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Porphyromonas gingivalis-Induced Neuroinflammation in Alzheimer's Disease

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"Chronic" periodontitis and its keystone pathogen *Porphyromonas gingivalis* have repeatedly been associated with Alzheimer's disease (AD). Pathological hallmarks in AD are brain accumulations of amyloid-beta and neurofibrillary tangles consisting of aggregated and hyperphosphorylated tau. In addition, neuroinflammation induced by *P. gingivalis* has increasingly been recognized as a factor in the pathogenesis of AD. The present mini-review discusses possible mechanisms for the induction of neuroinflammation by *P. gingivalis* in AD, involving factors such as pro-inflammatory mediators, amyloid-beta, tau, microglia, cathepsin B, and protein kinase R. Inflammagens of *P. gingivalis* such as lipopolysaccharide and gingipains are also discussed.

Keywords: amyloid-beta, tau, microglia, cathepsin B, protein kinase R, lipopolysaccharide, gingipains

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INTRODUCTION

"Chronic" periodontitis is a disease affecting the supporting tissues of the teeth. Untreated, it may end with tooth loss. It is a widely prevalent disease in adults all over the world (Eke et al., 2016) and has in several reports been associated with Alzheimer's disease (AD) (for a review, see Olsen, 2021). *Porphyromonas gingivalis*, which is considered a keystone bacterium in "chronic" periodontitis (Socransky et al., 1998; Darveau et al., 2012; Hajishengallis et al., 2012), has been detected in the brains of subjects with AD together with its toxic proteases—gingipains (Dominy et al., 2019). Also, *P. gingivalis* DNA was found in AD brains and cerebrospinal fluid of clinical AD patients. In other studies, *P. gingivalis* lipopolysaccharide (LPS) was detected in human AD brains and in the brains from transgenic mice serving as AD models (Poole et al., 2013; Ishida et al., 2017).

Several animal studies have indicated that *P. gingivalis* can induce neuroinflammation in the brain of AD patients (see later), and neuroinflammation has increasingly been suggested to have a substantial role in the progression of the neuropathological changes taking place in AD (Ilievski et al., 2018). This mini-review will deal with neuroinflammation in AD induced by *P. gingivalis* and possible mechanisms for this induction.

NEUROINFLAMMATION AND *Porphyromonas gingivalis*

Alzheimer's disease is our commonest neurological disease characterized by cognitive decline and accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NTFs). Neuroinflammation has increasingly been considered as another hallmark of AD. *P. gingivalis*-LPS-induced neuroinflammation was proposed to play an important role in the cognitive impairment of C57BL/6 mice (Zhang et al., 2018). Hu et al. (2020) found that periodontitis induced by

P. gingivalis-LPS promoted neuroinflammation by activating the Toll-like receptor 4/nuclear factor-kappa B signaling pathway and was associated with learning and memory impairment in Sprague-Dawley rats. In another study, *P. gingivalis* periodontal infection was proposed to cause cognitive impairment by releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1β in the brain tissues of middle-aged mice (Ding et al., 2018). Similarly, Memedovski et al. (2020) reported that *P. gingivalis* LPS induced classical and alternative activation of rat brain microglia with concomitant release of cytokines and chemokines.

AMYLOID-BETA AND *Porphyromonas gingivalis*

Amyloid-beta is known to be an activator of microglia. On the one hand, microglia can release inflammatory mediators such as inflammatory cytokines, complement components, chemokines, and free radicals that all contribute to Aβ production and accumulation. On the other hand, microglia can play a beneficial role in generating anti-Aβ antibodies and stimulating the clearance of Aβ plaques (Cai et al., 2014). According to these authors, a vicious cycle of inflammation occurs between Aβ accumulation, activated microglia, and microglia inflammatory mediators, which promotes Aβ deposition and neuroinflammation. This idea diverges from the general notion that Aβ production and neuroinflammation are independent processes.

Nie et al. (2019) reported that chronic exposure to *P. gingivalis* LPS led to the accumulation of Aβ in the brain of middle-aged mice. Such exposure also induced peripheral Aβ accumulation in inflammatory monocytes/macrophages. This suggested that monocytes/macrophages can serve as a circulating pool of Aβ in patients with periodontitis. Similarly, Leira et al. (2019) reported that *P. gingivalis*-induced LPS in periodontitis produced increased serum levels of Aβ peptides. In mice, oral *P. gingivalis* infection caused brain colonization and increased production of the amyloid plaque component $A\beta_{1-42}$ (Dominy et al., 2019). Importantly, the neuroinflammation established by *P. gingivalis* in the mice could be reduced by gingipain inhibition.

TAU PROTEIN AND *Porphyromonas gingivalis*

As mentioned, NFTs are created from hyperphosphorylated tau—a protein that stabilizes microtubules (for a review, see Kinney et al., 2018). In AD, hyperphosphorylated tau is removed from microtubules resulting in a collapse of the microtubule structure and thereby disrupted cellular functions for protein trafficking and cellular morphology, formation of tau aggregates, loss of neuronal function, and apoptosis.

There is a clear relationship between *P. gingivalis* and tau. Gingipains may cleave procaspase-3 to activate caspase-3 (Urnowey et al., 2006). The latter has been associated with tau phosphorylation (Chu et al., 2017) and tau cleavage (Sandhu et al., 2017). Dominy et al. (2019) found tau to be a target of gingipain proteolysis and suggested that tau pathology in AD brains may be caused by transneural spread of *P. gingivalis*, tau damage by gingipain proteolysis, and activation of human proteases. They also hypothesized that gingipains might be a driver of a compensatory increase in tau production of AD patients.

Tang et al. (2021) confirmed that peripheral *P. gingivalis* infection caused tau hyperphosphorylation, preventing tau from fulfilling its role as a microtubule-stabilizing protein, leaving it to self-assembly. In *P. gingivalis*-injected rats, the severity of phosphorylated tau at the AD-related sites Thr181 and Thr231 and the number of activated astrocytes were greater than in the hippocampus. Also, the levels of IL-1β, IL-6, and TNF-α in the rat serum and hippocampus were increased. Furthermore, the activity of protein phosphatase 2A (PP2A) was significantly inhibited in the hippocampus of these rats. Inhibition of PP2A and application of a PP2A promoter efficiently decreased IL-1β-induced tau hyperphosphorylation in HT-22 cells. Although systemic inflammation was identified as the driver of tau phosphorylation, the specificity of *P. gingivalis* producing this effect was not assessed. Laurent et al. (2018) and Didonna (2020) emphasized tauopathies and neuroinflammatory processes as a vicious circle that works together in the pathogenesis of AD. A link between pro-inflammatory cytokine signaling and hyperphosphorylation of tau has also been reported (Domingues et al., 2017). Of note, usnic acid derivatives were found to inhibit tau aggregation and neuroinflammation (Shi et al., 2020).

A novel mechanism of tau-seed-affected microglia was demonstrated by activation of the NLRP3–ASC inflammasome (Stancu et al., 2019). This inflammasome is an important sensor of innate immunity. Olsen and Singhrao (2016) and Olsen and Yilmaz (2016) reviewed the plausible contribution of specific bacteria playing a role in influencing the activity of the NLRP3 inflammasome in AD progression. *P. gingivalis* was found to have several mechanisms for modulating innate immunity by limiting the activation of the NLRP3 inflammasome. Among them, ATP-/$P2X_7$-signaling is associated not only with periodontitis but also with the development of several systemic diseases, including AD.

MICROGLIA AND *Porphyromonas gingivalis*

Hu et al. (2020) observed that *P. gingivalis* LPS-induced periodontitis caused learning and memory impairment in rats through neuroinflammation induced by significant activation of microglia and astrocytes in the brain cortex. Microglia activation may precede tau pathology (Yoshiyama et al., 2007). Memedovski et al. (2020) reported that 18-h *in vitro* stimulation with ultrapure *P. gingivalis* LPS caused classical and alternative activation of rat brain microglia with the release of cytokines and chemokines.

The gingipains Rgp and Kgp have important effects on brain-residing microglia, being responsible for *P. gingivalis*-induced cell migration of microglia and expression of pro-inflammatory

mediators by activating the protease-activated receptor 2 (Liu et al., 2017; Nonaka and Nakanishi, 2020). The subsequent activation of phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase/ERK pathways resulted in cell migration and inflammatory response in microglia. Here, the gingipains of *P. gingivalis* cooperatively contributed to cell migration of microglia toward the infected site (brain) and induction of neuroinflammation after reaching it.

The interaction between genetic factors, microglia, and *P. gingivalis* was reviewed by Olsen and Singhrao (2020). It was suggested that genes for apolipoprotein, clusterin, CD33, triggering receptor expressed on myeloid cells-2, tyrosine kinase binding protein (TYR-OBP), and complement receptors could affect microglia. Most of these genes can also be affected by *P. gingivalis via* its mastering of immune suppression.

CATHEPSIN B AND *Porphyromonas gingivalis*

Cathepsin B (CatB), a lysosomal cysteine protease, was suggested to have an important role in the initiation of neuroinflammation and neural dysfunction after chronic systemic exposure to LPS from *P. gingivalis* in mice. Thus, Wu et al. (2017) found that such exposure to *P. gingivalis* LPS induced AD-like phenotypes, including microglia-mediated neuroinflammation, intracellular Aβ accumulation in neurons, and reduced learning and memory functions in middle-aged mice in a CatB-dependent manner. As already mentioned, chronic systemic *P. gingivalis* infection induced Aβ accumulation in inflammatory monocytes/macrophages. This occurred *via* activation of CatB/nuclear factor kappa B signaling (Nie et al., 2019). CatB has been suggested as a potential therapeutic target for preventing the initiation and progression of periodontitis-related AD (Nakanishi et al., 2020).

PROTEIN KINASE R AND *Porphyromonas gingivalis*

Protein kinase R (PKR) is a 551 amino acid protein responsible for a key part of the defense against bacterial and viral infections in neurons (Dabo and Meurs, 2012; Marchal et al., 2014). This inflammation-associated kinase protein directly phosphorylates several abnormal and disease-modifying residues within tau, such as Thr181, Ser199/202, Thr231, Ser396, Ser404, and Ser409 (Reimer et al., 2021). The PKR-mediated phosphorylations actively dislocate tau from microtubules in cells. Also, PKR overexpression and knockdown increased and decreased, respectively, tau protein and mRNA levels in cells. It was noteworthy that acute encephalopathy in wild-type mice, induced by intracranial Langat virus infection, resulted in robust inflammation and PKR upregulation, which was followed by abnormally phosphorylated full-length and truncated tau. PKR can be capable of triggering pathological modification of tau independent of other kinases after brain inflammation. This might be the initial pathological seed in tauopathies such as AD and in chronic encephalopathy with severe inflammation. PKR inhibition reduced phosphorylation of soluble tau in the brain of transgenic rTg4510 tau mice (Reimer et al., 2021). Inhibition of PKR also prevented long-term potentiation and memory impairment in AD mouse models (Hwang et al., 2017). Furthermore, PKR inhibition reduced neuronal loss, motor deficits, and memory deficits in mice models of AD (Mouton-Liger et al., 2015; Segev et al., 2015; Reimer et al., 2021).

A direct relationship between *P. gingivalis* and PKR has not yet been demonstrated. However, PKR, a ubiquitously expressed serine–threonine kinase, is activated by indirect binding to bacterial LPS or pro-inflammatory cytokines such as TNF-α, IL-1, and interferon-gamma (for a review, see Reimer et al., 2021). PKR directly regulates tau, and activation of PKR has been associated with different tauopathies such as AD, Parkinson's disease, and Huntington' disease (Peel et al., 2001; Chang et al., 2002; Bando et al., 2005; Paquet et al., 2012; Lourenco et al., 2013; Ma et al., 2013). Because PKR is activated indirectly by LPS and specific cytokines, this could contribute to the correlation of "chronic" periodontitis and *P. gingivalis* brain levels with AD (Reimer et al., 2021). Bacterial infections and inflammation could also make neurons vulnerable to degeneration and thus initiate the onset of neurodegenerative diseases such as AD (Deleidi and Isacson, 2012). In this situation, activated PKR could initiate abnormal tau phosphorylation.

CONCLUDING REMARKS

Neuroinflammation seems to have a substantial role in the pathogenesis of AD. This supports neuroinflammation as a third disease hallmark of the disease. *P. gingivalis* with its inflammagens, gingipains, and LPS, both detected in the brains of AD subjects, could be major factors inducing neuroinflammation. *P. gingivalis* particularly affects Aβ, tau, microglia, CatB, and possibly PKR. A vicious cycle of inflammation probably occurs between several of these players where the interaction is complex and not yet fully understood.

Although not specifically related to *P. gingivalis*, PKR stands out as an inflammation-associated kinase of particular interest because it is ubiquitously expressed and an important part of the defense against bacterial infections in neurons. It is activated indirectly by LPS and specific pro-inflammatory cytokines and has been linked to AD. PKR is co-localized with abnormally phosphorylated tau in AD brains and directly regulates tau expression. Thus, PKR activated by *P. gingivalis*-induced brain infection/inflammation/pro-inflammatory cytokines may precede tau phosphorylation and thus participate in the etiology of AD. This should be studied.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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