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Deciphering dysbiosis: Bacteriome and mycobiome imbalances in oral mucosal dysplasia and oral cancer

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ABSTRACT

The oral microbiome has emerged as a critical determinant in the pathogenesis of various oral diseases, including oral mucosal dysplasia and oral cancer. Dysbiosis, characterized by imbalances in the composition and function of the bacteriome and mycobiome, has been implicated in the initiation and progression of these conditions. This review aims to elucidate the intricate relationship between dysbiosis and oral mucosal dysplasia and cancer. We explore the alterations in bacterial and fungal communities associated with dysplastic lesions and malignant transformations within the oral cavity. Additionally, we discuss the potential mechanisms by which dysbiotic changes contribute to the development of oral neoplasms, including microbial-mediated inflammation, immune modulation, and carcinogenic metabolite production. Understanding the dynamics of bacteriome and mycobiome dysbiosis in oral diseases is essential for developing novel diagnostic and therapeutic strategies to combat these conditions. By deciphering dysbiosis, we may pave the way for personalized approaches to oral cancer prevention and management, ultimately improving patient outcomes and quality of life.

Keywords: oral microbiome, dysbiosis, oral mucosal dysplasia, oral cancer

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INTRODUCTION

The oral cavity harbours a complex and diverse microbial ecosystem known as the oral microbiome, which plays a crucial role in maintaining oral health and homeostasis. Recent advancements in high-throughput sequencing technologies have unveiled the intricate composition and functionality of this microbiome, shedding light on its involvement in various oral diseases. Among these diseases, oral mucosal dysplasia and oral cancer represent significant challenges to global public health, with rising incidence rates and substantial morbidity and mortality [1].

Dysbiosis, characterized by imbalances in the composition, diversity, and function of the oral microbiome, has emerged as a key contributor to the pathogenesis of oral mucosal dysplasia and cancer. While dysbiosis was initially associated with bacterial communities (bacteriome), emerging evidence suggests that fungal populations (mycobiome) also play a pivotal role in oral disease development and progression. Understanding the interplay between the bacteriome and mycobiome dysbiosis in oral mucosal dysplasia and cancer is essential for elucidating the underlying mechanisms and identifying novel diagnostic and therapeutic targets [2-4].

In this review, we aim to provide a comprehensive overview of the current understanding of bacteriome and mycobiome dysbiosis in oral mucosal dysplasia and cancer. We will delve into the alterations observed in bacterial and fungal communities associated with dysplastic lesions and malignant transformations within the oral cavity. Moreover, elucidating the role of dysbiosis in oral mucosal dysplasia and cancer may provide insights into broader aspects of microbial pathogenesis and facilitate the development of personalized therapeutic interventions tailored to individual patients.

LITERATURE REVIEW

Effects of microbial dysbiosis on oral mucosa

Microbial dysbiosis, characterized by disruptions in the balance and composition of the oral microbiome, exerts multifaceted effects on the oral mucosa. These effects can significantly impact oral health and contribute to the development and progression of various oral diseases, including oral mucosal dysplasia. Here are some key effects of microbial dysbiosis on the oral mucosa.

Inflammation:

Dysbiotic microbial communities can trigger an inflammatory response in the oral mucosa. This inflammatory state is often characterized by the production of pro-inflammatory cytokines and chemokines, leading to tissue damage and increased susceptibility to diseases such as gingivitis and periodontitis [5].

Epithelial barrier dysfunction:

Dysbiosis can compromise the integrity of the oral mucosal epithelial barrier. Disruption of this barrier allows for increased penetration of microbial pathogens and their by-products into the underlying tissues, exacerbating inflammation and promoting tissue damage.

Immune dysregulation:

Dysbiotic oral microbiota can perturb the balance of the local immune response within the oral mucosa. This dysregulation may result in impaired immune surveillance and clearance of pathogens, as well as aberrant immune activation, contributing to chronic inflammation and tissue destruction [6].

Alterations in metabolite production:

Dysbiotic microbial communities produce an array of metabolites that can directly influence the oral mucosa. For example, certain bacterial metabolites, such as short-chain fatty acids and volatile sulfur compounds, have been implicated in mucosal inflammation, epithelial damage, and carcinogenesis.

Modulation of cell signaling pathways:

Dysbiosis can affect various signaling pathways within oral mucosal cells, influencing cellular processes such as proliferation, differentiation, and apoptosis. Dysregulated signaling pathways may promote dysplastic changes in the oral epithelium and facilitate the progression to oral cancer [7].

Induction of genotoxicity:

Some dysbiotic microorganisms possess genotoxic properties, capable of directly damaging the DNA of oral mucosal cells. Genotoxic insults may lead to the accumulation of genetic mutations and genomic instability, predisposing cells to malignant transformation.

Promotion of angiogenesis and tissue remodeling:

Dysbiotic microbial communities can stimulate angiogenesis and tissue remodelling processes within the oral mucosa. These changes may create a microenvironment conducive to tumour growth and invasion in cases of oral cancer [8].

Dysbiosis in oral squamous cell carcinoma

Dysbiosis in Oral Squamous Cell Carcinoma (OSCC) refers to alterations in the composition and function of the oral microbiome that are associated with the development and progression of this malignancy. Research in recent years has highlighted the intricate relationship between dysbiotic microbial communities and OSCC, shedding light on the potential role of the oral microbiome in oral cancer pathogenesis. Here are some key aspects of dysbiosis in OSCC.

Altered microbial composition:

Studies have revealed shifts in the oral microbiome composition in individuals with OSCC compared to healthy controls. These alterations often involve changes in the relative abundance of specific bacterial taxa, with an enrichment of potentially pathogenic species and a decrease in beneficial commensal microbes.

Dysfunctional microbial communities:

Dysbiosis in OSCC is not only characterized by changes in microbial abundance but also by disruptions in microbial community structure and function. Dysfunctional microbial communities may exhibit reduced diversity, altered metabolic profiles, and dysregulated interactions with the host environment.

Inflammatory microenvironment:

Dysbiotic oral microbiota can promote a pro-inflammatory milieu within the oral mucosa, contributing to chronic inflammation, a hallmark of OSCC. Microbial-induced inflammation may further fuel tumorigenic processes by facilitating immune evasion, angiogenesis, and tissue remodeling [9].

Modulation of tumor microenvironment:

Dysbiotic microbial communities can influence the tumor microenvironment in OSCC, affecting various cellular and molecular processes associated with cancer progression. Microbial metabolites, virulence factors, and extracellular vesicles may directly interact with tumor cells and stromal components, modulating signaling pathways related to proliferation, invasion, and metastasis.

Immune dysregulation:

Dysbiosis in OSCC may perturb the balance of the local immune response, impairing anti-tumor immunity and promoting immune tolerance. Dysbiotic microbial communities can influence immune cell function, cytokine production, and regulatory T cell activity, thereby facilitating immune evasion by tumor cells [10].

Potential biomarkers and therapeutic targets:

Dysbiotic microbial signatures have been proposed as potential biomarkers for OSCC detection, prognosis, and treatment response prediction. Additionally, targeting dysbiotic microbial communities or their associated pathways may represent novel therapeutic strategies for OSCC management, either alone or in combination with conventional therapies [11].

Oral tumor associated microbiota

Oral tumor-associated microbiota refers to the distinct microbial communities that are found within and around oral tumors, including both benign and malignant lesions. Research in recent

years has highlighted the significant role of the oral microbiome in the development, progression, and clinical outcomes of various oral tumors, including Oral Squamous Cell Carcinoma (OSCC) and other malignancies. Here are some key aspects of oral tumor-associated microbiota:

Diversity and composition:

Studies have demonstrated alterations in the diversity and composition of microbial communities associated with oral tumors compared to healthy oral tissues. These alterations often involve shifts in the relative abundance of specific bacterial and fungal taxa, with enrichment of certain pathogenic species and reduction of beneficial commensals [12].

Tumor microenvironment interactions:

Oral tumor-associated microbiota can interact with the tumor microenvironment, influencing various cellular and molecular processes involved in tumor initiation, progression, and metastasis. Microbial metabolites, virulence factors, and extracellular vesicles may directly impact tumor cells, stromal cells, and immune cells within the tumor microenvironment.

Inflammatory signaling:

Oral tumor-associated microbiota can induce and sustain a pro-inflammatory milieu within the tumor microenvironment, contributing to chronic inflammation, which is known to promote carcinogenesis. Microbial-induced inflammation may further drive tumor progression by enhancing angiogenesis, tissue remodeling, and immune evasion mechanisms [13].

Immunomodulation:

Oral tumor-associated microbiota can modulate the host immune response, influencing anti-tumour immunity and immune surveillance mechanisms. Dysbiotic microbial communities may impair immune cell function, alter cytokine production, and promote immune tolerance, thereby facilitating immune evasion by tumour cells.

Diagnostic and prognostic biomarkers:

Specific microbial signatures associated with oral tumors have been proposed as potential biomarkers for disease detection, prognosis, and treatment response prediction. Characterizing the oral tumor-associated microbiota may provide valuable insights into the molecular mechanisms underlying tumor development and progression, as well as novel diagnostic and therapeutic opportunities [14].

Therapeutic targets:

Targeting oral tumor-associated microbiota or their associated pathways represents a promising approach for cancer therapy. Modulating the composition and function of microbial communities within the tumour microenvironment may enhance treatment efficacy, reduce treatment-related side effects, and improve patient outcomes.

Salivary dysbiosis and oral squamous cell carcinoma

Salivary dysbiosis refers to an imbalance in the microbial communities present in saliva. This dysbiosis can lead to alterations in the oral microbiome, potentially contributing to various oral health issues, including Oral Squamous Cell Carcinoma (OSCC). OSCC is the most common type of oral cancer, arising from the squamous cells lining the oral cavity and oropharynx. The development of OSCC is multifactorial, with various factors contributing to its onset, including tobacco and alcohol use, Human Papilloma Virus (HPV) infection, genetic predisposition, and environmental factors [15]. The oral microbiome plays a crucial role in maintaining oral health, and disruptions in its composition and function have been implicated in the pathogenesis of several oral diseases, including OSCC. Saliva acts as a reservoir for microorganisms, and alterations in the microbial community structure can impact the local environment of the oral cavity, potentially promoting carcinogenesis.

Research suggests that certain bacteria associated with salivary dysbiosis, such as *Porphyromonas gingivalis,* Fusobacterium nucleatum, and Streptococcus mitis, may be involved in the development and progression of OSCC. These bacteria can induce chronic inflammation, produce carcinogenic metabolites, and modulate the host immune response, thereby contributing to the pathogenesis of OSCC.

Role of candida species in oral dysplasia

Candida species, particularly Candida albicans, are opportunistic fungi commonly found in the oral cavity. While Candida colonization is considered normal in healthy individuals, alterations in the oral environment can lead to candidiasis, an overgrowth of Candida that can manifest as oral thrush or other mucosal infections. In the context of oral dysplasia, which refers to abnormal changes in the cells of the oral mucosa that may progress to oral cancer, the role of Candida species is of interest but not entirely clear. Some studies have suggested a potential association between Candida colonization and oral dysplasia, while others have found conflicting results or no significant association.

Several mechanisms have been proposed to explain the potential involvement of Candida species in oral dysplasia.

Chronic inflammation:

Candida colonization can induce chronic inflammation in the oral mucosa through the release of various virulence factors and activation of the host immune response. Chronic inflammation is a known risk factor for the development of dysplasia and cancer.

Production of carcinogenic metabolites:

Candida species can produce carcinogenic metabolites, such as acetaldehyde, through the metabolism of ethanol, which is commonly found in alcoholic beverages. Acetaldehyde has been implicated in the progression of oral dysplasia and carcinogenesis [16].

Interaction with epithelial cells:

Candida species can interact with oral epithelial cells through adhesion mechanisms and the secretion of enzymes and toxins. These interactions may disrupt normal cellular processes and contribute to the development of dysplasia [17].

Immune modulation:

Candida colonization can modulate the host immune response in the oral cavity, potentially creating an immunosuppressive environment that promotes the growth and progression of dysplastic lesions.

Role of *Porphyromonas gingivalis* in oral dysplasia

Porphyromonas gingivalis is a Gram-negative anaerobic bacterium commonly associated with periodontal disease, a chronic inflammatory condition affecting the tissues supporting the teeth. While its primary role is in periodontitis, there is emerging evidence suggesting its potential involvement in the development and progression of oral dysplasia and oral cancer [18]. Several mechanisms have been proposed to explain the potential role of *Porphyromonas gingivalis* in oral dysplasia.

Chronic inflammation:

Porphyromonas gingivalis can induce chronic inflammation in the oral mucosa through the activation of inflammatory pathways and the production of virulence factors such as Lipo Poly Saccharide (LPS) and gingipains. Chronic inflammation is a known risk factor for the development of dysplasia and cancer [19-21].

Immune modulation:

Porphyromonas gingivalis can modulate the host immune response in the oral cavity, potentially creating an immunosuppressive environment that promotes the growth and progression of dysplastic lesions. This bacterium can evade host immune defenses and interfere with immune cell function, contributing to the persistence of inflammation and tissue damage [22].

Genomic instability:

Porphyromonas gingivalis has been shown to induce genomic instability in oral epithelial cells through various mechanisms, including the production of Reactive Oxygen Species (ROS) and the inhibition of DNA repair processes. Genomic instability is a hallmark of cancer development and can promote the accumulation of genetic mutations leading to dysplasia and carcinogenesis.

Promotion of angiogenesis:

Porphyromonas gingivalis may promote angiogenesis, the formation of new blood vessels, in the oral mucosa through the secretion of pro-angiogenic factors. Increased angiogenesis can facilitate the growth and spread of dysplastic lesions by providing nutrients and oxygen to the proliferating cells [23].

Challenges and future directions

Understanding dysbiosis dynamics:

Investigating the temporal dynamics of dysbiosis in Oral Mucosal Dysplasia (OMD) and oral cancer is crucial. Longitudinal studies tracking changes in the bacteriome and mycobiome composition over time can provide insights into the progression of dysplasia to malignancy and identify microbial markers of disease progression [24, 25].

Microbial interactions:

Exploring the interactions between bacteria and fungi in the oral microbiome and their role in OMD and oral cancer is essential. Synergistic or antagonistic relationships between different microbial species may influence disease development and progression.

Host-microbiome interactions:

Understanding how dysbiosis interacts with the host immune system and epithelial cells in the oral mucosa is critical. Elucidating the mechanisms by which dysbiotic microbiota contribute to inflammation, genomic instability, and immune evasion can provide novel therapeutic targets for preventing or treating OMD and oral cancer.

Microbial metabolites:

Investigating the metabolic products of dysbiotic microbiota and their effects on host cells is important. Microbial metabolites such as short-chain fatty acids, lipopolysaccharides, and secondary metabolites can modulate host immune responses and contribute to carcinogenesis in the oral mucosa.

Diagnostic biomarkers:

Identifying reliable biomarkers for early detection and risk stratification of OMD and oral cancer is a major challenge. Integrating multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, can facilitate the discovery of novel biomarkers associated with dysbiosis-driven carcinogenesis [26].

Personalized therapeutics:

Developing personalized therapeutic strategies targeting dysbiotic microbiota holds promise for the prevention and treatment of OMD and oral cancer. Precision medicine approaches based on individual microbial profiles, host genetics, and clinical characteristics can optimize treatment outcomes and minimize adverse effects.

Clinical translation:

Translating research findings into clinical practice requires rigorous validation in large, diverse patient cohorts. Collaborations between researchers, clinicians, and industry partners are essential for conducting robust clinical trials evaluating the efficacy and safety of microbiome-based interventions for OMD and oral cancer [27].

Addressing these challenges and pursuing future directions

in deciphering dysbiosis in the oral mucosa can advance our understanding of the pathogenesis of OMD and oral cancer and facilitate the development of innovative diagnostic, preventive, and therapeutic strategies.

CONCLUSION

In conclusion, the investigation of dysbiosis in the oral mucosa, particularly focusing on bacteriome and mycobiome imbalances, offers significant insights into the pathogenesis of Oral Mucosal Dysplasia (OMD) and oral cancer. Through advancements in high-throughput sequencing technologies and bioinformatics analyses, researchers have unveiled complex microbial communities inhabiting the oral cavity and their potential contributions to disease development and progression. In essence, unraveling the intricate interplay between microbial communities and the host mucosal environment in OMD and oral cancer represents a pivotal area of research with profound implications for disease prevention, diagnosis, and treatment. By embracing interdisciplinary collaborations and leveraging cutting-edge technologies, we can harness the potential of the oral microbiome to advance precision medicine approaches and improve patient outcomes in oral oncology.

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