

UDC 616-006.61;577.2;579.61

# The Oral Microbiome in the Development of Oral Cancer

E. S. Kolegova<sup>a, \*</sup>, A. A. Schegoleva<sup>a</sup>, L. A. Kononova<sup>b</sup>, and E. V. Denisov<sup>a</sup>

<sup>a</sup> Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, 634009 Russia

<sup>b</sup> Siberian State Medical University, Tomsk, 634050 Russia

\*e-mail: elenakolegova@oncology.tomsk.ru

Received August 30, 2023; revised October 23, 2023; accepted October 26, 2023

**Abstract**—Oral cancer is an aggressive and rapidly progressive disease. The oral cavity is home to over 700 species of microorganisms that regulate metabolism, immune function, and health. There are three types of mechanisms by which bacteria may participate in carcinogenesis. First, bacteria cause chronic inflammation, which stimulates the production of cytokines, including interleukins, interferons, and tumor necrosis factor. Second, bacteria can interact directly with host cells by secreting toxins or by binding to membrane receptors. Finally, the production of metabolites by bacteria may also contribute to carcinogenesis. The importance of the bacteria level and composition in the transition of oral precancerous lesions to cancer has been demonstrated. The relationships of changes in microbiome composition with smoking, inflammation in healthy individuals, as well as with the development of oral cancer in patients, have been studied.

**Keywords:** microbiome, oral cancer, inflammation, smoking, immunity

**DOI:** 10.1134/S0026893324020092

## INTRODUCTION

Oral cancer (OC) is one of the most common malignant neoplasms of the head and neck organs. [1]. The number of newly diagnosed cases of this pathology in Russia over the past 10 years has increased by 17% [2]. In addition to high morbidity, OC is characterized by an aggressive course; every year, about 180000 people worldwide die from OC, including people of working age [1, 2].

The human microbiota is an evolutionarily developed ecological system of various microorganisms inhabiting the open cavities of the body [3]. Microorganisms are an important link in the regulation of metabolism, immune function, and human health [3, 4]. It is believed that bacteria most strongly affect the cells of the intestines, skin, and mucous membranes [4]. The mucous membrane provides host protection from invading pathogens and also creates an environment for beneficial bacteria [5]. Disruption of the mucous membrane, for example by infection with harmful bacteria, can contribute to an inflammatory and carcinogenic environment [6].

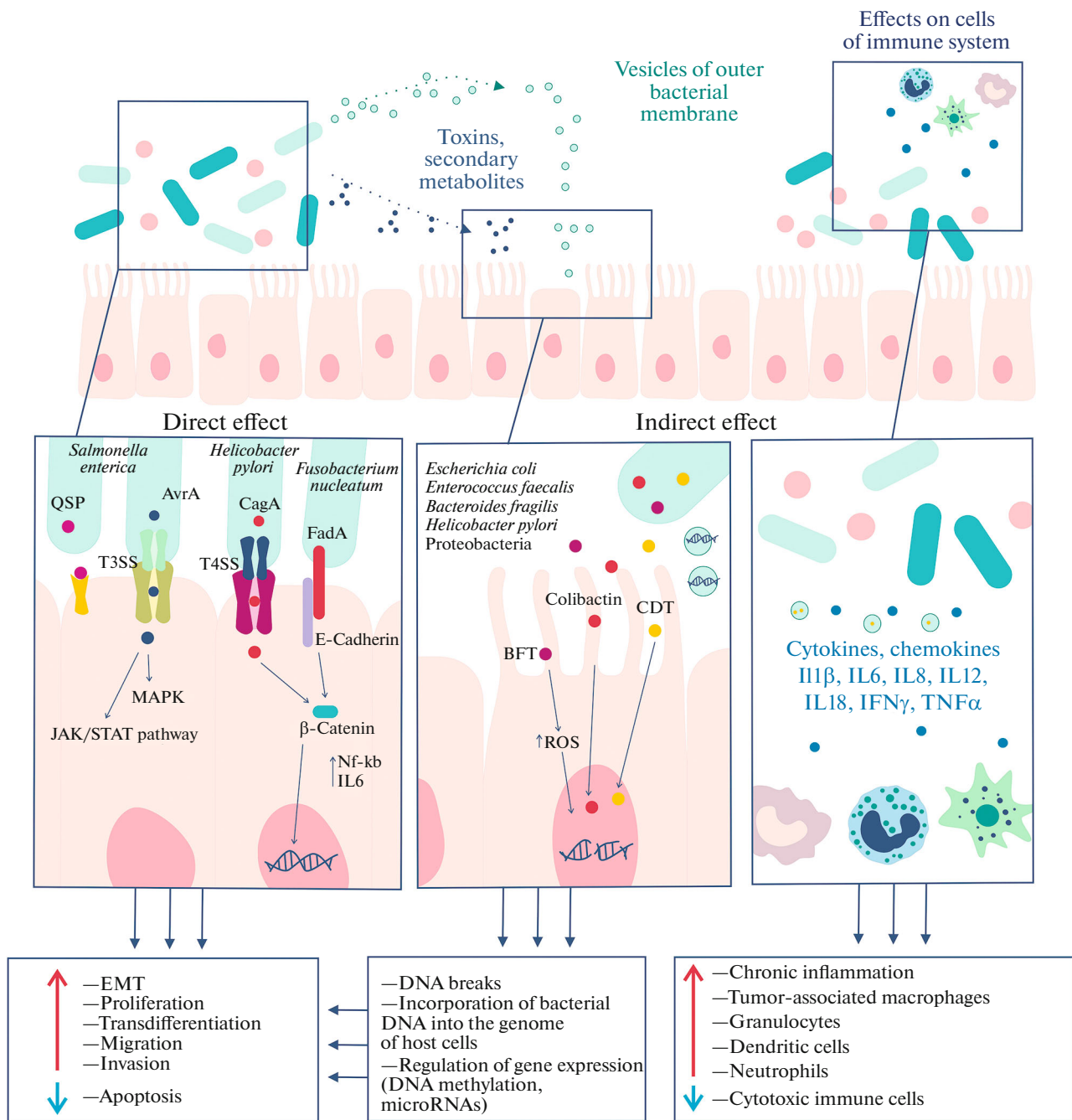
Bacteria play an important role in the pathogenesis of human diseases, including carcinogenesis [5]. Currently, active study of the influence of pathogenic microorganisms on cell proliferation, transformation, genetic instability, and tumor microenvironment occurs [7].

Three types of carcinogenic effects of bacteria on host cells have been described. Bacteria can contribute

to carcinogenesis both through direct interaction with host cells and indirectly, through the synthesis of toxins and metabolites, as well as influencing the immune system and stimulating inflammation [3, 5, 8–10] (Fig. 1).

## THE DIRECT IMPACT OF THE MICROBIOME ON HOST CELLS

When interacting directly with a host cell, bacteria secrete toxins, bind to membrane receptors and induce various signaling cascades [3, 10]. For example, *Fusobacterium nucleatum* binds to host epithelial and endothelial cells via the adhesion molecule FadA (*F. nucleatum* adhesin A), thereby ensuring the induction of pro-inflammatory signaling pathways mediated by nuclear factor NF- $\kappa$ B and IL6, and promoting OC invasion [11, 12]. As well, *F. nucleatum* may induce the epithelial–mesenchymal transition (EMT) [13]. Direct interaction between *F. nucleatum* and E-cadherin leads to DNA damage during epithelial cell proliferation, their acquisition of stemness and loss of cell polarity due to increased expression of E-cadherin/ $\beta$ -catenin-induced transcription factors [14, 15]. Another bacterium, *Helicobacter pylori*, bring the endothelial cell cytotoxin CagA (Cytotoxin-associated gene A) using the type IV secretion system (T4SS, Type IV Secretion System) [16]. CagA binds to E-cadherin and causes accumulation of  $\beta$ -catenin, which in turn leads to transdifferentiation of gastric epithelial



**Fig. 1.** Mechanisms of microbiome influence on host cells. ROS, reactive oxygen species; BFT, *Bacteroides fragilis* Toxin; CagA, Cytotoxin-associated gene A; CDT, Cytotolethal Distending Toxin; FadA, *Fusobacterium nucleatum* adhesin A; QSP, Quorum Sensing Peptides; T3SS, Type III Secretion System; T4SS, Type IV Secretion System.

cells and the development of precancerous intestinal metaplasia [17]. The bacterium *Bacteroides fragilis* secretes metalloproteinase BFT (Bacteroides Fragilis Toxin) and causes chronic inflammation and damage to intestinal tissues by altering intestinal cell tight junctions through cleavage of E-cadherin and activation of Wnt/β-catenin/NF-κB signaling pathways [18–20]. *Salmonella enterica*, using the type III secretion system (T3SS, Type III Secretion System), transfers the

effector protein AvrA into epithelial cells, which promotes the activation of the MAPK, Wnt/β-catenin and JAK/STAT signaling pathways, EMT, proliferation, cell transdifferentiation, cell cycle arrest and inhibition of apoptosis [21, 22]. *Bacillus* sp., *Enterococcus faecium* and *Escherichia coli* produce Quorum sensing (QSP) system peptides, which influence host epithelial cells through growth factors, promote tumor formation and metastasis of tumor cells [23]. Thus,

QSP peptides synthesized by *Bacillus* are capable of inducing invasion, EMT, and angiogenesis [23, 24].

### INDIRECT IMPACTS OF THE MICROBIOME ON HOST CELLS

Bacteria can initiate carcinogenesis by metabolizing various bioactive molecules secreted by host cells [3]. Thus, bacterial lipopolysaccharides and acetate stimulate EMT and angiogenesis, promoting the development of tumors [25]. Microorganisms metabolize host-secreted compounds such as secondary bile acids (deoxycholic and lithocholic acids) and contribute to the development of colorectal cancer and hepatocellular carcinoma [25]. Gallic acid of microbial origin induces mutations in the *TP53* gene and, as a consequence, the occurrence of malignant tumors in the distal intestine [26].

Another mechanism for the indirect effect of the microbiome on host cells is the bacterial delivery system, which consists of outer membrane vesicles of predominantly Gram-negative bacteria. This system allows bacteria to transfer genetic material, immunomodulatory molecules, virulence factors, and toxins into the host's bloodstream [3, 27–29].

#### *The Effect on the Host Cell Genome*

Many bacteria, in the process of evolution, have acquired the ability to damage DNA, thereby inducing genetic changes and contributing to carcinogenesis [30, 31]. *E. coli*, *B. fragilis*, and *H. pylori*, *Enterococcus faecalis* and proteobacteria cause DNA double-strand breaks, aneuploidy, cell cycle arrest, and abnormal cell division [32]. Colibactin and the cytolethal toxin CDT (Cytolethal Distending Toxin) mechanically damage DNA, while BFT acts indirectly by increasing the level of reactive oxygen species [32, 33]. DNA strand breaks and genomic instability allow bacterial DNA to integrate into the genome of the host cell. Bacterial genes initiate the transformation of healthy cells into tumor cells, stimulating the activity of oncogenes and inhibiting tumor suppressor genes [34].

Bacteria can make epigenetic changes to the host genome. Thus, exposure to commensal microbiota leads to local changes in the methylation of DNA regulatory elements in intestinal epithelial cells [35]. Bacterial microRNAs penetrate human cells and regulate gene expression in them. The bacterium *F. nucleatum* promotes increased proliferation and invasiveness of colorectal cancer cells and carcinogenesis through the TLR4/MYD88 signaling pathway, which leads to activation of NF- $\kappa$ B and increased miR21 expression in intestinal mucosal cells [36].

The ability of microbes to both directly and indirectly cause DNA damage and genome instability makes the microbiome both a potential risk factor for cancer and a target for anticancer therapy [37–39].

#### *Interaction with the Immune System*

Immune-bacterial interactions occur on mucosal surfaces, lymphoid organs, and tumor microenvironments [3]. Numerous bacteria induce the development of a protumor immune response [40–42]. *H. pylori* causes chronic inflammation by promoting the secretion of IL6, IL1 $\beta$ , TNF $\alpha$ , IFN $\gamma$ , and the toxin VacA (Vacuolating cytotoxin A) [43, 44]. Membrane vesicles produced by *F. nucleatum* cause chronic inflammation by stimulating the secretion of IL6, IL8, IL18, and TNF $\alpha$  by colon epithelial cells [15, 45].

Intratumoral bacteria can directly inhibit antitumor immunity by suppressing the infiltration of cytotoxic immune cells and blocking their ability to kill tumor cells [40, 46, 47]. Decreased numbers of T cells in the tumor microenvironment result in a weakened immune system and inability to target a tumor [3]. In addition, commensal bacteria recruit large numbers of inflammatory cells, including tumor-associated macrophages, regulatory T cells, granulocytes, and myeloid-derived suppressor cells, resulting in a proinflammatory tumor microenvironment. [41, 48–50].

Colonization of the stomach by the bacteria *H. pylori* causes an inflammatory response and recruits dendritic cells, macrophages, neutrophils, and lymphocytes to the gastric mucosa [44]. *Erythrobacter ramosus* and *B. fragilis* located in the ileum promote the induction of follicular T helper cells through the activation of dendritic cells and the release of IL1 and IL12 [51]. Bacteria entering the mucous membranes affect the activity of Th17 cells [52–54], playing an important role in the antitumor immune response [55]. The bacterium *Porphyromonas gingivalis* expresses chemokines such as CCL2 and CXCL2, which recruit myeloid suppressor cells and promote tumor progression [56, 57]. As well, *P. gingivalis* and *F. nucleatum* activate the binding of PD-L1 to PD-1, which leads to inhibition and apoptosis of T cells [56, 58]. *F. nucleatum*, interacting with the TIGIT receptor of immune cells, suppresses the activity of NK and T cells, creating a pro-inflammatory microenvironment that supports the progression of colorectal cancer [59]. In addition, this bacterium helps to increase the population of CD11b myeloid cells, tumor-associated neutrophils and macrophages in tumors of various locations [57].

Thus, bacteria secrete virulence factors, cause physical binding-induced signaling, and recruitment of immune cells, which together may contribute to carcinogenesis. Understanding these mechanisms is critical for the development of new methods for diagnosing and treating cancer [3, 10].

### THE ROLE OF THE MICROBIOME IN THE DEVELOPMENT OF ORAL CANCER

A number of studies have described the role of the microbiome in the development of oral diseases,

including OC [60–62]. Well-established risk factors for OC include smoking, alcohol, and chronic inflammation. These factors also influence the oral microbiome, which, in turn, can contribute to the occurrence of OC, its progression, or, conversely, regression.

### Normal Oral Microbiome

The Expanded Human Oral Microbiome Database contains information on approximately 772 species of prokaryotic microorganisms and is second only to the gastrointestinal microbiome. It is important to emphasize that the human microbiome can be divided into two parts, the main and the variable parts. The core microbiome consists of predominant species that exist in “healthy conditions,” while the variable microbiome evolves in response to lifestyle and nutritional patterns, and also depends on the genotypic characteristics of individuals [63–66].

Profiling of 16S rDNA isolated from a “healthy” oral cavity identified six types of bacteria: Bacillota (formerly Firmicutes), Actinomycetota (formerly Actinobacteria), Pseudomonadota (formerly Proteobacteria), Fusobacteriota (formerly Fusobacteria), Bacteroidota (formerly Bacteroidetes), and Spirochaetota (formerly Spirochaetes), representing 96% of the total number of microorganisms [67]. However, Bacillota accounts for a maximum of 36.7%, followed by Bacteroidota (17.1%), Pseudomonadota (17.1%), Actinomycetota (11.6%), Spirochaetota (7.9%), and Fusobacteriota (5.2%) [68]. The main genera of bacteria inhabiting a healthy oral cavity include Gram-positive *Abiotrophia*, *Actinomyces*, *Bifidobacterium*, *Corynebacterium*, *Eubacterium*, *Lactobacillus*, *Peptostreptococcus*, *Propionibacterium*, *Pseudoramibacter*, *Rothia*, *Streptococcus*, *Stomatococcus*, and Gram-negative *Campylobacter*, *Capnocytophaga*, *Desulfobacter*, *Desulfovibrio*, *Eikenella*, *Fusobacterium*, *Hemophilus*, *Lep-totrichia*, *Moraxella*, *Neisseria*, *Prevotella*, *Selemonas*, *Simonsiella*, *Treponema*, *Veillonella*, and *Wolinella* [63]. Although all of these bacteria are commensal, some of them are considered pathogenic. The transition of commensal microflora to pathogenicity often depends on the number of these microorganisms in the composition of oral biofilms [69].

Various factors such as dietary habits, tobacco and alcohol use, stress, hormonal imbalance, puberty, poor oral hygiene, diabetes and gum disease disrupt the structure of the local bacterial community and can lead to the development of cancer [64, 65].

### Changes in the Microbiome Due to Smoking

In the microbiome of active smokers, there is a significant decrease in the abundance of Pseudomonadota and an enrichment of Bacillota and Actinomycetota compared to individuals who have never smoked [70]. However, changes in the microbiome associated with smoking have a temporary effect; former smokers

have the same general composition of the oral microbiome as individuals who have never smoked [70].

There are several potential mechanisms by which smoking may alter the microbiome profile: increased salivary acidity [71, 72], formation of anaerobic conditions [73], influence on the adhesion of bacteria to the surfaces of mucous membranes [74], and impaired host immunity [75].

Currently, there is a trend towards the use of electronic cigarettes, which also affect the microflora of the oral cavity: the content of *Porphyromonas* and *Veillonella* species increases; beta diversity, which characterizes the similarity/difference of species composition, changes significantly compared to those who have never smoked or smoked tobacco cigarettes [76, 77]. Smoking e-cigarettes significantly increases the levels of IL-6 and IL-1b in saliva, making epithelial cells more susceptible to infection [76].

The risk of developing OC, oropharynx and hypopharynx cancer in smokers is 4–5 times higher than in nonsmokers. Alcohol acts synergistically with tobacco, resulting in an approximately 35-fold increase in the risk of OC in heavy smokers (>2 packs/day) who drink alcohol (>4 drinks/day) [78].

### Changes in the Microbiome during Inflammation

If the change in the microbial community during smoking is secondary, then during inflammation a change in the microbiome often becomes its cause. The main oral infections include periodontitis and caries.

Since the 1950s, the microbiota of the periodontal pocket has been studied using cultural methods. Researchers sought to identify microbial species that are critical to the onset and progression of the disease. Historically defined microorganisms of the “red complex” are *P. gingivalis*, *Tannerella forsythia* (previously *Bacteroides forsythus*), and *Treponema denticola* [79]. These species were considered most associated with deep periodontal pocket disease. The cluster of species with a less stringent association with periodontal disease, identified as the “orange complex,” includes *Prevotella* spp., *Fusobacterium* spp., and *Parvimonas micra* (previously *Peptostreptococcus micros*) [79].

A special role in the pathogenesis of periodontitis is assigned to *P. gingivalis*, a small anaerobic bacterium of the oral cavity that causes polymicrobial inflammatory disease and associated systemic conditions [80]. Thus, one low-abundance species can disrupt the homeostasis of the entire oral microbiome, causing inflammation. This concept has been called the polymicrobial synergy and dysbiosis model. According to this model, periodontitis is initiated by a synergistic and dysbiotic microbial community rather than by select pathogens such as the “red complex.” One of the fundamental requirements for the emergence of a

potentially pathogenic community is the ability of certain species, called “keystone pathogens,” to modulate the host response in such a way as to weaken immune surveillance and tip the scales from homeostasis to dysbiosis [81]. On the other hand, the development of pathogenic microflora requires the expression of various molecules, for example, corresponding adhesins, cognate receptors, proteolytic enzymes, and pro-inflammatory surface structures/ligands, which in combination act as community virulence factors to nutritionally support the pro-inflammatory microbial community [81].

All this makes us think about the possible specific prevention of periodontitis through vaccination or the use of probiotics. It has been shown that human immunization with monoclonal antibodies to *P. gingivalis* temporarily prevents colonization by these microorganisms [82]. It has also been found that periodontitis increases the likelihood of leukoplakia formation in the oral cavity in a dose-dependent manner. [83]. Leukoplakia is the most common precancerous lesion of the oral cavity, whose prevalence in the world ranges from 1.1 to 3.6% [84]. Patients with periodontitis, even those who have never smoked, have a several times higher risk of developing cancer than healthy people. [85].

#### *Changes in the Microbiome in Oral Cancer*

Recognized risk factors for OC include tobacco use, alcohol use, betel nut use, and older age. However, about 15% of all cases of OC are not associated with any known risk factors [86]. This has led to speculation about other possible contributing factors, including the microbiome.

Many studies have compared the microbiome profile in tumor tissue from patients with OC and in normal tissue from healthy donors. Despite the great heterogeneity of the results, it was possible to identify a number of microorganisms whose content increases with OC: *Fusobacterium*, *Streptococcus*, *Prevotella*, *Peptostreptococcus*, *Porphyromonas gingivalis*, *Capnocytophaga gingivalis*, and *T. denticola* [87–89]. Single studies have been published showing that in healthy individuals, compared with OC patients, *S. gordonii* [90], *S. mitis* [91], *Veillonella* [62], *Neisseria* [92], *Lautropia* [62], and *Haemophilus parainfluenzae* may predominate [91]. When studying the microbiome in patients with oral leukoplakia (facultative precancer), a specific microbiome profile was also discovered, in particular, an enrichment of Bacillota and Actinomycetota [93].

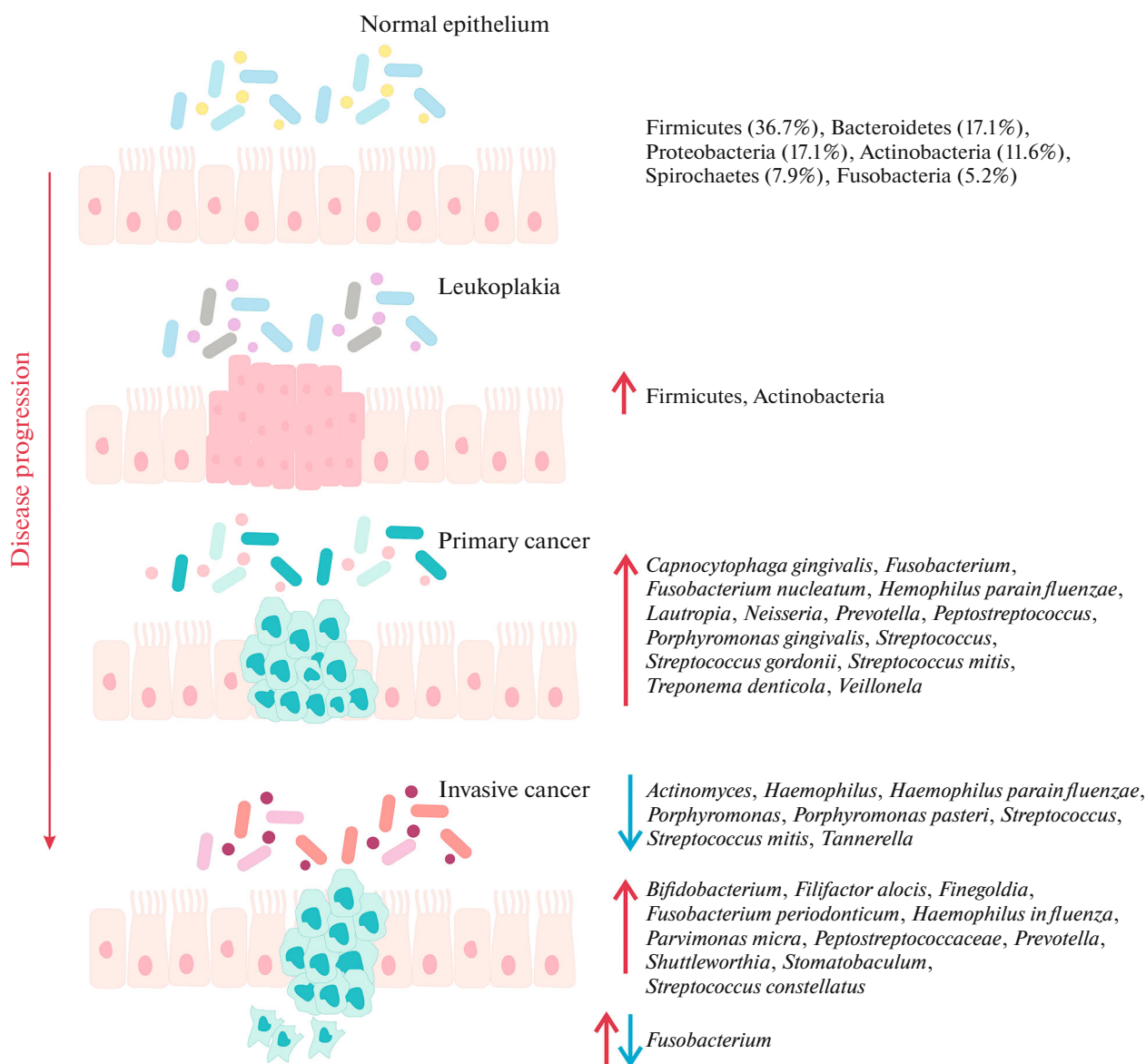
The results of experimental studies conducted on a mouse model have been published, confirming the role of at least the bacteria *P. gingivalis* and *F. nucleatum* in OC development [94, 95]. These studies have a similar design: mice were randomly divided into two groups: a group receiving only the carcinogen 4NQO

(4-nitroquinoline-1-oxide), and a group in which, in addition to the carcinogen, mice were infected *P. gingivalis* or *P. gingivalis* + *F. nucleatum*. Both studies demonstrated that these microorganisms contribute to carcinogenesis: mice in the challenged group developed more and larger tumors.

One of the key characteristics of ecosystems such as the oral microbiome is its biodiversity, which is assessed using alpha and beta diversity indices. Alpha diversity is an indicator of the complexity of communities, characterizing species richness and the evenness of the quantitative participation of species in the community. Beta diversity characterizes the similarity/difference between different groups. A number of studies have shown that healthy areas adjacent to tumors exhibit higher alpha diversity than tumor tissue [96]. At the same time, data were published indicating higher alpha and beta diversity in patients with OC compared to healthy donors [97, 98].

The microbiome profile differs not only between patients with OC and healthy people, it also dynamically changes during tumor progression. In particular, at the genus level, the number of *Fusobacterium* increases, while the number of bacteria of the genus *Streptococcus*, *Haemophilus*, *Porphyromonas*, and *Actinomyces* decreases as cancer progresses [96, 97]. The number of species *F. periodonticum*, *P. micra*, *S. constellatus*, *H. influenza*, and *Filifactor alocis* gradually increases as OC progresses from the first stage to the fourth [97]. At the same time, the quantity *S. mitis*, *Haemophilus parainfluenzae* and *Porphyromonas pasteri* decreases with increasing OC size and prevalence [97]. A significant increase in the content was revealed *Prevotella*, *Stomatobaculum*, *Bifidobacterium*, Peptostreptococcaceae *Shuttleworthia* and *Finegoldia*, and decline in *Tannerella* and *Fusobacterium* in patients with regional metastases compared to cases without metastases [99].

There is currently a problem with OC rejuvenation. Since the 1990s, the incidence of OC in patients under 45–50 years of age has been constantly increasing [1, 2, 100]. It has been hypothesized that young adults have a distinct bacterial profile that favors tumor progression. A comparative analysis of the microbiome of 40 patients with OC was carried out, half of whom were younger than 50 years old, the other half were over 60 years old: the main taxa in young adults were Betaproteobacteria, Burkholderiales, Ralstonia, Burkholderiaceae, and Rhizobiales, while in patients over 60 years of age they were Enterobacteriaceae, Enterobacterales, Sphingobacteriia, Sphingobacteriales, and Pedobacter [101].



**Fig. 2.** Changes in the composition of the oral microbiota during the development of oral cancer.

## CONCLUSIONS

Imbalance of the oral microbiota may be a key link through which commensal bacteria promote the development of OC. The results of studies indicate that the microbiome changes at the early stage of malignant transformation and is significantly transformed during tumor progression (Fig. 2). Microbiome data can be used to develop new methods for the diagnosis, prognosis, and prevention of OC, for example, through the use of vaccines, antimicrobials, or probiotics. Bacterial-mediated OC therapy, which causes fewer side effects compared to conventional methods of tumor therapy, may become a promising direction. However, given the variability of the oral microbiome even under normal conditions, care must

be taken to ensure that diagnostic and prognostic approaches are reproducible and repeatable.

## ABBREVIATIONS

OC, oral cancer; EMT, epithelial-mesenchymal transition.

## FUNDING

The work was carried out with the financial support of the Grant of the President of the Russian Federation no. MK-1940.2022.3.

ETHICS APPROVAL AND CONSENT  
TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

## CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

## REFERENCES

- Siegel R.L., Miller K.D., Fuchs H.E., Jemal A. 2022. Cancer statistics, 2022. *CA: Cancer J. Clin.* **72**, 7–33.
2022. *Sostoyanie onkologicheskoi pomoshchi naseleniyu Rossii v 2021 godu.* (The State of Cancer Care for the Russian Population in 2021). Kaprin A.D., Starinsky V.V., Shakhzadova A.O., Eds. Moscow: Herzen Moscow Research Institute of Oncology—Branch of the National Medical Research Center of Radiology of the Health Ministry of Russia.
- Cullin N., Azevedo Antunes C., Straussman R., Stein-Thoeringer C.K., Elinav E. 2021. Microbiome and cancer. *Cancer Cell.* **39**, 1317–1341.
- Yangyanqiu W., Shuwen H. 2022. Bacterial DNA involvement in carcinogenesis. *Front. Cell Infect. Microbiol.* **12**, 996778.
- Nokhandani N., Poursheikhani A., Alhosseini M.N., Davoodi H. 2021. Bacteria in carcinogenesis and cancer prevention: A review study. *Int. J. Cancer Manage.* **14**.  
<https://doi.org/10.5812/ijcm.107956>
- Whisner C.M., Athena Aktipis C. 2019. The role of the microbiome in cancer initiation and progression: How microbes and cancer cells utilize excess energy and promote one another's growth. *Curr. Nutr. Rep.* **8**, 42–51.
- Gaines S., Williamson A.J., Hyman N., Kandel J. 2018. How the microbiome is shaping our understanding of cancer biology and its treatment. *Semin. Colon Rectal Surg.* **29**, 12–16.
- Chang A.H., Parsonnet J. 2010. Role of bacteria in oncogenesis. *Clin. Microbiol. Rev.* **23**, 837–857.
- Contreras A.V., Cocom-Chan B., Hernandez-Montes G., Portillo-Bobadilla T., Resendis-Antonio O. 2016. Host-microbiome interaction and cancer: Potential application in precision medicine. *Front. Physiol.* **7**, 606.
- Liu J., Zhang Y. 2022. Intratumor microbiome in cancer progression: Current developments, challenges and future trends. *Biomark. Res.* **10**, 37.
- Han Y.W., Shi W., Huang G.T., Kinder Haake S., Park N.H., Kuramitsu H., Genco R.J. 2000. Interactions between periodontal bacteria and human oral epithelial cells: *Fusobacterium nucleatum* adheres to and invades epithelial cells. *Infect. Immun.* **68**, 3140–3146.
- Han Y.W., Redline R.W., Li M., Yin L., Hill G.B., McCormick T.S. 2004. *Fusobacterium nucleatum* induces premature and term stillbirths in pregnant mice: Implication of oral bacteria in preterm birth. *Infect. Immun.* **72**, 2272–2279.
- Zhang S., Li C., Liu J., Geng F., Shi X., Li Q., Lu Z., Pan Y. 2020. *Fusobacterium nucleatum* promotes epithelial-mesenchymal transition through regulation of the lncRNA mir4435-2hg/mir-296-5p/Akt2/Snai1 signaling pathway. *FEBS J.* **287**, 4032–4047.
- Guo P., Tian Z., Kong X., Yang L., Shan X., Dong B., Ding X., Jing X., Jiang C., Jiang N. 2020. FadA promotes DNA damage and progression of *Fusobacterium nucleatum*-induced colorectal cancer through up-regulation of Chk2. *J. Exp. Clin. Cancer Res.* **39**, 1–13.
- Rubinstein M.R., Wang X., Liu W., Hao Y., Cai G., Han Y.W. 2013. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/ $\beta$ -catenin signaling via its FadA adhesin. *Cell Host Microbe.* **14**, 195–206.
- Odenbreit S., Püls J., Sedlmaier B., Gerland E., Fischer W., Haas R. 2000. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. *Science.* **287**, 1497–1500.
- Murata-Kamiya N., Kurashima Y., Teishikata Y., Yamahashi Y., Saito Y., Higashi H., Aburatani H., Akiyama T., Peek R., Azuma T. 2007. *Helicobacter pylori* CagA interacts with E-cadherin and deregulates the  $\beta$ -catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene.* **26**, 4617–4626.
- Parida S., Wu S., Siddharth S., Wang G., Muniraj N., Nagalingam A., Hum C., Mistriotis P., Hao H., Talbot C.C., Jr., Konstantopoulos K., Gabrielson K.L., Sears C.L., Sharma D. 2021. A procarcinogenic colon microbe promotes breast tumorigenesis and metastatic progression and concomitantly activates Notch and  $\beta$ -catenin axes. *Cancer Discovery* **11**, 1138–1157.
- Cheng W.T., Kantilal H.K., Davamani F. 2020. The mechanism of *Bacteroides fragilis* toxin contributes to colon cancer formation. *Malays. J. Med. Sci.* **27**, 9.
- Wu S., Morin P.J., Maouyo D., Sears C.L. 2003. *Bacteroides fragilis* enterotoxin induces *c-myc* expression and cellular proliferation. *Gastroenterology.* **124**, 392–400.
- Lu R., Bosland M., Xia Y., Zhang Y.-G., Kato I., Sun J. 2017. Presence of *Salmonella avra* in colorectal tumor and its precursor lesions in mouse intestine and human specimens. *Oncotarget.* **8**, 55104.
- Wu S., Ye Z., Liu X., Zhao Y., Xia Y., Steiner A., Petrof E.O., Claud E.C., Sun J. 2010. *Salmonella typhimurium* infection increases p53 acetylation in intestinal epithelial cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* **298**, G784–G794.
- Wynendaele E., Verbeke F., D'Hondt M., Hendrix A., Van De Wiele C., Burvenich C., Peremans K., De Wever O., Bracke M., De Spiegeleer B. 2015. Crosstalk between the microbiome and cancer cells by quorum sensing peptides. *Peptides.* **64**, 40–48.
- De Spiegeleer B., Verbeke F., D'Hondt M., Hendrix A., Van De Wiele C., Burvenich C., Peremans K., De Wever O., Bracke M., Wynendaele E. 2015. The quorum sensing peptides PhrG, CSP and EDF promote angiogenesis and invasion of breast cancer cells in vitro. *PLoS One.* **10**, e0119471.
- Rossi T., Vergara D., Fanini F., Maffia M., Bravaccini S., Pirini F. 2020. Microbiota-derived me-

- tabolites in tumor progression and metastasis. *Int. J. Mol. Sci.* **21**, 5786.
26. Kadosh E., Snir-Alkalay I., Venkatachalam A., May S., Lasry A., Elyada E., Zinger A., Shaham M., Vaalani G., Mernberger M. 2020. The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic. *Nature*. **586**, 133–138.
  27. Cañas M.-A., Giménez R., Fábrega M.-J., Toloza L., Baldomà L., Badia J. 2016. Outer membrane vesicles from the probiotic *Escherichia coli* nissle 1917 and the commensal ECOR12 enter intestinal epithelial cells via clathrin-dependent endocytosis and elicit differential effects on DNA damage. *PLoS One*. **11**, e0160374.
  28. Chmiela M., Walczak N., Rudnicka K. 2018. *Helicobacter pylori* outer membrane vesicles involvement in the infection development and *Helicobacter pylori*-related diseases. *J. Biomed. Sci.* **25**, 1–11.
  29. Zakhazhevskaya N.B., Tsvetkov V.B., Vanyushkina A.A., Varizhuk A.M., Rakitina D.V., Podgorsky V.V., Vishnyakov I.E., Kharlampieva D.D., Manuvera V.A., Lisitsyn F.V. 2017. Interaction of *Bacteroides fragilis* toxin with outer membrane vesicles reveals new mechanism of its secretion and delivery. *Front. Cell. Infect. Microbiol.* **7**, 2.
  30. Imai S., Ooki T., Murata-Kamiya N., Komura D., Tahmina K., Wu W., Takahashi-Kanemitsu A., Knight C.T., Kunita A., Suzuki N., Del Valle A.A., Tsuboi M., Hata M., Hayakawa Y., Ohnishi N., Ueda K., Fukayama M., Ushiku T., Ishikawa S., Hatakeyama M. 2021. *Helicobacter pylori* CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis. *Cell Host Microbe*. **29**, 941–958.e910.
  31. Pleguezuelos-Manzano C., Puschhof J., Rosendahl Huber A., van Hoeck A., Wood H.M., Nomburg J., Gurjao C., Manders F., Dalmasso G., Stege P.B., Paganelli F.L., Geurts M.H., Beumer J., Mizutani T., Miao Y., van der Linden R., van der Elst S., Garcia K.C., Top J., Willems R.J.L., Giannakis M., Bonnet R., Quirke P., Meyerson M., Cuppen E., van Boxtel R., Clevers H. 2020. Mutational signature in colorectal cancer caused by genotoxic *pks<sup>+</sup> E. coli*. *Nature*. **580**, 269–273.
  32. Arthur J.C., Gharraibeh R.Z., Mühlbauer M., Perez-Chanona E., Uronis J.M., McCafferty J., Fodor A.A., Jobin C. 2014. Microbial genomic analysis reveals the essential role of inflammation in bacteria-induced colorectal cancer. *Nat. Commun.* **5**, 4724.
  33. Kipanyula M.J., Seke Etet P.F., Vecchio L., Farahna M., Nukenine E.N., Nwabo Kamdje A.H. 2013. Signaling pathways bridging microbial-triggered inflammation and cancer. *Cell. Signal.* **25**, 403–416.
  34. Riley D.R., Sieber K.B., Robinson K.M., White J.R., Ganesan A., Nourbakhsh S., Dunning Hotopp J.C. 2013. Bacteria-human somatic cell lateral gene transfer is enriched in cancer samples. *PLoS Comput. Biol.* **9**, e1003107.
  35. Ansari I., Raddatz G., Gutekunst J., Ridnik M., Cohen D., Abu-Remaileh M., Tuganbaev T., Shapiro H., Pikarsky E., Elinav E., Lyko F., Bergman Y. 2020. The microbiota programs DNA methylation to control intestinal homeostasis and inflammation. *Nat. Microbiol.* **5**, 610–619.
  36. Yang Y., Weng W., Peng J., Hong L., Yang L., Toiyama Y., Gao R., Liu M., Yin M., Pan C., Li H., Guo B., Zhu Q., Wei Q., Moyer M.P., Wang P., Cai S., Goel A., Qin H., Ma Y. 2017. *Fusobacterium nucleatum* increases proliferation of colorectal cancer cells and tumor development in mice by activating Toll-like receptor 4 signaling to nuclear factor- $\kappa$ B, and up-regulating expression of microRNA-21. *Gastroenterology*. **152**, 851–866.e824.
  37. Fulbright L.E., Ellermann M., Arthur J.C. 2017. The microbiome and the hallmarks of cancer. *PLoS Pathog.* **13**, e1006480.
  38. Bhatt A.P., Redinbo M.R., Bultman S.J. 2017. The role of the microbiome in cancer development and therapy. *CA—Cancer J. Clin.* **67**, 326–344.
  39. Hsiao Y.-C., Liu C.-W., Yang Y., Feng J., Zhao H., Lu K. 2023. DNA damage and the gut microbiome: From mechanisms to disease outcomes. *DNA*. **3**, 13–32.
  40. Nejman D., Liviyan I., Fuks G., Gavert N., Zwang Y., Geller L.T., Rotter-Maskowitz A., Weiser R., Mallel G., Gigi E., Meltzer A., Douglas G.M., Kamer I., Gopalakrishnan V., Dadosh T., Levin-Zaidman S., Avnet S., Atlan T., Cooper Z.A., Arora R., Cogdill A.P., Khan M.A.W., Ologun G., Bussi Y., Weinberger A., Lotan-Pompan M., Golani O., Perry G., Rokah M., Bahar-Shany K., Rozeman E.A., Blank C.U., Ronai A., Shaoul R., Amit A., Dorfman T., Kremer R., Cohen Z.R., Harnof S., Siegal T., Yehuda-Shnaidman E., Gal-Yam E.N., Shapira H., Baldini N., Langille M.G.I., Ben-Nun A., Kaufman B., Nissan A., Golan T., Dadiani M., Levannon K., Bar J., Yust-Katz S., Barshack I., Peeper D.S., Raz D.J., Segal E., Wargo J.A., Sandbank J., Shtental N., Straussman R. 2020. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science*. **368**, 973–980.
  41. Jin C., Lagoudas G.K., Zhao C., Bullman S., Bhutkar A., Hu B., Ameh S., Sandel D., Liang X.S., Mazzilli S., Whary M.T., Meyerson M., Germain R., Blainey P.C., Fox J.G., Jacks T. 2019. Commensal microbiota promote lung cancer development via  $\gamma$ DT cells. *Cell*. **176**, 998–1013.e1016.
  42. Forbes N.S. 2010. Engineering the perfect (bacterial) cancer therapy. *Nat. Rev. Cancer*. **10**, 785–794.
  43. Baik S.C., Youn H.S., Chung M.H., Lee W.K., Cho M.J., Ko G.H., Park C.K., Kasai H., Rhee K.H. 1996. Increased oxidative DNA damage in *Helicobacter pylori*-infected human gastric mucosa. *Cancer Res*. **56**, 1279–1282.
  44. Bagheri N., Salimzadeh L., Shirzad H. 2018. The role of T helper 1-cell response in *Helicobacter pylori*-infection. *Microb. Pathog.* **123**, 1–8.
  45. Engevik M.A., Danhof H.A., Ruan W., Engevik A.C., Chang-Graham A.L., Engevik K.A., Shi Z., Zhao Y., Brand C.K., Krystofiak E.S., Venable S., Liu X., Hirschi K.D., Hyser J.M., Spinler J.K., Britton R.A., Versalovic J. 2021. *Fusobacterium nucleatum* secretes outer membrane vesicles and promotes intestinal inflammation. *mBio*. **12** (2), e02706–20.
  46. Parhi L., Alon-Maimon T., Sol A., Nejman D., Shhadeh A., Fainsod-Levi T., Yajuk O., Isaacson B., Abed J., Maalouf N., Nissan A., Sandbank J., Yehuda-



- Shnaidman E., Ponath F., Vogel J., Mandelboim O., Granot Z., Straussman R., Bachrach G. 2020. Breast cancer colonization by *Fusobacterium nucleatum* accelerates tumor growth and metastatic progression. *Nat. Commun.* **11**, 3259.
47. Abreu M.T., Peek R.M., Jr. 2014. Gastrointestinal malignancy and the microbiome. *Gastroenterology*. **146**, 1534–1546.e1533.
48. Pushalkar S., Hundeyin M., Daley D., Zambirinis C.P., Kurz E., Mishra A., Mohan N., Aykut B., Usyk M., Torres L.E., Werba G., Zhang K., Guo Y., Li Q., Akkad N., Lall S., Wadowski B., Gutierrez J., Kochen Rossi J.A., Herzog J.W., Diskin B., Torres-Hernandez A., Leinwand J., Wang W., Taunk P.S., Savadkar S., Janal M., Saxena A., Li X., Cohen D., Sartor R.B., Saxena D., Miller G. 2018. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. *Cancer Discovery*. **8**, 403–416.
49. Kostic A.D., Chun E., Robertson L., Glickman J.N., Gallini C.A., Michaud M., Clancy T.E., Chung D.C., Lochhead P., Hold G.L., El-Omar E.M., Brenner D., Fuchs C.S., Meyerson M., Garrett W.S. 2013. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe*. **14**, 207–215.
50. Campbell C., McKenney P.T., Konstantinovskiy D., Isaeva O.I., Schizas M., Verter J., Mai C., Jin W.B., Guo C.J., Violante S., Ramos R.J., Cross J.R., Kadaveru K., Hambor J., Rudensky A.Y. 2020. Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. *Nature*. **581**, 475–479.
51. Roberti M.P., Yonekura S., Duong C.P.M., Picard M., Ferrere G., Tidjani Alou M., Rauber C., Iebba V., Lehmann C.H.K., Amon L., Dudziak D., Derosa L., Routy B., Flament C., Richard C., Daillère R., Fluckiger A., Van Seuning I., Chamaillard M., Vincent A., Kourula S., Opolon P., Ly P., Pizzato E., Becharef S., Paillet J., Klein C., Marliot F., Pietrantonio F., Benoist S., Scoazec J.-Y., Dartigues P., Hollebecque A., Malka D., Pagès F., Galon J., Gomperts Boneca I., Lepage P., Ryffel B., Raoult D., Eggermont A., Vanden Berghe T., Ghiringhelli F., Vandenabeele P., Kroemer G., Zitvogel L. 2020. Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer. *Nat. Med.* **26**, 919–931.
52. Dutzan N., Kajikawa T., Abusleme L., Greenwell-Wild T., Zuazo C.E., Ikeuchi T., Brenchley L., Abe T., Hurabielle C., Martin D., Morell R.J., Freeman A.F., Lazarevic V., Trinchieri G., Diaz P.I., Holland S.M., Belkaid Y., Hajishengallis G., Moutsopoulos N.M. 2018. A dysbiotic microbiome triggers Th17 cells to mediate oral mucosal immunopathology in mice and humans. *Sci. Transl. Med.* **10** (463), eaat0797.
53. Pandiyan P., Bhaskaran N., Zou M., Schneider E., Jayaraman S., Huehn J. 2019. Microbiome dependent regulation of Tregs and Th17 cells in mucosa. *Front. Immunol.* **10**, 426.
54. Zhang C., Xu C., Gao L., Li X., Zhao C. 2021. *Porphyromonas gingivalis* lipopolysaccharide promotes T-hel per17 cell differentiation by upregulating Delta-like ligand 4 expression on CD14<sup>+</sup> monocytes. *Peer J.* **9**, e11094.
55. Marques H.S., de Brito B.B., da Silva F.A.F., Santos M.L.C., de Souza J.C.B., Correia T.M.L., Lopes L.W., Neres N.S.M., Dórea R., Dantas A.C.S., Morbeck L.L.B., Lima I.S., de Almeida A.A., Dias M.R.J., de Melo F.F. 2021. Relationship between Th17 immune response and cancer. *W. J. Clin. Oncol.* **12**, 845–867.
56. Guo Z.C., Jumatai S., Jing S.L., Hu L.L., Jia X.Y., Gong Z.C. 2021. Bioinformatics and immunohistochemistry analyses of expression levels and clinical significance of *CXCL2* and *TANs* in an oral squamous cell carcinoma tumor microenvironment of *Prophyromonas gingivalis* infection. *Oncol. Lett.* **21**, 189.
57. Gholizadeh P., Eslami H., Kafil H.S. 2017. Carcinogenesis mechanisms of *Fusobacterium nucleatum*. *Biomed. Pharmacother.* **89**, 918–925.
58. Gao Y., Bi D., Xie R., Li M., Guo J., Liu H., Guo X., Fang J., Ding T., Zhu H., Cao Y., Xing M., Zheng J., Xu Q., Xu Q., Wei Q., Qin H. 2021. *Fusobacterium nucleatum* enhances the efficacy of PD-L1 blockade in colorectal cancer. *Signal. Transduct. Target Ther.* **6**, 398.
59. Gur C., Ibrahim Y., Isaacson B., Yamin R., Abed J., Gamliel M., Enk J., Bar-On Y., Stanietzky-Kaynan N., Copenhagen-Glazer S., Shussman N., Almogy G., Cuapio A., Hofer E., Mevorach D., Tabib A., Ortenberg R., Markel G., Miklič K., Jonjic S., Brennan C.A., Garrett W.S., Bachrach G., Mandelboim O. 2015. Binding of the Fap2 protein of *Fusobacterium nucleatum* to human inhibitory receptor tigit protects tumors from immune cell attack. *Immunity*. **42**, 344–355.
60. Gholizadeh P., Eslami H., Yousefi M., Asgharzadeh M., Aghazadeh M., Kafil H.S. 2016. Role of oral microbiome on oral cancers, a review. *Biomed. Pharmacother.* **84**, 552–558.
61. Rajagopala S.V., Vashee S., Oldfield L.M., Suzuki Y., Venter J.C., Telenti A., Nelson K.E. 2017. The human microbiome and cancer. *Cancer Prev. Res.* **10**, 226–234.
62. Zhao H., Chu M., Huang Z., Yang X., Ran S., Hu B., Zhang C., Liang J. 2017. Variations in oral microbiota associated with oral cancer. *Sci. Rep.* **7**, 11773.
63. Deo P.N., Deshmukh R. 2019. Oral microbiome: Unveiling the fundamentals. *J. Oral. Maxillofac. Pathol.* **23**, 122–128.
64. Kilian M., Chapple I.L., Hannig M., Marsh P.D., Meuric V., Pedersen A.M., Tonetti M.S., Wade W.G., Zaura E. 2016. The oral microbiome—an update for oral healthcare professionals. *Br. Dent. J.* **221**, 657–666.
65. Takeshita T., Kageyama S., Furuta M., Tsuboi H., Takeuchi K., Shibata Y., Shimazaki Y., Akifusa S., Nishimura T., Kiyohara Y., Yamashita Y. 2016. Bacterial diversity in saliva and oral health-related conditions: The Hisayama Study. *Sci. Rep.* **6**, 22164.
66. Zaura E., Nicu E.A., Krom B.P., Keijser B.J. 2014. Acquiring and maintaining a normal oral microbiome: Current perspective. *Front. Cell. Infect. Microbiol.* **4**, 85.

67. Turnbaugh P.J., Ley R.E., Hamady M., Fraser-Liggett C.M., Knight R., Gordon J.I. 2007. The human microbiome project. *Nature*. **449**, 804–810.
68. Dewhirst F.E., Chen T., Izard J., Paster B.J., Tanner A.C., Yu W.H., Lakshmanan A., Wade W.G. 2010. The human oral microbiome. *J. Bacteriol.* **192**, 5002–5017.
69. Morrison A.G., Sarkar S., Umar S., Lee S.T.M., Thomas S.M. 2023. The contribution of the human oral microbiome to oral disease: A review. *Microorganisms*. **11** (2), 318.
70. Wu J., Peters B.A., Dominianni C., Zhang Y., Pei Z., Yang L., Ma Y., Purdue M.P., Jacobs E.J., Gapstur S.M., Li H., Alekseyenko A.V., Hayes R.B., Ahn J. 2016. Cigarette smoking and the oral microbiome in a large study of American adults. *ISME J.* **10**, 2435–2446.
71. Grover N., Sharma J., Sengupta S., Singh S., Singh N., Kaur H. 2016. Long-term effect of tobacco on unstimulated salivary pH. *J. Oral Maxillofac. Pathol.* **20**, 16–19.
72. Kanwar A., Sah K., Grover N., Chandra S., Singh R.R. 2013. Long-term effect of tobacco on resting whole mouth salivary flow rate and pH: An institutional based comparative study. *Eur. J. Gen. Dent.* **2**, 296–299.
73. Kenney E.B., Saxe S.R., Bowles R.D. 1975. The effect of cigarette smoking on anaerobiosis in the oral cavity. *J. Periodontol.* **46**, 82–85.
74. Brook I. 2011. The impact of smoking on oral and nasopharyngeal bacterial flora. *J. Dent. Res.* **90**, 704–710.
75. Sopori M. 2002. Effects of cigarette smoke on the immune system. *Nat. Rev. Immunol.* **2**, 372–377.
76. Pushalkar S., Paul B., Li Q., Yang J., Vasconcelos R., Makwana S., González J.M., Shah S., Xie C., Janal M.N., Queiroz E., Bederoff M., Leinwand J., Solarewicz J., Xu F., Abozeria E., Guo Y., Agualló D., Gomez C., Kamer A., Shelley D., Aphinyanaphongs Y., Barber C., Gordon T., Corby P., Li X., Saxena D. 2020. Electronic cigarette aerosol modulates the oral microbiome and increases risk of infection. *iScience*. **23**, 100884.
77. Yang I., Rodriguez J., Young Wright C., Hu Y.J. 2023. Oral microbiome of electronic cigarette users: A cross-sectional exploration. *Oral Dis.* **29**, 1875–1884.
78. Dal Maso L., Torelli N., Biancotto E., Di Maso M., Gini A., Franchin G., Levi F., La Vecchia C., Serraino D., Polesel J. 2016. Combined effect of tobacco smoking and alcohol drinking in the risk of head and neck cancers: A re-analysis of case-control studies using bi-dimensional spline models. *Eur. J. Epidemiol.* **31**, 385–393.
79. Socransky S.S., Haffajee A.D., Cugini M.A., Smith C., Kent R.L., Jr. 1998. Microbial complexes in subgingival plaque. *J. Clin. Periodontol.* **25**, 134–144.
80. Hajishengallis G., Liang S., Payne M.A., Hashim A., Jotwani R., Eskin M.A., McIntosh M.L., Alsam A., Kirkwood K.L., Lambris J.D., Darveau R.P., Curtis M.A. 2011. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. *Cell Host Microbe*. **10**, 497–506.
81. Hajishengallis G., Lamont R.J. 2012. Beyond the red complex and into more complexity: The polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Mol. Oral Microbiol.* **27**, 409–419.
82. Persson G.R. 2005. Immune responses and vaccination against periodontal infections. *J. Clin. Periodontol.* **32** (Suppl 6), 39–53.
83. Meisel P., Holtfreter B., Biffar R., Suemnig W., Kocher T. 2012. Association of periodontitis with the risk of oral leukoplakia. *Oral Oncol.* **48**, 859–863.
84. Petersen P.E., Bourgeois D., Ogawa H., Estupinan-Day S., Ndiaye C. 2005. The global burden of oral diseases and risks to oral health. *Bull. W. Health Organ.* **83**, 661–669.
85. Tezal M., Sullivan M.A., Hyland A., Marshall J.R., Stoler D., Reid M.E., Loree T.R., Rigual N.R., Merzianu M., Hauck L., Lillis C., Wactawski-Wende J., Scannapieco F.A. 2009. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. *Cancer Epidemiol. Biomarkers Prev.* **18**, 2406–2412.
86. Chocolatewala N., Chaturvedi P., Desale R. 2010. The role of bacteria in oral cancer. *Indian J. Med. Paediatr. Oncol.* **31**, 126–131.
87. Fitzsimonds Z.R., Rodriguez-Hernandez C.J., Bagaitkar J., Lamont R.J. 2020. From beyond the pale to the pale riders: The emerging association of bacteria with oral cancer. *J. Dent. Res.* **99**, 604–612.
88. Karpiński T.M. 2019. Role of oral microbiota in cancer development. *Microorganisms*. **7** (1), 20.
89. Mauceri R., Coppini M., Vacca D., Bertolazzi G., Panzarella V., Di Fede O., Tripodo C., Campisi G. 2022. Salivary microbiota composition in patients with oral squamous cell carcinoma: a systematic review. *Cancers (Basel)*. **14** (21), 5441.
90. Ohshima J., Wang Q., Fitzsimonds Z.R., Miller D.P., Sztukowska M.N., Jung Y.J., Hayashi M., Whiteley M., Lamont R.J. 2019. *Streptococcus gordonii* programs epithelial cells to resist ZEB2 induction by *Porphyromonas gingivalis*. *Proc. Natl. Acad. Sci. U. S. A.* **116**, 8544–8553.
91. Al-Hebshi N.N., Nasher A.T., Maryoud M.Y., Homeida H.E., Chen T., Idris A.M., Johnson N.W. 2017. Inflammatory bacteriome featuring *Fusobacterium nucleatum* and *Pseudomonas aeruginosa* identified in association with oral squamous cell carcinoma. *Sci. Rep.* **7**, 1834.
92. Hayes R.B., Ahn J., Fan X., Peters B.A., Ma Y., Yang L., Agalliu I., Burk R.D., Ganly I., Purdue M.P., Freedman N.D., Gapstur S.M., Pei Z. 2018. Association of oral microbiome with risk for incident head and neck squamous cell cancer. *JAMA Oncol.* **4**, 358–365.
93. Schmidt B.L., Kuczynski J., Bhattacharya A., Huey B., Corby P.M., Queiroz E.L., Nightingale K., Kerr A.R., DeLacure M.D., Veeramachaneni R., Olshen A.B., Albertson D.G. 2014. Changes in abundance of oral microbiota associated with oral cancer. *PLoS One*. **9**, e98741.
94. Binder Gallimidi A., Fischman S., Revach B., Bulvik R., Maliutina A., Rubinstein A.M., Nussbaum G., Elkin M. 2015. Periodontal pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum*

- promote tumor progression in an oral-specific chemical carcinogenesis model. *Oncotarget*. **6**, 22613–22623.
95. Wu J.S., Zheng M., Zhang M., Pang X., Li L., Wang S.S., Yang X., Wu J.B., Tang Y.J., Tang Y.L., Liang X.H. 2018. *Porphyromonas gingivalis* promotes 4-nitroquinoline-1-oxide-induced oral carcinogenesis with an alteration of fatty acid metabolism. *Front. Microbiol.* **9**, 2081.
96. Shin J.M., Luo T., Kamarajan P., Fenno J.C., Rickard A.H., Kapila Y.L. 2017. Microbial communities associated with primary and metastatic head and neck squamous cell carcinoma—a high *Fusobacterial* and low *Streptococcal* signature. *Sci. Rep.* **7**, 9934.
97. Yang C.Y., Yeh Y.M., Yu H.Y., Chin C.Y., Hsu C.W., Liu H., Huang P.J., Hu S.N., Liao C.T., Chang K.P., Chang Y.L. 2018. Oral microbiota community dynamics associated with oral squamous cell carcinoma staging. *Front. Microbiol.* **9**, 862.
98. Yang J., He P., Zhou M., Li S., Zhang J., Tao X., Wang A., Wu X. 2022. Variations in oral microbiome and its predictive functions between tumorous and healthy individuals. *J. Med. Microbiol.* **71** (8). <https://doi.org/10.1099/jmm.0.001568>
99. Eun Y.G., Lee J.W., Kim S.W., Hyun D.W., Bae J.W., Lee Y.C. 2021. Oral microbiome associated with lymph node metastasis in oral squamous cell carcinoma. *Sci. Rep.* **11**, 23176.
100. Tota J.E., Anderson W.F., Coffey C., Califano J., Cozen W., Ferris R.L., St John M., Cohen E.E., Chaturvedi A.K. 2017. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. *Oral Oncol.* **67**, 146–152.
101. Zhang Z., Feng Q., Li M., Li Z., Xu Q., Pan X., Chen W. 2022. Age-related cancer-associated microbiota potentially promotes oral squamous cell cancer tumorigenesis by distinct mechanisms. *Front. Microbiol.* **13**, 852566.

**Publisher’s Note.** Pleiades Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.