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Review Article

Aggregatibacter Actinomycetemcomitans, an Aggressive Oral Bacteria - A Review

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ABSTRACT

Aggregatibacter actinomycetemcomitans, an oral commensal which is also an opportunist pathogen has a distinct racial bias and a surprising range of potential virulence factors and virulence mechanisms. It is a pathogen not only in the periodontium but also in some non oral infections, possesses several virulence determinants which contribute to its ability to colonize the oral cavity, persist in the periodontal pocket, resist and evade host defenses, cause destruction to soft and hard tooth-supporting tissues, and interfere with host tissue repair after infection. The purpose of this review is to elaborate the microbiological aspects of this bacteria which makes it clinically significant.

Keywords: Aggregatibacter actinomycetemcomitans, aggressive periodontitis, leukotoxin

I INTRODUCTION

More than 500 cultivable bacterial species have been isolated from the gingival crevices of human beings, [1] but the actual species count may be thousands, since a wide proportion of bacteria remains uncultivable or unidentified. [2] The sub gingival bacterial flora consists of facultatively anaerobic gram positive species in the healthy oral cavity, but in gingivitis the proportion of gram negative bacteria increases. [3] In periodontitis , only 10 to 30 species, mainly gram negative anaerobic bacteria, are putative pathogens. [4] Three species Actinobacillus actinomycetemcomitans , Porphyromonas gingivalis and Bacteroides forsythus are presently considered as periodontal pathogens and primary etiological agents in periodontitis (World Workshop in Periodontics 1996). Additional putative periodontal pathogens include Prevotella intermedia, Prevotella nigrescens, Campylobacter rectus , Fusobacterium

nucleatum , Peptostreptococcus micros and spirochetes (American Academy of Periodontology 1992 , Haffajee & Socransky 1994 , World Workshop in Periodontics 1996)

II HISTORICAL PERSPECTIVE

A. actinomycetemcomitans was first isolated and identified in 1912 by Klinger. [5] It was so named because of its consistent association with Actinomyces israelii in actinomycotic infections. In 1934 Klaber reported that this organism occurred only in association A. israelli. Heinrich and Pulverer (1959) reported that 30% of actinomycotic lesions contained this organism. However King and Tatum in 1962 reported instances of infection with A.actinomycetemcomitans unconnected with diagnosed actinomycosis. They considered this organism to be an important etiologic agent of endocarditis. [6] Since that time more cases of A.actinomycetemcomitans endocarditis have been reported (Mitchell & Gillespie 1964, Goss et al 1967 , Affias et al 1978). It has also been reported in brain abscess (Martin et al 1967), urinary tract et al infection (Townsend & Glenwatter 1969), infection of thyroid gland (Burgher et al 1973) osteomyletis (Muhle et al 1979). A. actinomycetemcomitans was first recognized as a possible periodontal pathogen by its increased frequency of detection and higher numbers in lesions of localized juvenile periodontitis (Newman et al 1976, Slots 1976, Newman & Socransky 1977, Slots et al 1980, Mandell & Socransky 1981, Zambon et al 1983, Chung et al 1989) [7]

III TAXONOMIC CLASSIFICATION

Aggregatibacter (previously Actinobacillus actinomycetemcomitans), a member of family Pasteurellaceae, [8] has been recognized as one of the key pathogens in periodontitis. This bacterium was first isolated from human cervicofacial actinomycosis together with Actinomyces and was thus described as Bacterium actinomycetemcomitans by Klinger in 1912. [9] Later Lieske in 1921 reclassified as Bacterium comitans. During the past 95 years , the taxonomic position has met several changes . In 1929 , Topley and Wilson changed the genus name to Actinobacillus although Bacterium actinomycetemcomitans had a weak resemblance to Actinobacillus lignirersiii , the type species of the genus Actinobacillus . In the name Actinobacillus actinomycetemcomitans , the new genus name refers to the star shaped structure (Greek actis "ray ") in the centre of the colonies of rod shaped cells.

King & Tatum (1962) [10] described the close phenotypic similarity of Actinobacillus actinomycetemcomitans with H. aphrophilus, and Actinobacillus actinomycetemcomitans was subsequently reassigned to the genus Haemophilus as Haemophilus actinomycetemcomitans by Potts et al 1985. [11] The genus change was however, not favoured , as Actinobacillus actinomycetemcomitans was not closely related to Haemophilus influenza , the type species of the genus Haemophilus. [12] The difference between Actinobacillus actinomycetemcomitans and Haemophilus influenzae is based on a number of chemotaxonomic characteristics as well as on 16S rRNA gene sequence phylogeny . Therefore the previous genus Actinobacillus was reinstated. [13]

Phylogenetic analysis of the three Pasteurellaceae genera , Actinobacillus - Haemophilus – Pasteurella , based on 16SrRNA gene sequences , revealed that Actinobacillus actinomycetemcomitans is closely related Haemophilus aphrophilus and Haemophilus paraaphrophilus and that these three species together with

Haemophilus segnis formed a single phylogenetic cluster . Due to their phylogeny and their typical phenotypic charecteristics - the autoaggregation, the species Actinobacillus actinomycetemcomitans, Haemophilus aphrophilus , Haemophilus paraaphrophilus and Haemophilus segnis were recently reclassified to a novel genus Aggregatibacter by Norskov – Lauritsen and Kilan; 2006. [14]

Taxonomic classification: Full lineage:

Domain	Bacteria
Phylum	Proteobacteria
Class	Gammaproteobacteria
Order	Parteurellales
Family	Pasteurellaceae
Genus	Aggregatibacter
Species	actinomycetemcomitans
Taxonomic I D	*714*
Type strain	*ATCC33384* *NCTC 9710*

IV CULTURAL CHARECTERISTICS

A actinomycetemcomitans is a small non motile Gram negative coccobacillus. It is capnophilic and facultatively anaerobic, it grows well in 5% CO2 in air or anaerobically and growth into well developed colonies takes 24-48hrs. On solid growth media, fresh A. actinomycetemcomitans isolates adhere to agar and form circular colonies 0.5 to 1mm in diameter with slightly irregular edges.

Fresh oral isolates of A. actinomycetemcomitans are invariably fimbriated and form small (~1mm), rough surface, translucent colonies, with an internal star shaped morphology. Repeated subculturing of the clinical isolates results in a spontaneous change from rough to smooth colony morphology as represented by A. actinomycetemcomitans strains from American Type Culture Collection. [15]

The rough colony morphology and the tight adherence (autoaggregation phenotype) have been attributed to the presence of long and bundled fimbriae on the cell surface . Colonies of the smooth variants lack the star like inner structure and the cells do not express fimbriae. [16] The non fimbriated smooth colony variants grow as large , round opaque colonies on agar.

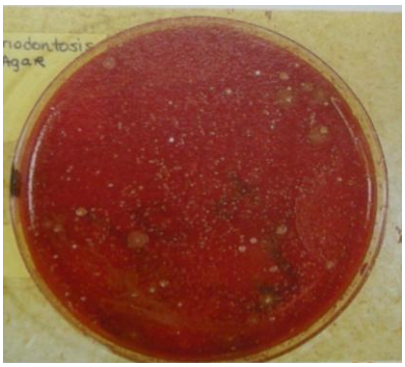
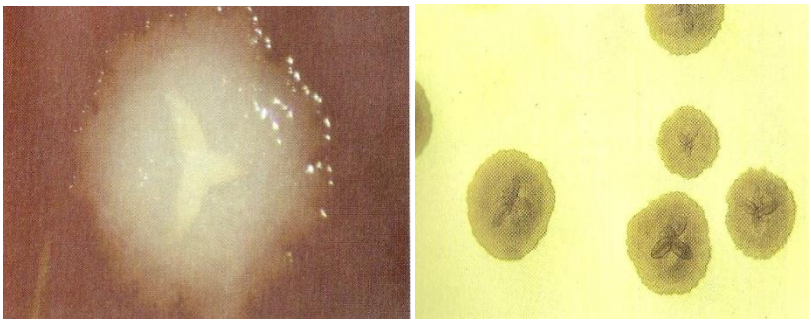


Figure 1 : Photograph of a primary isolation plate of a sub gingival plaque sample from a diseased site from a subject with LJP. The majority of small round convex colonies on this plate are isolates of A. actinomycetemcomitans

Occasionally the rough to smooth transition goes through an intermediate phase in which the colonies are translucent but smooth surfaced. Genes for the fimbriae biogenesis of A.

actinomycetemcomitans reside in the 12-kb flp operon that contains 14 genes flp-1-flp-2-tadV- rcpCAB-tadZABCDEFG. The transcription - initiation points of the operon were located at 101 and 102 nucleotides upstream of flp – 1



A B

Figure-2. Colony morphology of an A. actinomycetemcomitans strain on A. specific medium, and B , a nonspecific medium The internal star is easily seen

V BIOCHEMICAL CHARECTERISTICS

- Lack of growth on Mac Conkey and other enteric agars
- Catalase production : + ve
- Nitrate reduction : + ve
- Oxidase negative : + ve (occasional strains may be weakly positive)
- Urease : - ve
- Indole production : - ve
- X V factor requirement : - ve
- Glucose , Fructose , Mannose : strong fermentation
- Acid production from maltose , mannitol and xylose varies
- Non – haemolytic

Based on the variability in fermenting maltose, mannitol, xylose and dextrin A. actinomycetemcomitans strains have been grouped into 10 biotypes

Growth on chocolate and blood agar:

- Grows slowly
- Visible colonies appear after 48 to 72 hrs
- Colonies are small, smooth , translucent, non haemolytic and have slightly irregular edge
- Fresh clinical isolates are adherent to the agar , difficult to emulsify
- Prolonged incubation (5 to 7) days – colonies may develop a central density that appears as four or six pointed star. This characteristic is lost on repeated subcultures and the colonies become less adherent

Growth in broth:

- Growth is scant and adherent to sides of the tube

VI FACTORS INFLUENCING THE GROWTH AND VIABILITY OF A. ACTINOMYCETEMCOMITANS

The addition of increasing concentrations of yeast extract to bacteriological medium increased the growth rate of several A. actinomycetemcomitans strains.The addition of L- cysteine resulted in bacterial growth rates comparable to those with yeast extract. Thiamine increased the growth of several A. actinomycetemcomitans strains but did not result in growth rates comparable to those with yeast extract. The addition of physiological concentrations of steroid hormones to bacteriological medium enhanced the growth of A.

actinomycetemcomitans. Additional iron compounds and fat soluble vitamins had no influence on A. actinomycetemcomitans growth. The optimal pH range for A. actinomycetemcomitans was between pH 7.0 – 8.0 in a medium containing 0.5 – 1 % NaCl. Several interesting observations on the viability of A.actinomycetemcomitans were made . A rapid reduction of A.actinomycetemcomitans a viability occurred following suspension in distilled water . The presence of detergent Triton X – 100 at concentrations above 2% (u/v) also decreased the viability of A. actinomycetemcomitans within 10 min. [17]

VII VIRULENCE FACTORS

Virulence factors

- Leukotoxin
- Endotoxin
- Collagenase
- Bacteriocin
- Cytolethal distending toxin
- Adhesins
- Neutrophil inhibitor
- Fc binding proteins

A. actinomycetemcomitans is one of the few oral bacteria capable of colonizing buccal mucosa as well as dental plaque. The establishment of A.actinomycetemcomitans in the human oral cavity is dependent on appropriate attachment sites for initial colonisation and is influenced by the interacting microflora and various host factors

Aa colonisation factors;

- Pili or fimbriae
- Capsule
- Interactions with other bacteria
- Vesicles

➢ **Fimbriae (pili):** They are thin surface appendages that serve as adhesion determinants for initial attachment of A. actinomycetemcomitans to oral surface.

➢ **Bacterial interactions:** Bacterial interactions or interbacterial antagonism seem to be another determinant of oral colonisation of A. actinomycetemcomitans.

Hillman and co – workers (1982, 1985, 1987) showed that certain species such as Streptococcus sanguis , Actinomyces naeslundi genospecies 2 and Streptococcus uberis produced factors that were inhibitory to the growth of A. actinimycetemcomitans. The mechanism of inhibition was shown to be hydrogen peroxide formation by the " beneficial species ", which either directly or via a host peroxidase system inhibited the pathogen.

Stevens et al. (1987) and Hammond et al (1987) demonstrated the reverse antagonism. A. actinomycetemcomitans was shown to specifically inhibit the growth of S. sanguis, S. uberis, and A. naeslundii genospecies 2 (but not other species) by the production of a bacteriocin. This mutual antagonism is highly specific and its outcome may strongly influence whether a subject or a site will exhibit disease due to A. actinomycetemcomitans.

➢ **Vesicles:** Aa elaborates numerous vesicles or " blebs" on the cell surfaces. Their role in initial colonisation, if any , remains to be determined .

➢ **Plasmids and Bacteriophages:** Plasmids and bacteriophages are genetic elements that may alter the physiological properties of a microorganism , contribute to virulence , modify taxonomic status , and spread biological properties

among different strains, species , and genera.

About 5 percent of clinical isolates of A. actinomycetemcomitans show small or larger cryptic (i.e., with unknown function) plasmids .

VIRULENCE FACTORS:

It must be emphasized that , although a large numbers of 'virulence factors' of A. actinomycetemcomitans have been identified, there have been no in- vivo studies with isogenic mutants to establish that any of these proteins are implicated in tissue pathology.

Leukotoxin: A actinomycetemcomitans leukotoxin was found in the end of 1970's. It is a 116kDa protein and a member of the RTX (repeats in toxin) family whose cellular receptor is the beta 2 – integrin , LFA-1, thus accounting for its selective effect on leukocytes (although only those from primates) .

The gene operon that produces A. actinomycetemcomitans leukotoxin is designated as lkt. The leukotoxin operon consists in transcription order , of four genes – lktC, A, B and D . The lktA protein is the active toxin and this has to be acylated, by lktC and an acyl carrier protein, to be biologically active. The other two proteins (lktB and lktD) are responsible for transport and secretion of lktA . Interestingly , although different strains of A.actinomycetemcomitans express different levels of leukotoxin, they all have the genes for leukotoxin operon . The differences in leukotoxin expression appear to be due to transcriptional regulation since there is a direct correlation between the level of leukotoxin and the amount of lkt RNA in a given strain. The RTX leukotoxins are secreted , and the only exception to this is the lkt toxin of A. actinomycetemcomitans which has been thought to be entirely cell associated ; either bound to cell surface – associated nucleic acids or within membranous vesicles which bud from the bacterium's surface. This means that the bacterium itself is toxic to target cells. A.actinomycetemcomitans leukotoxin specifically kills leucocyte function associated antigen bearing cells such as polymorphonuclear leucocytes and macrophages, whereas other types of cells (e.g.: epithelial and endothelial cells, fibroblasts, erythrocytes and platelets) are resistant to lysis.

The leukotoxin mediated killing is extremely rapid (a matter of minutes) and is caused by formation of pores in the cell membrane of target cells.. Cell lysis might be induced by the rapid formation of highly conducive ion channels that lead to membrane depolarization , loss of intracellular K+ , osmotic swelling and subsequent cell death .Some A. actinomycetemcomitans strains produce higher amounts of leukotoxin than the others. Best known of the high producers are the JP2 – like clones , first reported for the strain JP2 that was recovered from an African – American individual with localized juvenile periodontitis. Molecular analysis of lkt operon revealed that a 530- bp deletion in the promoter region of the lktA genes is a possible reason for enhanced leukotoxin production in these strains. Except for the JP-2 like strains , also strains without the 530-bp deletion in the promoter region can produce elevated amounts of leukotoxin A. actinomycetemcomitans produces higher amounts of leukotoxin in anaerobic conditions than in aerobic conditions which is due to the presence of a 35 – bp oxygen response element that

represents leukotoxin production in aerobic conditions.

Superantigens:

Superantigens are generally bacterial proteins that activate T cells bearing specific V beta T- cell receptors. One consequence of such activation is that the T cells apoptose and thus superantigens can be considered as immunosuppresants.

Cytolethal distending toxin :

The cytolethal distending toxin (CDT) is a cell cycle – modulatory protein with immunosuppressive function . This toxin is the product of a three gene operon (cdtA, cdtB, cdtC) which is found in a range of bacteria including Escherichia coli , Shigella spp., Campylobacter spp., Helicobacter spp.

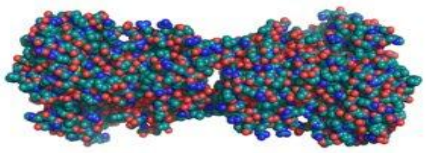


Figure 5: Crystal structure of cytolethal distending toxin

The mechanism of action of this toxin is believed to be due to nuclease activity of cdtB . In some, as yet unexplained manner, cdtA and cdtC are believed to facilitate the entry of cdtB into host cells. The cdtB is believed to enter into the nucleus and degrade chromosomal DNA, thus inducing cell cycle arrest in G2/M phase via specific checkpoint kinases .

Fc binding proteins:

The role of Fc receptors found on the bacterial surfaces and those released in soluble form during growth is not well established. However, in vitro studies suggest that these molecules may function to inhibit complement activation.

Chemotactic inhibitor:

Neutrophils are recruited to infected areas by following a concentration gradient of chemotactic signals. Disruption or inhibition of neutrophil chemotaxis is advantageous for the infecting organism. A. actinomycetemcomitans has been shown to be capable of inhibiting chemotaxis.

Immunosuppressive factor:

A. actinomycetemcomitans has been shown to produce a protein capable of inhibiting DNA, RNA, and protein synthesis in human T cells activated by mitogens or antigens. The purified protein is capable of inhibiting IgG and IgM production by human B cells and affects immunoglobulin production by interfering with the early stage of cell activation. Although the exact mechanism by which immunosuppressive factor (ISF) acts to cause immunosuppression is not known, it appears that this factor affects both B lymphocytes and T- regulatory cells.

Lipopolysaccharide:

A. actinomycetemcomitans lipopolysaccharide (LPS) has been extensively charecterised both structurally and functionally.

- LPS is toxic to human NK cells
- LPS induces the production of cytokines such as IL-6 , IL-8 , IL-1B and TNFA from different host cells, thus promoting inflammatory reaction.
- It also induces bone resorption in vitro and in vivo, which may enhance progression of periodontitis
- actinomycetemcomitans LPS may also contribute to destruction of periodontal connective tissue by

activating the pathways that lead to stimulation of matrix metalloproteinases and plasminogen activator.

- Recently, A. actinomycetemcomitans LPS has shown to induce foam cell formation and cholesteryl ester accumulation in murine macrophages which suggests that it also has proatherogenic activity.

Cytokine inducer proteins secreted by bacterium:

- **Cell stress protein, chaperonin 60 :**
  - Potent bone degrading molecule . This molecular chaperone, which is normally intracellular, appears to be secreted by this bacterium and stimulates bone resorption by acting as an osteoclast " growth factor"
- **Heat shock proteins:**
  - Several authors have reported in A. actinomycetemcomitans the presence of HSPs including GroEL- like (HSP-60) and DnaK like (HSP -70) proteins. Protein homologous to GroEL-like HSP found in the surface associated material of A. actinomycetemcomitans has osteolytic activity by murine bone resorption assay. Purified native GroEl – like HSP from A.actinomycetemcomitans promotes epithelial cell proliferation at lower HSP concentrations, but has a toxic effect on epithelial cells at higher HSP concentrations.

As mentioned above, bacterial and human HSPs share high sequence homology. Antibodies raised against GroEl – like proteins from A.actinomycetemcomitans , P. gingivalis and B. forsythus show a high level of cross reactivity to each other. [18, 19]

Actinomycetemcomitin: A new bacteriocin produced by A. actinomycetemcomitans

Lima FL et al 2008 isolated a bacteriocin named as actinomycetemcomitin from A.actinomycetemcomitans P (7-20) strain that is active against Peptostreptococcus anaerobius ATCC 27337. Actinomycetemcomitin was produced during exponential and stationary growth phases and its amount decreased until it disappeared during the decline growth phase.

VIII DIAGNOSTIC METHODS

Commercial diagnostic kits:

1. **Evalusite (Kodak)** This is a number of enzyme linked immunosorbant assays (ELISA) using antibodies to detect antigens for A.actinomycetemcomitans. The reactions are carried out in a simple chair side reaction kit. Subgingival plaque samples are reacted with the antibodies and detection substrate in a multilevel reaction dish.
2. **Omnigene (Omni Gene, Inc) and BTD (Biotechnica Diagnostics , Inc)** These are DNA probe systems for a number of subgingival bacteria. A paper point sample of subgingival plaque is placed in a container provided and mailed off to the company for assay.

Selective medium for isolation of A.actinomycetemcomitans:

Socransky et al 1981 developed a selective medium , malachite green bacitracin agar , for the isolation of A.actinomycetemcomitans. the medium consists of Trypticase soy agar 40 gm/l , bacitracin 128µg/ml , malachite green 8µg/ml and 5% defibrinated sheep blood. The medium, when incubated in an atmosphere of air plus 10% CO_2 for 5 days, permitted greater than 80% recovery of pure cultures of A.actinomycetemcomitans when compared with a non selective media. [20]

Slots et al 1982 developed TSBV (tryptic soy- serum – bacitracin – vancomycin) agar. TSBV agar contained (per litre) 40 g of tryptic soy agar , 1 g of yeast extract , 100 ml of horse serum , 75 mg of bacitracin and 5 mg of vancomycin. The TSBV medium suppressed most oral species and permitted significantly higher recovery of A.actinomycetemcomitans than non selective blood agar medium. [21]

Martijn van Steenbergen T J et al 1986 compared the two selective media Malachite green bacitracin agar (MGB agar) and tryptic soy serum bacitracin vancomycin (TSBV) agar . The highest recovery was found on TSBV agar plates cultured in air - 5% CO_2 both for plaque samples from periodontal pockets and for pure cultures. [22]

Tsuzukibashi O et al 2008 developed a novel selective medium designated as AASM . It was prepared by adding 200µg/ml of vancomycin and 10µg/ml of bacitracin to AAGM , which contains dextrose , sodium bicarbonate , trypticase soy , yeast extract and agar. They showed that all serotypes (a-f) of A.actinomycetemcomitans strains grow well and the average growth recovery of A.actinomycetemcomitans on AASM medium was 94.4% [23]

Phenotypic typing methods

Biotyping: Serological typing:

Upto now six A. actinomy-cetemcomitans serotypes have been designated (a through f). The serological specificity is defined by six structurally and antigenically distinct O-polysaccharide components of their respective lipopolysaccharide molecules (Page et al., 1991; Perry et al., 1996a, b; Kaplan et al., 2001). However 3% to 8% of A. actinomycetemcomitans isolates remain non serotypeable. [24]

Most periodontal patients with A. actinomycetemcomitans infections harbor only one serotype. Multiple serotypes (or serotypeable and non serotypeable isolates) are found in less than 10% of the subjects. The serotype distribution of A. actinomycetemcomitans in oral cavities of periodontal patients seems to be heterogenous:

- serotype a in 25%
- serotype b in 29 %
- serotype c in 23 to 26 %
- serotype d in 3 to 4 %
- serotype e in 6 to 10 % and
- non serotypeable isolates in 3 to 5 % of subjects. [25]

The only study on the A. actinomycetemcomitans serotype distribution in non oral infections suggested the predominance of serotype c in 72 % of subjects. [26] The serotype specificity is located in the lipopolysaccharide (LPS) O – antigen . The chemical structures of the LPS – O antigen of A.actinomycetemcomitans have been resolved for all six serotypes. While serotypes a, b, c, e and f contain repeated disaccharide or trisaccharide units in their O- antigens ; Serotype d has tetrasaccharide repeating units. [27]

Phylogenetic analysis of A. actinomycetemcomitans strains have revealed genetic diversity among the serotypes . Based on the 16SrRNA gene sequencing, arbitrarily primed polymerase chain reaction and PCR and / or restriction endonuclease analysis of certain genes or gene clusters, three distinct phylogenetic lineages of A. actinomycetemcomitans serotypes have been distinguished . Serotype b and c each form separate lineages and the third lineage consists of serotypes a, d, e and f. [28] It has been suggested that the genetic dissimilarities among A. actinomycetemcomitans serotypes may relate to variation in virulence potential and to the specific associations between certain serotypes or genotypes and periodontitis. For eg: while serotype c is dominant in periodontally healthy individuals serotypes a and/ or b are most frequently found in periodontitis than in health and serotype b and c in non – oral infections . There seems to be , however, geographic / racial / ethnic differences in the serotype distribution in periodontitis. Serotypes d, e and f are only rarely isolated from any population. Association have also been reported between periodontitis and certain restriction fragment length polymorphisms (RFLP) genotypes and AP-PCR genotypes .

Phage typing: Different strains within a species have different sensitivities for the lytic activity of bacteriophage. Phage typing is not available for A.actinomycetemcomitans. [20]

Molecular typing methods:

- Restriction enzyme analysis (REA)
- Restriction fragment length polymorphism (RFLP)
- Ribotyping: Pulse field gel electrophoresis (PFGE)
- Arbitrarily primed (AP)-PCR
- Amplified fragment length polymorphism (AFLP)

These methods have been successfully used to type A.actinomycetemcomitans

IX PRO- ATHEROGENETIC PROPERTIES OF A.ACTINOMYCETEMCOMITANS

An association between cardiovascular and periodontal disease may be due to lipopolysaccharide (LPS) promoted release of inflammatory mediators, adverse alterations in lipoprotein profile and an imbalance in cholesterol homeostasis. Laura Lakio et al in 2006 studied the proatherogenic properties of LPS preparations from serotypes b and d strains on macrophages (RAW 264.7) . A. actinomycetemcomitans LPS preparations induced a time dependant release of TNF – α and IL-1β . LPS induced foam cell formation and cholesterol ester accumulation from native low density lipoprotein in following order A. actinomycetemcomitans strains JP2 (serotype b) > Y_4 (serotype b) > IDH781 (serotype d) mRNA expression levels of scavenger receptor class B , type I and ATP- binding cassette transporter -1 receptors mediating cholesterol efflux from macrophages were decreased by LPS preparations. The result suggest that the pro -atherogenic potential of A.actinomycetemcomitans LPS may depend on the infecting strain and correlate with the periodontopathogenic potential of the pathogen. [29]

X A.ACTINOMYCETEMCOMITANS AND AGGRESSIVE PERIODONTITIS

Localised Aggressive periodontitis

This species was first recognized as a possible periodontal pathogen by its increased frequency of detection and high numbers in lesions of localized juvenile

periodontitis (Newman et al. 1976, Slots 1976, Newman & Socransky 1977, Slots et al. 1980, Mandell & Socransky 1981, Zambon et al 1983, Chung et al 1989) when compared with numbers in plaque samples from other clinical conditions including periodontitis, gingivitis and health. Majority of subjects with Localised Juvenile Periodontitis demonstrated elevated serum antibody response to this species and that there was local synthesis of antibody to this species. When subjects with LJP were treated successfully, the species was eliminated or lowered in level, while treatment failures were associated with failure to lower the numbers of the species in treated sites. The species induced disease in experimental animals.

XI CONCLUSION

A. actinomycetemcomitans is a bacterium with an array of diverse potential virulence characteristics, including multiple immune evasion mechanisms and novel mechanisms for binding to host matrices and invading host cells, any one of which may play a crucial role in the local tissue pathology of LAP. Our understanding of this organism still lags behind that of enteric pathogens, largely because methods for genetic manipulation have only just become available and the genome sequence, while almost complete, still awaits annotation. With the availability of such methodology and genome information we should begin to see rapid advances in understanding how A. actinomycetemcomitans produces such profound, but local, pathology and shed light on its ability to induce systemic pathology such as the recent report of glomerulonephritis caused by this bacterium.

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