrier, such as macrophages. Prophagocytic, antiphagocytic, and proapoptotic processes seem to be of particular importance in this context. This chapter describes the pathogenicity mechanisms and clinical presentations of selected bacterial foodborne pathogens as well as the associated diseases in humans.

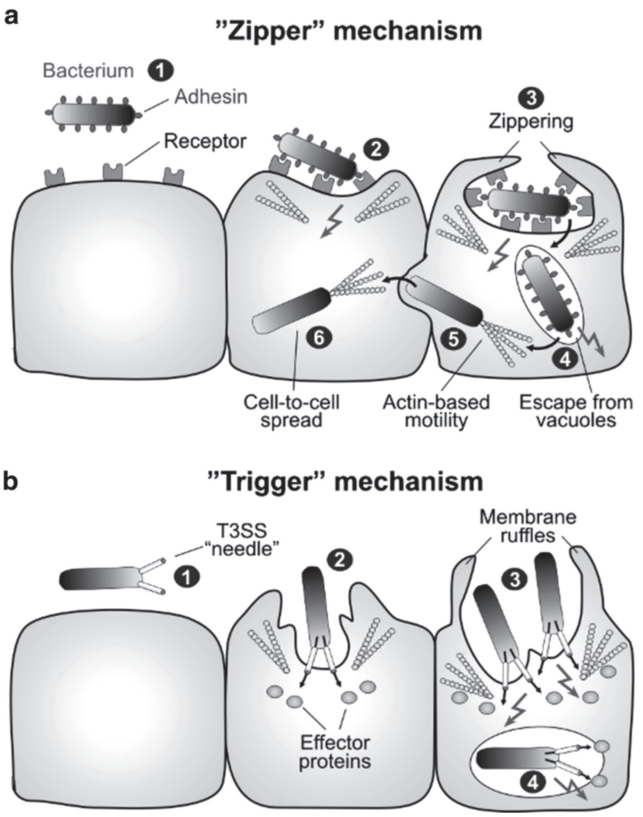


Fig. 1 Primary mechanisms of bacterial invasion into nonphagocytic host cells. Schematic representation of the two different routes of entry by intracellular bacterial pathogens. The pathogens induce their own uptake into target cells by subversion of host cell signaling pathways using the "zipper" and "trigger" mechanism, respectively. (**a**) Bacterial GI pathogens commonly colonize the gastric epithelium (step 1). The zipper mechanism of invasion involves the high-affinity binding of bacterial surface adhesins to their cognate receptors on mammalian cells (step 2), which is required to initiate cytoskeleton-mediated zippering of the host cell plasma membrane around the bacterium (step 3). Subsequently, the bacterium is internalized into a vacuole. Some bacteria developed strategies to survive within or to escape from this compartment (step 4). A well-known example of this invasion mechanism is *Listeria,* which escapes into the cyotsol and triggers actin-based motiliy (step 5) involved in the cell-to-cell spread of the bacteria (step 6). (**b**) The trigger mechanism is used by *Shigella* or *Salmonella* spp., which also colonize the gastric epithelium (step 1). These pathogens use a sophisticated type III secretion system (T3SS) and translocate multiple injected effector proteins into the host cell cytoplasm (step 2). These factors manipulate a variety of signaling events, including the activation of small Rho GTPases and actin-cytoskeletal reorganization, to induce membrane ruffling and subsequently bacterial uptake (step 3). As a consequence of this signaling, the bacteria are internalized into a vacuole (step 4), followed by the induction of different signaling pathways to establish infection including actin-based motility, entry into macrophages, and others. For more details, see text

2 *Salmonella* spp.

Salmonella spp. are Gram-negative bacilli that are members of the enterobacteriaceae family. Due to old nomenclature, the genus was originally split into three species: *Salmonella typhi* (the cause of typhoid fever), *Salmonella cholaesuis* (primarily a pathogen in swine), and *Salmonella enteritidis* (a common cause of diarrheal infections in humans and animals) (Salyers and Whitt 1994). Today it is commonly accepted that there are only two species: *Salmonella enterica* and *Salmonella*

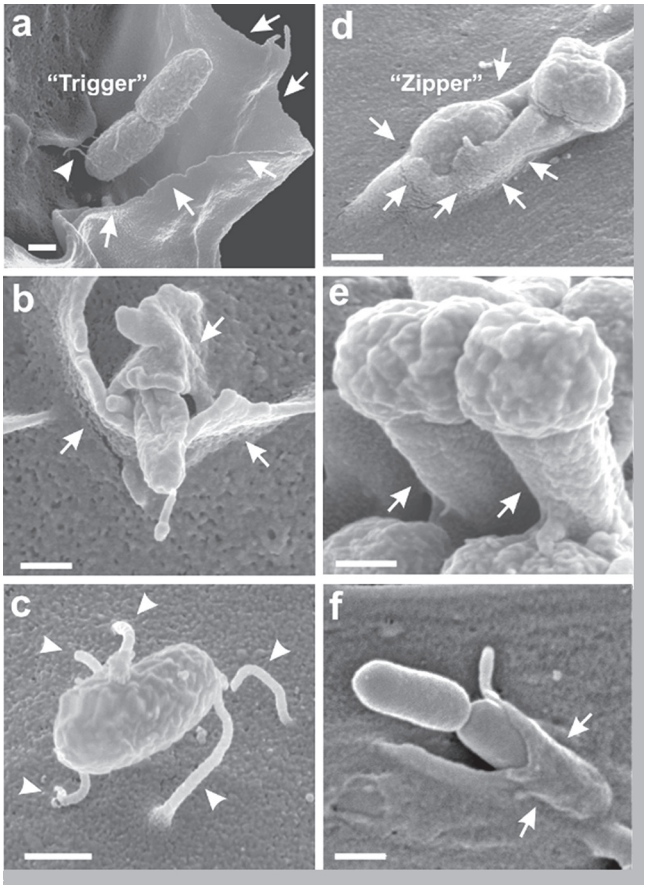


Fig. 2 Scanning electron micrographs of enteric bacterial pathogens interacting with epithelial cells in vitro. Selected examples include (**a**) *Salmonella enterica*, (**b**) *Campylobacter jejuni*, (**c**) *Shigella flexneri*, (**d**) *EHEC*, (**e**) *EPEC*, and (**f**) *Listeria monocytogenes*. The induction of membrane dynamics in cases of *Salmonella, Campylobacter,* and *Listeria* is indicated with arrows. *Salmonella* is a typical bacterium invading gastric epithelial cells by the trigger mechanism as indicated. The *arrows* for EHEC and *Listeria* indicate the tight engulfment of bacteria, which exhibit typical features of the zipper mechanism of invasion. EPEC induces classical actin-pedestal formation, as shown for two bacteria in panel (**e**) (*arrows*). *Arrowheads* indicate the presence of typical T3SS injection needles at the bacterial surface as observed for *Salmonella* and *Shigella*. Each *bar* represents 500 nm. For more details, see text

bongori (Boyd et al. 1996). *Salmonella enterica* was then classified into seven subspecies (I, II, IIIa, IIIb, IV, VI, and VII) containing more than 2,500 serovars according to the typing of different antigens. *Salmonella* spp. are able to infect numerous hosts and cause a broad spectrum of diseases in humans and animals, ranging from intestinal inflammation and gastroenteritis up to systemic infections and typhoid fever (Haraga et al. 2008; Tsolis et al. 2008). *Salmonella* spp. are the cause of sporadic food poisoning in developed countries but are especially prevalent in developing countries, where sanitation is poor and dairy and water supplies are contaminated with the bacterium. Animal food is also frequently contaminated with *Salmonella* spp. and may lead to infection in or colonization of domestic animals (Crump et al. 2002). Thus, most outbreaks in humans are associated with the consumption of contaminated eggs, egg products, poultry, and meat products (Mao et al. 2003). However, the pathogen is occasionally also detected in vegetables or fruits (Fang et al. 1991). The infective dose is moderate; approximately 10^2–10^3 ingested bacterial cells are sufficient to cause

disease. Historically, the discussion about *Salmonella* spp. is divided into typhoid and nontyphoid species. Patients with typhoid (enteric) fever, usually caused by *S. typhi*, suffer from fever persisting over several days, abdominal pain, and headache (Lamps 2007). Abdominal rash ("rose spots"), delirium, hepatosplenomegaly, and leukopenia are also fairly common. In the second or third week after infection, watery diarrhea begins and may progress to severe GI bleeding and even perforation. In contrast, nontyphoid *Salmonella* (e.g., *S. enteritidis, S. typhimurium, S. muenchen, S. anatum, S. paratyphi,* and *S. give*) generally cause a milder, often self-limited gastroenteritis with vomiting, nausea, fever, and watery diarrhea (McGovern and Slavutin 1979; Boyd 1985; Pegues et al. 1995; Kelly and Owen 1997; Kraus et al. 1999). In the United States, about 1.5 million cases of nontyphoid *Salmonella* infection are reported each year, and 95% of those cases are related to food (Mead et al. 1999). This accounts for about 10% of foodborne enteric diseases in the United States. Although most *Salmonella* infections in developed countries resolve by antibiotic treatment and supportive care, enteric infections may progress to septicemia and death, particularly in the elderly, very young children, or patients who are debilitated. Delayed treatment is associated with higher mortality (Pegues et al. 1995). During infection, any level of the GI tract may be involved, but the ileum, appendix, and right colon are preferentially affected. The bowel wall is enlarged, with raised nodules corresponding to hyperplasic Peyer's patches. Apthoid ulcers overlying Peyer's patches, linear ulcers, discoid ulcers, or full-thickness ulceration and necrosis often occur when infection continues (McGovern and Slavutin 1979; Boyd 1985; Pegues et al. 1995; Kelly and Owen 1997; Kraus et al. 1999). In infections with nontyphoid *Salmonella*, the overall findings are rather uncomplicated. The lesions can be focal, and occasionally the mucosa is grossly normal or only mildly hyperemic and edematous. The pathological features are most often those of acute self-limited colitis, although severe cases may have significant crypt distortion.

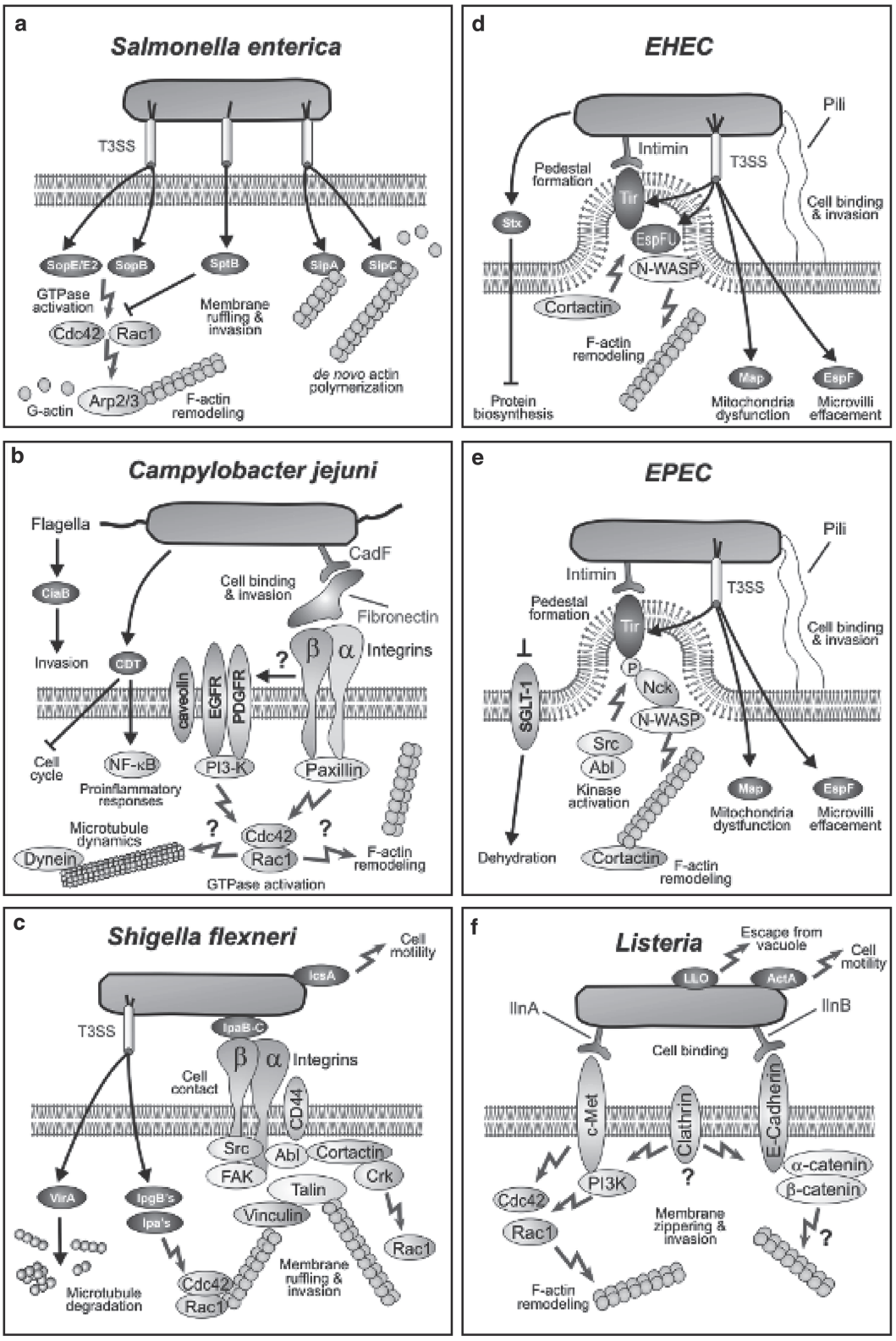
Salmonella infections are dominated by their profound capabilities to invade host cells by a trigger mechanism and to proliferate intracellularly (Fig. 2a). All known *Salmonella* are highly invasive, facultative intracellular pathogens that preferentially enter the microfold cells (M cells) overlying small intestinal Peyer's patches (Jepson and Clark 2001) although they can also enter and pass through epithelial cells of the intestinal tract in vivo and in cultured polarized epithelial cells in vitro. In addition, *Salmonella* can penetrate the intestinal epithelial barrier by uptake into DCs that protrude into the intestinal lumen (Niess et al. 2005). Once the bacteria have crossed the epithelium, they either are present inside the DCs or are quickly taken up by those cells or macrophages within the lamina propria. Once internalized, macrophages then transport the bacteria from the GI tract to the bloodstream, ultimately leading to a systemic infection. Early studies have shown that neutrophils begin to accumulate underneath the epithelium within several hours of infection, indicating a rapid immune response to infection (Takeuchi 1967). The molecular basis of *Salmonella's* virulence has been approached by screens for attenuated mutants, which lead to the identification and characterization of multiple genes involved in host cell entry and intracellular survival, replication, and spread. Many important virulence traits are clustered within the so-called *Salmonella* pathogenicity islands (SPIs) (Gal-Mor and Finlay 2006; Gerlach and Hensel 2007). In general, pathogenicity islands are large chromosomal regions that are present in pathogenic bacteria; they confer virulence properties and are absent in nonvirulent strains. They were first discovered in uropathogenic *E. coli* and since then have also been found in the chromosomes of many foodborne pathogens (Hacker et al. 2004; Gal-Mor and Finlay 2006). *Salmonella* strains can encode up to 17 SPIs (called SPI1–SPI17), and the availability of genome sequences of several *S. enterica* serotypes revealed serovar-specific SPIs (Gerlach and Hensel 2007). The best-characterized pathogenicity islands are SPI1 and SPI2. While SPI1 and SPI2 encode T3SSs with well-established roles in invasion (Patel and Galan 2005) and intracellular lifestyle (Kuhle and Hensel 2004), respectively, the role of many other putative SPIs still has to be elucidated. The events during the invasion of host cells have been studied in great detail both on the cellular and molecular levels. The two T3SSs (T3SS-1 and T3SS-2) can be described as multiprotein complexes spanning the inner and outer membranes of the Gram-negative bacterium to

form needlelike injection devices for effector proteins. These effector proteins modify signaling events of the host cell, leading to multiple responses, most notably rearrangements in the actin network (Patel and Galan 2005; Schlumberger and Hardt 2006). The best-characterized T3SS-1 effector proteins are SopE, SopE2, and SopB, which act in concert to activate small Rho GTPases Cdc42 and Rac1 in the host cell, by mimicking the action of eukaryotic G-nucleotide exchange factors either directly (SopE/E2) or indirectly by the generation of phosphatidyl inositol phosphates (PIPs). The activated GTP-bound forms of Cdc42 and Rac1 act synergistically to stimulate the conversion of host monomeric actin (G-actin) into filamentous actin (F-actin) by an actin-polymerization machinery, the Arp2/3 (actin-related proteins 2 and 3) complex. In addition, the effectors SipA and SipC interact directly with actin, thus inducing de novo polymerization and stabilization of F-actin. Another effector, SptB, counteracts this signaling as a GTPase-activating protein (GAP), thus inactivating Cdc42 and Rac1 (Patel and Galan 2005; Schlumberger and Hardt 2006). It has been proposed that SptB may downregulate GTPase functions once the bacteria have successfully entered the host cell. A simplified model of this signaling is shown in Fig. 3a. As a result of this complex manipulation scenario, local membrane ruffles are formed that ultimately trigger the engulfment and internalization of the bacteria, a process called *macropinocytosis*. Recent studies demonstrated that this invasion phenotype is also closely linked to trafficking along microtubule networks and the induction of intestinal inflammation by *Salmonella* (Hapfelmeier and Hardt 2005; Gerlach and Hensel 2007).

3 *Campylobacter jejuni*

Campylobacter infections of the human GI tract are recognized as the leading causes of enteric bacterial infection (Nachamkin et al. 2008), which may be responsible for as many as 400–500 million bacterial gastroenteritis cases worldwide each year (Friedman et al. 2000). Statistical data show that *Campylobacter* infections of humans cause a considerable use of medication and health service burden. In the United States, it has been estimated that *Campylobacter*-associated illnesses cost up to $6.2 billion per year (Forsythe 2000). Remarkably, in many studies in the United States and other industrialized countries, *Campylobacters* were found to cause diarrheal disease more than two to seven times as frequently as *Salmonella* and *Shigella* species or pathogenic *E. coli* (Allos 2001; Tam 2001). The genus of this Gram-negative bacterium currently comprises 17 species; two of them, *C. jejuni* and *C. coli*, are most frequently isolated from infected humans. *Campylobacter jejuni* is a typical zoonotic pathogen, as it can be found as part of the normal GI flora in numerous mammals and birds. Thus, *C. jejuni* may contaminate poultry, beef, veal, pork, water, and milk during food processing, as mainly transmitted by the fecal–oral route (Potturi-Venkata et al. 2007). The infective dose is relatively moderate: As few as 500 ingested bacteria can cause symptomatic disease. *Campylobacter* remain highly motile in the intestinal mucus, and their microaerobic nature promotes survival in the mucus layer. As a consequence of infection, the bacteria colonize the ileum and colon, where they can interfere with normal secretory and absorptive functions in the GI tract. This may cause certain intestinal diseases typically associated with fever, malaise, abdominal pain, and

Fig. 3 Bacterial attachment, injection of toxins, and effector proteins involved in signal transduction and host cell invasion. Schematic representation of the initial interactions between selected pathogens and host cell leading to injection of bacterial virulence factors or triggering signaling pathways, which eventually result in bacterial uptake. The signaling of selected pathogens is shown in a simplified manner. Major bacterial and host cell factors of infections with (**a**) *Salmonella*, (**b**) *Campylobacter*, (**c**) *Shigella*, (**d**) *EHEC*, (**e**) *EPEC,* and (**f**) *Listeria* are summarized. For details, see text


a
Salmonella enterica
T3SS
SopE/E2
SopB
SptB
SipA
SipC
GTPase activation
Cdc42
Rac1
Membrane ruffling & invasion
G-actin
Arp2/3
F-actin remodeling
de novo actin polymerization
b
Campylobacter jejuni
Flagella
CadF
CiaB
Cell binding & invasion
Fibronectin
Invasion
CDT
Integrins
caveolin
EGFR
PDGFR
Cell cycle
NF-κB
Proinflammatory responses
PI3-K
Paxillin
Microtubule dynamics
Dynein
Cdc42
Rac1
F-actin remodeling
GTPase activation
c
Shigella flexneri
Cell motility
IcsA
T3SS
IpaB-C
Integrins
Cell contact
CD44
Src
Abl
Cortactin
FAK
Crk
Talin
Vinculin
VirA
IpgB's
Ipa's
Rac1
Cdc42
Rac1
Membrane ruffling & invasion
Microtubule degradation
d
EHEC
Pili
Intimin
T3SS
Pedestal formation
Tir
Cell binding & invasion
Stx
EspFU
N-WASP
Cortactin
F-actin remodeling
Map
EspF
Protein biosynthesis
Mitochondria dysfunction
Microvilli effacement
e
EPEC
Pili
Intimin
T3SS
Pedestal formation
Tir
Cell binding & invasion
P
Nck
N-WASP
SGLT-1
Src
Abl
Kinase activation
Map
EspF
Mitochondria dysfunction
Microvilli effacement
Dehydration
Cortactin
F-actin remodeling
f
Listeria
Escape from vacuole
Cell motility
LLO
ActA
InlA
InlB
Cell binding
c-Met
Clathrin
E-Cadherin
α-catenin
β-catenin
PI3K
Cdc42
Rac1
Membrane zippering & invasion
F-actin remodeling

watery diarrhea that often contains blood and leukocytes (Wassenaar and Blaser 1999; Poly and Guerry 2008). Endoscopic findings are commonly nonspecific and include friable colonic mucosa with associated erythema and hemorrhage. Histological examination shows features of acute self-limited colitis, including a neutrophilic infiltrate in the lamina propria (Lamps 2007). Symptoms generally appear within 1–5 days of exposure and may last for 4–10 days. Most of these infections are self-limited as mentioned above, particularly in healthy persons, although relapse is common. In addition, individuals exposed to *C. jejuni* may develop postinfection sequelae, including Reiter's reactive arthritis or peripheral neuropathies such as Miller–Fisher and Guillain–Barré syndromes (Blaser and Engberg 2008). In contrast to the situation found in infected humans, *C. jejuni* is considered to be a commensal bacterium in chicken and other avian species. In particular, poultry is thought to be an important natural reservoir for *Campylobacters* that is supported by their perfect adaptive characteristics. For example, the optimal growth temperature of *C. jejuni* (42°C) is the same as that of the avian intestine. However, experimental infection of chicken with *C. jejuni* can also lead to diarrhea, but this is not typical. It appears that the human response to *C. jejuni* infection is more symptomatic than that of chicken. However, the molecular basis for the different outcomes of *C. jejuni* infection in humans versus chickens is not well understood and one of the pressing questions to be solved in the future.

Accumulating research work over the last few years has indicated that *C. jejuni* perturbs the normal absorptive capacity of the intestine by damaging epithelial cell function either directly by cell invasion and/or the production of toxin(s) or indirectly via the initiation of an inflammatory response (Ketley 1997; Wooldridge and Ketley 1997). The cytolethal distending toxin (CDT) is considered an important *C. jejuni* virulence factor that encodes a nuclease that damages DNA and causes cell-cycle arrest (Hickey et al. 2000; Lara-Tejero and Galan 2000). This toxin is essential for persistent infection of the GI tract and increases the severity of mucosal inflammation in susceptible mouse strains in vivo (Ge et al. 2008), and it was shown to play a role in *Campylobacter*-induced NF-κB activation and secretion of the proinflammatory chemokine interleukin-8 (IL-8) using polarized T84 human colonic epithelial cells as the in vitro model (Zheng et al. 2008). Early studies of intestinal biopsies from patients and in vitro infection of cultured human intestinal epithelial cells have demonstrated that *C. jejuni* is able to invade gut tissue cells (van Spreeuwel et al. 1985; Oelschlaeger et al. 1993; Wooldridge et al. 1996). Numerous studies demonstrated that *C. jejuni* encode a variety of adhesins, including CadF, JlpA, and PEB1 (Pei et al. 1998; Konkel et al. 2001; Poly and Guerry 2008). For example, CadF is a well-characterized bacterial outer membrane protein that binds fibronectin, an important extracellular matrix protein and bridging molecule, to integrin receptors (Moser et al. 1997). It has been described that host cell invasion of *C. jejuni* is one of the primary reasons for tissue damage in humans that involves a microtubule-dependent process (Oelschlaeger et al. 1993; Hu and Kopecko 1999). *C. jejuni* triggers membrane ruffling in cultured intestinal epithelial cells (INT-407) followed by invasion in a very specific manner, first with its tip followed by the end of the flagellum, and shows features of both the trigger and zipper mechanisms (Fig. 2b). Maximal adherence and invasion of INT-407 cells by *C. jejuni* require CadF and are accompanied with increased levels of tyrosine phosphorylation of host cell proteins (Biswas et al. 2004; Hu et al. 2006), such as the integrin-associated protein paxillin (Monteville et al. 2003). Interestingly, CadF is also involved in the activation of the small Rho GTPases Rac1 and Cdc42, which are required for the entry process (Krause-Gruszczynska et al. 2007). In addition, it has been shown that mutation of genes in the flagellar export system and ciaB (*Campylobacter* invasion antigen B), as well as deletion of the *kpsS* and *waaF* genes, which play a role in the biosynthesis of capsular polysaccharide and lipooligosaccharide, respectively, resulted in reduced bacterial adhesion and invasion in vitro, suggesting that these factors also play important roles in the host cell entry process (Karlyshev et al. 2000; Kanipes et al. 2004; Guerry 2007; Hu and Kopecko 2008; Larson et al. 2008). Host membrane caveolae, heterotrimeric G proteins, and certain protein kinases (EGF- and PDGF-receptor, phosphatidylinositol 3-kinase [PI3-K], and others) are also important for epithelial cell invasion of *C. jejuni* (Wooldridge

et al. 1996; Hu et al. 2006; Watson and Galán 2008). A model of this signaling is shown in Fig. 3b. Once internalized in epithelial cells, *C. jejuni* colocalize specifically with microtubules and dynein (Hu and Kopecko 1999) and are able to survive for extended periods of time and ultimately induce a cytotoxic response in vitro (Konkel et al. 1992; Day et al. 2000). The *C. jejuni*-containing intracellular vacuole deviates from the canonical endocytic pathway, and thus may avoid delivery into lysosomes and subsequent bacterial killing (Watson and Galán 2008). The intracellular survival of *C. jejuni* may enhance its ability to evade the host immune system, cause relapse of the acute infection, and establish long-term persistent infections (Lastovica 1996; Day et al. 2000). However, the molecular mechanisms of *C. jejuni* host cell invasion as well as the complex interplay of different bacterial factors are still not clear and are currently under investigation in many research labs.

4 *Shigella* spp.

Shigellosis is an acute GI disorder caused by infections with species of the genus *Shigella*. *Shigella* spp. are human-adapted Gram-negative pathogens, capable of colonizing the gastric epithelium. *Shigella dysenteriae* is the most common species isolated, although cases of *S. sonnei* and *S. flexneri* infection are increasingly being reported in several countries. These pathogens are generally ingested from fecally contaminated water, but person-to-person transmission is also possible. The infective dose is very low, with as few as 10–100 bacteria (Acheson and Keusch 1995). The symptoms of shigellosis range from mild watery diarrhea to severe inflammatory bacillary dysentery, as characterized by strong abdominal cramps, fever, and stools containing blood and mucus (Jennison and Verma 2004; Niyogi 2005). Infants and small children, homosexuals, and malnourished patients are most commonly affected by *Shigella* infections (Lamps 2007). About 5–15% of all diarrheal episodes worldwide can be attributed to an infection with *Shigella* spp., including 1.1 million fatal cases (Kotloff et al. 1999). The disease is usually self-limiting but may become life-threatening if the infected person is immunocompromised or if adequate medical care is not available. Thus, two thirds of all episodes and deaths occur in children under 5 years old, especially in the developing world. Like salmonellosis, the gross and microscopic features of shigellosis may mimic chronic idiopathic inflammatory bowel disease (Lamps 2007). Besides the mentioned symptoms, perforation and hemolytic-uremic syndrome have also been described. The large bowel is typically affected (often the left colon most severely), but the ileum may also be involved. The mucosa is hemorrhagic, and variably ulcerated, sometimes with pseudomembranous exudates (Speelman et al. 1984). Early shigellosis has features of acute self-limited colitis with cryptitis, crypt abscesses (often superficial), and ulceration (Lamps 2007). Apthoid ulcers similar to Crohn's disease are variably present. As the infection and disease continue, mucosal destruction arises by the infiltration of neutrophils and other inflammatory cells into the lamina propria. Marked architectural distortion can be commonly observed, leading to diagnostic confusion with chronic idiopathic inflammatory bowel disease (Mathan and Mathan 1991). The differential diagnosis of early shigellosis is primarily that of other enteric infections, particularly enteroinvasive *E. coli* and *Clostridium difficile*. Later on in the course of the disease, it may be extremely difficult to distinguish shigellosis from Crohn's disease or ulcerative colitis both endoscopically and histologically (Lamps 2007). Although a simple combination of oral rehydration and antibiotics commonly leads to the rapid resolution of these infections, the emergence of multidrug-resistant *Shigella* strains and a continuous high disease incidence imply that shigellosis is still an unsolved global health problem (Sansonetti 2006).

Shigella spp. express neither classical adherence factors on their surface nor flagella. Following ingestion, the bacteria rapidly move through the small intestine to the colon and rectum, where they cross the epithelial barrier through M cells. In contrast to *Salmonella*, *Shigella* preferentially enters M cells of the colorectal mucosa rather than the distal small intestine. The specific receptors that

account for this selectivity are unknown, but in vitro studies with cultured cells have demonstrated that β_1-integrins and CD44 receptor may play a role in the initial contact of *Shigella* with its host cell (Nhieu et al. 2005; Ogawa et al. 2008). In this way, *Shigella* breaches the epithelial barrier and immediately enters the macrophages that reside within the microfold-cell pocket. Once within the macrophages, the infecting bacteria disrupt the phagosomal membrane and disseminate from the phagosome into the macrophage cytoplasm, where they multiply and induce rapid apoptotic cell death in a caspase-1-dependent manner (Phalipon and Sansonetti 2007; Ogawa et al. 2008; Schroeder and Hilbi 2008). Bacteria released from dead macrophages can enter the surrounding enterocytes using a T3SS (Fig. 2c) that is encoded on a large virulence plasmid. T3SS-dependent injection of the Ipa effector proteins (IpaA-D) initiates actin-cytoskeletal and membrane remodeling processes that engulf the bacteria by macropinocytic ruffles (Nhieu et al. 2005). Exploring the process of how Ipa proteins alter the host cytoskeleton to induce the uptake process revealed that a complex of IpaB and IpaC binds the $\alpha_1\beta_5$-integrin receptor and the hyaluron receptor CD44 and induce actin rearrangements at the site of bacterial attachment (Watarai et al. 1996) (Fig. 3c). Earlier work demonstrated that IpaA binds to the focal adhesion protein vinculin and induces the recruitment of F-actin and the depolymerization of actin stress fibers (Bourdet-Sicard et al. 1999), but a recent study also showed that IpaA increases the activity of the small GTPase RhoA and decreases integrin affinity for extracellular matrix ligands by interfering with talin recruitment to the integrin's cytoplasmic tail (Demali et al. 2006). *Shigella* entry through the Ipa proteins further implicates the recruitment and activation of multiple other factors such as the tyrosine kinases FAK and Src, cortactin, Crk, Rac or Cdc42, which mediate massive actin polymerization in the vicinity of the original cup via the Arp2/3-complex (Burton et al. 2003; Bougneres et al. 2004). In addition, a new class of G-nucleotide exchange effector proteins has recently been discovered in *Shigella* that is also involved in invasion. Remarkably, IpgB1 functions to activate Rac1, and IpgB2 stimulates cellular responses activating RhoA (Huang et al. 2009). Using this multifactorial mechanism, *Shigella* invades the enterocytes. As soon as a bacterium is surrounded by a membrane vacuole within these cells, it disrupts the vacuolar membrane and escapes into the cytoplasm. *Shigella* movement is then triggered by the bacterial surface protein IcsA. IcsA has a high affinity to a major regulator of the actin-polymerization machinery, N-WASP (neuronal Wiskott–Aldrich syndrome protein), which recruits and activates the Arp2/3-complex (Phalipon and Sansonetti 2007; Ogawa et al. 2008; Schroeder and Hilbi 2008). The formation of actin tails pushes *S. flexneri* through the host cell cytoplasm, a process that is enhanced by secreting the T3SS-effector protein VirA, which is a protease of α-tubulin that destroys the surrounding microtubules (Yoshida et al. 2006). *Shigella* can multiply in the epithelial cell cytoplasm and move both intra- and intercellularly, and so infection of the intestinal epithelium by *Shigella* also elicits strong inflammatory and other responses (Phalipon and Sansonetti 2007; Ogawa et al. 2008; Schroeder and Hilbi 2008).

5 *Escherichia coli*

The famous laboratory strain K-12 and other nonpathogenic *Escherichia coli* isolates are common members in the normal GI microbial community. However, during evolution, some of these *E. coli* strains accumulated pathogenicity islands and other virulence elements in their genomes by horizontal DNA-transfer events (Hacker et al. 2004). Important examples of this category are enterohemorrhagic *E. coli* (EHEC) and enteropathogenic *E. coli* (EPEC), two emerging foodborne pathogens. One hallmark of EHEC and EPEC infections is their ability to colonize the gut mucosa and produce characteristic attaching and effacing lesions (A/E lesions), resulting in diarrheal and other diseases. A/E lesions are characterized by effacement of the intestinal brush border microvilli and close attachment of the bacterium to the enterocyte plasma membrane, leading to the formation of a

characteristic pedestal-shaped, localized membrane protrusion that can extend up to 10 μm outwards from the cell periphery (Knutton et al. 1987). One of the most common strains of EHEC is O157:H7. This pathogen gained worldwide attention in 1993 when a massive outbreak in the United States was linked to contaminated hamburgers. EHEC O157:H7 is still the most relevant serotype in such foodborne outbreaks; however, an increased incidence of infections caused by non-O157:H7 was observed in other countries (Gerber et al. 2002). Since cattle have been shown to be a major reservoir of EHEC, raw food such as ground beef and milk are the most common sources of infection. A variety of other food types, such as fermented meat products, raw salad vegetable products, unpasteurized fresh fruit juice, and water, as well as person-to-person contact have also been linked to EHEC outbreaks (Olsen et al. 2002; Mao et al. 2003). Although pathogenic *E. coli* are not particularly resistant to harsh environmental conditions, some reports indicate that EHEC can tolerate a wide range of pH and water conditions as well as low temperature, indicating that there is considerable potential for these organisms to survive in and on food (Chikthimmah and Knabel 2001; Hancock et al. 2001). Because an infective dose of EHEC and EPEC is low (<100 bacteria), even the minimal contamination of food is of concern. When it comes to an infection, the bacteria can induce diarrhea, which is usually bloody, with severe abdominal cramps and mild or no fever. However, nonbloody, watery diarrhea may also occur in some cases. Only one third of infected persons have fecal leukocytes. Children and the elderly are at particular risk of serious illness, including the hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura (Griffin et al. 1990; Kelly et al. 1990; Lamps 2007). Endoscopically, patients may have bowel edema, erosions, ulcers, and hemorrhage, and the right colon is usually more severely affected. The edema may be so marked as to cause obstruction, and surgical resection may be required to relieve this or to control bleeding. The lamina propria and submucosa contain marked edema and hemorrhage, with associated mucosal acute inflammation, cryptitis, crypt abscesses, ulceration, and necrosis. Crypt withering, such as that seen in other causes of ischemia, is often seen as well. Microthrombi may be observed within small vessels, and pseudomembranes are occasionally present (Griffin et al. 1990; Kelly et al. 1990; Lamps 2007).

The pathogenicity potential of EHEC is closely connected to the production of Shiga toxins (Stx1 and/or Stx2), which are related to the exotoxin of *Shigella dysenteriae* serotype-1 (Cleary 2004; Scheiring et al. 2008). These toxins act as inhibitors of protein biosynthesis and have profound effects on the signal transduction and immunological response in eukaryotic cells. In addition to the secretion of Shiga toxins, the production of EHEC hemolysin, serine protease, enterotoxin (EAST), catalase, pili, and other factors have also been implicated in the pathogenesis (Donnenberg and Whittam 2001; Vallance et al. 2002; Mao et al. 2003). In particular, EHEC O157:H7 produces long bundles of polar type-4 pili that mediate binding of the bacteria to epithelial cells and eventually cause bacterial invasion (Xicohtencatl-Cortes et al. 2009). Indeed, we could show that at least some EHEC bacteria can enter epithelial cells in vitro using a zipper-like mechanism (our unpublished data) (Fig. 2d). In addition, A/E lesions caused by both EHEC and EPEC in vivo are dependent on a T3SS that injects numerous effector proteins directly into host cells. The best-described effectors are encoded on the locus of enterocyte effacement (LEE) pathogenicity islands and display high levels of multifunctionality. The recent completion of the EPEC genome sequence suggests that there are at least 21 injected proteins (Dean and Kenny 2009). This T3SS acts together with the outer membrane adhesion molecule intimin to trigger actin-pedestal formation (Fig. 2e). Each of the two pathogens injects its own receptor called Tir (translocated intimin receptor), a T3SS effector molecule. Translocated Tir then inserts into the host cell plasma membranes, forming a hairpin loop, and interacts with intimin, both of which are required to trigger the actinpolymerization into focused pedestals just beneath attached bacteria. Despite similarities between the Tir molecules and the host components that associate with pedestals, EPEC-Tir and EHEC-Tir are not functionally interchangeable. Injected EPEC-Tir is tyrosine-phosphorylated by host cell kinases (mainly by members of the Src, Tec, and Abl kinase families) to mediate the binding of Nck, a host adaptor protein implicated

in actin signaling. In contrast, EHEC-Tir cannot be phosphorylated, and pedestals are formed independently of Nck but require translocation of another bacterial factor (TccP/EspF[U]) in addition to Tir to trigger actin signaling (Campellone and Leong 2003; Backert and Selbach 2005; Hayward et al. 2006; Frankel and Phillips 2008; Dean and Kenny 2009). Otherwise, EPEC- and EHEC-induced pedestals are very similar. They are composed of F-actin and a variety of signaling factors, including actin-regulatory proteins such as N-WASP, Arp2/3, cortactin, and others, as well as numerous adaptor and focal adhesion proteins (Fig. 3d, e). However, the physiological significance of pedestal formation in vivo is unknown. One could predict that such a tight interaction between the bacterium and the host cell should severely impair the ingestion of bacteria by immune cells, which could be a possible strategy (albeit unique). Interestingly, EPEC directly inhibits phagocytosis, but the T3SS effectors triggering this antiphagocytic activity are unknown (Celli and Finlay 2002). In the light of these findings, it is remarkable that EPEC is able to invade nonphagocytic epithelial cells using Map and Tir effectors by synergistic mechanisms (Jepson et al. 2003). Particularly, the Map effector protein has two distinct functions within host cells: targeting mitochondria to elicit dysfunction and mediating Cdc42-dependent filopodia formation involved in host entry (Jepson et al. 2003). The promotion of EPEC invasion by Tir appears to involve interaction with intimin but is independent of pedestal formation. Finally, the phenomenon of effacement by EPEC has been shown to require the cooperative action of three injected effectors (Map, EspF, and Tir) as well as intimin and leads to the retention (not the release) of the detached microvilli structures (Dean et al. 2006). As a consequence of this, EPEC rapidly inactivates the sodium-d-glucose cotransporter (SGLT-1), which provides a plausible explanation for the rapid onset of severe watery diarrhea, given the crucial role of SGLT-1 in the daily uptake of approximately 6 L of fluids from the normal intestine (Dean et al. 2006). Given the multitude of EHEC and EPEC effectors, there are many more signaling pathways induced by these pathogens, and they need to be studied in more detail in future research (Campellone and Leong 2003; Hayward et al. 2006; Frankel and Phillips 2008; Dean and Kenny 2009).

6 *Listeria monocytogenes*

Listeriosis is an animal-borne and foodborne human disease that is caused by pathogenic bacteria of the genus *Listeria.* There are seven species within this genus, including *L. monocytogenes*, *L. ivanovii*, *L. innocua*, *L. seeligeri*, *L. welshimeri*, *L. grayii,* and *L. murrayi*. However, only two of them are pathogenic: *Listeria monocytogenes* can cause disease in both humans and animals, and *L. ivanovii* causes disease predominantly in sheep (Mead et al. 1999; Roberts and Wiedmann 2003; Mao et al. 2003). Although relatively uncommon, *L. monocytogenes* infections are almost exclusively foodborne (99%) and are mainly caused by the consumption of contaminated food products (Mead et al. 1999). *Listeria* species are Gram-positive, nonspore-forming rods that are commonly observed in the environment where they developed highly adaptive characteristics during their evolution. *Listeria* species can grow over a wide range of temperatures (1–45°C) and pHs (4.3–9.6), and even at salt concentrations of up to 10% (Seeliger and Jones 1986; Johnson et al. 1988). This ability to survive and multiply under conditions frequently used for food preservation makes *Listeria* particularly problematic to our food industry. Thus, *L. monocytogenes* is a common food contaminant and a major cause of food recalls due to bacterial contamination and outbreaks, particularly in developed countries and possibly worldwide (Mead et al. 1999; Farber and Peterkin 1991). These outbreaks are commonly linked to a wide variety of foods, including refrigerated foods, ready-to-eat foods (e.g., hot dogs, cold cuts), fresh vegetables, apple cider, and dairy products such as cheese (Hitchins and Whiting 2001; Asperger et al. 2001). The frequent occurrence of *L. monocytogenes* in food, coupled with a high mortality rate of 20–30% in those developing listeriosis, make these infections a serious

public health concern (Mead et al. 1999; Farber and Peterkin 1991). *Listeria monocytogenes* causes *sepsis* and *meningitis*, usually affecting specific high-risk subgroups of the population such as the elderly, the immunocompromised, and fetuses. These diseases are due to *Listeria's* capacity to breach three host barriers during infection: the intestinal, the placental, and the blood–brain barriers. However, infection with *L. monocytogenes* in otherwise healthy individuals commonly causes self-limited gastroenteritis (Wing and Gregory 2002; Doganay 2003; Hof 2004). Listeriosis in animals, furthermore, represents not only a financial burden for the livestock industry but also a possible link between *Listeria* in the environment and human disease.

Listeria monocytogenes has evolved highly sophisticated strategies to infect its mammalian host and to survive as a facultative intracellular pathogen (Tilney and Portnoy 1989; Wing and Gregory 2002; Hamon et al. 2006; Dussurget 2008). At the cellular level, *Listeria* enters by a zipper mechanism characterized by a tight apposition of the plasma membrane around the entering bacteria (Fig. 2f). Two remarkable surface proteins, called internalin A and B (InlA and InlB), are crucial for mediating bacterial entry into mammalian cells. These adhesins interact with host cell transmembrane receptors, E-cadherin, and the hepatocyte growth factor receptor (c-Met), respectively (Fig. 3f). These interactions initiate a series of signaling events involving PI3-K, Cdc42, Rac, and possibly catenins and other factors, leading to actin polymerization, membrane invagination, and bacterial internalization. Investigations into InlA- and InlB-mediated entries have demonstrated that *Listeria* fully usurps the host cell cytoskeletal machinery (Rottner et al. 2005; Hamon et al. 2006; Bosse et al. 2007; Dussurget 2008). Moreover, recent studies have highlighted a role for the endocytic protein clathrin in *Listeria* InlB-mediated actin polymerization and entry, revealing a new role for this factor in bacteria-induced host entry. Furthermore, comparative studies have demonstrated that the clathrin-mediated endocytosis machinery is also used in the InlA–E-cadherin pathway and for the invasion of other bacteria that enter by the zipper mechanism (Cossart and Veiga 2008). In contrast, the clathrin-mediated endocytic machinery is not used by bacteria such as *Salmonella* that enter by the trigger mechanism (Cossart and Veiga 2008). However, the internalization process of *Listeria* results in the formation of intracellular vacuoles carrying the bacteria. A third bacterial protein, listeriolysin-O, rapidly lyses these vacuoles, releasing *Listeria* into the cytosol of the infected cell, where the bacterium can replicate. Certain phospholipases, which are secreted by *Listeria*, also play a role in this context (Hamon et al. 2006; Dussurget 2008). Similar to IcsA in *Shigella*, a fourth *Listeria* protein called ActA triggers a very efficient actin-polymerization process at the posterior pole of the bacterium that pushes the bacterium forward and allows active movement within the infected cell (Rottner et al. 2005). From time to time, intracellular bacteria may contact the membrane that allows *Listeria* to invade neighboring cells (Tilney and Portnoy 1989). This direct cell-to-cell spread allows bacteria to disseminate in the infected organism. Interestingly, most of the virulence proteins that have been identified in *L. monocytogenes* are under tight control of the transcriptional regulator PrfA, which is regulated by environmental conditions (Johansson et al. 2002). Finally, it has to be mentioned that *Listeria* infection induces a variety of other host cell signaling events and has also been established as a very useful model system to study host T cell responses (Pamer 2004).

7 Summary

Foodborne infections are a large health and economic problem worldwide. The WHO calculated that there were about 4.5 billion incidences of diarrhea that caused 1.8 million deaths in the year 2002. Approximately 99% of the cases occurred in developing countries, where poor hygiene and limited access to clean drinking water promote the spread of enteric diseases. Malnutrition and the lack of appropriate medical intervention contribute to the high mortality rate, especially for young children, the elderly, and immunocompromised persons. Infections with a large number of bacterial, viral, and

parasitic pathogens have been implicated in these diseases. In this chapter we focused on foodborne bacterial pathogens and summarized important strategies and signaling mechanisms that result in colonization of the GI epithelium, where the bacteria can multiply and spread. We highlighted the strategies of important GI pathogens, with an emphasis on species such as *Salmonella, Campylobacter, Shigella, Escherichia,* and *Listeria* that represent paradigms of host–pathogen interactions. However, there are a variety of other foodborne bacteria, such as *Yersinia* or *Clostridium,* that are discussed elsewhere. Recognition of the genetic and functional bases of bacterial foodborne pathogenicity and analyses of cross-talks on the level of molecular signaling cascades between these pathogens and their mammalian target cells have illuminated the diversity but also common strategies of these interactions. Entire genome sequences are now available for many microbes that cause foodborne diseases, and the development of themed and whole-genome DNA microarrays as well as improved proteomics techniques might provide effective new tools for rapidly detecting and identifying such organisms, assessing their biological diversity, and understanding their ability to trigger certain diseases. However, since there are also substantial interactions between commensal and pathogenic bacteria, more information about individual members constituting the normal gut flora is also needed. Collective genomes (microbiome) of the human microbiota have now become important targets to be studied in both microbiology and human biology. The generated data will be accumulated and evaluated in future studies, including the International Human Microbiome Project. This information also provides fresh insights into the metabolic capacity and versatility of microbes, for example, specific metabolic pathways that might contribute to the growth and survival of pathogens in a range of niches, such as food-processing environments and the human host. Different concepts are emerging about how pathogens function, both within foods and in interactions with the host. The future should bring the practical benefits of genome sequencing and molecular infection research to the field of microbial food safety, including new strategies and tools for the identification and control of emerging foodborne pathogens.

References

Acheson, D.W.K., and G.T. Keusch. 1995. *Shigella* and enteroinvasive *E. coli*. In *Infections of the gastrointestinal tract*, ed. M.J. Blaser, P.D. Smith, and J.I. Ravdin, 763–784. New York: Raven.

Allos, B.M. 2001. *Campylobacter jejuni* infections: update on emerging issues and trends. *Clinical Infectious Diseases* 32: 1201–1206.

Alouf, J.E., and M.R. Popoff. 2005. *The comprehensive sourcebook of bacterial protein toxins*, 3rd ed. London: Academic.

Asperger, H., M. Wagner, and E. Brandl. 2001. An approach towards public health and food-borne human listeriosis—The Austrian *Listeria* monitoring. *Berliner und Münchener Tierärztliche Wochenschrift* 114: 446–452.

Backert, S., and W. Koenig. 2005. Interplay of bacterial toxins with host defence: molecular mechanisms of immunomodulatory signalling. *International Journal of Medical Microbiology* 295: 519–530.

Backert, S., and M. Selbach. 2005. Tyrosine-phosphorylated bacterial effector proteins: the enemies within. *Trends in Microbiology* 13: 476–484.

Beutler, B., Z. Jiang, P. Georgel, K. Crozat, B. Croker, S. Rutschmann, X. Du, and K. Hoebe. 2006. Genetic analysis of host resistance: toll-like receptor signaling and immunity at large. *Annual Review of Immunology* 24: 353–389.

Biswas, D., H. Niwa, and K. Itoh. 2004. Infection with *Campylobacter jejuni* induces tyrosine-phosphorylated proteins into INT-407 cells. *Microbiology and Immunology* 48: 221–228.

Blaser, M.J., and J. Engberg. 2008. Clinical sspects of *Campylobacter jejuni* and *Campylobacter coli* infections. In *Campylobacter*, ed. I. Nachamkin, C.M. Szymanski, and M.J. Blaser, 99–121. Washington, DC: ASM Press.

Boquet, P., and E. Lemichez. 2003. Bacterial virulence factors targeting Rho GTPases: parasitism or symbiosis? *Trends in Cell Biology* 13: 238–246.

Bosse, T., J. Ehinger, A. Czuchra, S. Benesch, A. Steffen, X. Wu, K. Schloen, H.H. Niemann, G. Scita, T.E. Stradal, C. Brakebusch, and K. Rottner. 2007. Cdc42 and phosphoinositide 3-kinase drive Rac-mediated actin polymerization downstream of c-Met in distinct and common pathways. *Molecular and Cellular Biology* 27: 6615–6628.

Bougneres, L., S.E. Girardin, S.A. Weed, A.V. Karginov, J.C. Olivo-Marin, J.T. Parsons, P.J. Sansonetti, and G.T. Van Nhieu. 2004. Cortactin and Crk cooperate to trigger actin polymerization during *Shigella* invasion of epithelial cells. *The Journal of Cell Biology* 166: 225–235.

Bourdet-Sicard, R., M. Rudiger, B.M. Jockusch, P. Gounon, P.J. Sansonetti, and G.T. Nhieu. 1999. Binding of the *Shigella* protein IpaA to vinculin induces F-actin depolymerization. *The EMBO Journal* 18: 5853–5862.

Boyd, J.F. 1985. Pathology of the alimentary tract in *Salmonella typhimurium* food poisoning. *Gut* 26: 935–944.

Boyd, E.F., F.S. Wang, T.S. Whittam, and R.K. Selander. 1996. Molecular genetic relationships of the *salmonellae*. *Applied and Environmental Microbiology* 62: 804–808.

Burns, D., J.T. Barbieri, B.H. Iglewski, and R. Rappuoli. 2003. *Bacterial protein toxins*. Washington, DC: ASM Press.

Burton, E.A., R. Plattner, and A.M. Pendergast. 2003. Abl tyrosine kinases are required for infection by *Shigella flexneri*. *The EMBO Journal* 22: 5471–5479.

Campellone, K.G., and J.M. Leong. 2003. Tails of two Tirs: actin pedestal formation by enteropathogenic *E. coli* and enterohemorrhagic *E. coli* O157:H7. *Current Opinion in Microbiology* 6: 82–90.

Celli, J., and B.B. Finlay. 2002. Bacterial avoidance of phagocytosis. *Trends in Microbiology* 10: 232–237.

Chen, L.F., and W.C. Greene. 2004. Shaping the nuclear action of NF-κB. *Nature Reviews Molecular Cell Biology* 5: 392–401.

Chikthimmah, N., and S.J. Knabel. 2001. Survival of *Escherichia coli* O157:H7, *Salmonella typhimurium* and *Listeria monocytogenes* in and on vacuum packaged Lebanon bologna stored at 3.6 and 13.0 degrees C. *Journal of Food Protection* 64: 958–963.

Cleary, T.G. 2004. The role of Shiga-toxin-producing *Escherichia coli* in hemorrhagic colitis and hemolytic uremic syndrome. *Seminars in Pediatric Infectious Diseases* 15: 260–265.

Cossart, P., and P.J. Sansonetti. 2004. Bacterial invasion: the paradigms of enteroinvasive pathogens. *Science* 304: 242–248.

Cossart, P., and E. Veiga. 2008. Non-classical use of clathrin during bacterial infections. *Journal of Microscopy* 231: 524–528.

Crump, J.A., P.M. Griffin, and F.J. Angulo. 2002. Bacterial contamination of animal feed and its relationship to human food-borne illness. *Clinical Infectious Diseases* 35: 859–865.

Day Jr., W.A., J.L. Sajecki, T.M. Pitts, and L.A. Joens. 2000. Role of catalase in *Campylobacter jejuni* intracellular survival. *Infection and Immunity* 68: 6337–6345.

Dean, P., and B. Kenny. 2009. The effector repertoire of enteropathogenic *E. coli*: ganging up on the host cell. *Current Opinion in Microbiology* 12: 101–109.

Dean, P., M. Maresca, S. Schüller, A.D. Phillips, and B. Kenny. 2006. Potent diarrheagenic mechanism mediated by the cooperative action of three enteropathogenic *Escherichia coli*-injected effector proteins. *Proceedings of the National Academy of Sciences of the United States of America* 103: 1876–1881.

Demali, K.A., A.L. Jue, and K. Burridge. 2006. IpaA targets beta1 integrins and rho to promote actin cytoskeleton rearrangements necessary for *Shigella* entry. *Journal of Biological Chemistry* 281: 39534–39541.

Doganay, M. 2003. Listeriosis: clinical presentation. *FEMS Immunology and Medical Microbiology* 35: 173–175.

Donnenberg, M.S., and T.S. Whittam. 2001. Pathogenesis and evolution of virulence in enteropathogenic and enterohemorrhagic *Escherichia coli*. *The Journal of Clinical Investigation* 107: 539–548.

Dussurget, O. 2008. New insights into determinants of *Listeria monocytogenes* virulence. *International Review of Cell and Molecular Biology* 270: 1–38.

Eckburg, P.B., E.M. Bik, C.N. Bernstein, E. Purdom, L. Dethlefsen, M. Sargent, S.R. Gill, K.E. Nelson, and D.A. Relman. 2005. Diversity of the human intestinal microbial flora. *Science* 308: 1635–1638.

Eckmann, L., and M.F. Kagnoff. 2005. Intestinal mucosal responses to microbial infection. *Springer Seminars in Immunopathology* 27: 181–196.

Fang, G., V. Araujo, and R.L. Guerrant. 1991. Enteric infections associated with exposure to animals or animal products. *Infectious Disease Clinics of North America* 5: 681–701.

Farber, J.M., and P.I. Peterkin. 1991. *Listeria monocytogenes*, a food-borne pathogen. *Microbiological Reviews* 55: 476–511.

Forsythe, S.J. 2000. Food poisoning microorganisms. In *The microbiology of safe food*, ed. S.J. Forsythe, 87–148. Abingdon: Blackwell Science.

Frankel, G., and A.D. Phillips. 2008. Attaching effacing *Escherichia coli* and paradigms of Tir-triggered actin polymerization: getting off the pedestal. *Cellular Microbiology* 10: 549–556.

Friedman, C.R., J. Neimann, H.C. Wegener, and R.V. Tauxe. 2000. Epidemiology of *Campylobacter jejuni* infections in the United States and other industrialized nations. In *Campylobacter*, ed. I. Nachamkin and M.J. Blaser, 121–138. Washington, DC: ASM Press.

Gal-Mor, O., and B.B. Finlay. 2006. Pathogenicity islands: a molecular toolbox for bacterial virulence. *Cellular Microbiology* 8: 1707–1719.

Ge, Z., D.B. Schauer, and J.G. Fox. 2008. *In vivo* virulence properties of bacterial cytolethal-distending toxin. *Cellular Microbiology* 10: 1599–1607.

Gerber, A., H. Karch, F. Allerberger, H.M. Verweyen, and L.B. Zimmerhackl. 2002. Clinical course and the role of shiga toxin-producing Escherichia coli infection in the hemolytic-uremic syndrome in pediatric patients, 1997–2000, in Germany and Austria: a prospective study. *The Journal of Infectious Diseases* 186: 493–500.

Gerlach, R.G., and M. Hensel. 2007. *Salmonella* pathogenicity islands in host specificity, host pathogen-interactions and antibiotics resistance of *Salmonella enteric*a. *Berliner und Münchener Tierärztliche Wochenschrift* 120: 317–327.

Ghosh, S., and M.S. Hayden. 2008. New regulators of NF-kappaB in inflammation. *Nature Reviews Immunology* 8: 837–848.

Griffin, P.M., L.C. Olmstead, and R.E. Petras. 1990. *Escherichia coli* 0157:H7-associated colitis: a clinical and histological study of 11 cases. *Gastroenterology* 99: 142–149.

Guerry, P. 2007. *Campylobacter* flagella: not just for motility. *Trends in Microbiology* 15: 456–461.

Hacker, J., B. Hochhut, B. Middendorf, G. Schneider, C. Buchrieser, G. Gottschalk, and U. Dobrindt. 2004. Pathogenomics of mobile genetic elements of toxigenic bacteria. *International Journal of Medical Microbiology* 293: 453–461.

Hamon, M., H. Bierne, and P. Cossart. 2006. *Listeria monocytogenes*: a multifaceted model. *Nature Reviews Microbiology* 4: 423–434.

Hancock, D., T. Besser, J. Lejeune, M. Davis, and D. Rice. 2001. The control of VTEC in the animal reservoir. *International Journal of Food Microbiology* 66: 71–78.

Hapfelmeier, S., and W.D. Hardt. 2005. A mouse model for *S. typhimurium*-induced enterocolitis. *Trends in Microbiology* 13: 497–503.

Haraga, A., M.B. Ohlson, and S.I. Miller. 2008. *Salmonellae* interplay with host cells. *Nature Reviews Microbiology* 6: 53–66.

Hayward, R.D., J.M. Leong, V. Koronakis, and K.G. Campellone. 2006. Exploiting pathogenic *Escherichia coli* to model transmembrane receptor signalling. *Nature Reviews Microbiology* 4: 358–370.

Hickey, T.E., A.L. McVeigh, D.A. Scott, R.E. Michietutti, A. Bixby, S.A. Carroll, A.L. Bourgeois, and P. Guerry. 2000. *Campylobacter jejuni* cytolethal distending toxin mediates release of interleukin-8 from intestinal epithelial cells. *Infection and Immunity* 68: 6535–6541.

Hitchins, A.D., and R.C. Whiting. 2001. Food-borne *Listeria monocytogenes* risk assessment. *Food Additives and Contaminants* 18: 1108–1117.

Hof, H. 2004. An update on the medical management of listeriosis. *Expert Opinion on Pharmacotherapy* 5: 1727–1735.

Hooper, L.V., and J.I. Gordon. 2001. Commensal host-bacterial relationships in the gut. *Science* 292: 1115–1118.

Hornef, M.W., M.J. Wick, M. Rhen, and S. Normark. 2002. Bacterial strategies for overcoming host innate and adaptive immune responses. *Nature Immunology* 3: 1033–1040.

Hu, L., and D.J. Kopecko. 1999. *Campylobacter jejuni* 81–176 associates with microtubules and dynein during invasion of human intestinal cells. *Infection and Immunity* 67: 4171–4182.

Hu, L., and D.J. Kopecko. 2008. Cell biology of human host cell entry by *Campylobacter jejuni*. In *Campylobacter*, ed. I. Nachamkin, C.M. Szymanski, and M.J. Blaser, 297–313. Washington, DC: ASM Press.

Hu, L., J.P. McDaniel, and D.J. Kopecko. 2006. Signal transduction events involved in human epithelial cell invasion by *Campylobacter jejuni* 81–176. *Microbial Pathogenesis* 40: 91–100.

Huang, Z., S.E. Sutton, A.J. Wallenfang, R.C. Orchard, X. Wu, Y. Feng, J. Chai, and N.M. Alto. 2009. Structural insights into host GTPase isoform selection by a family of bacterial GEF mimics. *Nature Structural and Molecular Biology* 16: 853–860.

Jennison, A.V., and N.K. Verma. 2004. *Shigella flexneri* infection: pathogenesis and vaccine development. *FEMS Microbiology Reviews* 28: 43–58.

Jepson, M.A., and M.A. Clark. 2001. The role of M cells in *Salmonella* infection. *Microbes and Infection* 3: 1183–1190.

Jepson, M.A., S. Pellegrin, L. Peto, D.N. Banbury, A.D. Leard, H. Mellor, and B. Kenny. 2003. Synergistic roles for the Map and Tir effector molecules in mediating uptake of enteropathogenic *Escherichia coli* (EPEC) into non-phagocytic cells. *Cellular Microbiology* 5: 773–783.

Johansson, J., P. Mandin, A. Renzoni, C. Chiaruttini, M. Springer, and P. Cossart. 2002. An RNA thermosensor controls expression of virulence genes in *Listeria monocytogenes*. *Cell* 110: 551–561.

Johnson, J.L., M.P. Doyle, R.G. Cassens, and J.L. Schoeni. 1998. Fate of *Listeria monocytogenes* in tissues of experimentally infected cattle and in hard salami. *Applied and Environmental Microbiology* 54: 497–501.

Kanipes, M.I., L.C. Holder, A.T. Corcoran, A.P. Moran, and P. Guerry. 2004. A deep-rough mutant of *Campylobacter jejuni* 81–176 is noninvasive for intestinal epithelial cells. *Infection and Immunity* 72: 2452–2455.

Karlyshev, A.V., D. Linton, N.A. Gregson, A.J. Lastovica, and B.W. Wren. 2000. Genetic and biochemical evidence of a *Campylobacter jejuni* capsular polysaccharide that accounts for Penner serotype specificity. *Molecular Microbiology* 35: 529–541.

Kelly, J.K., and D.A. Owen. 1997. Bacterial diarrheas and dystenteries. In *Pathology of infectious diseases*, ed. D.H. Connor, F.W. Chandler, and D.A. Schwartz, 421–429. Stamford: Appleton & Lange.

Kelly, J., A. Oryshak, M. Wenetsek, J. Grabiec, and S. Handy. 1990. The colonic pathology of *E. coli* 0157:H7 infection. *The American Journal of Surgical Pathology* 14: 87–92.

Ketley, J.M. 1997. Pathogenesis of enteric infection by *Campylobacter*. *Microbiology* 143: 5–21.

Knutton, S., D.R. Lloyd, and A.S. McNeish. 1987. Adhesion of enteropathogenic *Escherichia coli* to human intestinal enterocytes and cultured human intestinal mucosa. *Infection and Immunity* 55: 69–77.

Konkel, M.E., S.F. Hayes, L.A. Joens, and W. Cieplak Jr. 1992. Characteristics of the internalization and intracellular survival of *Campylobacter jejuni* in human epithelial cell cultures. *Microbial Pathogenesis* 13: 357–370.

Konkel, M.E., M.R. Monteville, V. Rivera-Amill, and L.A. Joens. 2001. The pathogenesis of *Campylobacter jejuni*-mediated enteritis. *Current Issues in Intestinal Microbiology* 2: 55–71.

Kotloff, K.L., J.P. Winickoff, B. Ivanoff, J.D. Clemens, D.L. Swerdlow, P.J. Sansonetti, G.K. Adak, and M.M. Levine. 1999. Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies. *Bulletin of the World Health Organization* 77: 651–666.

Kraus, M.D., B. Amatya, and Y. Kimula. 1999. Histopathology of typhoid enteritis: morphologic and immunophenotypic findings. *Modern Pathology* 12: 949–955.

Krause-Gruszczynska, M., M. Rohde, R. Hartig, H. Genth, G. Schmidt, T. Keo, W. Koenig, W.G. Miller, M.E. Konkel, and S. Backert. 2007. Role of the small Rho GTPases Rac1 and Cdc42 in host cell invasion of *Campylobacter jejuni*. *Cellular Microbiology* 9: 2431–2444.

Kuhle, V., and M. Hensel. 2004. Cellular microbiology of intracellular *Salmonella enterica*: functions of the type III secretion system encoded by *Salmonella* pathogenicity island 2. *Cellular and Molecular Life Sciences* 61: 2812–2826.

Lamps, L.W. 2007. Infective disorders of the gastrointestinal tract. *Histopathology* 50: 55–63.

Lara-Tejero, M., and J.E. Galan. 2000. A bacterial toxin that controls cell cycle progression as a deoxyribonuclease-1 like protein. *Science* 290: 354–357.

Larson, C.L., J.E. Christensen, S.A. Pacheco, S.A. Minnich, and M.E. Konkel. 2008. *Campylobacter jejuni* secretes proteins via the flagellar type III secretion system that contribute to host cell invasion and gastroenteritis. In *Campylobacter*, ed. I. Nachamkin, C.M. Szymanski, and M.J. Blaser, 315–332. Washington, DC: ASM Press.

Lastovica, A.J. 1996. *Campylobacter*/*Helicobacter* bacteraemia in Cape Town, South Africa 1977–95. In *Campylobacters, helicobacters and related organisms*, ed. D.G. Newell, J.M. Ketley, and R.A. Feldman, 475–479. New York: Plenum Press.

Liston, A., and S. McColl. 2003. Subversion of the chemokine world by microbial pathogens. *BioEssays* 25: 478–488.

Mao, Y., C. Zhu, and E.C. Boedeker. 2003. Food-borne enteric infections. *Current Opinion in Gastroenterology* 19: 11–22.

Mathan, M.M., and V.I. Mathan. 1991. Morphology of rectal mucosa of patients with shigellosis. *Reviews of Infectious Diseases* 13(Suppl. 4): 314–318.

McGovern, V.J., and L.J. Slavutin. 1979. Pathology of *Salmonella colitis*. *The American Journal of Surgical Pathology* 3: 483–490.

Mead, P.S., L. Slutsker, V. Dietz, L.F. McCaig, J.S. Bresee, C. Shapiro, P.M. Griffin, and R.V. Tauxe. 1999. Food-related illness and death in the United States. *Emerging Infectious Diseases* 5: 607–625.

Monack, D.M., A. Mueller, and S. Falkow. 2004. Persistent bacterial infections: the interface of the pathogen and the host immune system. *Nature Reviews Microbiology* 2: 747–765.

Monteville, M.R., J.E. Yoon, and M.E. Konkel. 2003. Maximal adherence and invasion of INT 407 cells by *Campylobacter jejuni* requires the CadF outer-membrane protein and microfilament reorganization. *Microbiology* 149: 153–165.

Moser, I., W. Schroeder, and J. Salnikow. 1997. *Campylobacter jejuni* major outer membrane protein and a 59-kDa protein are involved in binding to fibronectin and INT-407 cell membranes. *FEMS Microbiology Letters* 157: 233–238.

Nachamkin, I., C.M. Szymanski, and M.J. Blaser. 2008. *Campylobacter*. Washington, DC: ASM Press.

Nhieu, G.T., J. Enninga, P. Sansonetti, and G. Grompone. 2005. Tyrosine kinase signaling and type III effectors orchestrating *Shigella* invasion. *Current Opinion in Microbiology* 8: 16–20.

Niess, J.H., S. Brand, X. Gu, L. Landsman, S. Jung, B.A. McCormick, J.M. Vyas, M. Boes, H.L. Ploegh, J.G. Fox, D.R. Littman, and H.C. Reinecker. 2005. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science* 307: 254–258.

Niyogi, S.K. 2005. Shigellosis. *Journal of Microbiology* 43: 133–143.

Oelschlaeger, T.A., P. Guerry, and D.J. Kopecko. 1993. Unusual microtubule-dependent endocytosis mechanisms triggered by *Campylobacter jejuni* and *Citrobacter freundii*. *Proceedings of the National Academy of Sciences of the United States of America* 90: 6884–6888.

Ogawa, M., Y. Handa, H. Ashida, M. Suzuki, and C. Sasakawa. 2008. The versatility of *Shigella* effectors. *Nature Reviews Microbiology* 6: 11–16.

Olsen, S.J., G. Miller, T. Breuer, M. Kennedy, C. Higgins, J. Walford, G. McKee, K. Fox, W. Bibb, and P. Mead. 2002. A waterborne outbreak of *Escherichia coli* O157:H7 infections and hemolytic uremic syndrome: implications for rural water systems. *Emerging Infectious Diseases* 8: 370–375.

Palm, N.W., and R. Medzhitov. 2009. Pattern recognition receptors and control of adaptive immunity. *Immunological Reviews* 227: 221–233.

Pamer, E.G. 2004. Immune responses to *Listeria monocytogenes*. *Nature Reviews Immunology* 4: 812–823.

Patel, J.C., and J.E. Galan. 2005. Manipulation of the host actin cytoskeleton by *Salmonella* – all in the name of entry. *Current Opinion in Microbiology* 8: 10–15.

Pédron, T., and P. Sansonetti. 2008. Commensals, bacterial pathogens and intestinal inflammation: an intriguing ménage à trois. *Cell Host and Microbe* 3: 344–347.

Pegues, D.A., E.L. Hohmann, and S.I. Miller. 1995. *Salmonella* including *S. typhi*. In *Infections of the gastrointestinal tract*, ed. M.J. Blaser, P.D. Smith, and J.I. Ravdin, 785–809. New York: Raven.

Pei, Z., C. Burucoa, B. Grignon, S. Baqar, X.Z. Huang, D.J. Kopecko, A.L. Bourgeois, J.L. Fauchere, and M.J. Blaser. 1998. Mutation in the peb1A locus of *Campylobacter jejuni* reduces interactions with epithelial cells and intestinal colonization of mice. *Infection and Immunity* 66: 938–943.

Phalipon, A., and P.J. Sansonetti. 2007. Shigella's ways of manipulating the host intestinal innate and adaptive immune system: a tool box for survival? *Immunology and Cell Biology* 85: 119–129.

Poly, F., and P. Guerry. 2008. Pathogenesis of *Campylobacter*. *Current Opinion in Gastroenterology* 24: 27–31.

Potturi-Venkata, L.P., S. Backert, S.L. Vieira, and O.A. Oyarzabal. 2007. Evaluation of logistic processing to reduce cross-contamination of commercial broiler carcasses with *Campylobacter* spp. *Journal of Food Protection* 70: 2549–2554.

Roberts, A.J., and M. Wiedmann. 2003. Pathogen, host and environmental factors contributing to the pathogenesis of listeriosis. *Cellular and Molecular Life Sciences* 60: 904–918.

Rottner, K., T.E. Stradal, and J. Wehland. 2005. Bacteria-host-cell interactions at the plasma membrane: stories on actin cytoskeleton subversion. *Developmental Cell* 9: 3–17.

Salyers, A.A., and D.D. Whitt. 1994. *Bacterial pathogenesis*. Washington, DC: ASM Press.

Sansonetti, P.J. 2004. War and peace at mucosal surfaces. *Nature Reviews Immunology* 4: 953–964.

Sansonetti, P.J. 2006. Shigellosis: an old disease in new clothes? *PLoS Medicine* 3: e354.

Scheiring, J., S.P. Andreoli, and L.B. Zimmerhackl. 2008. Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). *Pediatric Nephrology* 23: 1749–1760.

Schlumberger, M.C., and W.D. Hardt. 2006. *Salmonella* type III secretion effectors: pulling the host cell's strings. *Current Opinion in Microbiology* 9: 46–54.

Schroeder, G.N., and H. Hilbi. 2008. Molecular pathogenesis of *Shigella* spp.: controlling host cell signaling, invasion, and death by type III secretion. *Clinical Microbiology Reviews* 21: 134–156.

Seeliger, H.P.R., and D. Jones. 1986. Listeria. In *Bergey's manual of systematic bacteriology*, ed. J. Butler, 1235–1245. Baltimore: Williams and Wilkins.

Sougioultzis, S., and C. Pothoulakis. 2003. Bacterial infections: small intestine and colon. *Current Opinion in Gastroenterology* 19: 23–30.

Speelman, P., I. Kabir, and M. Islam. 1984. Distribution and spread of colonic lesions in shigellosis: a colonoscopic study. *Journal of Infectious Diseases* 150: 899–903.

Stecher, B., and W.D. Hardt. 2008. The role of microbiota in infectious disease. *Trends in Microbiology* 16: 107–114.

Takeuchi, A. 1967. Electron microscope studies of experimental *Salmonella* infection. I. Penetration into the intestinal epithelium by Salmonella typhimurium. *The American Journal of Pathology* 50: 109–136.

Tam, C.C. 2001. *Campylobacter* reporting at its peak year of 1998: don't count your chickens yet. *Communicable Disease and Public Health* 4: 194–199.

Tato, C.M., and C.A. Hunter. 2002. Host-pathogen interactions: subversion and utilization of the NF-κB pathway during infection. *Infection and Immunity* 70: 3311–3317.

Thanassi, D.G., and S.J. Hultgren. 2000. Multiple pathways allow protein secretion across the bacterial outer membrane. *Current Opinion in Cell Biology* 12: 420–430.

Tilney, L.G., and D.A. Portnoy. 1989. Actin filaments and the growth, movement, and spread of the intracellular bacterial parasite. Listeria monocytogenes. *The Journal of Cell Biology* 109: 1597–1608.

Tsolis, R.M., G.M. Young, J.V. Solnick, and A.J. Bäumler. 2008. From bench to bedside: stealth of enteroinvasive pathogens. *Nature Reviews Microbiology* 6: 883–892.

Vallance, B.A., C. Chan, M.L. Robertson, and B.B. Finlay. 2002. Enteropathogenic and enterohemorrhagic *Escherichia coli* infections: emerging themes in pathogenesis and prevention. *Canadian Journal of Gastroenterology* 16: 771–778.

van Spreeuwel, J.P., G.C. Duursma, C.J. Meijer, R. Bax, P.C. Rosekrans, and J. Lindeman. 1985. *Campylobacter colitis*: histological immunohistochemical and ultrastructural findings. *Gut* 26: 945–951.

Wassenaar, T.M., and M.J. Blaser. 1999. Pathophysiology of *Campylobacter jejuni* infections of humans. *Microbes and Infection* 1: 1023–1033.

Watarai, M., S. Funato, and C. Sasakawa. 1996. Interaction of Ipa proteins of *Shigella flexneri* with alpha5beta1 integrin promotes entry of the bacteria into mammalian cells. *The Journal of Experimental Medicine* 183: 991–999.

Watson, R.O., and J.E. Galán. 2008. *Campylobacter jejuni* survives within epithelial cells by avoiding delivery to lysosomes. *PLoS Pathogens* 4: e14.

Wing, E.J., and S.H. Gregory. 2002. *Listeria monocytogenes*: clinical and experimental update. *Journal of Infectious Diseases* 185: 18–24.

Wooldridge, K.G., and J.M. Ketley. 1997. *Campylobacter* – host cell interactions. *Trends in Microbiology* 5: 96–102.

Wooldridge, K.G., P.H. Williams, and J.M. Ketley. 1996. Host signal transduction and endocytosis of *Campylobacter jejuni*. *Microbial Pathogenesis* 21: 299–305.

World Health Organization. 2004. Global burden of disease (GBD) 2002 estimates. WHO, Geneva, Switzerland. http://www.who.int/topics/global_burden_of_disease/en/.

Xicohtencatl-Cortes, J., V. Monteiro-Neto, Z. Saldaña, M.A. Ledesma, J.L. Puente, and J.A. Girón. 2009. The type 4 pili of enterohemorrhagic *Escherichia coli* O157:H7 are multipurpose structures with pathogenic attributes. *Journal of Bacteriology* 191: 411–421.

Yoshida, S., Y. Handa, T. Suzuki, M. Ogawa, M. Suzuki, A. Tamai, A. Abe, E. Katayama, and C. Sasakawa. 2006. Microtubule-severing activity of *Shigella* is pivotal for intercellular spreading. *Science* 314: 985–989.

Zheng, J., J. Meng, S. Zhao, R. Singh, and W. Song. 2008. *Campylobacter*-induced interleukin-8 secretion in polarized human intestinal epithelial cells requires *Campylobacter*-secreted cytolethal distending toxin- and Toll-like receptor-mediated activation of NF-kappaB. *Infection and Immunity* 76: 4498–4508.

http://www.springer.com/978-1-4614-1176-5

Microbial Food Safety
An Introduction
Oyarzabal, O.A.; Backert, S. (Eds.)
2012, X, 262 p., Hardcover
ISBN: 978-1-4614-1176-5