Bacterial Surface Components and Toxins in Cancer Development: Mechanisms of Oncogenesis and Therapeutic Implications

Chandan Sarkar[1], Abul Hasnat[2], Md Mostafizur Rahman[3], Mashsharat Maliha[4], Bikom Chandra Singha[5], Tufael[6*]

Abstract

Background: Cancer arises from genetic alterations, often influenced by environmental and lifestyle factors, including microbial infections. While the link between viruses such as HPV and HBV and cancer is well-established, the involvement of bacteria in cancer development remains less explored. Growing evidence suggests that bacterial surface components, toxins, and effector proteins play a crucial role in altering host signaling pathways, ultimately driving oncogenesis. Methods: This review consolidates current research on how bacteria interact with host cells, with a particular focus on bacterial surface molecules, toxins, and their roles in immune evasion, cellular invasion, and oncogenic signaling. Both experimental studies and epidemiological data are evaluated to better understand the connection between bacterial infections and cancer formation. Results: Surface molecules from bacteria like Helicobacter pylori CagL and Fusobacterium nucleatum FadA have been found to disrupt key host pathways, such as β-catenin and Wnt signaling, leading to cellular transformation. Similarly, lipopolysaccharides (LPS) from Gram-negative bacteria promote inflammation-driven tumorigenesis through TLR4 activation. Bacterial toxins, including cytolethal distending toxin (CDT) and diphtheria toxin, cause genomic instability, interfere with apoptotic pathways, and activate proliferative signals, further establishing bacterial infections as contributors to cancer progression. Conclusion: Bacterial infections contribute to cancer development through a combination of immune modulation, DNA damage, and disruption of cellular signaling pathways. A deeper understanding of these mechanisms offers promising avenues for developing preventive measures and targeted therapies to counter microbial-driven oncogenesis. The pivotal role of the microbiome in cancer biology highlights the need for future research to unravel the intricate interactions between bacteria and host cells, fostering advancements in cancer prevention and treatment strategies.

Keywords: Microbial oncogenesis, Bacterial surface components, Cancer signaling pathways, Inflammation-driven tumorigenesis, Bacterial toxins, genomic instability.

Significance | Understanding bacterial contributions to cancer reveals novel mechanisms of oncogenesis, enabling targeted prevention, diagnostics, and therapeutic strategies against infection related malignancies.

*Correspondence. Tufael, Department of Biochemistry, Ibn Sina Diagnostic and Imaging Center, Dhaka, Bangladesh.
E-mail: tofayelahmed083@gmail.com

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1. Introduction

Di It involves a series of genetic alterations that lead to the disturbance in the normal processes governing cell growth and cell survival (Wu et al., 2016). A wide range of external agents, including physical factors like ultraviolet and radio waves, as well as lifestyle

Author Affiliation.
[1] Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh.
[2]Mymensingh Medical College, Mymensingh, Bangladesh.
[3]Department of Biological Sciences, St. John's University, New York, United States.
[4]Department of Medicine, Bangladesh Agricultural University, Mymensingh, Bangladesh.
[5]Department of Microbiology and Hygiene, Bangladesh Agricultural University, Mymensingh, Bangladesh.
[6]Department of Biochemistry, Ibn Sina Diagnostic and Imaging Center, Dhaka, Bangladesh.

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choices such as tobacco use, smoking, and alcohol consumption, contribute to the genetic changes that can lead to cancers, including HIV-2023 (Parkin et al., 2011; Siegel 2015; Koh et al., 1996). At least 75% of causes are linked to alcohol and tobacco use (Blot et al., 1988), and approximately 65–86% of the incidence of skin cancer is attributed to sun exposure (Khoury et al., 2013). In addition to the viral genomes identified by Bosch et al. (1995), exogenous factors have been found in various tumor tissues, which observation was supported by numerous epidemiological studies. (Salam et al.,2024) Viral infections, for instance, HPV, HBV (El-Serag, 2012), and HCV virus, are responsible for nearly 90% of causes related to cervical cancer and about 80% of hepatocellular carcinoma, respectively (Neuveut et al., 2010). An apparently stronger argument for the relationship between viral infections and cancer arises from studies demonstrating how viruses exploit the host cell environment for their replication (Münger et al., 2004). This process activates mammalian growth-promoting genes, which trigger uncontrolled cell division- a hallmark of cancer (Mostafa, Sheweita, & O'Connor, 1999). Hepatitis B virus (HBV) contributes to the development of cancer mainly through its HBx protein, which interferes with the cell's ability to repair DNA. This disruption makes the genome unstable, increasing the chances of liver cancer (Table 1). Similarly, human papillomavirus types 5 and 8 (HPV 5 & 8) also play a role in cellular changes that can lead to cancer (Krump et al., 2018). They contribute to genetic instability through viral integration and activate various signaling pathways and cellular genes involved in cancer development, proliferation, inflammation, and immune response (Jahan et al., 2015).

Viruses represent merely one microbiome component that takes advantage of the mammalian host in their infectious life cycle. Disease-causing fungi, parasitic worms, and bacteria interact quite extensively with mammalian host cells competing for survival (Mughini-Gras et al., 2018). These microorganisms do not usually leave a genetically manipulable signature, nor do they integrate into mammalian genes in the manner of viruses (Lofgren et al., 2011). Nonetheless, epidemiological associations are well-established between a wide range of microbial infections and the development of cancers (Bhowmik et al., 2021). Such infections are linked to the development of specific types of cancers. For instance, Schistosoma haematobium infections have been linked to bladder cancer (Lee et al., 2008). Similarly, Helicobacter pylori infections are associated with gastric cancer, chronic Salmonella typhi infections are related to gallbladder carcinoma, and Salmonella enteritidis (Figure 3) infections have been connected to colon carcinoma (Vannucci et al., 2008). Various recent studies have shown tumor-promoting properties in the microbiota in different models, including germ-free and antibiotic-treated animal models, with special emphasis on gastric, colon, and liver cancers (Li et al., 2012; Tufael et al., 2024). However, recent discoveries exhibit that artificial intelligence tools are frequently utilized to identify microbial patterns and analyze host- microbiome interactions, highlighting their role in tumorigenesis (Rahman et al., 2024). Furthermore, the increasing use of technology for smart health monitoring is revolutionizing data collection in the medical field. This advancement assists in the early detection of illnesses, including cancer risk assessment, by providing real-time health data and enhancing decision-making (Dapito et al., 2012; Rahman et al., 2024).

Due to the extreme diversity of the microbiome-host interactions, such functions cannot be precisely defined. It has been documented that pathogenic bacteria can manipulate the cellular environment of human host cells in various ways during their infection cycle. This review will discuss bacterial surface components, protein toxins, and effector proteins interacting with host cells, their potential modulation of key host cell signaling pathways, and how these interactions might influence cancer development (Bhowmik et al., 2021).

2. Bacterial cell-surface components and cancer development

The outermost layer of bacteria, which makes direct contact with host cells, comprises complex formations, including various antigenic components that interact with both innate and adaptive immune responses of the host (Abeyta et al.,2003). Consequently, pathogenic bacteria have developed a diverse array of outer surface modifications to evade immune detection and enhance their survival. To avoid immune recognition and elimination, Gram-negative bacteria encase their complex outer surface macromolecules within a polysaccharide-rich capsule (Geno et al.,2015). These capsules restrict complement activation by protecting underlying membrane structures in pathogenic strains of *Escherichia coli*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, and others (Tran et al.,2005). Capsules also prevent engulfment by phagocytic immune cells (Gewirtz et al.,2004). Unencapsulated variants of these bacteria seldom cause invasive infections and exhibit reduced virulence in several infection models because of increased susceptibility to opsonophagocytic clearance (Kawasaki et al.,2004). Beyond their protective capsules, numerous bacterial pathogens have altered their surface-exposed molecules, such as lipopolysaccharides, peptidoglycans, and flagella to minimize immune detection. For instance, *H. pylori* possesses LPS surface molecules containing "underacylated" lipid A, which is a poor substrate for the host's Toll-like receptor 4, thus evading innate immune sensing (Popp et al.,2001). *H. pylori* also generate modified flagellin molecules that are not detected by TLR5, preventing TLR5-mediated interleukin-8 secretion and subsequent immune signaling (Meenan et al.,2007). *Salmonella typhimurium* expresses lipid A deacetylase PagL and a lipid A palmitoyltransferase PagP to modify lipid A, leading to a hundredfold reduction in lipid A-mediated TLR4 activation and

Table 1. Epidemiological and experimental evidence for a link between microbial infections and cancer.

Infectious agent	Type of micro-organism	Cancer type
Epstein–Barr virus	Virus	Nasopharyngeal carcinoma, Burkitt lymphoma, immune suppression-related non-Hodgkin lymphoma, Hodgkin lymphoma, extranodal natural killer/T-cell lymphoma (nasal type)
Hepatitis B virus	Virus	Hepatocellular carcinoma
Hepatitis C virus	Virus	Hepatocellular carcinoma, non-Hodgkin lymphoma
Kaposi sarcoma herpesvirus	Virus	Kaposi sarcoma, primary effusion lymphoma
Human immunodeficiency virus 1	Virus	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, carcinoma of the cervix, anus, conjunctiva
Human papillomavirus type 16	Virus	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil
Human T-cell lymphotropic virus type 1	Virus	Adult T-cell leukaemia and lymphoma
Merkel cell polyomavirus	Virus	Merkel cell carcinoma
Opisthorchis viverrini	Trematode	Cholangiocarcinoma
Clonorchis sinensis	Helminth	Cholangiocarcinoma
Schistosoma haematobium	Trematode	Urinary bladder cancer
Helicobacter pylori	Bacterium	Non-cardia gastric carcinoma, low-grade B-cell MALT gastric lymphoma
Aflatoxin (B1)	Mould (Aspergillus flavus)	Liver cancer
Salmonella Typhi	Bacterium	Gallbladder carcinoma
Salmonella Enteritidis	Bacterium	Colon carcinoma in the ascending and transverse parts of the colon
Chlamydia trachomatis	Bacterium	Carcinoma of the cervix and ovaries

nuclear factor-κB activation (Raibaud et al.,2005). These cases show how bacterial pathogens modify their outer surfaces to avoid immune detection. Disease-causing bacteria that thrive within host cells produce surface proteins that facilitate both attachment to and internalization within those cells. For instance, pathogenic *Neisseria* species express various surface adhesins that enable selective interaction with specific cell types, allowing them to exploit specialized host cell environments (Wiedemann et al.,2012). Similarly, fibronectin-binding proteins of *Staphylococcus aureus* and *Borrelia burgdorferi* mediate bacteria-host cell interactions by forming tandem β-zippers that trigger bacterial uptake by non-phagocytic cells (Tabassam et al.,2009).

These surface-mediated attack strategies generally aim to enhance bacterial survival within the host by evading the immune system and invading host cells. However, to exert further control over host cell machinery, bacterial surface molecules also manipulate host cell signaling pathways and compromise cell integrity, which can inadvertently lead to cellular malignancies. *H. pylori's* CagL, a type IV pilus adhesin, facilitates bacterial adherence to gastric epithelial cells and triggers a signaling cascade that increases gastrin secretion (Polk et al.,2010). This results in hypergastrinemia, a significant risk factor for gastric adenocarcinoma. CagL binds β5-integrin, thereby manipulating integrin-linked kinase complexes and the downstream rapidly accelerated fibrosarcoma kinase, mitogen-activated protein kinase kinase, and extracellular signal-regulated kinase pathways (Franco et al.,2008). *H. pylori's* outer inflammatory protein A activates epidermal growth factor receptor and stimulates Akt and β-catenin signaling, a phenotype observed in various cancers, including gastric cancer. OipA inactivation reduces β-catenin nuclear localization *in vitro* and decreases cancer incidence

in animal models (Ishijima et al.,2011). Additionally, *H. pylori's* blood group antigen-binding adhesin BabA can bind human Lewis(b) surface epitopes, indirectly increasing mRNA levels of proinflammatory cytokines chemokine ligand 5 and IL-8, and the precancer-related factors CDX2 and MUC2. *Fusobacterium nucleatum's* fusobacterium adhesion A binds to E-cadherin's extracellular domain, inducing E-cadherin phosphorylation and internalization (Rubinstein et al.,2013). This releases β-catenin, activating β-catenin–T-cell factor/LEF downstream in the Wnt signaling pathway, regulates the transcription of genes related to apoptosis, cellular expansion, and transformation (Kostic et al.,2012). High *F. nucleatum fadA* expression levels in patients with colon adenomas or adenocarcinomas correlate with upregulated expression of oncogenic and inflammatory genes interconnected with the Wnt signaling pathway (Castellarin et al.,2012). Lipopolysaccharide, the major surface-exposed component of Gram-negative bacteria, activates signaling cascades that contribute to cancer development (Coleman et al.,2017). Present in both pathogenic and commensal bacteria, LPS plays a key role in activating TLR4. TLR4-mediated signaling is crucial for activating numerous downstream pathways underlying various inflammatory and immune responses. It can also promote the development of adenomatous polyposis coli-dependent and inflammation-associated colorectal cancers in mice (Rakoff-Nahoum et al.,2007). The role of TLR signaling in intestinal tumorigenesis has been investigated by crossing myeloid differentiation primary response 88-deficient mice (with impaired TLR4 signaling) with ApcMin/+ mice (mimicking sporadic cancer and familial adenomatous polyposis) (Abreu et al.,2010). These MyD88-deficient × ApcMin/+ mice exhibited reduced tumor number and size compared to ApcMin/+ controls, suggesting that TLR4 signaling promotes tumor growth (Fink et al.,2014). Tumor tissues from MyD88-deficient mice showed lower expression of *Cox2*, a gene involved in inflammation, indicating its role in reduced tumor formation (Wang et al.,2010). Furthermore, Cox2 inhibitors like aspirin reduce colorectal cancer risk in individuals overexpressing *15-PGDH*, which encodes an enzyme that disrupts Cox2 activity. Studies with germ-free and wild-type mice demonstrated that TLR4 activation by LPS from intestinal microbiota contributes to injury- and inflammation-driven hepatocellular carcinoma by activating proliferative and anti-apoptotic signals (Costa et al.,2015). These animal study findings are supported by human studies detecting enhanced TLR4/MyD88 complex expression in 20% of colorectal patient samples (Murphy et al.,2011).

3. Bacterial toxin-mediated host cell transformation

To facilitate immune evasion, rapid replication, and dissemination, pathogenic bacteria utilize not only immune-evasion tactics to elude clearance by host cells but also implement mechanisms aimed at the destruction of immune cells. A notable tactic involves the secretion of protein toxins characterized by their cytolytic effects. These toxins are frequently expressed from bacterial pathogenicity islands and are secreted via specialized secretion systems that enable their translocation across the bacterial outer membrane (Rosadi et al.,2016). The interaction between protein toxins and host cells typically adheres to a well-defined sequence of events, as exemplified by the diphtheria toxin. This toxin, secreted by Corynebacterium diphtheriae in the form of a singular polypeptide chain, comprises three distinct subunits. It binds to the heparin-binding epidermal growth factor-like receptor of the host, initiating its internalization through the endosomal pathway (Cortes-Bratt et al.,2000). Within the confines of the endosome, the transmembrane domain of the toxin unfolds, promoting its translocation to the cytosolic side of the endosomal membrane. The disulfide linkage between the A and B fragments of the toxin is subsequently reduced, resulting in the liberation of the C-domain into the cytoplasm. The C-domain then undergoes a conformational refolding into its enzymatically active state and catalyzes the NAD+-dependent ADP-ribosylation of the host elongation factor 2 (EF-2), thereby obstructing protein synthesis and ultimately precipitating cell death (Guerra et al.,2008). Pathogenic bacteria predominantly exploit toxin-mediated approaches to cultivate a conducive environment within host cells; however, their toxins may inadvertently facilitate oncogenesis (Putze et al.,2009). Toxin-induced carcinogenesis can transpire through diverse mechanisms, including the promotion of genomic instability, evasion of apoptosis signaling, and activation of proliferative signaling pathways (Nougayrede et al.,2006). Genomic instability is most frequently instigated by bacterial protein toxins that induce double-stranded DNA breaks (DSBs) in host cells. Notable examples of such toxins include cytolethal distending toxin (CDT), colibactin, Shiga toxin, and endonucleases. CDT, secreted by Gram-negative bacteria such as S. Typhi, E. coli, Shigella dysenteriae, and Campylobacter jejuni, is composed of three subunits: CdtA, CdtB, and CdtC. While CdtA and CdtC facilitate cellular uptake and delivery, CdtB is responsible for the enzymatic activity that induces DSBs (Cuevas-Ramos et al.,2010). Following binding and internalization, CdtB is retrogradely transported through the endosomal and Golgi apparatus to the endoplasmic reticulum (ER), where it translocates into the cytosol via ER-associated degradation pathways. Once within the cytoplasm, CdtB penetrates the nucleus and instigates DSBs (Buc et al.,2013). These breaks activate DNA damage responses (DDR), resulting in G1-S cell cycle arrest in epithelial and endothelial cells, G1-S and G2-M arrest in fibroblasts, and apoptosis in hematopoietic cells, which exhibit heightened sensitivity to CDT (Dejea et al.,2018). While this mechanism may effectively eliminate immune cells, thus benefiting bacterial persistence, prolonged exposure to low doses of CDT can disrupt DDR functionality,

hindering the efficient detection and repair of DNA damage (Arthur et al.,2012). Simultaneously, the activation of MAPK signaling through NET1 and RhoA enhances the survival of the damaged cells (Fig. 2A). Consequently, these cells accrue mutations and deletions during the repair process, culminating in genomic instability and fostering the emergence of cancer (Wu et al.,2007).In addition to CDT toxins, the DNA-interacting colibactin toxin has also been implicated in the generation of double-stranded DNA breaks (DSBs) and the induction of genomic instability (Figure 2). Colibactin is secreted by E. coli strains belonging to the phylogenetic group B2, which harbor the polyketide synthetase (pks) island (Nelson et al.,2004). These *E. coli* strains induce DSBs in eukaryotic cells, activating DNA damage checkpoint pathways such as ATM, CHK1, and CHK2. This leads to G2-to-M phase cell cycle arrest. However, as a side effect, colibactin-producing bacteria cause incomplete DNA repair, chromosomal instability, and anchorage-dependent colony formation phenotypes that promote cancer development (Wu et al.,2009).Epidemiological studies further support this, showing a higher prevalence of colibactin-producing *E. coli* in colorectal tumor biopsies (Rhee et al.,2009). Additionally, studies in colitis-susceptible IL-10-deficient mice revealed that colonization with colibactin-producing *E. coli* increased invasive carcinoma formation, whereas deletion of the pks island reduced tumor multiplicity and invasiveness (Toprak et al.,2006).

Beyond toxins inducing DSBs and genomic instability, other bacterial toxins contribute to carcinogenesis by promoting resistance to cell death and stimulating proliferative signaling. Such toxins are typically secreted by intracellular pathogenic bacteria that benefit from host cell survival (Nakayama et al.,2009). For instance, *Bacteroides fragilis* toxin (BFT) binds to intestinal epithelial cell receptors, triggering cell proliferation by cleaving the tumor suppressor protein E-cadherin (Sokolova et al.,2008).E-cadherin plays a crucial role in forming intercellular junctions and regulating proliferation and differentiation through β-catenin/Wnt and NF-κB signaling pathways (Fig. 2B) (McCracken et al.,2014). BFT has been shown to induce acute and chronic colitis in C57BL/6 mice and colon tumors in *ApcMin*/+ mice, a model for human colon carcinoma. Similarly, *Helicobacter pylori* has been shown to trigger a multi-step inflammatory cascade involving IL-17R, NF-κB (Figure 1), and STAT3 signaling, promoting carcinogenesis (Xu et al.,2012). Epidemiological studies corroborate these findings, showing enterotoxigenic *B. fragilis* is more common in colorectal cancer (CRC) patients (40%) compared to only 10–20% in the healthy population (Wang et al.,2014).

Additionally, *H. pylori* toxins such as vacuolating cytotoxin A (VacA) have been implicated in gastric cancer risk. VacA, similar to *H. pylori* outer membrane protein OipA, activates the EGFR receptor, triggering PI3K-Akt signaling and inactivating glycogen synthase kinase 3β. This prevents β-catenin degradation, enhancing Tcf/LEF-mediated transcription and transformation and promoting cell growth (Fredlund et al.,2014). Another key *H. pylori* virulence factor, cytotoxin-associated gene A (CagA), interacts with the c-Met receptor via type IV pilus cell-surface adhesion CagL, stimulating epithelial proliferation, as demonstrated in human gastric organoids (Senerovic et al.,2014). Both phosphorylated and unphosphorylated CagA interact with multiple host proteins involved in MEK, ERK, NF-κB, and β-catenin pathways, all of which are central to cell proliferation and cancer development (Henry et al.,2006).

4. Bacterial effector proteins that mediate host cell transformation

Many intracellular bacterial pathogens have modified molecular strategies to establish long term infections within the protective surroundings of host cells. This involves controlling various stages of the intracellular infection cycle, including host cell entry (via receptor-mediated endocytosis or phagocytosis), intracellular survival and expansion, along with its release from the infected cell (Shaughnessy et al.,2007). Following internalization, bacterial cargo typically travels through the endosomal system, which often leads to a highly degradative organelle known as the phagolysosome. In order to prevent phagolysosomal degradation, intracellular bacterial pathogens have developed various mechanisms, broadly categorized into two pathways: escaping the phagosome/entering the cytosol, or hijacking and modifying the phagosome to suit their needs (Santic et al.,2008). Cytosolic pathogens such as *Listeria*, *Shigella flexneri*, *Rickettsia*, and *Francisella* rapidly escape the phagosome to enter the host cytosol, thus avoiding lysosomal fusion and degradation (Ozanic et al.,2015)(Chong, et al.,2008). This typically involves secreting bacterial effector proteins that induce pore formation in the endolysosomal vacuole, leading to its rupture (Rajashekar et al.,2014). For example, *S. flexneri* secretes the effector protein Invasion plasmid antigen B, which forms ion channels in eukaryotic membranes, mediating potassium influx and subsequent endolysosomal leakage. *Listeria* secretes listeriolysin-O, a protein that creates small membrane perforations, causing Ca2+ leakage from vacuoles, increasing vacuolar pH, and preventing vacuolar maturation. *Francisella tularensis* also escapes into the host cytoplasm. After phagocytic uptake by macrophages, *F. tularensis* resides in the Francisella-containing phagosome, which matures from an early endosome-like phagosome to a more acidic late endosomal phagosome. Inhibiting FCP acidification delays *F. tularensis* escape into the cytosol, suggesting that further acidification during phagosome maturation stimulates *F. tularensis* to express unique, yet-unidentified factors that disrupt the phagosomal membrane (Beuzon et al.,2000).

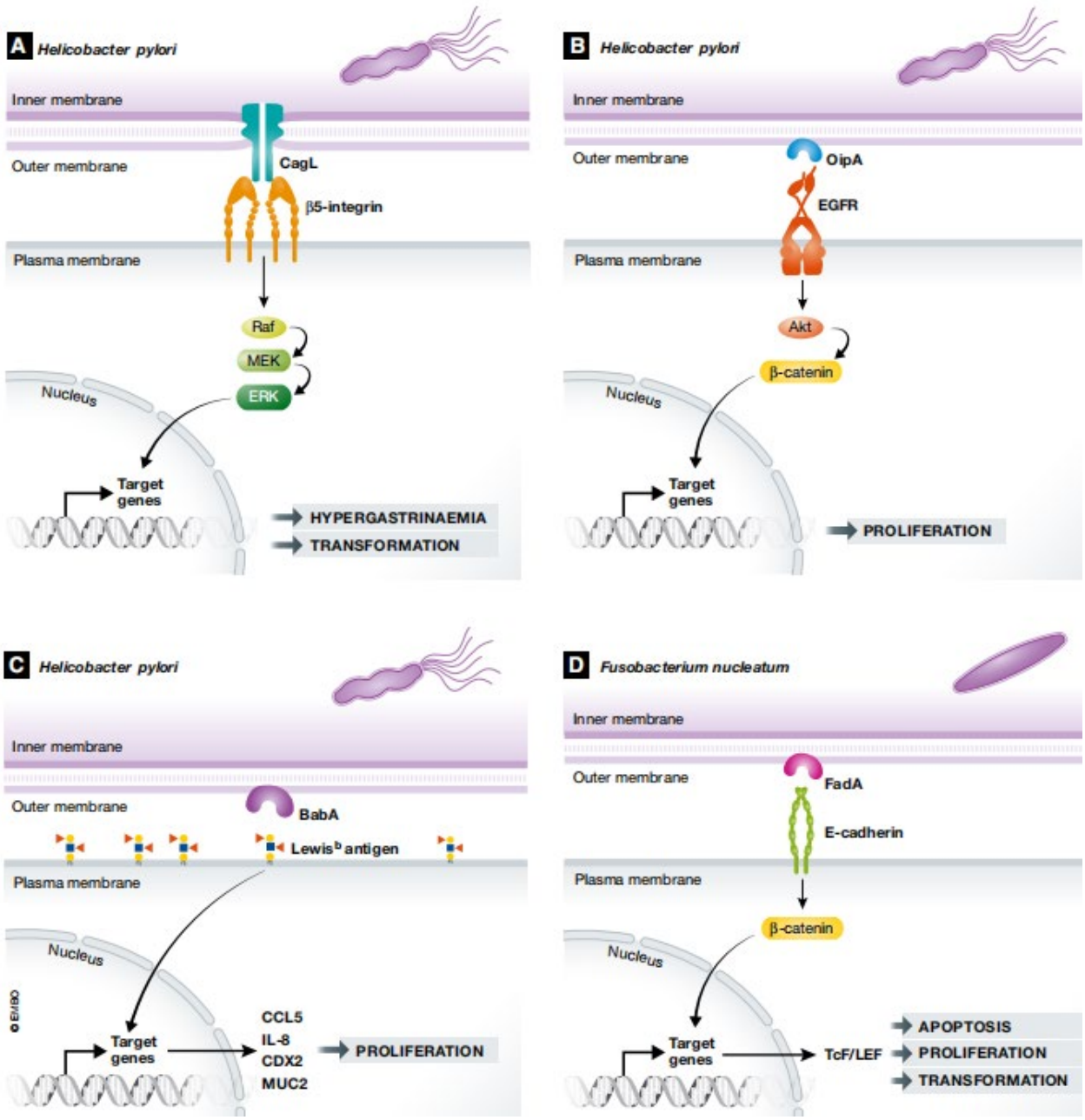


Figure 1. Bacterial outer-surface components that manipulate host cell signalling cascades involved in cellular malignancy. (A) Helicobacter pylori uses CagL, a protein that binds to β5-integrin, triggering a chain reaction that activates the Raf, MEK, and ERK pathways. These pathways play a crucial role in stimulating gastrin production and promoting cellular transformation, which may contribute to gastric cancer.(B) Another H. pylori protein, OipA, interacts with the EGFR (epidermal growth factor receptor), leading to the activation of the Akt and β-catenin signaling pathways. This results in increased cell proliferation, creating conditions favorable for tumor development.(C) H. pylori BabA binds to Lewis(b) surface epitopes on human cells, leading to increased levels of CCL5, IL-8, CDX2, and MUC2. These molecules are involved in inflammation and cell proliferation, which may contribute to the progression of gastric disease and cancer.(D) Fusobacterium nucleatum produces FadA, a protein that binds to E-cadherin. This disrupts normal cell adhesion and releases β-catenin, which then activates the Tcf/LEF transcription factors. These factors regulate genes responsible for cell survival, proliferation, and transformation, contributing to colorectal cancer development.

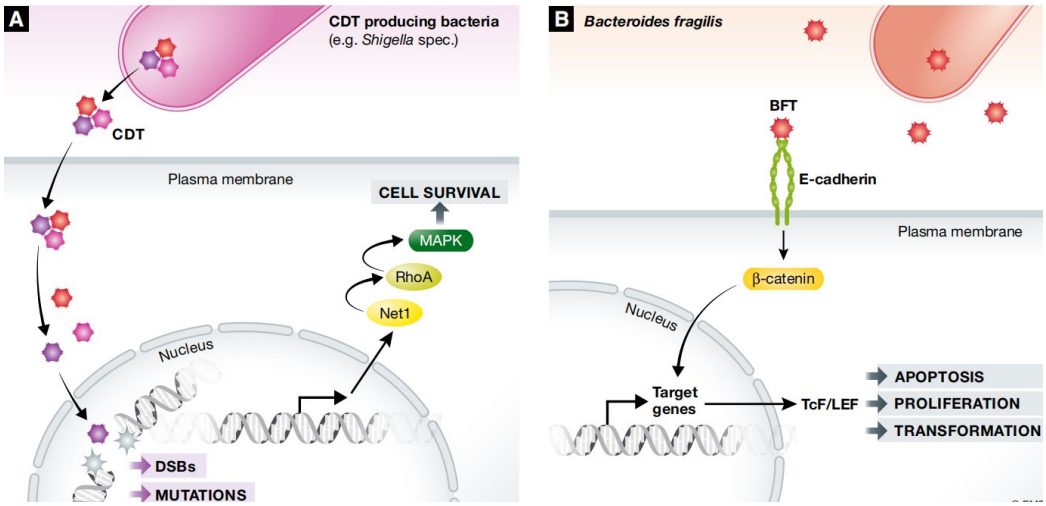


Figure 2. Host cell signalling pathways involved in cell growth and transformation manipulated by bacterial toxins. (A) The CdtB subunit of the CDT toxin plays a significant role in damaging DNA. Once inside the nucleus, it causes double-strand breaks (DSBs) and disrupts the function of DNA damage response (DDR) sensors, making it harder for the cell to repair itself. At the same time, proteins NET1 and RhoA become activated, leading to the upregulation of MAPK signaling, which helps the cell survive despite the DNA damage.(B) Bacteroides fragilis produces a toxin called BFT, which binds to E-cadherin, a protein involved in cell-to-cell adhesion. This interaction triggers a cascade of cellular signaling events, promoting proliferation and transformation. Specifically, BFT activates the β-catenin/Wnt and NF-κB pathways—both of which are linked to uncontrolled cell growth and cancer development.

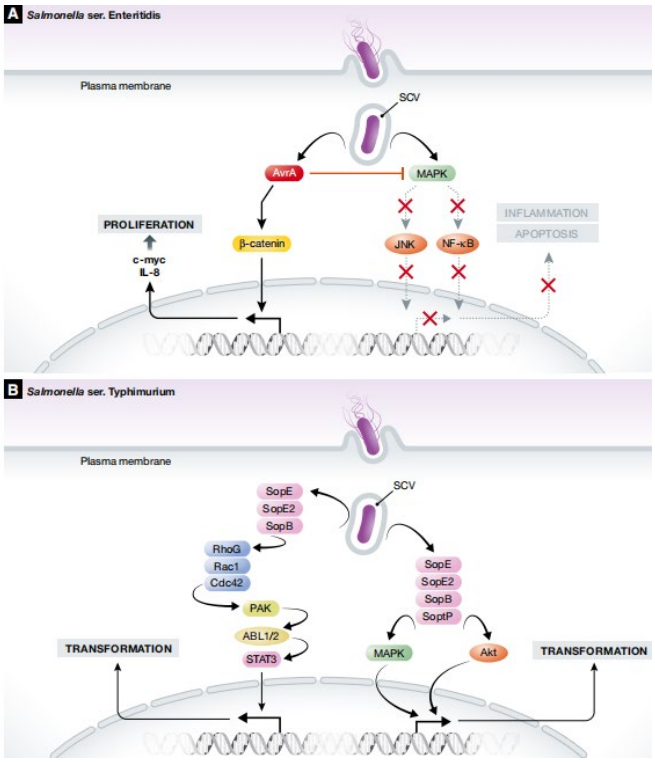


Figure 3. Examples of bacterial effector proteins involved in cellular transformation. Here are some examples of bacterial effector proteins involved in cellular transformation: (A) Salmonella Enteritidis produces an effector protein called AvrA, which plays a dual role in cellular processes. It stabilizes β-catenin, leading to the activation of the Wnt signaling pathway, which promotes cell proliferation. At the same time, AvrA inhibits JNK and NF-κB signaling pathways, which are typically involved in inflammation and apoptosis. By suppressing these pathways, AvrA helps infected cells evade programmed cell death and sustain uncontrolled growth.
(B) Salmonella Typhimurium utilizes several effector proteins SopB, SopE, and SopE2 to manipulate host cell signaling. These proteins activate small GTPases (RhoG, Rac1, and Cdc42), which in turn stimulate PAK kinases. These kinases phosphorylate members of the Abl kinase family, ultimately activating the STAT3 transcription factor, a key player in cellular transformation. Additionally, SopB, SopE, SopE2, and SptP contribute to the activation of MAPK and Akt signaling pathways. These pathways have been shown to drive the transformation of premutated fibroblasts and gallbladder organoids, highlighting their potential role in cancer development.

Unlike bacteria that escape the phagosome, some pathogenic bacteria exploit the phagosome to create a favorable niche for replication. *Legionella pneumophila* is a prime example, as it redirects the Legionella-containing phagosome to the endoplasmic reticulum (ER) by secreting bacterial proteins through the Dot-Icm secretion system. This strategic rearrangement prevents lysosomal degradation and enables *Legionella* to replicate within the phagosome (Sindhwani et al.,2017). Similarly, *Salmonella* an intracellular pathogen manipulates phagosomal maturation after internalization into host cells. *Salmonella* resides in a membrane-bound vacuolar compartment known as the Salmonella-containing vacuole (SCV), which matures and acquires features of late endocytic compartments, including acidification, but remains non-bactericidal. Key *Salmonella* effectors—SifA, SseJ, SseG, SseF, SopD2, and PipB2—alter host cell processes to transform the SCV into a replication-permissive compartment (Lu et al.,2016). SifA, a crucial effector (Lu et al.,2017), interacts with the host GTPase effector Arl8b and the SifA and kinesin-interacting protein (SKIP). This interaction drives the formation of Salmonella-induced filaments (SIFs), an extensive tubular membrane network that delivers nutrients to the SCV while simultaneously preventing antimicrobial activity (Lu et al.,2014). By facilitating constant mixing with late endosomes and lysosomes, this network disrupts the delivery of antimicrobial agents, ensuring *Salmonella* survival and replication (Ye et al.,2007).

Intracellular pathogenic bacteria utilize effector proteins to significantly alter host cell integrity during their intracellular life cycle, and some of these infections have been epidemiologically associated with specific cancer types. For example, *Salmonella Typhi* has been associated with gallbladder cancer, while *Salmonella Enteritidis* is associated with colon cancer (Sun et al.,2004).These bacteria introduce effector proteins into host cells, hijacking cellular pathways and, depending on the pathway targeted, potentially promoting cancer formation (Jones et al.,2008). One such effector, AvrA, an acetyltransferase expressed by *Salmonella*, is implicated in colon cancer. AvrA modulates host signaling pathways by stabilizing β-catenin, thereby enhancing signaling and driving epithelial cell proliferation (Fig. 3A) (Trosky et al.,2004).Additionally, AvrA suppresses immune responses and apoptosis through inhibition of the JNK and NF-κB signaling pathways (Trosky et al.,2007). Similar to AvrA, orthologues like YopJ (*Yersinia pestis*), VopA (*Vibrio parahaemolyticus*), and AopP (*Aeromonas salmonicida*) interact with critical host signaling pathways. YopJ attenuates the ERK, p38, JNK, and IKK pathways, reducing cytokine production (Siddique et al., 2024) and anti-apoptotic factors (Fehr et al.,2006). VopA inhibits ERK, p38, and JNK signaling but not IKK (Hannemann et al.,2013), while AopP specifically targets the IKK pathway (Kuijl et al.,2007).

In epithelial cells infected by *S. Typhimurium*, the effector proteins SopE, SopE2, and SopB manipulate Rho-family GTPases, p21-activated kinase (PAK), and ABL tyrosine kinase, which activate STAT3 and alter transcription regulation, leading to cellular transformation (Fig. 3B) (Kuo et al.,2013). Additionally, transformation can occur through the activation of MAPK and AKT pathways mediated by SopE, SopE2, SopB, and SptP (Fig. 3B) (Melenotte et al.,2016). These pathways enable the transformation of fibroblasts and gallbladder organoids with pre-transformed phenotypes characterized by p53 inactivation and MYC oncogene overexpression (Fulbright et al.,2017). Supporting this evidence, pathology studies on gallbladder carcinoma samples from Indian patients showed *S. Typhi* DNA along with pre-transformed molecular signatures similar to those observed in laboratory experiments. Furthermore, oral infection of *ApcMin*/+ mice with *S. Typhimurium* led to the development of colorectal adenocarcinomas, demonstrating a dependency on *Salmonella* effectors (Louis et al.,2014).

5. Conclusion

While bacterial infections may play a role in the etiology of neoplasia, this phenomenon is frequently an inadvertent outcome of the bacterial life cycle rather than a selective advantage for the microorganisms involved. Neoplastic processes generally ensue subsequent to the bacterium's departure from the host organism, with the bacterial manipulation of host cellular mechanisms serving merely as one phase in the intricate, multi-faceted sequence of cellular transformation. Persistent infections, exemplified by those instigated by Salmonella or Mycobacterium tuberculosis, have been shown to augment the likelihood of tumorigenesis, particularly in the context of pre-transformed cellular populations. As scholarly investigations persist in elucidating the bacterial mechanisms linked to malignancy, we acquire critical understanding regarding the pathways through which pathogens facilitate cellular transformation. These revelations may facilitate the development of prophylactic strategies, such as the integration of antimicrobial therapy within oncological treatment protocols, especially in instances where bacterial viability sustains the transformed phenotype. Such methodologies possess the capacity to augment extant cancer treatment modalities and refine screening initiatives, thereby presenting novel prospects for the prevention and management of cancer.

Author contributions

C.S. and T. conceptualized and developed the methodology. A.H. and M.M.R. prepared the original draft and reviewed and edited the writing M.M. and B.C.S. analyzed the data and reviewed and edited the writing.

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Competing financial interests

The authors have no conflict of interest.

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