

## Review Article

# The Four Horsemen in Colon Cancer

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Received 8 June 2019; Accepted 26 August 2019; Published 29 September 2019

Guest Editor: Hironori Yoshiyama

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Worldwide, neoplasms of the gastrointestinal tract have a very high incidence and mortality. Among these, colorectal cancer, which includes colon and rectum malignancies, representing both highest incidence and mortality. While gallbladder cancer, another neoplasm associated to gastrointestinal tract occurs less frequently. Genetic factors, inflammation and nutrition are important risk factors associated with colorectal cancer development. Likewise, pathogenic microorganisms inducing intestinal dysbiosis have become an important scope to determine the role of bacterial infection on tumorigenesis. Interestingly, in human biopsies of different types of gastrointestinal tract cancer, the presence of different bacterial strains, such as *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica* have been detected, and it has been considered as a high-risk factor to cancer development. Therefore, pathogens infection could contribute to neoplastic development through different mechanisms; including intestinal dysbiosis, inflammation, evasion of tumoral immune response and activation of pro-tumoral signaling pathways, such as  $\beta$  catenin. Here, we have reviewed the suggested bacterial molecular mechanisms and their possible role on development and progression of gastrointestinal neoplasms, focusing mainly on colon neoplasms, where the bacteria *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica* infect.

## 1. Introduction

Worldwide, neoplasms affecting gastrointestinal tract are among the most frequent in incidence and mortality [1]. Gastrointestinal tract neoplasms are including: colon, rectum, stomach, pancreas, biliary tract and esophagus [2]. The main factors associated with development of gastrointestinal tract malignancies are alcohol consumption and smoking [3–5], high fat diets [6–9]; as well as, ageing, gender and race [10–13]. In addition, pathogenic microorganisms such as viruses and bacteria infecting the gastrointestinal tract, are being studied as possible triggers for development of neoplasms. In this regard, the role of *Helicobacter pylori* in the development of gastric cancer has been extensively studied [14]. However, other bacteria have also been associated with development of gastrointestinal neoplasms, especially in colon, rectum and gallbladder. This review describes the possible roles of *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica* on cancer

development. These bacteria have been considered as emerging pathogenic bacteria associated with development of colorectal cancer, which includes colon and rectum neoplasms, [15]. Here, we have focused on colon cancer, a neoplasia with a very high incidence on worldwide population, registering in 2018; 850,000 new cases and a mortality rate of 550,000 individuals [1].

## 2. *Fusobacterium nucleatum*

*Fusobacterium nucleatum* (*F. nucleatum*) is an adherent and invasive Gram-negative anaerobic bacterium. *F. nucleatum* resides mainly in oral cavity and is usually associated with periodontal disease [16]. Nevertheless, in last years, this bacterium has been detected in primary lesions [17], biopsies [18, 19], and stools [20] of patients with colon cancer, so bacterium has also been linked to development and progression of this neoplasia. In addition, different regions of human colon are colonized by *F. nucleatum* [21]. However,

in patients with colon cancer, *F. nucleatum* has been located mainly on cecum and rectum [22, 23], where it is preferentially localized into tumor tissue [24, 25]. An important factor associated with *F. nucleatum* recruitment into tumor is over-expression of Gal-GalNAc molecules by tumor cells, which promote bacterial adhesion via Fap2 protein [26]. Likewise, high levels of anti-*Fusobacterium* IgA and IgG antibodies have been detected in sera of colon cancer patients [27], which could be used as biomarkers in early diagnosis of this neoplasia. Additionally, infection by *F. nucleatum* has been associated with a low survival of colon cancer patients [28], as well as increased resistance to chemotherapy treatment [29].

Previous studies have reported the association of *F. nucleatum* and colon cancer, although the presence of this bacterium in infected people is highly variable and inconsistent. In this regard, infection with *F. nucleatum* has been detected in 15% of North American population with colon cancer, while more than 60% of infected patients have been found in Chinese population [25, 28, 30, 31]. Interestingly, common characteristics found in all colon cancer patients with *F. nucleatum* infection were microsatellite instability (MSI), methylation phenotype of CpG island (CIMP), as well as *BRAF* and *KRAS* genes mutations [23, 25, 32].

On the other hand, infection with *F. nucleatum* in C57BL/6 APC<sup>Min/+</sup> mice induced tumorigenesis regardless of colitis development [20], unlike the infection by enterotoxigenic *Bacteroides fragilis*, which initially produces colitis and subsequently tumors [33]. Therefore, several mechanisms inducing tumor by *F. nucleatum* have been proposed, including  $\beta$  catenin signaling pathway activation, which is upregulated in colon cancer [34]. In this pathway,  $\beta$  catenin is phosphorylated by PAK-1 through *F. nucleatum*-TLR4 interaction [35]. Likewise, binding of *F. nucleatum* FadA adhesin to E-cadherin expressed on host cells activates the Wnt/ $\beta$  catenin pathway promoting cell proliferation [36]. Additionally, a significant decrease on expression of TOX family proteins (thymocyte selection-associated high-mobility group box) after *F. nucleatum* infection has been shown [37]. These proteins regulate important cellular functions such as growth, apoptosis, DNA repair and metastatic processes [38]. Interestingly, an important decrease on TOX family proteins expression has been associated with advanced tumors.

Another mechanism associated with development and progression of colon cancer induced by *F. nucleatum* have been linked to inflammation. Thus, in colon cancer patients infected with *F. nucleatum*, an important increase on TNF- $\alpha$  and IL-10 expression levels have been shown in adenomas, a precursor lesion of colon cancer [17]; while into tumor, IL-6 and IL-8 increased levels were induced by *F. nucleatum*. Both IL-6 and IL-8 are proinflammatory cytokines regulated by NF- $\kappa$ B transcription factor, a link between inflammation and cancer; and NF- $\kappa$ B activation has been also shown in colon cancer [18, 36]. Additionally, *F. nucleatum* infection increased the chemokine CCL20 expression [39], a chemokine related with both colon cancer progression [40], and Th17+ lymphocytes mediated inflammatory

response [41]. Likewise, *F. nucleatum* induced inflammation could be regulated by microRNAs, such as miR-135b; because a correlation between *F. nucleatum* and miR-135b overexpression in colon cancer patients has been found [42]. So it has suggested that miR-135b could also be used as a biomarker in early detection of colon cancer [43]. However, the role of *F. nucleatum* in development and progression of colon cancer remains to be understood.

Finally, microsatellite instability (MSI) in colon cancer has been linked to capability to evade immune response by *F. nucleatum* infected tumor cells [31]. In this fact, CD3+ [32], and T CD4+ lymphocytes subsets were decreased into the tumor after *F. nucleatum* infection [37], but proportions of T CD8+, CD45RO+, or FOXP3+ lymphocytes subsets were not modified [32]. In addition, the binding of *F. nucleatum* Fap2 protein with TIGIT [44], a receptor with tyrosine-based inhibitory motif (ITIM) expressed on NK cells [45], leads to an important decreased on lymphocytes infiltration into tumor. This way, tumor is protected from an effective immune cells attack [44]. The proposed mechanisms are summarized in Figure 1(a).

### 3. *Escherichia coli*

*Escherichia coli* (*E. coli*) is a Gram-negative bacterium widely distributed in nature, including human intestinal microbiome. The *E. coli* strains are classified into 5 phylogenetic groups: A, B1, B2, D, and E [46]. The main *E. coli* strains associated with human disease belong to B2 group and are also related to colon cancer [47, 48]. To date, the role of pathogenic *E. coli* strains in carcinogenesis is not completely known; however, chronic inflammation in gastrointestinal tract that they promote has been suggested as the trigger mechanism [49]. Because, this chronic inflammation induces pathologies such as Crohn's disease [50], an important risk factor to develop colon cancer [51]. Alternatively, molecular mechanisms induced directly by bacteria have been described. *In vitro* studies have shown that pathogenic strains such as Adherent-Invasive *Escherichia coli* (AIEC) and Enteropathogenic *Escherichia coli* (EPEC), secrete cyclomodulin colibactin [52] and effector protein EspF [53], respectively, which are involved in development and progression of colon cancer. Although the specific mechanisms associated to colon cancer induced by pathogenic *E. coli* have started to become elucidated recently. The molecular mechanisms associated to colon cancer and pathogenic *E. coli* are described in Figure 1(b).

**3.1. Adherent-Invasive *Escherichia coli*.** The main pathogenic *E. coli* strain found in tumor tissue from colon cancer patients is Adherent-Invasive *Escherichia coli* or AIEC [54]. On infection, AIEC binds to CEACAM6 (cellular adhesion receptor associated to carcinoembryonic antigen) [55], which is overexpressed on intestinal epithelial cells of both Crohn's disease and colon cancer patients [56]. To date, it is still unknown what induces overexpression of CEACAM6 on the intestinal epithelium in these patients, although it has been shown that IL-6 is related to induction of CEACAM6

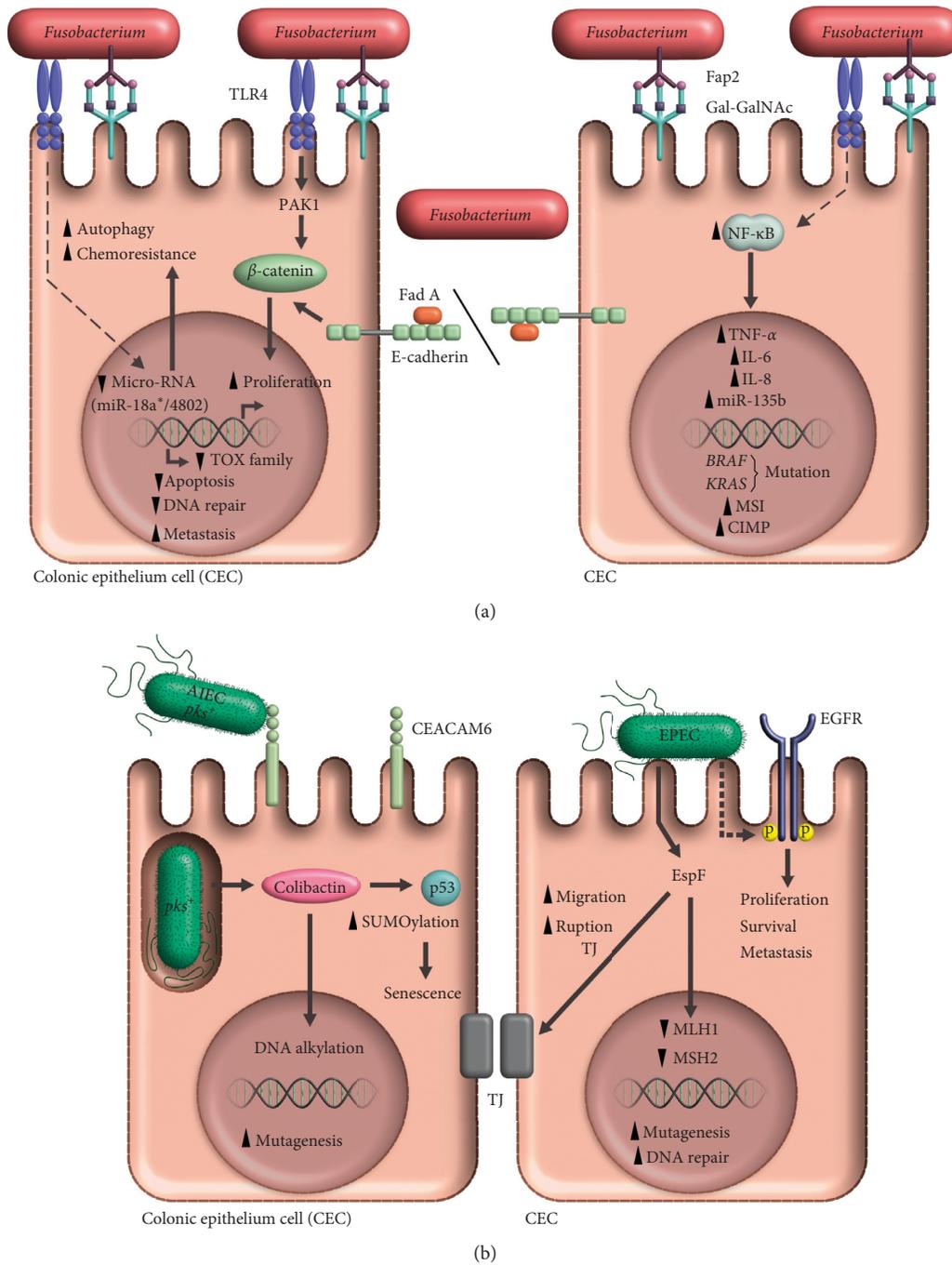


FIGURE 1: Oncogenic activity of *Fusobacterium nucleatum* and *Escherichia coli*. (a) Gal-GalNAc overexpression in colon cells promotes the recruitment of *Fusobacterium nucleatum* via the Fap2 protein. After interacting with TLR4, the bacterium activates the protein PAK 1 and in turn,  $\beta$  catenin; the latter can also be activated through the effect of FadA on E-Cadherin. Activation of these signaling pathways promotes cellular proliferation and decreases proteins of the TOX family, which are associated with decreased apoptosis, failures in DNA repair and increased metastases. Likewise, bacterial interaction with TLR4 and its signaling via MYD88, modulates specific microRNAs that activate the autophagy associated with chemotherapy resistance. Also, *Fusobacterium nucleatum* increases the inflammatory process characterized by the presence of cytokines such as TNF- $\alpha$ , IL-6 and IL-8, that are regulated by the transcription factor NF- $\kappa$ B, whose increased activation has also been documented in colon cancer. *Fusobacterium nucleatum* has also been shown to be associated with the development of mutations in the genes *BRAF* and *KRAS*, microsatellite instability (MSI) and the methylation phenotype in CpG islands (CIMP). (b). The Adherent Invasive *Escherichia coli* strain (AIEC) colonizes the intestinal epithelium and uses CEACAM6 to invade the cells of the colonic epithelium; once internalized, it produces colibactin, a cyclomodulin encoded by the *pks* island, that damages DNA by alkylation and promotes the development of mutations. Colibactin also fosters cellular senescence by favoring SUMOylation of p53. Infection with the Enteropathogenic *Escherichia coli* (EPEC) strain, promotes the autophosphorylation of EGFR, a protein associated with an increase in proliferation, survival and metastases; it also decreases the expression of the DNA repair proteins, MLH1 and MSH2, and favors the rupture of tight junctions, a process involved in the development of metastases. All these EPEC-dependent mechanisms have been associated with the EspF protein.

expression [57]. Additionally, it well is known that infection with AIEC stimulates IL-6 production [58]. Taking all these finding together, it is suggested that AIEC could regulate its own infective capacity on intestinal epithelium by both increasing IL-6 production and CEACAM6 expression, and when bacterium has penetrated and invaded the intestinal epithelium, carcinogenesis could be induced through secretion of colibactin, although the true mechanism is not completely known.

**3.2. Colibactin and the *pks* Island.** Colibactin is a cyclo-modulin encoded in the genotoxic *pks* island (polyketide island). The *pks* island has been found in different *E. coli* strains [59, 60]. Colibactin is a secondary metabolite produced by non-ribosomal peptide synthetase (NRPS)-polyketide synthase (PKS) (NRPS-PKS). Although the synthesis of colibactin is not completely known, it has been shown that a multi-enzymatic complex is required in which several genes of *pks* island participate [61, 62]. The main role of colibactin in carcinogenesis has been associated with DNA damage [63], by acting as an alkylating agent [64, 65], inducing DNA mutations and promoting tumor development.

On the other hand, because of the synthesis of colibactin has not yet been achieved, which has prevented the understanding of the molecular mechanism of this cyclo-modulin, most studies designed to evaluate the role of colibactin in carcinogenesis have been limited to study the *pks* island function. *In vitro* infection of cell lines with *E. coli pks+* strains induced a cell cycle arrest, aneuploidy and tetraploidy [66, 67]; as well as, cell senescence via miR-20a-5P, which inhibits the expression of SUMO-specific protease 1 (SENP-1) [52]. SENP-1 is a protein that induce deSUMOylation of p53 [68], an important transcription factor involved in regulation of cellular senescence and development of colon cancer [69]. On the other hand, the role of the *pks* island has been evaluated in experimental murine models. The inflammatory environment in mice intestinal epithelium induced upon infection, both spreading of *E. coli pks+* and increased risk of colon cancer were produced [49, 70]. In a xenotransplant murine model, infection with *E. coli pks+* strains lead to a significant increase in tumor size, while infection with *E. coli pks-*strains do not [52].

**3.3. Enteropathogenic *Escherichia coli*.** Enteropathogenic *Escherichia coli* or EPEC, is the second pathogenic strain of *E. coli* associated to colon cancer [71, 72], and it has been suggested that EPEC infection might be involved in some molecular pathways involved in colorectal tumorigenesis [72]. *In vitro* studies have shown that infection with EPEC stimulates macrophage-inhibitory cytokine-1 (MIC-1) production, a cytokine related to metastasis by inducing both, increasing survival and spreading of tumor cells through a GTPase Rho A-dependent pathway [73]. Likewise, autophosphorylation of EGFR receptor, was induced upon EPEC infection [74]; this is a upstream activator of both prosurvival phosphoinositide 3-kinase/Akt and proinflammatory mitogen-activated protein (MAP) kinase pathways. These molecular mechanisms have been

associated with colon cancer [75], and poor prognosis in patients [76].

However, it has been shown that EPEC can degrade EGFR receptor via EspF protein [77]; this effector protein is internalized to epithelial cells through the *E. coli* type III secretion system [78]. Interestingly, this process can be inhibited by EspZ, another protein that is also internalized into epithelial cell through the same secretion system [77]. On the other hand, EspF has also been associated with other mechanism inducing cancer, such as decreasing levels of DNA repair proteins MLH1 and MSH2 (mismatch repair MMR) [53, 71], which are widely related to colon cancer [79]. Further, EspF could also contribute to colon cancer metastasis by promoting detachment and dissemination of tumor cells through rupturing tight junction proteins such as Occludin and Claudin on intestinal epithelium [80].

Finally, other proteins produced by pathogenic *E. coli* strains and related to carcinogenesis have been studied. These proteins include: (1) *Cytolethal distending toxin* (CDT), which blocks cell cycle [81], and induces malignant transformation of epithelial cells [82], (2) *Cycle inhibiting factor* (Cif), which induces nuclear DNA elongation on cells and stimulates DNA synthesis even when infected cells are not actively dividing [83] and (3) *Cytotoxic Necrotizing Factor 1* (CNF1), which induces gene transcription and cellular proliferation by GTPases activation [84].

#### 4. *Bacteroides fragilis*

The *bacteroides* is a normal inhabitant of human intestine and represent about 30% of intestinal microbiota [85]. These bacteria have a very important role on mucosal immune system development [86], and intestinal homeostasis [87]. *Bacteroides fragilis* (*B. fragilis*) is classified within *bacteroides* species and is an anaerobic Gram-negative bacterium colonizing about 0.5% to 2% of whole human intestine [86, 88, 89]. Two *Bacteroides fragilis* strain has been described: (a) non-toxigenic *B. fragilis* or NTBF and (b) toxigenic *B. fragilis* or ETBF, which is characterized by a 6 kb pathogenicity island encoding to a metalloproteinase, also known as *B. fragilis* toxin (BFT) or fragilysin [90], of which 3 isoforms have been identified [91].

It has been shown that while NTBF has a protective effect against the development of colitis and colon cancer [92], ETBF has been associated with a wide variety of clinical manifestations ranging from a simple diarrhea to inflammatory bowel disease and colitis [93], both considered as high-risk factors to develop colon cancer. ETBF has already been associated to colon cancer [88], because bacteria has been detected in stool and biopsies obtained from colon cancer patients [94], particularly in early cancer stages [95]. However, a very low proportion of ETBF has been detected in stools from healthy individuals [96].

Although role of enterotoxigenic *B. fragilis* in development of colon cancer has not been completely described; different studies have shown that carcinogenesis induced by ETBF is through BFT toxin, which is present in ETBF but not in NTBF bacteria strains. BFT toxin is a multifunctional protein; thus, it could induce to tumorigenesis through

several mechanisms including activation of c-Myc [97], and consequently an increase on spermine oxidase (SMO) expression [98], an enzyme increasing reactive oxygen species (ROS), which favors cellular injury and carcinogenesis.

Another possible mechanism of ETBF toxin-mediated carcinogenesis, could be through host immune system dysregulation, inducing the recruitment and accumulation of Treg lymphocytes in intestinal lamina in response to bacteria [99], which subsequently suppress the mucosal Th1 response and polarizing to Th17 lymphocytes response [100] by increasing IL-17 secretion [33]. Interestingly, increased levels of IL-17 have been detected on early weeks post-infection, after that; its expression was decreased. However, in APC<sup>Min/+</sup> mice, the early and temporary increased on IL-17 was enough to trigger tumorigenesis [101]. On this regards, it has been suggested that activation of Stat3 [102] and NF- $\kappa$ B [103] pathways by immune responding cells and colonic epithelial cells (CECs) may be involved [104]. Furthermore, ETBF also polarizes IL-17-secreting TCR $\gamma\delta$ + T lymphocytes [105], promoting the differentiation and recruitment of myeloid-derived suppressor cells (MDSC) into the tumor [106, 107], which has been associated with a poor prognosis of colon cancer patients [108]. Because IL-17 up regulates CXCL1, CXCL2 and CXCL5 chemokines expression, also has been involved on MDSC recruitment [104]. Additionally, T lymphocyte proliferation is inhibited by high levels of Nitric Oxide (NO), and arginase 1 (Arg1) a potent metabolic enzyme induced and produced by an increase on MDSC population [107], this way several mechanisms of evasion of anti-tumor immune response by tumor cells are generated.

Finally, ETBF could trigger carcinogenesis through  $\beta$  catenin pathway activation, by disrupting the adherent E-cadherin gap junctions, similar than *F. nucleatum*, [109, 110]. The molecular carcinogenic mechanisms of ETBF are summarized in Figure 2(a).

## 5. *Salmonella enterica*

*Salmonella enterica* represents a broad range of bacteria, including serotypes such as *Salmonella* Typhi (*S. Typhi*), *Salmonella* Paratyphi (*S. Paratyphi*), *Salmonella* Enteritidis (*S. Enteritidis*) and *Salmonella* Typhimurium (*S. Typhimurium*) [111]. In recent years, development of colon cancer [112], gallbladder cancer [113], and other gastrointestinal tract neoplasms have been associated with *Salmonella enterica* infection. Also, It has been found that bacteria may modulate host immune response [114], promoting carcinogenesis by both DNA damage and increasing proliferation, as well as cell migration through induction of chronic inflammation [115]. At least, two proteins of *Salmonella enterica* have been associated with an increased risk of developing colon cancer. The former is typhoid toxin; a cyclomodulin sharing features with the *E. coli* CDT [116], increasing cellular survival and promoting intestinal dysbiosis [117]. Both mechanisms are involved with development of inflammatory bowel disease and colon cancer [118]. The second protein is AvrA, an effector protein secreted by bacteria through type III Secretion System [119], and it has been detected in stool samples from colon cancer patients [120].

Thus, the main protein of *Salmonella enterica* associated with carcinogenesis is AvrA. It has been suggested that most important role of AvrA in colon cancer may be related to inflammatory and immune response dysregulation, through several mechanisms such as: inhibition of NF- $\kappa$ B signaling pathway [121], inhibition of IL-12, INF- $\gamma$  and TNF- $\alpha$  secretion [122], inhibition of IL-6 transcription and increasing on IL-10 transcription [123]. On the other hand, AvrA has been associated to tumors on intestinal epithelium through activation of Wnt/ $\beta$  catenin, inducing cellular proliferation [124], by both  $\beta$  catenin phosphorylation (activation) and deubiquitination (decreased degradation) [125]. These mechanism are important in signaling pathway associated with colon cancer development [126]. Likewise, JAK/STAT signaling pathway is activated by AvrA [127], which regulates several mechanisms such as: apoptosis, cellular proliferation and differentiation, as well as inflammatory response, all these important events involved in carcinogenesis [128]. Additionally, the function of p53 transcription factor is affected by AvrA acetyl transferase activity [129], leading to cell cycle arrest and inhibition of apoptosis by decreasing pro-apoptotic proteins (such as Bax), dependent of p53 acetylation [130]. The carcinogenic mechanisms associated to *Salmonella enterica* are summarized in Figure 2(b).

**5.1. *Salmonella enterica* and Gallbladder Cancer.** Gallbladder cancer is the main type of neoplasia affecting the biliary tract. Worldwide, the incidence of this neoplasia is low. Interestingly, it has been shown that gallbladder cancer occurs more frequently in geographic regions with a high incidence of *Salmonella* infection [113, 131–134]. Therefore, a greater interest has been generated in searching for a possible association between *Salmonella* infection and development of gallbladder cancer. On this respect, Typhoidal *Salmonella* serotypes as *S. Typhi* and *S. Paratyphi* have been detected in most of the biopsies from patients with gallbladder cancer [113, 135–137], however, DNA traces of Non-typhoidal *Salmonella* serotypes as *S. Typhimurium* and *S. Choleraesuis* have also been found in gallbladder cancer biopsies [135]. These findings have suggested that *Salmonella* (which may be undetected for years, because it can produce biofilm on cholesterol biliary stones [138]), could represent an important risk factor in development of gallbladder cancer [132], because inflammation and epithelial injury associated to cholelithiasis is induced by *Salmonella* [139] and cholelithiasis is a common clinical manifestation in most patients with gallbladder cancer [137]. However, the mechanism triggering carcinogenesis by *Salmonella enterica* in gallbladder is not completely known, but it has been suggested that a chronic inflammation of gallbladder is induced [140], after bacteria arrival to gallbladder from either blood circulation or bile [141].

Additionally, recruitment of some immune cells, including activated macrophages expressing COX-2 is increased upon *Salmonella enterica* infection [142]. COX-2 is an important enzyme that promotes the development of gastrointestinal tract tumors [143, 144]. Also, bacteria induced inflammation leads to mutations of *TP53* gene,

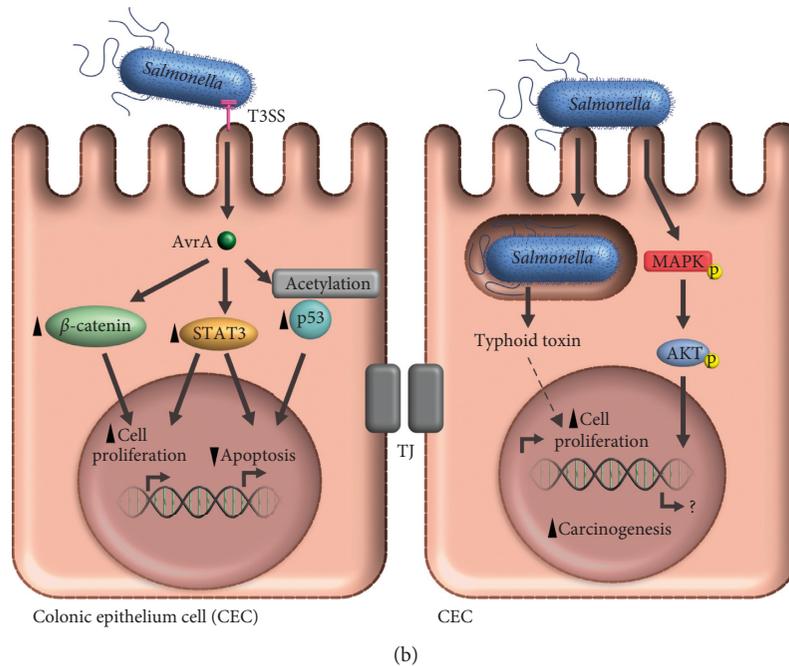
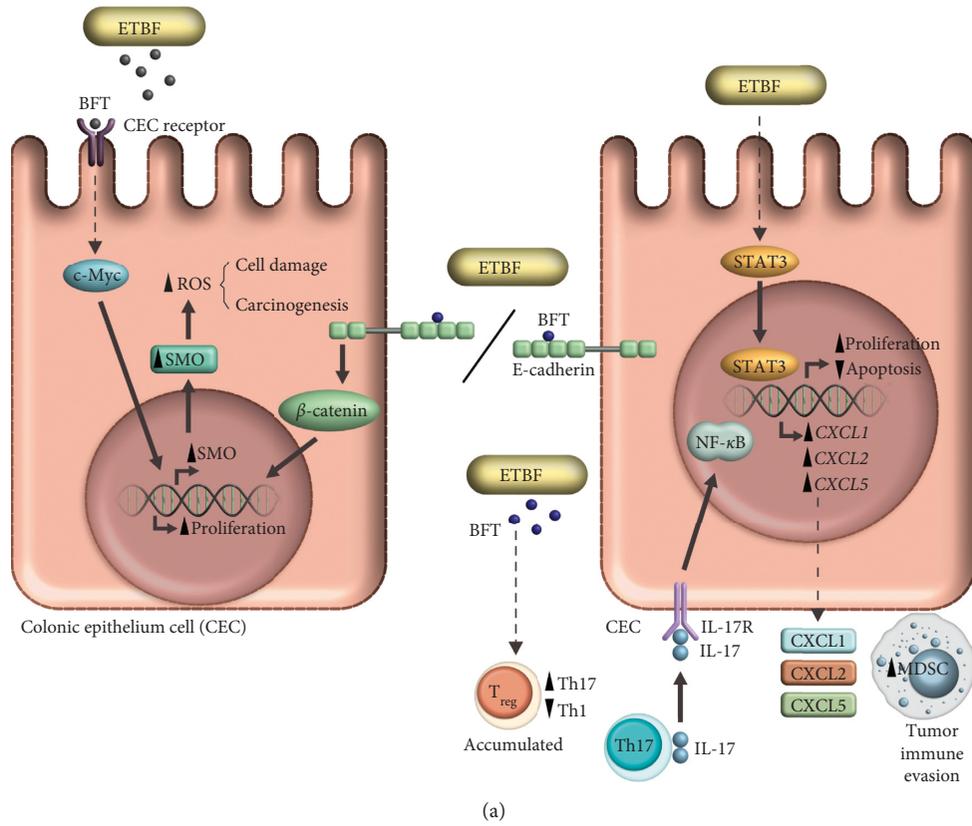


FIGURE 2: Oncogenic activity of *Bacteroides fragilis* and *Salmonella enterica*. (a) Enterotoxigenic *Bacteroides fragilis* (ETBF) stimulates carcinogenesis in colonic epithelium through the BFT toxin. This toxin leads to an increase in reactive oxygen species (ROS) by inducing spermine oxidase expression via c-Myc. Likewise, BFT cuts E-cadherin, thus activating  $\beta$  catenin which stimulates cellular proliferation. BFT also modulates the host's immune response by promoting Treg lymphocytes to polarize the response to Th17 lymphocytes, thus increasing IL-17 secretion which in turn, activates NF- $\kappa$ B in the colonic epithelium; this results in the secretion of the chemokines CXCL1, CXCL2 and CXCL5 that recruit MDSC, thus favoring evasion from the immune response. The presence of ETBF has also been associated with STAT3 activation. (b). *Salmonella enterica* releases two proteins that promote carcinogenesis: the typhoid toxin that induces cellular proliferation, and the AvrA protein that is internalized via the Type 3 Secretion System(T3SS). AvrA activates the  $\beta$  catenin and STAT3 pathways, and also causes the acetylation of p53. Additionally, *Salmonella enterica* leads to the activation of the MAPK/AKT pathway. The activation of these pathways promotes an increase in proliferation and cellular differentiation, and decreases apoptosis.

increasing the risk of developing gallbladder cancer [145]. Finally, *in vitro* infection of cell lines and gallbladder organoids with *S. Typhimurium*, led to malignant transformation through MAPK and AKT signaling pathways activation. Similarly, *in vivo* activation of these signaling pathways resulted in tumor development in mice [134].

## 6. Conclusions

Recently, the number of publications referring an association between pathogenic bacteria and development of gastrointestinal tumors, has increased exponentially. The best example and widely reported is *Helicobacter pylori* and gastric cancer. However, emerging bacteria such as *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica* have also been involved in development of cancer, particularly colon cancer.

In this review, it is suggested that infection by pathogenic bacteria may be a high-risk factor associated with the development of neoplasms in gastrointestinal tract. Mechanisms such as, inflammation, modulation and evasion of immune response and activation of signaling pathways, such as the  $\beta$ -catenin pathway; all are potential triggers of carcinogenesis.

The inducing tumor mechanisms can be evaluated in murine models, such as APC<sup>Min/+</sup>, a specific mice model to study intestinal tumorigenesis [146]. In this experimental model, developing colon cancer mechanisms by *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica* have been identified. However, effects of coinfection with these bacteria and tumor development remains to be analyzed, because ETBF and *E. coli pks+* strains have been found simultaneously in patients with adenomatous polyps, a precursor lesion of colon cancer [147]. Nevertheless, ETBF is a very common bacterium in colon cancer patients but also in healthy individuals [96], so it remains to be elucidated whether ETBF has a role on induction of carcinogenesis. Another possible mechanism through bacteria may trigger cancer is by biofilm. This structure produced by a community of bacteria, more common in ascending colon [148], could increase carcinogenic metabolites concentration, such as polyamines [149], which are related to an important increase on reactive oxygen species. In addition, biofilm has been associated with decreased expression of E-cadherin on colonic epithelial cell, an over activation of IL-6 and Stat3 in epithelial cell [148], all these mechanisms are involved in colon cancer. The mechanisms above described, are used by *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica*. Therefore, further studies are required to understand the specific roles of these four bacteria in development of neoplasms on gastrointestinal tract, specifically in colon cancer.

## 7. Future Perspectives

Worldwide, colon cancer has very high incidence and mortality. Here we have described that infection with either bacteria such as *F. nucleatum*, *E. coli*, *B. fragilis* or *S. enterica* represent an important risk factor that promote cell

transformation (carcinogenesis). In this regards, detection of promoting carcinogenesis bacterial proteins, such as cyclomodulin, colibactin, BFT, AvrA or EspF may be used as a biomarker for early detection of colon cancer, as it has been proposed for Fap2 [150]. Because early detection of tumor can increase both healing and survival. Moreover, it would generate new and appropriate strategies to block bacterial proteins activity, thus complementing the traditional treatment to neoplasms of gastrointestinal tract.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

## Acknowledgments

R. L. P. Acknowledges support from CONACYT (CB-2013-01-222446, INFR-2015-01-255341, PN-2015-01-1537) and Federal Funds (HIM-2016-114 SSA. 1333, HIM-2017-041 SSA. 1325).

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