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Opinion

Possibility of Polymicrobial Synergy and Dysbiosis of Periodonto Pathogens in the Oral Squamous Cell Carcinoma Tumour Microenvironment

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Opinion

At least 15% of oral cancer is suspected to be associated with chronic inflammation. Hence, the role of infection associated inflammation in oral cancer gained much attention [1-3]. Recent past epidemiological evidence, facilitated the emergence of poor oral hygiene as an independent risk factor for oral squamous cell carcinoma (OSCC) [4-6]. Periodontitis is the most devastating outcome of poor oral hygiene [7]. In several epidemiological studies, periodontitis reported to be associated with increased risk of OSCC [8-12]. Periodontitis is an inflammatory disease of the periodontium with polymicrobial aetiology [13]. Interestingly, carcinogenic attributes of two periodontopathogenic bacteria *Fusobacterium nucleatum* [3] and *Porphyromonas gingivalis* [3] have been investigated by number of in vivo and in vitro experiments. Promising evidence has been obtained, thus inhibition of apoptosis, activation of uncontrolled cell proliferation, promotion of cell migration/ invasion as well production of carcinogenic virulence factors reported to be responsible for oral carcinogenesis [3]. Evidently, these two periodonto pathogens have been associated with oral, pancreatic and colorectal (CRC) cancers by facilitating chronic inflammation and suppressing immuno surveillance [3].

Contemporary advancements in omics technologies: metagenomics, metatranscriptomics, metaproteomics and metabolomics have overcome the inherent limitations in conventional culture techniques and closed ended molecular techniques such as PCR and DNA-DNA hybridization, and provided an extra ordinary opportunity to understand the unexpected versatility of microbial ecosystems, including different micro habitats in humans [3]. Furthermore, to appreciate the genetic potential of microbes to adopt to harsh environments, subsequently, maintaining the stability and dynamic equilibrium in any micro-ecosystem, Thus, 'Hypothetical Models' have been proposed to explain the progression of inflammatory poly microbial diseases in the oral cavity (40,41), to emphasize the importance of the contribution of virulence factors of low abundance microbial species in 'poly microbial infections' which can act synergistically with over presented marker genera. This phenomenon is termed as 'polymicrobial synergy' [13-15] which helps to maintain a persistent inflammation in the oral cavity [13].

The term "keystone" has been introduced in the ecological literature to characterize species whose effects on their communities are disproportionately large, relative to their abundance and which are thought to form the "keystone" of the community's structure [13-15]. The 'Keystone Pathogen Hypothesis' holds that certain low abundance microbial pathogens could orchestrate inflammatory diseases by remodeling a 'normobiome' into a 'dysbiome' (44). 'Dysbiosis' is the term use in microbial ecology to define a state of imbalance that is characterized by compositional and functional changes of microbiota in disease conditions, compared with healthy state [3,14,15], Dominance of 'key stone' pathogens are commonly found in dysbiosis [3,13].

Against this backdrop, Key-Stone Pathogen [14] mediated Polymicrobial Synergy and Dysbiosis (PSD) model [13] has been

developed and validated to explain the progression of periodontitis, based on alpha-diversity and species composition. Meanwhile, oral microbiome appears as a cofactor in the initiation and progression of oral cancer with established etiological factors namely: smoked and smokeless tobacco addiction, arecanut and arecanut based product usage and alcohol consumption, according to the latest epidemiological and laboratory evidence [3]. Moreover, numerous periodontopathogens were included in the microbiome profiles of oral cancer patients [3].

Hence, it is justifiable to assume the possibility of polymicrobial synergy and dysbiosis mediated by periodonto pathogens in the OSCC tumour microenvironment. Metagenomic and metatranscriptomic studies, based on the large cohort study design are much warranted to explore the possible association of polymicrobial synergy and dysbiosis mediated by periodontopathogens in the OSCC tumour microenvironment. This opinion highlights the importance of investigating epidemiological and laboratory evidence to confirm the hypothesis proposed to understand the versatility of metagenome in OSCC tumour microenvironment. This will widen the horizon of available knowledge of the role of periodonto pathogens in oral carcinogenesis and strengthen the epidemiological evidence of significant association of periodontitis with oral cancer. Furthermore, provide the rationale for the improvement of oral hygiene status before surgery/chemotherapy /radiotherapy of OSCC patients for a better prognosis in the era of personalized or precision medicine.

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Conflict of Interest

The authors declare no conflict of interest.

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