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Review Article

Aggregatibacter actinomycetemcomitans- A periodontopathogen

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ABSTRACT

Aggregatibacter actinomycetemcomitans is a gram-negative oral pathobiont that is associated with severe form of periodontitis. This bacterium has various virulence factors which enables the bacterium to colonize the oral cavity, invade and evade the host defences. Leukotoxin and cytolethal distending toxin are the important virulence factors that causes periodontal destruction. Periodontal infections with *Aggregatibacter actinomycetemcomitans* seems to be refractory to conventional therapy and systemic antibiotics. Hence, leukotoxin represents an ideal anti-virulence target and inhibition of its immunosuppressive activity would eliminate the colonization advantage provided to the bacteria by the toxin.

Key message: This review provides a comprehensive update of *Aggregatibacter actinomycetemcomitans* with an emphasis on its virulence factors leukotoxin and cytolethal distending toxin and its role in periodontal destruction and recent developments in the management.

1. Introduction

Periodontitis is a chronic inflammatory disease associated with loss of the supporting connective tissue and alveolar bone around the teeth. According to the Global Burden of Disease Study, severe periodontal disease was the 11^{th} most prevalent condition in the world and the prevalence ranges from 20% to 50%. It is one of the major causes of tooth loss which can compromise mastication, aesthetics, and quality of life.[1–3]

The etiology of periodontal diseases are multi-factorial and periodontopathogens plays an important role in the initiation of periodontal disease. In 1996, three bacteria, *Aggregatibacter actinomycetemcomitans*, Tannerella forsythia and *Porphyromonas gingivalis*, were officially designated as aetiological agents of periodontitis.[4] The aim of this review is to provide a comprehensive update of *Aggregatibacter actinomycetemcomitans* with an emphasis on its virulence factors leukotoxin and cytolethal distending toxin and its role in periodontal destruction and recent developments in the management.

2. Aggregatibacter actinomycetemcomitans

Aggregatibacter actinomycetemcomitans is a member of the *Pasteurellaceae* family and it is a gram-negative, capnophilic and facultative anaerobic bacillus. Inclusion of *Aggregatibacter actinomycetemcomitans* as an etiological agent of periodontitis was based on prevalence studies in healthy and periodontally diseased subjects, the presence of bacterial virulence determinants that have the potential to promote disease, and the presence or absence of circulating antibodies in affected patients and healthy groups.[4]

It is one of the main causative organism of aggressive form of periodontal disease and was initially considered to be the sole causative agent of localised aggressive periodontitis.[5] Recent work by Fine et al in 2019, has hypothesized that *Aggregatibacter actinomycetemcomitans* may instead promote the development of an alliance of specific microorganisms that cause symptoms of the disease.[6]

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3. History

1. The bacteria was first isolated from a cervicofacial actinomycotic lesion in 1912 by Klinger and was designated as *Bacterium actinomycetemcomitans*.[7]
2. It was designated as *Actinobacillus actinomycetemcomitans* in 1929 by Topley and Wilson.[8] The term *Actinobacillus* connotes the internal star-shaped morphology when viewed under a microscope and the short rod like or bacillary nature of individual cells. The name *actinomycetemcomitans* arises from its association with an actinomycete and frequent isolation from actinomycotic lesions along with *Actinomyces israelii*.
3. Pulverer in 1959 was the first to demonstrate that *Actinobacillus* actinomycetemcomitans was part of the normal oral flora and indicated that *Actinobacillus* actinomycetemcomitans could colonize teeth, musoca and the oropharynx.[9]
4. Leukotoxin was discovered by Tsai et al in 1979.[10]
5. Norskov-Lauritsen and Kilian in 2006 reclassified *Actinobacillus actinomycetemcomitans* as *Aggregatibacter actinomycetemcomitans*. *Aggregatibacter* refers to the rod shaped bacterium that aggregate with others.[11]

4. Serotypes

1. Non-oral strains of *Aggregatibacter actinomycetemcomitans* were classified into three serotypes (a, b, c) on the basis of a heat-stable antigen by King and Tatum in 1962.[12]
2. Differences in surface antigens and leukotoxin production were used by Taichman in 1982to classify *Aggregatibacter actinomycetemcomitans* into four serogroups.[13]
3. Five serotypes of *Aggregatibacter actinomycetemcomitans* were identified and designated as a, b, c, d and e, leaving 3-8% of clinical isolates non-serotypeable.[5]
4. Kaplan et al in 2001 reported serotype f.[14]
5. Takada et al in 2010 reported serotype g.[15]
6. A systematic review by Brígido et al., stated that serotypes a, b, and c are globally dominant, serotypes d and e are rare and the distribution patterns of *Aggregatibacter actinomycetemcomitans* vary among subjects of different ethnicity and geographic regions and their association with various periodontal conditions remains unclear.[16]
7. Joshi et al.,found that there was presence of multiple serotype in the same individual and combination of any serotype with herpes virus was associated with increased severity of disease.[17]
8. Claesson et al., found that serotype b was more prevalent in Sweden.[18]
9. Setty et al., found that that serotype c was more predominant in periodontal disease in India.[19]
10. Sudhakar et al., found that serotype b and serotype e were predominant in chronic periodontitis patients and serotype b was predominant in aggressive periodontitis patients.[20]

5. Virulence factors of Aggregaticbacter actinomycetemcomitans

Aggregatibacter actinomycetemcomitans has many virulence factors that play an important role in the initiation and progression of periodontal disease.

5.1.

5.1.1. Factors that promote colonization and persistence in the oral cavity

1. Adhesins
2. Autotransporter proteins
3. Fimbriae
4. Bacteriocins
5. Antibiotic resistance

5.1.2. Factors that interfere with the host defences

1. Leukotoxin
2. Chemotactic inhibitors
3. Immunosuppressive proteins
4. Fc-binding proteins

5.1.3. Factors that destroy host tissues

1. Cytolethal distending toxin
2. Collagenase
3. Lipopolysaccharide
4. Inflammatory mediators

5.1.4. Factors that inhibit host repair of tissues

1. Inhibitors of fibroblast proliferation
2. Inhibitors of bone formation

Leukotoxin and cytolethal distending toxin are unique to *Aggregatibacter actinomycetemcomitans* and causes periodontal breakdown.

6. Leukotoxin

The leukotoxin of *Aggregatibacter actinomycetemcomitans* is one of the main virulence factors of this bacterium which can destroy host immune tissues. It is a large pore-forming toxin and belongs to the repeats-in-toxin (RTX) family. The operon of this toxin consists of four coding genes determined as ltxC, ltxA, ltxB, and ltxD. ltxC encodes the components of the post-translational acylation of toxin, while ltxA encodes approximately 113 KDa protein which is the structural protein of the toxin and LtxB and LtxD

are required for transporting the toxin to the bacterial outer membrane.[21]

LtxA consists of 1,055 amino acids, and has been divided into four functional domains. The hydrophobic domain (residues one–420) consists primarily of hydrophobic residues and contains the reported cholesterol binding site ($CRAC^{336}$). The central domain (residues 421–730) contains two lysine residues, K^{562} and K^{687}, that are post-translationally acylated. The repeat domain (residues 731–900) contains 14 copies of the repeats-in-toxin specific repeated amino acid motif. The C-terminal domain (residues 901–1,055) plays a role in secretion. Epitopes of the neutralizing anti-LtxA monoclonal antibodies are found in the central, repeat, and C-terminal domains.[22]

7. Leukotoxin and periodontal disease

7.1. Host cells targeted by leukotoxin

Leukotoxin specifically targets human immune cells such as polymorphonuclear leukocytes, monocytes, macrophages and lymphocytes.[23,24] Leukotoxin also acts on hematopoietic cells and endothelial cells.

7.2. Receptors of leukotoxin

Leukotoxin interacts with erythrocytes and endothelial cells but the toxin is able to interact with human immune cells at a much lower concentration and with much faster kinetics. This host cell type specificity of leukotoxin suggests that the toxin recognizes a specific component on human white blood cells that is not present on other cell types. Lymphocyte function-associated antigen-1 integrin is identified as the functional receptor for leukotoxin. However, additional receptors might be involved in leukotoxin recognition of other cell types or that might play a supplementary role in the interaction of leukotoxin with human immune cells.[23]

7.2.1. Lymphocyte function-associated antigen-1 (LFA-1)

Lymphocyte function-associated antigen-1 is a transmembrane glycoprotein that functions as an adhesion and signalling receptor on the surface of leukocytes. It is composed of two non-covalently associated subunits: CD11a and CD18 and it is one of the four members of the β2 integrin family.[22]

In lymphocytes, both CD11a and CD18 are critical for leukotoxin to induce its toxic effects. Leukotoxin has a strong binding affinity for regions of the cytosolic domains on both CD11a and CD18. Specifically, leukotoxin binds to peptides representative of an N-terminal region of the CD11a cytosolic domains and to a peptide representing an intermediate region of CD18. Although leukotoxin seems to have a strong affinity for the cytoplasmic domains of LFA-1, these interactions may not play a significant role in leukotoxin -mediated cytotoxicity.[24,25]

7.2.2. P2 receptors

Reports of leukotoxin -mediated hemolysis prompted studies to identify a receptor for leukotoxin on erythrocytes. Munksgaard et al.,hypothesized that leukotoxin interacts with P2X receptors in an ATP-dependent manner to mediate lysis. P2X antagonists, including pyridoxalphosphate-6-azolphenyl-2′,4′-disulfonic acid (PPADS), inhibited leukotoxin -mediated hemolysis.[26] A similar effect was identified in human monocytes. P2X inhibitors have also been demonstrated to interfere directly with oligomerization of the Staphylococcus aureus α-toxin which had been reported to require P2X receptor activation.[27]

7.2.3. Fas receptor

Di Franco et al.,demonstrated that leukotoxin kills lymphoma cells in a caspase-8-dependent manner.[28] The authors then screened a number of receptors and proteins that can activate caspase-8, and identified the death receptor, Fas, as an essential component in the leukotoxin -mediated killing of these cells. The researchers also observed decreased antibody binding when cells were pre-treated with the toxin, suggesting that leukotoxin binds directly with the Fas receptor. In a recent investigation by Vega et al., the researchers further identified the importance of the Fas receptor for leukotoxin cytotoxicity in lymphocytes.[24]

7.3. Interaction of leukotoxin with cholesterol

One of the critical interactions between leukotoxin and host cells is the binding to cholesterol. Removal of cholesterol from the host cell membrane with methyl-β-cyclodextrin significantly inhibited the ability of leukotoxin to kill the cell.[29,30]

7.4. Mechanism of action of leukotoxin in causing periodontal destruction

Interaction of *Aggregatibacter actinomycetemcomitans* leukotoxin with T-, B-lymphocytes, polymorphonuclear leukocytes, and macrophages leads to cell lysis. Leukotoxin-induced cell death in macrophages involves several steps before the cell lysis occurs.[31]

1. Leukotoxin binds to lymphocyte function-associated antigen-1
2. Induces extracellular release of ATP
3. The released ATP binds to the $P2X_7$-receptor
4. Subsequently causes efflux of potassium
5. The inflammasome complex is formed and activated
6. Promotes the cleavage and activation of a cysteine proteinase called caspase
7. The cleaved caspase1 is then responsible for activation
8. And release of abundant levels of active interleukin-1β and interleukin-18
9. The secreted interleukin-1β, from leukotoxin exposed macrophages, was mainly the biologically active form

and could act as the major activator of bone resorption.

In neutrophils, leukotoxin activates degranulation causing a massive release of lysosomal enzymes, net-like structures, and matrix metallo proteinases and induces apoptosis in lymphocytes. Net-like structures can also be released from the leukotoxin exposed neutrophils under anaerobic conditions and contain citrullinated proteins with sequence homology to proteins found in inflamed joints.[32–34]

Variations in gene that encodes for leukotoxin which leads to increased leukotoxin production and periodontal destruction

The ltxCABD gene operon encoding the leukotoxin is controlled by one promoter, referred to as the leukotoxin promoter. It has a full length of approximately 1106–1112 base pairs. Some isolates which belongs to the JP2 clone or the JP2 genotype are characterized by lacking almost half of the full-length promoter (530 base pair). This genotype was initially believed to only be present in individuals of North or West African origin but it has also been detected in individuals of other origins.[35–38]

The JP2 genotype produces increased amounts of the leukotoxin and strains of this genotype have been demonstrated to be highly leukotoxic. Individuals colonized by this genotype are at increased risk for development of an aggressive form of periodontitis.[39,40]

JP2 genotype strains share a specific gel electrophoresis banding pattern in arbitrarily primed polymerase chain reaction, referred to as AP-PCR genotype 1. Non-JP2 AP-PCR genotype 1 strains also express high leukotoxin levels and are associated with periodontal attachment loss progression. All AP-PCR genotype 1 strains, carry the cagE gene locus. This gene sequence has been suggested as a suitable diagnostic marker for carriers of highly virulent *Aggregatibacter actinomycetemcomitans* serotype b and which are at increased risk of developing an aggressive form of periodontitis and appears not to be present in any of the other serotypes.[41,42]

Two additional promoter variants of *Aggregatibacter actinomycetemcomitans* have been reported, one lacking 640 base pair instead of the typical 530 base pair and one promoter that carries an 886-base pair insertion sequence, referred to as IS1301.[43]

Claesson et al., identified and characterized two additional ltxCABD promoter types of *Aggregatibacter actinomycetemcomitans* serotype b, being one, which contains a 172-base pair duplication, whereas the other lacks 230 base pair and therefore has a deletion.[44] The leukotoxin expression was significantly higher for the JP2 genotype strain, HK1651, the 640-base pair deletion type and the 230-base pair deletion type.

There was low production of leukotoxin by *Aggregatibacter actinomycetemcomitans* with a complete leukotoxin promoter. It is due to the fact that a transcriptional repressor, can bind to a region in the promoter which leads to decreased secretion of leukotoxin. This region in the promoter is not present in JP2 genotype strains due to their 530-base pair deletion. Recently, it was reported that the specific region of the promoter that is crucial for the binding of this putative repressor is 100 base pair, present within the 530-base pair region, that is absent in the JP2 genotype strains. 230 base pair deletion in strain 046-19 was found to be located within the same 530-base pair region.[44,45]

8. Anti- leukotoxin strategies to prevent periodontal destruction

Aggregatibacter actinomycetemcomitans has shown resistance to common antibiotic treatments. Hence, leukotoxin represents an ideal anti-virulence target and inhibition of its immunosuppressive activity would eliminate the colonization advantage provided to the bacteria by the toxin.[22,46]

8.1. Receptor blocking

Leukotoxin has a variety of receptors used to target host cells. Since both cholesterol and lymphocyte function-associated antigen-1 have been established to be required for cytotoxicity, preventing the toxin from interacting with either may provide a way to inhibit the toxin's activity.[22]

8.2. Cholesterol inhibition

A peptide was synthesized by Koufos in 2016.[47] It inhibited LtxA activity by blocking the binding of the toxin with cholesterol and it also blocked the internalization of the toxin and cytotoxicity. Peptide competed with the toxin for potential binding sites, interrupting the interaction of LtxA with cholesterol.[30]

8.3. Lymphocyte function-associated antigen-1 inhibition

A series of peptides was synthesized based on the β-strands of lymphocyte function-associated antigen-1. Four of the five peptides inhibited leukotoxin cytotoxicity in THP-1 cells.[48]

8.4. Catechins and small molecules

DRAQ5 altered the host cell membrane property and inhibited leukotoxin from embedding in the bilayer which demonstrated that small molecules like catechins have potential as anti-toxin agents.[49]

Catechins are polyphenols commonly found in foods like green tea, cocoa, red wine and variety of fruits and vegetables, and are attributed to numerous health benefits due to their antioxidant and antimicrobial properties.[50]Epigallocatechin gallate was found to have

the strongest effect against leukotoxin but remarkably, five of the catechins were shown to significantly inhibit cytotoxicity in THP-1 cells when the toxin was pre-treated with the catechins.[22,51]

9. Cytolethal distending toxin

The cytolethal distending toxin consists of subunits CdtA, CdtB, and CdtC. While CdtA and CdtC subunits mediate the internalization of the CdtB into the cell, the latter is translocated to the nucleus, causing its deleterious effects on the host cells. This subunit is functionally homologous to deoxyribonuclease I, hence it can cause DNA damage. It is postulated that CdtB internalization occurs through a mechanism involving the recognition of cell membrane cholesterol by both CdtC and CdtB.[52]

10. Cytolethal distending toxin and periodontal disease

Aggregatibacter actinomycetemcomitans expresses a cytolethal distending toxin and is the only known oral species with this property. An estimated 66% to 86% of its strains express a cytolethal distending toxin, and its presence has been associated with the occurrence of periodontal disease. It is very plausible that its pathogenic effects are related to its capacity to cause DNA damage, cell cycle arrest, and eventually apoptosis to the intoxicated cells.[53,54]

The deleterious effects of cytolethal distending toxin on cells of the immune system denote an impairment of the local immunity, which may compromise the capacity of the periodontium to recognize and eliminate the bacterial challenge, be it *Aggregatibacter actinomycetemcomitans* or other microbial constituents of the biofilm community.[54]

Another potentially pathogenic mechanisms activated by cytolethal distending toxin is the stimulation of pro-inflammatory and osteolytic cytokine production by the intoxicated host cells. Cytolethal distending toxin induces receptor activator of nuclear factor kappa-*B* ligand expression and production in periodontal connective tissue cells, such as gingival fibroblasts and periodontal ligament cells, as well as T-cells. This implies that the cytolethal distending toxin may increase the levels receptor activator of nuclear factor kappa-*B* ligand in the periodontal tissues and therefore potentiate bone destruction by this action. The induction of inflammatory and bone-destructive molecular cascades in the periodontium by cytolethal distending toxin may well constitute an additional mechanism through which *Aggregatibacter actinomycetemcomitans* is involved in the etiopathogenesis of periodontitis. On the other side of the bone remodeling equilibrium, when cytolethal distending toxin acts directly on pre-osteoclasts, it may also induce apoptosis and hinder their differentiation to osteoclastic cells, thereby contributing a dysbalanced bone remodeling equilibrium that leads to periodontal breakdown.[55]

11. Conclusion

Aggregatibacter actinomycetemcomitans possesses traits that enable it to colonize, invade, avoid the host-defensive strategies and cause tissue destruction. Leukotoxin and cytolethal distending toxin are the major virulence factors that are involved in periodontal destruction. Future research should be directed towards development of strategies against these toxins.

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14. Conflicts of Interest

All contributing authors declare no conflict of interest.

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