



Mini Review

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Oral Microbiome and Response to Immunotherapy: Is It Time To Pay Attention?

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Abstract

Microbiome studies have shown associations between the presence of certain bacteria in the gut and response to checkpoint inhibition (CPI) therapies in cancer patients. Studies looking at any such potential associations between oral microbiome and response to CPI therapies are lacking. Oral cavity is an important microbial habitat. Microbes present in the oral cavity influence not only the local and systemic immune homeostasis; but also the gastrointestinal microbial diversity. If associations exist between specific gut microbes and response to CPI therapies, it is reasonable to assume that such relationships exist between oral microbes and therapy response in cancer patients. Since the findings from such studies will have resounding implications on patient selection for therapies and prophylactic or therapeutic modulation of microbes for prevention or treatment of malignancies; it is crucial that dental and oral research community pays attention and joins this research effort to identify associations and elucidate mechanisms of oral microbial determinants of CPI therapy responses in cancer patients.

Keywords: Oral microbiome; Immunotherapy; Checkpoint inhibition; Resistance to therapy; Determinants of response; Biomarkers; Oral squamous cell carcinoma

Abbreviations: PD-1: Programmed Death Receptor 1; PD-L1: Programmed Death-Ligand 1; CTLA-4: Cytotoxic T-lymphocyte-Associated Protein 4; CPI: Checkpoint Inhibition; TME: Tumor Microenvironment; OSCC: Oral Squamous Cell Carcinoma; HNSCC: Head and Neck Squamous Cell Carcinoma

Introduction

The field of cancer therapies has benefitted immensely from the recent advances in immunotherapeutic approaches. The understanding of the role of checkpoint molecules, such as PD-1/PD-L1, and CTLA-4 in mediating immunosuppression in the tumor microenvironment (TME) has led to development of antibodies that block these molecules and enhance anti-tumor immunity [1]. The success of these inhibitors has been highlighted by FDA approval of checkpoint blocking antibodies for use in patients with non-small-cell lung cancer, metastatic melanoma, classical Hodgkin's lymphoma, renal cell carcinoma, and metastatic or recurrent head and neck squamous cell carcinoma [2]. Despite this, majority of patients don't benefit from these treatments and identification of biomarkers of response has been slow. Studies have focused on understanding the innate barriers or the therapy induced adaptive resistances that hamper therapeutic response [3,4]. In line with that, susceptibility factors are being explored to inform

the therapy response prediction and patient stratification. Among many, presence of specific microbes in the gut has been identified as potential determinant of therapeutic response to checkpoint inhibitor therapy in cancer patients [5-8]. What remains unexplored however is the contribution of specific microbes of the oral cavity in determination of success or failure of such therapies.

Discussion

High expression of PD-1/PD-L1 has been associated with poor outcomes in oral squamous cell carcinoma patients [9-11]. PD-1 blockade has been shown to prevent the development of carcinogen-induced oral premalignant lesions and prevent the malignant transformation [12,13]. While clinical studies of PD-1 blockade exclusively on oral squamous cell carcinoma (OSCC) are not available, study on head and neck squamous cell carcinoma (HNSCC) has shown that a subset of patients benefit from this treatment; leading to the approval of PD-1 blocking antibody for

patients with platinum-refractory recurrent and/or metastatic HNSCC [14,15]. These findings, however, further highlight that a majority of the patients do not respond to this therapy. Many recent studies have focused on identifying the determinants of response or failure to checkpoint blockade therapies. Such studies are lacking in the case of oral squamous cell carcinoma.

The field of microbiome research has gained momentum as of late, in part due to the studies showing associations between the presence of specific bacterial species in the gut and response to checkpoint blockade immunotherapy. One early study showed that presence of the commensal *Bifidobacterium* improved the efficacy of PD-L1 blockade therapy through a mechanism that depended on dendritic cell mediated priming of CD8+ T cells and their accumulation in the tumors [7]. Similarly, another study showed that anti-tumor activity of CTLA-4 blockade was enhanced by the presence of *Bacteroides* spp. (*B. fragilis*). This enhanced response was associated with presence of T-cells specific for these bacteria [8]. Melanoma patients that responded to PD-1 blockade immunotherapy were shown to have a presence of abundant *Ruminococcaceae/Faecalibacterium* in their gut [5]. Another study found that abundance of *Akkermansia muciniphila* in gut associated with response to PD-1 blockade in an IL-12 dependent manner [6]. The importance of gut microbiota in modulating therapy response was highlighted by the fact that consumption of antibiotics was associated with poor response to PD-1 blockade [6]. While the exact mechanism that underscores the efficacy of checkpoint inhibitors in presence of these bacterial species is unknown, heightened immune responses, including T cell infiltration into the tumors, secondary to the colonization of these bacterial species is thought to be the responsible factor [6-8].

Studies have demonstrated associations between presence of microbes and risk of squamous cell carcinomas [16-18]. Higher abundance of *Corynebacterium* and *Kingella*, which have the ability to metabolize carcinogens, has been shown to associate with decreased risk of HNSCC [16]. *Porphyromonas Gingivalis* and *Fusobacterium nucleatum*, however, were found to promote oral carcinogenesis in preclinical models [19].

Porphyromonas Gingivalis, *Fusobacterium nucleatum* and *Actinomyces* were shown to be increased in tumor sites of OSCC patients [20]. *Fusobacterium* were found to not only be enriched but also gradually increase in abundance with the progression of OSCC [17,18]. Despite these findings, whether the presence and abundance of these microbes is causative to OSCC or if their presence is rather facilitated by microenvironment changes with OSCC progression remains to be determined. Additionally, it is essential that contributions of other factors such as emotional stress of the patients, which play a crucial role in determining the composition of oral microbes as well as promoting the risk of periodontal diseases through behavioral and systemic changes [21], be considered while studying and establishing associations between oral microbes and risk of tumor development and progression. As such, psychological therapies may lend towards decreased risk of such microbial colonization and unveil whether true causal associations exist between these microbes and oral cancers development and progression.

Composition of oral microbiome has also been shown to associate with increased or decreased risk of developing pancreatic cancer. Specifically, presence of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* associated with higher risk of pancreatic cancer while the presence of *Fusobacteria* and *Leptotrichia* associated with decreased risk of pancreatic cancer [22]. Similar studies are also available for other gastrointestinal cancer such as esophageal cancer [23]. While the associations of particular bacterial species with increased risk of cancers have been attributed to the persistent inflammation in response to these bacteria; if and how the presence of any microbial species confers resistance against development of malignancies is unknown. More importantly, whether presence of any specific oral microbe is associated with enhanced response to checkpoint blockade therapies remain to be determined.

Conclusion

Oral cavity is an extension of gastrointestinal system and represents a major habitat for microbes. Changes in microflora in the oral cavity affect both the local and systemic immune homeostasis and associations of oral microflora with oral and gastrointestinal cancers have been made. With recent studies showing correlations between presence of specific bacterial species in gut and response to checkpoint inhibitor therapies in various cancers, microbiome studies have started to focus on microbial biomarkers of response. Oral microbiome, on the other hand, has not yet been studied for the potential role of microbes on the success or failure of checkpoint inhibitor therapy response. It is essential that research studies be undertaken to detect relationship between oral microbes and response to checkpoint inhibitor therapies against oral and other cancers. Not only should such studies focus on identifying the oral microbial biomarkers or determinants of response to checkpoint blockade therapies, but also on elucidating the mechanisms inherent to the bacterial subspecies that regulate the outcome. Insights gained will not only allow for prophylactic and therapeutic modulation of microbes to prevent or treat oral cancers, but also inform rational combination of cancer therapies for successful clinical outcomes. Research on gut microbiome and association with immunotherapy responses has gained momentum. It is time for dentists and oral research community to pay attention and jump this research bandwagon.

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