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REVIEW

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Understanding the characteristics of the host genome and microbiome interaction in oral squamous cell carcinoma: a narrative review

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Abstract

Background: Oral health status is directly associated with microbes present within it. The abundance of microbes at the OSCC site is more than at its control site, representing its possible role in the progression of OSCC development. Dysbiosis of oral microbiota could be a crucial etiological risk factor in the elevation of OSCC. This study aimed to analyze and assess: a) positive regulator microbes of oral cancer and their abundance at the cancer site, b) pathways involved in positive regulator microbes, and c) identification of the most virulent oral oncogenic microbe.

Main body: It is obtained from several studies that microbes belonging to *Prevotella, Fusobacterium, Alloprevotella, Capnocytophaga, Porphyromonas, Campylobacter, and Aggregatibacter* are detected to be more in number contrast to healthy sites. *Fusobacterium nucleatum, Porphyromonas gingivalis, and Candida albicans* show molecular pathways linked with OSCC development. Genes encoding for virulent factors like FimA, Gingipains, lipopolysaccharide (*P. gingivalis)*, FadA, Fap2 (*F. nucleatum*), and zymosan (*C. Albicans*) are directly involved in elevating oral cancer.

Conclusion: Mostly, the genes that are involved in promoting oral cancer are the genes that generally encode cell wall proteins. The cell wall proteins that is FadA, Fap, and FimA interact with the host's cell and hamper the normal regulation pathway, which leads to activation of cell proliferating pathways, down-regulates apoptotic pathways, cytoskeleton rearrangement, and upregulates the cell cycle checkpoint regulators; as a result, progression of oral cancer occurs.

Keywords: Oral microbes, Oral cancer, OSCC, Carcinogenic pathway

1 Background

The buccal cavity is the most diverse reservoir of microbes comprehending symbiotic, commensal, and pathogenic organisms. The microbes in the buccal cavity/oral cavity determine the fitness of oral health. Over time with the progress of techniques, it has been evaluated that about 600 species encompass the oral ecological community. Gerald et al. [1].

The oral cavity is predominantly enriched by Proteobacteria and Firmicutes, which is about 19.26% and 53.83%, respectively. It is espied that there is a shift of oral microbiome in preoral cancer and oral cancer patients compared with normal individuals, and microflora changes metabolic pathway to influence oral health. Zixuan et al. [2].

OSCC—Oral squamous cell carcinoma, is one of the most common types of oral cancer, approximately ninety percent of total oral cancer Tendon et al. [3]. Wang et al.

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[4] The reoccurrence rate in OSCC ranges from 32.7 to 44.9% [4]. Mathur et al. [5] consumption of alcohol, poor oral hygiene, tobacco smoking, unhealthy diet, and microbial infection are the etiological factor that boosts the risk of OSCC [5]. Some unknown etiological factors are responsible for OSCC development as it has been seen that persons who have never drank or smoked also face OSCC Kruse et al. [6]. It is obtained from the data that genes of OSCC-associated bacterium have a potential role in bacterial chemotaxis, flagellar assembly, and lipopolysaccharide (LPS) synthesis are concentrated in the tumor site [7].

Streptococcus spp. is found to be significantly less in number on the surface of oral squamous cell carcinoma-OSCC lesions. The tumor site of the oral cavity is hiked up with *Campylobacter*, *Fusobacterium, Capnocytophaga, Prevotella, and Peptostreptococcus.* Su et al. [8]. *Carnobacteriaceae*, *Actinomycetaceae, Micrococcaceae*, and *Streptococcaceae* are low in number in OSCC patients. Zhang et al. [9].

Periodontitis patients are more prone to develop oral squamous cell carcinoma. Yufei et al. [10]. Considering the carcinogenic property, a study was conducted to determine the relationship between OSCC microflora and periodontitis. The positive and negative regulator microbes of periodontitis were tested against the HSC-3 cell line. Positive regulator microbes of periodontitis express a high amount of IL-6, cyclin-D1, IL-8, and MMP-9 and show more proliferative activity than control and negative regulator microbes of periodontitis. Xiaoyu Hu et al. [11]. This review analyzes the oral microbiota of OSCC patients and the pathway associated with the OSCC advancement to establish the link between the particular positive regulator of OSCC bacteria and molecular mechanisms. These positive regulator microorganisms might be employed as biomarkers to identify and prevent OSCC in its early stages.

2 Pathway used by the positive regulator of oral cancer

2.1 *Porphyromonas gingivalis*

Porphyromonas gingivalis resides in the subgingival site and is a Gram-negative anaerobic bacteria involved in promoting anti-apoptotic pathway by increasing the expression of anti-apoptotic genes and by blocking the pro-apoptotic genes, as represented in Fig. 1. *Porphyromonas gingivalis* activates PI3/Akt pathway, which enhances cancer. Mao et al. [12].

Sandros et al. [13] Some essential virulent factors like endotoxin, gingipains, and fimbriae of *Porphyromonas gingivalis* provoke secretion of various chemokines and tumor necrosis factor-alpha (TNF-α). Yilmaz et al. [14] FimA fimbriae found on the surface of *Porphyromonas gingivalis*, which have a role in rearranging cytoskeleton by interacting with beta 1 integrin on the host cell membrane and cause invasion of the cell. Amano et al. [15] Fimbriae also cause inflammation by inducing the host cell secretion of IL-1, IL-6, IL-8, and TNF-α. Inaba et al. [16] Gingipains convert ProMMP9 to activated MMP9, and MMP9 makes carcinoma cells migrate and show invasiveness property by degrading the basement membrane.

Tang et al. [17] *Porphyromonas gingivalis* alters the pathway, which is linked with the regulation of cell cycles like cyclins, PI3K, and p53. LPS (lipopolysaccharide) of *P. gingivalis* is involved in the downregulation of p53. Groeger et al. and Kuboniwa et al. [18, 19] *Porphyromonas gingivalis* activate NF-κB and MAPK pathways which are associated with cell proliferation.

Metabolites like "Butyric acid" (Chang et al. [20]) and "Acetaldehyde" (Olsen et al. [21]) are synthesized by PG, whose effect can promote cancer by causing mutation in the nucleotides. Kurita-Ochiai et al. [22] Butyric acid also provokes apoptosis of T- cell and B-cells in the absence of P^{53}.

Gabrilovich et al. [23] Myeloid-derived suppressor cells are linked with metastasis and found abundantly at the OSCC site, inhibiting the activation of T cells. PG induces the growth of myeloid-derived suppressor cells at the OSCC site through cytokine and interleukins-mediated pathway.

Nucleoside diphosphate kinase is secreted by *P. gingivalis*, which blocks the ATP-dependent pathway via purinergic receptor $P2X_7$ [23].

Porphyromonas gingivalis adhere to the host cell membrane through integrin-mediated receptor binding. It activates Akt/ PI3K pathway and promotes the cell proliferation process. It upregulates the anti-apoptosis gene expression and down-regulates pro-apoptotic gene expression.

2.2 *Fusobacterium nucleatum*

Peyret-Lacombe et al. [24] *F. nucleatum* is a Gram-negative anaerobic bacteria involved in producing various chemokines like IL-6, IL8, IL1β, IL6, and IL1α interact with oral epithelial cell and promotes carcinogenesis by the 'START' mediated pathway as depleted in Fig. 2. START, in turn, inhibits the expression of apoptotic genes and upregulates the cell survival genes. *F. nucleatum* also interacts with toll-like receptors present on the oral epithelial cell, and its entry is straightforward for the invasion process. Like PG, *F. nucleatum* is found copiously at the OSCC site than at the control site [25].

Fardini et al. [26] With the help of FadA, the adhesion molecule, *F. nucleatum*, binds with the host cell, disrupts the host's membrane integrity by disrupting its

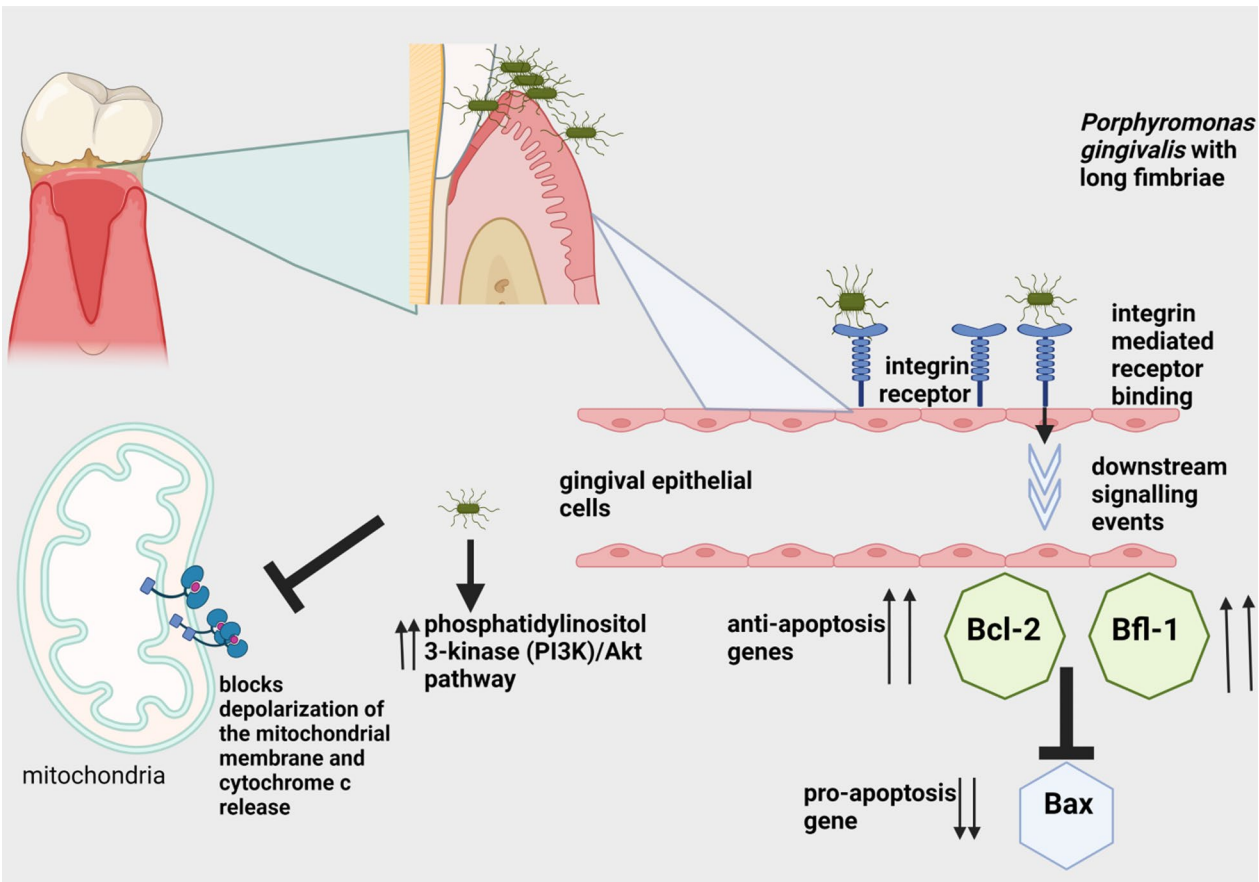

Fig. 1 *Porphyromonas gingivalis* carcinogenic signaling pathway

tight junction proteins and is also able to invade cells like colonic and placental epithelial cells, keratinocytes, T-cells and macrophages by expressing Fap2 and FadA Han et al. [27]. Abed et al. [28] *F. nucleatum* attaches to the host cell through an adhesion molecule that is Fap2, which binds with the oligonucleotide that is Gal-GalNAc of the host cell. Coppenhagen-Glazer et al. [29] Fap2 is also associated with oral biofilm formation.

F. nucleatum activates P^{38}, which activates a series of proteins like matrix metalloproteinase-9 and MMP-13 and heat shock protein-27 (HSP-27). MMP-9 and MMP-13 are observed to cause metastasis [30]. *F. nucleatum* also promotes the JNK and TLR-2 signaling pathways [31].

LPS (lipopolysaccharide) at the cell wall of *F. nucleatum* upregulates the expression of genes encoding IL-8, which in turn causes inflammation and lesion made in the gingiva cell through cytokine-mediated damaging. [32, 33].

Yost et al. [34] Fusobacterium shows high RNA expression at tumor sites than at healthy sites. Mostly virulent expressing genes transcript more at OSCC site.

BD-1-beta defensin-1and BD-2-beta defensin-2 are antimicrobial peptides generally produced by epithelial cells of salivary glands whose expression is elevated when it detects the presence of LPS and TNF-alpha. [33–35].

F. nucleatum and *Porphyromonas gingivalis* act cooperatively to skip from the host's immune system and found that *F. Nucleatum* can increase the invasive potential of *Porphyromonas gingivalis* [36, 37]. Huang et al. [38] *F. nucleatum* produces ammonia from aspartate and glutamate and makes the environment neutral, which is suitable for *P.gingivalis* colonization as *P. gingivalis* is an acid intolerant microbe.

2.3 *Candida albicans*

Candida albicans is a saprophytic fungus generally found in the oral cavity, vagina, and GI tract (gastrointestinal) [39]. The presence of Candida in the deeper site of OSCC, which is about 74%, clarifies its role in OSCC occurrence [40]. Under certain specific conditions, *Candida albicans* become pathogenic and can cause acute and chronic infection (candidiasis), especially in immunosuppressive patients [41]. According to

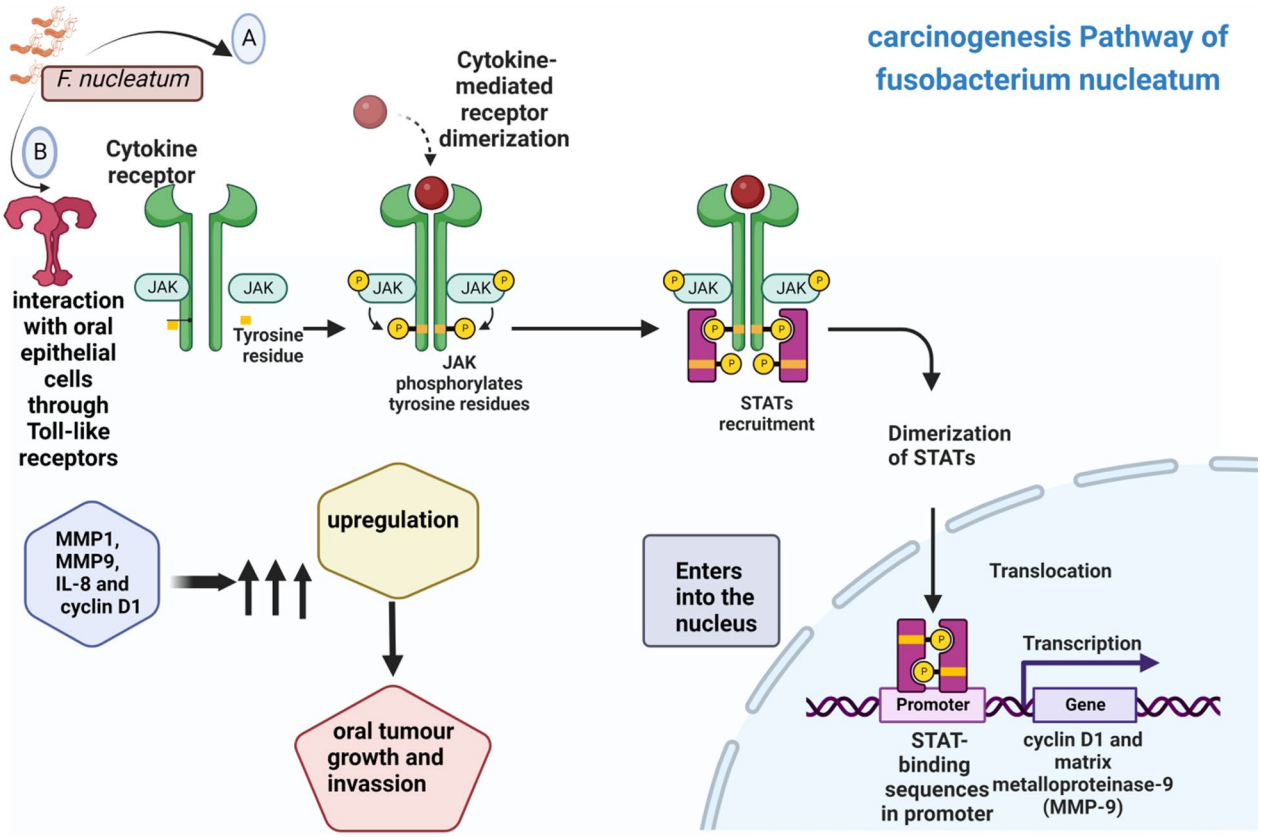

Fig. 2 Carcinogenic pathway associated with *Fusobacterium nucleatum*

Chen et al. [42] , *Candida albicans* contains zymosan in the cell wall, is glycan in nature and can be easily recognized by pattern recognition receptors. OSCC expresses TLR (mostly TLR3 and TLR4). Activation of TLR leads to activation of adaptor molecules like MyD88, which ultimately triggers the NF-κB pathway that promotes tumor progression. Abdullah et al. [43] Leukoplakic lesions, a pre-cancerous state, are caused by *Candida albicans*. The ECE1 gene of *Candida albicans* encodes candidalysin toxin and triggers NF-κB and MAPK pathways. ECE1gene expression was found to be more during macrophage attack by the host cell and escapes from macrophage attack by switching its morphological form in the phagosome [44, 45] (Fig. 3).

The ECE1 gene of *Candida albicans* encodes candidalysin protein, which is very toxic. It damages the host's cell membrane. As a result, cytokine secretion triggers APCs to differentiate and form a lesion, which ultimately turns into cancer. Candida albicans develops hyphae and secretes candidalysin when it is swallowed by macrophages, causing additional harm to the host immune cell. Candida albicans activate the NF-kB and MAPK pathways via TLR and adaptor protein activation.CA: *Candida albicans* (Table 1).

3 Positive regulators and their interaction with the host at the OSCC site

It is observed that the deeper tissue is generally sterile, and microbes colonize on the surface layer of mucosal epithelium in healthy individuals. However, microbes can evade the mucosal barrier and seem to colonize themselves on the deeper tissue under certain circumstance. [46, 47]. Aerobic bacteria, obligate anaerobic bacteria, and facultative anaerobic species are abundantly present at the OSCC site, but facultative anaerobic species are more frequently found [48].

The expression of genes regulating bacterial mobility, LPS synthesis, bacterial chemotaxis, and flagella assembly was high and played an essential role at the OSCC site (7). Moghimi et al. [49] found an up-regulation of microbial genes like bspA, fadA, *and* interpain A, which correlates with CXCL10, MMP9, NCLN, and DIAPH1 genes.

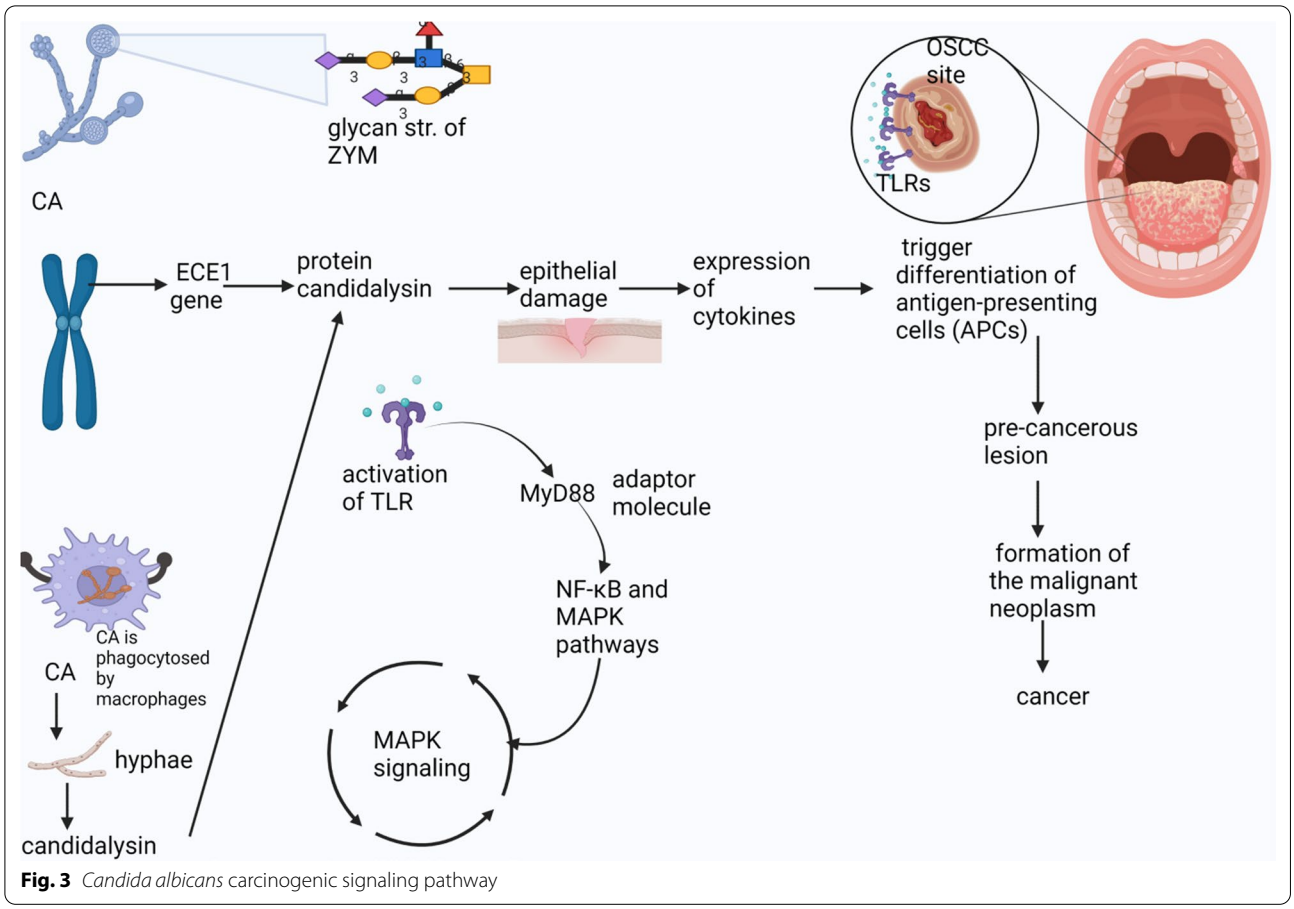

Fig. 3 *Candida albicans* carcinogenic signaling pathway

Table 1 Microbial profile at OSCC site against control site

Sl no	Microbes	Abundance in OSCC site	Abundance in a healthy site	Sample type	References
1	Prevotella	11.02%	7.92%	Bilateral buccal mucosal biopsy	Zhang et al. [9]
2	Fusobacterium	10.98%	3.27%		
3	Alloprevotella	4.79%	2.30%		
4	Porphyromonas	3.13%	1.95%		
5	Capnocytophaga	3.43%	1.58%		
6	Aggregatibacter	2.59%	0.92%		
7	Campylobacter	1.66%	0.61%		
8	Selenomonas	1.31%	0.70%		
9	Acinetobacter	12%		Biopsy	Zhang et al. [54]
10	Fusobacterium	9%			
11	Campylobacter	6%			
12	Prevotella	6%			
13	Firmicutes	85%	74.6%		Pushalkar Smruti et al. [55]
14	Parvimonas	7.5	0.6		Torralba et al. [56]
15	Veillonella	6.6	12.6		
16	Streptococcus	17.9	34.8		
17	Mogibacterium	0.6	0.2		

4 Interaction of virulent microbes at the OSCC site

P. gingivalis and *F. nucleatum* employ different invasion methods. According to studies, *P. gingivalis* enters host cells using the endocytic route and lipid rafts; likewise, *F. nucleatum* enters host cells through numerous adhesins and a "zipper" mechanism [50].

FomA of *F. nucleatum* assists in bacterial co-aggregation and biofilm formation and is advantageous for bacterial invasion into host cells. It binds to the Fc portion of human IgG [51]. *F. nucleatum* assists *P. gingivalis* in invading host cells [52].

However, on the other hand, it has been found that *P. gingivalis* prevented *F. nucleatum* from invading oral epithelial cells by decreasing the production of the adhesion-related proteins FadA and FomA by secreting proteases [50].

Although *P. gingivalis* inhibits the invasion process of *F. nucleatum*, those bacterial mixtures abundantly found at the OSCC site are now a question of research. It may be due to the involvement of a particular strain of *P. gingivalis* that inhibit the *F. nucleatum* invasion process. More research is needed focusing on those areas.

A study report observed that *C. albicans* SN152's hyphal development is inhibited by *F. nucleatum* ATCC 23,726 in a contact-dependent manner [53]. Whether all strains of *C. albicans* inhibit *F. nucleatum* or not, which particular strain of *Candida albicans* is involved in promoting oral cancer needs to be studied. These are the research gap that needs to be focused on in future research.

5 Conclusion

Although many microbes are found to be more at the OSCC site than the control site, few positive regulator microbes like *Porphyromonas gingivalis*, *Candida albicans*, and *Fusobacterium nucleatum* are associated with host cell membrane damage and tissue invasion, which activates signaling pathways like MAPK and PI3K. Among these microbes, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* are found to be more virulent oncogenic bacteria. Moreover, the interrelation between these microbes of different strains needs to be screened. The virulent strains of these microbes may lead to dysplasia of the oral cavity, which might further lead to various inflammatory pathways and later develops into cancer. Positive regulator microbes of OSCC activate pathways associated with cell growth, proliferation, survival, differentiation, and motility, increasing the risk of OSCC. These microbes suppress the pro-apoptotic gene expression and upregulate the anti-apoptotic gene expression; as a result, the survival chance of cells increases. The drug can be developed as a future therapeutic intervention strategy by targeting virulent expressing genes responsible for promoting cancer. The validation of the OSCC-associated microbiota as a biomarker might have significant implications for future oral cancer screening, early detection and treatment.

Abbreviations

OSCC: Oral squamous cell carcinoma; LPS: Lipopolysaccharide; IL: Interleukin; MMP 9: Matrix metallopeptidase 9; CXCL10: C-X-C Motif chemokine ligand 10; TNF: Tumor necrosis factor.

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Author contributions

The concept was given by RB. She also examined and revised the paper. SL conducted the literature review and wrote the manuscript. SB guided in making diagrams. All authors read and approved the final manuscript.

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Availability of Data and Material

All the data were collected from Scopus, google scholar and PubMed for this study.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Competing interests

The authors declare that they have no Competing interests.

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