

Bifacial Relationship between Periodontal Diseases and Alzheimer's Disease- Is *Porphyromonas gingivalis* the Missing Link?

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Abstract

Alzheimer's disease represents a significant public health challenge for the world population, and its prevalence likely to increase as the population ages. Periodontal diseases considered as a risk factor for various systemic diseases and there is extensive data on an association between periodontitis and Alzheimer's disease. The bacterial burden caused by periodontal diseases, in particular, *Porphyromonas gingivalis*, has an immense role in the pathology of Alzheimer's disease. This review uncovers the role of periodontal disease as a risk for Alzheimer's disease and points up *Porphyromonas gingivalis* as a missing link in the pathology of Alzheimer's disease.

Keywords: Alzheimer's Disease; Periodontal Disease; *Porphyromonas gingivalis*; Leptomeningeal; Blood-Brain Barrier

Introduction

This review is aiming at evaluating the bifacial relationship between Periodontal disease (PD) and Alzheimer's Disease (AD) and identify the role of *Porphyromonas gingivalis* as the missing link in their bifacial relationship. Various studies have shown that periodontal diseases are coupled to the initiation and progression of Alzheimer's Disease. They also suggest that the leptomeningeal cells have an essential role in the transduction of inflammatory signals to the brain-resident microglia to initiate neuroinflammation. Also, senescent-type microglia exaggeratedly responds to systemic inflammation. A substantial number of adults are affected with periodontitis, which acts as a significant supplier of covert systemic inflammation within the population. This literary criticism highlights our current understanding of the link between periodontitis and AD [1-3].

AD could also be a neurodegenerative disease afflicting a large population across the world. It is projected that, in the next 40 - 50 years as a result of the population ages and therefore, the life-span increases; AD will afflict approximately more than one hundred million people [4,5]. Susceptibility to develop AD depends upon genetic and environmental factors [2]. Whereas the actual factors concerned among the etiology and pathogenesis of AD are not well characterized, inflammation is believed to play a significant role [6].

Periodontal diseases have been linked directly with diabetes, respiratory infections, rheumatoid arthritis, osteoporosis, obesity and adverse pregnancy outcomes like preterm birth and low birth weight. Most recently, PD has also been associated with the etiology of AD.

Periodontal diseases are heterogeneous, affecting the supporting structures of the teeth. Microorganisms among the plaque cause various types of periodontal diseases and include dental plaque-induced gingival diseases or periodontal disease, chronic and aggressive

periodontitis. A balance between microorganisms populating the dental biofilm and host immune response [5,7], maintains the health of periodontal tissue. In periodontitis, the balance between host response and bacterial equilibrium is disturbed, resulting in an uncontrolled inflammation characterized by the assembly of high levels of inflammatory mediators like IL-1, IL-6, IL-17 and TNF- α and low levels of anti-inflammatory molecules like IL-10.

The keystone periodontal pathogen

Porphyromonas gingivalis (*P. gingivalis*) has been propositioned as the keystone periodontal infectious agent in causing periodontal diseases associated with inflammophilic microbiota. An inflammatory pathology may be a disease condition where the host's immune defenses persistently encounter invading pathogens or bacterial virulence factors. The host's defense failure in the gingival tissues, results in the keystone inflammophilic microbe, *P. gingivalis*, colonizing the subgingival areas and eventually spreading to distant organs [7].

Implications of inflammation in the brain

The brain is immunologically privileged because of a physical blood-brain barrier (BBB) and due to the absence of a lymphatic system, displays low levels of molecules that are crucial to antigen presentation. Thus, throughout neurodegeneration, the brain depends less on the recruitment of peripheral adaptive immune surveillance cells, more on the resident central nervous system (CNS) cells to recognize and mount a response against the invading pathogens [8,9]. Although astrocytes and neurons can cope with infection, the microglial cells function as the primary protective guardians of a healthy brain.

Susceptibility to microbial infection seems to extend throughout advancing age and just before the clinical diagnosis of dementia. This can be because, throughout aging, microglia seem to develop functional defects; therefore, it can be argued that when age is a significant risk factor (as in AD), infections will play a significant role within the specific processes resulting in dementia [10].

Immune evasion strategies of *P. gingivalis*

A surplus data of numerous studies suggested the concept that *P. gingivalis* is a master evader of the host's immune system. The biofilm structure provides a physical barrier against the immune cells of the host [8,11-14]. Additionally, a variety of active mechanisms are employed by bacteria, including degradation of complement fragments, recruitment of hosts regulatory proteins (Factor H, C4 binding protein), and protection by the bacterial cell wall. The trypsin-like protease (Gingipains) secreted by *P. gingivalis* can degrade C3 and C5, thereby preventing C3b deposition on the bacterial cell walls; therefore, *P. gingivalis* is resistant to destruction by complement system [10]. The strains of *P. gingivalis* can evade the innate immune recognition by degrading complement component C3.

The immune invasion strategies of *P. gingivalis* are of great importance not only in PD but to systemic diseases also as this bacterium, and its virulence factors access the systemic organs. In doing so, byproducts/virulence factors of *P. gingivalis* and any inflammatory mediators generated within the blood will potentially reach remote body organs. Dental procedures like tooth extraction, periodontal surgery, scaling and root planning and also the tooth brushing and flossing may be the causal factors for the oral bacteria invading into the systemic circulation [8].

Communication routes between the brain and the immune system

Routes by which systemic immune signals are often transmitted to the brain are intensively studied. Some of them are as follows:

1. The direct pathway involves the circumventricular organs, which are specialized regions lacking a contiguous blood-brain barrier (BBB). The production and release of pro-inflammatory cytokines by macrophage-like cells expressing Toll-like receptors (TLRs) occur in the CVOs by Pathogen-Associated Molecular Patterns, with the cytokines entering the brain through volume diffusion properties.

2. The second route utilizes the IL-1 receptors located on the endothelial cells of brain capillaries and perivascular macrophages. The activation of the IL-1 receptors by current cytokines initiates cytokine release into the brain, without the physical entry of the BBB constituents.
3. A third route consists of cytokine transporters gaining access to the brain through a saturable transport system due to by inundation of cytokine transporters into the systemic circulation.
4. A fourth route involves systemic immune signals are transmitted via the autonomic nervous system. Systemic cytokines directly stimulate primary afferent nerves, like the vagal nerves, which, in turn, activate central pathways concerned in sickness behavior.

In addition to those four “classical” routes, it has been further found that the other possible route through the leptomeningeal pathway could even be considered. The leptomeningeal brain parenchymal covering plays a role by providing a physical boundary at the cerebrospinal fluid-blood barrier. The activation of leptomeningeal cells by circulating cytokines induces the assembly and release of pro-inflammatory cytokines into the brain [11,12]. Thus, they transmit signals from systemic immune cells into the brain-resident microglia.

The toll-like receptor 2 (TLR2), TLR4, TNF-α expressions are mainly reported within the gingival macrophages of chronic periodontitis patients, and it had been found that leptomeningeal cells can transmit the inflammatory signals from peripheral macrophages to resident brain microglia in response to *P. gingivalis* LPS stimulation.

After treatment with the conditioned medium from *P. gingivalis* LPS-stimulated macrophages, the mean expression levels of IL-1b and TNF-a secreted by meningeal fibroblasts were considerably over those after treatment with *P. gingivalis* LPS alone. Furthermore, the mean expression levels of IL-1b and TNF-a secreted by activated microglia after treatment with the conditioned medium from *P. gingivalis* LPS-treated leptomeningeal cells were considerably beyond those after treatment with *P. gingivalis* LPS alone.

These observations recommend that the leptomeningeal cells transmit systemic inflammatory signals from macrophages to brain-resident microglia by secreting inflammatory mediators during periodontitis [15,16].

Figure 1 illustrates the transduction of periodontal microorganism inflammatory signals to brain-resident microglia through the leptomeninges. During chronic disease, IL1β and TNF-α secreted by macrophages and periodontal bacterial components, including LPS and Flagellin, activate IL-1R/TNFR and TLRs, which are localized on the surface of the leptomeninges. These factors successively activate senescent-type microglia in the brain. When cellular activation, senescent-type microglia secrete proinflammatory molecules, like IL-1b, to extend the expression and activity of BACE1, increased the inflated accumulation of Ab. Furthermore, IL-1b secreted from activated senescent-type microglia conjointly accelerates the tangle formation through tau hyperphosphorylation. These pathological features of AD might impair neuronal functions and promote cognitive deficits.

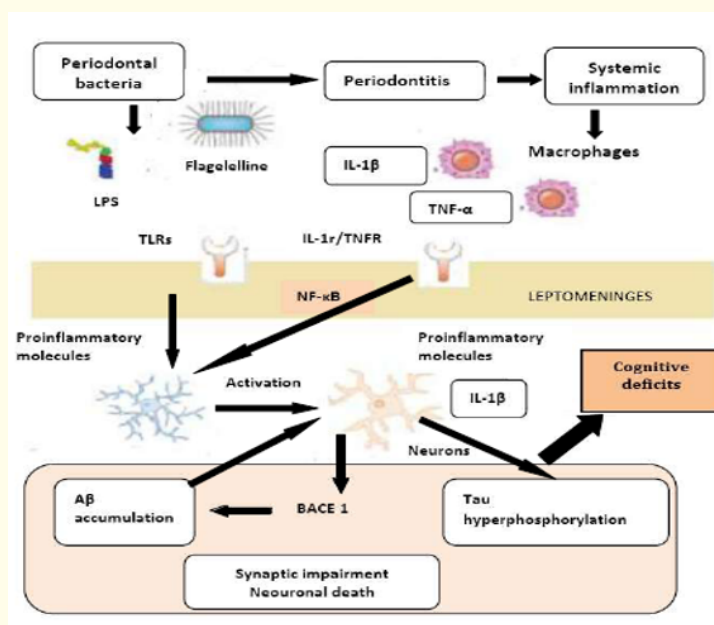


Figure 1: Illustration of the transduction of periodontal microorganism inflammatory signals to brain-resident microglia through the leptomeninges [1].

Conclusion

It is proposed that the bacterial and inflammatory burden due to the various periodontal diseases may be a causal factor for the inflammation in the brain and contributes to the initiation or progression of Alzheimer's Disease. Although no direct evidence associates PD to AD, indirect findings suggest this risk. To conclude, maintaining a healthy oral hygiene practice and managing periodontal disease with the help of proper maintenance therapy throughout life is likely to reduce the unnecessary burden of Alzheimer's Disease in older individuals.

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