Aggregatibacter actinomycetemcomitans

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TAXONOMY AND CLASSIFICATION:

KINGDOM: Bacteria

PHYLUM: Proteobacteria

CLASS: Gammaproteobacteria

ORDER: Pasteurellales

FAMILY: Pasteurellaceae

GENUS: Aggregatibacter

SPECIES: actinomycetemcomitans

Gram-negative, Fastidious, Facultative anaerobe, Capnophiles, Non-motile, Non-hemolytic, Non-spore forming, and Coccoid to rod shaped; Member of normal microbiota of HACEK group found in Oral-pharyngeal region, Causes adolescent periodontal disease[1].

KEY FACTS:

- BSL-2 pathogen; first identified as *Bacterium actinomycetemcomitans* by Klinger in 1912. Changed into *Actinobacillus actinomycetemcomitans* (Aa). Based on 16 rRNA analysis, and auto-aggregation properties re-classified as "Aggregatibacter"[2].
- Single chromosome of Median Genome size (Mb) - 2.12758; Median protein count - 1959; Median G+C content: 44.4 (Out of Nine Full length sequences)[3].
- Tight-adherence (tad) locus and production of β (1, 6)-linked N-acetyl-D-glucosamine contributes to adherence, and histone-like nucleoid-structuring (H-NS) protein promotes multispecies biofilm formation [4]. Secretes Dispersin B, a glycoside hydrolase which degrades PIA/PNAG at its β (1,6)-linkage.
- Translucent appearance form central star-shaped colonies. Optimum growth 37°C; ceases at 22°C; Able to ferment fructose, glucose, maltose, and mannose, Oxidase and catalase positive, can reduce nitrate, does not hydrolyze esculin and hippurate sodium, No production of H₂S and indole[5].

DISEASE FACTS:

- Seven Biotypes: I, II, VI, IX or X, V and VIII. Biotype II and X most prevalent in periodontal patients; Healthy subjects show biotype II, VI, X[6].
- Worldwide one third populations infected with bacteria. Clinical samples susceptible to cefuroxime, cefazolin, and tetracycline but displayed poor susceptibility to clindamycin and azithromycin. Isolates resistant to metronidazole.
- Leukothera™ (Actinobac Biomed Inc.) – purified Leukotoxin as natural targeted biologic to treat hematologic malignancies, autoimmune diseases, and HIV infection targeting activated WBC. Leukothera™ completed GMP manufacturing and GLP toxicity testing[7].
- Rhesus Primate study shows direct correlation of leukotoxin production and attachment factor expression and progression of disease [8]

INFOGRAPHIC VIRULENCE MECHANISMS:

Aggregatibacter actinomycetemcomitans secretes two exotoxins; **C**ytotolethal **D**istending **T**oxin (CDT) which activates osteoclast cells, and disrupts macrophage function by inhibiting phagocytic activity, and production of cytokine. Mechanistically, activated osteoclast cells bind Toll like receptor 2 (TLR2) and TLR4 on macrophage cell surface which in turn initiates c-Jun N- terminal kinase (JNK), extracellular signal – regulated kinase (ERK), p38 mitogen activated protein kinases (MAPKs), and nuclear factor –κB (NF-κB) intracellular signaling cascades that regulate pro inflammatory-cytokine transcription. Activation of NF-κB promotes nuclear translocation of p50, and p65[9]. Further, p65 bind with DNA to activate IL-1β, IL6, TNF-α, IL-10 and IL-12 to damage immune cells. Secreted Leukotoxin A (**LtxA**) induces LFA-1 integrin (CD11a/CD18) mediated internalization of toxin and apoptosis in human immune cells [10].

Further, LtxA enhances ROS (**R**eactive **O**xygen **S**pecies) activity and cause cell damage in PMNs. Aa outer membrane proteins, Omp100 and OmpA1 may allow activation of Factor H and C4 binding protein (C4bp), respectively. This would result in down regulation of alternative, classical, and **M**annose **B**inding **L**ectin (MBL) pathway of complement activation. **O**uter **M**embrane **V**esicles (OMVs) carry NOD-1 and NOD-2 activates peptidoglycan (PGN), which can be internalized into non-phagocytic human cells to induce gingival fibroblasts [10].

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