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The Roles for Fusobacterium Nucleatum in Human Colorectal Carcinogenesis

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Abstract

Colorectal cancer (CRC) is one of the most common malignant tumors. There are many risk factors involved in CRC. According to recent findings, Fusobacterium nucleatum (F. nucleaum) are closely related to the progression of CRC. Studies have found that F. nucleaum may contribute to the development and prognosis of inflammation and CRC. The factors of the pathogenicity of *F. nucleaum* include its adhesion, its metabolite butyric acid, the cell factor of the host, and so on. Underlying mechanisms of F. nucleatum in CRC remain to be established.

Keywords: Colorectal cancer (CRC); Fusobacterium nucleatum; Pathogenicity; Adhesion; Butyric acid

Introduction

The Roles for Fusobacterium Nucleatum in Human Colorectal Carcinogenesis

Colorectal cancer (CRC) is one of the most common malignant tumors [1]. Intestinal microorganisms can affect the development of intestinal tumors by regulating the proliferation and differentiation of intestinal epithelial cells, providing nutrition, participating in angiogenesis and apoptosis [2-6]. In recent years, more and more evidences have shown that some *Fusobacterium*, especially *Fusobacterium nucleatum (F. nucleaum*), are closely related to the progression of CRC. F. nucleaum, gram-negative obligate anaerobe, periodontal pathogenic bacteria, widely exists in the dental plaque biofilm, which plays an important role in the formation, metabolism and succession of biofilm. *F. nucleaum* is invasive, adhesive and proinflammatory, and has a high detection rate in oral and systemic infectious diseases [7]. To explore the roles for *F. nucleatum* in colorectal carcinogenesis has become a research hotspot recently and attracts more and more attention. In this paper, studies in correlation between *F. nucleatum* and colorectal cancer are reviewed.

F. nucleatum Biological Characteristics and Distribution

F. nucleatum is a gram-negative, nonspore-specific obligate anaerobe with sharp ends and a spindle-shaped center. The optimum growth temperature of *F. nucleatum* was 37°C, and the colony on the blood plate was flat, irregular edge and convex translucent, which was like glass or bread crumbs. *F. nucleatum* is a normal flora of the human and animal oral, upper respiratory, intestinal and urogenital tracts, and can also be isolated from clinical specimens of each infection site.

Pathogenic Mechanisms of *F. Nucleatum*

The Adhesion and Invasion of *F. Nucleatum*: *F. nucleatum* can adhere to the surface of epithelial cells, fibroblasts, endothelial cells and other host cells and bind to saliva macromolecules, extracellular matrix proteins, antibody IgG, et al. It interferes with the key components of host cell mucosal barrier to regulate the expression of host cell mucin and stimulate a series of host reactions to cause disease [8]. *F. nucleatum* can adhere to and invade host cells by secreting many adhesins such as Fap2 and RadD and enhance the adhesion and invasion of copolymers to epithelial cells [9]. Han et al. found that a new adhesive FadA（Fusobacterium nucleatum adhesin A） can bind to the surface protein of KB cells in oral mucosa [10]. In 2007, Xu et al. constructed FadA gene deficient and complementary strains. The results showed that the binding capacity of FadA gene deficient strains to cells decreased by 70%-80%, while that of complementary strains increased by 3-4 times, which proved that FadA was closely related to the adhesion of *F. nucleatum* [11]. Fardini et al. found that the receptor of FadA was Endothelial cadherin (E-cadherin). The essential condition for *F. nucleatum* to attach cells efficiently was that there was cadherin on the surface of the host cell membrane [12].

Interaction between *F.Nucleatum* and Host Immune Cells: The effect of *F. nucleatum* on immune cells is mainly manifested in two aspects: immunosuppression and promoting inflammation.

The human immune system mainly has three lines of defense, the most important of which is the cellular immunity in the third line. Fap 2 and Rad D secreted by *F. nucleatum* can induce apoptosis of human T lymphocytes and loss of cellular immunity, resulting in tumor immune escape [13]. Butyric acid, a metabolite of *F. nucleatum*, can also induce apoptosis of host monocytes and lymphocytes [14]. Swidsinski et al. detected the bacterial flora in 70 cases of acute appendicitis. It was found that the presence of *F. nucleatum* in mucosal lesions was positively correlated with the severity of appendicitis and did not exist in cecum biopsy tissues of healthy and disease-control subjects [15]. This can largely prove that *F. nucleatum* can promote inflammation.

Interaction between *F. nucleatum* and Host Epithelial Cells: Adhesion to epithelial cells is important for bacterial colonization. Invasion allows bacteria not only to escape the host's immune surveillance, but also to spread to deeper tissues. The effect of *F. nucleatum* on epithelial cells is mainly manifested in promoting epithelial cell proliferation and inflammatory reaction. *F. nucleatum* can promote colonic epithelial cells proliferation and inflammation by secreting FadA binding E-cadherin and invading epithelial cells, which can activate the β-catenin signaling pathway and lead to increased expression of transcription factors, oncogenes, Wnt genes and inflammatory genes, as well as growth stimulation of colorectal cancer cells [16]. Studies have shown that *F. nucleatum* can invade the epithelial cells of esophageal cancer and promote the proliferation of tumor cells by stimulating the production of inflammatory cytokine IL-6 [17]. Wang kun et al. [18] found that the expression levels of proinflammatory cytokines IL-1β、IL-8 and TNF-α in human intestinal epithelial cells (Caco-2) infected with *F. nucleatum* were significantly higher than that in the control group at both transcriptional and protein levels, and the expression level of proinflammatory cytokines was the highest 6 hours after infection. These results indicated that *F. nucleatum* could promote epithelial cell inflammation.

***F. nucleatum* Promotes Colorectal Carcinogenesis:** Studies found that the detection rate of *F. nucleatum* in oral cavity, feces and tumor tissues of CRC patients were higher than that of healthy people [19-22]. Flanagan et al. [23] and Kostic et al. [22] provide strong evidence for the relationship between *F. nucleatum* and CRC. Kostic et al. [24] confirmed that the number of *F. nucleatum* in the stool of patients with colon adenocarcinoma and CRC was significantly higher than that of healthy people, and the number of *F. nucleatum* in the CRC group was significantly higher the colon adenocarcinoma group. Flanagan et al. [23] found that the number of *F. nucleatum* was not significantly different in different tumor sites (colon or rectum) and tumor stages. However, in different stages of CRC progression, the number was significantly different. The number of *F. nucleatum* increased gradually from tubular adenoma to villous adenoma, and then to highly dysplasia, and there was significant difference between them. These results indicated that the high number of *F. nucleatum* was closely related to the progress of adenoma and the process of adenoma transformation into cancer. Survival analysis showed that the mean survival time of the patients (2 years) with a high number of *F. nucleatum* was significantly less than that of the patients (>3 years) with or without a low number of *F. nucleatum*, suggesting that the level of *F. nucleatum* could be an independent prognostic factor for CRC.

Molecular mechanism of *F. nucleatum* in the development of colorectal cancer

Surface adhesion protein (FadA) is the main component mediating *F. nucleatum* adhesion and invasion [11], it adheres to and invades different types of host cells by binding to the corresponding regions of different types of cadherin [12]. Rubinstein et al found that the binding of FadA to epithelial cadherin (E-Cadherin) mediates the adhesion and invasion of *F. nucleatum*. The interaction between FadA and E-Cadherin plays an important role in *F. nucleatum* promoting the growth of colorectal cancer [16]. E-Cadherin is a tumor suppressor that acts through β-catenin [25]. The binding of FadA to E-Cadherin increased phosphorylation of E-Cadherin and decreased phosphorylation of β-catenin. Then β-catenin aggregates in the cytoplasm and translocate to the nucleus, resulting in increased transcriptional activation regulated by β-catenin and increased expression of proinflammatory and oncogenic genes. Inflammation plays an important role in the development of CRC. *F. nucleatum* can activate NF-kappa B by retinoic acid-inducible gene-I (Rig-I), a cytoplasmic receptor associated with RNA virus recognition, and cause an increased expression of the pro-inflammatory genes, leading to an inflammatory response [26]. The increased activation of NF-kappa B was consistent with the increased abundance of Clostridium [24], suggesting that inflammation induced by *F. nucleatum* further enhances the tumorigenic potential of *F. nucleatum* [16].

Butyrate is a product of dietary fiber fermented and decomposed by intestinal microorganisms, which plays an important role in maintaining intestinal health, including regulating host immune response, reducing DNA oxidative damage of intestinal epithelial cells, inducing differentiation and apoptosis of cells suffering DNA damage [27]. More importantly, butyrate inhibits the release of inflammatory factors and protects the intestinal mucosal barrier [28,29]. In cancer microenvironment, the decrease of *F. nucleatum* butyrate metabolism has a synergistic effect on promoting inflammatory response [30]. Whether there is a bidirectional effect between *F. nucleatum*-induced inflammation and tumor development remains to be further studied.

Conclusion

Although there is increasing evidence that Clostridium is associated with CRC, the abundance of Clostridium in tumors is increased in only a few patients, and the relative abundance is significantly different in different patients [24]. *F. nucleatum* can also be detected in healthy human tissues, and its abundance may be high, so it is not feasible to use *F. nucleatum* as a single biological marker at present. The specific mechanism *between F. nucleatum* and colorectal cancer still needs to be clarified. In the future, *F. nucleatum* may be used as a marker to predict disease progression and prognosis. In addition, butyric acid is the main metabolite of Clostridium, some studies showed that butyric acid has a protective effect on CRC, but other studies indicated that butyrate can promote the development of colon cancer. Its role in tumor development is

complex and depends on host genotypes, microbial composition, and the presence of other metabolites [31]. Therefore, it remains to be confirmed whether butyric acid plays a role in promoting the development of colon tumors by *F. nucleatum*. The study of *F. nucleatum*'s effect on the development and prognosis of colorectal tumors provides a new idea for the prevention and treatment of CRC.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108.
2. Chen HM, Yu YN, Wang JL, Lin YW, Kong X, et al. (2013) Decreased dietary fiber intake and structural alteration of gut microbiota in patients with advanced colorectal adenoma. Am J Clin Nutr 97: 1044-1052.
3. Geng J, Fan H, Tang X, Zhai H, Zhang Z (2013) Diversified pattern of the human colorectal cancer microbiome. Gut Pathog 5(1): 2.
4. Shen XJ, Rawls JF, Randall T, Burcal L, Mpande CN, et al. (2010) Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas. Gut Microbes 1: 138-147.
5. Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, et al. (2011) Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One 6: e16393.
6. Wang T, Cai G, Qiu Y, Fei N, Zhang M, et al. (2012) Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. Isme j 6: 320-329.
7. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, et al. (2012) Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res 22: 299-306.
8. Han YW, Shi W, Huang GT, Kinder Haake S, Park NH, et al. (2000) Interactions between periodontal bacteria and human oral epithelial cells: Fusobacterium nucleatum adheres to and invades epithelial cells. Infect Immun 68: 3140-3146.
9. Hashemi Goradel N, Heidarzadeh S, Jahangiri S, Farhood B, Mortezaee K, et al. (2018) Fusobacterium nucleatum and colorectal cancer: A mechanistic overview. J Cell Physiol.
10. Han YW, Ikegami A, Rajanna C, Kawsar HI, Zhou Y, et al. (2005) Identification and characterization of a novel adhesin unique to oral fusobacteria. J Bacteriol 187: 5330-5340.
11. Xu M, Yamada M, Li M, Liu H, Chen SG, et al. (2007) FadA from Fusobacterium nucleatum utilizes both secreted and nonsecreted forms for functional oligomerization for attachment and invasion of host cells. J Biol Chem 282: 25000-25009.
12. Fardini Y, Wang X, Temoin S, Nithianantham S, Lee D, et al. (2011) Fusobacterium nucleatum adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity. Mol Microbiol 82: 1468-1480.
13. Kaplan CW, Ma X, Paranjpe A, Jewett A, Lux R, et al. (2010) Fusobacterium nucleatum outer membrane proteins Fap2 and RadD induce cell death in human lymphocytes. Infect Immun 78: 4773-4778.
14. Abe K (2012) Butyric acid induces apoptosis in both human monocytes and lymphocytes equivalently. J Oral Sci 54: 7-14.
15. Swidsinski A, Dorffel Y, Loening Baucke V, Theissig F, Ruckert JC, et al. (2011) Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/necrophorum. Gut 60: 34-40.
16. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, et al. (2013) Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling via its FadA adhesin. Cell Host Microbe 14: 195-206.
17. Baba Y, Iwatsuki M, Yoshida N, Watanebe M, Baba H (2017) Review of the gut microbiome and esophageal cancer: Pathogenesis and potential clinical implications. 1: 99-104.
18. Wang k, Jia y, Zhu P, Li Q, Mao X (2015) Fusobacterium nucleatum induces inflammation and apoptosis in cultured intestinal epithelial Caco-2 cells. Immunological Journal 31: 331-338.
19. Chen W, Liu F, Ling Z, Tong X, Xiang C (2012) Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. PLoS One 7: e39743.
20. McCoy AN, Araujo Perez F, Azcarate Peril A, Yeh JJ, Sandler RS, et al. (2013) Fusobacterium is associated with colorectal adenomas. PLoS One 8: e53653.
21. Warren RL, Freeman DJ, Pleasance S, Watson P, Moore RA, et al. (2013) Co-occurrence of anaerobic bacteria in colorectal carcinomas. Microbiome 1: 16.
22. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, et al. (2012) Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 22: 292-298.
23. Flanagan L, Schmid J, Ebert M, Soucek P, Kunicka T, et al. (2014) Fusobacterium nucleatum associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome. Eur J Clin Microbiol Infect Dis 33: 1381-1390.
24. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, et al. (2013) Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 14: 207-215.
25. Bryant DM, Stow JL (2004) The ins and outs of E-cadherin trafficking. Trends Cell Biol 14: 427-434.
26. Lee P, Tan KS (2014) Fusobacterium nucleatum activates the immune response through retinoic acid-inducible gene I. J Dent Res 93: 162-168.
27. Scharlau D, Borowicki A, Habermann N, Hofmann T, Klenow S, et al. (2009) Mechanisms of primary cancer prevention by butyrate and other products formed during gut flora-mediated fermentation of dietary fibre. Mutat Res 682: 39-53.
28. Hofmanova J, Strakova N, Vaculova AH, Tylichova Z, Safarikova B, et al. (2014) Interaction of dietary fatty acids with tumour necrosis factor family cytokines during colon inflammation and cancer. 2014: 848632.
29. Kozubik A, Louis P, Hold GL, Flint HJ (2014) The gut microbiota, bacterial metabolites and colorectal cancer. Mediators Inflamm 12: 661-672.
30. Baba H, Zackular JP, Rogers MA, Ruffin MT, Schloss PD (2014) The human gut microbiome as a screening tool for colorectal cancer. Ann Gastroenterol Surg 7: 1112-1121.
31. Irrazabal T, Belcheva A, Girardin SE, Martin A, Philpott DJ (2014) The multifaceted role of the intestinal microbiota in colon cancer. Mol Cell 54: 309-320.

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