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Indirect Targeting of Cancers via Oral Microbiome Modification

Salvador Vale*

Unidad de Investigación, Laboratorio Trinidad, Tlaxcala 90, Mexico DF, Mexico

Abstract

The aim of this manuscript is to call attention that the modification of the oral microbiome, a possible issue nowadays, can reduce the incidence of some cancers even distant of the oral location. Although with possibly inconsistent effects in the treatment of established cancers, their potential preventive role will open new avenues of research and have important implications for clinical science.

Keywords: Cancer; Oral microbiome; Gut microbiome transplantation; Oral topical arginine

Introduction

The aim of this manuscript is to call attention that the modification of the oral microbiome, a possible issue nowadays, can reduce the incidence of some cancers even distant of the oral location. Although with possibly inconsistent effects in the treatment of established cancers, their potential preventive role will open new avenues of research and have important implications for clinical science.

The human microbiome, referring to the collective genome of all bacteria, archaea, fungi, protists and viruses residing in and on the human body, has attracted substantial attention in human health and diseases and its relevance has been comprehensively recognized. Increasing evidence has demonstrated that correcting several type of dysbiosis can suppress or collaborate in diseases control in may pathological states as Crohn´s disease [1,2] or in their treatments [3]. The gut biomass is the largest microbiome unit in humans and in vertebrates in general; however, other compartment microbiome like those presenting in the urothelial mucosa, the skin, the vaginal, and so on, has additional contribution in several diseases.

In recent years, the oral microbiome has prompted increasing attention since it appears not only to be a strong indicator of dental health, but also contributes to the increased risk of other serious disease like oral cancer [4,5]. Moreover, periodontal disease has been shown promoting several neoplastic diseases in distant sites [6,7].

The mechanism for this association is not clear. Periodontal pathogens could travel extra-orally in saliva via ingestion to infect the gastrointestinal organs (from esophageal to colonic tissues). These pathogens could also permeate through diseased periodontal tissues into the overall circulation, reaching distant sites. Accordingly, numerous scientific reports show periodontal pathogen isolates in various organ systems like arteries, lymph nodes, lung aspirates, precancerous esophageal and gastric or colon/colorectal lesions. At the target site, periodonto-pathogens may stimulate a tolerant microenvironment favorable to cancer progression [8,9]. Chronic periodontitis is generally detected in older subjects compared to more aggressive forms, has slower rates of progression and destruction, and is associated with thicker and more complex biofilms [10].

Hoare et al. [10] states "the oral microbiome is formed by hundreds of microbial species, including bacteria, fungi, archaea and viruses, which coexist in specific and organized arrangements in the different habitats of the oral cavity. Oral sub-habitats include the mucosa, covered by keratinized and non-keratinized stratified squamous epithelium, the papillary surface of the tongue dorsum and the hard structures of teeth, which are comprised by those above (supragingival) and below (subgingival) the gingival margin". Periodontal diseases are inflammatory situations that affect the supporting structures of teeth also. Beyond gingival inflammation, further inflammation, as observed in periodontitis, results in damage of the connective tissue accessory, alveolar bone resorption and eventual tooth loss. In a recent report, marginal increased total cancer risks were observed for breast, lung, esophagus, gallbladder, and skin melanoma linked to periodontal disease [7].

The case of molecular subtypes in colorectal cancer (CRC)

The enrichment of *Porphyromonas gingivalis*, that can promote oral cancer, has been associated with promotion of CRC. This micro-organism is a known to be a biofilm former that co-aggregates with Treponema denticola and Tannerrella forsythia. Formation of such biofilms in extra-intestinal infections facilitates synergistic pathogenicity, and the high enrichment of these bacteria in CRC suggests that similar community synergy may be occurring in the tumor microenvironment. As a matter of fact, biofilms facilitate the invasion of the mucous layer. A study by Dejea et al. [11] found that biofilms were present in >90% of right-sided CRC. Two further oral bacteria, *P. micra* and *P. stomatis*, have been identified in metagenomics studies as markers of CRC using fecal samples, and have been described in an oral-microbe-induced colorectal tumorigenesis model [12] underlining the potential role of oral polymicrobial communities in the development of a subset of CRC, and the importance of considering CRC heterogeneity when studying mechanisms of CRC pathogenesis.

Therapeutic perspectives

Studies regarding genetically modified strains of S. mutans in the prevention and/or treatment of caries are published [13]. In the same line, there are studies evaluating the effect of non-genetically modified strains that may antagonize native pathogens; for example, a nasal spray containing a mixture of S. sanguinis, S. mitis and S. oralis showed potential as a beneficial alternative for acute otitis media in children [14].

***Corresponding author:** Dr. Salvador Vale, MD, Unidad de Investigación, Laboratorio Trinidad, Tlaxcala 90, Mexico DF, México, Tel: (55)55933714; E-mail: svalemayorga@yahoo.com.mx

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Another strategy that utilizes the bacterial replacement principles for the treatment of dysbiotic disorders is gut microbiome transplantation. This approach has been mainly directed towards the restoration of the intestinal microbiota after antibiotic treatment, which alters the indigenous community structure and allows colonization by pathogens such as *Clostridium difficile* [15]. "Fecal transplantation has been tested as a therapy for *C. difficile* - associated diarrhea with excellent clinical results, showing restoration of bacterial diversity in stool samples and a decrease in symptomatology with a much more superior performance than vancomycin treatment, which has been the standard of care [10]". Also, some promising results have been obtained for other conditions such as metabolic syndrome, obesity, ulcerative colitis and irritable bowel syndrome.

Although the above cited approaches are promising strategies, a distinct confined therapy within the oral cavity will be valuable. This is the case of local treatment with arginine-containing dentifrice that normalized the oral microbiota of active caries individuals similar to that of caries-free controls in terms of microbial structure, abundance of typical species, enzymatic activities of glycolysis and alkali-generation related enzymes and their corresponding transcripts [16]. In addition, combinatory use of arginine with fluoride could better enrich alkali-generating Streptococcus sanguinis and suppress acidogenic/aciduric Streptococcus mutans, and thus significantly delay the demineralizing ability of saliva-derived oral biofilm [16].

Conclusion

Hoare et al. [10] have mentioned that the Colgate-Palmolive-Company has developed a Pro-Argin technology that contains 8% arginine in its toothpaste against tooth hypersensitivity as well as a mouthwash with the same formula. Interestingly, topical arginine in the mouth shows beneficial effects regarding the construction of a healthier microbiome, enriching the alkali-generating Streptococcus sanguinis and suppressing acidogenic/aciduric Streptococcus mutans. Although the initial perspective is promising, further prospective studies are needed to disclose if improving the oral microbiome via administration of arginine-fluoride agents will diminish the incidence of distant malignancies. It is possible that combinatorial approaches like adding gut microbiome transplantation may develop additional results in this setting. I hope these data could arouse the concern of people on this health problem.

Conflict of Interest

I declare to have no direct or indirect commercial financial incentive associated with any data described in this manuscript.

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