International Journal of Dentistry and Oral Science (IJDOS)
ISSN: 2377-8075

Role of Treponema Denticola in Oral Cancer - A Review on Direct and Indirect Mechanisms

Review Article

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Abstract

The *Treponemadenticola*, an oral spirochete is implicated in causation of periodontal disease. The same is implicated in carcinogenesis via a number of potential mechanisms. The oral microbial dysbiosis, promotion of tumorigenesis, aiding in cell migration, enhancement of tumor depth or contribution in invasion were cited before. The tumorsphere modifications and co-existing inflammatory mediator allured Macrophage (M2) alterations were additionally described as contributory to oral cancer biology. The isolation and associations of *T denticola* and *impacted* direct and indirect mechanisms in oral carcinogenesis is presented in this review.

Keywords: Cancers; Mouth; Oral Cavity; Oral Cancer; Oral Squamous Cell Carcinoma; Triponema Denticola.

Introduction

Oral cancer as defined by the World Health Organization and International Agency for Research and Cancer, as the cancer of the 'as the cancer of lips, mouth and tongue' [1]. Oral cancer is health burden in the Indian subcontinent, ranking among the top three types of cancer in the country [1]. The difference in incidence is due to variations in ageing of population, the regional differences in the occurrence of risk factor and genetic makeup of individual to cancer treatments. Globally, oral cancer is the 6th common type of cancer, of which India contributes to almost 1/3rd of the total burden [2]. Oral squamous cell carcinoma (OSCC) is the predominate histological type of all types of oral cancer, with often in found association with pre-existing potentially malignant disorders or pre-cancers of oral cancer [2]. The habits of tobacco consumption (smokeless or smoked tobacco), betel-quid chewing, poor oral hygiene, and sustained infections (human papillomavirus) are some of the risk factors of oral cancer [1, 2]. Lack of knowledge, variations in exposure to the environment, and behavioral risk factors indicate a wide variation in the global incidence and increases the mortality rate [2, 3].

Periodontitis, a chronic inflammatory disease of tooth-attachment system or perodontium is associated with local or systemic factors and reported to be mediated by a bacterial dysbiosis, unfavorable host-bacterial interactions and characterized by destruction of periodontal tissues. The advanced stages of periodontitis are associated with specific microbes which also have role in tumor progression [4-6]. The microbes namely Treponema denticola, Porphyromonas gingivalis and Tannerella forsythia are pathogenic in the etiology of periodontal disease [4]. The Oral spirochete, *T. denticola* notable in periodontal disease, is also detectable levels in healthy gingival plaque, however the levels of *T. denticola* increase with the severity of periodontitis [5].

The oral microbiota contributes to carcinogenesis via a number of potential mechanisms. The genome sequencing based studies showed the presence of microbial patterns that are site-specific,

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Received: November 30, 2020
Accepted: December 30, 2020
Published: January 12, 2021

Citation: Sriram Kaliamoorthy, R Saranyan, Aishwarya Durai. Role of Treponema Denticola in Oral Cancer - A Review on Direct and Indirect Mechanisms. *Int J Dentistry Oral Sci.* 2021;8(1):1367-1370. **doi:** http://dx.doi.org/10.19070/2377-8075-21000270

which might be considered as normal oral microbiota and disease specific when isolated or liked to one disease [7]. The dysbiosisor loss of microbial diversity leads to the loss of beneficial microbes with simultaneous extension of pathogenic microbes. This intern leads to enhancement of carcinogenesis as hypothesized earlier [8, 9]. The three most common archetypes proposed to describe the pathogenesis involving microbiota in the development of cancer are: trigger of chronic inflammation (immune responses will promote tumor growth), alteration of atmosphere (toxic metabolites) and virus latency abrogation that lead to malignancies. [10-12]. The evidence on these 3 mechanism or any further flow of events for commonly inhibiting periodontal pathogens is not sound.

However, given the paucity of knowledge in this area considering the *T. denticola*, and periodontitis and oral cancer often occur together in geriatric patients, we had collected evidence based mechanism in this aspect. The microbe has been implicated in various mechanisms by which concern tumor progression, invasion and metastasis. The aim of this review is to update knowledge on these aspects of the microbe pertaining to novel mechanisms in OSCC. The identification of each of such mechanism may pave way to better understanding and adjunctive treatment options for management of OSCC.

Role of *T denticola* in Mechanisms of Oral Cancer/OSCC

(i) Promotion of OSCC related tumorigenesis (*in vivo* mice models). *In vitro* murine model data showed that, mice injected with pathogen-challenged OSCC cells exhibited greater tumor burden compared with the pathogen-free control counterparts. The data was from dissected tumors obtained from mice injected with oral cancer cell lines(UM-SCC-14A) challenged with control medium or media containing different concentrations of *T. denticola, P. gingivalis or F. nucleatum* [4]. This evidence shows that periodontal microbes have a direct role in carcinogenesis. However, a validation by *in viv*o studies is warranted before endorsing this association.

(ii) Promotion of OSCC cell migration: Kamarajan et al., had studied the effects of pathogenic oral bacteria, *T. denticola, P. gingivalis, and F. nucleatum*, on OSCC cell migration and invasion using a scratch migration assay and matrigel invasion assay. The T. denticolawas found to significantly increased OSCC cell migration and invasion in two different OSCC cell lines [4]. Another study had shown that *T denticola*-chymotrypsin-like proteinase (Td-CTLP) werenoted in 95% of early-stage mobile tongue SCC.The Toll-like receptors (TLRs) are pattern recognition receptors (PRRs), the role of which in development of periodontal disease and cancer pathogenesis was reported earlier [13, 14]. The TLRs and the adaptor molecule MyD88 in *T. denticola*-mediated OSCC cell migration was examined in a study. The study had reported that *T. denticola* induced (i) increased expression of integrin alpha V, (iii) phosphorylated FAK, TLR2 and 4 and MyD88, and (iii) Induced suppression of MyD88 abrogates *T. denticola*-induced migration. The stable suppression of MyD88 prevents *T. denticola*-induced FAK phosphorylation and TLR/MyD88. Also, integrin/FAK crosstalk was reported to occur leading to aggressive pathogen-enhanced OSCC phenotype formation [5]. These two evidence again supports that periodontal microbe (*T denticola*)to have a direct role in carcinogenesis.

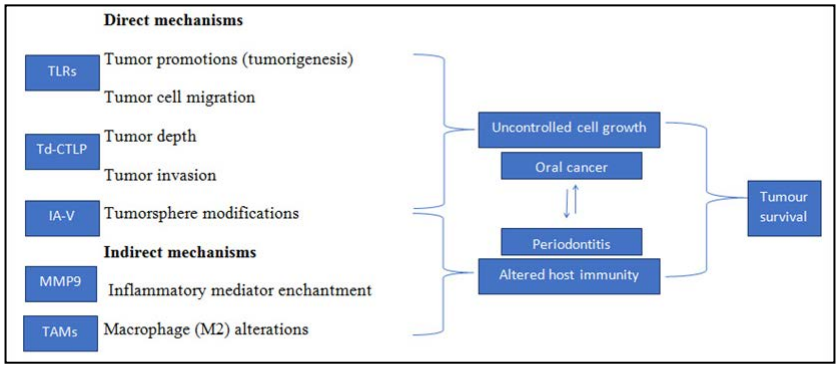
(iii) Tumor depth and invasion: The *Td*-CTLPpositivity was reported to be significantly associated with invasion depth, tumour diameter and the expression of, toll-like receptors (TLR-7, TLR-9) and c-Myc(a gene often noted in cancer progression). The higher *Td*-CTLP immunopositivity in patients below 60 years old was reported to be associated with a predicted early oral cancer relapse, which again can be postulated as direct association of periodontal microbe to cancer prognosis. The T denticola and its CTLP were shown in early-stage mobile tongue SCC(MTSCC) carcinoma and may contribute to carcinogenesis, and therefore provide novel perspectives into intervention and therapeutic measures of MTSCC [5]. The *T. denticola* virulence stems are represented by a protease complex 'dentilisin'. The dentilisin contributes to *T. denticola* adherence, followed by cytotoxic effects on epithelial cells (liked to ulceration/ breach formation), invasion or penetration of epithelial tissue and evasion of complement-mediated bactericidal activity [4, 5]. The dentilisin based effects also can be grouped as 'direct mechanism' of *T denticola* carcinogenesis.

(iv) Tumour atmosphere (tumorsphere) modifications: The three periodontal pathogens were reported to have significantly enhanced tumorsphere formation while *T. denticola* was promoting OSCC progression while *P. gingivalis* was toxic to OSCC cell growth [4]. The molecular mechanisms of *T. denticola* showed that expression of integrin alpha V (IA-V), which were upregulated upon challenge of OSCC cells with pathogenic bacteria compared to controls. This upregulation facilities the actions of enhanced tumorsphere formation and cell migration [4].

(v) Inflammatory mediators in carcinogenesis: The periodontal microbes (including *T denticola*) cause a Chronic inflammation that inturn can induce cell proliferation and the activation of signaling pathways such as (MAPK/ ERK) or can also inhibit apoptosis by modulation of the expression of Bcl- 2 family genes [15, 16]. A persistence of infection can induce DNA damage in proliferating cells through the production of toxic substances such as reactive oxygen species (ROS). Consequently, tissue regeneration results in DNA damage and permanent genomic alterations in proliferating cells [17]. The inflammatory or pro-inf-mammatory cytokines such as IL-6, IL- 8, IL-1β, and TNF-α has been demonstrated in cancers [15, 17, 18] and periodontitis [4, 6, 15]. The matrix metalloproteinase (MMP) system is responsible for degradation of tissue in both normal and pathological processes, including tumour invasion and metastasis. The presence of subgingival micro-organisms in GCF, particularly T. denticola, appeared toinduce a host response with an increased release of MMP-8 and MMP-9 in the test sites [19, 20].

(vi) Macrophage(M2) and Cell alteration: The M2 macrophages promote tumor development by producing IL- 10, IL-13 and TGF-β [18]. Besides, the proportion of M1-type macrophages and M2-type macrophages plays a critical role in the status of gingival tissue and development of periodontitis. The T denticola has direct role in modifications of tumour atmosphere and signaling for cell proliferation [5]. *T. denticola* may participate in the PMN-dependent extracellular matrix degradation during the course of periodontal inflammation by triggering the secretion and activation of matrix [20]. The role of *T denticola* is indirect but leads to periodontis and thus, alteration of macrophages. Additionally,

Figure 1. *T denticola* and oral carcinogenesis mechanisms.



Abbreviations: *IA-V, integrin alpha V; MMP9, matrix metalloproteinase -9; TAMs, tumor associated macrophages; Td-CTLP, Tdenticola-chymotrypsin-like proteinase;TLRs, Toll like receptors.*

interactions between tumor-associated macrophages (TAMs) and cancer cells play important roles in the regulation of tumor microenvironment. TAMs initiate and support tumor development via signaling molecules and pathways such as growth factors, cytokines and chemokines [21]. The M2 cell alterations and inflammatory process set out in periodontitis is indirect mechanism that have role of *T denticola*, while the rest seem to be directly involved with OSCC carcinogenesis. Figure 1

Isolation and Associations In Other Cancers and Current Evidence

The Td-CTLP were reported to be present in majority of orodigestivetumour samples. Td-CTLP was found to convert pro MMP-8 and -9 into their active forms. In addition, Td-CTLP was able to degrade the proteinase inhibitors TIMP-1, TIMP-2, and a-1-antichymotrypsin, as well as complement C1q. The orodigestivetumours which were reported to have an association of td-CTLP using immunohistochemistry included were Oral, tonsillar, oesophageal, gastric, pancreatic, and colon cancers [22, 23]. A meta-analysis suggested that different periodontal bacteria infection correlated with different incidence of cancer: Porphyromonas-gingivalis and Prevotella intermedia infection was associated with high incidence of cancer, while there is no obvious relationship between the *T denticol*a infection and incidence of cancer owing to lack of studies as opposed to P ginigvalis. The meta-analysis had cleared showed odds of having poor cancer related prognosis with *T denticola* (OR=1.30; 95% CI: 0.99–1.72) and also highlighted that improvement of oral hygiene and treatment of periodontal disease should also be taken into consideration in the prevention and treatment strategies for cancer [24].

Conclusion

The mini review has identified mechanism by which T denticola is involved with carcinogenesis or tumor progression of OSCC. The direct mechanisms promotion tumorigenesis/cell migration/tumor depth/invasion and tumorsphere modifications while inflammatory mediator enchantment and Macrophage (M2) alterations are indirect mechanisms. Further research is needed to investigate the specific microbial associations and need or role of periodontal therapy with regard to OSCC prognosis.

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