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Review Article

Aggregatibacter (Actinobacillus) actimycetemcomitans leukotoxin and human periodontitis – A historic review with emphasis on JP2

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Abstract *Aggregatibacter (Actinobacillus) actimycetemcomitans (Aa)* is a gram-negative bacterium that colonizes the human oral cavity and is causative agent for localized aggressive (juvenile) periodontitis (AgP). In the middle of 1990s, a specific JP2 clone of belonging to the cluster of serotype b strains of *Aa* with highly leukotoxicity (leukotoxin, LtxA) able to kill human immune cells was isolated. JP2 clone of *Aa* was strongly associated with in particularly in rapidly progressing forms of aggressive periodontitis. The JP2 clone of *Aa* is transmitted through close contacts. Therefore, AgP patients need intense monitoring of their periodontal status as the risk for developing severely progressing periodontitis lesions are relatively high. Furthermore, timely periodontal treatment, including periodontal surgery supplemented by the use of antibiotics, is warranted. More importantly, periodontal attachment loss should be prevented by early detection of the JP2 clone of *Aa* by microbial diagnosis testing and/or preventive means.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

One can detail several cellular, humoral, and metabolic prerequisites that enable polymorphonuclear leukocytes (PMNs) to attack and destroy microbial parasites, and much information also has been gained on how and why PMNs act as mediators of tissue damage in numerous inflammatory disorders. But hardly anything is known about the function of PMNs in inflammatory conditions of the tissue that support teeth in their sockets. PMNs have long been recognized as conspicuous elements in such lesions, but one still cannot define specifically the pathobiological significance of local leukocytosis in the etiology and development of periodontal diseases. The deposition and retention of bacterial plaque (biofilms) on the cervical surfaces of teeth is the principal etiologic factor in the initiation of gingivitis. There is little doubt that the progression of the disease process leading to pocket formation and bone loss is dependent upon the continued presence of bacteria in the subgingival area. PMNs can be seen in diseased tissues during the very earliest and the most advanced stages of tissue breakdown [1—7]. The mechanisms that account for the constant influx of PMNs into diseased gingiva have been the subject of numerous studies [8—12]. It would appear that whole plaque, individual plaque bacteria, or their products can exert a chemotactic effect on PMN migration by acting directly or indirectly on the cells by activating the complement system, leading to the generation of chemotactic peptides. For example, gram-positive oral bacteria [13], gram-negative endotoxins [12], or antigen—antibody complexes consisting of plaque antigens and host antibodies [14] can trigger sequential activation of complement. PMNs also contain lysosomal proteases that are capable of cleaving chemotactic split products from specific complement components [15]. The release of such enzymes from PMNs that have contacted plaque bacteria or their products has been postulated as an additional pathway to ensure delivery of PMNs to the gingival area [16].

Having established that PMNs are in direct contact with plaque deposits, it seems reasonable to suspect that these cells kill plaque bacteria that could be potentially harmful to the host [17]. Although PMN phagocytosis of plaque bacteria has been observed in the gingival crevice or pocket [17,18], the response had never been fully characterized on a quantitative or on a functional basis. Which plaque organisms are phagocytized by PMNs? Does ingestion of these bacteria result in death or growth restriction of these parasites? Do engulfed organisms play a role in the pathogenesis of local tissue injury? Is phagocytosis the only mechanism whereby PMNs potentially influence the establishment of plaque bacteria? It is true that more exaggerated or accelerated forms of gingival and periodontal diseases can be seen in some individuals with various abnormalities in PMN function. Yet these clinical descriptions offer no specific insight into the significance of PMNs as mediators of host defense in the oral cavity.

Circumstantial evidence suggests that the PMN could act as an effector mechanism of tissue destruction in periodontal diseases. PMNs degranulation can be readily observed in inflamed gingival tissues and fluids [3,5,18]; to some degree, this probably accounts for the relatively high levels of lysosomal hydrolases that can be measured in the sites [19].

In the years of 1970s, Taichman et al. have been interested in characterizing the destructive potentials of PMNs in periodontal diseases. They have conducted a series of experiments in which PMNs are exposed to whole plaque, to specific plaque bacteria, and to various components of these organisms to determine whether these stimuli are capable of activating PMN lysosome release and to learn more about the nature of PMN-bacterial interaction. All these experiments suggest that the PMNs release reaction in response to plaque reflects an active and selective secretory process rather than nonspecific enzyme leakage from dying cells [20—26].

The discovery of *Aa*-leukotoxin

In 1979, we first reported that a gram-negative anaerobic rod referred to as *Actinobacillus Y4* which was isolated from dental plaque of a patient with juvenile periodontitis [27]. *Y4* is capable of killing PMNs [28,29] (Fig. 1 and Fig. 2) and has the potential to promote periodontal lesions in monoinfected rats [30]. Considering that *Actinobacillus* as *Y4* has adverse effects on PMNs and that PMNs are predominant inflammatory cells in the gingival sulcus/pocket the interaction of *Actinobacillus* and PMNs may have crucial impaction for the initiation and/or perpetuation of juvenile (aggressive) periodontitis. Therefore, we conducted new series of studies in and isolated *Actinobacillus* from juvenile periodontitis (JP) patients.

First, we examined leukotoxic activity in different strains of the bacterium *Actinobacillus actinomycetemcomitans (Aa)* type culture strains and dental plaque isolates from JP in man [31]. The majority of *Aa*, as well as sonic extracts prepared from these organisms, rapidly destroyed PMNs, shown by the extracellular release of lactate dehydrogenase from PMNs and degenerative ultrastructural alterations. Whereas toxic and non-toxic strains of *Aa* shared common antigens, immunologic analyses revealed a unique antigen in sonic extracts of leukotoxic organisms. Thus, *Aa*-derived leukotoxin may be an etiologic vector in JP.

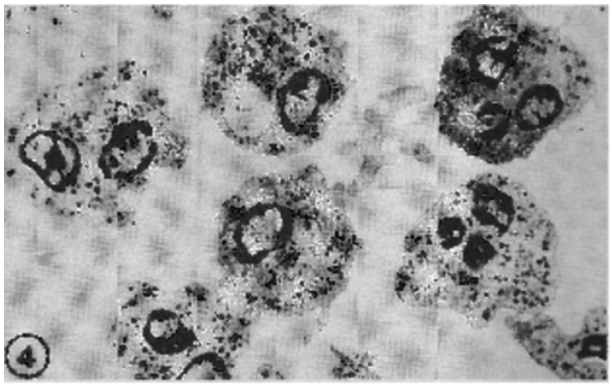

Figure 1. Normal human peripheral blood PMNs (Adopted from Infect Immun, 25:427—439, 1979) [29].

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