Published in final edited form as:
Curr Opin Microbiol. 2015 February ; 0: 141–147. doi:10.1016/j.mib.2014.11.013.

Fusobacterium nucleatum: a commensal-turned pathogen

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Abstract

Fusobacterium nucleatum is an anaerobic oral commensal and a periodontal pathogen associated with a wide spectrum of human diseases. This article reviews its implication in adverse pregnancy outcomes (chorioamnionitis, preterm birth, stillbirth, neonatal sepsis, preeclampsia), GI disorders (colorectal cancer, inflammatory bowel disease, appendicitis), cardiovascular disease, rheumatoid arthritis, respiratory tract infections, Lemierre's syndrom and Alzheimer's disease. The virulence mechanisms involved in the diseases are discussed, with a particular emphasis on its colonization, systemic dissemination, and induction of host inflammatory and tumorigenic responses. The FadA adhesin/invasin conserved in *F. nucleatum* is a key virulence factor and a potential diagnostic marker for *F. nucleatum*-associated diseases.

With the advancement of microbial detection technologies, an increasing number of previously overlooked microorganisms have been discovered to play important roles in human diseases. *Fusobacterium nucleatum*, a Gram-negative anaerobe, is such an emerging pathogen that is quickly attracting attention of the medical and research communities. *F. nucleatum* is ubiquitous in the oral cavity, absent or infrequently detected elsewhere in the body under normal conditions [1,2]. Under disease conditions, however, *F. nucleatum* is one of the most prevalent species found in extra-oral sites [3]. *F. nucleatum* is a heterogeneous species with five proposed subspecies (ss), i.e. *ss animalis*, *ss fusiforme*, *ss nucleatum*, *ss polymorphum*, and *ss vincentii*, whose prevalence in disease vary [3–6]. This article reviews the infections implicating *F. nucleatum*, along with the virulence mechanisms involved.

Diseases implicating *F. nucleatum*

Summarized in Table 1 are diseases in which *F. nucleatum* has been implicated.

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Oral infections

F. nucleatum is one of the most abundant species in the oral cavity, in both diseased and healthy individuals [7–10]. It is implicated in various forms of periodontal diseases including the mild reversible form of gingivitis and the advanced irreversible forms of periodontitis including chronic periodontitis, localized aggressive periodontitis and generalized aggressive periodontitis [8–15] (Table 1). It is also frequently associated with endodontic infections such as pulp necrosis and periapical periodontitis [16–22] (Table 1). The prevalence of *F. nucleatum* increases with the severity of disease, progression of inflammation and pocket depth [8,14,23]. Among the five subspecies, *ss fusiforme* and *ss vinvcentii* are more frequently associated with health while *ss nucleatum* with disease [24,25]. In addition to the periodontal sites, *F. nucleatum* is detected in saliva, with its quantities increased in patients with gingivitis and periodontitis, compared to the healthy controls [11,26]. Serum antibody titers to *F. nucleatum* have been reported to be elevated in diseased patients [27].

The abundance of *F. nucleatum* is affected by environmental factors. Smoking increases the abundance in both periodontally healthy and diseased individuals [28,29]. Among patients with chronic periodontitis, those with uncontrolled type-2 diabetes have higher levels of *F. nucleatum* [30].

Animal studies support a causative role of *F. nucleatum* in periodontal infections. Mono-infection of mice with *F. nucleatum* induces periodontal bone loss or abscess [31]. When *F. nucleatum* is co-infected with other oral species, e.g. *Tannerella forsythia*, *Porphyromonas gingivalis* and *Streptococci*, respectively, synergy in virulence is observed as evidenced by enhanced bone loss, abscess, or death [32–36].

Adverse pregnancy outcomes

Adverse pregnancy outcome (APO) is a broad term including preterm labor, chorioamnionitis, preterm premature rupture of membranes, preeclampsia, miscarriage, intrauterine growth retardation, low birth weight, stillbirth, neonatal sepsis, etc. *F. nucleatum* is one of the most prevalent species and by far the most prevalent oral species implicated in APO [30]. It has been detected in a wide variety of placental and fetal tissues including amniotic fluid, fetal membranes, cord blood, neonatal gastric aspirates, fetal lung and stomach, associated with chorioamnionitis, preeclampsia, preterm birth, stillbirth, and early-onset neonatal sepsis [37–45] (Table 1). A case report of term stillbirth caused by oral *F. nucleatum* provides the first human evidence that the bacteria originated from the mother’s subgingival plaque and translocated to the placenta and fetus, causing acute inflammation leading to the fetal demise [38]. *F. nucleatum* has been detected as a predominant species in amniotic fluid and fetal membrane associated with preterm birth [39,43,46,47], and in cord blood associated with early-onset neonatal sepsis [37]. Concurrent detection of *F. nucleatum* in matching amniotic fluid and cord blood indicates its ability to spread to different placental and fetal compartments [37].

F. nucleatum is frequently detected in amniotic fluid and cord blood by culture-independent methods in cases of idiopathic preterm birth and presumed neonatal sepsis, i.e. the patients

display the symptoms of disease but the hospital culture results are negative [37,39]. The prevalence of *F. nucleatum* detected in cord blood from neonatal sepsis equals or is higher than that of *E. coli* and Group B Streptococcus, placing *F. nucleatum* on the same importance scale as these two well-recognized neonatal pathogens [37]. These findings point to the urgent need to update the microbial diagnostic technologies employed by hospital laboratories.

It has been postulated that *F. nucleatum* translocates from the maternal oral cavity to the intrauterine cavity via hematogenous transmission [48–50]. This hypothesis is supported by results from animal studies [51,52]. Hematogenous injection of *F. nucleatum* resulted in specific colonization and proliferation of the bacteria in the fetoplacental unit without causing systemic infections. The bacteria colonized initially in the decidua by crossing the endothelium, followed by spread to amniotic fluid, fetus and fetal membrane, mimicking chorioamnionitis, eventually leading to preterm and term fetal death [51]. The pattern and duration of infection, as well as the pathology of the mouse placenta, correspond to those of the stillbirth case described above [38]. The inflammatory responses observed in infected mouse placentas are also consistent with those in humans [51,52]. A recent report that the human placenta harbors a low abundant microbiome closely mimicking the human oral microbiome provides further support for hematogenous transmission [53].

Among the five subspecies, only two have been detected in intrauterine infections, with the overwhelming majority belonging to *ss animalis*, and an occasional few belonging to *ss polymorphum. F. nucleatum* is often detected together with other oral species as mixed infections, indicating co-translocation from the oral cavity [37,39,42]. These observations are supported by animal studies in which a variety of cultivated and uncultivated oral species are found to co-translocate to the mouse placenta [54]. The majority of oral species translocated to the murine placenta were oral commensals, supporting the notion that commensals in the oral cavity may become pathogens elsewhere. Accurate identification of species/subspecies involved in APO will make it plausible for early and accurate diagnosis to identify individuals at risk [55].

A large body of literature supports the link between periodontal disease and APO [48]. A few studies conducted in South America, Europe, and U.S. improve birth outcome following repeated periodontal treatment or daily use of antibacterial mouth rinse [56–58]. Unfortunately, several large-scale multi-center intervention studies employing a single-treatment therapy during the second trimester fail to demonstrate efficacy [59–61]. It is possible that the one-time treatment is insufficient for disease resolution, and a daily regimen to control inflammation and oral bacterial load might be more effective [48,49].

GI disorders

The GI disorders discussed here include colorectal cancer (CRC), inflammatory bowel disease (IBD) and appendicitis (Table 1). It is only recently that *F. nucleatum* has been linked to CRC, yet the field is fast growing. *F. nucleatum* was first discovered to be enriched in CRC carcinomas and the rectal swabs of CRC patients [62–65]. Subsequent studies report that levels of *F. nucleatum* are also elevated in adenomas, in stools of patients with adenoma and carcinoma, and associated with stages of colorectal neoplasia development [66–70]. As

in APO, *F. nucleatum* is often detected in conjunction with other oral species, suggesting an oral source of infection [71]. The question arises whether *F. nucleatum* is a passenger or a driver of colorectal tumorigenesis [72,73]. Rubinstein et al. demonstrate that *F. nucleatum* stimulates CRC cancer growth by modulating the E-cadherin/β catenin signaling via its unique FadA adheisn (see below). Kostic et al. report that *F. nucleatum* potentiates colorectal tumorigenesis in $Apc^{min/+}$ mice. Together, these studies support a causal role of *F. nucleatum* in CRC [74,75].

IBD has been recognized as a risk factor for CRC. Thus, it is not surprising that the same microorganisms are implicated in both diseases. *F. nucleatum* has been detected in colonic biospsies of patients with IBD [76,77]. *F. nucleatum* strains isolated from inflamed tissues of the IBD patients are more invasive than those from the normal tissues [77]. Several studies have reported association of *F. nucleatum* in appendicitis [78–80]. Co-occurrence of *F. nucleatum* with other oral taxa has been observed [80]. The mechanisms of *F. nucleatum* in IBD and appendicitis have not been elucidated.

Other infections

Fusobacterium nucleatum is associated with a wide spectrum of infections and abscesses including infections of the head and neck (Lemierre's syndrome, acute and chronic mastoiditis, chronic otitis and sinusitis, tonsillitis, peritonsillar and retropharyngeal abscesses, postanginal cervical lymphadenitis, periodontitis), brain, lungs, abdomen, pelvis, bones, joints, and blood, which has been recently reviewed elsewhere [81,82]. *Fusobacterium*, especially *F. necrophorum* and *F. nucleatum*, is a major cause of the well-known Lemierre's Syndrome, a rare form of upper airways infection with a life threatening secondary septic thrombophlebitis of internal or external jugular veins, usually developed in previously healthy young adults [81,83].

F. nucleatum has been implicated in cardiovascular diseases (CVD) [3]. It is frequently detected in the atherosclerotic plaques, and is also one of the most common periodontal pathogens detected in ruptured cerebral aneurysm [84–86]. The frequency of detecting *F. nucleatum* in atherosclerotic plaques and blood vessels is directly related to the severity of periodontal disease [87].

Additional diseases that *F. nucleatum* has been involved in include rheumatoid arthritis and Alzheimer's disease [88,89]. Periodontal treatment has been shown to improve clinical outcomes of rheumatoid arthritis [90].

Virulence mechanisms of *F. nucleatum*

How can an oral commensal be implicated in so many infections within and outside the mouth? The answer lies in several key virulence mechanisms *F. nucleatum* possesses, which can be broadly classified into two groups and reviewed below: (1) colonization and dissemination, and (2) induction of host responses. The readers can in addition refer to a previous review [82].

Colonization and dissemination

F. nucleatum is an adhesive bacterium. It coaggregates with various microbial species in the oral cavity, playing a key role in dental plaque formation [91]. *F. nucleatum* encodes several adhesins for interspecies interactions, including Fap2, RadD, and aid1 [92–94]. *F. nucleatum* also binds to a variety of mammalian cells, i.e. epithelial and endothelial cells, PMNs, monocytes, erythrocytes, fibroblasts, HeLa cells and NK cells, as well as host molecules such as salivary macromolecules, extracellular matrix proteins, human IgG, and cadherins [82,95]. Furthermore, *F. nucleatum* invades epithelial and endothelial cells [51,96]. Adherence and invasion are essential mechanisms for colonization, dissemination, evasion of host defense, and induction of host responses. Invasion of endothelial cells by *F. nucleatum* in mouse placenta has been observed [51]. The invasiveness of *F. nucleatum* varies widely among different strains, and has been shown as directly related to the IBD disease status [77,97].

So far, only one adhesin, FadA, has been identified to bind host cells, and remains to be the best-characterized virulence factor identified from *F. nucleatum* [82]. FadA exists in two forms, the intact pre-FadA consisting of 129 amino-acid (aa) residues and the secreted mature FadA (mFadA) consisting of 111 aa residues [98]. The crystal structure of mFadA reveals a predominantly alpha-helical hairpin structure, with the monomers linked together in a head-to-tail pattern via a novel leucine-chain motif [98]. Pre-FadA and mFadA form an active complex, FadAc, for host-cell binding and invasion [68,98,99].

FadA is uniquely encoded by two closely related species, *F. nucleatum* and *F. periodonticum*, absent in most other species of *Fusobacterium* [100]. Thus, FadA is a potential diagnostic marker for specific detection of *F. nucleatum* and *F. periodonticum*. FadA is more frequently detected in the dental plaque samples from patients with gingivitis and periodontitis than the normal controls [13]. In a proof-of-concept study, the *fadA* gene level is shown to be step-wise elevated from colon tissues of normal individuals to adenomas, and from adenomas to carcinomas [68]. The *fadA* levels in the normal tissues adjacent to adenoma and carcinoma are higher than those from individual without tumor or inflammation, indicating a field effect [68].

FadA is not only an adhesin but also an invasin [98]. It is required for binding and invasion of both normal and cancerous host cells, and for colonizing the murine placentas [51,68,82,96,101]. FadA binds to cell-junction molecules, the cadherins. FadA binds to VE-cadherin on the endothelial cells and to E-cadherin on epithelial and colorectal cancer cells [68,101]. Because cadherins are widespread in various tissues and cells, FadA binding to cadherins is likely the reason why it can colonize numerous tissues and body sites. FadA binding to VE-cadherin on endothelial cells causes the latter to migrate from cell-cell junction to intracellular compartments, increasing the permeability of the endothelial layer [101]. Thus, FadA allows both direct invasion into the host cells and pericellular invasion via loosened cell-cell junctions. It is postulated that this is the mechanism employed for systemic dissemination [101]. Furthermore, the increased endothelial permeability allows other bacteria in the vicinity to penetrate through, a likely reason why *F. nucleatum* is often found in mixed infections at extra-oral sites. It has been shown in vitro that *F. nucleatum*

facilitates both intra-cellular and inter-cellular invasion of other species, such as *Streptococcus cristatus* and *E. coli* [101,102].

Induction of host responses

F. nucleatum elicits a variety of host responses [82]. It induces human b-defensin 2 from oral epithelial cells via FAD-I [103], stimulates factors predisposing to atherosclerosis by GroEL [65], and activates lymphocyte apoptosis by Fap2 and RadD [94]. *F. nucleatum* is a potent stimulator of inflammatory cytokines, IL-6, IL-8, and TNFα [96,104]. Binding of *F. nucleatum* to NK cells activates inflammatory responses involved in periodontal disease [31]. It is reported that *F. nucleatum* activates the immune responses through retinoic acid-inducible gene I (RIG-I) [105]. During periodontal health, the pro- and anti-inflammatory factors are maintained under homeostasis. Once disseminated outside the oral cavity and under dysbiosys, *F. nucleatum* induces exacerbated inflammation thus turning into a pathogen. For example, *F. nucleatum* stimulates TLR4-mediated inflammatory responses in the placentas of pregnant mice, causing fetal demise [51,52]. Suppression of inflammation protects the fetuses, even in the presence of bacterial colonization [52]. In colorectal cancer cells, *F. nucleatum* activates not only inflammatory responses, but also oncogenes and Wnt gene expressions, all of which are hallmarks of tumorigenesis [68]. *F. nucleatum* modulates the tumor-immune microenvironment and selectively expands myeloid cells in $Apc^{min/+}$ mice [66].

FadA plays a key role in induction of the tumorigenic responses. A synthetic peptide that prevents FadA from binding to E-cadherin blocks tumorigenic responses [68]. Induction of inflammatory responses requires internalization of FadA in the cancer cells while activation of Wnt and oncogenes does not [68]. It is possible that FadA interacts with intracellular components, such as RIG-I, to activate the inflammatory responses.

Concluding remarks

As a fastidious anaerobe, cultivation of *F. nucleatum* has been difficult. Hence, although cultivable, *F. nucleatum* is frequently missed in routine culture employed by hospital laboratories. The recent discovery of this opportunistic commensal in a wide spectrum of human disease is due largely to the employment of culture-independent methods. In addition, not all subtypes of *F. nucleatum* are equally prevalent in diseases. Thus, it is crucial to update microbial detection technologies in clinical practice for accurate diagnosis of disease and for identification of individuals at risk. The involvement of *F. nucleatum* in some of the diseases discussed above is still at the stage of association, with no established causal roles. Further more, since *F. nucleatum* is prevalent in periodontal disease, the link between periodontal health and these human diseases needs to be explored. It is hopeful that with an increasing attention on this emerging commensal-turned pathogen, an output of research findings on the pathogenesis mechanisms of *F. nucleatum*, its detection, and the connection between oral health and various human diseases can be anticipated in the coming years.

Acknowledgement

The author acknowledges funding from the National Institutes of Health RO1 DE014924 and RO1DE023332.

References

1. Aagaard K, Riehle K, Ma J, Segata N, Mistretta TA, Coarfa C, Raza S, Rosenbaum S, Van den Veyver I, Milosavljevic A, et al. A metagenomic approach to characterization of the vaginal microbiome signature in pregnancy. PLoS One. 2012; 7:e36466. [PubMed: 22719832]
2. Segata N, Haake SK, Mannon P, Lemon KP, Waldron L, Gevers D, Huttenhower C, Izard J. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biol. 2012; 13:R42. [PubMed: 22698087]
3. Han YW, Wang X. Mobile Microbiome: Oral Bacteria in Extra-oral Infections and Inflammation. J Dent Res. 2013 **This paper advocates a novel concept that the microbiome is mobile rather than static and provides a comprehensive review on how oral bacteria, including *F. nucleatum*, can translocate to extra-oral sites to cause infections.
4. Gharbia SE, Shah HN. Fusobacterium nucleatum subsp. fusiforme subsp. nov. and Fusobacterium nucleatum subsp. animalis subsp. nov. as additional subspecies within Fusobacterium nucleatum. Int J Syst Bacteriol. 1992; 42:296–298. [PubMed: 1581188]
5. Gharbia SE, Shah HN. Heterogeneity within *Fusobacterium nucleatum* proposal of four subspecies. Lett. Appl. Microbiol. 1990; 10:105–108.
6. Allen-Vercoe E, Strauss J, Chadee K. Fusobacterium nucleatum: an emerging gut pathogen? Gut Microbes. 2011; 2:294–298. [PubMed: 22067936]
7. Field CA, Gidley MD, Preshaw PM, Jakubovics N. Investigation and quantification of key periodontal pathogens in patients with type 2 diabetes. J Periodontal Res. 2012; 47:470–478. [PubMed: 22220967]
8. Moore WE, Moore LV. The bacteria of periodontal diseases. Periodontol 2000. 1994; 5:66–77. [PubMed: 9673163]
9. Griffen AL, Beall CJ, Campbell JH, Firestone ND, Kumar PS, Yang ZK, Podar M, Leys EJ. Distinct and complex bacterial profiles in human periodontitis and health revealed by 16S pyrosequencing. ISME J. 2012; 6:1176–1185. [PubMed: 22170420]
10. Loozen G, Ozcelik O, Boon N, De Mol A, Schoen C, Quirynen M, Teughels W. Inter-bacterial correlations in subgingival biofilms: a large-scale survey. J Clin Periodontol. 2014; 41:1–10. [PubMed: 24102517]
11. Saygun I, Nizam N, Keskiner I, Bal V, Kubar A, Acikel C, Serdar M, Slots J. Salivary infectious agents and periodontal disease status. J Periodontal Res. 2011; 46:235–239. [PubMed: 21261620]
12. Feng X, Zhang L, Xu L, Meng H, Lu R, Chen Z, Shi D, Wang X. Detection of eight periodontal microorganisms and distribution of Porphyromonas gingivalis fimA genotypes in chinese patients with aggressive periodontitis. J Periodontol. 2014; 85:150–159. [PubMed: 23646850]
13. Liu P, Liu Y, Wang J, Guo Y, Zhang Y, Xiao S. Detection of fusobacterium nucleatum and fadA adhesin gene in patients with orthodontic gingivitis and non-orthodontic periodontal inflammation. PLoS One. 2014; 9:e85280. [PubMed: 24416378]
14. Yang NY, Zhang Q, Li JL, Yang SH, Shi Q. Progression of periodontal inflammation in adolescents is associated with increased number of Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythensis, and Fusobacterium nucleatum. Int J Paediatr Dent. 2014; 24:226–233. [PubMed: 24025042]
15. Kistler JO, Booth V, Bradshaw DJ, Wade WG. Bacterial community development in experimental gingivitis. PLoS One. 2013; 8:e71227. [PubMed: 23967169]
16. Didilescu AC, Rusu D, Anghel A, Nica L, Iliescu A, Greabu M, Bancescu G, Stratul SI. Investigation of six selected bacterial species in endo-periodontal lesions. Int Endod J. 2012; 45:282–293. [PubMed: 22077868]
17. Fujii R, Saito Y, Tokura Y, Nakagawa KI, Okuda K, Ishihara K. Characterization of bacterial flora in persistent apical periodontitis lesions. Oral Microbiol Immunol. 2009; 24:502–505. [PubMed: 19832803]

18. Siqueira JF Jr, Rocas IN, Paiva SS, Magalhaes KM, Guimaraes-Pinto T. Cultivable bacteria in infected root canals as identified by 16S rRNA gene sequencing. Oral Microbiol Immunol. 2007; 22:266–271. [PubMed: 17600539]
19. Triches TC, de Figueiredo LC, Feres M, de Freitas SF, Zimmermann GS, Cordeiro MM. Microbial profile of root canals of primary teeth with pulp necrosis and periradicular lesion. J Dent Child (Chic). 2014; 81:14–19. [PubMed: 24709428]
20. Topcuoglu N, Bozdogan E, Kulekci G. Presence of oral bacterial species in primary endodontic infections of primary teeth. J Clin Pediatr Dent. 2013; 38:155–160. [PubMed: 24683780]
21. Rocas IN, Siqueira JF Jr, Debelian GJ. Analysis of symptomatic and asymptomatic primary root canal infections in adult Norwegian patients. J Endod. 2011; 37:1206–1212. [PubMed: 21846535]
22. Siqueira JF Jr, Rocas IN. The microbiota of acute apical abscesses. J Dent Res. 2009; 88:61–65. [PubMed: 19131319]
23. Riep B, Edesi-Neuss L, Claessen F, Skarabis H, Ehmke B, Flemmig TF, Bernimoulin JP, Gobel UB, Moter A. Are putative periodontal pathogens reliable diagnostic markers? J Clin Microbiol. 2009; 47:1705–1711. [PubMed: 19386852]
24. Lourenco TG, Heller D, Silva-Boghossian CM, Cotton SL, Paster BJ, Colombo AP. Microbial signature profiles of periodontally healthy and diseased patients. J Clin Periodontol. 2014; 41:1027–1036. [PubMed: 25139407]
25. Gharbia SE, Shah HN, Lawson PA, Haapasalo M. Distribution and frequency of Fusobacterium nucleatum subspecies in the human oral cavity. Oral Microbiol Immunol. 1990; 5:324–327. [PubMed: 2098710]
26. Zhou X, Liu X, Li J, Aprecio RM, Zhang W, Li Y. Real-time PCR quantification of six periodontal pathogens in saliva samples from healthy young adults. Clin Oral Investig. 2014
27. Vincent JW, Suzuki JB, Falkler WA Jr, Cornett WC. Reaction of human sera from juvenile periodontitis, rapidly progressive periodontitis, and adult periodontitis patients with selected periodontopathogens. J Periodontol. 1985; 56:464–469. [PubMed: 3869650]
28. Moon JH, Lee JH, Lee JY. Subgingival microbiome in smokers and non-smokers in Korean chronic periodontitis patients. Mol Oral Microbiol. 2014
29. Mason MR, Preshaw PM, Nagaraja HN, Dabdoub SM, Rahman A, Kumar PS. The subgingival microbiome of clinically healthy current and never smokers. ISME J. 2014
30. Casarin RC, Barbagallo A, Meulman T, Santos VR, Sallum EA, Nociti FH, Duarte PM, Casati MZ, Goncalves RB. Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis. J Periodontal Res. 2013; 48:30–36. [PubMed: 22762355]
31. Chaushu S, Wilensky A, Gur C, Shapira L, Elboim M, Halftek G, Polak D, Achdout H, Bachrach G, Mandelboim O. Direct recognition of Fusobacterium nucleatum by the NK cell natural cytotoxicity receptor NKp46 aggravates periodontal disease. PLoS Pathog. 2012; 8:e1002601. [PubMed: 22457623]
32. Kuriyama T, Nakagawa K, Kawashiri S, Yamamoto E, Nakamura S, Karasawa T. The virulence of mixed infection with Streptococcus constellatus and Fusobacterium nucleatum in a murine orofacial infection model. Microbes Infect. 2000; 2:1425–1430. [PubMed: 11099928]
33. Nagashima H, Takao A, Maeda N. Abscess forming ability of streptococcus milleri group: synergistic effect with Fusobacterium nucleatum. Microbiol Immunol. 1999; 43:207–216. [PubMed: 10338189]
34. Settem RP, El-Hassan AT, Honma K, Stafford GP, Sharma A. Fusobacterium nucleatum and Tannerella forsythia induce synergistic alveolar bone loss in a mouse periodontitis model. Infect Immun. 2012; 80:2436–2443. [PubMed: 22547549]
35. Polak D, Wilensky A, Shapira L, Halabi A, Goldstein D, Weiss EI, Houri-Haddad Y. Mouse model of experimental periodontitis induced by Porphyromonas gingivalis/Fusobacterium nucleatum infection: bone loss and host response. J Clin Periodontol. 2009; 36:406–410. [PubMed: 19419440]
36. Kesavalu L, Sathishkumar S, Bakthavatchalu V, Matthews C, Dawson D, Steffen M, Ebersole JL. Rat model of polymicrobial infection, immunity, and alveolar bone resorption in periodontal disease. Infect Immun. 2007; 75:1704–1712. [PubMed: 17210663]

37. Wang X, Buhimschi CS, Temoin S, Bhandari V, Han YW, Buhimschi IA. Comparative microbial analysis of paired amniotic fluid and cord blood from pregnancies complicated by preterm birth and early-onset neonatal sepsis. PLoS One. 2013; 8:e56131. [PubMed: 23437088]

38. Han YW, Fardini Y, Chen C, Iacampo KG, Peraino VA, Shamonki JM, Redline RW. Term stillbirth caused by oral *Fusobacterium nucleatum*. Obstet Gynecol. 2010; 115:442–445. [PubMed: 20093874] *This is the first report of *F. nucleatum* originating from the mother's oral cavity causing stillbirth.

39. Han YW, Shen T, Chung P, Buhimschi IA, Buhimschi CS. Uncultivated bacteria as etiologic agents of intra-amniotic inflammation leading to preterm birth. J Clin Microbiol. 2009; 47:38–47. [PubMed: 18971361]

40. Bohrer JC, Kamemoto LE, Almeida PG, Ogasawara KK. Acute chorioamnionitis at term caused by the oral pathogen Fusobacterium nucleatum. Hawaii J Med Public Health. 2012; 71:280–281. [PubMed: 23115747]

41. Gauthier S, Tetu A, Himaya E, Morand M, Chandad F, Rallu F, Bujold E. The origin of Fusobacterium nucleatum involved in intra-amniotic infection and preterm birth. J Matern Fetal Neonatal Med. 2011; 24:1329–1332. [PubMed: 21314291]

42. Dixon NG, Ebright D, Defrancesco MA, Hawkins RE. Orogenital contact: a cause of chorioamnionitis? Obstet Gynecol. 1994; 84:654–655. [PubMed: 9205437]

43. Cahill RJ, Tan S, Dougan G, O'Gaora P, Pickard D, Kennea N, Sullivan MH, Feldman RG, Edwards AD. Universal DNA primers amplify bacterial DNA from human fetal membranes and link Fusobacterium nucleatum with prolonged preterm membrane rupture. Mol Hum Reprod. 2005

44. Weible DR, Randall HW Jr. Evaluation of amniotic fluid in preterm labor with intact membranes. J Reprod Med. 1985; 30:777–780. [PubMed: 4067950]

45. Barak S, Oettinger-Barak O, Machtei EE, Sprecher H, Ohel G. Evidence of periopathogenic microorganisms in placentas of women with preeclampsia. J Periodontol. 2007; 78:670–676. [PubMed: 17397314]

46. Chaim W, Mazor M. Intraamniotic infection with fusobacteria. Arch Gynecol Obstet. 1992; 251:1–7. [PubMed: 1550388]

47. Hill GB. Preterm birth: associations with genital and possibly oral microflora. Ann Periodontol. 1998; 3:222–232. [PubMed: 9722706]

48. Han YW. Oral health and adverse pregnancy outcomes - what's next? J Dent Res. 2011; 90:289–293. [PubMed: 21041548]

49. Han YW. Can oral bacteria cause pregnancy complications? Womens Health (Lond Engl). 2011; 7:401–404. [PubMed: 21790330]

50. Hill GB. Investigating the source of amniotic fluid isolates of fusobacteria. Clin Infect Dis. 1993; 16(Suppl 4):S423–S424. [PubMed: 8324160]

51. Han YW, Redline RW, Li M, Yin L, Hill GB, McCormick TS. Fusobacterium nucleatum induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. Infect Immun. 2004; 72:2272–2279. [PubMed: 15039352] *This is the first animal study elucidating the role of *F. nucleatum* in adverse pregnancy outcome.

52. Liu H, Redline RW, Han YW. Fusobacterium nucleatum induces fetal death in mice via stimulation of TLR4-mediated placental inflammatory response. J Immunol. 2007; 179:2501–2508. [PubMed: 17675512]

53. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Sci Transl Med. 2014; 6:237ra265.

54. Fardini Y, Chung P, Dumm R, Joshi N, Han YW. Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. Infect Immun. 2010; 78:1789–1796. [PubMed: 20123706]

55. Abad C, Antczak DF, Carvalho J, Chamley LW, Chen Q, Daher S, Damiano AE, Dantzer V, Diaz P, Dunk CE, et al. IFPA Meeting 2010 Workshop Report I: Immunology; ion transport; epigenetics; vascular reactivity; epitheliochorial placentation; proteomics. Placenta. 32(Suppl 2):S81–S89. [PubMed: 21227506]

56. Jeffcoat M, Parry S, Gerlach RW, Doyle MJ. Use of alcohol-free antimicrobial mouth rinse is associated with decreased incidence of preterm birth in a high-risk population. Am J Obstet Gynecol. 2011; 205:382 e381–382 e386. [PubMed: 22083060]
57. Lopez NJ, Da Silva I, Ipinza J, Gutierrez J. Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. J Periodontol. 2005; 76:2144–2153. [PubMed: 16277587]
58. Radnai M, Pal A, Novak T, Urban E, Eller J, Gorzo I. Benefits of periodontal therapy when preterm birth threatens. J Dent Res. 2009; 88:280–284. [PubMed: 19329465]
59. Macones GA, Parry S, Nelson DB, Strauss JF, Ludmir J, Cohen AW, Stamilio DM, Appleby D, Clothier B, Sammel MD, et al. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). Am J Obstet Gynecol. 2010; 202:147 e141–147 e148. [PubMed: 20113691]
60. Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006; 355:1885–1894. [PubMed: 17079762]
61. Offenbacher S, Beck JD, Jared HL, Mauriello SM, Mendoza LC, Couper DJ, Stewart DD, Murtha AP, Cochran DL, Dudley DJ, et al. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. Obstet Gynecol. 2009; 114:551–559. [PubMed: 19701034]
62. Marchesi JR, Dutilh BE, Hall N, Peters WH, Roelofs R, Boleij A, Tjalsma H. Towards the human colorectal cancer microbiome. PLoS One. 2011; 6:e20447. [PubMed: 21647227]
63. Chen W, Liu F, Ling Z, Tong X, Xiang C. Human intestinal lumen and mucosaassociated microbiota in patients with colorectal cancer. PLoS One. 2012; 7:e39743. [PubMed: 22761885]
64. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012; 22:299–306. [PubMed: 22009989]
65. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, Ojesina AI, Jung J, Bass AJ, Tabernero J, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res. 2012; 22:292–298. [PubMed: 22009990]
66. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, et al. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-Immune microenvironment. Cell Host Microbe. 2013; 14:207–215. [PubMed: 23954159]
67. McCoy AN, Araujo-Perez F, Azcarate-Peril A, Yeh JJ, Sandler RS, Keku TO. Fusobacterium is associated with colorectal adenomas. PLoS One. 2013; 8:e53653. [PubMed: 23335968]
68. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe. 2013; 14:195–206. [PubMed: 23954158] **This study elucidates *F. nucleatum* as an etiologial factor of colorectal cancer and FadA as a key virulence factor driving colorectal tumorigenesis.
69. Flanagan L, Schmid J, Ebert M, Soucek P, Kunicka T, Liska V, Bruha J, Neary P, Dezeeuw N, Tommasino M, et al. Fusobacterium nucleatum associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome. Eur J Clin Microbiol Infect Dis. 2014; 33:1381–1390. [PubMed: 24599709]
70. Mira-Pascual L, Cabrera-Rubio R, Ocon S, Costales P, Parra A, Suarez A, Moris F, Rodrigo L, Mira A, Collado MC. Microbial mucosal colonic shifts associated with the development of colorectal cancer reveal the presence of different bacterial and archaeal biomarkers. J Gastroenterol. 2014
71. Warren RL, Freeman DJ, Pleasance S, Watson P, Moore RA, Cochrane K, Allen-Vercoe E, Holt RA. Co-occurrence of anaerobic bacteria in colorectal carcinomas. Microbiome. 2013; 1:16. [PubMed: 24450771]
72. Tjalsma H, Boleij A, Marchesi JR, Dutilh BE. A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. Nat Rev Microbiol. 2012; 10:575–582. [PubMed: 22728587]
73. Keku TO, McCoy AN, Azcarate-Peril AM. Fusobacterium spp. and colorectal cancer: cause or consequence? Trends Microbiol. 2013; 21:506–508. [PubMed: 24029382]

74. Zhu Q, Jin Z, Wu W, Gao R, Guo B, Gao Z, Yang Y, Qin H. Analysis of the intestinal lumen microbiota in an animal model of colorectal cancer. PLoS One. 2014; 9:e90849. [PubMed: 24603888]

75. Allen-Vercoe E, Jobin C. Fusobacterium and Enterobacteriaceae: Important players for CRC? Immunol Lett. 2014

76. Tahara T, Shibata T, Kawamura T, Okubo M, Ichikawa Y, Sumi K, Miyata M, Ishizuka T, Nakamura M, Nagasaka M, et al. Fusobacterium Detected in Colonic Biopsy and Clinicopathological Features of Ulcerative Colitis in Japan. Dig Dis Sci. 2014

77. Strauss J, Kaplan GG, Beck PL, Rioux K, Panaccione R, Devinney R, Lynch T, Allen-Vercoe E. Invasive potential of gut mucosa-derived fusobacterium nucleatum positively correlates with IBD status of the host. Inflamm Bowel Dis. 2011; 17:1971–1978. [PubMed: 21830275]

78. Swidsinski A, Dorffel Y, Loening-Baucke V, Theissig F, Ruckert JC, Ismail M, Rau WA, Gaschler D, Weizenegger M, Kuhn S, et al. Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/necrophorum. Gut. 2011; 60:34–40. [PubMed: 19926616]

79. Swidsinski A, Dorffel Y, Loening-Baucke V, Tertychnyy A, Biche-Ool S, Stonogin S, Guo Y, Sun ND. Mucosal invasion by fusobacteria is a common feature of acute appendicitis in Germany, Russia, and China. Saudi J Gastroenterol. 2012; 18:55–58. [PubMed: 22249094]

80. Zhong D, Brower-Sinning R, Firek B, Morowitz MJ. Acute appendicitis in children is associated with an abundance of bacteria from the phylum Fusobacteria. J Pediatr Surg. 2014; 49:441–446. [PubMed: 24650474]

81. Brook I. Fusobacterial infections in children. Curr Infect Dis Rep. 2013; 15:288–294. [PubMed: 23616183]

82. Han, YW. *Fusobacterium nucleatum* interaction with host cells. In: Kolenbrander, P., editor. Oral microbial communities : genomic inquiry and interspecies communication. ASM press; 2011.

83. Williams MD, Kerber CA, Tergin HF. Unusual presentation of Lemierre's syndrome due to Fusobacterium nucleatum. J Clin Microbiol. 2003; 41:3445–3448. [PubMed: 12843117]

84. Ford PJ, Gemmell E, Chan A, Carter CL, Walker PJ, Bird PS, West MJ, Cullinan MP, Seymour GJ. Inflammation, heat shock proteins and periodontal pathogens in atherosclerosis: an immunohistologic study. Oral Microbiol Immunol. 2006; 21:206–211. [PubMed: 16842503]

85. Figuero E, Sanchez-Beltran M, Cuesta-Frechoso S, Tejerina JM, del Castro JA, Gutierrez JM, Herrera D, Sanz M. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. J Periodontol. 2011; 82:1469–1477. [PubMed: 21453047]

86. Pyysalo MJ, Pyysalo LM, Pessi T, Karhunen PJ, Ohman JE. The connection between ruptured cerebral aneurysms and odontogenic bacteria. J Neurol Neurosurg Psychiatry. 2013; 84:1214–1218. [PubMed: 23761916]

87. Elkaim R, Dahan M, Kocgozlu L, Werner S, Kanter D, Kretz JG, Tenenbaum H. Prevalence of periodontal pathogens in subgingival lesions, atherosclerotic plaques and healthy blood vessels: a preliminary study. J Periodontal Res. 2008; 43:224–231. [PubMed: 18326058]

88. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, Dawson D 3rd. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimers Dement. 2012; 8:196–203. [PubMed: 22546352]

89. Temoin S, Chakaki A, Askari A, El-Halaby A, Fitzgerald S, Marcus RE, Han YW, Bissada NF. Identification of oral bacterial DNA in synovial fluid of patients with arthritis with native and failed prosthetic joints. J Clin Rheumatol. 2012; 18:117–121. [PubMed: 22426587]

90. Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, Askari A. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. J Periodontol. 2009; 80:535–540. [PubMed: 19335072]

91. Rickard AH, Gilbert P, High NJ, Kolenbrander PE, Handley PS. Bacterial coaggregation: an integral process in the development of multi-species biofilms. Trends Microbiol. 2003; 11:94–100. [PubMed: 12598132]

92. Kaplan A, Kaplan CW, He X, McHardy I, Shi W, Lux R. Characterization of aid1, a novel gene involved in Fusobacterium nucleatum interspecies interactions. Microb Ecol. 2014; 68:379–387. [PubMed: 24643713]

93. Kaplan CW, Lux R, Haake SK, Shi W. The Fusobacterium nucleatum outer membrane protein RadD is an arginine-inhibitable adhesin required for inter-species adherence and the structured architecture of multispecies biofilm. Mol Microbiol. 2009; 71:35–47. [PubMed: 19007407]

94. Kaplan CW, Ma X, Paranjpe A, Jewett A, Lux R, Kinder-Haake S, Shi W. Fusobacterium nucleatum outer membrane proteins Fap2 and RadD induce cell death in human lymphocytes. Infect Immun. 2010; 78:4773–4778. [PubMed: 20823215]

95. Bachrach G, Ianculovici C, Naor R, Weiss EI. Fluorescence based measurements of Fusobacterium nucleatum coaggregation and of fusobacterial attachment to mammalian cells. FEMS Microbiol Lett. 2005; 248:235–240. [PubMed: 15993010]

96. Han YW, Shi W, Huang GT, Kinder Haake S, Park NH, Kuramitsu H, Genco RJ. Interactions between periodontal bacteria and human oral epithelial cells: Fusobacterium nucleatum adheres to and invades epithelial cells. Infect Immun. 2000; 68:3140–3146. [PubMed: 10816455]

97. Manson McGuire A, Cochrane K, Griggs AD, Haas BJ, Abeel T, Zeng Q, Nice JB, MacDonald H, Birren BW, Berger BW, et al. Evolution of invasion in a diverse set of fusobacterium species. MBio. 2014; 5

98. Xu M, Yamada M, Li M, Liu H, Chen SG, Han YW. FadA from Fusobacterium nucleatum utilizes both secreted and nonsecreted forms for functional oligomerization for attachment and invasion of host cells. J Biol Chem. 2007; 282:25000–25009. [PubMed: 17588948]

99. Temoin S, Wu KL, Wu V, Shoham M, Han YW. Signal peptide of FadA adhesin from Fusobacterium nucleatum plays a novel structural role by modulating the filament's length and width. FEBS Lett. 2012; 586:1–6. [PubMed: 22108653]

100. Han YW, Ikegami A, Rajanna C, Kawsar HI, Zhou Y, Li M, Sojar HT, Genco RJ, Kuramitsu HK, Deng CX. Identification and characterization of a novel adhesin unique to oral fusobacteria. J Bacteriol. 2005; 187:5330–5340. [PubMed: 16030227]

101. Fardini Y, Wang X, Temoin S, Nithianantham S, Lee D, Shoham M, Han YW. Fusobacterium nucleatum adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity. Mol Microbiol. 2011; 82:1468–1480. [PubMed: 22040113] *This is the first study revealing cadherins as receptor for FadA.

102. Edwards AM, Grossman TJ, Rudney JD. Fusobacterium nucleatum transports noninvasive Streptococcus cristatus into human epithelial cells. Infect Immun. 2006; 74:654–662. [PubMed: 16369022]

103. Gupta S, Ghosh SK, Scott ME, Bainbridge B, Jiang B, Lamont RJ, McCormick TS, Weinberg A. Fusobacterium nucleatum-associated beta-defensin inducer (FAD-I): identification, isolation, and functional evaluation. J Biol Chem. 2010; 285:36523–36531. [PubMed: 20847052]

104. Park SR, Kim DJ, Han SH, Kang MJ, Lee JY, Jeong YJ, Lee SJ, Kim TH, Ahn SG, Yoon JH, et al. Diverse Toll-like receptors mediate cytokine production by Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans in macrophages. Infect Immun. 2014; 82:1914–1920. [PubMed: 24566622]

105. Lee P, Tan KS. Fusobacterium nucleatum activates the immune response through retinoic acid-inducible gene I. J Dent Res. 2014; 93:162–168. [PubMed: 24334410]

Highlights

- *F. nucleatum* is an oral commensal implicated in oral infections, adverse pregnancy outcomes, GI disorders, and various other human diseases.
- *F. nucleatum* can disseminate systemically colonizing different body sites.
- *F. nucleatum* elicit a spectrum of host responses including inflammation.
- The FadA adhesin/invasin of *F. nucleatum* binds to cadherins and is a key virulence factor.

Table 1

Diseases *F. nucleatum* associated with.

Diseases		References
Oral Infections	Chronic Periodontitis	[8–11]
	Aggressive Periodontitis	[8,11,12]
	Gingivitis	[8,11,13–15]
	Endodontic Infections	[16–22]
Adverse Pregnancy Outcomes	Chorioamnionitis	[38–40,42]
	Preterm Birth	[39,41–44,46,47]
	Stillbirth	[38]
	Neonatal Sepsis	[37]
	Preeclampsia	[45]
GI Disorders	Colorectal Cancer	[62–71]
	Inflammatory Bowel Disease	[76,77]
	Appendicitis	[78–80]
Other Infections	Atherosclerosis	[84,85,87]
	Cerebral Aneurysm	[86]
	Lemierre’s Syndrome	[81,83]
	Other Respiratory Tract Infections	[81]
	Organ Abscesses	[81]
	Rheumatoid Arthritis	[89]
	Alzheimer’s	[88]