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Inflammation and Alzheimer's disease: Possible role of periodontal diseases

Angela R. Kamer[a,*], Ronald G. Craig[a,b], Ananda P. Dasanayake[c], Miroslaw Brys[d], Lidia Glodzik-Sobanska[d], Mony J. de Leon[d,e]

[a]*Department of Periodontology and Implant Dentistry, College of Dentistry, New York University, New York, NY, USA*
[b]*Department of Basic Sciences and Craniofacial Biology, College of Dentistry, New York University, New York, NY, USA*
[c]*Department of Epidemiology and Health Promotion, College of Dentistry, New York University, New York, NY, USA*
[d]*Department of Psychiatry, School of Medicine, New York University, New York, NY, USA*
[e]*Nathan Kline Institute, Orangeburg, NY, USA*

Abstract The molecular and cellular mechanisms responsible for the etiology and pathogenesis of Alzheimer's disease (AD) have not been defined; however, inflammation within the brain is thought to play a pivotal role. Studies suggest that peripheral infection/inflammation might affect the inflammatory state of the central nervous system. Chronic periodontitis is a prevalent peripheral infection that is associated with gram-negative anaerobic bacteria and the elevation of serum inflammatory markers including C-reactive protein. Recently, chronic periodontitis has been associated with several systemic diseases including AD. In this article we review the pathogenesis of chronic periodontitis and the role of inflammation in AD. In addition, we propose several potential mechanisms through which chronic periodontitis can possibly contribute to the clinical onset and progression of AD. Because chronic periodontitis is a treatable infection, it might be a readily modifiable risk factor for AD.

Keywords: Alzheimer's disease; Inflammation; Periodontitis; Pathogenesis model

1. Introduction

Alzheimer's disease (AD) is one of the leading causes of dementia afflicting the elderly. In the United States, approximately 4.5 million patients are currently diagnosed with AD. The prevalence of AD increases with age from 4% in the 65 to 75 years age group to 19% in the 85 to 89 years age group, and the incidence of AD increases from 7/1000 in the 65 to 69 years age group to 118/1000 in the 85 to 89 years age group. Undoubtedly, as the population ages and life span increases, the prevalence of AD will increase even further and in 50 years is predicted to include approximately 14 million people. Although the above statistics underscore AD as a major public health concern, the prevalence of AD will not significantly decrease unless new approaches to treatment emerge that can delay the onset, slow the progression, or reverse the disease process. Efforts to identify treatable factors involved in the initiation and progression of AD are therefore of paramount importance.

Early onset AD is thought to be genetically determined, whereas late onset or sporadic AD, which includes the majority of patients, is believed to result from the interaction of genetic and environmental factors. Age is a significant risk factor for AD. Other risk factors for late onset AD identified to date include family history, education, high fat diet, hypertension, diabetes, history of head trauma, and susceptibility genes such as *APOE*. Among them, age, family history, and *APOE* ε4 allele are accepted risk factors. The others are possible and are still being investigated. Table 1 presents odds ratios for selected risk factors.

*Corresponding author. Tel.: 212-998-9868; fax: 212-995-4603.
E-mail address: ark5@nyu.edu

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Table 1
Risk Factors for AD

Risk factor	Odds ratio	Source
Family history of AD or dementia	4.6–6.6	Hall et al,[1] 1998, Brayne et al,[2] 1998
ApoE 4 at least 1 allele	2.6–4.6	Farrer et al,[3] 1997
Hyperhomocystinemia	3.7–4.5	Clarke et al,[4] 1998, Quadri et al,[5] 2004
Head trauma	1.1–3.6	Fleminger et al,[6] 2003 (review)
Severe atherosclerosis	3.0	Hofman et al,[7] 1997
Smoking	2.4	Tyas et al,[8] 2003
Hypertension	2.3	Kivipelto et al,[9] 2001
Hyperlipidemia	2.1	Kivipelto et al,[9] 2001
Depression	1.7–1.8	Andersen et al,[10] 2005, Speck et al,[11] 1995
Diabetes	1.4	Brayne et al,[2] 1998

NOTE. Odd ratios for AD risk factors are presented. Family history and *APOE* with an e4 allele are accepted risk factors. The other risk factors are possible and are being investigated. References are also given. These references are different from those references cited in the text.

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Some of the above risk factors for AD are immutable, but the identification of modifiable risk factors might hold the potential for intervention, thus limiting the prevalence and morbidity of AD in the future. Although the molecular mechanisms involved in the etiology and pathogenesis of AD have not been completely characterized, inflammation within the central nervous system (CNS) is thought to play a pivotal role. Central to the role of inflammation in AD is the hypothesis that peripheral infection/inflammation might alter the inflammatory state in the brain. Indeed, preliminary studies have shown that peripheral infections might hasten the onset and progression of AD [1], although the specific mechanisms and pathways involved have not been defined. The intent of this article is to review the role of inflammation in the pathogenesis of AD and suggest the contribution of periodontal disease to the clinical onset and progression of AD.

2. The association of inflammation with AD

2.1. Inflammatory mechanisms in AD

A prominent hypothesis forwarded to explain the pathogenesis of AD is the inflammatory hypothesis [2], whose central theme is a self-perpetuating progressive inflammation in the brain culminating in neurodegeneration. At present, no local inciting inflammatory factors for AD are accepted. It has been suggested that inflammation might be induced by the pathologic features of AD, including Aβ-amyloid 1-42 peptide (Aβ42) found in senile plaques, hyperphosphorylated tau protein (P-Tau) comprising the neurofibrillary tangles, or components of degenerated neurons [3]. These pathologic changes are believed to stimulate glial cells to produce proinflammatory cytokines including tumor necrosis factor (TNF)–α, interleukin (IL)-1β, IL-6, and inflammation reactive proteins such as C-reactive protein (CRP). Elevated proinflammatory cytokines and CRP might then act via paracrine and/or autocrine pathways to stimulate glial cells to further produce additional Aβ42, P-Tau, and proinflammatory molecules. Thus, a positively reinforcing cycle is established in which inflammatory mediators play a dual role by both stimulating glial cells and activating molecular pathways, leading to neurodegeneration [2]. Several lines of evidence support this model. Senile plaques are associated with reactive astrocytes and activated microglial cells [3] and immunoreact with antibodies against TNF-α, IL-1β, IL-6, CRP, and complement proteins [3]. TNF-α, IL-1β, and IL-6 are capable of stimulating the synthesis of Aβ42 and the phosphorylation of tau protein**,** and Aβ42 and P-Tau can stimulate the production of TNF-α, IL-1β, and IL-6 by glial cells [2–5].

Clinical studies in support of the role of inflammation in the pathogenesis of AD, although limited, have investigated the value of CRP (an acute phase protein whose synthesis is regulated by proinflammatory cytokines in response to infection/inflammation) and other systemic inflammatory markers in predicting the onset of AD. Elevated CRP increased the risk of both developing AD [6] and of cognitive decline in various populations [7]. A nested case-control study of 1,050 subjects from the Honolulu-Asia Aging Study reported that higher levels of CRP increased the risk of developing AD 25 years later [8]. Proinflammatory cytokines as predictors of AD have also been investigated, however with conflicting results. For example, elevated IL-6 moderately increased the risk of AD, even after adjusting for age, gender, smoking, body mass index, medications, and diabetes, and correlated with disease severity [9]. AD subjects with elevated IL-1β were at increased risk of cognitive decline compared with those with low IL-1β [10], whereas the presence of a composite genotype characterized by the presence of IL-1α-889 and IL-1β+3953 polymorphisms conferred an almost 11-fold increased risk of developing AD [11], presumably as a result of increased

IL-1 levels. However, other studies failed to demonstrate that elevated IL-6 and CRP were associated with cognitive decline. The variation in results from the above studies, however, is not unexpected. Differences exist in the timing, duration, and nature of the inflammatory processes. In addition, inflammation is the summation of multiple signaling and effector pathways that interact with each other, resulting in the stimulation or inhibition of the inflammatory response. For example, some mediators might not be increased, but they might lead to an elevated inflammatory response as a result of their interaction with other molecules. Therefore, the lack of detection, the increase or decrease in one specific proinflammatory cytokine might not reflect the inflammatory response. IL-6, IL-1β, and TNF-α are often in the effector pathways; therefore, they are the most studied, but they do not represent the complete inflammatory phenotype. Therefore, new methodologies such as multiplex analysis may be needed to evaluate the expression of proinflammatory and anti-inflammatory molecules.

Additional support for the inflammatory hypothesis comes from studies reporting that nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) might be effective in slowing the onset of AD. For example, the Baltimore and Rotterdam studies reported that anti-inflammatory drugs taken for at least 2 years before the onset of dementia were effective in its delay [12,13], and a meta-analysis supported these findings [14]. In addition to the beneficial effect of the NSAIDs, animal studies showed that peroxisome proliferator activated receptor gamma (PPAR-γ) agonists are effective in reducing the activated glial cells and therefore impact AD. PPAR-γ agonists are transcription factors with a role in reducing the expression of proinflammatory molecules including IL-1β and TNF-α. Taken together, these studies suggest that inflammation plays a significant role in the pathogenesis of AD, and at least some forms of anti-inflammatory methods reduce the onset of AD. However, randomized control studies failed to support the role of all NSAIDs in modifying the risk for AD [15,16], and alternate explanations have been forwarded [17]. Most of the clinical trials used specific NSAIDs such as cyclooxygenase 2 (COX-2) inhibitors as anti-inflammatory drugs [16], whereas the patients sampled in epidemiologic studies used COX-1/2 inhibitors. These results suggest that the effect of NSAIDs depends on the drug itself. Perhaps nonspecific and specific NSAIDS might have multitudes of effects, some of them independent of their COX-1/2 inhibitory activity, or the role of COX-1 and COX-2 enzymes in the pathogenesis of AD is far from clear. For example, COX-1 inhibitors at effective concentration and right duration might stimulate the PPAR-γ agonists and therefore inhibit the proinflammatory mediators, whereas COX-2 inhibitors might increase the synthesis of Aβ42 peptide, a process in conflict with an anti-AD effect. Clinical trials with COX-1 inhibitors did not hold positive findings, probably because of low dosage and high dropout rates [15]. Therefore, these results do not indicate that the anti-inflammatory methods are not effective but suggest that only some NSAIDs might be effective if administered properly. These studies do not refute the inflammatory hypothesis of AD or the beneficial effect of anti-inflammatory protocols in AD, but they suggest that much more has to be learned about these methods and their mechanism of action.

2.2. Peripheral inflammatory mechanisms in the pathogenesis of AD

One of the hallmarks of AD is the presence of activated glial cells that produce significant levels of inflammatory molecules. At low levels these molecules might have a protective role. However, when expressed at high levels as in AD, they can induce neurodegeneration [18], suggesting the hypothesis that processes capable of up-regulating the expression of inflammatory molecules will contribute to the progression of the AD. Proinflammatory molecules derived from the periphery might increase the brain inflammatory molecule pool by at least two mechanisms, via systemic circulation and/or neural pathways. Proinflammatory molecules in the systemic circulation might enter the CNS by multiple routes. They might enter the CNS via areas of the brain that lack a blood-brain barrier (BBB) (circumventricular organs). But they might also enter the CNS in the areas with BBB by (1) crossing through fenestrated capillaries of the BBB, (2) using cytokine-specific transporters, (3) increasing the BBB permeability, or (4) activating brain endothelial cells to produce cytokine-inducing signaling molecules such as nitric oxide or prostanoids. Once in the brain, proinflammatory molecules might directly increase the local proinflammatory cytokine pool or indirectly stimulate glial cells to synthesize additional proinflammatory cytokines. If glial cells are already primed or activated as in AD, stimulation by peripherally derived proinflammatory cytokines would result in amplified, exaggerated responses and overexpression of proinflammatory molecules. Neuronal pathways are another mechanism through which cytokines derived from peripheral inflammatory sources might affect the brain proinflammatory cytokine pool [19]. Peripheral cytokines can stimulate afferent fibers of peripheral nerves, leading to increased levels of brain cytokines, or they can enter the brain via channels or compartments associated with peripheral nerves. Interestingly enough, even if the elevated concentrations of these cytokines are only local and not systemic, they still might increase brain cytokines [20]. This mechanism has also been described in the oral cavity, suggesting that proinflammatory molecules originating in oral cavity might affect the brain via neural pathways. Still another mechanism by which peripheral proinflammatory molecules might induce inflammatory changes in the brain is by activating peripheral inflammatory cells such as T cells and macrophages that then gain access to the brain and contribute to the inflammatory process.

In addition to peripheral proinflammatory molecules, bacterial products can also indirectly increase the brain proinflammatory cytokine pool. The lipopolysaccharide (LPS) of gram-negative bacteria is a readily recognized, pathogen-associated molecular pattern that triggers the innate immune response and increases peripheral proinflammatory cytokines by activating the CD14 receptor. Studies have shown that CD14 receptors are present on areas of the brain that are exposed to the systemic circulation such as the circumventricular areas, leptomeninges, and choroid plexus. On intravenous injection with LPS, CD14 receptors are up-regulated not only in areas exposed to the LPS but also throughout the brain [21], demonstrating that LPS is capable of influencing the CD14 profile in the brain even in the absence of direct contact between LPS and CD14. There, CD14 can be activated by LPS derived from invasive bacteria or AD amyloid-β protein, thus increasing further brain cytokines and hypothetically contributing to the inflammatory burden of AD.

2.3. Peripheral infection in the pathogenesis of AD

Several bacterial pathogens have been proposed to directly act as triggers or cofactors in the etiology/pathogenesis of AD [22]. A prospective pilot study showed impairment of cognitive function in AD patients for at least 2 months after the resolution of a systemic infection [10], whereas the presence of peripheral infections increased the risk of delirium in patients with AD [23]. Among twins, individuals with a history of severe peripheral infections experienced earlier onset of AD, and subjects with higher CRP levels were at greater risk for the development of AD [8]. Few studies on the role of specific bacteria in the pathogenesis of AD have been conducted, and most have focused on *Chlamydia pneumoniae* and spirochetes. However, reports for both pathogens have been contradictory. Whereas one study reported that *C pneumoniae* was present in 17 of 19 postmortem brain samples of patients diagnosed with AD but only in 1 of 18 non-AD age-matched control specimens [24], other studies failed to report this association. *Borrelia burgdorferi* spirochetes were detected in blood and cerebrospinal fluid of AD patients, with *B burgdorferi* antigens co-localized with beta-amyloid deposits, and it was observed that glial and neuronal cells exposed to *B burgdorferi* synthesized βamyloid precursor protein and P-taus [25]. Although other studies failed to replicate these findings, these results suggest that spirochetes are not only capable of reaching the brain, but they are also capable of producing pathology characteristic of AD. Spirochetes are also present in the oral cavity, and *Treponema denticola* is a prominent periodontal pathogen associated with moderate to severe periodontitis [26]. *Treponema* species including *T denticola* were detected in 14 of 16 postmortem AD specimens but only detected in 4 of 18 age-matched non-AD specimens. Furthermore, specimens from AD subjects had a greater number of *Treponema* species than controls [27]. These results suggest that bacteria, including periodontopathic bacteria, can invade the brain. The mechanism by which bacterial invasion occurs is not known. Two mechanisms have been proposed. One mechanism is by systemic circulation, and the other mechanism is by way of peripheral nerve pathways. Periodontopathic bacteria could potentially use both pathways. Oral treponemas identified in the trigeminal ganglia are supportive of the neuronal pathways [27]. Oral bacteria are detected in the systemic circulation, particularly when heavy bacterial plaques are present. The occurrence of brain abscesses caused by oral bacteria and the detection of *T denticola* in the brain of an experimental endodontic infection model suggest the potential of these bacteria for reaching the brain [28].

3. Periodontal diseases as a source of systemic inflammation

3.1. Pathogenesis of periodontal disease

Periodontal diseases are a group of inflammatory diseases that affect the supporting tissues of the dentition. The most prevalent periodontal diseases are caused by the interaction of specific bacteria with components of the host immune response in disease-susceptible individuals and are currently classified as plaque-induced gingival diseases and chronic and aggressive periodontitis. Plaque-induced gingival diseases are inflammatory diseases limited to the gingiva (gingivitis), nearly pandemic in children and young adults, and are reversible with treatment. In contrast, chronic and aggressive periodontitis are irreversible, destructive forms of periodontal disease that ultimately result in tooth loss. In periodontitis, the inflammatory process extends from the gingiva to include deeper connective tissues, resulting in the loss of connective tissue and bone largely through the activation of host-derived osteoclasts and matrix metalloproteinases. Recruited into the connective tissue adjacent to the pocket epithelium is an intense inflammatory cell infiltrate consisting of polymorphonuclear leukocytes, monocyte/macrophages, and T and B cells mediated by a multitude of cytokines and chemokines, most of them produced by the inflammatory cells themselves [29]. Clinically, destruction of the periodontal ligament and surrounding alveolar bone in periodontitis creates deep, ulcerated pockets around affected teeth. The total surface area of the inflamed periodontal pockets within a single subject with moderate to severe periodontitis has been estimated to range from 8 to 20 cm^2, depending on the number of teeth affected. Thus, the inflamed ulcerated periodontal pocket can be a very significant source of inflammatory and pathogen-derived mediators. It is estimated that 35% of dentate adults in the United States between 30 and 90 years of age have periodontitis, and the prevalence of periodontitis increases with age to afflict approximately 50% of people older than the age of 55

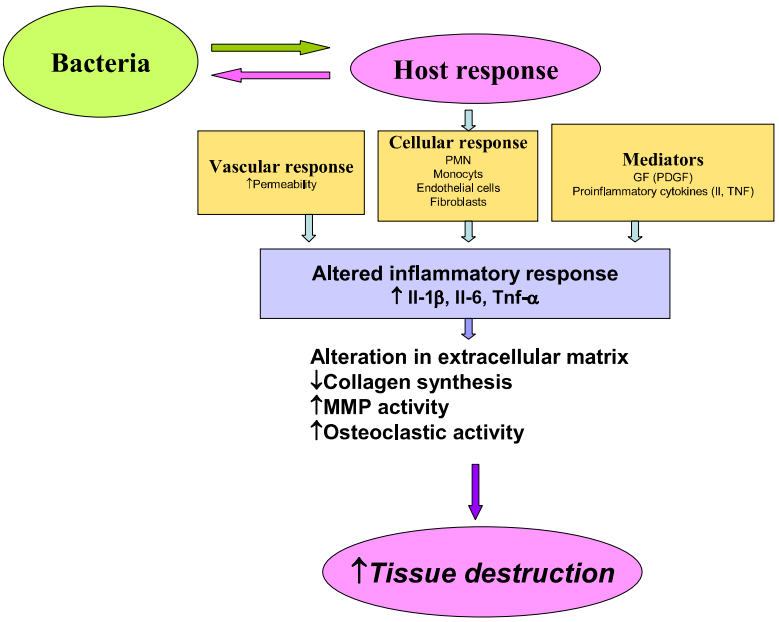

Fig. 1. Pathogenesis of periodontitis. Main theme of this model is the maintenance of a fine balance between bacterial plaque and the host response to this bacterial challenge. In disease-susceptible individuals, periodontal bacteria activate an innate and adaptive immune response including cell targeting and local release of inflammatory mediators such as IL-1, IL-6, and TNF-α, resulting in tissue destruction.

[30]. Therefore, chronic periodontitis can be a significant source of covert peripheral inflammation within the general population.

3.2. Host pathogen interactions

Approximately one dozen periodontal pathogenic species have been identified as necessary for the initiation, maintenance, and progression of periodontitis. However, the presence of these bacterial species is not sufficient for disease progression but appears to be dependent on the host's inflammatory and immune response to these pathogens (Fig. 1). Within the periodontal pocket, bacteria exist in a stratified, complex ecosystem or dental biofilm, consisting of microorganisms and their components (endotoxin/LPS, virulence factors, etc) embedded in an extracellular matrix of polysaccharides, proteins, and inorganic compounds. The structure of the dental biofilm favors periodontal bacterial cell growth while providing protection from host defense mechanisms and exogenously derived antibacterials. The profile of bacterial species within the dental biofilm varies between sites and individuals [31]. In health, the majority of bacteria are gram-positive aerobes. In plaque-induced gingivitis, 50% of bacteria are gram-positive, but with increasing inflammation, a shift toward increasing numbers of gram-negative bacteria occurs. In periodontitis, approximately 85% of bacteria are gram-negative [31], with *Aggregatibacter actinomycetemcomitans* (*Actinobacillus actinomycetemcomitans), Tannerella forsythensis, Porphyromonas gingivalis, and T denticola* considered prime periodontal pathogens [31]. The later three are all gram-negative anaerobic species, and *P gingivalis*, *A actinomycetemcomitans,* and *T denticola* are capable of tissue invasion. Periodontal bacteria and their products can gain access to the circulation particularly in the presence of ulcerated pockets, resulting in bacteremia and systemic dissemination of bacterial products.

The host response to subgingival periodontal pathogens engages both innate and adaptive immune responses, resulting in the alteration of local vasculature, generation of an inflammatory response, immune cell priming [32], and the secretion of proinflammatory cytokines including IL-1, IL-6, and TNF-α. In periodontal health, bacteria and host response are in balance. In gingivitis, the bacterial challenge elicits an innate immune response in the adjacent gingival tissue that is able to limit bacterial-induced pathology. In periodontitis, the balance between bacteria and host response is disrupted, resulting in increased inflammatory infiltrate and the production of proinflammatory cytokines including IL-1, IL-6, and TNF-α. Tissue destruction occurs mainly by activation of osteoclasts, matrix metalloproteinases, and other proteinases by the host inflammatory response. The occurrence and expression of periodontitis reflect the heightened proinflammatory reaction mounted by the host to bacterial challenge and suggest a significant host-dependent response in the pathogenesis of periodontitis (Figure 1). Indeed, this hypothesis is supported by studies reporting specific polymorphisms in genes coding for inflammatory molecules (for example, the presence of IL-1α-889 and IL-1β+3953 polymorphisms) are at higher risk of having severe periodontal disease [33].

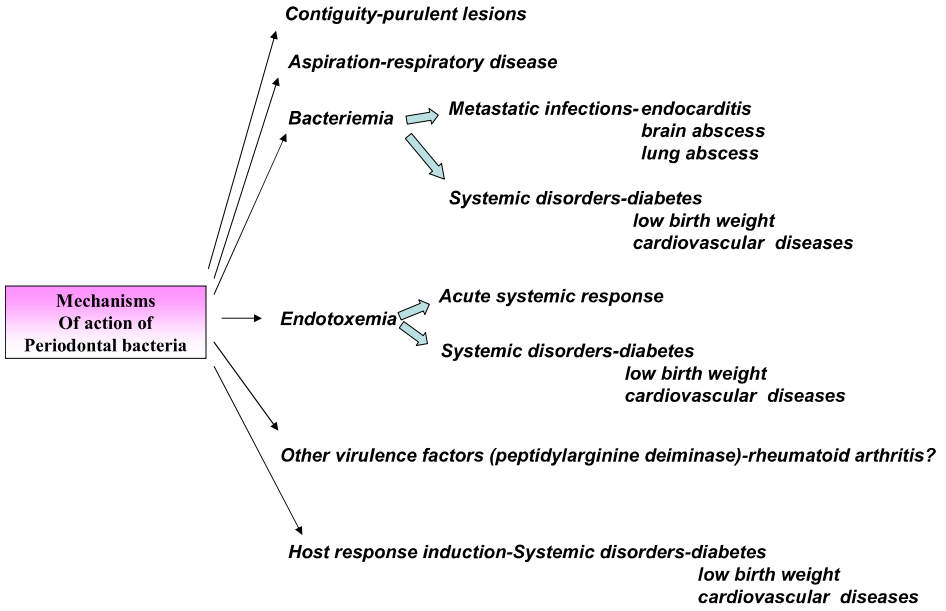

Fig. 2. Possible mechanisms of actions of periodontal bacteria. Periodontal bacteria might induce distant pathology by at least six mechanisms: (1) direct spreading of a periodontal suppurant lesion to neighboring spaces; (2) by aspiration; (3) by bacteremia and direct spread to various sites; (4) by endotoxemia; (5) by releasing virulence factors into the circulation; and (6) by stimulating the production of pathogenic molecules by the host (CRP, inflammatory mediators, etc).

3.3. Mechanisms of actions of periodontal bacteria

In view of the profile of bacterial species associated with periodontitis and the unique availability of the periodontal pocket to the circulation and to nervous tissue, it is not surprising that periodontitis can have significant systemic effects. Periodontal bacteria can elicit systemic effects through at least 6 mechanisms (Fig. 2). First, periodontal bacteria can directly induce pathology by invasion into contiguous body spaces, and Ludwig's angina is an extreme example of this type of pathology. Second, bacteria and its products can be aspirated and induce pulmonary pathology [34]. Third, periodontal bacteria might gain access to the systemic circulation and subsequently colonize a distant anatomic site. For example, periodontal bacteria have been implicated in several systemic diseases including endocarditis and brain and lung abscesses [35]. In these examples, periodontal bacteria can be isolated and cultured from the affected sites. Bacterial endotoxin or other bacterial products (virulence factors) might also gain access to the systemic circulation and affect various pathologic processes at distant sites. Still another mechanism involves the host response. Challenged by bacteria, the host produces a multitude of mediators including cytokines that gain access to the circulation. Collectively, these mechanisms account for many systemic disorders with an inflammatory basis.

Indeed, chronic adult periodontitis has been associated with several conditions including increased risk of delivery of pre-term low birth weight infants [36], atherosclerotic complications including myocardial infarction and stroke [37], respiratory diseases [34], poorly controlled diabetes mellitus [38], and possibly with AD [39].

3.4. Periodontal infection can induce systemic pathology

A single periodontal pocket can harbor as many as 300 million organisms [31]. Largely consisting of gram-negative bacterial species, periodontal bacteria can incite systemic effects through bacteremia, endotoxemia, and virulence factor release into the circulation. Both minor and major oral surgical procedures might result in bacteremia. For example, suture removal induces bacteremia only in 5% of subjects, tooth extraction in 58% to 100% of subjects, and periodontal procedures in 10% to 70% of subjects, depending on the severity of periodontal disease and on the type of procedures performed. In addition, bacteremia might also result from routine daily procedures including flossing, brushing, and mastication in subjects with periodontitis comparable to those induced by dental procedures [40]. Moreover, the frequent nature of bacteremias from routine procedures might lead to cumulative bacterial exposures that greatly exceed those caused by professional dental procedures [40]. This is especially true when local infection persists as in chronic periodontitis.

Periodontal pathogens might also be capable of inciting pathology at distant sites. For example, *A actinomycetemcomitans*, *P gingivalis*, and *T denticola* are capable of invading multiple cell types. Studies showed that *P gingivalis* not only invaded human aortic endothelial cells but also induced production of proinflammatory molecules. More-

over, these bacteria have been recovered at distant sites including atherosclerotic plaques and brain tissues [27,41]. These results are not surprising because most periodontal pathogenic species are gram-negative, colonize subgingival dental biofilm adjacent to the ulcerated periodontal pocket, and are capable of proteolytic enzyme synthesis that can degrade the host basement membrane and gain access to the systemic circulation. Several periodontal bacterial species have been associated with inflammatory systemic diseases. An epidemiologic study from Finland reported that the risk of coronary heart disease was increased 50% in subjects with an elevated antibody response to *P gingivalis* and *A actinomycetemcomitans* [42], whereas a second study reported that subjects whose subgingival biofilm tested positive for periodontal bacteria were more likely to have carotid atherosclerosis as measured by intima-media thickening [43]. These reports support a role for periodontal pathogenic bacteria in systemic inflammatory diseases.

Endotoxin is a prominent component of dental plaque, is present on roots of periodontally involved teeth, and can be released into the circulation during professional and nonprofessional dental procedures. In addition, bacteremia might be accompanied or followed by endotoxemia. Only a few studies have assessed endotoxemia of oral origin but have demonstrated that it can be induced by normal mastication, and its prevalence and level depend on the severity and extent of periodontal disease. Endotoxemia was present in 40% of subjects with severe periodontitis compared with 12% of subjects without periodontal disease. Moreover, endotoxemia might be accompanied by elevation in TNF-α, IL-6, CRP [44], and possible fever, suggesting that endotoxemia of oral origin might induce a systemic acute phase response.

Finally, periodontitis might exert systemic effects through elevation of proinflammatory cytokines and other inflammatory mediators. A growing number of studies have reported an elevation of CRP in subjects with moderate to severe periodontitis [45]. For example, data from the Third National Health and Nutrition Examination Survey reported that subjects with extensive periodontal disease were more likely to have CRP values $>$10 mg/L (13%) when compared with subjects without periodontal disease (6%), and subjects with periodontitis also had significantly higher CRP levels (mean, 4.5 vs 3.3 mg/L) [46]. Periodontal therapy resulted in decreased CRP levels and was more likely to occur in subjects who were responsive to periodontal treatment. Although studies have reported a relationship between the severity of periodontitis and CRP, other studies have reported elevated CRP only associated with severe periodontitis [46]. A limited number of studies have examined the association between periodontitis and systemic levels of IL-1β, IL-6, and TNF-α and suggest that a higher proportion of subjects with periodontitis have higher levels of plasma IL-6. Both levels of plasma IL-6 and TNF-α decreased after periodontal treatment, suggesting that these proinflammatory markers reflect periodontal infections. The plasma levels of IL-1 and TNF-α appear to depend on the severity of inflammation; therefore, they might be more difficult to detect if periodontal disease is not severe or extensive.

4. Hypothetical contributions of periodontitis to AD onset and progression

On the basis of the contribution of moderate to severe periodontitis to systemic inflammation and the potential role of inflammation in the etiology and progression of AD, we propose that chronic periodontitis might be a risk factor in the incidence and progression of AD. Periodontitis is a chronic inflammatory disease resulting in years of locally increased proinflammatory molecules that surround the trigeminal cranial nerve endings. Periodontitis results also in years of systemic host exposure to proinflammatory cytokines and other systemic markers of inflammation such as CRP. Therefore, hypothetically, periodontal-derived cytokines could reach the brain by both systemic and neural pathways and amplify brain cytokine pools. Periodontal pathogens associated with moderate to severe periodontitis are gram-negative anaerobic species, rich in endotoxin/LPS that can stimulate proinflammatory cytokines and CD14 activity. In addition, several bacteria associated with severe or progressive periodontitis are capable of invading tissues including *A actinomycetemcomitans, P gingivalis*, and *T denticola*. *T denticola* is from the same class as *T palidum,* known to invade brain tissue and to induce chronic inflammation, cortical atrophy, and amyloid deposition in subjects with syphilis. In fact, *Treponema* species have been detected in the trigeminal ganglia, brainstem, and cortex of human brain, and AD donors were more likely to have *Treponema* and more *Treponema* species than controls, suggesting that oral bacteria are capable of invading brain tissue perhaps via peripheral nerve fibers [27]. Because this is the only study investigating the presence of oral bacteria in the brain, replication is necessary.

Clinical studies investigating the relationship between periodontitis and AD are warranted. A recently published study in this journal showed that in monozygotic twins discordant for AD, the presence of tooth loss earlier in life constituted an increased risk for AD (odds ratio, 5.5) [39]. Although this study used tooth loss as an exposure, periodontal disease is a major reason for tooth loss. More importantly, this study assessed the loss of teeth years before the diagnosis of AD, suggesting that oral disease and perhaps periodontal disease exposure might significantly impact the incidence and prevalence of AD. Therefore, these results, although not conclusive, point toward the possibility that periodontal disease might impact the expression and progression of AD, and this relationship should be investigated.

We propose that periodontal disease with significant inflammatory burden might enhance the pool of inflammatory

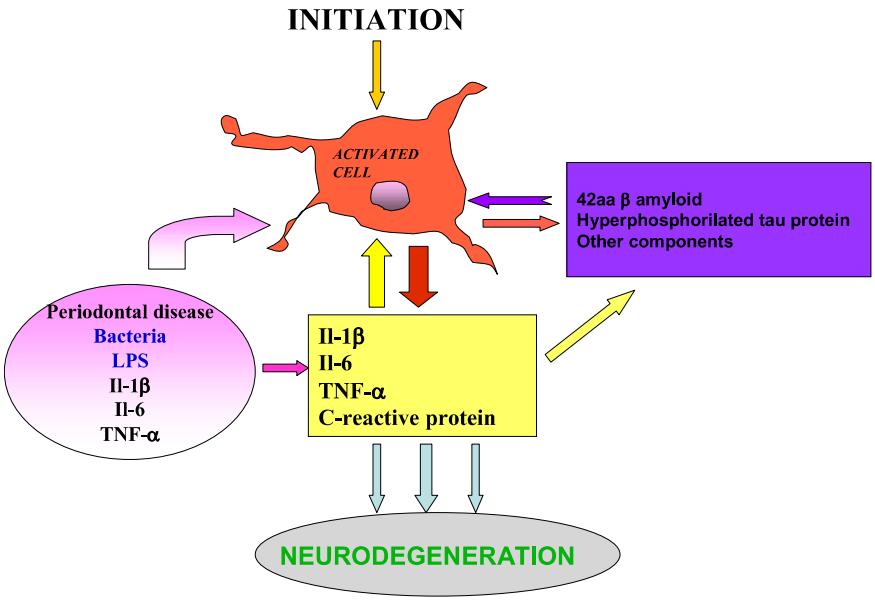

Fig. 3. Model for periodontal disease–induced progression of AD. Central theme of AD pathogenesis is the inflammation as illustrated by intensive production of inflammatory molecules such as IL-1β, IL-6, TNF-α, and CRP. Periodontal disease might affect the progression of AD directly by bacterial invasion or indirectly through bacterial products (LPS) or host response molecules (cytokines, CRP), resulting in elevation of brain inflammatory molecules. These molecules would further amplify the inflammatory signal by activating the already primed glial cells and increase production of molecules such as β-amyloid peptide, P-taus, and ultimately activate pathways leading to degeneration.

molecules in the brain and contributes to the progression of AD (Fig. 3). According to our model, cytokines are produced locally during periodontal inflammation and are systemically due to periodontal endotoxemia. These cytokines will act on the already primed glial cells, resulting in an amplified reaction and progression of AD. Another way to increase brain inflammatory molecule pool is by the direct action of bacteria or bacterial products as demonstrated by *T palidum*. The progression of AD might manifest clinically as earlier onset or as more severe disease.

Inflammation is a prominent component of both AD and chronic periodontitis. Hyperinflammatory genotypes, as evidenced by IL-1α-889 and IL-1β+3953 polymorphisms, have been associated with both AD and chronic periodontitis. Indeed, Offenbacher [47] in the dental literature and McGeer and McGeer [48] in the neurologic literature have suggested that an inflammatory trait characterized by an amplified inflammatory response to an injurious stimulus might result in disease initiation and progression. Therefore, another possibility exists that periodontitis and AD, although separate entities, converge to a common pathogenic base (effector), a hyperinflammatory response to β-amyloid peptide in AD and to periodontal pathogens in periodontitis. As suggested by Korman [33], an amplified inflammatory response would not cause the disease but modify its expression (onset, severity, rate of progression). Future studies should address these questions.

The significance of the possible involvement of periodontitis in AD onset and progression is that periodontal infections are treatable; therefore, periodontitis might be a modifiable risk factor for AD. Studies assessing the role of anti-inflammatory drugs in reducing the risk of AD taught us valuable lessons, that is, anti-inflammatory modulation might prevent AD if the protocol proved to be anti-inflammatory, was longer in duration, and proved not to have unwanted effects (pro-amylogenesis) [49]. Perhaps the anti-inflammatory methods have to be better profiled and activated earlier in the disease process for them to be effective. Therefore, combining periodontal disease treatment with studies of AD biomarkers [50] years before AD onset might be effective in delaying it.

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