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Research Progress on Oral Microbiota and Oral Cancer

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Abstract: With the development of technology, although it has become easier to detect and treat oral cancer, it still causes significant harm to people's lives. Therefore, it is urgent for researchers to clarify the mechanisms behind oral cancer and identify early detection signatures. Previous research has shown a connection between bacteria and the occurrence of cancer detected in other human organs, such as the intestinal tract and stomach. Subsequently, the potential principles of how oral bacteria increase the happening of oral cancer has attracted considerable interest from researchers. This article briefly introduces different signatures of oral bacteria in various human body conditions, such as variations in distribution and composition. Additionally, this passage summarizes the latest research results about the relationship between bacteria and the occurrence of oral cancer.

Keywords: oral bacteria, oral squamous cell carcinoma, OSCC

1. Introduction

About 30 trillion bacteria live inside or on the surface of each human body, which equals to approximately one bacterium for each cell. These bacteria constitute a complex and delicate ecosystem that fluctuates within the dynamic microenvironment, maintaining a symbiotic relationship with the human host. Human beings' normal functions, such as digestion and immune response, cannot be maintained without bacteria. Furthermore, certain signatures presented by bacteria, such as composition and distribution, change as cancer progresses. Bacteria's number in the mouth is small, accounting for just 1%, as previous reports have indicated; however, their concentrations should not be neglected (109 bacteria per mL in saliva and 10^11 bacteria per mL in dental plaque) [1,2]. Moreover, the diversion of oral bacteria ranks second in the human body, just behind the intestines, with around 700 species observed. A balance in oral bacteria contributes to physiological, metabolic, and immunological functions that help maintain homeostasis through the formation of a mucosal barrier. Recently, alterations in oral bacteria have been detected in many illnesses. It has been reported that the occurrence of oral squamous cell carcinoma (OSCC) is significantly associated with oral bacteria. As for malignant tumor in oral cavity, OSCC ranks the most, representing 2% of all tumors worldwide [3,4]. However, it is still unclear exactly how oral bacteria lead to the occurrence of OSCC, and further study and research are needed. This article focuses on the signatures of oral bacteria, including the distribution and composition of bacteria in healthy individuals, those with pre-existing lesions, and those diagnosed with OSCC. Current hypotheses regarding the effect of oral bacteria to the occurrence of OSCC are discussed, containing the stimulation of excessive inflammatory reactions, inhibition of apoptosis, promotion of tumor cell

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invasion, and emission of carcinogenic substances. Additionally, the related mechanisms are introduced and explained.

2. Healthy Oral Bacteria

Bacteria migrate to the oral cavity at a very early stage. With various species of bacteria living in such a small space, the environment of the oral cavity is quite complicated. Early in the fetal period, bacteria are transferred between the mother and infant at the foeto-maternal interface. Bacteria in the human body develop and gradually distribute to different parts after birth. The oral cavity creates a perfect living condition for bacteria, which has a moderate pH of 6.5–7 and an average temperature of 37°C. Various places in oral cavity all provide suitable conditions for bacteria to grow. Particularly, the extracellular polymeric matrix (EPM), known as biofilm in the oral cavity, is composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA). Up to 95% of bacteria live in biofilms, creating a highly active and complex ecosystem. Because the oral cavity has continuous exposure to the external environment, these bacteria change dynamically. However, most of the time, the bacterial composition is stable, with only slight fluctuations [4]. According to previous reports, the most common bacterial species include Streptococcus, Gemella, Eubacterium, Selenomonas, Veillonella, Actinomyces, Atopobium, Rothia, Neisseria, Eikenella, Campylobacter, Porphyromonas, Prevotella, Granulicatella, Capnocytophaga, Fusobacterium, Leptotrichia, and Streptococcus mitis [5]. These can be classified into six main phyla: Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, and Spirochaetes [4]. Due to different structures and environments, bacterial categories and concentrations vary across multiple oral sites. Additionally, the distribution and composition of bacteria also have association with factors such as physiological conditions, geographical location, and racial characteristics [2]. These complex ecosystems play important roles in normal human activities. For example, these bacteria work harmoniously to ensure that human body could steadily assimilate nutrients such as sugars and protein. Glycosidic enzymes are indispensable parts in these processes, which are produced by bacteria, such as sialidase, N-acetylglucosaminidases, β-galactosidase, mannosidases, α-fucosidase, exo-proteolytic, and endo-proteolytic activities [6]. These bacteria also help keep oral state of cleanness by reducing pathogens' adherence to the mucosal surface. This role is facilitated by bacteria emitting Immunoglobulin A (IgA), the dominant class of antibodies in the gastrointestinal mucosa, which is a key component of the gastrointestinal barrier [7].

3. The Oral Bacteria and Oral Cancer

The composition and distribution of oral bacteria vary significantly as people's health conditions change (Table 1). When internal or external factors cause the imbalance of bacteria in the oral cavity, dysbiosis occurs. According to previous research, these abnormalities are directly linked to OSCC. Oral leukoplakia, which shows symptoms of having a white spot on the oral mucosa, is regarded as the most common pre-existing lesion with malignant potential for OSCC. AMER A et al. compared the bacterial composition between oral leukoplakia tissue and healthy mucosal tissue from the same patient to identify early markers of malignant progression. The results show that, compared with contralateral normal sites, leukoplakia samples have higher levels of Proteobacteria and Fusobacteria and lower levels of Firmicutes. Additionally, nearly 35% of samples from leukoplakia sites are colonized by Candida spp. [8]. Lee et al. studied bacterial differences between normal individuals, patients with epithelial precursor lesions, and cancer patients. Results show that the dominant bacterial species belonged to one of five phyla: Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria. These phyla were present consistently in all individuals. However, the abundance of Megasphaera, Escherichia, and Atopobium differed among three groups mentioned

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above. Contrasted with the normal group, the abundance of Blautia, Dorea, Faecalibacterium, and Phascolarctobacterium increased in the epithelial precursor lesion group. Additionally, there was a huge increase in the abundance of Bacteroides, Escherichia, Cloacibacillus, Gemmiger, Oscillospira, and Roseburia in samples having epithelial precursor lesion and cancer [9]. Cancer progression has been divided into four phases based on the degree of severity. Yang et al. compared samples from individuals in healthy conditions and patients in different phases of OSCC. They found that the quantity of Fusobacteria increased largely as oral cancer progressed from the healthy controls (2.98%) to OSCC stage 1 (4.35%) and stage 4 (7.92%). At the genus level, Fusobacterium periodonticum, Parvimonas, Streptococcus constellatus, Haemophilus influenzae, and Filifactor alocis have connection with OSCC, and their quantities gradually increased from phase 1 to phase 4. However, the quantities of Streptococcus mitis, Haemophilus parainfluenzae, and Porphyromonas pasteri show inverse relationship with the development of OSCC [10].

Table 1: Variations of Predominant Bacteria Found in Oral Cancer.

Name	Absolute Quantitative Variations in Oral Cancer	Name	Absolute Quantitative Variations in Oral Cancer
Bacteroides	Elevated	Escherichia	Elevated
Cloacibacillus	Elevated	Gemmiger	Elevated
Oscillospira	Elevated	Roseburia	Elevated
Fusobacterium periodonticum	Elevated	Parvimonas	Elevated
Streptococcus constellatus	Elevated	Haemophilus parainfluenzae	Reduced
Filifactor alocis	Elevated	Streptococcus mitis	Reduced
Haemophilus influenza	Elevated	Porphyromonas pasteri	Reduced

4. Mechanism

The mechanism by which bacterial dysbiosis induces the development of OSCC has been studied for a long time. During bacterial dysbiosis, substances from the bacteria themselves or emitted by the bacteria can stimulate diverse responses in the host, which may lead to OSCC (Table 2).

4.1. Excessive Inflammation

Angiogenesis, tumor progression, and metastasis are all linked to inflammation caused by infection. Oral dysbiosis may facilitate the development of both local and systemic inflammation, which can be exacerbated by inflammation, thus resulting in a vicious cycle. Flagella on the surface of bacteria and cytotoxins (e.g., ExoU) are strongly associated with OSCC-related inflammation. Bacterial endotoxins released by gram-negative bacteria can activate pattern recognition receptors (PRRs) such as TLRs (particularly TLR4). These can activate signaling pathways which cause inflammation such as nuclear factor kappa B (NF-kB), Wnt, and JAK-STAT3 cascades, which extend the influence of bacteria on cancer development. The inflammatory response also involves various cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and matrix metalloproteinases MMP-9. Among these, IL-1β has attracted significant attention. IL-1β can cause inflammation by activating

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osteoclast formation and activating endothelial cells to excrete vascular endothelial growth factor (VEGF) and other proangiogenic factors (e.g., TNF). IL-1β also acts as a promoter of inflammation due to its ability to release TNF and IL-6. IL-6 leads bone to resorb and causes generations of acute-phase proteins, chemokines, and PGE2. IL-6 could cause oxidative stress and significant H2O2 accumulation in mitochondria, causing mitochondrial trauma. Mitochondria are indispensable organelles for most eukaryotic cells, and the mitochondrial genome has high relevance with carcinogenesis and cancer metastasis. Increased contents of reactive oxygen species (ROS) and stabilization of hypoxia-inducible factor-1 (HIF-1) are associated with mutations in the mitochondrial genome. These variations in both coding and noncoding areas, could accelerate tumorigenicity, cell motility, and metastasis. Low concentrations of bacteria-induced TNF-α have been reported to be associated with tumor promotion. TNF-α is a key cytokine in the process of generating reactive oxygen species (ROS), leukotrienes, prostaglandins, and metalloproteinases, which can damage DNA and have been shown to be linked to cancer progression. Additionally, osteogenic cells and fibroblasts significantly decrease, primarily due to TNF-α [11–13].

4.2. Inhibition of Apoptosis

Cancer cells' ability to inhibit apoptosis can lead to long-term proliferation and chemoresistance. Porphyromonas gingivalis (P. gingivalis) has been shown to participate in inhibiting apoptosis in host cells and then lead to the occurrence of cancer. Research suggests that P. gingivalis might exert its effect by stimulating the JAK1/STAT3 and PI3K/Akt signaling pathways in epithelial cells. These pathways regulate intrinsic mitochondrial apoptosis processes [14]. Jungnam Lee et al. found that a homologue of the conserved nucleoside-diphosphate kinase (Ndk) family of multifunctional enzymes, secreted by P. gingivalis, can regulate specific host molecular pathways, then bring variations such as less synthesis of reactive oxygen species (ROS). Lower concentration of ROS could enable bacterial survive in human gingival epithelial cells (GECs). By comparing P. gingivalis-Ndk protein constructs with an isogenic P. gingivalis-Ndk-deficient mutant strain, they observed that P. gingivalis-infected GECs show rising levels of phospho-heat-shock protein 27 (HSP27) compared with the Ndk-deficient strain. Thus, they concluded that P. gingivalis inhibits host cell apoptosis by HSP27 [15].

4.3. Promotion of Tumor Cell Invasion

Tumor cells can also activate key pathways to release substances that damage human tissue, thereby facilitating invasion. Suchitra Singh et al. found that P. gingivalis can promote tumor cell invasion. Their results show that pathways such as ERK 1/2–Ets1, p38/HSP27, and PAR2/NF-κB are stimulated after P. gingivalis' infection. The extracellular signal-regulated kinase 1/2 (ERK1/2) pathway has been shown to be associated with tumors. It can elevate the invasive and metastatic capabilities of cancer cells, equip cancer cells with the ability to resist chemotherapy and radiation, and regulate tumorigenic potential by maintaining cancer stem cells. E26 transformation-specific (Ets) transcription family members take part in various biological processes, including tumor-causing transformation, angiogenesis, differentiation, and apoptosis. Ets1 can be activated by Ets transcription factors, which are downstream of ERK1/2. P38 is a multifunctional kinase that regulates various cellular functions. It has effect in cell proliferation, differentiation, stress response, apoptosis, and cell migration and survival. It has been shown to be associated with tumor occurrence. Protease-activated receptor 2 (PAR2) is a G protein-coupled receptor (GPCR) that is primarily activated by trypsin-like serine proteases to start signal transduction pathways (Ca2+ release, ERK1/2 phosphorylation, RhoA activation, cAMP down-regulation, and β-arrestin1/2 recruitment), which mediate both physiological and pathological processes, such as cancer. The activation of these pathways leads to the generation of matrix metalloproteinases (MMP-9). P. gingivalis also synthesis

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gingipains and cysteine proteinases, which can degrade the basement membrane and extracellular matrix, allowing tumor cells to enter the systema lymphaticum and blood vessels. In this way, it enables tumor cells to spread further, accelerating cancer progression [16,17].

4.4. Production of Carcinogenic Substances

Additionally, bacteria can generate other substances with carcinogenic effects. Bacteria such as Lactobacillus, Lactococcus, Bifidobacterium, Streptococcus, Leuconostoc, and Pediococcus can produce lactic acid. Lactic acid, such as lactate, is associated with cancer development, maintenance, and metastasis. Tumor cells can utilize lactate as an energy source and transport it to nearby cancer cells, close stroma, and vascular endothelial cells, which induces reprogramming in metabolism. High concentrations of lactic acid in the tumor microenvironment can also block lactate export in T cells, thereby destroying their proper physiologic function. Mark R. Hellmich et al. found that there is an obvious increasing expression of various hydrogen sulfide (H2S)-producing enzymes in cancer cells no matter the type of tissue. H2S can enhance tumor development and diffusion by boosting cellular bioenergetics, activating pathways in proliferation, migration, and invasion, and strengthen tumor angiogenesis [13].

Table 2: Pathways and Substances Mentioned in Different Hypotheses.

Hypothesis	Pathway	Substance
Excessive Inflammation	Nuclear factor-κB (NF-κB) Wnt JAK-STAT3	flagella cytotoxins (ExoU) endotoxins IL-1β, IL-6 tumor necrosis factor-α (TNF-α) matrix metalloproteinases MMP-9 vascular endothelial growth factor (VEGF) proangiogenic factors (TNF) acute phase proteins chemokines PGE2 H2O2 oxygen compounds (ROS) leukotrienes prostaglandins metalloproteinases
Inhibition of Apoptosis	JAK1/STAT3 PI3K/Akt	phospho-heat-shock protein 27 (HSP27)
Promotion of Tumor Cells' Invasion	ERK 1/2-Ets 1 p38/HSP27 PAR2/NF-KB	Ets 1 p38 protease-activated receptor 2 (PAR2) matrix metalloproteinases MMP-9 gingipains cysteine proteinases
Production of Carcinogenic Substances		lactic acid (lactate) H2S

5. Conclusion

Bacteria are indispensable to human beings. Under healthy conditions, bacteria participate in many physiological activities of the human body. The composition and distribution change when the balance is disrupted in the oral cavity. Bacterial variations in the oral cavity have obvious effect in the occurrence of OSCC. It is hypothesized that this leads to cancer through four mechanisms: (1) excessive inflammation; (2) inhibition of apoptosis; (3) promotion of tumor cell invasion; and (4) production of carcinogenic substances. However, further research is needed to determine the exact mechanisms behind the occurrence of OSCC.

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