Oral Squamous Cell Carcinoma Tumour Microenvironment as the Ideal Niche for Keystone Periodontal Pathogens

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Findings on functional prediction of metagenome demonstrated more consistence than compositional profiles of bacteriome associated with Oral Squamous Cell Carcinomas (OSCC)s [1]. Moreover, speculations on functional capacity of the metagenome of polymicrobial, inflammatory diseases, using hypothetical models based on core community ecological theories, gained much attention in the recent past [2,3]. Evidently, keystone pathogen mediated polymicrobial synergy and dysbiosis (PSD) model developed for periodontitis provides the rationale on successful colonization of periodontal bacteria in the immunosuppressive OSCC tumour microenvironment [2]. This efficacious colonization seems to be more of a consequence of oral carcinogenesis than a cause in most instances with known aetiology. It has been demonstrated that the oral microbiome acts as a co-factor in the initiation and progression of oral cancer with well-known life style related modifiable risk factors [3,4]. However, those initial ‘apprentice’ might convert to ‘expert’ as they can enhance the carcinogenesis with their inflammophilic, carcinogenic, immunogenic and toxic attributes as the time progressed, according to the latest in-vitro and in-vivo experiments [5]. In light of these stirring findings, it is worthwhile to highlight the intrinsic factors which may facilitate the successful colonization of keystone periodontal pathogens in OSCC tumour microenvironment.

The term ‘keystone’ has been widely used in hypothetical ‘ecological models’ to provide quantitative insight into microbial ecology using the ongoing developments in ‘omics’ technologies [6]. Especially, to appreciate the contribution of the minority or the low abundance microbial species for a common purpose—that is the enhancement of the virulence [7]. Accurately, 688 bacterial species were detected by nucleotide sequencing of 16S rRNA marker gene which is common to bacteria and archaea, in a published metagenomic data of 25 OSCC cases and 27 fibro epithelial polyp (FEP) controls from a case-control study conducted in Sri Lanka by Perera and colleagues [1]. However, handful taxa Capnocytophaga, Pseudomonas, Atopobium and Campylobacter concisus, Prevotella salivae, Prevotella loeschii and Fusobacterium oral taxon 204 were able to flourish accounting as differently abundant taxa, enriched in the OSCC tumour microenvironment [1], without giving any opportunity to the red complex major periodontal pathogens; Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola to overpower them [1]. Furthermore, the species richness and alpha diversity of OSCC tissues were reported to be less than that of the FEP controls, though it was not statistically significant [1] Inability of proper surface decontamination with 70% alcohol may be a reason not to obtain a statistically significant result. The loss of species richness and alpha diversity could be considered as a characteristic feature of the keystone periodontopathogen mediated (PSD) model. Individual members of the community seems to be physiologically compatible without much antagonism when considering their metabolism [7]. Vigorous multiplication and metabolism of colonizers were indicated by the enrichment of lipopolysaccharides (LPS), energy metabolism, membrane and intracellular structural molecules, chromosome, peptidases restriction enzymes pathways, in the OSCC tumour microenvironment [1]. As all of us aware, LPS is one of the major components of the outer membrane of Gram-negative bacteria of the probable keystone periodonto-pathogenic genera of Fusobacterium, Prevotella, Veillonella and Selenomonas [5]. This virulent factor is a heat stable (endotoxin), which can induce inflammatory responses in the host [8]. Another immunogenic virulent factor, flagellum is the organ of locomotion of Fusobacterium, Campylo-
bacter, Selanomonas and Capnocytophaga genera and Prevotella species and other motile bacteria. Flagellin is the structural component of the flagellum with a proinflammatory immune stimulation capacity [9]. Apparently, periodontal pathogenic [7] Campylobacter, Parviomonas, Selanomonas and Olsenella genera which were presented in low abundance in OSCC tumour microenvironment in the same study but much higher proportions compared with the FEP microenvironment, can be considered as the most eligible candidates to become ‘keystone periodontal pathogens’ in the PSD model [10,11], with a genetic potential of LPS biosynthesis, flagella assembly, bacterial chemotaxis, peptidases, chromosomes, restriction enzymes etc.

Several important intrinsic factors in the OSCC tumour microenvironment comprising redox potential, availability of nutrients, pH, temperature, attachment ligands and immune elements inevitably govern the colonization process [1]. The hypoxic [12] and necrotic tissues provide a favorable environment with the ideal redox potential for the anaerobic respiration [5]. Anaerobes do not have cytochrome oxidase or oxygenases thus, they cannot use molecular oxygen for respiration [5]. Hence, anaerobic Fusobacterium, Prevotella, Veillonella, Parviomonas, Selanomonas and Olsenella are anaerobes found as ideal colonizers of the OSCC tumour microenvironment. Moreover, Capnocytophaga and Campylobacter have shown the adaptability to the OSCC tumour microenvironment with their capnophilic [13] and microaerophilic [14] types of respiration respectively. Availability of nutrients is another important intrinsic factor which govern the colonization of microbes [1]. Thus, inflammophilic bacteria nourish from proteinaceous substrates derived from inflammatory tissue breakdown [15] using peptidase [16]. It is reasonable to hypothesize the assemblage of physiologically compatible community members in attachment ligands, with ‘cross talks’ with each other through a range of diffusible molecules which assist the coordination of gene expression among the microbial community members [17]. Many of these gram negative periodontal bacteria found to be communicated via autoinducer 2 molecules [17]. Several periodontal pathogens have been shown to activate inflammatory pathways to worsen the existing immunosuppressive status [18] in the OSCC tumour microenvironment, retarding the immunosurveillance and immuno editing processes. Thus, they can thrive well in OSCC tumour microenvironment as pathobiont avoiding immune elimination by immune elements. These mesophiles can grow well in average core temperature at 37°C ± 0.5 to 1°C in OSCC tumour microenvironment Furthermore, these proteolytic and asaccharolytic anaerobes can thrive well in slightly alkaline pH due to the production of H₂S (hydrogen sulphide) as the end product by proteolytic metabolism [19].

In conclusion, this commentary provides meaningful explanation on high burden of chronic periodontitis in OSCC patients [1] using a hypothetical model of keystone periodontopathogens mediated polymicrobial synergy and dysbiosis (PSD). OSCC tumour microenvironment appears as an ideal niche with hypoxic, necrotic conditions for keystone periodontopathogens, which are capable of nourishing on inflammatory tissue breakdown-derived nutrients. It seems, they have migrated from periodontal pockets to OSCC tumour microenvironment, searching for ‘greener pastures’ for them to be nourished and flourished. These periodontal pathobionts do depend on the host for their nutritional requirements, thus they are hunting for nutrients for their metabolism to boosts the virulence. Moreover, this type of evidence synthesis demonstrates important public health and clinical management implications. Assessing and intervening oral hygiene and periodontal disease status of oral cancer patients with risk habit intervention would be a fay forward to improve the prognosis.

**Figure 1:** OSCC tumour microenvironment as a favourable niche for periodontal pathogens.
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Bibliography


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