Japanese Dental Science Review 57 (2021) 20–26

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Review Article

Etiology of aggressive periodontitis in individuals of African descent

Akihiro Yoshida[a,*], Amal Bouziane[b], Samir Erraji[b], Leila Lakhdar[b], Meryem Rhissassi[b], Hideo Miyazaki[c], Toshihiro Ansai[d], Masanori Iwasaki[e], Oumkeltoum Ennibi[b]

[a] Department of Oral Microbiology, Faculty of Dentistry, Matsumoto Dental University, Shiojiri, Japan
[b] Department of Periodontology, School of Medicine Dentistry, Mohammed V University, Rabat, Morocco
[c] Department of Dental Technology, Meirin College, Niigata, Japan
[d] Division of Community Oral Health Development, Kyushu Dental University, Kitakyushu, Japan
[e] Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

ARTICLE INFO

Article history:
Received 1 October 2020
Received in revised form
22 December 2020
Accepted 30 December 2020

Keywords:
Aggressive periodontitis (AgP)
Aggregatibacter actinomycetemcomitans
Th17
Genetic predisposition
African descent

ABSTRACT

Aggressive periodontitis (AgP) is a form of periodontitis that affects adolescents and has a significantly higher prevalence in individuals of African descent. AgP typically shows familial aggregation, suggesting a genetic predisposition. Young age, good health status, rapid attachment loss, and familial aggregation are the primary features of this disease. AgP has been closely linked to specific bacterial strains of *Aggregatibacter actinomycetemcomitans*. *A. actinomycetemcomitans* strains isolated from patients with AgP produce leukotoxin (LtxA), which specifically affects polymorphonuclear leukocytes in primates, especially humans. High-throughput 16S rRNA gene sequencing and bioinformatics analyses revealed differences in the subgingival microbiota between patients with AgP and those with chronic periodontitis (ChP). The genera *Atopobium* and *Prevotella* show increased prevalences in AgP than in ChP. According to AgP susceptibility, several single nucleotide polymorphisms have been detected in different genes in individuals of African descent. Interleukin (IL)-1α and IL-1β genetic polymorphisms may be associated with the severity of both ChP and AgP. An elevated serum level of IL-17 produced by Th17 cells may be a characteristic of AgP. Analyses of the relationships among bacteria, host defenses, genetic predisposition, and numerous other factors are required to understand the progression of this disease.

1. Introduction

Aggressive periodontitis (AgP) is rapidly progressing periodontitis that occurs in systemically healthy individuals [1]. This form of periodontitis is characterized by pronounced attachment loss and vertical alveolar bone destruction and early onset in childhood or adolescence, whereas chronic periodontitis (ChP), a common form of periodontitis, occurs after 30 years old [1,2]. AgP typically shows familial aggregation, suggesting a genetic predisposition [3–5]. Young age, good health status, rapid attachment loss, and familial aggregation are the primary features of this disease [1,2]. Localized AgP (LAgP) affects the periodontal tissues of the incisors and first molars [3,4]. In general, LAgP occurs around puberty, whereas generalized AgP (GAgP) usually occurs before 30 years of age but sometimes occurs at older ages [3,4]. GAgP can be localized initially but over time will affect other teeth in addition to the incisors and first molars, eventually becoming generalized [3,4].

The reported prevalence rates of AgP vary considerably among studies. A meta-analysis revealed a higher AgP prevalence of 4.2% (95% confidence interval [CI] 2.0–7.1) in Africa, with a rate of 4.0% (95% CI 0.9–9.1) in South Africa, compared with 1.2% (95% CI 0.5–2.2) in Asia, 0.8% (95% CI 0.4–1.4) in North America, and 0.1% (95% CI 0.1–0.2) in Europe. The prevalence of LAgP appears to be higher in individuals of African descent (6.9%) compared with Hispanic (1.92%) and Caucasian (0.14%) populations [6,7].

Unlike ChP, LAgP has been closely linked to specific strains of a single organism, *Aggregatibacter actinomycetemcomitans* [8–10]. *A. actinomycetemcomitans* strains isolated from patients with AgP tend to produce significant levels of leukotoxin (LtxA), whereas strains isolated from healthy subjects tend to produce much lower levels of this LtxA [11–13]. Exotoxin-producing bacteria are very rare in the oral microbiome. Of the highly leukotoxic strains, the JP2 clone differs genetically from the others. A 530-bp deletion in the promoter region of the LtxA operon containing the *ltxA* gene was found in the JP2 clone, which resulted in increased LtxA produc-

* Corresponding author at: Department of Oral Microbiology, Faculty of Dentistry, Matsumoto Dental University, 1780 Gobara Hirooka, Shiojiri, 399-0781, Japan.
E-mail address: akihiro.yoshida@mdu.ac.jp (A. Yoshida).

https://doi.org/10.1016/j.jdsr.2020.12.001

tion [14–16]. LtxA binds specifically to human leukocytes, causing toxicity [16–18]. Thus, LtxA has immunosuppressive activity and is suspected to be closely associated with AgP. Neutrophils from humans, great apes, and most Old World monkeys are susceptible to LtxA, whereas polymorphonuclear leukocytes (PMNs) from the prosimii, New World monkeys, and lesser apes are not susceptible to LtxA [19,20]. These data suggest that LtxA has specificity for particular primate PMNs and is especially potent against human leukocytes. This specificity of LtxA limits the ability to produce animal experimental models of *A. actinomycetemcomitans* infection, which has hampered AgP research. In addition to LtxA, *A. actinomycetemcomitans* expresses cytolethal distending toxin (CDT) and is the only known oral species to do so. The pathogenic effects of this toxin are DNA damage, cell cycle arrest, and apoptosis of the intoxicated cells [21]. The surface of *A. actinomycetemcomitans* is covered by lipopolysaccharide (LPS), a potent pro-inflammatory molecule. A previous review gives the detailed virulence-related properties of *A. actinomycetemcomitans* LPS and other virulence factors [21].

LAgP has etiologically and clinically unique characteristics compared with ChP. In the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions, periodontitis was reclassified into three categories: necrotizing periodontitis, periodontitis as a manifestation of systemic disease, and periodontitis. The final category includes most cases of periodontitis, including ChP and AgP, as a single category [22,23]. The workshop attendees agreed on a classification framework for periodontitis further characterized based on a multidimensional staging and grading system [22,23]. Staging is dependent upon the severity of disease at presentation, while grading provides supplemental information about biological features of the disease [22,23]. Thus, ChP and AgP are classified as the same disease in the current classification of periodontal disease. However, the purpose of this review is to consider the etiology of AgP by comparing it with ChP. Therefore, it will be described based on the previous classification.

This nonsystematic review presents the clinical, epidemiological, microbiological, immunological, and genetic characteristics of AgP (LAgP/GAgP). The characteristics that are distinct from those of ChP will contribute to clarification of the features of, and development of preventive and therapeutic approaches for, this disease.

2. Clinical characteristics of aggressive periodontitis

ChP is the most common form of advanced periodontal disease affecting the general population and is a major cause of tooth loss after the age of 30 years (Table 1) [1,2]. ChP is classified as generalized when it affects more than 10 of the 32 teeth in the human dentition and as localized when fewer teeth are involved [3,4]. On the other hand, LAgP affects systemically healthy children or adolescents and is associated with significant and rapid progression of bone loss localized to the permanent incisors and first molars [3,4]. Patients with LAgP have low levels of supragingival plaque and inflammation despite deep periodontal pockets and severe bone loss, whereas those with ChP have moderate to severe inflammation with plaque and calculus. In GAgP, the disease can be localized to the incisors and first molars initially and then affects the other teeth over time [3,4]. It is still unclear why LAgP affects only the incisors and first molars. The eruption ages of the first incisors (upper: 7–8 years, lower: 6–7 years) and first molars (upper and lower: 6–7 years) are almost same and may explain why LAgP is limited to these teeth. The biological events occurring at this age may influence the localization of LAgP. In addition, AgP shows familial aggregation, suggesting a genetic predisposition. In addition to its predominance in young healthy patients with rapid attachment loss and familial aggregation, AgP has a number of other specific characteristics compared with ChP, including distinct racial tropism [24]. A study by the National Institute of Dental and Craniofacial Research in 1987, performed in 11,007 children aged 14–17 years in the USA, reported 15.1- and 24.6-fold higher incidences of LAgP and GAgP, respectively, in African American than white children [25]. A study of 1200 high school students in Sudan showed that the prevalence of AgP was significantly higher in students of African heritage compared with those of Afro-Arabian descent (6% vs. 2.3%, respectively, $P = 0.01$) [26]. Thus, individuals of African descent are more sensitive to AgP than are Caucasians and Asians. Although this strict tropism is a major characteristic of AgP, the reason for the increased prevalence of AgP in individuals of African descent is still unclear. At present, no disease-specific biomarkers are available to distinguish between ChP and AgP.

3. Epidemiology of aggressive periodontitis

Data from the 2009–2012 National Health and Nutrition Examination Survey (NHANES) cycles estimated that over 46% of the adult population in the United States has periodontitis and concluded that periodontitis is ubiquitous in elderly individuals [26]. Previous epidemiological studies of AgP showed that its prevalence varies among racial groups and/or countries [25–28]. However, direct comparisons are not possible due to differences in conditions (study population, evaluation criteria, etc.) among studies. Taking these differences into account, the prevalence of AgP ranges from 0.13%, according to a survey performed in Iran, to 9.9%, according to a survey performed in Brazil [29,30]. The wide range among countries is reasonable considering that this infectious disease shows racial tropism. The prevalence of LAgP is much lower than that of ChP in most populations, with a prevalence of >50%. Many investigations have reported a higher prevalence of LAgP in individuals of African and Middle Eastern descent and a relatively low prevalence in individuals of Caucasian and Asian descent [31,32].

4. *Aggregatibacter actinomycetemcomitans* as a causative microorganism of aggressive periodontitis

A. actinomycetemcomitans, a gram-negative coccobacillus and nonmotile component of the oral microflora [33], was recovered from the subgingival plaque of some patients with LAgP from Africa, the Middle East, Brazil, and the USA [34–39]. In contrast, this organism was not recovered from LAgP patients in Asian populations, including Japan and China, or in Caucasian populations [24]. These findings suggest that LAgP has no significant association with this organism in patients from these regions. There are a number of possible explanations for these differences. Some strains of *A. actinomycetemcomitans* show enhanced production of LtxA characterized by a 530-bp deletion in the promoter region of the LtxA operon [34,40]. Of 326 isolates from 29 countries, including those in Asia, Europe, Africa, South America, and North America, 38 belonged to a single clone of serotype b with a 530-bp deletion in the promoter region of the LtxA operon. Among these 38 isolates, 36 were associated with LAgP. Research regarding the geographic dissemination of this clone revealed that all subjects carrying this clone had a genetic affiliation with African populations [24,41]. These results suggest that AgP in some adolescents of African descent is associated with this clone of *A. actinomycetemcomitans*, and that *A. actinomycetemcomitans* has racial tropism. There is a marked contrast in the etiology of LAgP between Caucasians and patients genetically associated with certain African populations. Haubek et al. reported that AgP may represent two different types of disease with distinct etiologies and epidemiologies

Table 1
Characteristics of aggressive periodontitis and chronic periodontitis.

	Aggressive periodontitis	Chronic periodontitis	Sources
Locus	Locarized: first molars and incisors	All tooth	3, 4
Age	Up to 30 years	After 30 years	1, 2
Clinical features	Rapid and vertical bone loss Low levels of supragingival plaque and inflammation	Slow and horizontal bone loss Moderate to severe inflammation with plaque and calculus	1, 2
Epidemiologic	Rare (prevalence 0.1−2%)	Common (prevalence 40−50%)	6, 7
Race	African-Americans, Middle Easterners, Hispanic	No specific ethnic distribution	6, 7
Microbiological	*Aggregatibacter actinomycetemcomitans*	Anaerobic gram-negative rods	8, 9, 10
Genetic	Familial aggregation	No familial aggregation	1, 2, 3, 4, 5

[24]. In the first type, a diverse array of *A. actinomycetemcomitans* clones found worldwide act as opportunistic pathogens, whereas the second is a particular clonal type of *A. actinomycetemcomitans* serotype b characterized by the 530-bp promoter deletion and acts as an exogenous pathogen [24]. *A. actinomycetemcomitans* is dominant in patients with AgP in Brazil, whereas *Porphyromonas gingivalis* is abundant in the subgingival plaque and saliva of Chinese patients with AgP [42–45]. In research performed in the U.S., the detection rate of *A. actinomycetemcomitans* was high in African American and Hispanic populations, lower in Asian, Pacific Islander, and Caucasian populations, and negligible in Native American and Alaskan Native populations [24]. That longitudinal study concluded that the presence of *A. actinomycetemcomitans*, *Streptococcus parasanguinis*, and *Filifactor alocis* together at a site is an indicator of future bone loss in LAgP [46]. These data clearly indicate the racial tropism of *A. actinomycetemcomitans*. However, a LAgP has also been observed in non-African or non-Hispanic populations, races in which *A. actinomycetemcomitans* has not been detected [47]. Based on these observations, we speculated that the LAgP has a distinct etiology, and that the so-called AgP disease state differs among races. That is, there may be two different disease states, i.e., *A. actinomycetemcomitans*-related and -unrelated AgP, which need to be clarified among different racial groups.

5. Comparison of the microbiome between aggressive periodontitis and chronic periodontitis

As described above, the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions grouped the diseases previously recognized as ChP or AgP under the same category as “periodontitis” [22,23]. Previous studies attempted to identify microbiological elements that allow differential diagnosis between AgP and ChP, but the suggestion that AgP has a distinct microbiological pathogenesis from that of ChP has not been confirmed [48] A systematic review revealed that 13 of 56 articles reported that *A. actinomycetemcomitans* was elevated in AgP compared with ChP in subgingival microbiota, while *Fusobacterium nucleatum*, *Parvimonas micra*, and *Campylobacter rectus* were elevated in AgP in a few studies [49]. None of these species were elevated in ChP. However, of these studies, most did not find a statistical difference between AgP and ChP [49]. Therefore, this systematic review suggested an association of *A. actinomycetemcomitans* with AgP. However, no bacterial species studied to date is specific to AgP and ChP or can distinguish between them. One polymerase chain reaction (PCR)-based study revealed a relationship between the presence of highly toxic or low toxic strains of *A. actinomycetemcomitans* in the subgingival microbiota and the occurrence of AgP [50]. The prevalence of JP2 and non-JP2 clones was analyzed in 180 young African-Americans with/without LAgP in north Florida [50]. Of the 60 LAgP subjects, JP2 was positive in 45 (75%) diseased sites and 34 (56.67%) healthy sites. JP2 carriage was detected in 16 (26.67%) of 60 healthy siblings (HS) and 24 (40%) in 60 unrelated healthy controls (HC). Non-JP2 was equally positive (n = 11, 18.33%) in both diseased and healthy sites of LAgP subjects: 6 (10%) HS sites and 3 (5%) HC sites. Thus, the presence of the JP2 sequence is strongly associated with LAgP-diseased sites in young African-American, significantly more so than non-JP2 [50]. High-throughput 16S rRNA gene sequencing and bioinformatics analyses revealed differences in the subgingival microbiota between AgP and ChP; the genera *Pseudoramibacter*, *Wolinella*, *Lactococcus*, *Klebsiella*, and *Bulleidia* were more abundant in ChP, while *Atopobium* and *Prevotella* were more abundant in AgP. Within the limitation of the small sample size ($n = 3$), that study indicated a shift in the subgingival microbiome between healthy subjects and patients with AgP/ChP [48].

Research regarding the microbiota has progressed with the development of microbiological methodologies. For example, the development of anaerobic culture techniques revealed the contribution of anaerobic bacteria to periodontal disease. However, bacteria that could not be cultured using anaerobic culture techniques or culture media have been eliminated from among the etiological candidates. Therefore, the results obtained using new methodologies involve bias, and interpretation of the results has changed accordingly. At present, the most commonly used method is next-generation 16S rRNA gene sequencing. However, the data obtained represent the periodontal condition according to the extent of disease progression. Therefore, it is necessary to follow changes in the microbiome from disease onset to final progression. It will be necessary to characterize the dynamic changes in the subgingival microbiome during the disease course in both AgP and ChP.

6. Genetic factors associated with aggressive periodontitis

As described above, the incidence of AgP is higher among individuals of African descent. Therefore, there are ethnic disparities among patients with AgP worldwide. The etiology of infectious disease is related to the interaction between microorganisms and host immunity. This is also true for periodontitis, which is a major infectious disease. Periodontal pathogens are oral commensals, and periodontitis is considered an endogenous infection. However, there are high degrees of interindividual susceptibility to such commensals, but the differences in periodontal pathogens composing the individual microbiota cannot explain the differences in disease severity. Multifactorial diseases, such as periodontitis, include multiple biological pathways that may contribute to similar clinical phenomena. The gene variants associated with these pathways are considered susceptibility or disease-modifying loci. The number and types of relevant genetic variants may vary depending on the periodontitis form and ethnicity. Several studies investigating the associations between gene variants (polymorphisms) and AgP susceptibility have been reported [51–54]. Polymorphisms can cause alterations in the proteins encoded by the affected genes or in their expression. These variants result in alterations of host immune responses and susceptibility to pathogens. Single nucleotide polymorphisms (SNPs), which are relevant in periodontitis, are thought to affect genes encoding cytokines and cytokine receptors, regula-

Table 2
Characteristics of Leukocyte adhesion deficiency-I.

	Descriptions	Sources
Pathophysiology	Rare disorder of leukocyte adhesion and transmigration	73
Cause of disease	Mutations in the ITGB2 gene encoding for the β2 integrin component, CD18	73
Outcome of illness	Severe LAD-I (<2% of CD18-expressing neutrophils): infant mortality Moderate LAD-I (2%−30% of CD18-expressing neutrophils): recurrent infections of skin and mucosal surfaces	73
Intraoral findings	Recurrent painful oral ulcers that often impede eating	76
Periodontitis	The most frequent (>50%), severe, early onset (prepubertal periodontitis)	77, 78
Characteristics of periodontitis	Severe inflammation (enlarged gingiva), rapid loss of alveolar bone, tooth mobility, complete bone loss and tooth loss	79, 80
Subgingival microbiome	Reduced microbial diversity: a bacterium not typically found in subgingival plaque was also detected in LAD-I patients (Pseudomonas aeruginosa). Periodontitis-associated species in the LAD-I microbiome: *Parvimonas micra*, *Porphyromonas endodontalis*, *Eubacterium brachy*, *Treponema* species.	81
Inflammations	Exaggerated IL-23 and IL-17 signature within the inflammatory periodontitis lesions	82

tors of immunity. Several SNPs in different genes with positive and negative associations with AgP have been evaluated in populations of African descent [55–67]. Interleukin (IL)-1 is a proinflammatory mediator mainly released by monocytes, macrophages, and dendritic cells (DCs). Genetic polymorphisms in IL-1α and IL-1β have been suggested to be associated with the severity of ChP and AgP [59,64,67]. In addition, polymorphisms in the genes encoding lactoferrin, vitamin D receptor, glycosyltransferase 6 (expressed in leukocytes involved in GATA3 signaling in immune cell development), and other proteins have been examined [68–71]. However, the associations are controversial due to differences in conditions among studies (country, sample numbers, etc.).

Genome-wide association studies in AgP samples from populations in Germany and the Netherlands validated the associations of AgP/ChP with SNPs in the sialic acid binding Ig-like lectin 5 gene and downstream of the defensin alpha 1 and alpha 3 locus [72]. These results highlight the roles of innate and adaptive immunity in the etiology of periodontitis.

Some hereditary diseases associated with immunodeficiency cause periodontitis. Leukocyte adhesion deficiency type I (LAD-I) is an autosomal recessive immunodeficiency disorder characterized by mutations in the CD18 subunit of β2 integrins, receptors expressed on leukocytes, which lead to impaired adhesion and chemotaxis (Table 2) [73,74]. LAD-I is invariably associated with recurrent skin infections that can be chronic and refractory to treatment [75]. In addition to these infections, LAD-I patients typically have oral ulcers, which cause severe pain and periodontitis, leading to complete loss of adult teeth in almost all patients [75–79]. Defects in neutrophil recruitment in LAD-I patients exhibiting LAD-I-associated periodontitis are associated with excessive production of predominantly T-cell-derived IL-17 in the periodontal tissue [80]. Previous investigation has reported that subgingival microflora of LAD-I is distinct from that of other types of periodontal disease [81]. As periodontitis-associated species in the LAD-I subgingival microbiome, *Parvimonas micra*, *Porphyromonas endodontalis*, *Eubacterium brachy* and *Treponema* species are included [81]. In addition, *Pseudomonas aeruginosa*, a bacterium not typically found in subgingival plaque is detected in LAD-I [81]. Thus, very characteristic bacteria are found in the subgingival flora of LAD-I patients. In LAD-I patients, a dominant IL-23/IL-17 signature is seen at sites of inflammation. Local treatment with ustekinumab, an antibody that binds to the p40 subunit of IL-23 and IL-12 and blocks the activity of these cytokines inhibiting IL-23-dependent IL-17 production, was administered to LAD-I patients. After 1 year of treatment, the patient showed resolution of the inflammatory lesions [82]. Additionally, the subgingival plaque microbiota in patients with LAD-I is quite different from that in patients with ChP [81]. The diversity of the subgingival microflora is reduced in LAD-I patients [81]. Although LAD-I periodontitis and AgP are distinct clinical entities with different etiologies, the etiology of LAD-I periodontitis may provide insight to elucidate the etiology of AgP.

7. Immunology of aggressive periodontitis

There have been a number of in vitro investigations of the immune responses of innate and acquired immune cells to *A. actinomycetemcomitans*. However, the analyses of immune responses in AgP patients have been insufficient. The first line of periodontal defense is provided by non-hematopoietic host barriers, including gingival epithelial cells, resident gingival fibroblasts, and periodontal ligament fibroblasts [83]. One candidate causative pathogen of AgP, *A. actinomycetemcomitans*, colonizes the gingival sulcus by attaching to the sulcular/junctional epithelial cells. *A. actinomycetemcomitans* invades through the epithelium via proapoptotic virulence mechanisms, penetrates into the subgingival connective tissue, and stimulates epithelial cells and fibroblasts to secrete proinflammatory cytokines. These barriers are normally engaged continuously in the response to dental plaque under conditions of preclinical physiological inflammation [83]. The host inflammatory responses play an important role in disease initiation and progression, and individuals with AgP are characterized by a hyperresponsive inflammatory phenotype. The levels of calprotectin, colony stimulating factor 1, macrophage migration inhibitory factor, monokine induced by interferon γ, and matrix metalloprotease (MMP)-8 in serum and saliva were measured in patients with AgP or gingivitis and healthy controls in Turkey [84]. The levels of calprotectin and MMP-8 in serum and the level of MMP-8 in saliva were elevated in the patients with AgP [84]. Following the initial colonization, innate immune cells derived from myeloid hematopoietic cells, neutrophils, monocytes, and DCs are recruited into the periodontal tissue, local sites of infection, and perpetuate the host inflammatory response. There is accumulating evidence for the presence of neutrophils in gingival lesions and in root surfaces in AgP. Increased respiratory burst activities and nitric oxide synthase activities in neutrophils, and superoxide production and chemiluminescence in peripheral polymorphonuclear leukocytes, have been reported in AgP patients [85]. These neutrophil features might render individuals more susceptible to periodontitis upon subgingival microbial colonization. In addition, excessive local and systematic inflammatory responses specific to macrophage inflammatory protein 1α (MIP-1α/CCL3) and bacterial lipopolysaccharide have been reported in AgP patients [86].

On the other hand, DCs, which are involved in the innate immune system, are the most potent antigen-presenting cells that activate naïve T cells, and the play a critical role as effectors in the induction of adaptive immunity. There are three types of immature DCs, Langerhans cells, submucosal DCs, and plasmacytoid DCs, in periodontal tissue [87]. Langerhans cells constitute a distinct population and differentiate into mature DCs following antigen capture.

DCs play critical roles in the initiation and amplification of adaptive immune systems by antigen presentation [88]. Immature and mature DCs in gingival tissue obtained from patients with AgP or ChP and healthy controls were compared, and immature DCs were shown to be more abundant in AgP patients than in ChP patients and healthy controls [88]. Conversely, mature DCs were more abundant in ChP patients than in AgP patients and healthy controls [88]. There is evidence that immature DCs undergo transdifferentiation into osteoclasts, and that DC-derived osteoclasts are present during immune interactions with $CD4^+$ T cells and microbial products under inflammatory conditions. These observations suggest that DCs are involved in inflammation-induced osteoclastogenesis and bone loss in periodontal disease [89]. However, further functional studies of increased numbers of immature DCs in AgP periodontal tissue are required.

Naïve T cells are induced to differentiate into effector T cells upon antigen presentation by antigen-presenting cells. The level of IL-17 was reported to be significantly higher in the serum from patients with LAgP or GAgP than in that from healthy controls [90]. These results indicate the dominance of Th17 subsets in patients with LAgP or GAgP and suggest that IL-17 production by Th17 cells may be a characteristic of AgP. Despite the lack of comparison with ChP, the elevated IL-17 level in AgP is consistent with neutrophil infiltration in the periodontal lesions of AgP. IL-17 produced by Th17 cells stimulates epithelial cells and fibroblasts to produce chemokines, such as CXCL8, and recruit neutrophils to sites of bacterial colonization. In addition, Th17 cells possess osteoclastogenic ability attributed mainly to their production of IL-17, which stimulates the expression of the pro-bone resorptive factor, receptor activator of nuclear factor κB ligand, in fibroblasts, which acts as a signal for osteoclast differentiation and maturation [90,91]. Recently, periodontitis was shown to be characterized by alveolar bone resorption as a consequence of Th17/Treg (regulatory T cells) imbalance due to increased Th17 and decreased Treg numbers, protective against $CD4^+$ T cells, in periodontal tissue [91]. However, the roles of Th17 and IL-17 in AgP are still unclear, and further functional studies are required.

8. Etiology of aggressive periodontitis

Despite the limited number of studies in AgP, it is clear that periodontal disease is a complex process involving multiple factors. Bacteria, host defenses, and genetic predisposing factors play distinct roles in the susceptibility to AgP. The relationships among these factors have not been clarified. In addition, numerous factors, including lifestyle-related factors (e.g., local diets in North Africa or the Mediterranean diet) and hormone imbalances during adolescence (e.g., sex hormones such as androgens and estrogens) may modify the onset and progression of this disease.

9. Conclusions

AgP has a characteristic pathophysiology in its onset and progression compared with ChP. This review presents evidence obtained from previous investigations regarding the etiology of AgP. However, these pathological conditions are described independently, and the interrelationships between these pathological conditions and factors involved in the pathological condition formation have not been analyzed. Clarifying the relationships between factors involved in disease pathogenesis may help elucidate the pathogenic mechanism of AgP. The mechanisms underlying AgP onset and progression have yet to be clarified. However, the unique characteristics of AgP will facilitate further studies to obtain clinical, epidemiological, microbiological, immunological, and genetic insights into this disease.

Conflict of interest

The authors declare that there are no conflicts of interest associated with this work.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (B) (grant number 18H02974) to A.Y. from the Japan Society for the Promotion of Science.

References

[1] Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1–6.
[2] Albander JM. Aggressive periodontitis: case definition and diagnostic criteria. Periodontol 2000 2014;65:13–26.
[3] Albandar JM, Brown LJ, Löe H. Clinical features of early-onset periodontitis. J Am Dent Assoc 1997;128(10):1393–9.
[4] Albandar JM, Brown LJ, Genco RJ, Löe H. Clinical classification of periodontitis in adolescents and young adults. J Periodontol 1997;68:545–55.
[5] Gronert K, Kantarci A, Levy BD, Clish CB, Odparlik S, Hasturk H, et al. A molecular defect in intracellular lipid signaling in human neutrophils in localized aggressive periodontal tissue damage. J Immunol 2004;172:1856–61.
[6] Bouziane A, Hamdoun R, Abouqal R, Ennibi O. Global prevalence of aggressive periodontitis: a systematic review and meta-analysis. J Clin Periodontol 2020;47:406–28.
[7] Susin C, Haas AN, Albandar JM. Epidemiology and demographics of aggressive periodontitis. Periodontol 2000 2014;65:27–45.
[8] Kamma JJ, Nakou M, Gmür R, Baehni PC. Microbiological profile of early onset/aggressive periodontitis patients. Oral Microbiol Immunol 2004;19:314–21.
[9] Cappelli DP, Ebersole JL, Kornman KS. Early-onset periodontitis in Hispanic-American adolescents associated with *A. actinomycetemcomitans*. Community Dent Oral Epidemiol 1994;22:116–21.
[10] Müller HP, Eickholz P, Heinecke A, Pohl S, Müller RF, Lange DE. Simultaneous isolation of *Actinobacillus actinomycetemcomitans* from subgingival and extracrevicular locations of the mouth. J Clin Periodontol 1995;22:413–9.
[11] Haubek D, Ennibi OK, Poulsen K, Poulsen S, Benzarti N, Kilian M. Early-onset periodontitis in Morocco is associated with the highly leukotoxic clone of *Actinobacillus actinomycetemcomitans*. J Dent Res 2001;80:1580–3.
[12] Haraszthy VI, Hariharan G, Tinoco EM, Cortelli JR, Lally ET, Davis E, et al. Evidence for the role of highly leukotoxic *Actinobacillus actinomycetemcomitans* in the pathogenesis of localized juvenile and other forms of early-onset periodontitis. J Periodontol 2000;71:912–22.
[13] Califano JV, Pace BE, Gunsolley JC, Schenkein HA, Lally ET, Tew JG. Antibody reactive with *Actinobacillus actinomycetemcomitans* leukotoxin in early-onset periodontitis patients. Oral Microbiol Immunol 1997;12:20–6.
[14] Sampathkumar V, Velusamy SK, Godboley D, Fine DH. Increased eukotoxin production: characterization of 100 base pairs within the 530 base pair leukotoxin promoter region of *Aggregatibacter actinomycetemcomitans*. Sci Rep 2017;7:1887.
[15] Yoshida A, Ennibi OK, Miyazaki H, Hoshino T, Hayashida H, Nishihara T, et al. Quantitative discrimination of *Aggregatibacter actinomycetemcomitans* highly leukotoxic JP2 clone from non-JP2 clones in diagnosis of aggressive periodontitis. BMC Infect Dis 2012;12:253.
[16] Johansson A. *Aggregatibacter actinomycetemcomitans* leukotoxin: a powerful tool with capacity to cause imbalance in the host inflammatory response. Toxins (Basel) 2011;3:242–59.
[17] Nygren P, Balashova N, Brown AC, Kieba I, Dhingra A, Boesze-Battaglia K, et al. *Aggregatibacter actinomycetemcomitans* leukotoxin causes activation of lymphocyte function-associated antigen 1. Cell Microbiol 2019;21:e12967.
[18] Lally ET, Kieba IR, Sato A, Green CL, Rosenbloom J, Korostoff J, et al. RTX toxins recognize a beta2 integrin on the surface of human target cells. J Biol Chem 1997;272:30463–9.
[19] Taichman NS, Simpson DL, Sakurada S, Cranfield M, DiRienzo J, Slots J. Comparative studies on the biology of *Actinobacillus actinomycetemcomitans* leukotoxin in primates. Oral Microbiol Immunol 1987;2:97–104.
[20] Taichman NS, Shenker BJ, Tsai CC, Glickman LT, Baehni PC, Stevens R, et al. Cytopathic effects of *Actinobacillus actinomycetemcomitans* on monkey blood leukocytes. J Periodontal Res Suppl 1984;19:133–45.
[21] Belibasakis GN, Maula T, Bao K, Lindholm M, Bostanci N, Oscarsson J, et al. Virulence and pathogenicity properties of *Aggregatibacter actinomycetemcomitans*. Pathogens 2019;8:222.
[22] Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification. J Periodontol 2018;89(Suppl 1):S1–8.
[23] Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and

conditions - introduction and key changes from the 1999 classification. J Clin Periodontol 2018;45(Suppl 20):S1–8.
[24] Haubek D, Dirienzo JM, Tinoco EM, Westergaard J, López NJ, Chung CP, et al. Racial tropism of a highly toxic clone of *Actinobacillus actinomycetemcomitans* associated with juvenile periodontitis. J Clin Microbiol 1997;35:3037–42.
[25] Löe H, Brown LJ. Early onset periodontitis in the United States of America. J Periodontol 1991;62:608–16.
[26] Elamin AM, Skaug N, Ali RW, Bakken V, Albandar JM. Ethnic disparities in the prevalence of periodontitis among high school students in Sudan. J Periodontol 2010;81:891–6.
[27] Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol 2015;86:611–22.
[28] Susin C, Haas AN, Albandar JM. Epidemiology and demographics of aggressive periodontitis. Periodontol 2000 2014;65:27–45.
[29] Sadeghi R. Prevalence of aggressive periodontitis in 15-18 year old school-children in Tehran, Iran. Community Dent Health 2010;27:57–9.
[30] Corraini P, Pannuti CM, Pustiglioni AN, Romito GA, Pustiglioni FE. Risk indicators for aggressive periodontitis in an untreated isolated young population from Brazil. Braz Oral Res 2009;23:209–15.
[31] Albandar JM, Tinoco EMB. Global epidemiology of periodontal diseases in children and young persons. Periodontol 2000 2002;29:153–76.
[32] Jenkins WM, Papapanou PN. Epidemiology of periodontal disease in children and adolescents. Periodontol 2000 2001;26:16–32.
[33] Zambon JJ. *Actinobacillus actinomycetemcomitans* in human periodontal disease. J Clin Periodontol 1985;12:1–20.
[34] Haubek D, Poulsen K, Kilian M. Microevolution and patterns of dissemination of the JP2 clone of *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*. Infect Immun 2007;75:3080–8.
[35] Elamin A, Albandar JM, Poulsen K, Ali RW, Bakken V. Prevalence of *Aggregatibacter actinomycetemcomitans* in Sudanese patients with aggressive periodontitis: a case-control study. J Periodontal Res Suppl 2011;46:285–91.
[36] Jentsch H, Cachovan G, Guentsch A, Eickholz P, Pfister W, Eick S. Characterization of *Aggregatibacter actinomycetemcomitans* strains in periodontitis patients in Germany. Clin Oral Invest 2012;16:1589–97.
[37] Haubek D. The highly leukotoxic JP2 clone of *Aggregatibacter actinomycetemcomitans*: evolutionary aspects, epidemiology and etiological role in aggressive periodontitis. APMIS Suppl 2010;130:1–53.
[38] Ennibi OK, Benrachadi L, Bouziane A, Haubek D, Poulsen K. The highly leukotoxic JP2 clone of *Aggregatibacter actinomycetemcomitans* in localized and generalized forms of aggressive periodontitis. Acta Odontol Scand 2012;70:318–22.
[39] Chen C, Wang T, Chen W. Occurrence of *Aggregatibacter actinomycetemcomitans* serotypes in subgingival plaque from United States subjects. Mol Oral Microbiol 2010;25:207–14.
[40] Haubek D, Poulsen K, Westergaard J, Dahlèn G, Kilian M. Highly toxic clone of *Actinobacillus actinomycetemcomitans* in geographically widespread cases of juvenile periodontitis in adolescents of African origin. J Clin Microbiol 1996;34:1576–8.
[41] Haubek D, Poulsen K, Asikainen S, Kilian M. Evidence for absence in Northern Europe of especially virulent clonal types of*Actinobacillus actinomycetemcomitans*. J Clin Microbiol 1995;33:395–401.
[42] Roman-Torres CV, Aquino DR, Cortelli SC, Franco GC, Dos Santos JG, Corraini P, et al. Prevalence and distribution of serotype-specific genotypes of *Aggregatibacter actinomycetemcomitans* in chronic periodontitis Brazilian subjects. Arch Oral Biol 2010;55:242–8.
[43] Tinoco EM, Beldi MI, Loureiro CA, Lana M, Campedelli F, Tinoco NM, et al. Localized juvenile periodontitis and *Actinobacillus actinomycetemcomitans* in a Brazilian population. Eur J Oral Sci 1997;105:9–14.
[44] Li Y, Feng X, Xu L, Zhang L, Lu R, Shi D, et al. Oral microbiome in chinese patients with aggressive periodontitis and their family members. J Clin Periodontol 2015;42:1015–23.
[45] Cui X, Liu J, Xiao W, Chu Y, Ouyang X. Subgingival microbiome in Chinese patients with generalized aggressive periodontitis compared to healthy controls. Arch Oral Biol 2019;101:92–9.
[46] Fine DH, Markowitz K, Fairlie K, Tischio-Bereski D, Ferrendiz J, Furgang D, et al. A consortium of *Aggregatibacter actinomycetemcomitans*, *Streptococcus parasanguinis*, and *Filifactor alocis* is present in sites prior to bone loss in a longitudinal study of localized aggressive periodontitis. J Clin Microbiol 2013;51:2850–61.
[47] Marazita ML, Burmeister JA, Gunsolley JC, Koertge TE, Lake K, Schenkein HA. Evidence for autosomal dominant inheritance and race-specific heterogeneity in early onset periodontitis. J Periodontol 1994;65:623–30.
[48] Heller D, Silva-Boghossian CM, do Souto RM, Colombo AP. Subgingival microbial profiles of generalized aggressive and chronic periodontal diseases. Arch Oral Biol 2012;57:973–80.
[49] Montenegro SCL, Retamal-Valdes B, Bueno-Silva B, Duarte PM, Faveri M, Figueiredo LC, et al. Do patients with aggressive and chronic periodontitis exhibit specific differences in the subgingival microbial composition? A systematic review. J Periodontol 2020;91:1503–20.
[50] Burgess D, Huang H, Harrison P, Aukhil I, Shaddox L. *Aggregatibacter actinomycetemcomitans* in african americans with localized aggressive periodontitis. JDR Clin Trans Res 2017;2:249–57.
[51] Harris TH, Wallace MR, Huang H, Li H, Mohiuddeen A, Gong Y, et al. Association of P2RX7 functional variants with localized aggressive periodontitis. J Periodontal Res Suppl 2020;55:32–40.
[52] Taiete T, Casati MZ, Martins L, Andia DC, Mofatto LS, Coletta RD, et al. Novel rare frameshift variation in aggressive periodontitis: exomic and familial-screening analysis. J Periodontol 2020;91:263–73.
[53] Hashim NT, Linden GJ, Ibrahim ME, Gismalla BG, Lundy FT, Hughes FJ, et al. Replication of the association of GLT6D1 with aggressive periodontitis in a Sudanese population. J Clin Periodontol 2015;42:319–24.
[54] Taiete T, Casati MZ, Stolf CS, Corrêa MG, Santamaria MP, Andere NMRB, et al. Validation of reported GLT6D1 (rs1537415), IL10 (rs6667202), and ANRIL (rs1333048) single nucleotide polymorphisms for aggressive periodontitis in a Brazilian population. J Periodontol 2019;90:44–51.
[55] Diehl SR, Wang Y, Brooks CN, Burmeister JA, Califano JV, Wang S, et al. Linkage disequilibrium of interleukin-1 genetic polymorphisms with early-onset periodontitis. J Periodontol 1999;70:418–30.
[56] Walker SJ, Van Dyke TE, Rich S, Kornman KS, di Giovine FS, Hart TC. Genetic polymorphisms of the IL-1alpha and IL-1beta genes in African-American LJP patients and an African-American control population. J Periodontol 2000;71:723–8.
[57] Fu Y, Korostoff JM, Fine DH, Wilson ME. Fc gamma receptor genes as risk markers for localized aggressive periodontitis in African-Americans. J Periodontol 2002;73:517–23.
[58] Zhang Y, Syed R, Uygar C, Pallos D, Gorry MC, Firatli E, et al. Evaluation of human leukocyte N-formylpeptide receptor (FPR1) SNPs in aggressive periodontitis patients. Genes Immun 2003;4:22–9.
[59] Guzman S, Karima M, Wang HY, Van Dyke TE. Association between interleukin-1 genotype and periodontal disease in a diabetic population. J Periodontol 2003;74:1183–90.
[60] Velliyagounder K, Kaplan JB, Furgang D, Legarda D, Diamond G, Parkin RE, et al. One of two human lactoferrin variants exhibits increased antibacterial and transcriptional activation activities and is associated with localized juvenile periodontitis. Infect Immun 2003;71:6141–7.
[61] Pontes CC, Gonzales JR, Novaes Jr AB, Taba Júnior M, Grisi MF, Michel J, et al. Interleukin-4 gene polymorphism and its relation to periodontal disease in a Brazilian population of African heritage. J Dent 2004;32:241–6.
[62] Nibali L, Donos N, Brett PM, Parkar M, Ellinas T, Llorente M, et al. A familial analysis of aggressive periodontitis—clinical and genetic findings. J Periodontal Res Suppl 2008;43:627–34.
[63] Jordan WJ, Eskdale J, Lennon GP, Pestoff R, Wu L, Fine DH, et al. A non-conservative, coding single-nucleotide polymorphism in the N-terminal region of lactoferrin is associated with aggressive periodontitis in an African-American, but not a Caucasian population. Genes Immun 2005;6: 632–5.
[64] Trevilatto PC, de Souza Pardo AP, Scarel-Caminaga RM, de Brito Jr RB, Alvim-Pereira F, Alvim-Pereira CC, et al. Association of IL1 gene polymorphisms with chronic periodontitis in Brazilians. Arch Oral Biol 2011;56:54–62.
[65] Hashim NT, Linden GJ, Ibrahim ME, Gismalla BG, Lundy FT, Hughes FJ, et al. Replication of the association of GLT6D1 with aggressive periodontitis in a Sudanese population. J Clin Periodontol 2015;42:319–24.
[66] Wu X, Offenbacher S, López NJ, Chen D, Wang H-Y, Rogus J, et al. Association of interleukin-1 gene variations with moderate to severe chronic periodontitis in multiple ethnicities. J Periodontal Res Suppl 2015;50: 52–61.
[67] Boukortt KN, Saidi-Ouahrani N, Boukerzaza B, Ouhaibi-Djellouli H, Hachmaoui K, Benaissa FZ, et al. Association analysis of the IL-1 gene cluster polymorphisms with aggressive and chronic periodontitis in the Algerian population. Arch Oral Biol 2015;60:1463–70.
[68] Jordan WJ, Eskdale J, Lennon GP, Pestoff R, Wu L, Fine DH, et al. A non-conservative, coding single-nucleotide polymorphism in the N-terminal region of lactoferrin is associated with aggressive periodontitis in an African-American, but not a Caucasian population. Genes Immun 2005;6:632–5.
[69] Nibali L, Parkar M, D'Aiuto F, Suvan JE, Brett PM, Griffiths GS, et al. Vitamin D receptor polymorphism (-1056 Taq-I) interacts with smoking for the presence and progression of periodontitis. J Clin Periodontol 2008;35:561–7.
[70] Hashim NT, Linden GJ, Ibrahim ME, Gismalla BG, Lundy FT, Hughes FJ, et al. Replication of the association of GLT6D1 with aggressive periodontitis in a Sudanese population. J Clin Periodontol 2015;42:319–24.
[71] Schaefer AS, Richter GM, Nothnagel M, Manke T, Dommisch H, Jacobs G, et al. A genome-wide association study identifies GLT6D1 as a susceptibility locus for periodontitis. Hum Mol Genet 2010;19:553–62.
[72] Munz M, Willenborg C, Richter GM, Jockel-Schneider Y, Graetz C, Staufenbiel I, et al. A genome-wide association study identifies nucleotide variants at SIGLEC5 and DEFA1A3 as risk loci for periodontitis. Hum Mol Genet 2017;26:2577–88.
[73] Hanna S, Etzioni A. Leukocyte adhesion deficiencies. Ann N Y Acad Sci 2012;1250:50–5.
[74] Movahedi M, Entezari N, Pourpak Z, Mamishi S, Chavoshzadeh Z, Gharagozlou M, et al. Clinical and laboratory findings in Iranian patients with leukocyte adhesion deficiency (study of 15 cases). J Clin Immunol 2007;27:302–7.
[75] Almarza Novoa E, Kasbekar S, Thrasher AJ, Kohn DB, Sevilla J, Nguyen T, et al. Leukocyte adhesion deficiency-I: a comprehensive review of all published cases. J Allergy Clin Immunol Pract 2018;6, 1418-1420.e10.
[76] Yashoda-Devi BK, Rakesh N, Devaraju D, Santana N. Leukocyte adhesion deficiency type I—a focus on oral disease in a young child. Med Oral Patol Oral Cir Bucal 2011;16:e153–7.
[77] Meyle J. Leukocyte adhesion deficiency and prepubertal periodontitis. Periodontol 2000;1994(6):26–36.

[78] Dababneh R, Al-Wahadneh AM, Hamadneh S, Khouri A, Bissada NF. Periodontal manifestation of leukocyte adhesion deficiency type I. J Periodontol 2008;79:764–8.
[79] Roberts MW, Atkinson JC. Oral manifestations associated with leukocyte adhesion deficiency: a five-year case study. Pediatr Dent 1990;12:107–11.
[80] Moutsopoulos NM, Konkel J, Sarmadi M, Eskan MA, Wild T, Dutzan N, et al. Defective neutrophil recruitment in leukocyte adhesion deficiency type I disease causes local IL-17-driven inflammatory bone loss. Sci Transl Med 2014;6:229ra40.
[81] Moutsopoulos NM, Chalmers NI, Barb JJ, Abusleme L, Greenwell-Wild T, Dutzan N, et al. Subgingival microbial communities in Leukocyte Adhesion Deficiency and their relationship with local immunopathology. PLoS Pathog 2015;11:e1004698.
[82] Moutsopoulos NM, Zerbe CS, Wild T, Dutzan N, Brenchley L, DiPasquale G, et al. Interleukin-12 and Interleukin-23 blockade in leukocyte adhesion deficiency type 1. N Engl J Med 2017;376:1141–6.
[83] Nibali L. Aggressive periodontitis: microbes and host response, who to blame? Virulence 2015;6:223–8.
[84] Lira-Junior R, Öztürk VÖ, Emingil G, Bostanci N, Boström EA. Salivary and serum markers related to innate immunity in generalized aggressive periodontitis. J Periodontol 2017;88:1339–47.
[85] Guentsch A, Puklo M, Preshaw PM, Glockmann E, Pfister W, Potempa J, et al. Neutrophils in chronic and aggressive periodontitis in interaction with Porphyromonas gingivalis and *Aggregatibacter actinomycetemcomitans*. J Periodontal Res Suppl 2009;44:368–77.
[86] Preedy VR, Patel VB. Macrophage inflammatory Protein-1 alpha (MIP-1 alpha)/CCL3: as a biomarker. Gen Methods Biomarker Res Appl 2015:223–49.
[87] Cutler CW, Jotwani R. Dendritic cells at the oral mucosal interface. J Dent Res 2006;85:678–89.
[88] Tesmer LA, Lundy SK, Sarkar S, Fox DA. Th17 cells in human disease. Immunol Rev 2008;223:87–113.
[89] da Motta RJG, Tirapelli C, da Silva RJ, Villafuerte KRV, Almeida LY, Riveiro-Silva A, et al. Immature, but not mature, dendritic cells are more often present in aggressive periodontitis than chronic periodontitis: an immunohistochemical study. J Periodontol 2016;87:1499–507.
[90] Schenkein HA, Koertge TE, Brooks CN, Sabatini R, Purkall DE, Tew JG. IL-17 in sera from patients with aggressive periodontitis. J Dent Res 2010;89:943–7.
[91] Cafferata EA, Terraza-Aguirre C, Barrera R, Faúndez N, González N, et al. Interleukin-35 inhibits alveolar bone resorption by modulating the Th17/Treg imbalance during periodontitis. J Clin Periodontol 2020;47:676–88.