

THE IMPACT OF ORAL MICROBIOME IN MAINTAINING ORAL HEALTH AND PREVENTING DISEASE

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ABSTRACT

Among the vast array of microbial communities that inhabit in the human body ,one of the most diverse and complex microorganisms are oral microbes , including over 700 species of bacteria, numerous viruses, fungi and protozoa[1,2,3]. The oral microbiome plays an important role to maintains a normal oral physiological environment[4]. Dysbiosis of the oral microbiome has been linked to various oral and systemic diseases. The connection between the host and microorganisms significantly shapes the microbial composition which ultimately affecting the host's overall health.[5,6,7] Numerous studies have consistently indicates that the microbiome is closely linked to various types of cancer including oral cancer, prostate cancer, oral squamous cell carcinoma (OSCC) and also diseases like periodontal disease , diabetes and etc.[8] Also, research has demonstrated that cancer progression can, in turn, alter the composition of the human microbiome. The main risk factors for cancer of the oral cavity are the consumption of tobacco and alcohol. The effect of carcinogens on the oral mucosa creates an area prone to malignant transformation.[9,10,11] The immune-inflammatory response of the host in periodontitis is primarily marked by a physiological acute inflammatory reaction (gingivitis) to both supragingival and subgingival

plaque, maintained by innate immune system cells.[12] *Fusobacterium* plays an crucial role in the bacterial impact on OSCC where as it had the ability to co-adhere with other species and form an association network centered around itself in patients of the cancer group. [14,15] We will discuss the complex relationships between the oral microbiome and various oral health conditions and how these microbes are used to improve human health and the future aspects of these microbes in this paper.

Keywords: *Oral microbes, Oral disease, Periodontal disease, OSCC, Microbial Dysbiosis*

Introduction

Among the vast array of microbial communities that inhabit the human body, the oral microbes are one of the most diverse and complex microorganisms, including over 700 species of bacteria, numerous viruses, fungi and protozoa. The oral microbiome plays an important role to maintains a normal oral physiological environment. [1,2,3] It also influences the maintenance and development of oral tissues, including teeth and gums. Furthermore, it produces antimicrobial compounds and maintains the level of the oral ecosystem which contributes to the breakdown and digestion of food, modulation of the immune system, and protection against pathogens.[16] Here we have shown the examples of oral microorganisms through the figure given below.

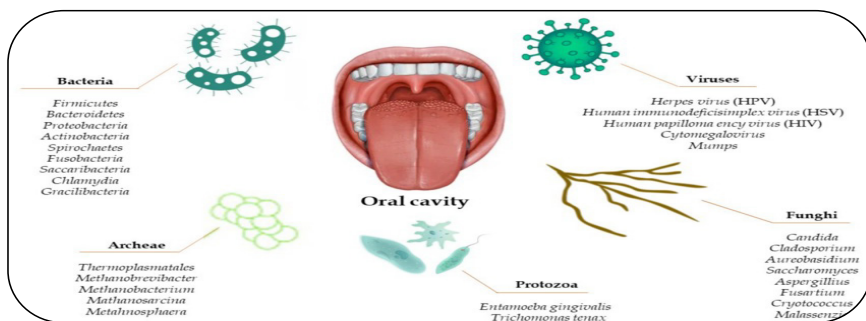


Fig: Diagrammatic representation of oral microbiome[48]

Dysbiosis of the oral microbiome has been connected to various oral and systemic diseases. The partnership between

the host and microorganisms significantly shapes the microbial composition which ultimately affecting the host's overall health. [17,18,] Numerous studies have consistently indicate that the microbiome is closely linked to various types of cancer including oral cancer, prostate cancer, oral squamous cell carcinoma (OSCC) and also diseases like periodontal disease, diabetes and etc. Furthermore, research has shown that cancer progression can, in turn, alter the composition of the human microbiome. The investigation of microorganisms as possible disease-fighting strategies has been prompted by the connection between the microbiome and cancer. [19,20,21] Particularly several microbes have been recognized as:

1. Pathogenic agents, are microorganisms that aid in the onset and advancement of illnesses. For example -*Porphyromonas gingivalis*, is a type of bacteria that causes periodontal disease and other related diseases in mouth. [22]
2. Diagnostic markers, microorganisms that can be utilized to show whether a disease is present or is progressing. For instance, mouth samples can be used to detect the Human Papillomavirus (HPV), this type of virus can be used to diagnose disorders associated to HPV, including oral cancer. [23]
3. Therapeutic targets, microorganisms which can be used to stop or cure illnesses. For example, antifungal drugs can be used to treat the fungus *Candida albicans*. [24]

In this review we will talk about the complex relationships between the oral microbiome and various oral health conditions and how these microbes are used to improve human health and the future aspects of these microbes.

Oral Disease

The oral cavity contains the second most abundant collection of microorganisms in the body, next only to the gastrointestinal tract. The oral microbiome contributes to the balance of physiologic, metabolic, and immunological functions that help to maintain homeostasis through the formation of a mucosal barrier. Oral microbiome alterations have been observed in various conditions, such as Oral cancer,

Periodontal disease, Oral squamous cell carcinoma (OSCC), Diabetes Cardiovascular disease and etc.

Oral Cancer

Many of studies have been set aside to the significance of heredity in oral carcinogenesis. Several genes are involved in genetic tendency of oral cancer. Gene polymorphisms participating in the metabolism of xenobiotic factors which are the external, foreign materials that the body does not naturally create, For example cytochrome P450 1A1 (CYP1A1) [25] and glutathione S-transferase mu 1 (GSTM1) [26,27] are blamed for the increase of relative danger in the carriers. Individuals with alcohol dehydrogenase 3 genotype are prone to the development of oropharyngeal cancers. Oral cancer is becoming more common, especially in women and young people. Every year, between 350,000 and 400,000 new cases are diagnosed worldwide. The fundamental risk factors for cancer of the oral cavity are the consumption of tobacco and alcohol. The effect of carcinogens on the oral mucosa creates an area prone to malignant transformation. The risk factors are consumption of alcohol and tobacco use, cannot account for the variations in incidence, since oral cancer often develops in individuals without a background of alcohol or tobacco exposure [28,29]. Frequently, the disturbance of similar signalling pathways leads to the molecular pathogenesis of cancer of the oral cavity that promote oncogenesis which occurs against a backdrop of tumor suppressor inactivation. In high frequency of oral cancer the inactivations of p53 and CDKN2A tumor suppressor happened. [30]

Periodontal Disease

Periodontal disease is a type of chronic inflammatory condition which affecting about 15–45% of people worldwide. The host's immune-inflammatory response in periodontitis is primarily marked by a physiological acute inflammatory reaction (gingivitis) to both supragingival and subgingival plaque, maintained by innate immune system cells. [12] During this stage, the resident cell population produces cytokines such as tumour necrosis factor (TNF)- α , interleukin (IL)-1 β , and interleukin (IL)-6, which mainly aid in promoting

cell migration to infection sites, increasing the expression of neutrophil adhesion molecules on internal vessel surfaces, and increasing the synthesis of other proinflammatory cytokines. [31,32] The removal of plaque results in the gradual resolution of inflammation and the return to individual homeostasis. The activation of acquired immunity follows the clearance of plaque. This process, which is controlled by adaptive-immunity cytokines, including interferon (IFN)- γ , interleukin (IL)-2, and interleukin (IL)-4, occurs through antigen processing and presentation by lymphocytes, macrophages, and dendritic cells. The gradual breakdown of periodontal tissues are the cause in the loss of bone tissues and the deterioration of ECM. [33,34] Bone resorption occurs due to a changing balance between osteogenesis and osteoclastogenesis, tipping towards the latter, which is regulated by a complex pathway induced by inflammation that includes the receptor RANK, its ligand (RANKL), IL-1 β , IL-6, and TNF- α [34]. The increased expression of 23 Zn²⁺- and Ca²⁺-dependent enzymes known as matrix metalloproteinases (MMPs) causes the destruction of extracellular matrix (ECM). [35] In healthy periodontal tissues, where they take part in specific physiological processes including tissue growth and turnover, these enzymes usually show a modest expression level. Additionally, MMPs contribute to pathological processes such as the degradation of connective tissue in periodontitis, which results in the breakdown of collagen in the gingival and periodontal ligaments [47].

Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma is the most prevalent malignant epithelial tumour that affects the oral cavity. (OSCC) [36]. In the past few years, research has centered on the involvement of oral bacteria in OSCC and their compositional alterations. Generally speaking, oral bacteria can contribute to the formation of OSCC by encouraging angiogenesis and cell proliferation, affecting normal apoptosis, aiding invasion and metastasis, and supporting cancer stem cells. The dorsum of the tongue and the palatal mucosa are viewed as low-risk zones, while the floor of the mouth and the ventrolateral tongue are regarded as high-risk areas. According to studies,

Fusobacterium may play a crucial role in the bacterial impact on OSCC because it can co-adhere with other species and create a self-centred association network in cancer patients.[14,16] Certain oral bacteria, like *P. gingivalis* and *F. nucleatum*, are involved in various pathways that aid in the development of OSCC. Additionally, inflammation might play a role in the process, with several inflammatory cytokines like IL-6, IL-8, TNF- α , and PGE influencing the tumor microenvironment, potentially facilitating tumor progression.[37]

Microbial Dysbiosis In Disease Condition

Dysbiosis is defined by an alteration in the microbiome that leads to an imbalance in the microbiota, modifications in their functional makeup and metabolic processes, or a variation in their local distribution. Dysbiosis in the oral microbiome may play a role in the onset of various oral and systemic conditions, such as dental caries [4,5], periodontitis [12], oral and other cancers [7,8,9], cardiovascular issues [38], and diabetes [39]. It is linked to a rise in harmful bacteria and a matching decline in helpful bacteria. This insight has prompted significant research aimed at interventions to rebuild microbial health and equilibrium in the oral microbiome, such as prebiotics, probiotics, and antimicrobial agents, serving as potential therapeutic methods for addressing and averting oral dysbiosis and related diseases.

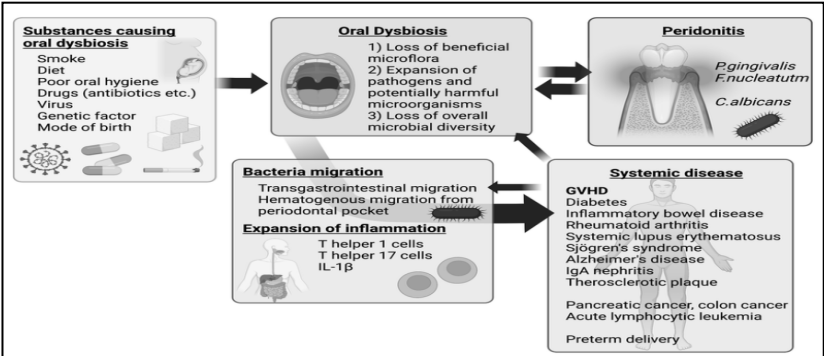


Fig: Oral dysbiosis [46]

Use of microbes to improve health

Numerous studies have reported that microbiota is made up of several microorganisms that reside in the gastrointestinal system and oral cavity. Many bacteria find that the oral cavity offers the best conditions for growth since it consistently maintains the right temperature and humidity. Saliva released into the mouth contains antimicrobial elements: agglutinins that adhere to oral bacteria like *S. mutans* and support phagocytosis by inducing bacterial clustering [40]; lysozymes that lead to cell lysis by disrupting the cell walls [41,42]; lactoferrin that hinders biofilm development by enhancing twitching, a unique surface movement, through iron chelation [59]; and peroxidase, which demonstrates antimicrobial properties by obstructing the bacteria's glycolytic pathway. To protect against infections brought on by new pathogens like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), oral sIgA may therefore be crucial [43,44]. sIgA attaches to oral bacteria like *Streptococcus mitis*, [45] *Streptococcus oralis*, and *S. mutans*, which feature epitopes acknowledged by sIgA, thereby selectively attracting these specific bacteria to the mucus layer on the mouth's mucosal surfaces.

The oral microbiota can affect how well the body digests specific foods. Additional variables include food extracts (such as red wine) and eating habits (vegetarian or not). [46] Here, we demonstrate the potential effects of food extracts and dietary patterns on body health. Yomo gyutto, or fermented Japanese mugwort, is a type of probiotic fermented milk (Batavito). Probiotic yoghurt, probiotic petit-suisse cheese, probiotic milk, and Italian Grana Padano (GP) cheese all controlled the oral microbiota or decreased the quantity of oral microorganisms, which prevented or improved dental caries and periodontal disease. Additionally, fermented milk reduced inflammation and changed the gut and mouth microbiome.

Conclusion

There are many different types of microorganisms that make up the oral microbiome, which includes bacteria, fungus, viruses, and archaea. When infections disrupt the symbiotic

connections that make up the oral microbiome and result in dysbiosis, a once-healthy state can turn unhealthy and raise the chance of comorbidities. The importance of the oral microbial community in preserving systemic and oral health is becoming more widely recognized. Additionally, contemporary lifestyle choices such as smoking, eating an unbalanced diet, and poor oral hygiene are major contributors to the disruption of the oral microbiome's delicate balance and the development of oral diseases like periodontal disease, particularly in people who are genetically and epigenetically susceptible. By creating oral probiotics and modifying the oral microbiota, we can improve dental health in future while also improving overall health. Also in future by using metagenomics we can identify more oral microbes in the early stage of disease and by analyzing the sequence further research like target specific oral microbes to treat disease and advance research between microbes and disease and probiotics. The intergration of metagenomics and oral microbes research will revolutionize to understand about the oral health and disease and also develop effective treatment and also helps to early identification of life threatening disease and etc.

References:

- Dewhirst , F.E. et al. (2010) The human oral microbiome. *J. Bacteriol.*, 192 , 5002–5017
- M. Kilian The oral microbiome - friend or foe? *Eur. J. Oral Sci.*, 126 (Suppl. 1) (2018), pp. 5-12
- Verma D., Garg P.K., Dubey A.K. Insights into the human oral microbiome. *Arch. Microbiol.* 2018;200:525–540. doi: 10.1007/s00203-018-1505-3.
- Gomez A., Nelson K.E. The Oral Microbiome of Children: Development, Disease, and Implications Beyond Oral Health. *Microb. Ecol.* 2017;73:492–503. doi: 10.1007/s00248-016-0854-1.
- Gholizadeh P., Eslami H., Yousefi M., Asgharzadeh M., Aghazadeh M., Kafil H.S. Role of oral microbiome on oral cancers, a review. *Biomed. Pharmacother.* 2016;84:552–558. doi: 10.1016/j.biopha.2016.09.082.
- Irfan M., Delgado R.Z.R., Frias-Lopez J. The Oral Microbiome and Cancer. *Front. Immunol.* 2020;11:591088. doi:

10.3389/fimmu.2020.591088.

Slocum C., Kramer C., Genco C.A. Immune dysregulation mediated by the oral microbiome: Potential link to chronic inflammation and atherosclerosis (Review) *J. Med.* 2016;280:114–128. doi: 10.1111/joim.12476.

G. Hajishengallis, Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response *Trends Immunol.* (2014)

Wang, Shengran; Tan, Xiao¹; Cheng, Juan¹; Liu, Zeyang¹; Zhou, Huiping²; Liao, Jiyuan²; Wang, Xijun²; Liu, Hongyun². Oral microbiome and its relationship with oral cancer. *Journal of Cancer Research and Therapeutics* 20(4):p 1141-1149, August 2024. | DOI: 10.4103/jcrt.jcrt_44_24

Williams HK. Molecular pathogenesis of oral squamous carcinoma. *Mol Pathol.* 2000;53:165–72. doi: 10.1136/mp.53.4.165.

Mehrotra R, Yadav S, et al. Oral squamous cell carcinoma: etiology, pathogenesis and prognostic value of genomic alterations. *Indian J Cancer.* 2006;43:60–6. doi: 10.4103/0019-509x.25886.

Papapanou, P.N.; Sanz, M.; Buduneli, N.; Dietrich, T.; Feres, M.; Fine, D.H.; Flemmig, T.F.; Garcia, R.; Giannobile, W.V.; Graziani, F.; et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J. Periodontol.* 2018, 89 (Suppl. S1), S173–S182.

He, J.; Li, Y.; Cao, Y.; Xue, J.; Zhou, X. The oral microbiome diversity and its relation to human diseases. *Folia Microbiol.* 2015, 60, 69–80.

Sharma P, Saxena S, Aggarwal P. Trends in the epidemiology of oral squamous cell carcinoma in Western UP: an institutional study. *Ind J Dent Res.* 2010;21:316–9. doi: 10.4103/0970-9290.70782.

Mehrotra R, Yadav S, et al. Oral squamous cell carcinoma: etiology, pathogenesis and prognostic value of genomic alterations. *Indian J Cancer.* 2006;43:60–6. doi: 10.4103/0019-509x.25886.

Group TNHW, Peterson J, Garges S, Giovanni M, McInnes P, Wang L, et al. The NIH Human Microbiome Project. *Genome Res* (2009) 19:2317–23. doi: 10.1101/gr.096651.109

Contaldo M., Fusco A., Stiuso P., Lama S., Gravina A.G., Itró A., Federico A., Itró A., Dipalma G., Inchingolo F., et al. Oral Microbiota and Salivary Levels of Oral Pathogens in Gastro-Intestinal Diseases: Current Knowledge and Exploratory Study. *Microorganisms*. 2021;9:1064. doi: 10.3390/microorganisms9051064.

Whitmore SE, Lamont RJ. Oral Bacteria and Cancer. *PLoS Pathog* (2014) 10:e1003933. 10.1371/journal.ppat.1003933

Del Giudice C., Vaia E., Liccardo D., Marzano F., Valletta A., Spagnuolo G., Ferrara N., Rengo C., Cannavo A., Rengo G. Infective Endocarditis: A Focus on Oral Microbiota. *Microorganisms*. 2021;9:1218. doi: 10.3390/microorganisms9061218.

Arthur JC, Gharaibeh RZ, Mühlbauer M, Perez-Chanona E, Uronis JM, McCafferty J, et al. Microbial genomic analysis reveals the essential role of inflammation in bacteria-induced colorectal cancer. *Nat Commun* (2014) 5:4724. 10.1038/ncomms5724

K. Nagy et al. The microflora associated with human oral carcinomas *Oral Oncol.* (1998)

Gholizadeh, P.; Eslami, H.; Yousefi, M.; Asgharzadeh, M.; Kafil, H.S. Role of oral microbiome on oral cancers, a review. *Biomed Pharm.* 2016, 84, 552–558.

Seitz, H.K.; Becker, P. Alcohol metabolism and cancer risk. *Alcohol. Res. Health* 2007, 30, 38–41, 44–47.

arsonnet J. *Helicobacter pylori* and gastric cancer. *Gastroenterol Clin North Am* (1993) 22:89–104.

Bhatelia K, Singh K, Singh R. TLRs: linking inflammation and breast cancer. *Cell Signal* (2014) 26:2350–7. 10.1016/j.cellsig.2014.07.035

Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, et al. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Res* (2012) 22:292–8. 10.1101/gr.126573.111

Ohadian Moghadam S, Momeni SA. Human microbiome and prostate cancer development: current insights into the prevention and treatment. *Front Med* (2020) 14(3):1–22. 10.1007/s11684-019-0731-7

Cekici A., Kantarci A., Hasturk H., Van Dyke T.E. Inflammatory and immune pathways in the pathogenesis of

periodontal disease. *Periodontology* 2000. 2014;64:57–80. doi: 10.1111/prd.12002.

Checchi V., Maravic T., Bellini P., Generali L., Consolo U., Breschi L., Mazzoni A. The Role of Matrix Metalloproteinases in Periodontal Disease. *Int. J. Environ. Res. Public Health*. 2020;17:4923. doi: 10.3390/ijerph17144923.

Kato T., Yamazaki K., Nakajima M., Date Y., Kikuchi J., Hase K., Ohno H., Yamazaki K. Oral Administration of *Porphyromonas gingivalis* Alters the Gut Microbiome and Serum Metabolome. *mSphere*. 2018;3:e00460-18. doi: 10.1128/mSphere.00460-18.

Page, R.C.; Schroeder, H.E. Pathogenesis of inflammatory periodontal disease. A summary of current work. *Lab. Investig.* 1976, 34, 235.

Kuo, L.-C.; Polson, A.M.; Kang, T. Associations between periodontal diseases and systemic diseases: A review of the inter-relationships and interactions with diabetes, respiratory diseases, cardiovascular diseases and osteoporosis. *Public Health* 2008, 122, 417–433.

Kilian M., Chapple I.L., Hannig M., Marsh P.D., Meuric V., Pedersen A.M., Tonetti M.S., Wade W.G., Zaura E. The oral microbiome – An update for oral healthcare professionals. *BDJ*. 2016;221:657. doi: 10.1038/sj.bdj.2016.865.

Papapanou P.N., Sanz M., Buduneli N., Dietrich T., Feres M., Fine D.H., Flemmig T.F., Garcia R., Giannobile W.V., Graziani F., et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J. Periodontol.* 2018;89((Suppl. S1)):S173–S182. doi: 10.1002/JPER.17-0721.

Di Stefano M., Polizzi A., Santonocito S., Romano A., Lombardi T., Isola G. Impact of Oral Microbiome in Periodontal Health and Periodontitis: A Critical Review on Prevention and Treatment. *Int. J. Mol. Sci.* 2022;23:5142. doi: 10.3390/ijms23095142.

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.; et al. Oral Microbiota Community Dynamics Associated with Oral Squamous Cell Carcinoma Staging. *Front. Microbiol.* 2018, 9, 862.

Karpiński, T.M. Role of Oral Microbiota in Cancer Development. *Microorganisms* 2019, 7, 20.

Maciel S.S., Feres M., Gonçalves T.E.D., Zimmermann G.S., Da Silva H.D.P., Figueiredo L.C., Duarte P.M. Does obesity influence the subgingival microbiota composition in periodontal health and disease? *J. Clin. Periodontol.* 2016;43:1003–1012. doi: 10.1111/jcpe.12634.

Perera, M. et al. (2018) Inflammatory bacteriome and oral squamous cell carcinoma . *J. Dent. Res.* , 97 , 725 –732.

R. Sinha, H. Ahsan, M. Blaser, J.G. Caporaso, J.R. Carmical, A.T. Chan, A. Fodor, M.H. Gail, C.C. Harris, K. Helzlsouer, C. Huttenhower, R. Knight, H.H. Kong, G.Y. Lai, D. Hutchinson, L. LeMarchand, H. Li, M.J. Orlich, J. Shi, A. Truelove, M. Verma, E. Vogtmann, O. White, W. Willett, W. Zheng, S. Mahabir, C. Abnet, Next steps in studying the human microbiome and health in prospective studies, Bethesda, MD, May 16-17, 2017, *Microbiome*, 6 (1) (2018), p. 210

F.E. Dewhirst, The oral microbiome: critical for understanding oral health and disease

J. Calif. Dent. Assoc. 44 (7) (2016), pp. 409-410

Gomez A., Nelson K.E. The Oral Microbiome of Children: Development, Disease, and Implications Beyond Oral Health. *Microb. Ecol.* 2017;73:492–503. doi: 10.1007/s00248-016-0854-1.

Di Stefano M., Polizzi A., Santonocito S., Romano A., Lombardi T., Isola G. Impact of Oral Microbiome in Periodontal Health and Periodontitis: A Critical Review on Prevention and Treatment. *Int. J. Mol. Sci.* 2022;23:5142. doi: 10.3390/ijms23095142.

[44]Fan X., Alekseyenko A.V., Wu J., Peters B.A., Jacobs E.J., Gapstur S.M., Purdue M.P., Abnet C.C., Stolzenberg-Solomon R., Miller G., et al. Human oral microbiome and prospective risk for pancreatic cancer: A population-based nested case-control study. *Gut.* 2018;67:120–127. doi: 10.1136/gutjnl-2016-312580.

Brandtzaeg, P. Secretory Immunity with Special Reference to the Oral Cavity. *J. Oral Microbiol.* 2013, 5, 20401.

https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.researchgate.net%2Ffigure%2FSchematic-of-oral-dysbiosis-Oral-dysbiosis-is-affected-by-environmental-and-genetic_fig1_369111148&psi

g=AOvVaw01rKhczw-BjVMYrShzP4vj&ust=173688345410900
0&source=images&cd=vfe&opi=89978449&ved=0CBQQjRxqF
woTCPDJ956584oDFQAAAAAdAAAAABAE

ostalonga M., Herzberg M.C. The oral microbiome and the
immunobiology of periodontal disease and caries. *Immunol.*
Lett. 2014;162:22–38. doi: 10.1016/j.imlet.2014.08.017.

[https://www.google.com/
url?sa=i&url=https%3A%2F%2Fwww.researchgate.
net%2Ffigure%2FComposition-of-the-human-oral-microbiota_](https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.researchgate.net%2Ffigure%2FComposition-of-the-human-oral-microbiota_)