World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

From dysbiosis to tumor progression: the microbiome's role in head and neck squamous cell carcinoma (HNSCC)

Anshika Srivastava *, Bhavika Sain, Abhilasha Fenin, Ashmeen Kaur and Aarohi Punj

Department of Oral Pathology, Adesh Institute of Dental Sciences & Research, Bathinda-151001, Punjab, India.

World Journal of Advanced Research and Reviews, 2025, 26(02), 2555-2562

Publication history: Received on 30 March 2025; revised on 14 May 2025; accepted on 17 May 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.26.2.1782

Abstract

Head and neck squamous cell carcinoma (HNSCC) is one of the leading health issues globally. Oral cavity harbors a rich variety of microbes, which are in charge of preserving homeostasis under healthy circumstances. Imbalance among this microbial community—is referred to as oral dysbiosis—that has the potential to cause oncogenesis by chronic inflammation, immune modulation, and genotoxic effect. Pathogenic bacteria, including *Porphyromonas gingivalis, Fusobacterium nucleatum* and *Treponema denticola* have been linked with the development & progression of tumors. Dysbiotic microenvironment is capable of causing DNA damage, inducing epithelial-mesenchymal transition, and remodeling the tumor microenvironment, hence facilitating cancer development and progression. The current review aims at tackling the multifaceted relationship between oral dysbiosis and head and neck squamous cell carcinoma (HNSCC) in light of underlying molecular mechanisms, potential diagnostic application and therapeutic measures.

Keywords: Oral cavity; Squamous cell carcinoma; Oral dysbiosis; Carcinogenic; Tumor; *Porphyromonas gingivalis; Fusobacterium nucleatum*; Tumor microenvironment; Oncogenesis

1. Introduction

Head and neck squamous cell cancer (HNSCC) ranks amongst the most frequent malignant malignancies of the head & neck [1], qualifying it to become a prime universal health focus area. This life-threatening cancer has bleak prospects when treated with advanced generations of radiochemotherapy treatments; therefore, there is a need for early recognition with intensified efforts towards therapeutic treatment [2]. Risk factors such as tobacco use, alcohol consumption, and infection with human papillomavirus (HPV) are established, but there is emerging evidence to support the involvement of the oral microbiome in carcinogenesis [3].

The human oral cavity contains a rich microbial community that includes bacteria, fungi, viruses, and archaea and is essential in ensuring oral and systemic health [4]. Under healthy states, commensal bacteria like *Streptococcus* and *Veillonella* play roles in immune homeostasis and pathogen resistance. Yet, alterations in microbial balance—also known as oral dysbiosis—can result in chronic inflammation, immune evasion, and tumor-promoting actions [5]. Interestingly, opportunistic pathogens like *Porphyromonas gingivalis, Fusobacterium nucleatum,* and *Treponema denticola* have been shown to promote oncogenic pathways through immune modulation, bacterial metabolites, and genotoxic effects [6]. Some recent studies indicate that oral microbial dysbiosis can be both a biomarker and a target for therapeutic intervention for HNSCC [7]. Elucidating the tumor-microbiome relationship is pivotal to the development of precision oncology. In this review, the complex interaction between oral dysbiosis and HNSCC is discussed, highlighting carcinogenesis mechanisms, diagnostic, and novel therapeutic approaches.

* Corresponding author: Dr. Anshika Srivastava

2. Oral microbiome

The oral cavity shelters a dynamic and multifaceted microbial community consisting of more than 700 species of bacteria, in addition to fungi, viruses, and archaea [8]. This microbial community is vital to both oral and systemic health, as it monitors immune responses, inhibits colonization by pathogenic microbes, and contributes to vital metabolic processes [9]. Oral homeostasis depends on a balanced oral microbiome, but microbial composition disturbances—oral dysbiosis—can cause a number of diseases, such as periodontitis and caries, and possibly head and neck squamous cell carcinoma (HNSCC) [10].

2.1. Composition of the Oral Microbiome

The oral microbiota comprises commensal and pathogenic microbes that are in harmony with the host in a finely tuned balance. Commensal bacteria like Streptococcus, Veillonella, Rothia, and Neisseria, which play roles in immune modulation and preventing pathogen overgrowth [9], are mostly found in healthy individuals. They serve to maintain oral pH, break down dietary constituents, and communicate with the immune system to modulate inflammatory processes [11].

Dysbiosis, on the other hand, involves an accumulation of pathogenic species such as *Porphyromonas gingivalis, Fusobacterium nucleatum,* and *Treponema denticola*—microbes that are well known for their involvement in periodontitis and, more recently, in carcinogenesis [12]. They play roles in immune evasion, chronic inflammation, and the production of oncogenic metabolites [6].

2.2. The Microbiome's Role in Immune Homeostasis

The oral microbiome is also important in modulating immune responses. Immune system activity is controlled by commensal bacteria through the stimulation of pattern recognition receptors (PRRs), e.g., Toll-like receptors (TLRs), to ensure immune homeostasis [13]. Immune tolerance is enhanced by a healthy microbiome through cytokine regulation, including interleukin-10 (IL-10), which is anti-inflammatory [14]. On the other hand, oral dysbiosis may interfere with immune regulation to induce a pro-inflammatory condition with increased levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8)—all of which play a role in tumor growth [15]. Bacterial dysbiosis-induced chronic inflammation could be responsible for the development of a microenvironment favouring carcinogenesis, facilitating malignant transformation of the oral epithelium [16].

2.3. Dysbiosis as a Disease Precursor

Oral dysbiosis is long established in periodontal disease and caries, but growing evidence indicates that it plays a role in systemic diseases such as cardiovascular disease, diabetes, and even neurodegenerative disorders [17]. Of particular interest, recent evidence has shown that microbial dysbiosis has a strong association with the development of HNSCC, and it is proposed that certain bacterial communities may play a role in cancer initiation and progression [18].

For example, *F. nucleatum*—a periodontitis-associated bacterium—has been found to induce epithelial-mesenchymal transition (EMT), facilitate immune evasion, and enhance resistance to apoptosis in cancer cells [19]. Likewise, *P. gingivalis* can cause DNA damage and suppress normal repair mechanisms of epithelial cells, further aiding carcinogenesis [20].

These data indicate that preservation of oral microbial homeostasis is not merely critical for avoidance of periodontal disease but potentially also holds relevance for prevention of cancer. Further elucidation of the function of the microbiome in the regulation of the immune system and disease development can open the way for new diagnostics and therapies aiming at microbial dysbiosis.

3. Oral dysbiosis and carcinogenesis

There have been numerous studies performed in recent times to ascertain the connection between oral dysbiosis and carcinogenesis that drew monumental attention [21]. Oro-pathogens can manipulate the tumor microenvironment by several ways, i.e., chronic inflammation, immunosuppression, bacterial metabolism, and genotoxicity directly [22]. These processes grant a supporting niche for the malignant transformation [23].

3.1. Mechanisms linking dysbiosis to HNSCC

3.1.1. Chronic Inflammation and Carcinogenesis

Inflammation is a body's natural procedure which occurs in response to any infection or injury to promote better & faster healing . It can be acute or chronic. Chronic inflammation is well-established hallmark of cancer [24]. *P. gingivalis* and *F. nucleatum* trigger the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, leading to production of pro-inflammatory cytokines i.e. interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) [25]. Inflammation lasting for longer duration produces reactive oxygen & nitrogen species (ROS & RNS), inducing DNA damage, genomic instability, and epigenetic modifications— which are the primary events in carcinogenesis [24].

3.1.2. Microbial Metabolites and Oncogenesis

Oral bacteria yield metabolites that may contribute to oncogenesis. For instance, some anaerobic bacteria, for instance, *F. nucleatum* and *P. gingivalis*, produce short-chain fatty acids (SCFAs) like butyrate and propionate, which could compromise epithelial cell integrity and amplify tumor-promoting pathways [25]. Moreover, nitrosamine formation by Neisseria and Haemophilus species is of specific interest. Nitrosamines are established carcinogens that result in DNA alkylation, mutagenesis, and enhanced oxidative stress, which play a role in malignant transformation [26].

3.1.3. Immune Evasion and Tumor Progression

Evasion of immune surveillance is one of the characteristics of cancer. Evasion occurs through mechanisms that have been developed by certain oral pathogens so that they may inhibit immune function and thus shield tumor cells from being detected. *P. gingivalis*, for instance, inhibits apoptosis of infected epithelial cells by interfering with Bcl-2 family proteins and thus allows long-term survival of transformed cells [27]. Moreover, *F. nucleatum* is found to interact with Toll-like receptors (TLRs) and β-catenin signaling, suppressing T-cell responses and promoting immune evasion [28]. Interactions like this result in uncontrollable cancer cell growth.

3.1.4. Genotoxic Effects and DNA Damage

Several oral pathogens produce a chemical named genotoxin which is responsible for causing DNA damage and genomic instability. For instance, *P. gingivalis* produces gingipains, a class of proteases that degrade host proteins and facilitate mutagenic changes [29]. Similarly, *F. nucleatum* has been linked to double-strand DNA breaks, which promote chromosomal instability—a key feature of cancer progression [3].

4. The microbiome-tumor microenvironment interplay in HNSCC

The tumor microenvironment (TME) plays a crucial role in cancer progression, influencing tumor cell proliferation, immune evasion, and therapeutic resistance. Several studies indicate that oral microbiota has the potential to shape the TME in HNSCC by modulating the inflammatory pathways, metabolic interactions & immune responses [30].

4.1. Inflammation-Driven Tumor Microenvironment

Persistent inflammation is one of the characteristics of the microenvironment of HNSCC, and oral pathogens play an active role in this inflammatory process. *Porphyromonas gingivalis* and *Fusobacterium nucleatum* cause chronic inflammatory signaling through the activation of the nuclear factor kappa B (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways [24]. These pathways result in increased pro-inflammatory cytokines like:

- **Tumor necrosis factor-alpha (TNF-α)** – It promotes angiogenesis and survival of tumor cell.
- **Interleukin-6 (IL-6) and Interleukin-8 (IL-8)** – Responsible for cancer cell proliferation and invasion.
- **Transforming growth factor-beta (TGF-β)** – Promotes epithelial-mesenchymal transition (EMT), facilitating metastasis [15].

4.2. Immunosuppressive Effects of Dysbiosis

The immune response is key to managing tumor growth, but oral pathogens have the ability to establish an immunosuppressive microenvironment supporting cancer growth (see figure 1) [13].

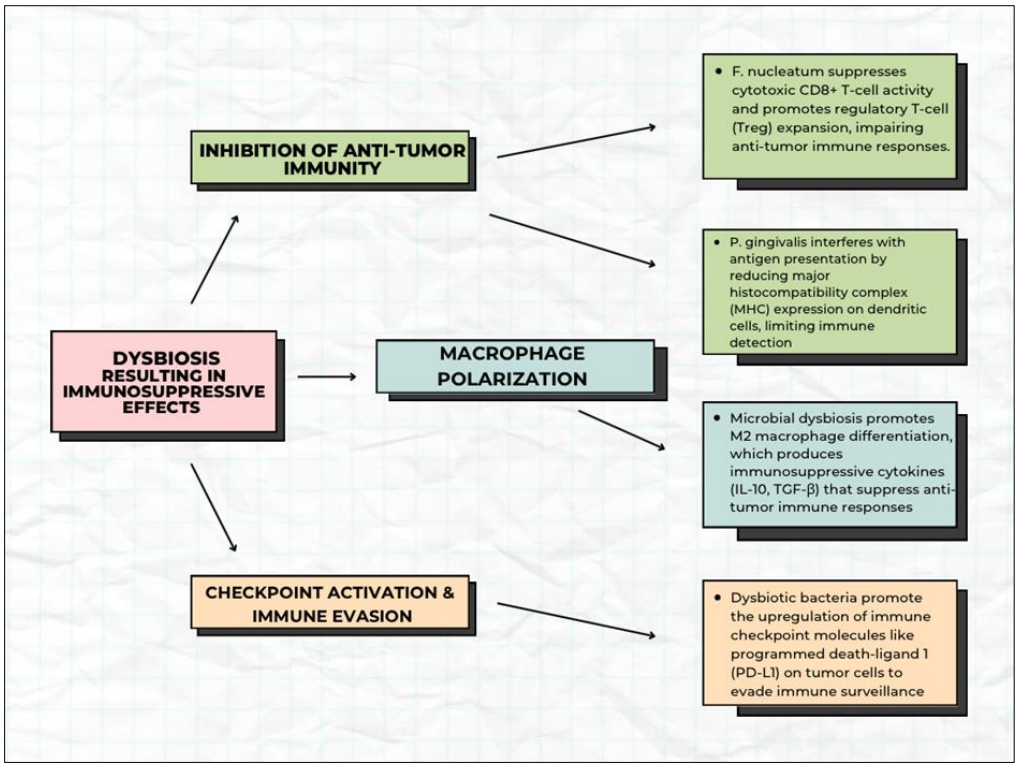

Figure 1 Flowchart representing the immunosuppressive effects caused by oral dysbiosis

The interplay of chronic inflammation, immune suppression, and checkpoint activation establishes a tumor - permissive microenvironment, making HNSCC resistant to immune-mediated clearance.

4.3. Microbial Metabolites and Tumor Metabolism

Oncogenic metabolites are produced by the oral pathogens to sustain the tumor growth. Metabolites like short chain fatty acids (SCFAs), polyamines & bacterial lipopolysaccharides (LPS) play an important role. These metabolic interactions underscore the ways in which oral microbiota affect tumor growth independent of direct infection, pointing to new directions for metabolic-targeted therapies in HNSCC treatment. Short chain fatty acids (SCFAs) like butyrate and propionate may play bivalent roles—both tumor suppressors during normalcy and tumor promoters during dysbiosis [31]. Polyamines like putrescine and spermidine from *P. gingivalis* promote cancer cell growth and apoptosis resistance [32]. Bacterial lipopolysaccharides (LPS) stimulate Toll-like receptors (TLRs) on immune and tumor cells, promoting tumor-facilitating inflammation [33].

4.4. Biofilms and Their Role in Tumor Aggressiveness

Biofilms are communities of microbes that are enclosed in an extracellular matrix. It acts as a “protective covering”for the encased microbes preventing them from harsh environment [34]. Biofilm bacteria produce a pro-tumorigenic niche through:

- Increased resistance to chemotherapy by elevated extracellular matrix production, which hinders drug penetration[35].
- Inducing epithelial-mesenchymal transition (EMT) and tumor invasion [35].
- Creating hypoxic conditions, resulting in vascularization and tumor growth [35].

Targeting biofilms by anti-biofilm agents or interfering with bacterial communication (quorum sensing inhibitors) is a new approach in microbiome-targeted cancer treatment.

5. The role of the microbiome in treatment response and resistance in HNSCC

The oral microbiome's composition has increasingly been understood as a critical determinant of treatment efficacy and resistance in head and neck squamous cell carcinoma (HNSCC). Dysbiosis can affect the effectiveness of

radiotherapy, chemotherapy, immunotherapy, and targeted therapies, influencing outcomes for patients. Exploring the role of the microbiome in therapeutic resistance may unlock new possibilities for personalized therapy strategies in HNSCC [7].

5.1. Microbiome and radiotherapy response

5.1.1. Microbial Modulation of Radiation Sensitivity

The bacterial ecosystem in the oral cavity can be easily altered by radiation, resulting in increased level of pathogenic microbes. These bacteria are involved in inflammation and delayed mucosal healing, impairing treatment compliance and patient outcome. On the other hand, some commensal bacteria (*Streptococcus* and *Lactobacillus spp*.) have radioprotective properties, which indicate that modulation of the microbiome may prevent mucositis severity [6].

5.1.2. Microbiome-Induced Radioresistance

P. gingivalis and *Treponema denticola* stimulate DNA damage repair mechanisms, ensuring tumor cell survival after radiation [10]. Moreover, tumor hypoxia, which is caused by the microbiota, also leads to radioresistance because hypoxic tumor cells are less sensitive to ionizing radiation [3]. Efficient strategies specifically targeting the microbes are probiotics & antibiotics to downgrade the level of bacterial population & enhance radiotherapy efficacy.

5.2. Chemotherapy and microbiome interactions

Chemotherapeutic drugs, such as cisplatin and 5-fluorouracil (5-FU) are widely used in the treatment of HNSCC. Nevertheless, the oral microbiome impacts drug metabolism, activity, and toxicity considerably.

5.2.1. Microbial Metabolism of Chemotherapeutic Agents

Microbial enzymes are known to modify metabolism of chemotherapy drugs, thereby altering drug effectiveness. For example, *Enterococcus faecalis* inactivates 5-FU, blunting its cytotoxic effect [17]. *P. gingivalis* is also known to trigger drug efflux pumps within cancer cells, reducing intracellular drug levels and leading to chemoresistance [11].

5.2.2. Microbiome Impact on Toxicity of Chemotherapy

Chemotherapy-induced oral mucositis is aggravated by microbiome dysbiosis, which results in an overgrowth of opportunistic pathogens that extend inflammation and raise secondary infections [36].

Microbiome modulation procedures like prebiotics and probiotics can mitigate mucositis and enhance chemotherapy tolerance [37]. In addition, new interventions like microbial engineering and dietary adjustments have potential in eradicating bacteria involved in chemoresistance.

6. Immunotherapy: the microbiome as a predictor of response

Immunotherapy & immune checkpoint inhibitors (ICIs) against PD-1/PD-L1 in particular, has revolutionized HNSCC treatment. Yet, the microbiome is an important determinant of response rates.

6.1. Microbiome Composition and Immunotherapy Response

Patients with a more diverse richness of commensal bacteria (*Lactobacillus* and *Bifidobacterium spp*.) have greater reactions to PD-1 inhibitors [7]. On the other hand, immune evasion and ICIs resistance is linked with pro-inflammatory species *F. nucleatum* and *P. gingivalis* [38].

6.2. Microbiome-Mediated Immune Modulation

Some bacterial metabolites, including short-chain fatty acids (SCFAs), modulate T-cell function and anti-tumor immune responses [39]. *F. nucleatum* also inhibits cytotoxic CD8+ T-cell function, weakening the effectiveness of immune checkpoint blockade [10].

6.3. Microbiome-Immune Therapy Synergy

Microbiome-directed treatments, such as fecal microbiota transplantation (FMT) and microbiome therapeutics, are being investigated to augment immunotherapy effectiveness [17]. Clinical trials have shown that patients who receive microbiome-modulating therapies in combination with ICIs have better survival rates.

7. Microbiome-based therapeutic strategies in HNSCC

As more evidence converges linking the dysbiosis of oral microbiome with HNSCC disease progression and chemoresistance, scientists are venturing to understand microbiome-manipulating therapeutic approaches for a better response in treatment. Several methods such as probiotics, prebiotics, antibiotics, bacteriophage therapy, transplantation of microbiota, and engineering of the microbiome have stepped forward as efficient adjuncts with traditional anticancer therapies.

Probiotics and Prebiotics are important in restoring the balance of microbes and enhancing immune response. There are beneficial strains of bacteria like *Lactobacillus* and *Bifidobacterium*, which have shown promise in inhibiting cancer-related pathogenic bacteria. Probiotics reduce inflammation, boost immunity in the gut and the mouth, and enhance overall treatment outcomes [40]. Prebiotics like dietary fiber and polyphenols feed the above-mentioned beneficial bacteria and help increase the healthy composition of the microbiome [41]. Research indicates that the addition of probiotic supplementation may alleviate mucositis induced by treatment and lower chemoradiotherapy complications [12]. Selective Antibiotic Therapy and Bacteriophage Treatment are also being investigated as precision-based methods to kill cancer-related bacteria without harming useful microbial communities. Pathogenic genera like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have been linked to tumor growth and immune suppression. It may be possible to decrease chemoresistance and increase the efficacy of immunotherapy by targeting these bacteria with narrow-spectrum antibiotics or bacteriophage therapy, which employs viruses to selectively destroy harmful bacteria. But selection must be done cautiously to prevent destabilizing the entire microbiome and thus potentially interfering with immune function and treatment efficacy [17].

Microbiota Transplantation has been in the spotlight as a promising approach to maximize the immune environment for cancer treatment. Fecal microbiota transplantation (FMT), where healthy gut microbiota are transplanted to regain microbial homeostasis, was found to be promising in enhancing response to immune checkpoint inhibitors in cancers like melanoma. In consideration of the robust relationship between gut and oral microbiomes, transplantation of oral microbiota (OMT) has been proposed for its efficacy to alter HNSCC-related tumor-associated dysbiosis. Through this measure, it has been suggested, enhanced immunotherapy rates, decrease in inflammatory cytokines, and better tumor microenvironment can be enhanced.

Microbiome Engineering and Metabolite-Based Therapies are novel strategies that utilize bacterial alterations for therapeutic intervention. Scientists are investigating the potential of genetically engineered commensal bacteria to target anticancer compounds directly to the tumor. Moreover, microbial metabolites, including short-chain fatty acids (SCFAs) and polyamines, have been recognized as crucial regulators of tumor growth and immune responses.

In general, incorporating microbiome-targeted therapies into HNSCC treatment regimens has the potential to transform cancer therapy. Reducing resistance to treatment, stimulating immune function, and minimizing adverse effects, these approaches hold much promise for customized cancer therapy.

Yet, more clinical trials must be conducted to demonstrate the safety, effectiveness, and long-term consequences of microbiome-based treatments. With advancing insights into the connection between the tumor and microbiome, the use of microbiome modulation could become a fundamental aspect of precision oncology for HNSCC patients.

8. Conclusion

Any oral or systemic illness develops based on the importance of oral microbiomes. The interactive relationship between oral microbiome functions as a significant indicator toward developing microbiome-based precise cancer therapy for HNSCC patients. The recognition of microbial treatment responses enables clinicians to develop improved treatment interventions that generate superior patient results. Future medical research should dedicate its efforts to integrated therapeutic approaches which focus on oral microbiome interventions through probiotic treatments, microbiome transplanted therapies, and bacterial inhibition methods into standard HNSCC clinical care. Better knowledge about these interactions will be vital for optimizing therapy efficacy while minimizing resistance to ensure improved survival rates.

Compliance with ethical standards

Disclosure of conflict of interest

The author declare that there is no potential conflict of interest with respect to the authorship and/or publication of this article.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.

[2] Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020 Nov 26;6(1):92.

[3] Guerrero-Preston, R., White, J. R., Godoy-Vitorino, F., et al. High-resolution microbiome profiling uncovers head and neck cancer risk factors within a Hispanic population. Front microbiol. 2016. 7(1): 596.

[4] Takahashi N, Nyvad B. The role of bacteria in the caries process: ecological perspectives. J Dent Res. 2011 Mar;90(3):294-303.

[5] Li Z, Liu Y, Zhang L. Role of the microbiome in oral cancer occurrence, progression and therapy. Microb Pathog. 2022 Aug;169:105638.

[6] Whitmore SE, Lamont RJ (2014) Oral Bacteria and Cancer. PLoS Pathog 10(3): e1003933.

[7] Hayes RB, Ahn J, Fan X, Peters BA, Ma Y, Yang L, et al. Association of Oral Microbiome With Risk for Incident Head and Neck Squamous Cell Cancer. JAMA Oncol. 2018 Mar 1;4(3):358-365.

[8] Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, et al. The human oral microbiome. J Bacteriol. 2010 Oct;192(19):5002-17.

[9] Wade WG. The oral microbiome in health and disease. Pharmacol Res. 2013 Mar;69(1):137-43.

[10] Marsh PD, Zaura E. Dental biofilm: ecological interactions in health and disease. J Clin Periodontol. 2017 Mar;44 Suppl 18:S12-S22.

[11] Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015 Jan;15(1):30-44.

[12] Irfan M, Delgado RZR, Frias-Lopez J. The Oral Microbiome and Cancer. Front Immunol. 2020 Oct 23;11:591088.

[13] Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010 Mar 19;140(6):805-20.

[14] Devaraja K, Aggarwal S. Dysbiosis of Oral Microbiome: A Key Player in Oral Carcinogenesis? A Critical Review. Biomedicines. 2025 Feb 12;13(2):448.

[15] Karpiński TM. Role of Oral Microbiota in Cancer Development. Microorganisms. 2019 Jan 13;7(1):20.

[16] Frank DN, Qiu Y, Cao Y, Zhang S, Lu L, Kofonow JM, Robertson CE, Liu Y, Wang H, Levens CL, Kuhn KA, Song J, Ramakrishnan VR, Lu SL. A dysbiotic microbiome promotes head and neck squamous cell carcinoma. Oncogene. 2022 Feb;41(9):1269-1280.

[17] Kitamoto S, Nagao-Kitamoto H, Jiao Y, Gillilland MG 3rd, Hayashi A, Imai J, et al. The Intermucosal Connection between the Mouth and Gut in Commensal Pathobiont-Driven Colitis. Cell. 2020 Jul 23;182(2):447-462.e14.

[18] Sarkar P, Malik S, Laha S, Das S, Bunk S, Ray JG, Chatterjee R, Saha A. Dysbiosis of Oral Microbiota During Oral Squamous Cell Carcinoma Development. Front Oncol. 2021 Feb 23;11:614448.

[19] Hashemi Goradel N, Heidarzadeh S, Jahangiri S, Farhood B, Mortezaee K, Khanlarkhani N, Negahdari B. Fusobacterium nucleatum and colorectal cancer: A mechanistic overview. J Cell Physiol. 2019 Mar;234(3):2337-2344.

[20] Mysak J, Podzimek S, Sommerova P, Lyuya-Mi Y, Bartova J, Janatova T, Prochazkova J, Duskova J. Porphyromonas gingivalis: major periodontopathic pathogen overview. J Immunol Res. 2014;2014:476068.

[21] Mivehchi H, Eskandari-Yaghbastlo A, Pour Bahrami P, Elhami A, Faghihinia F, Nejati ST, Kazemi KS, Nabi Afjadi M. Exploring the role of oral bacteria in oral cancer: a narrative review. Discov Oncol. 2025 Feb 26;16(1):242.

[22] Arneth B. Tumor Microenvironment. Medicina (Kaunas). 2019 Dec 30;56(1):15.

[23] de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell. 2023 Mar 13;41(3):374-403.

[24] Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019 Jul-Sep;18(3):121-126.

[25] Ou S, Wang H, Tao Y, Luo K, Ye J, Ran S, Guan Z, Wang Y, Hu H, Huang R. Fusobacterium nucleatum and colorectal cancer: From phenomenon to mechanism. Front Cell Infect Microbiol. 2022 Nov 29;12:1020583.

[26] Schlingemann J, Burns MJ, Ponting DJ, Martins Avila C, Romero NE, Jaywant MA, Smith GF, Ashworth IW, Simon S, Saal C, Wilk A. The Landscape of Potential Small and Drug Substance Related Nitrosamines in Pharmaceuticals. J Pharm Sci. 2023 May;112(5):1287-1304.

[27] Hajishengallis, G. (2015). Periodontitis: From microbial immune subversion to systemic inflammation. Nature Reviews Immunology, 15(1), 30-44.

[28] Dadgar-Zankbar L, Elahi Z, Shariati A, Khaledi A, Razavi S, Khoshbayan A. Exploring the role of Fusobacterium nucleatum in colorectal cancer: implications for tumor proliferation and chemoresistance. Cell Commun Signal. 2024 Nov 15;22(1):547.

[29] Ceccarelli F, Saccucci M, Natalucci F, Olivieri G, Bruni E, Iacono R, Colasanti T, Di Carlo G, Alessandri C, Uccelletti D, Russo P, Pilloni A, Conti F, Polimeni A. Porphyromonas gingivalis amount in the tongue biofilm is associated with erosive arthritis in systemic lupus erythematosus. Lupus. 2022 Jul;31(8):921-926.

[30] Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacol Ther. 2021 May;221:107753.

[31] Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol. 2024 Aug;24(8):577-595.

[32] Holbert CE, Cullen MT, Casero RA Jr, Stewart TM. Polyamines in cancer: integrating organismal metabolism and antitumour immunity. Nat Rev Cancer. 2022 Aug;22(8):467-480.

[33] Wang X, Quinn PJ. Lipopolysaccharide: Biosynthetic pathway and structure modification. Prog Lipid Res. 2010 Apr;49(2):97-107.

[34] Yin W, Wang Y, Liu L, He J. Biofilms: The Microbial "Protective Clothing" in Extreme Environments. Int J Mol Sci. 2019 Jul 12;20(14):3423.

[35] Choi E, Murray B, Choi S. Biofilm and Cancer: Interactions and Future Directions for Cancer Therapy. Int J Mol Sci. 2023 Aug 16;24(16):12836.

[36] Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. Neoplasia. 2004 Sep-Oct;6(5):423-31.

[37] Pulito C, Cristaudo A, Porta C, Zapperi S, Blandino G, Morrone A, Strano S. Oral mucositis: the hidden side of cancer therapy. J Exp Clin Cancer Res. 2020 Oct 7;39(1):210.

[38] Jiang SS, Xie YL, Xiao XY, Kang ZR, Lin XL, Zhang L, Li CS, Qian Y, Xu PP, Leng XX, Wang LW, Tu SP, Zhong M, Zhao G, Chen JX, Wang Z, Liu Q, Hong J, Chen HY, Chen YX, Fang JY. Fusobacterium nucleatum-derived succinic acid induces tumor resistance to immunotherapy in colorectal cancer. Cell Host Microbe. 2023 May 10;31(5):781-797.e9.

[39] Gholizadeh P, Eslami H, Yousefi M, Asgharzadeh M, Aghazadeh M, Kafil HS. Role of oral microbiome on oral cancers, a review. Biomed Pharmacother. 2016 Dec;84:552-558.

[40] Gupta V, Garg R. Probiotics. Indian J Med Microbiol. 2009 Jul-Sep;27(3):202-9.

[41] Mishra P, Badiyani VM, Jain S, Subramanian S, Maharaj SV, Kumar A, Singh BN. Prebiotics: Ignored player in the fight against cancer. Cancer Rep (Hoboken). 2023 Nov;6(11):e1870.