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Review Article

ROLE OF *FUSOBACTERIUM* IN COLORECTAL CANCER

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ABSTRACT
The human intestinal microbiota inhabits a complex and diverse environment populated by hundreds of different bacterial species. The human gut microbiota is increasingly recognized as a player in colorectal cancer (CRC). Recent studies have implicated over-abundance of *Fusobacterium* in association with colorectal adenomas and cancer. However, the precise mechanisms by which bacterial dysbiosis may be related to colorectal cancer are not known. This paper critically reviews the current evidence in association of *Fusobacterium* with colorectal adenomas and cancer.

Key Words: *Fusobacterium, Colorectal Cancer, Microbiota*

INTRODUCTION
The intestine harbors a massive and diverse microbiota which can reach a density of 10^{12}organisms/g and is comprised of more than 1000 species, including both anaerobes and aerobes, containing at least 100 times as many genes as within our own genome. Gut microbiota provides huge benefits to their host, including the breakdown of indigestible food, the supply of energy for colonicepithelial cells, and a barrier against invasive pathogenic bacteria; they also have a major impact on many host systems, particularly on the development of the intestine and the immune system (Liu *et al.,* 2013; Ley *et al.,* 2006; Belkaid and Naik, 2013).
16% of cancers are microbiological in etiology, which is to say the cancers are almost certainly due to viruses or bacteria. *Helicobacter pylori*, hepatitis B and C viruses, and human papilloma virus are thought to have caused just under 2 million cancers worldwide in 2008. And this is not even counting the cancers caused by aflatoxins.
If recent research is correct, it appears we may now be able to add another major cancer to the list of neoplastic diseases caused by a microbe. Colorectal cancer, which is on the rise in all developed countries and many developing ones, may turn out to be caused by a bacterium, an extraordinarily tiny bug called *Fusobacterium* spp. (Hausen, 2009; Polk and Peek, 2010; Parkin, 2006). Fuso bacteria are obligately anaerobic non-sporeforming gram-negative bacilli, forming part of the family Bacteroidaceae.*Fusobacterium* spp. are sensitive to kanamycin, and most strains fluoresce a chartreuse color (Benntt and Eeley, 1993; Stephen and Peter, 2006).
Several recent studies suggest a link between bacterial dysbiosis in the gut and colorectal adenomas and cancer. However, the precise mechanisms by which bacterial dysbiosis may be related to colorectal cancer (CRC) are not known (Sanapareddy *et al.*, 2012; Sobhani *et al.*, 2011; Keku *et al.,* 2013; McCoy *et al.*, 2013).

Fusobacterium spp.
The genus *Fusobacterium* is now defined in biochemical and genetic terms as encompassing Gram-negative non-sporing anaerobes with DNA G±C content of 27–33 mol% that produce butyric and propionic acids as major metabolic products. Many that conform to this description do not exhibit the classical fusiform appearance (Table 1).
The more significant members of the genus in human disease are *F. necrophorum* and *F. nucleatum*. Colonial appearance is also varied, but most fusobacteria produce moderate to large colonies, 1–3 mm in diameter, generally with an irregular or dentate edge. They vary from translucent to granular and opaque (Benntt and Eeley, 1993; Stephen and Peter, 2006; Citron, 2002).

Table 1: The main human sources of *Fusobacterium* isolates

Species	Mouth	Gastrointestinal tract	Clinical specimens
F. nucleatum	+	+	+
F. necrophorum	-	+	+
F. alocis	+	-	-
F. gonidiaformans	-	+	+
F. mortiferum	-	+	+
F. naviforme	+	-	+
F. necrogenes	-	+	-
F. periodonticum	+	-	-
F. prausnitzii	-	+	-
F. russii	-	+	-
F. sulci	+	-	-
F. ulcerans	-	-	+
F. varium	-	+	+

Fusobacteriumnucleatum

*F. nucleatum*is a Gram negative, nonspore forming, strictly anaerobic species of the *Fusobacteriaceae* family, which currently consists of 9 genera, including *Fusobacterium* and *Leptotrichia*. Within the *Fusobacterium* genus there are currently14 species described, several of which (including *F. nucleatum*) are known pathogens of man and animals (Citron, 2002; Kolenbrander *et al.,* 2006). *F. nucleatum*is a highly heterogeneous species and has been the subject of various schemes attempting to classify strains into subspecies or other groupings. Currently, five subspecies are recognized; *animalis, fusiforme, vincentii, polymorphum* and *nucleatum* (Strauss *et al.,* 2008). *F. nucleatum*is associated with many conditions and diseases.

It has been isolated from numerous inflammatory processes, including sinusitis, endocarditis, septic arthritis, tonsillitis and abscesses of the brain, skin and liver (Shammas *et al.,* 1993). The role of infectious agents in cancer etiology is increasingly recognized with an estimated 15% of the world's burden of cancer attributable to known bacterial and viral pathogens. Recently, two independent studies using metagenomics to probe the prevalence of potential infectious agents associated with colorectal cancer. Together both studies indicate that live, invasive *F. nucleatum* cells are associated with colorectal cancer (Parkin, 2006; Castellarin *et al.,* 2012; Kostic *et al.,* 2011).

Colorectal Cancer

Colorectal cancer, also known as colon cancer, rectal cancer, or bowel cancer, is a cancer from uncontrolled cell growth in the colon or rectum. Symptoms of colorectal cancer typically include rectal bleeding and anemia which are sometimes associated with weight loss and changes in bowel habits. Colorectal cancer is the third most common cancer and the fourth most common cancer cause of death globally, accounting for roughly 1.2 million new cases and 600000 deaths per year. Incidence is low at ages younger than 50 years, but strongly increases with age. Median age at diagnosis is about 70 years in developed countries.

The highest incidence is reported in countries of Europe, North America, and Oceania, whereas incidence is lowest in some countries of south and central Asia and Africa (Siegel *et al.,* 2012; Center *et al.,* 2009). 75-95% of colon cancer occurs in people with little or no genetic risk. Other risk factors include older age, male gender, high intake of fat, alcohol or red meat, obesity, smoking and a lack of physical exercise. People with inflammatory bowel disease (Crohn's disease) are at increased risk of colon cancer (Watson and Collins, 2011; Cunningham *et al.,* 2010). Several recent studies suggest a link between bacterial dysbiosis in the gut and colorectal adenomas and cancer (Sobhani *et al.,* 2011; Keku *et al.,* 2013; McCoy *et al.,* 2013; Castellarin *et al.,* 2012; Kostic *et al.,* 2011).

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Fusobacterium spp. and Colorectal Cancer

The microbiota exerts both beneficial and detrimental effects on host contributing to health or disease (Sekirov *et al.,* 2010). Recent studies have implicated over-abundance of *Fusobacterium* in association with colorectal adenomas and cancer. However, the precise mechanisms by which bacterial dysbiosis may be related to colorectal cancer are not known (Figure 1). In 1971, a study intended to identify associations between human microbiota composition and colorectal carcinogenesis, but it had to be abandoned because of technical difficulties. Later, Moore and co-workers reported that 13 bacterial species were significantly associated with a high risk of colon cancer and the Western diet (Sobhani *et al.,* 2011; Savage, 1977). In study Kostic *et al.,* (2011) *F. nucleatum* presence was confirmed in situ in tumor tissue (Kostic *et al.,* 2011).

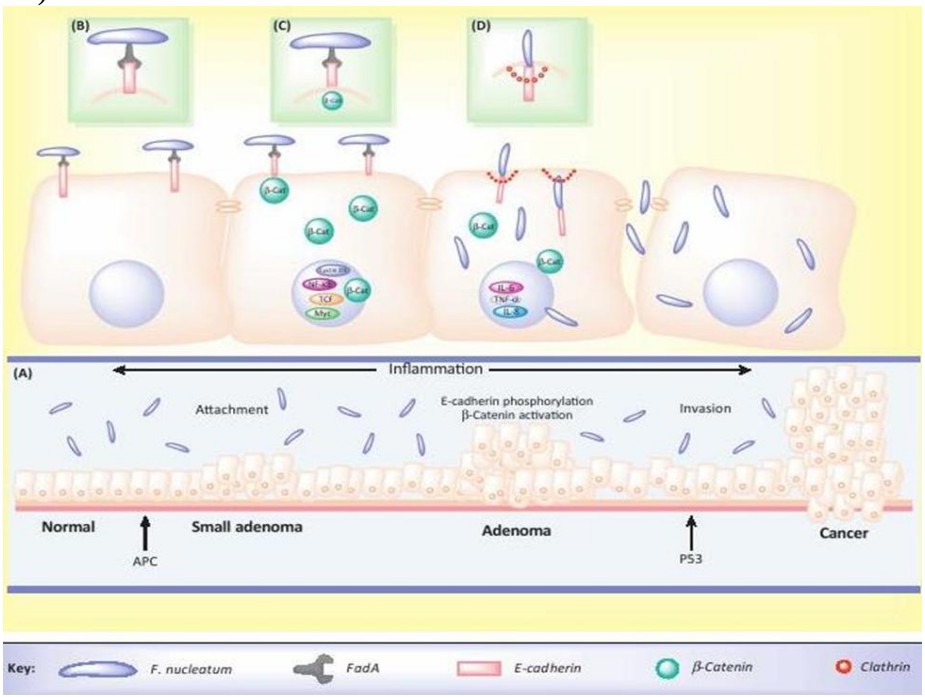

Figure 1: Potential mechanisms by which *Fusobacterium* promotes colorectal carcinogenesis. In the presence of APC mutation, *F. nucleatum* promotes oncogenesis in the colon via adhesinFadA through attachment, phosphorylation and invasion (A). FadA binds to E-cadherin on the surface of the cell, inhibiting its tumor-suppressor activity and activating b-catenin signaling (B). b-catenin phosphorylation is decreased, resulting in increased b-catenin in the cytoplasm and translocation into the nucleus where it modulates increased expression of LEF, TCF, NF-kb, and other oncogenes (C). *F. nucleatum* invades the cell via internalization of E-cadherin by clathrin (D) and stimulates (Keku *et al.,* 2013).

In the other study by Castellarin *et al.,* (2012) a *F. nucleatum* strain was recovered from a frozen biopsy sample and subsequently found to be invasive in Caco-2 cells (Castellarin *et al.,* 2012). In study, McCoy *et al.,* (2013) results support a link between the abundance of *Fusobacterium* in colonic mucosa and adenomas and suggest a possible role for mucosal inflammation in this process (McCoy *et al.,* 2013).

Conclusion

The human colon contains up to 10^{14} bacteria. They play a major role in the fermentation of residual food, the modulation of gut immune function, and protection against pathogens and diseases. Although the intestinal microbiota is largely beneficial, changes in bacterial populations or in the products of bacterial metabolism may contribute to disease. This review provides information about the role of *Fusobacterium*

in colorectal cancer. Recent studies have implicated over-abundance of *Fusobacterium* in association with colorectal adenomas and cancer. However, the precise mechanisms by which bacterial dysbiosis may be related to colorectal cancer are not known.

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