



Editorial

Advances in Biomarkers and Diagnostics in Periodontitis and Oral Diseases

Gaetano Isola

Department of General Surgery and Surgical-Medical Specialties, School of Dentistry, University of Catania,
Via S. Sofia 78, 95124 Catania, Italy; gaetano.isola@unit.it; Tel.: +39-095-378-2453

Introduction

Oral health is essential to general health and well-being at every stage of life [1]. A healthy mouth enables the nutrition of the physical body and enhances social interaction and promotes self-esteem and feelings of well-being [2]. The mouth serves as a “window” to the rest of the body, providing general health disorders signals. Oral and periodontal conditions have an impact on overall health and disease [3]. Bacteria from the mouth can cause infection in other parts of the body when the immune system has been compromised by disease or medical treatments (e.g., infective endocarditis) [4–6]. Systemic conditions and their treatment are also known to impact on oral health (e.g., reduced saliva flow, altered balance of oral microorganisms) [7,8].

The most important risk factors for oral cancer, the Oral Squamous Cell Carcinoma (OSCC) development, are tobacco use and extensive alcohol consumption. Moreover, infection with oncogenic types of human papillomavirus (HPV) has been identified as a significant risk factor for a subset of oral cancer [9,10].

The main reasons for failure in oral cancer treatment and the strongest adverse factors for prognosis are the spread to the regional lymph nodes and early development of local recurrence or second primary tumors [11]. Modern head and neck oncology can offer a plethora of treatment modalities including surgical resection with reconstructive options, radiotherapy (including proton therapy), conventional and targeted systemic treatment, and also, as of late, immunotherapy [12]. The success rates of treatments can significantly vary between particular patients. Thus, one of the biggest future challenges is to tailor multidisciplinary treatments such that they are based not only on clinical assessment of disease advancement determined by stage but also on the biological factors of the tumor.

Advances in genetics and molecular biology have improved our knowledge of cellular mechanisms, which provide insights into the pathophysiological processes that turn healthy epithelial cells into cancer. Potential biomarkers and therapeutic targets can be investigated to identify genetic signatures that could be used for early diagnosis, treatment personalization, and, finally, the prognosis for individual patients [13].

Numerous biomarkers are being utilized, including circulating tumor DNA (ctDNA), micro RNAs, extracellular vesicles, circulating tumor cells and endothelin receptor type B hypermethylation [14,15]. More than one-hundred salivary components have been reported to differ in concentration in patients with and without OSCC [16,17].

In this regard, saliva has been described as “the defender of the oral cavity” and provides for the protection of hard and soft tissues; aids taste, swallowing and digestion; and offers antimicrobial properties [18].

Saliva contains more than two thousand proteins, enzymes, electrolytes, small organic molecules, and antimicrobials. The whole saliva contains plasma-derived components, sloughed epithelial cells, microorganisms and their associated products, gingival

Citation: Isola, G.; Advances in Biomarkers and Diagnostics in Oral Cancer and Diseases. *Int. J. Environ. Res. Public Health* **2021**, *18*, 1886. <https://doi.org/10.3390/ijerph18041886>

Received: 9 February 2021

Accepted: 10 February 2021

Published: 15 February 2021

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

crevicular fluid, debris, and nasopharyngeal discharge. In the context of oral disease, the research, identification and use of salivary biomarkers is ongoing for many conditions. In this editorial, we will discuss some of the salivary biomarkers researched and used for periodontal disease and oral/oropharyngeal cancer [19].

The aim of the special issue “New Biomarkers and Diagnostics in Oral Cancer and Oral Diseases” was to provide insight into the recent advances in the field of oral cancer and oral diseases. More specifically, among published manuscripts, Mazurek-Mochol et al. examined the association between the IL-17F rs763780 and IL-17A rs2275913 polymorphisms and periodontitis in non-smoking and smoking patients to check if these polymorphisms could be a risk factor for periodontitis. Interestingly, they found a lack of statistically significant associations between IL-17F rs763780 and IL-17A rs2275913 polymorphisms and periodontitis in a European population [20].

Recently, an increasing number of reports in literature have focused attention on some salivary research initiatives, the key objective of which is to generate a growing appreciation of the importance of saliva for overall health and for the diagnosis of oral diseases, and also to encourage a call to action in scientists and leaders in oral health to obtain the benefits of salivary screening tests useful for an advance detection of oral disease that will definitely help to stratify the patient’s risk and to reduce the global burden according to the “personalized medicine” approach [21–24]. It is ever more apparent that addressing this challenge to improve oral health worldwide will require a closer and more robust engagement across sectors in the dental field and the adoption of an upstream approach to reduce the global burden of disease in general.

This diagnostic modality in the field of molecular biology has led to the discovery and potential of salivary biomarkers for the detection of oral cancers. Biomarkers are the molecular signatures and indicators of normal biological, pathological process, and pharmacological response to treatment, and hence may provide useful information for detection, diagnosis, and prognosis of the disease. Saliva’s direct contact with oral cancer lesions makes it a more specific and potentially sensitive screening tool, whereas there are more than 100 salivary biomarkers. However, because of sensitivity and specificity, as well as technical requirements and cost, the use of salivary biomarkers is promising and has been confined to the laboratory. However, future investigations will continue along different pathways using different techniques to better understand salivary biomarkers’ role in oral health and disease.

Author Contributions: Conceptualization, validation, writing—review and editing, G.I. The author has read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Hugo, F.N.; Kassebaum, N.J.; Marcenes, W.; Bernabé, E. Role of Dentistry in Global Health: Challenges and Research Priorities. *J. Dent. Res.* **2021**, doi:10.1177/0022034521992011.
2. Leira, Y.; Rodriguez-Yanez, M.; Arias, S.; Lopez-Dequidt, I.; Campos, F.; Sobrino, T.; D’Aiuto, F.; Castillo, J.; Blanco, J. Periodontitis is associated with systemic inflammation and vascular endothelial dysfunction in patients with lacunar infarct. *J. Periodontol.* **2019**, *90*, 465–474, doi:10.1002/jper.18-0560.
3. Yildiz Telatar, G.; Gurlek, B.; Telatar, B.C. Periodontal and caries status in unexplained female infertility: A case-control study. *J. Periodontol.* **2020**, doi:10.1002/JPER.20-0394.
4. Arweiler, N.B.; Marx, V.K.; Laugisch, O.; Sculean, A.; Auschill, T.M. Clinical evaluation of a newly developed chairside test to determine periodontal pathogens. *J. Periodontol.* **2020**, *91*, 387–395, doi:10.1002/JPER.19-0180.
5. Yang, M.; Li, L.; Soh, Y.; Heo, S.M. Effects of omega-3 fatty acids and aspirin on *Porphyromonas gingivalis*-induced periodontitis in rats. *J. Periodontol.* **2019**, *90*, 1307–1319, doi:10.1002/jper.19-0063.
6. Fang, D.; Yuran, S.; Reches, M.; Catunda, R.; Levin, L.; Febbraio, M. A peptide coating preventing the attachment of *Porphyromonas gingivalis* on the surfaces of dental implants. *J. Periodontal Res.* **2020**, *55*, 503–510, doi:10.1111/jre.12737.

7. Isola, G.; Polizzi, A.; Patini, R.; Ferlito, S.; Alibrandi, A.; Palazzo, G. Association among serum and salivary *A. actinomycetem-comitans* specific immunoglobulin antibodies and periodontitis. *BMC Oral Health* **2020**, *20*, 283, doi:10.1186/s12903-020-01258-5.
8. El-Sharkawy, H.; Elmeadawy, S.; Elshinnawi, U.; Anees, M. Is dietary melatonin supplementation a viable adjunctive therapy for chronic periodontitis?—A randomized controlled clinical trial. *J. Periodontal Res.* **2019**, *54*, 190–197, doi:10.1111/jre.12619.
9. Bagan, J.; Murillo-Cortes, J.; Leopoldo-Rodado, M.; Sanchis-Bielsa, J.M.; Bagan, L. Oral cancer on the gingiva in patients with proliferative leukoplakia: A study of 30 cases. *J. Periodontol.* **2019**, *90*, 1142–1148, doi:10.1002/JPER.18-0620.
10. Patil, S.; Warnakulasuriya, S. Blood-based circulating microRNAs as potential biomarkers for predicting the prognosis of head and neck cancer—a systematic review. *Clin. Oral Investig.* **2020**, *24*, 3833–3841, doi:10.1007/s00784-020-03608-7.
11. Dave, K.; Ali, A.; Magalhaes, M. Increased expression of PD-1 and PD-L1 in oral lesions progressing to oral squamous cell carcinoma: A pilot study. *Sci. Rep.* **2020**, *10*, 9705.
12. Sami, A.; Elimairi, I.; Stanton, C.; Ross, R.P.; Ryan, C.A. The Role of the Microbiome in Oral Squamous Cell Carcinoma with Insight into the Microbiome-Treatment Axis. *Int. J. Mol. Sci.* **2020**, *21*, 8061.
13. Ye, D.; Gajendra, S.; Lawyer, G.; Jadeja, N.; Pishey, D.; Pathagunti, S.; Lyons, J.; Veazie, P.; Watson, G.; McIntosh, S.; et al. Inflammatory biomarkers and growth factors in saliva and gingival crevicular fluid of e-cigarette users, cigarette smokers, and dual smokers: A pilot study. *J. Periodontol.* **2020**, *91*, 1274–1283, doi:10.1002/JPER.19-0457.
14. Assao, A.; Domingues, M.A.C.; Minicucci, E.M.; Marchi, F.A.; Coutinho-Camillo, C.M.; Oliveira, D.T. The relevance of miRNAs as promising biomarkers in lip cancer. *Clin. Oral Investig.* **2021**, doi:10.1007/s00784-020-03773-9.
15. Xu, G.Q.; Li, L.H.; Wei, J.N.; Xiao, L.F.; Wang, X.T.; Pang, W.B.; Yan, X.Y.; Chen, Z.Y.; Song, G.H. Identification and profiling of microRNAs expressed in oral buccal mucosa squamous cell carcinoma of Chinese hamster. *Sci. Rep.* **2019**, *9*, 15616.
16. Esteves, C.V.; de Campos, W.G.; Amorim Dos Santos, J.; Kobayashi Velasco, S.; Guerra, E.N.S.; Siqueira, W.L.; Lemos, C.A. Proteomic profile of saliva collected directly from ducts: A systematic review. *Clin. Oral Investig.* **2020**, *24*, 559–568, doi:10.1007/s00784-019-03165-8.
17. Lo Muzio, L.; Campisi, G.; Farina, A.; Rubini, C.; Pastore, L.; Giannone, N.; Colella, G.; Leonardi, R.; Carinci, F. Effect of p63 expression on survival in oral squamous cell carcinoma. *Cancer Investig.* **2007**, *25*, 464–469, doi:10.1080/07357900701509387.
18. Lam-Ubol, A.; Matangkasombut, O.; Trachootham, D.; Tarapan, S.; Sattabanasuk, V.; Talungchit, S.; Paemuang, W.; Phonyiam, T.; Chokchaitam, O.; Mungkung, O.O. Efficacy of gel-based artificial saliva on *Candida* colonization and saliva properties in xerostomic post-radiotherapy head and neck cancer patients: A randomized controlled trial. *Clin. Oral Investig.* **2020**, doi:10.1007/s00784-020-03484-1.
19. Ishikawa, S.; Wong, D.T.W.; Sugimoto, M.; Gleber-Netto, F.O.; Li, F.; Tu, M.; Zhang, Y.; Akin, D.; Iino, M. Identification of salivary metabolites for oral squamous cell carcinoma and oral epithelial dysplasia screening from persistent suspicious oral mucosal lesions. *Clin. Oral Investig.* **2019**, *23*, 3557–3563, doi:10.1007/s00784-018-2777-3.
20. Abate, A.; Cavagnetto, D.; Fama, A.; Matarese, M.; Bellincioni, F.; Assandri, F. Efficacy of operculectomy in the treatment of 145 cases with unerupted second molars: A retrospective case-control study. *Dent. J.* **2020**, *3*, 65. doi: 10.3390/dj8030065.
21. Mazurek-Mochol, M.; Kozak, M.; Malinowski, D.; Safranow, K.; Pawlik, A. IL-17F Gene rs763780 and IL-17A rs2275913 Polymorphisms in Patients with Periodontitis. *Int. J. Environ. Res. Public Health* **2021**, *18*, 1081, doi:10.3390/ijerph18031081.
22. Isola, G.; Polizzi, A.; Alibrandi, A.; Williams, R.C.; Leonardi, R. Independent impact of periodontitis and cardiovascular disease on elevated soluble urokinase-type plasminogen activator receptor (suPAR) levels. *J. Periodontol.* **2020**, doi:10.1002/JPER.20-0242.
23. Isola, G.; Lo Giudice, A.; Polizzi, A.; Alibrandi, A.; Murabito, P.; Indelicato, F. Identification of the different salivary Interleukin-6 profiles in patients with periodontitis: A cross-sectional study. *Arch. Oral Biol.* **2021**, *122*, 104997. doi: 10.1016/j.archoral-bio.2020.104997.
24. Raisanen, I.T.; Heikkinen, A.M.; Pakbaznejad Esmaeili, E.; Tervahartiala, T.; Pajukanta, R.; Silbereisen, A.; Bostanci, N.; Sorsa, T. A point-of-care test of active matrix metalloproteinase-8 predicts triggering receptor expressed on myeloid cells-1 (TREM-1) levels in saliva. *J. Periodontol.* **2020**, *91*, 102–109, doi:10.1002/JPER.19-0132.