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Oral Bacteria: Key Organism in Oral Cavity

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Abstract:

This paper discusses key factors in oral bacteria that enable oral bacteria to thrive within the oral cavity. The oral cavity provides an ideal environment for bacterial survival, and bacteria possess various techniques and mechanisms to enhance their persistence. These mechanisms can overwhelm the human immune system, making it challenging for the body to handle bacterial infections effectively. One key factor in bacterial infection is the adhesive properties of bacteria, facilitated by specialized adhesins that target salivary and epithelial proteins, leading to the formation of biofilms, such as dental plaque. Dental plaque is a combination of polymers from both bacterial and salivary sources. Additionally, bacteria require Quorum sensing to communicate among microbial cells, further promoting biofilm production. Biofilms present a formidable challenge as they offer multiple strategies to evade the host's defense mechanisms. Bacteria possess superior organelles that aid in survival, including fimbriae for attachment, endotoxin in the cell wall to enhance resistance to stress and host defenses, and capsules that reduce cell recognition by the immune system. The impact of oral bacteria on patients can range from mild to severe, with some cases being extremely dangerous and potentially lethal, often becoming untreatable when detected too late. Oral bacteria can disseminate to various anatomical systems through open pathways, ultimately leading to systemic diseases such as cardiovascular disease, pneumonia, and diabetes. Therefore, active oral health care is needed in order to maintain a healthy condition throughout life to ensure that oral bacteria do not become a threat to our overall well-being.

Keywords **—adhesin, biofilm, dental plaque, immune system, systemic diseases**

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INTRODUCTION

Bacteria play a significant role in oral health, contributing to Dental caries, Tartar, Gingivitis, and periodontitis due to inadequate dental hygiene. These microorganisms exhibit diverse characteristics, including the capacity to form intricate multi-dimensional structures known as biofilms, facilitating communication, and establishing bacterial communities. Varying bacterial species can exert different effects, with some being highly pathogenic, while others cause milder consequences.

Oral bacteria thrive within different regions of the oral cavity, including the cheeks, tongue surface, palate, tonsils,and gums. The oral environment provides an ideal habitat for unicellular microorganisms due to its consistent moisture, relatively neutral pH, and moderate temperature.Recognizing the significant role of bacteria in causing oral diseases emphasizes the importance of adopting good oral hygiene practices and daily care for teeth and mouth. An understanding of the pathology and biological attributes of bacteria that can harm our teeth prevents not only conditions like Tartar, tooth decay, and gum disease but also more serious systemic diseases.

I. ORAL BACTERIA COLONIZATION

A. Oral environment

Oral anatomy

The oral is the most frequently used part of the human body and performs many functions that are essential for the human body. It is related to the processing and digestion of food as its primary role, while its secondary functions encompass speech, respiration, aesthetics, and facial expression. Oral anatomy roughly confines the oral cavity and Perioral structure, including the face, neck, and head [1]. The oral cavity consists of two primary components:

1. Vestibule
2. The oral cavity proper.

The vestibule is a space surrounded by lips and cheeks on the external and the gums and teeth on the inside. It is kept moist from the secretion from the salivary glands. The vestibule communicates with the body through the oral sphincter and with the oral cavity proper on another side through a narrow space at the back of wisdom teeth when the mouth is closed. The oral cavity proper is the area that encompasses the upper and lower dental arches.

The oral cavity appropriately encircles the alveoli carrying the teeth. It communicates with the pharynx through a narrow intel. Its roof is constructed by the soft and hard palates, and the floor is established by the tongue. The oral cavity and Perioral structure can be categorized into two primary components:

1. Hard tissue
2. Soft tissue.

The hard tissue encompasses two sections: perioral bones and dentition. The perioral bones comprise the mandible, maxilla, and the other cranial components. The mandible serves as the lower jaw, being a movable, robust bone articulating with the rest of the skull through joints on either side. However, the maxilla, known as the upper jaw, remains immobile. The skull bones included bones of the facial skeleton and the cranium or bones surrounding and protecting the brain. The alveolus/alveolar process refers to the portion of the maxilla and mandible that supports the teeth. Dentition is the natural teeth in the jaw bones and its function is to assist in digestion in the mouth by breaking down a large portion of food into smaller fragments. It consists of three different types:

1. Primary dentition is the initial set of teeth that emerge in the oral cavity. Primary dentition included 20 in total and it is commonly known as ‘baby teeth’ or ‘deciduous teeth.

2. Permanent teeth are the subsequent set of teeth that emerge after Primary teeth have been shed. There are 32 Permanent teeth and it is called ‘adult teeth’ or ‘secondary teeth’.

3. Mixed dentition occurs when both primary and permanent teeth coexist, typically taking place between the age of 6 and 12 years.

Teeth have variations in size, location, and shape.

1. Incisors are front. Single-rooted teeth with sharp and thin edges were designed to cut food. There are 4 incisors.

2. Canines are corner teeth. They are 2 types collectively:

Firstly, Premolar is the teeth that have cusps that hold and grind food. The premolar is only included in the Permanent teeth set, Primary teeth don’t have a premolar.

Secondly, Molars are larger teeth with more cusps to help with chewing and grinding food. In each arch, there are four molar teeth and six molars in Permanent teeth.

The soft tissue of the oral cavity wraps the skeletal components, compressing with lips, cheeks, gums, tongue, salivary gland, and soft palate.

1. Lips are two pliable, perioral structures situated in both the upper and lower regions of the mouth, which encircle the oral opening and regulate mouth closure and opening. Lips contain muscle, blood vessels, nerves, areolar tissue, fat, and numerous of minor salivary glands. Lips also play a significant role in deglutition and speech.

2. Salivary glands are exocrine organs responsible for secreting saliva, aiding in the digestive process. There are three major pairs of salivary glands located in distinct areas of the oral cavity. Saliva is responsible for maintaining continual moisture within the oral cavity

3. Tongue is one of the sensory organs placed on the floor of the mouth, features numerous small papillae housing taste buds. The tongue is the principal organ responsible for taste perception and is also vital for speech, mastication, and the swallowing of food and beverages.

4. Cheeks are sheet-like structures that form the lateral aspects of the face and are combined with the lips anteriorly. Cheeks consist of muscle, fat, areolar tissue, blood vessels, and nerves and cover-up by the skin.

5. Gums are tissue that covers the alveolar processes and are enclosed by dense fibrous tissue. The gums are covered by a firm mucous membrane.

6. The palate comprises the anatomical structure forming the roof of the mouth and is divided into a hard and soft palate.

The hard palate is a bony vault of the oral cavity, bordered anteriorly and laterally by the alveolar arches. It is lined by a firm mucous membrane derived from the palatal periosteum and features a few corrugations known as rugae.

The soft palate is a mobile, soft tissue suspended from the posterior edge of the hard palate, creating an incomplete separation between the oral cavity and the pharynx.

B. Distribution of Oral Bacteria

Colonization of the host after transmission and access is crucial for the persistence of oral bacteria [2]. At the core of their survival in an open system like the oral cavity rely on the formation of dental biofilms on tooth surfaces. The plaque biofilm not only assist in retaining oral microorganisms but also provide protective functions. The biofilm can shield individual cells from harmful agents, and cells within a biofilm may exhibit distinct phenotypic traits that enhance their survival. Bacteria in dental plaque experience a wide range of known stresses and possibly some yet unidentified. However, other stresses are important to the persistence of an organism in dental plaque. For example, dental biofilms serve as a habitat for a diverse bacterial community, where the survival of a particular species or genetic strain hinges on its ability to compete with other populations, adapt its physiology, or maintain intrinsic resistance to environmental changes. Clearly, stages such as transmission, access, incorporation into, and the capacity to flourish within the biofilm of a host are all integral to the survival of an oral microorganism. The ability of bacteria to adhere to surfaces is a common strategy for thriving in natural habitats and represents an early phase in biofilm (dental plaque) development on teeth. Similar to organisms in other natural settings and medicine, oral bacteria possess surface molecules and appendages, acting as adhesins that recognize specific receptors on mucosal cells, other bacteria, and conditioning films on solid surfaces [3].

C. How Bacteria Grow in Our Mouth

Oral colonizing microorganisms exhibit remarkable adaptation to the diverse environmental niches within the oral cavity. Whether they contribute to one of the major oral diseases such as dental caries, pulp infections, or gingival/periodontal diseases, or reside as part of a commensal community, their capacity to thrive is paramount. Key to these infections is the ability to adhere to surfaces through an array of specialized adhesins that target salivary and epithelial proteins, glycans, and the formation of biofilms [4]. They must also withstand various physical stressors, including challenges posed by pH levels and oxidative stress. Possibly most strikingly, they have developed the ability to harvest both nutrient sources provided by both dietary intake and host-derived substances, such as proteins and surface glycans.

These bacteria feed on the sugars present in our food and beverages, leaving behind byproducts or dental plaque. Among the bacteria attracted to sugars, some convert them into acids, which can

contribute to surface tooth decay and subsequent plaque formation [5-6].

D. Adherent in Oral

Oral bacteria forms biofilms on implanted medical devices through a range of cell-surface proteins. There is evidence suggested that specific homophilic interactions mediated by these proteins play a significant role in cell aggregation during biofilm formation, yet the precise molecular mechanisms remain incompletely understood [7-8].

Out of the various microorganisms that make up biofilm, bacteria are by far the most prevalent. In fact, it is estimated that around 1,000 distinct species of bacteria reside in biofilm(plaque), making up around 70% of its dry weight [9].

E. Dental Plaque Formation

Dental plaque, an intricate biofilm that forms on the hard tissue within the oral cavity, is the result of a highly organized colonization process [10]. This process involves the initial adhesion of colonizing microorganisms to the enamel salivary pellicle, followed by secondary colonization through interbacterial adhesion. The development of plaque and its association with diseases like caries and periodontal disease are influenced by a variety of adhesins and molecular interactions.

Saliva plays a role as a medium in maintaining planktonic suspension. It serves multiple critical functions in relation to oral biofilm, acting as a medium for transporting planktonic bacteria within and between oral cavities [11]. During this transit, bacteria may face selective pressures. Salivary agglutinins can deter reattachment to surfaces, while antimicrobial proteins may lead to the attachment of dead cells. Salivary proteins form conditioning films on all oral surfaces, creating favorable conditions for microbial adherence. Saliva also contains chemical messengers that enable adherent cells to sense a critical density of conspecifics, triggering growth, and the formation of robust biofilms that can resist antimicrobial substances. Additionally, salivary macromolecules may undergo catabolism, and salivary flow can clear dietary substrates.

Bacteria employ intricate chemical signal systems that enable them to communicate within and between species[12]. One universal signal, referred to as AI-2, facilitates interspecies communication and exerts control over various processes, including the production of virulence factors, biofilm formation, and motility.

This signal system can lead to coordinated behaviors, which are categorized as Quorum Sensing (QS) [13]. QS is a process in which bacteria monitor their cell-population density by measuring the concentration of small secreted signal molecules known as autoinducers. As a population of quorum-sensing bacteria grows, individual organisms produce and secrete autoinducers into the extracellular environment. Consequently, the concentration of external autoinducers correlates with cell-population density. By monitoring this extracellular autoinducer concentration, bacteria can effectively assess their numbers and adjust the expression of target genes accordingly. QS has been demonstrated to play a pivotal role in bacterial pathogenesis by regulating the expression of various virulence factors that impact processes such as adhesion, invasion, and survival within tissues.

Bacteria possess the capacity to produce a wide variety of polymers, each serving a range of essential biological functions, including acting as reserve materials, forming protective capsules and slimes, and comprising components of the biofilm matrix[14].

II. ORAL BACTERIOME

A. Biodiversity in Oral Health

The compartmentalization involved in viewing the mouth separately from the rest of the body must cease, as oral health significantly impacts general health. It brings about substantial pain, suffering, dietary alterations, speech impediments, and influences one's overall quality of life and well-being [15]. Furthermore, it has repercussions on various chronic conditions. Physically and psychologically, oral health shapes an individual's

growth, life enjoyment, appearance, speech, mastication, taste perception, and social interactions, as well as their overall social well-being.

The oral microbiome represents a significant component of the human microbiome. Within the oral cavity, distinct niches with diverse microbial communities are observed. This encompasses a wide spectrum of microorganisms, encompassing bacteria, fungi, viruses, archaea, and protozoa, forming a complex ecological community that exerts influence on both oral and systemic health. Prevalent oral diseases, such as dental caries and periodontal diseases, are closely associated with microbiota [16]. In addition, mounting evidence supports the connection between disturbances in the oral ecosystem and systemic diseases like diabetes, cardiovascular conditions, and tumors.

The oral cavity boasts the second most complex microbiota in the human body, second only to the colon. The oral microbiome exhibits remarkable diversity, including bacteria, fungi, viruses, archaea, and protozoa. Approximately 700 species inhabit the oral cavity, with the majority being indigenous. Of these, roughly 54% have been cultured and named, 14% are cultivated but remain unnamed, and 32% are known solely as uncultivated phylotypes.

The oral ecosystem is intricate due to the presence of markedly distinct niches, including saliva, the soft tissues of the oral mucosa and tongue, and the hard tissues of teeth [17]. These diverse surfaces attract unique microbial communities, as each niche provides specific conditions and nutrients for the thriving microorganisms. Consequently, microbiomes from the same site among different individuals exhibit greater similarities than those from disparate sites.

Infections affecting the oral cavity can result from a variety of pathogens, encompassing bacteria, viruses, and fungi. While many of these infections remain localized, some have the potential to disseminate and evolve into systemic infection. Some of which are shown in Table 1.

Diseases	**Oral diseases**		
	Pathogen	**Sign of symptoms**	**transmission**
Dental caries	*Streptococcu smutans*	Discoloration, softening, and cavities in teeth	Non-transmissible ; Caused by bacteria of the normal oral microbiota
Gingivitis and periodontitis	*Porphyroma, streptococcu s, Actinomyces*	Inflammation and erosion of gums, bleeding, and halitosis lead to tooth loss in severe infections	Non-transmissible Caused by bacteria of the normal microbiota
Herpetic gingivostom atitis	Herpes simplex virus type I (HSV-1)	Lesions in mucous membranes of the mouth	Contact with saliva or direct contact with lesions of an infected individual
Mumps	Mumps virus (paramyxovir us)	Swollen of parotid glands, fever, headache, muscle pain, in more severe condition, encephalitis, meningitis	Contact with saliva or respiratory droplets of an infected individual
Oral thrush	*Candida albicans, Candida spp.*	White patches and pseudomembran es in the oral cavity, lead to bleeding	Non-transmissible Caused by overgrowth of Candida spp. in normal oral microbiota
Trench mouth	*Prevotella intermedia Fusobacteriu m species, Treponema vincenti, etc*	Erosion of gums, ulcers, substantial pain while chewing, halitosis	Non-transmissible Caused by members of the normal oral microbiota

Table 1. Example of oral diseases

B. New Technology to Find Bacteriome

The study of the oral microbiota requires culture-independent techniques, due to the fact that approximately one-third of the 700 bacterial species recognized in the human oral cavity have not been successfully grown in a laboratory setting. These techniques often involve the amplification of PCR and the high-throughput sequencing of the 16S ribosomal RNA genes (16S-HTS) or the metagenomic whole genome shotgun (WGS) sequencing [18]. After collecting samples, one method for identifying the taxonomy of bacteria and archaea involves amplifying and sequencing the 16S ribosomal RNA gene. This entails using culture-independent, high-throughput sequencing of

short genetic hypervariable regions, as exemplified by 454 pyrosequencing.

C. Bacteriome in Periodontal Diseases

Periodontal disease is a chronic disease in many of its forms, If, over the course of 20 years, the alveolar bone supporting a tooth root, measuring approximately 20 mm in length, were to deteriorate, the rate of bone loss would, on average, be around 1 mm per year, or less than one-tenth of a millimeter per month. It is improbable that this destruction would occur at a consistent rate; instead, it's likely that there would be periods of exacerbation and remission. The gradual pace of periodontal deterioration and the challenges in discerning its activity serve to complicate the elucidation of the factors driving this disease [19]. The oral cavity, akin to all external surfaces of the body and the gastrointestinal tract, hosts a substantial microflora that exists in symbiosis with a healthy host. The oral microflora includes hundreds of aerobic and anaerobic bacterial species. These organisms form intricate, mixed, interdependent colonies within biofilms on tooth surfaces (plaque). They are attached densely to the tooth's deeper layers, with more motile forms residing in the superficial layers. As dental plaque progresses towards a state associated with periodontal disease, the number of gram-negative and anaerobic bacteria increases. Encouragingly, substantial efforts have been invested in exploring the microflora associated with periodontal disease, employing various methodologies ranging from traditional culture-based techniques to contemporary approaches at the molecular, whole-genomic, and proteomic levels. Distinct clusters of bacterial species consistently coexist in subgingival locations, demonstrating consistent associations with disease. Infections within periodontal tissues by these and other microorganisms lead to the release of bacterial leucotoxins, collagenases, fibrinolysins, and other proteases. *Actinobacillus actinomycetemcomitans* is another species frequently linked to disease, particularly in young adults. Recently, *Candida albicans* and other fungi is likely to be a contributors to periodontal condition in immunocompromised individual.

III. ORAL BIOFILM

A. What is Biofilm

Biofilms can be defined as communities of microorganisms attached to a surface. The profound transformations microorganisms undergo during their shift from planktonic (freely swimming) entities to constituents of a multifaceted, surface-bound community are apparent. Biofilms present a substantial challenge in the realm of public health due to the heightened resilience of microorganisms associated with biofilms against antimicrobial agents and their potential to initiate infections in patients with implanted medical devices[20]. In nature, microorganisms exist primarily by attaching to and proliferating on both animate and inanimate surfaces, encompassing various forms such as those encountered in terrestrial and aquatic settings, the spectrum of implanted medical devices, as well as biological tissues like tooth enamel, cardiac valves, the lungs, and the middle ear. The shared feature of this adherent growth state is the formation of a biofilm. Biofilm formation is a process whereby microorganisms irreversibly attach to and grow on a surface and produce extracellular polymers that facilitate attachment and matrix formation. This sequence of events leads to a shift in the phenotype of these microorganisms concerning growth rate and gene expression. biofilm-associated microorganisms exhibit dramatically decreased susceptibility to antimicrobial agents. Cells that securely attach to surfaces, evading removal through gentle rinsing, commence cell division, form microcolonies, and release extracellular polymers that define a biofilm. These extracellular polymeric substances (EPSs) are primarily composed of polysaccharides and are discernible through microscopic examination and chemical analysis. EPSs function as the structural framework of the biofilm, characterized by significant hydration (98% water) and a strong adhesion to the underlying surface. The structure of the biofilm is not a mere homogeneous monolayer of slime but is heterogeneous, both in space and over time, with

"water channels" that allow transport of essential nutrients and oxygen to the cells thriving within the biofilm.

B. Why Does Bacteria Produces Biofilm

According to Darwin's theory of evolution, the only true driving force behind the actions of any organism is reproductive fitness. Any action hat augments propagation stands to endure within a species. The biofilm mode of growth may bestow a competitive edge in terms of reproductive fitness, given that biofilm bacteria exhibit a reduced growth rate compared to their planktonic counterparts thriving in nutrient-rich culture media. Nevertheless, outside the confines of the laboratory, bacteria rarely, if ever, find themselves in an environment as nutrient rich as culture media, and in these less-than-ideal conditions, the biofilm mode of growth imparts a multitude of advantages with respect to reproductive fitness[21]. It requires special type of signaling, known as Quorum sensing [13], among microbial cells and the transcription of a distinct set of genes in contrast to planktonic forms of the same microbial organisms.

A biofilm is constituted of microbial cells that firmly adhere to each other and to a stationary surface, whether living or non-living [22]. Bacterial biofilms predominantly exhibit pathogenic attributes and have the potential to induce nosocomial infections The structural matrix of the biofilm encompasses various substances, including proteins such as fibrin, polysaccharides like alginate, and extracellular DNA (eDNA) [23]. Beyond the protective aspect of the matrix, bacteria within biofilms can employ several survival strategies to circumvent the host's defence mechanisms. By entering a dormant state and eluding immune detection by the immune system, these bacteria can induce localized tissue damage, subsequently leading to an acute infection.

The National Institutes of Health (NIH) revealed that 65% of all microbial infections and 80% of chronic infections are associated with the development of biofilms. The process of biofilm formation has multiple stages, commencing with initial attachment to a living or inanimate surface, followed by microcolony formation, culminating in the development of three-dimensional structures, and concluding with detachment [24-25].

C. Biofilm in Oral

Biofilm infections are typically chronic in nature, given the resilience of biofilm-dwelling bacteria to the immune system, antibiotics, and other therapeutic interventions. Biofilm-related diseases may occur in various anatomical systems, including the auditory, digestive, and integumentary systems [26].

The Auditory System

Otitis media (OM) is defined as an inflammation of the middle ear cavity. It is one of the most common causes of infection among pre-school aged children and one of the most common causes of antibiotic prescription and surgical intervention. OM can be subdivided into acute OM (AOM), chronic supportive OM (CSOM), and OM with effusion (OME) [26-27]. These conditions can lead to temporary or permanent hearing loss. Colonization of the nasopharynx by otopathogenic bacteria such as *Streptococcus pneumoniae*, and non-typeable *Haemophilus influenzae* (NT-Hi), in early childhood considerably increases the risk of subsequent episodes of AOM and OME later in life.

The Digestive System

Sialolithiasis is a condition in which calcified masses, known as sialoliths or salivary stones, develop within a salivary gland [28]. These sialoliths can create an obstruction that hinders the normal flow of saliva, impacting the initial stages of the digestive process that commence in the mouth, aiding in the breakdown of carbohydrates [26]. This obstruction can lead to discomfort and swelling, affecting approximately 0.5% of the general population.

The Integumentary System

Wound infections, wounds emerge as detrimental conditions to living tissues, originating from factors like trauma (such as cuts, abrasions, burns, or surgical procedures) or as an outcome of underlying

medical conditions like diabetes [26]. Typically, the majority of wounds containing microorganisms recover successfully. However, sometimes microorganisms, and particularly bacteria, experience excessive proliferation, leading to an interruption in the healing process and consequential damage to the wound tissues, ultimately culminating in an infection. This susceptibility to infection is pertinent to both chronic and acute wounds, attributed to the compromised innate protective barrier function of the skin and dermal appendages.

D. Dental Plaque

Dental plaque refers to the heterogeneous assembly of microorganisms that resides on the tooth's surface, ensconced within a matrix comprising polymers derived from both bacterial and salivary sources. Following the thorough cleaning of a tooth's surface, a swift adsorption of proteins and glycoproteins forms a conditioning film on the tooth's surface[29]. The process of plaque formation hinges on the interplay between the initial bacterial settlers and this film, which is known as the acquired enamel pellicle. In order to facilitate the colonization of the tooth's surface, specific receptors on salivary molecules are only exposed to bacteria after these molecules have been absorbed to a surface.

E. Biofilm in Denture and Implant

The use of biomaterials to restore oral function poses a risk of biofilm formation, which can negatively impact oral health. For bacteria to survive in the oropharyngeal region, they must adhere to either soft or hard tissues to withstand shear forces. The rapid turnover of oral lining epithelia serves as an effective defence mechanism [30], preventing the buildup of extensive microbial populations. Biofilm tends to accumulate more on rough surfaces compared to smooth ones. Teeth, dentures, or endosseous implants [31], however, providing non-shedding surfaces can foster the development of thick biofilms. In general, these established biofilms maintain a dynamic equilibrium with the host.

IV. VIRULENT FACTORS IN ORAL BACTERIA

A. Fimbriae

Fimbriae, found predominantly in Gram-negative bacteria, are slender, hair-like protein appendages extending from the bacterial cell surface. Their primary functions include aiding in bacterial attachment to host cells, facilitating colonization, and fortifying resistance against host immune defences [32]. These functions collectively increase the likelihood of oral bacteria enduring within the oral cavity for extended periods.

B. Invasiveness of Flagella

The flagellum primarily serves as a motility organelle, enabling movement and chemotaxis in bacteria. Bacteria can have a single flagellum or multiple, which may be polar (located at one or several spots) or peritrichous (distributed across the bacterium). Comprising over 20 distinct proteins, the flagellar structure includes the basal body, which traverses the cell wall, the curved hook connecting it to the whip-like flagellar filament extending several micrometers from the bacterial cell [33]. Traditionally regarded as a motility organelle, flagella also serve various functions that vary among bacteria and across their life cycles. For instance, participate in biofilm formation, protein export, and adhesion. The major subunit, flagellin, of the flagellum plays a significant role in innate immunity and as a dominant antigen eliciting an adaptive immune response. Importantly, flagella have been observed to function as adhesins, contributing significantly to bacterial attachment and invasion into host cells. Bacterial adhesion is a critical initial step in bacterial colonization and persistence, whether they are pathogens or commensals. Bacteria express various adhesive surface structures such as capsule, fimbriae or pili, and several surface proteins. Typically, these adhesive structures are not expressed simultaneously with the flagellum, ensuring that motility and attachment occur sequentially [34]. Thus, bacteria transition from a motile to a sessile lifestyle, guided by different environmental

conditions like temperature, osmolarity, and pH, which regulate the expression of the flagellar master operon, flhDC (a heterohexameric complex that acts as a master regulator of flagellar biosynthesis genes in numerous bacteria) [35]. Regulation of flagellar expression occurs both temporally at the transcription level and during assembly. Furthermore, the flagellum functions as an export apparatus responsible for extracellular secretion of non-flagellar virulence-associated effector proteins. Consequently, the bacterial flagellum exerts diverse effects on bacterial virulence, including motility toward host targets, early biofilm formation for enhanced bacterial survival, secretion of virulence factors, initiation of adaptive and innate immune responses, and promotion of adherence and invasion.

C. Cell wall Releases Endotoxin

Gram-negative microorganisms exhibit distinct virulence factors and form products and by-products that are harmful to apical and periapical tissues. Among these, endotoxin, or lipopolysaccharide (LPS), is a component released by the majority of Gram-negative bacteria, residing within their outer cell wall membrane [36]. The outer layer of the cell wall is composed of an asymmetric phospholipid bilayer that contains the LPS, and the inner layer of the membrane includes glycerophospholipids. The presence of LPS enhances bacterial resistance to antimicrobial agents and environmental stresses.

Endotoxin, often referred to as LPS due to its chemical structure, does not directly cause damage to cells or tissues; rather, it stimulates competent cells to release chemical mediators. Research has established macrophages as the primary target of endotoxins. Consequently, endotoxins themselves are not inherently toxic but rather exert their effects based on the host's response.

Endotoxins from vital or nonvital, intact or fragmented bacteria influence macrophages, neutrophils, and fibroblasts, triggering the release of numerous bioactive chemical inflammatory mediators, such as tumor necrosis factor (TNF) [37]. Furthermore, LPS is cytotoxic and acts as a potent stimulator of nitric oxide production. Inflammation can occur as an immune response to an infectious agent or molecular hazard signal.

The inflammatory response involves multiple innate immunity receptors that induce transcriptional activation, resulting in the production of numerous cytokines, chemokines, and other inflammatory mediators. This cascade can ultimately lead to osteoclastogenesis through osteoblast-related activities [38]. The host's immune response effectively regulates bacterial load, maintaining low numbers at the sulcus. Nevertheless, alterations in oral hygiene practices or host responses can lead to inadequate management, resulting in the development of gingival inflammation, epithelial and connective tissue migration, and compromised attachment between the tooth and alveolar bone.

D. Capsule affects host immunity

Non-encapsulated strains mostly cause non-invasive, localized abscesses localized abscesses, while encapsulated strains are responsible for invasive, spreading phlegmonous infections. Capsules serve a protective role for bacteria by shielding them from phagocytosis and helping with cell attachment, subsequently facilitating biofilm formation [39]. Capsular antigens are also targeted by the immune system and play a role in cell recognition, reducing the ability of host immune effectors to access the bacteria. However, the act of encapsulation doesn't only act as a barrier. It has a direct impact on the microbial structures capable of triggering a host response. By concealing microbial surface components, encapsulation may enhance the virulence of a microorganism by diminishing the host's response. This results in a reduction of the clearance potential of the host, resulting in the prolonged survival of the bacterium and ultimately leading to a persistent, long-term inflammatory response.

E. PROTEASE ENZYME

Besides the ability to form biofilms, the production of harmful substances stands as a pivotal trait among dental pathogenic bacteria. Enzymes

directly inflict damage on tissues, including neutral phosphatases and collagenases. Leucotoxins and immunoglobulin-splitting substances evade the host's defence mechanisms [40]. Furthermore, osteoclast-activating alkaline and acid phosphatases indirectly contribute to the loss of the periodontal attachment apparatus. Proteases cleave peptide bonds and are classified based on their catalytic activity. Bacteria such as, P. gingivalisis able to secrete large amounts of proteolytic enzymes. Among these extracellular endopeptidases, cysteine proteases, termed gingipains, emerge as major virulence factors. While these activities are crucial for bacterial survival, they pose a pathogenic threat to the host [41]. Gingipains allow P. gingivalis to attach to host tissues by facilitating fimbriae maturation and also play a role in hemoglobin binding, essential for collecting heme and host amino acids – vital nutrient sources for the bacteria. These enzymes are able to break down a wide array of proteins, including collagens(a major component of periodontal conn ective tissue)and extracellular matrix proteins (fi bronectin and laminin). Successful eradication of infection by the host requires the influx of effector cells, killing of the pathogen, resolution of inflammation and finally remodeling of the extracellular matrix (ECM). Host-derived matrix metalloproteinases (MMPs) are necessary for the successful execution of these events. Matrix metalloproteinases (MMPs) are a group of enzymes responsible for the degradation of most extracellular matrix proteins during organogenesis, growth, and normal tissue turnover. In adult tissues, MMP expression and activity typically remain low, but they significantly increase in various pathological conditions, leading to inflammation and undesirable tissue degradation. Tissue reaction to bacteria triggers an excessive inflammatory reaction by the host. Inflammatory cells release matrix-degrading proteinases, including MMPs [42]. Various cell types, such as lymphocytes and granulocytes, but especially activated macrophages, produce MMPs. MMPs are initially secreted as proenzymes and require proteolytic cleavage for activation. They are regulated by a family of inhibitors known as tissue inhibitors of matrix metalloproteinases (TIMPs), which are constitutively produced by various cells. Excessive inflammation following infection can result in tissue damage, and MMPs are implicated in causing this immunopathological effect. Tissue destruction may promote the dissemination or persistence of pathogens by breaking down barriers to spread or by creating an immunoprivileged site that is poorly accessible to the host. MMPs have the capacity to degrade and modify nearly all matrix and basement membrane proteins during growth and normal tissue turnover. Elevated levels of MMPs, particularly neutrophil gelatinase B (MMP-9) and to a lesser extent neutrophil collagenase-2 (MMP-8), are considered potential markers for tissue destruction in inflammation.

F. VESICLE AND EXTRACELLULAR ENZYME

Bacterial extracellular vesicles (EVs) represent nanosized vesicles of bacterial origin enclosed by lipid bilayers, and they exert diverse influences on host environments. These EVs contain a myriad of bioactive compounds, encompassing microbe-associated molecular patterns (MAMPs), proteins, lipids, sugars, and nucleic acids specific to their originated bacteria, which they transfer to host cells. The immunostimulatory effects of bacterial EVs rely on the unique profiles of their molecular constituents. EVs from Gram-negative bacteria, for instance, carry lipopolysaccharides (LPS), a notable TLR4 ligand, and a prominent MAMP responsible for provoking proinflammatory responses in host cells [43]. Conversely, EVs from Gram-positive bacteria predominantly contain bacterial lipoproteins, recognized as primary TLR2 ligands. EVs sourced from probiotic strains are laden with immunomodulatory molecules that confer beneficial properties, such as the reduction of proinflammatory cytokines and the enhancement of epithelial barrier functions**.**

V. ORAL BACTERIA IN SYSTEMIC DISEASES

Teeth represent the sole non-shedding surfaces within the body, harboring bacterial populations that can exceed 10^{11} microorganisms per mg of dental plaque. In human endodontal and periodontal infections, complex microfloras are involved, encompassing approximately 200 species, with some encounters documenting more than 500 species. These infections are primarily anaerobic, with gram-negative rods emerging as the most prevalent isolates. The close proximity of these microfloras to the bloodstream can facilitate bacteremia and the systemic dissemination of bacterial products, components, and immunocomplexes [44]. Oral infections, particularly periodontitis, have the potential to impact the progression and pathogenesis of various systemic diseases such as cardiovascular disease, bacterial pneumonia, diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus. Periodontitis, as a significant oral infection, can influence the host's susceptibility to systemic diseases through three primary mechanisms: shared risk factors, subgingival biofilms serving as reservoirs of gram-negative bacteria, and the periodontium itself acting as a reservoir of inflammatory mediators.

A. CVD

Cardiovascular disease (CVD) refers to diseases of the circulatory system, including outcomes such as myocardial infarction and stroke. Oral bacteria can travel through the tissues in oral cavity into the bloodstream, all over the body, and into the heart valves and heart. The bacteria can trigger inflammation throughout the body which may cause a narrowing of important arteries which can lead to a heart attack and stroke [45]. Additionally, it may cause an infection in the bloodstream that could result in a heart attack. The endothelium is a thin layer of cells that lines the interior surface of blood vessels. It plays a crucial role in regulating blood flow, preventing clots, and maintaining overall vascular health. Individuals with poor oral hygiene are at a higher risk of developing bacteremia during periodontal procedures due to a higher bacterial burden. These bacteria can release toxins that directly affect the endothelial cells, impairing their function and leading to a condition known as endothelial dysfunction. Endothelial dysfunction is a precursor to atherosclerosis and other cardiovascular diseases. When the endothelium doesn't function properly, it becomes less effective at relaxing and contracting, leading to narrowed blood vessels and reduced blood flow. This sets the stage for the development of hypertension and other cardiovascular complications.

B. Pneumonia

Pneumonia is an acute lung infection, which can produce respiratory signs and symptoms, such as cough, short and fast breathing, production of secretion and chest pain.Additionally, it may give rise to non-specific systemic symptoms such as fever, fatigue, muscle ache, and diminished appetite. Bacteria are the most frequent cause of this infection. The lung is composed of multiple units formed through the gradual branching of the airways [46]. Generally, the lower respiratory tracts remain free of microbial contamination, despite the upper respiratory tract's secretions being heavily populated with microorganisms from the oral and nasal surfaces. The sterility in the lower respiratory tract is preserved through intact cough reflexes, the action of secretions in the tracheobronchial region, mucociliary transportation of inhaled microorganisms and particulate material from the lower respiratory tract to the oropharynx, as well as immune and non-immune defence mechanisms. Still, microorganisms can somehow gain access to the lower respiratory tracts via four potential routes: aspiration of oropharyngeal contents, inhalation of infectious aerosols, extension of infection from adjacent areas, and hematogenous spread from extrapulmonary infection sites.

Most commonly, bacterial pneumonia arises primarily due to the aspiration of oropharyngeal microbiota into the lower respiratory tract [47], with the failure of the host's defence mechanisms to eliminate these microorganisms, their subsequent proliferation, and the consequent tissue destruction. It is likely that most pathogens first colonize the surfaces of the oral cavity or pharyngeal mucosa before aspiration. These pathogens may colonize

from an external source or emerge after an overgrowth of the normal oral flora following antibiotic treatment. Pneumonia can result from infection by anaerobic bacteria. Dental plaque would seem to be a logical source of these bacteria, particularly in individuals with periodontal disease. Patient with Pneumonia would harbor a large number of subgingival bacteria, particularly anaerobic species.

C. Diabetes

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to an absolute or relative deficiency of insulin. Diabetes is commonly categorized as type 1, or insulin dependent, and type 2, non-insulin dependent.In insulin-dependent diabetes, the primary anomaly is the insufficient production of insulin due to the destruction of pancreatic beta cells. Conversely, non-insulin-dependent diabetes is characterized by resistance of target tissues to insulin's actions. The interplay of genetic predisposition and environmental factors influences both the development of the clinical syndrome and its timing. In insulin-dependent diabetes, environmental factors encompass elements such as viruses, dietary influences, immunological factors, and pancreatic diseases. In non-insulin-dependent diabetes, factors such as lifestyle, age, pregnancy, pancreatic pathology, as well as insulin secretion and resistance are involved [48]. Severe periodontal disease frequently coexists with severe diabetes mellitus, as diabetes serves as a risk factor for the development of severe periodontal disease. The accumulation of advanced glycation end products (AGEs) mediated by glucose affects the migration and phagocytic activity of mononuclear and polymorphonuclear phagocytic cells. This results in the establishment of a more pathogenic subgingival microflora. The maturation and progressive shift of the subgingival microflora towards a predominantly gram-negative composition leads to the formation of a chronic source of systemic challenge through ulcerated pocket epithelium. This, in turn, initiates both an "infection-mediated" pathway characterized by cytokine upregulation and a state of insulin resistance, which impacts pathways involved in glucose utilization.

Simultaneously, periodontal infection can induce a chronic state of insulin resistance, thereby contributing to a cycle of hyperglycemia, nonenzymatic irreversible glycation, AGE-protein binding, and accumulation. This amplifies the classical pathway of degradation, destruction, and proliferation of diabetic connective tissue. Consequently, the relationship between diabetes mellitus and periodontal disease or infection becomes bidirectional. A self-sustaining, two-way system of catabolic responses and tissue destruction ensues, leading to more severe periodontal disease and greater challenges in blood sugar control.

D. Rheumatoid

Rheumatoid arthritis (RA), is an autoimmune and inflammatory disease, wherein the immune system erroneously targets and assaults healthy cells in the body, provoking inflammation characterized by painful swelling in the affected areas. RA mainly targets joints, often multiple joints concurrently. Commonly afflicted joints in RA include those in the hands, wrists, and knees. In a joint affected by RA, the synovial lining becomes inflamed, resulting in damage to joint tissues. The development of RA can be attributed to a highly pathogenic oral flora bacterium, capable of sustaining a chronic bacteremia that may lead to harm in distant organs such as joints and the endocardium [49]. Periodontal pathogens, including P. gingivalis, exhibit the capacity to compromise epithelial integrity, infiltrate human endothelial cells, and influence both transcription and protein synthesis. Through these mechanisms, periodontal pathogens gain direct systemic access to the bloodstream [50]. Consequently, there is an elevation in the levels of specific antibodies and the presence of bacterial DNA in the blood and synovial fluid. Recent research has revealed that P. gingivalis has the ability to invade primary human chondrocytes isolated from knee joints, eliciting cellular effects. This invasion by P. gingivalis leads to a delay in cell cycle progression and an increase in cell apoptosis in these chondrocytes.

E. SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organ systems and presenting a wide range of clinical manifestations. Microbial infections and alterations in mucosal microbiota can exert an influence on the morbidity of individuals with systemic lupus erythematosus (SLE). Within the oral cavity, periodontal bacteria and disruptions in subgingival plaque composition provide continuous sources of inflammatory stimuli at the mucosal interface. Patients with SLE frequently encounter bacterial infections in various anatomical sites, including the respiratory tract, urinary tract, and skin. Apart from these locations, the gingival mucosal surface remains consistently exposed to a diverse array of bacteria found within dental plaque. The interface between dental plaque and the gingival epithelium serves as a site of continuous interaction between microorganisms and the innate immune system. Moreover, these bacteria have the potential to enter the systemic circulation through bleeding gums or by directly invading the gingival epithelium [51]. Dental plaque itself can act as a persistent source of compounds that mimic autoantigens.

Consequently, T cells reactive to autoantigens associated with lupus may be activated by peptides originating from bacteria found in dental plaque. Recent findings indicate that, in comparison to non-lupus controls, SLE patients exhibit significant imbalances in the composition of periodontal microbiota, featuring a higher proportion of pathogenic bacteria. As a result, the exposure of the immune system to dental plaque bacteria in SLE patients bears substantial potential for influencing the course of the disease.

CONCLUSIONS

the oral cavity provides an ideal environment for bacteria to thrive, characterized by its moderate moisture and pH levels. Within this environment, bacteria find numerous hiding spots and colonization sites, allowing them to flourish and form dental plaque, which is associated with various diseases, including periodontal disease. The oral bacteriome has a significant impact on overall health, and advances in technology, such as 16S ribosomal RNA gene sequencing, help identify and manage oral bacterial communities. Furthermore, the formation of oral biofilm is crucial for bacterial survival, as it can evade the host's immune system, leading to biofilm-related diseases in various systems of the human body, including the auditory, cardiovascular, and integumentary systems. The rapid proliferation of oral bacteria is attributed to virulent factors like Fimbriae, flagella, endotoxin, capsule, and enzymes. These factors contribute to the spread of bacteria and can lead to systemic diseases such as cardiovascular disease, pneumonia, diabetes, rheumatoid arthritis, and systemic lupus erythematosus. To maintain good overall health and prevent the severity of such diseases, oral hygiene is of utmost importance. It is always better to prevent oral bacterial infections through proper oral care than to confront the potential consequences of unchecked bacterial growth.

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