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Porphyromonas gingival is – details matter, it is worth waiting to get it right

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Abstract

Periodontitis is a prevalent disease characterized by loss of connective tissue attachment and bone around the teeth. Periodontal disease progression is episodic. More than 700 species of microorganisms colonize the oral cavity, but only a few of them are thought to be pathogenic. Porphyromonas gingival is a gram-negative anaerobic rod that is usually detected in the periodontal pockets of patients with severe periodontitis. P. gingival is has been highly implicated in the etiology of adult form of human periodontal diseases. As the periodontal diseases are of unique nature and have their own variety of flora of microorganisms, a thorough knowledge of the different microorganisms is a must. This review article will discuss about P. gingival is and its virulence factors in detail.

Keywords: Periodontitis, Porphyromonas gingival is, virulence factors, pathogenicity, oral microbota, periopathogens

Introduction

Oral microbiota contains the microorganisms found in the oral cavity, which consists of more than 700 different species with distinct subspecies. A healthy oral cavity is in a state of homeostasis, with a balance between the resident microbiota and host immune response. The disruption of this balance contributes to oral diseases like periodontal diseases. Periodontal disease is the sixth most prevalent disabling condition worldwide, causing alveolar bone resorption, formation of deep

periodontal pockets, tooth loosening, and is epidemiologically associated with several systemic diseases including atherosclerosis, diabetes and cardiovascular conditions.

Periodontal disease is a result of an exacerbated inflammatory response to normal microbiota triggered by the presence of dysbiotic species such as Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Prevotella Intermedia, Treponema denticola, Tannerella forsythia and Porphyromonas gingival is. The latter three species together constitute the 'red complex' which substantially contributes to subgingival biofilm and it is associated with severe forms of periodontal disease. P. gingival is a "keystone pathogen", which contributes to microbial imbalance and leads to disease progression, whereas T. denticola and T, forsythia act as 'pathobionts' that accelerate disease progression. This article discusses about Porphyromonas gingival is and its virulence factors in detail.

Porphyromonas gingival is

Among major periodontal pathogens, P. gingival is appears to be one of the prime etiological agents in the pathogenesis and progression of the inflammatory events of periodontal disease.[1] Formerly called Bacteroides gingival is, it is a gram-negative, anaerobic, non-motile, non-spore forming rod shaped bacteria, characterized by production of large amounts of cell-associated protoheme, forming black colonies on blood agar. This heme is obtained by the degradation of haemoglobin, by lysine- and arginine- specific proteinases called gingipains, and is collected by heme-binding proteins.

P. gingival is secretes a variety of proteases that degrade exogenous proteins to generate peptides; it is assachrolytic i. e it generates its metabolic energy by fermenting amino acids, a property decisive for its survival in deep periodontal pockets, where sugars are extremely scarce. It is also known to produce a wide array of virulence factors that could cause tissue destruction on their own or act through other mediators to induce inflammation.

Virulence factors

Virulence factors are molecules that exert detrimental effects on host cells, resulting in the establishment and maintenance of bacterial species (through symbiotic/parasitic relationship) with or within the confines of the host.[2] The bacterium must find an appropriate ecological niche (the site of activity), where the virulence factors can exert their effects on the host. This is influenced by the inherent pathogenic potential of a bacterium, its environment, and its interaction with the host. The virulence factors are multifactorial and they may include

- endotoxins, exotoxins, chemotactic substances, antigens, enzymes and proteins,
- exopolysaccharides in the capsule,
- molecules in the fimbriae,
- outer membrane proteins and vesicles,
- end products of metabolism,
- surface structures or ligands.

These virulence factors can damage the host at different stages of the bacterial life cycle, and aid in its:

- entry and exit into the host cells,
- colonization of the host,
- extraction of nutrients from the host,
- immune escape,
- immunosuppression,
- release of other virulence factors.

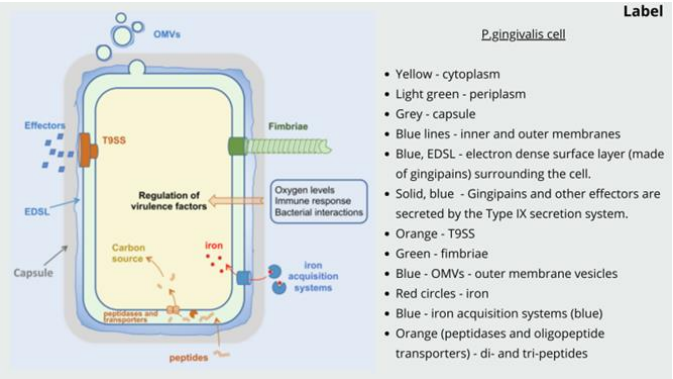

Figure 1: Major virulence factors of P. gingival is. (Courtesy: I. Lunar Silva et al, 2021)[3]

Capsule

Capsule is a layer of slime that lies outside the bacterial cell wall; secreted by the bacteria and diffuses into the surrounding medium. Capsular polysaccharides are highly hydrated molecules, which bind to lipid A on the cell surface, serving as adhesins. Capsule from different strains of P. gingival is were seen to be different in their sugar composition; usually composed of galactose, glucose, glucosamine, amino sugars, rhamnose, mannose and methyl pentose. These differences result in differences in adhesion capacity and virulence of strains. Based on the capacity of capsular polysaccharides (K-antigen) to generate systemic IgG antibody responses, six P. gingival is serotypes (K1 to K6) have been identified.[4] Increased capsulation causes increased resistance to phagocytosis, increased hydrophilicity, decreased autoagglutination, and decreased induction of polymorphonuclear leukocyte chemiluminescence.[5,6] Capsules may interact with surface protein to facilitate attachment to host cells. The level and mechanism of co-aggregation between P. gingival is and other periodontopathogens depends on the presence and type of capsule.[7] Encapsulated P. gingival is was able to modulate the host response to bacteria by reducing the synthesis of cytokines IL-1, IL-6, IL-8 by fibroblasts.[8] Capsule also contributes to increased bacterial survival by reducing the bactericidal effects of small antimicrobial peptide known as defensins.[9]

Lipopolysaccharide

Lipopolysaccharide (LPS) is a major component of the cell wall of P. gingival is. LPS is an endotoxin, known for its toxicity and ability to cause unwanted host inflammation. LPS consists of a distal polysaccharide 'O-antigen', a 'core' oligosaccharide, and a hydrophobic domain called lipid A. Lipid A is the biologically active region of LPS that could cause deregulation of the host innate immune system by interacting with both TLR 2 and 4.[10] P. gingival is lipid A structure exhibits different variations of acylation, in its structure: tetra-acylation and penta-acylation. As a consequence, P. gingival is LPS activates distinct signaling pathways and initates differential immune responses. The production of distinct P. gingival is LPS can be attributed to different P. gingival is strains and environmental factors, such as hemin levels, phosphate availability and incubation temperatures.[11]

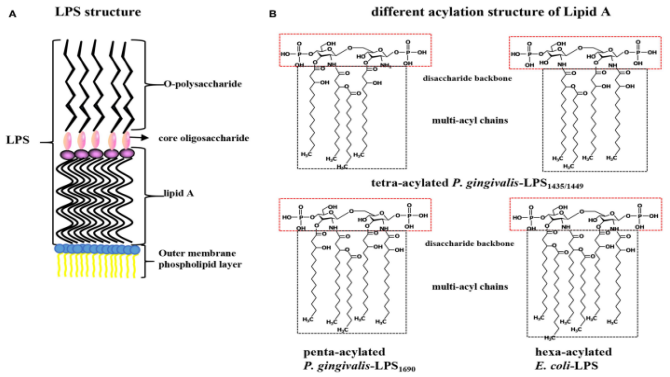

Figure 2: Lipopolysaccharide of P. gingival is (Courtesy: Jia et al, 2019)[12]

A. Structure of P. gingival is-LPS

B. Different acylation structures of P. gingival is and E. coli LPS.

- P. gingival is-LPS with tetra-acylated chains (LPS1435/1449) and penta-acylated chains (LPS1690).
- E. coli-LPS with hexa-acylated lipid A.

Immunopathogenesis of LPS

As P. gingival is LPS is poorly recognized by innate host defence system compared with LPS of other species, it disrupts the innate host surveillance by interfering with distribution of leukocytes in the vicinity of bacterial colonization. The ability of gingival epithelial cells to secrete chemokines IL-8 was paralyzed; thereby activation of neutrophils, eosinophils and basophils were affected.[13] This phenomenon known as chemokine paralysis results in resistance to oxidative burst killing by neutrophils. Without an effective innate immune defence, the number of periodontal bacteria can increase rapidly, resulting in periodontal disease. LPS also inhibits osteoblastic differentiation and mineralization in periodontal ligament stem cells that have a role in tissue regeneration.[14]

It has been shown that P. gingival is LPS circulates systemically in more than 50% of periodontal patients and triggers an inflammatory response in the left ventricle through MMP, causing cardiac dysfunction.[15] LPS also stimulates the production of thrombospondin-1, causing macrophage migration and modulation of host inflammatory response.[16]

Fimbriae

Fimbriae are proteinaceous, filamentous appendages that protrude outwards from the bacterial cell surface, and are involved in bacterial motility, adhesion to host cells and invasion into the cells or biofilm formation. P. gingival is expresses two forms of fimbriae[12]

1. Major / long / Fim A fimbriae (role in colonization and invasion)
2. Minor / short / Mfa1 fimbriae (possess proin flammatory capacity)

Based on the differences in the Fim A genes, P. gingival is fimbriae are classified into 6 genotypes (types I, I-b, II, III, IV, V).[17]

Biological properties of P. gingival is fimbriae

Fimbriae are responsible for binding the bacterium to the host tissues and saliva coated hydroxyapatite. The interaction of the fimbriae with certain proteins may be the first step in a signaling process that mediates uptake of the bacteria into host cells. The salivary proteins statherin and the salivary proline rich protein have been proposed as receptor proteins for fimbriae to bridge them to the tooth surface. Purified /recombinant fimbriae, monoclonal antibodies to P. gingival is fimbriae and synthetic peptides are effective in preventing the attachment of P. gingival is cells to saliva-coated hydroxyapatite and human buccal epithelial cells.[18-20]

Electron microscopy of P. gingival is strains that bound well to the host epithelial cells have revealed abundant peritrichously arranged fimbriae long and wide on their surface, whereas nonadherent strains had very few shorter fimbriae. P. gingival is fimbriae possess host cell specificity, in that they bind to epithelial cells, but not to red blood cells which is mediated by haemagglutinin.

Immunopathogenesis of fimbriae

P. gingival is fimbriae can signal through either TLR2 (Toll-like receptor-2) or TLR4. It can directly induce two distinct signaling pathways, mediating

- production of proinflammatory cytokines such as IL-6 and TNF-α
- expression of cell adhesion molecules, such as ICAM-1.[21]

Major fimbriae can exploit TLR2 signaling in order to interact with complement receptor 3 (CR3), in a novel 'inside-out' signaling pattern.[22] Signaling through TLR4 requires an additional co-stimulation of CD19 & MD-2.[23] The CR3 which is exploited by P. gingival is can interfere with the phagocytic process of bacteria mediated by IL-12, thereby increasing its viability and capacity to cause periodontitis. IL-12p70 acts to activate

T & NK cells that produce IFN-γ, which functions to activate the bactericidal function in macrophages. All these interactions collectively inhibit bacterial clearance.

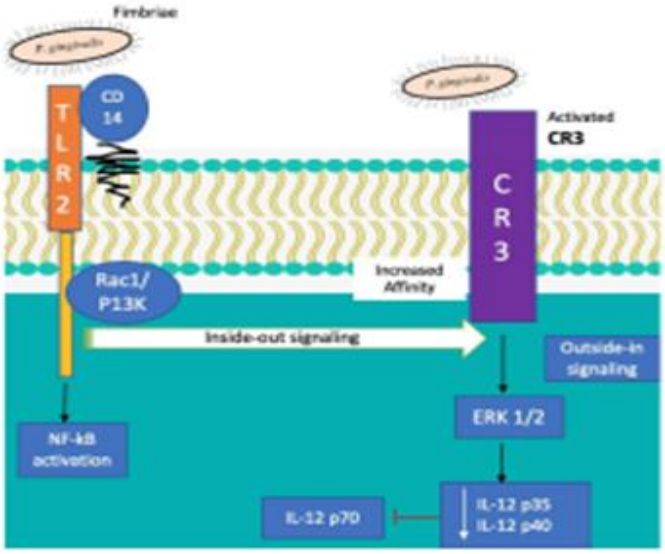

Figure 3: Interaction of P. gingival is with TLR2 and CR2 to undermine innate immunity.

(Courtesy: Septiwidyati et al, 2020)[24]

Outer membrane proteins (omps)

The cell membrane has two layers: outer membrane and inner membrane. Both layers have different composition and structure, and are separated by the periplasm. Inner membrane is a phospholipid bilayer with numerous integral proteins. Outer membrane is an asymmetrical layer with phospholipids and lipopolysaccharide in the inner and outer leaflet. Lipopolysaccharides and haemagglutinin are intimately associated with outer membrane. The most abundant OMPs are identified as porins and OmpA-like proteins. Porin proteins allow movement of various substances, thus making cell membrane, a selective barrier.

OMPs act as antigens to the host, as they are the most exposed region involved in specific recognition processes. OMPs also mediate the formation and maintenance of periodontal biofilms, through its interaction with periodontal microflora.[25] Analysis of OMP using SDS-PAGE revealed that the outer membrane consists of diverse array of proteins ranging in size 20-100 kDa.[26]

Table 1: Functions of OMPs

Sn.	OMPs	Functions
1	75 kDa major OMP[27]	stimulates activation of polyclonal B-cell and production of IL-1.
2	24 kDa called "fibroblast activating factor"[28]	gingival fibroblasts proliferating factor and stimulates bone resorption
3	40 kDa OMP[29]	adhesins in the aggregation of P. gingival is vesicles and Actinomyces viscous.
4	PG534[30]	important roles in producing active gingipains
5	LptO (PG0027)[31]	deacylation of P. gingival is LPS, to provide attachment to host cells. also plays important role in secretion of gingipains to the cell surface

Outer membrane vesicles (omvs)

Proteins are released from the outer membrane as single layered vesicles, which contain numerous enzymes that occur in the periplasmic region of intact cell. Vesicles fuse with outer membrane of other bacterial species, and release virulence factors resulting in impairment of target cells. P. gingival is OMVs are enriched in gingipains and other proteins anchored at the cell surface and hence participate in toxin delivery and pathogenicity.

Effects of P. gingival is OMVs

- P. gingival is OMVs can be internalized into cells by an actin-mediated pathway or fimbria-dependent lipid raft pathway, and can exert virulence by affecting different receptors on the host cell surface.
- P. gingival is OMVs can activate or degrade a variety of biologically active substances in host cells, inhibit cell proliferation, promote glycolysis, apoptosis, and cause host cells to produce a variety of inflammatory factors thereby promoting the formation of an inflammatory environment.[32]

Haemagglutinins

P. gingival is binding to erythrocytes with the help of hemagglutinins may serve a nutritional function as it utilizes heme for growth. P. gingival is produces at least 5 types of haemagglutinin molecules. 3 hag genes encoding haemagglutinins have been cloned. All haemagglutinin activity is related to haemagglutinin adhesin domains of RgpA, Kgp and HagA. Haemagglutinins also promote colonization by mediating the binding of bacteria to receptors on human cells, other than red blood cells.[33]

Hemin-binding proteins

P. gingival is utilizes for its growth, a broad range of hemin containing compounds such as haemoglobin, myoglobin, hemopexin, metha emoglobin, oxy haemoglobin and cytochrome C, and non-hemin iron sources, including ferric and ferrous inorganic iron and human transferrin. The characteristic pigmentation produced by P. gingival is colonies appears to be due to accumulation of hemin and serves as a mechanism for hemin storage, which provides a nutritional advantage for the survival of this pathogen in the iron-limited environment of the healthy periodontal pocket. P. gingival is possesses haemagglutinin, hemolysin and several enzymatic activities that aid in the acquisition of hemin or iron. The P. gingival is hemolysin may function to lyse erythrocytes in vivo, resulting in the liberation of hemin.[34] P. gingival is hemin may induce the production of new OMPs that may function in hemin binding and transport and may represent a novel mechanism for the acquisition of hemin.[2]

Proteinases

All the strains of P. gingival is produce a large number of hydrolytic, proteolytic and lipolytic enzymes, which is one of its potentially significant virulence characteristics. Many of these enzymes are either exposed

i) at the outer membrane of the bacterium where they are able to come into contact with host cells,

ii) within the periplasmic space capable of being transported to the cell surface,

iii)in the outer membrane vesicles, which are sloughed from the outer membrane during growth.

Several of these P. gingival is - associated proteases appear to be functionally important in the in-vivo environment and they include the trypsin-, thiol- and caseinolytic proteinases, and two peptidases, glycylpropyl dipeptidyl aminopeptidase and glycylpropyl peptidase. In the host, these enzymes could play a significant role in periodontal disease progression, including the dissemination of bacterial species to deeper tissues of the host, resulting in tissue invasion and the destruction of host tissue and cells.[2]

Gingipains

The majority of the enzymatic activity of P. gingival is against a broad range of host proteins is due to cysteine proteinases. Cysteine proteinases are thiol proteinases and comprise the group of endopeptidases. They rely on the presence of thiol group of a cysteine residue in the enzyme molecule for their catalytic activity.

Gingipains are cysteine proteinases which cleave substrates after arginine and lysine residues. Gingipains are either secreted in the environment or anchored to the cell surface.[35] They have been called trypsin-like enzymes.

Types of gingipains: They are of two types

1) Arginine-specific gingipains (Arg-gingipain – A / RgpA; Arg-gingipain – B / RgpB),

2) Lysine-specific gingipain (Lys-gingipain / Kgp).

Arg-gingipain is encoded by two genes: RgpA and RgpB; and Lys-gingipain, by one gene: Kgp.

Physiological functions of Gingipains

- Act as processing enzymes for various cell surface proteins of P. gingival is like proteinases, fimbrial components, haemoglobin-binding protein and haemagglutinin.[36]
- Energy source activation: the haemagglutination activity associated with Rgp genes, causes agglutination and lysis of erythrocytes, releasing protoheme, the absolute requirement for P. gingival is growth.[37]
- Gingipains carry out significant housekeeping functions important for bacterial cell physiology.

Pathological properties of Rgp and Kgp

1. Degradation of Type I and IV collagens, extracellular matrix proteins such as fibronectin and laminin which directly contribute to tissue destruction.[38,39]

2. Activation of kallikrein / kinin cascade

Arg-gingipains are very potent vascular permeability enhancement (VPE) factors, inducing kallikrein activity through plasma PR kallikrein activation and subsequent bradykinin release.[38] Hence gingipains contribute to GCF production and edema formation at periodontitis sites. Bradykinin may be involved in alveolar bone resorption by inducing prostaglandin production.

3. Dysregulation of coagulation cascade

Rgp activates coagulation factors IX, X and prothrombin, causing amplified production of thrombin.

- Enhances vascular permeability and induces leukocyte chemotaxis → GCF production and leukocyte accumulation at periodontitis site.
- Stimulates prostaglandin secretion by osteoblastic cells and IL-1 production.
- Stimulates bone resorption by osteoclasts.

4. Evasion of host defence systems

The role of gingipains in disruption of complement system is shown below.

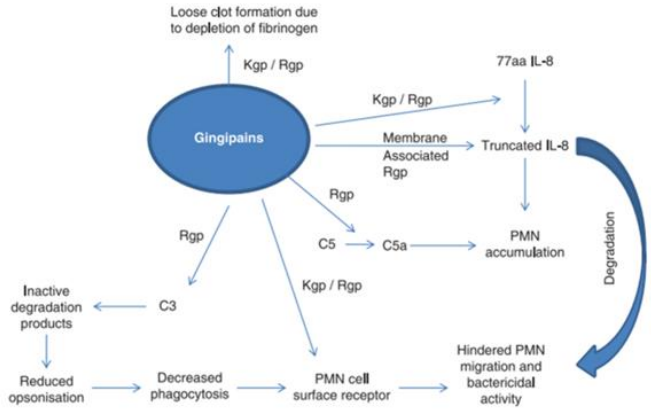

Figure 4: Effects of gingipains (Courtesy: Pandit et al, 2015)[40]

5. Pro- and anti-inflammatory effects

Gingipains inactivate IL-8, IL-6, IL-1β, TNF-α and IFN-γ. They activate immunoglobulins such as IgG, IgA and secretory IgA. Since gingipains are not inactivated by host proteinase inhibitors, they are highly damaging to host defence mechanisms.[41]

Aminopeptidases

P. gingival is the only periodontopathic microbiota to exhibit dipeptidyl aryl aminopeptidase activity.[42] It contained two additional aminopeptidases, N-CBz-glycyl-arginyl peptidase and glycyl-prolyl peptidase, which were thiol and serine activated proteinases respectively.

Caseinases

Caseinases hydrolyze the protein casein and exist in P. gingival is as 3 isoenzymes: Pase -A, -B, -C, displaying different cleavage patterns.[43] They are active against salivary and egg-white lysozyme and insulin chain B.

Collagenases

Type I collagen is resistant to destruction by majority of mammalian and bacterially synthesized proteolytic enzymes. The periodontal tissue destruction must be mediated by specific proteolytic enzymes, especially of collagenases. Collagenases are the most important of the P. gingival is proteolytic enzymes; when expressed in vivo, are major enzymes associated with soft tissue destruction, contributing to the clinical hallmark of periodontal disease - the destruction of periodontal connective tissue during inflammation.[2]

Activities of other p. gingival is enzymes

Apart from proteinases, several biosynthetic and degradative enzymes have been identified in P. gingival is strains.

- **Alkaline phosphatase**

P. gingival is alkaline phosphatase functions as a phosphoprotein phosphatase, as it is involved in the hydrolysis of casein and o-phosphoserine. Its activity has been positively correlated with periodontal disease activity, as well as with alveolar bone resorption in advanced periodontitis.

- **Superoxide dismutase**

P. gingival is being an obligate anaerobe, cannot grow in aerobic environment but can tolerate high levels of dissolved oxygen. It possesses the enzymes such as superoxide dismutase, peroxidase and catalase which are essential for detoxifying oxygen radicals. The presence of superoxide dismutase might be important to its ability to resist superoxide generation by neutrophils.

- **Sulfatase**

P. gingival is elaborates an extracellular sulfatase capable of removing the sulfate ester groups from the structural constituents of the cell membrane of gingival epithelium - sulfated glycosphingolipids, and from the glycosaminoglycan component of gingival connective tissue proteoglycans.

- **Heparinase and Chondroitinase**

P. gingival is also possesses heparinase and chondroitinase, for degradation of gingival proteoglycans such as chondroitin-4-sulfate and heparin sulfate.

- **Peptidyl arginine deiminase (PAD)**

Members of the Porphyromonas genus are the only bacteria known to produce and to secrete PAD, an enzyme involved in the citrullination of protein. Citrullinated proteins are targeted by the immune system and ultimately lead to autoimmune diseases. At the structural level, Porphyromonas PAD (PPAD) presents an organization similar to gingipains and is a significant factor in the development of experimental periodontitis and rheumatoid arthritis in mice.[44]

- **Sialidase**

A neuraminidase, functions as a potential virulence factor. Studies have demonstrated that sialidase-deficient of mutants of P. gingival is failed to produce an intact capsule, form less biofilm, have lower gingipain activity, cause rapid clearance by macrophages and exhibit reduced virulence in a mouse abscess model.[45]

Molecular analysis of p. gingival is enzymes

Molecular techniques including gene cloning and the construction of defined functional mutants have revealed a large number of proteolytic enzymes synthesized by P. gingival are strains.

Table 2: P. gingival is strain proteinase genes (Adapted from Holt et al, 1999)[2]

Strain	Genes	Enzymes
➢ 381	hagA, hagB, hagC, hagD	Haemagglutinin
	pgiIM	Methylase
	rgp	Arg-gingipain precursor
	381-kgp	Lys-gingipain (mature form)
	381-rgpB, 381-rgpA	Arg-gingipain
➢ 33277	Sod	Superoxide dismutase
	cpg R	Glutamate dehydrogenase
	rgpA, rgpB	Arg-gingipain
	ATCC 33217-rgpB	Arg-gingipain
➢ 53977	Sod	Superoxide dismutase
	prtC	Collagenase
	prtT	Trypsin like protease
➢ W83	tpr, Tpr	Thiol protease
	prtH	Protease
	gdh	Glutamate dehydrogenase
➢ 33277, W50, W12, W83	pgag1	PgAg1
➢ W50	prt1	Protease 1
	prpR1	Protease (polyprotein for Arg1)
	mcmA, mcmB	Methylmalonyl-CoA mutase
	W50-prtR	Arg-specific proteinase, adhesin
	W50 – prpR1, prpR2	Arg-x-proteases – R11A, R11B
	W50 – tla	R1 protease precursor
➢ H66	rgp1	Arg-gingipain-1
➢ H66, W50	kgp	Gingipain K
➢ W12	prtP	Porphypain

The haemagglutination events mediated by P. gingival is might be due to combined effects of at least three enzymes formed into a large protein complex. The Arg- and Lys-gingipains and several P. gingival is adhesion proteins have been found to be complexed together to form a “haemagglutination complex” all of which are transcribed from the same gene. The enzymatic activities of P. gingival is to be important virulence factors, is supported by genetic evidence linking the expression of the genes encoding various factors, which could act in a synergistic way to effect soft tissue destruction in periodontium.

The type ix secretion system

The type IX secretion system (T9SS), the key virulence factor of P. gingival is is a multiprotein transport apparatus, that trans locates effectors through the outer membrane and covalently attaches them on the anionic LPS at the cell surface, and indirectly participates to fimbriae assembly by secreting proteases that process fimbrial subunits.[3]

The T9SS is a secretion apparatus that is restricted to bacteria of the Bacteriodetes phylum. It is a two-step mechanism, in which effectors first close the inner membrane by the Sec pathway before being recruited and transported by the T9SS through outer membrane. Deletion of T9SS genes causes effector accumulation in the periplasm.[46] Periplasm-sequestered gingipains have shown partial enzymatic activity, but the requirement of an Ig-like domain for T9SS transport and the internal diameter of outer membrane translocon, suggest that T9SS effectors achieve proper folding in the periplasm, before translocation through the cell membrane.

In P. gingival is, C-terminal domains (CTD) are cleaved when effectors reach the cell exterior, and effectors are either released into the extracellular medium or anchored to the surface by covalent attachment to LPS. In wild-type P. gingival is, CTD proteins attached to the cell surface yield an additional electron-dense surface layer that can be observed by election microscopy.

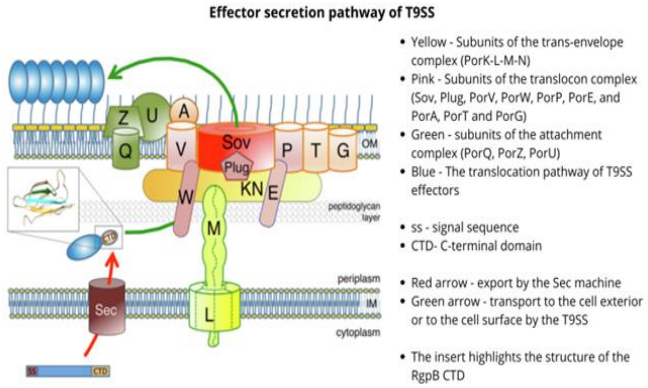

Figure 5: Organization and mechanism of action of the P. gingival is Type IX secretion system. (Courtesy: I Lunar Silva et al, 2021).[3]

T9SS components: For proper function of the T9SS, a set of 18 genes is necessary in P. gingival is. Except the porKLMNP locus, these genes are widespread within the genome.[47]

1. The T9SS trans-envelope core complex: The trans-envelope core complex comprises 4 subunits, Por -K, -L, -M, -N, which localize in the cell envelope. PorL and PorM are inner membrane proteins, while PorN is a periplasmic protein and PorK an outer membrane lipoprotein.

2. The T9SS translocon: The "PorV" complex and "Plug" complex are likely to represent two different states of the mechanism of transport; while the PorV complex may correspond to the open complex, prior to substrate engagement, the Plug complex may represent the pore after substrate release, occluded to preserve membrane permeability. A partner of PorV, named PorA was identified in P. gingival is and proposed to be a component of the translocon complex. PorA is absent in most T9SS bacteria and might be specific to gingipains.[49]

3. The attachment complex: Most of the T9SS substrate are anchored to the cell surface rather than being secreted into the extracellular medium. T9SS attachment complex consists of Por U, PorV, PorZ and PorQ subunits.

4. Additional T9SS components: Poorly characterized T9SS components associated to the outer membrane, include the PorP, PorT and PorG outer membrane β-barrels and the PorE, PorF and PorW outer membrane lipoproteins.

By blocking the T9SS, inhibitors will prevent cell surface exposure of gingipains and of PAD, and will indirectly hamper fimbriae biogenesis. Virulence blockers that target T9SS, will provide potential treatment against periodontitis. Hence understanding how the function of the different components of the T9SS apparatus, solving the structure of subunit or subcomplexes, and defining how effectors are recognized, selected, sorted and transported is of critical importance to rationally design molecules of peptides that will block the biogenesis or mode of action of T9SS.

Preventive strategies

Inhibitory compounds

Recent advances in the understanding of the pathogenic mechanisms of P. gingival is may lead to the development of novel strategies for eradication of P. gingival is and treatment for periodontal diseases in the future. Various compounds have been investigated to be potential inhibitors of P. gingival is pathogenesis.

Table 3: Effects of potential inhibitory compounds of P. gingival is

Sn.	Compounds	Effects
1	Quercetin, resveratrol, and related compounds catechin, epicatechin, orcinol and 4-allylphenol[49]	Inhibitory effect on the activity of P. gingival is fimbriae
2	Grape seed proanthocyanidin extracts[50]	Inhibitory effect on P. gingival is LPS
3	α-tocopherol[51]	counteracting the damaging effects of P. gingival is LPS by reducing inflammatory cytokines, increasing β-defensins, and promoting gingival fibroblast growth and migration
4	Tormentic acid; [52] Alpha-mangostin[53]	Inhibition of LPS-induced inflammatory response in human gingival fibroblasts, by inhibiting IL-6 and IL-8

		production
5	DX-9065a, proteinase inhibitor[54]	Activation of coagulation factor X which selectively reduced P. gingival is growth.
6	KYT-41, synthetic dual protease inhibitor[55]	Antibacterial and anti-inflammatory activity against P. gingival is, through inhibition of Rgp and Kgp proteases
7	Rhein, anthraquinone from rhubarb roots[56]	Antibacterial synergistic effect with polyphenols, causing downregulation of two protease genes, RgpA and Kgp
8	Theaflavins, polyphenols in black tea[57]	Inhibition of proteinase activities of gingipains
9	Polyphenols of Myrothamnus flabellifolia[58]	Anti-adhesive and cytoprotective effects, by interacting with P. gingival is OMPs
10	Streptococcal ArcA derived Anti-P. gingival is Peptide (SAPP)[59]	Inhibit P. gingival is colonization on the surface of Streptococcus gordonii, by repressing the expression of P. gingival is genes such as Fim A, mfA1, RgpA/B and Kgp
11	Epimedokoreanin B, prenylated flavonoid from Epimedium	Inhibitory activities against gingipains, host protein degradation, vascular permeability
	species[60]	enhancement, and haemagglutination
12	DANA (2-deoxy-2,3-didehydro-N-acetylneuraminic acid)[45]	sialidase inhibitory activity against P. gingival is, affecting its growth, biofilm formation and virulence; and inhibiting inflammation
13	Cratoxylum cochinchinense methanolic leaves extract (CCM)[61]	Inhibits the citrullination process of P. gingivitis PPAD

Vaccination against p. gingivitis

A common finding in patients with periodontitis is the presence of P. gingival is-specific antibodies in serum and GCF. The production of antibodies is the result of activation of the major host defence mechanism; but these antibodies are insufficient to clear P. gingival is infection. Immunization with several P. gingival is-specific antigens, such as capsular antigens, LPS, fimbriae, OMPs, haemmagglutinins and gingipains, has been shown to enhance the immune response against P. gingival is by the induction of specific antibodies and reduction of P. gingival is-induced bone loss in animal models. In general, these antigens of P. gingival is induce an overall inflammatory immune response as demonstrated in vitro for a wide variety of cell types and in vivo, in experimental animal models. Despite the strong and active inflammatory immune response generated by P. gingival is antigens, more research is needed to study the use of the same, as vaccine candidates, which, if used appropriately, may have utility as an adjunctive therapy in ameliorating chronic periodontitis.[40]

Conclusion

P. gingival is, the key stone pathogen - possesses all of the biological and chemical characteristics that make it an important member of the periodontopathic microbiota. It possesses and excretes numerous potentially toxic virulence factors, apart from its cell components and macromolecules that also function as virulence factors. Despite the huge data available on P. gingival is, it is not fully understood how P. gingival is escapes the host immune surveillance and thrive under the micro-ecologically imbalanced system by completely exploiting its virulence factors. Explaining the unique pathogenic mechanism of P. gingival is virulence factors is an strenuous task, and a significant amount of work remains, which requires the collaboration of researchers. It is believed that with the developmental leap of peri medicine, problems will ultimately be solved to provide effective and efficient treatment for patients with periodontitis and periodontal-associated systemic-diseases.

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