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Unmasking P. Gingivalis: The Oral Health Enemy Within

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Abstract

Porphyromonas gingivalis is a gram negative oral anaerobe that is involved in the pathogenesis of Periodontics, an inflammatory disease that destroys the tissues supporting the tooth, eventually leading to tooth loss. Porphyromonas gingivalis has can locally invade periodontal tissues and evade the host defence mechanisms. It utilizes a panel of virulence factors that cause deregulation of the innate immune and inflammatory responses. Moreover, the role of P. gingivalis as a keystone biofilm species in orchestrating a host response is highlighted.

Keywords: Porphyromonas Gingivalis Periodontitis.

Introduction

Porphyromonas gingivalis is the species most highly associated with the chronic form of periodontitis and can be detected in up to 85% of the disease sites.[1] The presence of p. gingivalis in a periodontal pocket may predict imminent disease prognosis.[2]

This species possesses a number of potential virulence factor such as cysteine, proteinases lipopolysaccharides, capsule and fimbriae.[3]

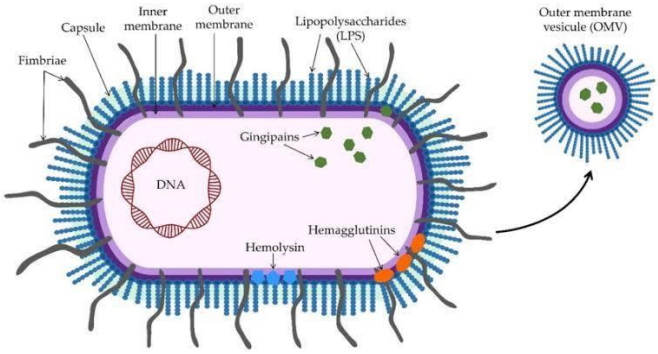
Collectively due to these properties of P. gingivalis is considered an "opportunistic pathogens" in line with the modified koch's postulates for oral infections such as periodontal disease[4].

P. gingivalis is most associated with chronic periodontitis. Its chronic persistence in the periodontium depends on its ability to evade host immunity without inhibiting the inflammatory response, which also benefits other periodontal bacteria.[5]

Moreover, experimental implicates of P. gingivalis in animal models induces an inflammatory response and periodontal bone loss[6].

Following periodontal treatment, a reduction of P. gingivalis number is associated with resolution of disease at the affected site[7].

Structure of P. gingivalis



P. gingivalis bacteria are Gram-negative, obligately anaerobic, non-motile, and nonperforming. Morphology can be short rod-shaped, or in broth culture, coccobacilli 0.5 µm by 1-2 µm in size. On solid media, colonies are generally smooth, shiny and convex.

Characteristics of P. gingivalis

P. gingivalis is a black pigmented, saccharolytic, non-motile, gram negative species that requires anaerobic condition for growth and the presence of heme or hemin and vitamin k in its nutrient milieu[8]. The black pigmentation of P. gingivalis colonies observed in blood agar culture is itself associated with the aggregation of heme on its cell surface[9].

P. gingivalis gains its metabolic energy by fermenting its amino acids, a property decisive for its survival in deep periodontal pockets where sugars are extremely scarce.[10] P.gingivalis is known to have a slightly alkaline Ph optimum growth in inflamed periodontal pockets which are also are alkaline. [11]

Virulence Factors

P. gingivalis is known to produce a repertoire of virulence factors that could penetrate the gingiva and cause tissue destruct directly or indirectly by induction of inflammation[12]. Colonization of host tissue could only happen in the presence of virulence factors such as capsules, lipo-polysaccharides (lps), fimbriae, gingipains.[13]

Capsule

Microbial adhesion are found as cell wall component or are associated with cell structure such capsule or fimbriae. A major virulence factors of P.gingivalis is considered to be its capsule also known as CPS or K antigen[15]. P. gingivalis capsule serves as a bacterial cell defence mechanism against phagocytosis and intra cellular death[16]. Encapsulated P.gingivalis shows a higher survival rate, due to its resistance to phagocytosis by macrophages and dendritic cells than those without capsules.[17]

Fimbriae

Fimbriae are thin, proteinaceous surface appendages that protrude from the outer membrane of the bacterial cell. These are 3-25micrometer long structures are harboured by most of the P. gingivalis strains. Studies showed that P. gingivalis expresses two distinct fimbriae on its cell surface. One consist of a subunit protein (named film A or frimdrillin) encoded by film A or gene (Termed long or major fimbriae) while the other subunits Mfa protein is encoded by the Mfa 1 gene (Termed short, minor or Mfa 1 fimbriae) even though the two fimbriae are antigenically distinct and differ in these amino acid composition, they are believed to contribute to the progress of periodontal inflammatory [15]. Type 1 (major) fimbriae have important role in colonisation and invasion where type 2 (minor) fimbriae possess a higher proinflamatory capacity.[16] Other properties of both major and minor fimbriae are the induction of proinflamatory cytokines and production of the matrix metalloproteinases (MMPs) such as IL-1, IL-6, IL-8, TNM-alpha and MMP-9 by various host cells. [17, 18]

Interestingly, major fimbriae can exploit TLR2 signalling in order to interact with compliment receptor 3 (CR3) in a novel "inside out "signalling pattern.

Gingipains

Gingipains are a group of cell surface cysteine proteinase of P. gingivalis that can also be present in secreted soluble form. They account for 85% of the total proteolytic activity of P.gingivalis[19]. Based on their substrate specificity, they are divided into arginine specific (Arg –x) and Lysine specific (Lys –x) gingipains.[20] Arginine specific gingipains have trypsin like activity and can degrade extracellular matrix components, including the integrin- fibronectin binding cytokine, immunoglobulin and complement factors. There are two types of Arg –x gingipains namely RgPA, which contains a proteolytic and an adhesion domain and RgPB, which contains only proteolytic domain.[20]

There is one type of lysine specific gingipains, KgP, which contains both a proteolytic and an adhesion domain. They are sequence similarities between the adhesion domains of KgP and RgPA. Gingipains can also stimulates 1L-6 production by oral epithelial cells and 1L8 production by gingival fibroblasts.[20]

Lipopolysaccharides

The outer cell membrane of gram negative bacteria, including P. gingivalis consists mainly of lipopolysaccharides (LPS) but for virulence of P.gingivalis the most important is LPS-A .Lipopolysaccharides belongs to the group of microbe associated molecular factors known by abbreviation MAMP.[21]

The term endotoxin is also used in the literature because of its ability to cause inflammatory reaction in the host organism. It consists of lipid-A, the nuclear oligosachride that forms the core of its structure, and the O specific polysaccharides[21]. P.gingivalis LPS exbit controversial features with regard to the induction of an inflammatory responds. A parts from being a weaker cytokine stimulator compared with the LPS of other gram negative (ie, enteropathogenic species). It can also antagonize the cytokine- stimulating capacity of other putative pathogens[21].

Like gram negative bacterial species P. gingivalis is sheated by an LPS, which is an outer membrane component recognised by host that can trigger intracellular signalling events[21].

The P.gingivalis LPS is a stimulator of proinflammatory response and bone resorption as demonstrated in experimental animal [21]. Structurally it exhibits unique features compared with LPS of other species[22]. These includes difference in the structure of O antigen between P.gingivalis strains that can confer antigenic differences[22].

The basic chemical structure of LPS is similar to that of other bacteria[22]. However the structure of P.gingivalis LPS shows difference acylacions, tetra- acylacions and penta acylacions, due to which P.gingivalis LPS activates specific signalling pathways and specific immune responses.[22]

Hemolysin And Hemagglutinin

P. gingivalis requires heme as a source of iron and protoporphyrin IX in order to survive within the host cell and establish infection[3]. Heme is located within the pigment on the cell surface of P. gingivalis in the form of µ-oxo bisheme. µ-oxo bisheme can be formed from heme in two ways. Heme from hemoglobin could react with molecular oxygen and other oxygen types or be formed from hematin molecules[9]. Heme sources are hemoproteins in saliva, gingival fluid, and erythrocytes.[6] The main mechanisms by which P. gingivalis supplies heme via hemagglutinin, hemolysin, and gingipains can also use heme acquisition systems of other bacteria[2]. The availability of heme greatly affects the growth and morphology of P. gingivalis and, thus, its virulence[7]. Cells grown under heme deficiency were in the shape of cocobacilii with few fimbriae. Still, they had many extracellular vesicles, while cells grown with excess heme are cocci with more fimbriae but fewer extracellular vesicles.[8] Heme also directly increases virulence through the increased production of cytotoxins, acids, and proteases.[11] Heme also affects the ability to bind further heme and the structure of lipopolysaccharides. P. gingivalis cells grown in the presence of µ-oxo bisheme have a layer of dimeric heme on their surface, which protects them from H2O2, which helps the cell survive in the presence of neutrophil-releasing H2O2,

extracellularly or intracellularly[19]. Accumulation of heme serves as a barrier for other oxidants. P. gingivalis grown under excess heme accumulates more FePPIX. P. gingivalis requires heme to stimulate growth and virulence, but also, an excessive amount of heme can adversely affect the cell, especially in the presence of excessive proteolysis.[24] Heme can be released from hemoglobin by the proteolytic action of Kgp. The formation of μoxo bisheme and its maintenance in this form is promoted by alkaline conditions, and P. gingivalis is known to have a slightly alkaline pH optimum growth in inflamed periodontal pockets, which are also alkaline.[13] The heme-binding domains (HA2) on gingipains, Kgp and HRgpA, and the adhesion domains on the hemagglutinin surface, HagA, can bind both heme and hemoglobin. HA2, Kgp, and HRgpA promote μ-oxo bisheme aggregation. P. gingivalis can agglutinate and hemolyze erythrocytes.[22] Its haemagglutinating activity is found in fimbriae, haemagglutinins, and gingipains. Iron is used more from hemoglobin than other sources[3]. Free heme may be derived from hemoglobin due to its release from erythrocytes degraded in the periodontal pocket by hemolysins and other proteases during gingival bleeding. After hemoglobin, albumin is the most abundant protein that carries heme without bleeding.[17]

Outer Membrane Vesicles (OMVS)

Gram-negative bacteria, during their growth, release outer membrane vesicles while maintaining the integrity of the outer membrane.[11] OMVs consist of outer membrane proteins, phospholipids, lipopolysaccharides, periplasm parts, DNA, and RNA.[16] Vesicles are involved in bacterial adaptation to stress, nutrient acquisition, and maintaining communication with other bacteria and host cells.[26] They are also responsible for invading host cells and destroying them through pathological mechanisms of avoiding host immune defenses and antibiotic resistance.[4] Various mechanisms can form outer membrane vesicles.[7] One of the formation mechanisms is during the growth of the bacterial cell. Due to growth, the bacterial cell wall is stimulated, and muramyl peptides are released, which, if not absorbed, are generated on the outer membrane and later released.[1] Vesicles are formed where the bond between the peptidoglycan and the outer membrane is weakened[14]. OMVs are accumulated along the outer membrane, containing virulence factors more strongly than in the parent bacterial cell.[24] OMVs can eliminate unwanted substances that accumulate under the influence of stressors and toxins, carry antigenic substances for the bacterium's interaction with host cells and drugs, and thus increase the viability of the bacterium.[5] OMVs penetrate better into deep tissues and activate the host's inflammatory response there, but their virulence depends on the amount of lipids, proteins, and nucleic acids.[22] Most P. gingivalis OMV proteins are membrane proteins, lipoproteins, and extracellular proteins.[27] OMVs also contain noncoding RNAs and lipoproteins that bind heme. P. gingivalis OMVs can return heme-filled OMVs to the biofilm and provide other bacteria in the plaque with nutrients, allowing other species to reproduce.[23] Other bacteria may also use oligosaccharides, monosaccharides, peptides, and amino acids produced by hydrolases in OMVs. FimA and Mfa1 found in OMVs serve to communicate P. gingivalis with other bacteria.[14] They have excellent communication with S. aureus and can inhibit other bacteria in the biofilm, such as S. gordonii, creating a favorable environment for P. gingivalis. Small RNAs within OMVs are considered mediators of host–guest communication due to their ability to modulate gene expression in multiple cells and species, for which they use many regulatory mechanisms.[6] Some of them are the capacity to bind protein targets and modify their function and blockage of the ribosome-binding site.[19] Bacterial sRNAs can be released into the environment and transferred to other microbes and host cells.[13] Specific for periodontal pathogens, msRNAs can deactivate anti-inflammatory host response by deactivating the expression of genes that encode cytokines such as IL-5 and IL-13. OMVs can be embedded in a cell in two different ways.[16] One way is actin-mediated, where OMVs use host cell receptors to initiate F-actin polymerization and, thus, enter the cell.[20] The second way is by fimbriae and the process of endocytosis, which depends on P13K, Rac1, and GTPase. Once they enter the host cell, OMVs can cause enormous damage.[19] They inhibit the

proliferation of endothelial cells and fibroblasts and angiogenesis, which slows down the healing process.[9] They activate pathogen recognition receptors (PRRs), leading to cytokine secretion and gingival epithelial apoptosis[22]. They stimulate macrophages to produce large amounts of proinflammatory factors such as interleukins IL-6, IL10, and IL-12p70, TNFα, and IFNb and activate caspase-1 and release LDH, ultimately resulting in cell apoptosis.[21]

Role in the periodontal disease

Periodontal diseases or periodontitis is defined as a bacterially induced inflammatory disease of tooth supporting tissue[23]. Pathology occurs when P.gingivalis binds to and accumulated on the tooth surface, leading to the development of a mixed biofilm[24]. The expansion of bacteria into the gingival sulcus and the formation of periodontal pocket.[24]

Inside this periodontal pocket lies the gingival crevicular fluid, an inflammatory exudate source of essential nutrients for P.gingivalis growth-present in low abundance in healthy individuals, but drastically increased during gum inflammation P.gingivalis[25]. Invades gingival epithelial cells via binding of its fimbriae to (beta1) antigrin on the host cell surface followed by a rearrangement of host actin cyto-skeleton.[25]

It inhibits 1L-8 expression by epithelial cells, creating what is known as "local chemokine paralysis ".[26] This mechanism induces a delay in neutrophil recruitment, which allows the proliferation of bacteria in this new niche, leading to an alteration of subgingival microbiome with respect to its composition and total bacterial count[27].

Conclusion

Porphyromonas gingivalis is a major pathogen of severe adult periodontitis. Porphyromonas gingivalis, an etiological agent in severe forms of periodontitis is a prominent component of oral microbiome and a successful colonizer of oral epithelium. This gram negative anaerobe can also exist within the most epithelium without the existences of overt disesase. Colonization of the most tissues could only happen in the presence of virulence factors such as fimbrae, capsules, lipopoly saccharides and gingipains. Complement manipulation by p.gingivalis may denote a coevolution strategy to support other species present in the biofilm, which may reciprocally provide further colonization opportunities and nutrient availability to p.gingivalis. Subsequent changes in the local micro-environment can differentially regulate expression of its virulence factors, and hence the proinflammatory or ant-inflamatory potentials of p.gingivalis. This is strongly indicated by recent evidence demonstrating, that even at low abundance, this species qualitatively and quantitatively affects the composition of the oral commensal micro bio ta, which are in turn required for p.gingivalis. Induced inflammatory bone loss. For this reasons, p.gingivalis is now considered a 'Key Stone' species in Subgingival biofilms.

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