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REVIEW
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Potential Bidirectional Relationship Between Periodontitis and Alzheimer's Disease

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Alzheimer's disease (AD) is the most prevalent form of dementia in the elderly population, representing a global public health priority. Despite a large improvement in understanding the pathogenesis of AD, the etiology of this disorder remains still unclear, and no current treatment is able to prevent, slow, or stop its progression. Thus, there is a keen interest in the identification and modification of the risk factors and novel molecular mechanisms associated with the development and progression of AD. In this context, it is worth noting that several findings support the existence of a direct link between neuronal and non-neuronal inflammation/infection and AD progression. Importantly, recent studies are now supporting the existence of a direct relationship between periodontitis, a chronic inflammatory oral disease, and AD. The mechanisms underlying the association remain to be fully elucidated, however, it is generally accepted, although not confirmed, that oral pathogens can penetrate the bloodstream, inducing a low-grade systemic inflammation that negatively affects brain function. Indeed, a recent report demonstrated that oral pathogens and their toxic proteins infect the brain of AD patients. For instance, when AD progresses from the early to the more advanced stages, patients could no longer be able to adequately adhere to proper oral hygiene practices, thus leading to oral dysbiosis that, in turn, fuels infection, such as periodontitis. Therefore, in this review, we will provide an update on the emerging (preclinical and clinical) evidence that supports the relationship existing between periodontitis and AD. More in detail, we will discuss data attesting that periodontitis and AD share common risk factors and a similar hyper-inflammatory phenotype.

Keywords: Alzheimer's disease, periodontitis, dysbiosis, neurodegeneration, dementia

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder affecting millions of people worldwide, with a frequency that is rapidly rising as the life expectancy increases and the world population becomes older (Brookmeyer et al., 2002, 2007; Sosa-Ortiz et al., 2012; Alzheimer's Association., 2016). Importantly, AD is characterized by neuronal loss with a slow and progressive decline in memory, language, and other cognitive skills, leading to the final stage of the disease, which is ultimately fatal (Alzheimer's Association 2016).

Despite decades of intense investigation, how degenerative neurodisorders, such as AD, develop remains unclear. Aggregates (plaques) of the amyloid-β peptide (AβP), as well as neurofibrillary tangles of the hyperphosphorylated protein, tau, are among the most sought-after therapeutic targets for AD (Braak and Braak, 1995; Long and Holtzman, 2019). However, many clinical trials investigating the effects of anti-amyloid drugs failed to demonstrate improvement in patients' cognitive performance and in countering the primary adverse events (Pinheiro and Faustino, 2019). Hence, there is an increasing interest in identifying new strategies to prevent and/or treat AD. For instance, several modifiable risk factors have been considered so far, such as physical inactivity, mood disorders, hypertension, diabetes mellitus, and obesity (Mayer et al., 2018). Moreover, many reports are now supporting the role of inflammation as a significant pathological driver of AD development and cognitive decline, with evidence that communication between the brain and peripheral immune systems also exists (Goldeck et al., 2016; Cao and Zheng, 2018; Alexandraki et al., 2019; Long and Holtzman, 2019; Tejera et al., 2019). In this sense, multiple studies have raised that an infectious hypothesis might underlie the pathogenesis of AD (Long and Holtzman, 2019). For instance, several studies have demonstrated the presence of herpesvirus (HSV) within the amyloid plaques and in the brains of AD patients (Jamieson et al., 1991; Jamieson et al., 1992; Wozniak et al., 2009; Carbone et al., 2014). In line with these data, HSV-1 particles can directly induce the fibrillization of Aβ42 *in vitro* (Ezzat et al., 2019). Moreover, two retrospective cohort studies demonstrated that HSV infection significantly increased the risk of developing all-cause dementia. Of note is that this risk was almost eliminated in patients treated with antiherpetics (Chen et al., 2018; Tzeng et al., 2018; Long and Holtzman, 2019).

Further to these viral effects on AD development, the research in the field has focused its attention on periodontitis, a chronic oral inflammatory condition, and its potential bidirectional link with AD (Kim and Amar, 2006; Kamer et al., 2008; Chen et al., 2017; Marchini et al., 2019; Long and Holtzman, 2019). Importantly, people with periodontitis have an increased risk of developing AD (Chen et al., 2017), and those with AD or dementia have impaired oral health, as a result of cognitive decline, and are more prone to develop chronic oral diseases, such as periodontitis, tooth loss, and mucosal lesions (Tada et al., 2006; Gonsalves et al., 2008; Noble J.M. et al., 2013; Maldonado et al., 2018). Mechanistically, periodontal pathogens not only invade the oral cavity but can also percolate through the epithelium of the periodontal pocket. From here, they can enter the bloodstream, where they can induce the release of several endotoxins and exotoxins, thus fueling infection in different compartments, including the brain (Nazir, 2017; Sudhakara et al., 2018; Bui et al., 2019; Dominy et al., 2019; Liccardo et al., 2019).

Thus, this review aimed to provide the readers with an update on the most recent findings that support the existence of a relationship between periodontitis and AD, with particular emphasis on the common risk factors, phenotype, and bidirectionality.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE: β-AMYLOID, TAU, AND APOE

AD is generally classified into two forms: the inherited and the sporadic one (Bekris et al., 2010; Dorszewska et al., 2016). Although there are differences in terms of the triggering factors and the proportion of the affected population, the underlying neuropathology of both conditions remains similar: with patients progressing from normal to mild cognitive impairment (MCI), followed by increasing dementia severity, eventually leading to the final stage of the disease that is ultimately fatal (Donev et al., 2009; Sperling et al., 2011; Scheltens et al., 2016; Davis et al., 2018). At a molecular level, both the sporadic and the inherited forms are characterized by the same diagnostic hallmarks such as AβP plaques and neurofibrillary tangles (Braak and Braak, 1995; Long and Holtzman, 2019).

AβP Plaques

In 1907, Alois Alzheimer, a German neurologist, reported the presence of a not well-identified substance in the cortex associated with a progressive behavioral and cognitive disorder (Alzheimer et al., 1995; O'Brien and Wong, 2011). Almost 80 years later, Glenner and Wong (1984) demonstrated that this substance was constituted by a ∼4 kDa peptide called AβP. AβP is a fragment derived from the proteolytic cleavage of the amyloid precursor protein (APP). APP is a transmembrane protein with a large ectodomain, a C-terminal (CT) membrane-bound domain and short intracellular domain (AICD) (Passer et al., 2000; Serpell, 2000; Gu et al., 2001; Weidemann et al., 2002; Kakuda et al., 2006; Walsh and Selkoe, 2007). Importantly, two main proteolytic pathways have been described for APP: the nonamyloidogenic and the amyloidogenic (Andrew et al., 2016; **Figure 1**). In the non-amyloidogenic pathway, α-secretase ADAM10 cleaves APP within the Aβ domain, generating a soluble proteolytic fragment, termed sAPPα, and a membrane-bound CT fragment (CTFα). Importantly, CTFα is subsequently processed by another proteolytic process that involved γ-secretases to generate p3 and the AICD. Conversely, in the amyloidogenic pathway, β-secretase 1, also known as β-site APP cleaving enzyme 1 (BACE1), and presenilin-containing γ-secretase (PS/γ-secretase) multi-subunit complex are involved in the generation of AβP (De Strooper et al., 1998; Struhl and Greenwald, 1999; Wolfe et al., 1999; Gu et al., 2001; De Strooper et al., 2012; Ben Halima et al., 2016; Andrew et al., 2016). More in detail, BACE1 cleaves APP, liberating a sAPPβ fragment and a

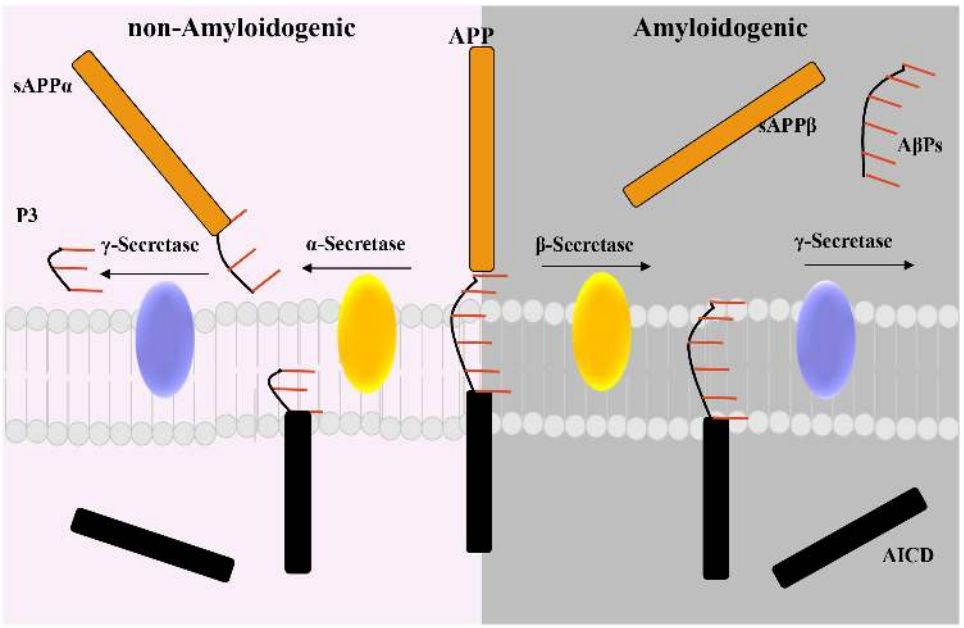

FIGURE 1 | Diagram of the non-amyloidogenic and the amyloidogenic proteolytic pathway for the amyloid precursor protein (APP). Non-amyloidogenic pathway: α-secretase cleaves the transmembrane protein APP to release the soluble APP fragment, sAPPα. The APP C-terminal fragment is then processed by γ-secretase to release an intracellular domain (AICD) and the P3 fragment. Amyloidogenic pathway: β-secretase processes APP to generate the soluble fragment, sAPP-β, then cleaved γ-secretase Aβ peptides (AβPs), and the AICD.

99-amino acid remaining CTF (CTFβ) (De Strooper et al., 2012; Andrew et al., 2016; Ben Halima et al., 2016). Then, the CTFβ is processed at the ε-site by PS/γ-secretase, thereby releasing the AICD (Andrew et al., 2016; Ben Halima et al., 2016). The AICD, either produced by α- or β-secretase, translocates into the nuclei of neurons. Here, it acts as a regulator of gene expression, including that of the Aβ-degrading neprilysin, or is degraded into the cytosol (Belyaev et al., 2010; Grimm et al., 2015; Multhaup et al., 2015). Importantly, different Aβ forms are generated by PS/γ-secretase cleavages at the ζ and γ sites that trim the transmembrane domain of CTFβ to liberate several forms of AβPs of variable lengths [from 38 (Aβ38) to 42 (Aβ42) amino acids] (De Strooper et al., 2012). In this regard, Aβ40 is the major product generated, along with minor amounts of Aβ38 and Aβ42 (De Strooper et al., 2012). However, besides these Aβ forms, it has been reported that, in this process, tiny amounts of Aβ37 and Aβ43 are also generated (De Strooper et al., 2012).

Importantly, although AβP's function is still debated and uncertain, these products are generated throughout life and appear to be normally stimulated by synaptic activity (Pearson and Peers, 2006). Conversely, dysregulation of the trimming process of APP can lead to a substantial increase in the levels of the insoluble Aβ42 isoform. This isoform is more prone to form oligomers, which correlate with synaptic dysfunction (Hayden and Teplow, 2013), protofibrils, or fibrils. Importantly, Aβ42 oligomers represent the most soluble and potent toxic conformers of AD (Haass and Selkoe, 2007), and their presence correlates with the severity of the disease (McLean et al., 1999). However, as recently suggested by Gulisano et al. (2018), Aβ42 oligomers are crucial both in physiological and pathological conditions. Indeed, only when present in excessive concentrations or for a prolonged time do these Aβ isoforms can negatively affect long-term potentiation (LTP) and memory. Conversely, low-dose administration positively affects synaptic plasticity and memory.

Thus, all the described processes, in a multitude, generate amyloid plaques resulting toxic to neurons and participating in synaptic destruction during the early stages of AD (Andrew et al., 2016). However, it is worth stressing that several studies are now supporting the idea that amyloid plaques are not the major toxic AβP entity, and amyloid plaques are not a direct indicator of AβP-induced brain damage in AD. For instance, the Arctic APP mutation (E693G) (Nilsberth et al., 2001) leads to enhanced Aβ protofibril formation and AD dementia. Still, no amyloid is visible on positron emission tomography (PET) imaging through the ^{11}C-labeled Pittsburgh Compound B (PiB) ligand (Schöll et al., 2012). Similarly, the Osaka mutation (E693Δ) in APP causes the aggregation of AβP with little amyloid accumulation on PiB-PET (Shimada et al., 2011). Similarly, transgenic mice carrying the Osaka mutation do not show, by immunohistochemistry, amyloid deposits (Tomiyama et al., 2010). Thus, several therapeutic strategies targeting Aβ have been tested in the last decades, such as secretase inhibitors, AβP aggregation inhibitors, and Aβ immunotherapy (Pinheiro and Faustino, 2019). However, almost all of these strategies have been discontinued, either because of side effects or the lack of sizable therapeutic effects. Nevertheless, the failure of past clinical trials targeting Aβ does not mean that Aβ is a wrong target. Indeed,

the current common concern is that AD patients must be treated at an earlier stage, i.e., right when the pathological "amyloid" cascade likely begins.

Tau Protein

The protein tau has been identified and purified in 1970 (Weingarten et al., 1975; Cleveland et al., 1977) as a microtubule-interacting protein that stabilizes the neuronal cytoskeleton. The tau protein structure is composed of four main regions: an acidic N-terminal (NT); a proline-rich region responsible for the binding to microtubules; four repeat domains (R1–4), also called microtubule-binding domains (MBDs) (Drewes et al., 1995; Sengupta et al., 1998; Gendron and Petrucelli, 2009); and a C-terminal (CT) region. Importantly, tau activity can be modulated by a wealth of posttranslational modifications (PTMs), such as acetylation, glycosylation, glycation, methylation, truncation, nitration, ubiquitination, and phosphorylation (Almansoub et al., 2019). However, phosphorylation is the most commonly described and investigated since it is centrally involved in the formation of pathologic aggregates. Indeed, the aggregation of tau has been correlated to a broad spectrum of neurological diseases, including AD, known as "tauopathies" (Congdon and Sigurdsson, 2018; Almansoub et al., 2019). This PTM is physiologically regulated by the balance between tau kinases and phosphatase activities (Martin et al., 2013). Importantly, among 85 phosphorylation sites, about 45 of these are phosphorylated in AD brains (Noble W. et al., 2013). More in detail, the early phosphorylation events, at specific serine residues such as Ser199, Ser202/205, and Ser262, can disrupt the association of tau with microtubules. This event, in turn, can lead to alterations in tau-dependent cellular functions with dysregulated axonal growth and vesicle and organelle transport (Gendron and Petrucelli, 2009; LaPointe et al., 2009; Congdon and Sigurdsson, 2018). Otherwise, phosphorylation at other serine residues, such as Ser396, has been suggested as a prominent subsequent event that correlates with the progression of AD (Congdon and Sigurdsson, 2018).

Like phosphorylation, tau acetylation may arise from multiple mechanisms, and the dysregulation of this process can chiefly contribute to neurodegeneration. For instance, acetylation appears to prevent the binding of ubiquitin and then tau turnover (Min et al., 2010). This event can prompt a rise in cytosolic tau levels that makes the protein prone to aggregation (Congdon and Sigurdsson, 2018). Finally, unlike other tau posttranslational modifications, *O*-GlcNAcylation seems to be protective against tau-induced pathology. Indeed, in the AD brain, the levels of *O*-GlcNAcylated tau are reduced when compared to those in healthy subjects (Liu et al., 2009). Thus, targeting these posttranslational modifications may offer new avenues to prevent tau aggregation, restoring the normal function of the protein.

Apolipoprotein E

Apolipoprotein E (ApoE) is a primary cholesterol carrier highly expressed in astrocytes and, to a lesser extent, in the microglia which mediates both the transport and delivery of lipids from a cell type to another (Mahley and Rall, 2000). In humans, three different alleles (ε2, ε3, and ε4) give rise to three different isoforms of ApoE, which differ in amino acids in positions 112 and 158: ApoE2 (Cys112 and Cys158), ApoE3 (Cys112 and Arg158), and ApoE4 (Arg112 and Arg158) (Mahley and Rall, 2000; Liu et al., 2013). Importantly, the single amino acid difference in the ApoE protein influences its ability to bind lipids, receptors, and also Aβ(REFF). Indeed, several studies have demonstrated that ApoE has a crucial role in Aβ aggregation and clearance influencing senile plaque formation and AD development (Ellis et al., 1996; Liu et al., 2013). In this context, several reports, including clinical, epidemiological, and genetic studies, have demonstrated an association between ApoE genotypes and AD. For instance, genome-wide association studies (GWAS) have confirmed that the ε4 allele of ApoE is one of the strongest genetic risk factors for AD (REFF). Indeed, the ε4 allele is significantly enriched in AD patients (Corder et al., 1993) and is associated with an increased Aβ plaque load in the brain (Schmechel et al., 1993), a higher brain atrophy (Agosta et al., 2009), and an earlier onset and accelerated progression of the disease (Shi et al., 2017).

Moreover, it has been shown that Aβ deposition and aggregation to form senile plaques are a phenomena predominantly observed in ApoE ε4 allele carriers compared with non-carriers (Schmechel et al., 1993; Polvikoski et al., 1995; Kok et al., 2009). In addition, ApoE ε4 carriers present lower Aβ42 levels in cerebrospinal fluids (CSFs) and higher PiB-positive imaging (Prince et al., 2004; Head et al., 2012).

NEUROINFLAMMATION IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

In addition to the two classic diagnostic hallmarks of AD, Aβ plaques and neurofibrillary tangles, the brain of patients with AD exhibits evidence of a sustained inflammatory response (Mandrekar and Landreth, 2010; Femminella et al., 2018, 2019). In the acute phase, inflammation in the brain represents an established defense against infections, toxins, and injury. However, a disruption in the equilibrium between the pro- and anti-inflammatory mediators results in a chronic inflammatory condition of the brain which is identified as a neuroinflammation (Mandrekar and Landreth, 2010). Importantly, this process is currently attributed to the accumulation of reactive microglia and astrocytes that, in AD, appears to be localized to amyloid deposits (Alzheimer et al., 1995; Bornemann et al., 2001; Stalder et al., 2001; Mandrekar and Landreth, 2010). Microglia are the resident phagocytes of the central nervous system that are activated in response to AβP accumulation, change their morphology to ameboid cells, migrate to the plaques, and release inflammatory mediators, starting the phagocytosis of the plaques (Kettenmann et al., 2011; Du et al., 2017; Wolf et al., 2017). However, while in the acute phase, the activation of microglia is neuroprotective; in chronic phase, it exacerbates neuroinflammation with consequent neurodegeneration (Solito and Sastre, 2012; Heppner et al., 2015; Zuroff et al., 2017; Kinney et al., 2018). Emerging evidences have demonstrated that astrocyte-mediated neuroinflammation is also involved in the pathogenesis of neurodegenerative diseases, including

AD (Verkhratsky et al., 2010; Colombo and Farina, 2016). Astrocytes are specialized glial cells involved in the production of neurotrophic factors and in the maintenance of the blood brain–barrier (BBB), which protect the central nervous system (CNS) from harmful molecules and cells (including pathogens) (Sofroniew and Vinters, 2010). In response to brain insults, these cells become activated, a process known as reactive astrogliosis, and they release reactive oxygen species (ROS), nitric oxide (NO), and pro-inflammatory molecules, including interleukins (ILs) and tumor necrosis factor (TNF) (Phillips et al., 2014; Neal and Richardson, 2018). Although initially this process is aimed at removing noxious stimuli, prolonged astrocyte activation causes detrimental effects, leading to neuronal dysfunction and cell loss (Steardo et al., 2015). Reactive astrogliosis is a hallmark of AD and is responsible for the exacerbation of AβP-induced neurotoxicity and increased tau phosphorylation (Garwood et al., 2011; Osborn et al., 2016).

The involvement of neuroinflammation in the pathogenesis of AD has been supported by observational and epidemiological studies demonstrating that chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) can exert beneficial roles in reducing the risk of AD (Ali et al., 2019). Moreover, mutations in the genes encoding for immune receptors, including triggering receptor expressed on myeloid cells 2 (TREM2) and myeloid cell surface antigen CD33, have been associated with an elevated risk of developing AD (Griciuc et al., 2013; Gratuze et al., 2018). TREM2 is a transmembrane immune receptor expressed on the surface microglia, and in AD, it is involved in the clearance of Aβ plaques (Boche et al., 2013; Jevtic et al., 2017; Lagarde et al., 2018). For this reason, an alteration in TREM2 function is reported as harmful and correlates with AD development. For instance, Wang and coworkers have demonstrated that TREM2 deficiency resulted in an increased AβP accumulation in the brain with reduced clustering of the microglia around the plaques (Wang et al., 2015). Importantly, the most common TREM2 mutation is the arginine 47 histidine (R47H) variant, which appears to be associated with a reduced microglial uptake of Aβ and an increased risk of AD development (Guerreiro et al., 2013; Jonsson et al., 2013; Tanzi, 2015; Hansen et al., 2018). In this regard, Cheng-Hathaway et al. (2018) demonstrated that AD mice heterozygous for the TREM2 R47H presented reduced immune cells and enhanced neuritic dystrophy around Aβ plaques. Importantly, other TREM2 variants have also been studied for their association with the risk of AD, including R62H (Huang et al., 2004; Guerreiro et al., 2013; Jonsson et al., 2013; Jin S.C. et al., 2014; Roussos et al., 2015; Ghani et al., 2016; Song et al., 2017; Sims et al., 2017). More in detail, Kleinberger et al. demonstrated, in human macrophages *in vitro*, that the TREM2 R62H variant led to an impairment of the phagocytic functions of TREM2 with a reduced uptake of Aβ-LDL complexes compared to wild-type control cells (Kleinberger et al., 2014; Yeh et al., 2016). Of note is that numerous recent findings suggest a link between tau protein aggregation and TREM2 dysfunction. For instance, in the CSF of AD patients, the levels of soluble TREM2 correlate with the amount of total and phosphorylated tau, but not with those of Aβ42 (Piccio et al., 2016). Importantly, either soluble TREM2 or the phosphorylated tau levels in the CSF are related to the cognitive decline and clinical progression of AD (de Leon et al., 2004; Buerger et al., 2006; Andersson et al., 2008; Ewers et al., 2019). Contrary to the protective role of TREM2, CD33 induces a negative response in AD because this receptor inhibits phagocytosis, thus reducing microglial uptake and clearance of Aβ (Griciuc et al., 2013). There is also evidence for the existence of a potential crosstalk between CD33 and TREM2. More in detail, Griciuc and coworkers have demonstrated, in a murine model of AD, that loss of CD33 resulted in a decreased Aβ pathology and improved cognition (Griciuc et al., 2019). However, these effects were significantly abrogated by additional TREM2 knockout (Griciuc et al., 2019). Conversely, TREM2 knockout mice presented increased Aβ pathology and exacerbated neurodegeneration, which was not rescued by additional knockout of CD33. Thus, the authors concluded that TREM2 acts downstream of CD33.

Importantly, an association between TREM2 and ApoE has also been discussed. For instance, Jendresen et al. (2017) have demonstrated that human ApoE protein contains a binding site for TREM2 (amino acids 130–149), and this binding is isoform-dependent. In line with this report, Atagi et al. (2015) showed that ApoE can increase the phagocytosis of apoptotic neurons *via* TREM2 binding.

Importantly, ApoE activity has also been associated with microglia function. Indeed, LaDu and colleagues have demonstrated that glial cells cultured from ApoE knockout (KO) mice show an increased production of pro-inflammatory markers in response to treatment with Aβ (LaDu et al., 2001). In line with these data, in 2003, Lynch et al. (2003) have demonstrated that intravenous administration of lipopolysaccharide (LPS) in animals expressing the ε4 allele resulted in a more significant systemic and brain inflammation compared with their ε3 allele counterparts. Analogously, in a tauopathy murine model, ApoE knockdown markedly reduced the activation of microglia and astrocytes (Shi et al., 2017). This evidence supports the role of ApoE in neurodegenerative disorders. In the same vein, in one report, Rodriguez and colleagues demonstrated a direct relationship between ApoE, neuroinflammation, and AD (Rodriguez et al., 2014). Indeed, in the cortex of transgenic mice expressing five familial AD mutations (FAD), these authors found that the ApoE genotype can influence both Aβ deposition and Aβ-induced glial activation. Consistent with this notion, NSAIDs have been shown to reduce AD risk only in ε4 allele carriers, further supporting the role of the *ApoE* genotype in AD progression and development (Szekely et al., 2008).

Finally, in addition to these mechanisms, chronic complement activation has been linked to neuroinflammation and AD (Fischer et al., 1995; Fischer and Popa-Wagner, 1996). In particular, recent pieces of evidence from GWAS have identified complement component receptor (CR1), which binds complement proteins C3b and C4b, as a risk factor for AD (Lambert et al., 2009). In line with these data, Brouwers and coworkers found four single-nucleotide polymorphisms (SNPs) in the CR1 locus that were associated

with elevated levels of Aβ in the CSF of patients with AD (Brouwers et al., 2012). Furthermore, intragenic duplication of low copy repeats (LCR) within the CR1 gene appears to be associated with an increased risk of late-onset AD (Kucukkilic et al., 2018).

ORAL DYSBIOSIS, INFLAMMATION, AND PERIODONTITIS

The microbiome plays a crucial role in human physiology influencing nutrition, immunity, organ development, and function (Sudhakara et al., 2018). In the last decades, the observation that several chronic diseases of the gastrointestinal tract and mouth are associated with the perturbation of microbiome (dysbiosis) has achieved growing attention from scientists. Thus, several studies have been designed to evaluate the potential association between dysbiosis and systemic diseases, including cardiovascular and neurological disorders (Beck and Offenbacher, 2005; Poole et al., 2013). Periodontitis is a chronic inflammatory disease caused by the abnormal growth and aggregation of different microorganisms (Kassebaum et al., 2014; Poole et al., 2015). In periodontitis, of the about 800 microorganisms identified so far, it appears that the vast majority of germs are Gram-positive (early colonizers), followed by Gram-negative bacteria (late colonizers). The latter are on the tooth surface, where they contribute to form the dental plaque (Belstrøm et al., 2014; Liccardo et al., 2019). These species include *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Prevotella intermedia*, *Campylobacter rectus*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Selenomonas* spp., *Parvimonas micra*, and *Eubacterium timidum* (Socransky et al., 1998; Belstrøm et al., 2014; Liccardo et al., 2019). Interestingly, poor oral hygiene results in the increase of the anaerobic environment in the dental plaque, promoting the proliferation of these pathogens and the release of their toxic factors. Moreover, defects in host immunoregulation enable pathogen proliferation and increase local inflammation (Barth et al., 2013). Paradoxically, also neutrophils, i.e., the most efficient phagocytes and primary cellular defense recruited to the periodontal pocket, participate in the pathogenesis of periodontitis (Hajishengallis, 2015). Indeed, these immune cell types release several molecules (antimicrobial peptides, enzymes, and reactive oxygen species) that cannot discriminate between pathogens and host tissue. Moreover, certain agents, such as *P. gingivalis*, may subvert neutrophil function, inhibiting the phagocytosis, thus expanding the inflammatory response (Sochalska and Potempa, 2017). Because of this process, additional mediators and cytokines are produced, and more neutrophils, T cells, and monocytes are recruited to the periodontium, leading to chronic local and systemic inflammation (Cekici et al., 2014; Hajishengallis, 2014; Hajishengallis, 2015). Importantly, T cells promote the release of several cytokines and inflammatory mediators, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-4, IL-10, and transforming growth factor β (TGF-β) (Graves, 2008). In addition to these inflammatory mediators, in response to pathogen infection, the gingival epithelial cells and fibroblasts release other cytokines and mediators [i.e., IL-1, IL-8, TNF-α, and prostaglandin E2 (PGE2)] that, in turn, recruit more macrophages and neutrophils. Moreover, these cells promote the expression of matrix metalloproteinases (MMPs), tissue-derived enzymes that participate in the extracellular matrix remodeling. Altogether, these processes result in the stimulation of osteoclasts with subsequent alveolar bone reabsorption (Neely et al., 2005; Jin J. et al., 2014). Periodontitis leads to systemic inflammation due to the direct infiltration of bacteria and their virulence factors into the bloodstream (Poole et al., 2013). For this reason, periodontitis has been linked to the onset and progression of disorders systemically, such as cancer, diabetes, and cardiovascular and neurological diseases (Hajishengallis, 2015; Liccardo et al., 2019). Importantly, virulence factors expressed by periodontal pathogens are important pathogenic determinants in the initiation, progression, and severity of the disease, and they are responsible for the local and systemic inflammatory response observed in patients with periodontitis. For instance, *P. gingivalis*, long considered as one of the most important members of the periodontopathic microbiota, presents a specific LPS (LPS-Pg), which is recognized by immune cells *via* Toll-like receptors 2 and 4 (TLR2/4), and toxic proteases called gingipains (gps) and other surface components such as carbohydrates and fimbriae (Potempa et al., 1995, 1997; Holt et al., 1999; Imamura, 2003; Hasegawa et al., 2008; Yilmaz, 2008; Guo et al., 2010). gps are cysteine proteases that comprise lysine-gp (Kgp) and arginine-gp A (RgpA) and B (RgpB) are released and transported to the outer bacterial membrane surfaces (Guo et al., 2010). In synergy with other virulence factors (Guo et al., 2010; Dominy et al., 2019) these proteases are crucially involved in *P. gingivalis* survival and pathogenicity, allowing the colonization and invasion of gingival/periodontal tissues as well as other tissues, systemically. Importantly, the initial colonization of cells, including fibroblasts, epithelial cells, and other bacteria, is mostly mediated by the coordination between gps and the fimbrial and non-fimbrial components. Moreover, gps play a critical role in iron and nutrient acquisition (*P. gingivalis* agglutinates erythrocytes and lyses them to release hemoglobin), tissue destruction (Guo et al., 2010), and in the inactivation of host defenses escaping phagocytosis from immune cells (i.e., neutrophils) (Maekawa et al., 2014). Analogously, *A. actinomycetemcomitans* produces numerous factors that have been well characterized, including adherence proteins, LPS, and toxins like the cytolethal distending toxin (CDT) and leukotoxin (LtxA) (Kolodrubetz et al., 1989; Lally et al., 1989; Shenker et al., 2005). Of note is that these toxins are involved in immune evasion mechanisms (Kachlany, 2010). Finally, *T. forsythia* expresses several proteases that contribute to bacterial virulence in multiple manners. For example, proteases participate in degrading the host periodontal tissue, modifying host cell proteins, thus allowing bacterial colonization. Moreover, all the above-mentioned factors are able to activate host degradative enzymes that process components involved in innate and adaptive immunity, thus blocking the host immune response (Sharma, 2010).

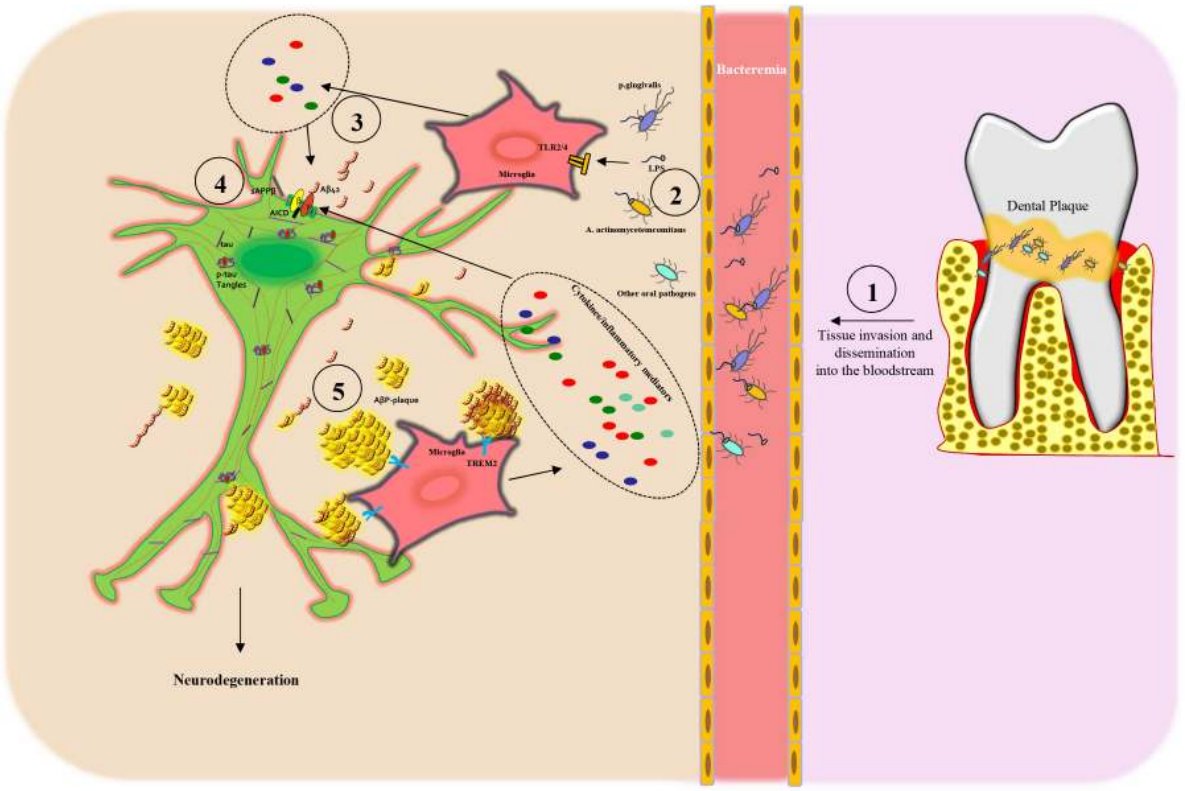

FIGURE 2 | Scheme of the proposed mechanism linking periodontitis to Alzheimer's disease: (1) Oral dysbiosis of the dental plaque leads to proliferation, tissue invasion, and then dissemination into the bloodstream of oral pathogens. (2) Next, the oral pathogens and their toxic molecules, such as lipopolysaccharide (LPS), bind to microglia *via* Toll-like receptors 2/4 (TLR2/4), inducing the release of cytokines (3) and inflammatory mediators that, in turn, lead to APP processing from neuronal cells. (3–4) Subsequently, the activation of β- and γ-secretase leads to an increased secretion of Aβ peptides (AβPs), in particular Aβ42 monomers and sAPPβ, outside of the cells and AICD intracellularly. (4) AβPs form oligomers, protofibrils, or fibrils and then amyloid plaques that are recognized by TREM2 receptors on the microglia plasma membrane, thus triggering an inflammatory response, which again stimulates AβP production. Dysfunctional neurons present also increased tau phosphorylation (p-tau) with the formation of neurofibrillary tangles (p-tau tangles). All these processes induce neuronal degeneration.

RELATIONSHIP BETWEEN PERIODONTITIS AND ALZHEIMER'S DISEASE

Although the brain is considered an immune-isolated environment, several shreds of evidence have indicated that systemic inflammation contributes to neurodegeneration through the microglial activation and release of pro-inflammatory molecules, thus driving AD progression (Perry et al., 2007; Holmes, 2013). For instance, Capsoni and colleagues, in 2012, have demonstrated that pathogen-free conditions can delay the onset of neurodegeneration in a murine model of nerve growth factor (NGF) deprivation (Capsoni et al., 2012). Furthermore, LPS, the main component of the membrane of Gram-negative bacteria, can be found in large amounts in the brain of AD patients compared to healthy controls (Zhan et al., 2016). In this context, several studies have found that LPS co-localized with AβPs (Aβ40/42) in the amyloid plaques and around vessels of the brain of AD patients (Zhan et al., 2018). And peripheral injection of LPS in mice can activate microglia, inducing the release of pro-inflammatory cytokines, such as interleukins and TNF-α (Godbout et al., 2005). In line with these data, Sheng et al. (2003) demonstrated that mice infused with LPS presented an increased neuroinflammation associated with the enhanced expression and processing of APP and Aβ40/42 levels inside neurons. Lastly, Lee and colleagues showed that in rTg4510 mice expressing a mutated tau protein (TauP301L) that develop tauopathy between 3 and 5 months of age, LPS infusion increases microglial activation and tangle formations (Lee et al., 2010). Thus, these reports indicate that bacteria can induce local inflammatory damage, which, in chronic condition, is a trigger of neuroinflammation, constituting a significant contributor of neurodegeneration and AD. For this reason, periodontal pathogens have been investigated for their involvement in AD development and progression. For instance, Chen and colleagues have demonstrated, in a retrospective study, that periodontitis exposure is associated with an about 1.7-fold increase in the risk of developing AD (Chen et al., 2017). Analogously, a recent study analyzing the National Health and Nutrition Examination Survey (NHANES) database demonstrated that subjects with mild to severe periodontitis presented a decreased cognitive function compared

with the healthy group (Sung et al., 2019). Mechanistically, this association has been demonstrated in a different number of studies. Kamer et al. (2009) have observed that elevated serum levels of TNF-α and serum antibodies to *P. gingivalis*, *A. actinomycetemcomitans*, and *T. forsythia* were present in AD patients compared to the controls. In line with these data, Sparks Stein and coworkers demonstrated that antibody levels to *F. nucleatum* and *P. intermedia*, at baseline, resulted significantly increased compared to the controls and correlated with a declined cognitive function in AD patients (Sparks et al., 2012). Furthermore, in a preclinical study from Ilievski and coworkers, it has been shown that in wild-type mice, *P. gingivalis* infection resulted in the neurodegeneration and formation of extracellular Aβ42 (Ilievski et al., 2018). Analogously, Díaz-Zúñiga et al. (2019) demonstrated that *in vitro* LPS (from *A. actinomycetemcomitans*) increased neuroinflammation *via* the activation of microglia and the subsequent increase in pro-inflammatory cytokines and chemokines coupled to the accumulation of Aβ42. Importantly, LPS from *P. gingivalis* (LPS-PG) binds to glial cells (Poole et al., 2013), and in the AD brain, it is co-localized with Aβ plaques (Zhan et al., 2016; Zhao et al., 2017). Of note is that a direct connection between oral dysbiosis and AD has been suggested by Poole et al. (2013), who reported the presence of periodontal pathogen components in AD subjects. Subsequently and in line with these data, Dominy et al. (2019) demonstrated that *P. gingivalis* and their virulence factors, gingipains, were exclusively detected in the brain of AD patients compared to the controls. Moreover, in this study, the authors demonstrated that in mice, this oral pathogen migrates from the mouth to the brain, increasing the production of Aβ42, exerting significant neurotoxic effects. Conversely, these processes were abolished following treatment with gingipain inhibitors. In this context, a phase II/III clinical trial has been designed and initiated in order to test the effects of the gingipain inhibitor COR388 in patients with a diagnosis of mild to moderate AD (NCT03823404).

Importantly, as discussed above, the ApoE genotype appears to be crucially involved in neuroinflammation, and as previously demonstrated, it can also contribute to enhancing *P. gingivalis* brain colonization. For example, in 2015, Poole and coworkers observed the presence of *P. gingivalis* DNA (Poole et al., 2015) in the brain of $ApoE^{null}$ mice infected at gingival levels with this Gram-positive pathogen. Interestingly, as demonstrated by Singhrao et al., in these mice, gingival infection with *P. gingivalis* also resulted in the early appearance of age-related granules (Singhrao et al., 2015). These data, in line with the results obtained in another study by Hafezi-Moghadam et al., suggest that the lack of functional ApoE protein and the increased systemic inflammation, observed in periodontitis, induce an impairment of the BBB (Hafezi-Moghadam et al., 2007; Singhrao et al., 2017; Ranjan et al., 2018).

Importantly, a dysfunctional BBB allows periodontal pathogens to access the systemic circulation (bacteremia) and invade the brain (Hafezi-Moghadam et al., 2007; Singhrao et al., 2017; Ranjan et al., 2018) and represents an early feature of AD and cognitive decline (Van de Haar et al., 2016; Carter, 2017). In aggregate, these data strengthen the potential relationship between periodontitis and AD development and progression (**Figure 2**).

CONCLUSION

In summary, periodontitis and AD often coexist. However, the current debate focuses on one main question: *what comes first*? Some studies have demonstrated that people with periodontitis present a major risk of developing AD (Chen et al., 2017); however, other reports suggest that those with AD or dementia suffer from inadequate oral health, stemming from cognitive decline, and are, therefore, more likely to develop periodontitis (Tada et al., 2006; Gonsalves et al., 2008; Maldonado et al., 2018). Thus, further studies are urgently needed to establish the *raison d'être* for the mutual association between periodontitis and AD. Along this line of reasoning, the trial (NCT03823404) discussed above shall give us the proof-of-concept of the beneficial role of oral pathogen blockade in human AD. Yet, while waiting for the publication of the trial outcome, we can ascertain, with no additional hesitation, that a more careful dental treatment effectively improves the quality of life/cognitive impairment of patients with mild AD (Rolim et al., 2014). Likewise, in decreasing the incidence of dementia in patients treated for dementia or periodontitis (Lee et al., 2017; Yoo et al., 2019). Therefore, oral hygiene care strategies should be included in the routine health care of patients with dementia and cognitive impairment and become a dominant part of adult oral health programs to avoid any extra-neuronal source of inflammation as well as to prevent the onset of neurodegeneration. Thus, these findings highlight the necessity to prevent the progression of periodontitis and encourage healthcare service at the national level.

AUTHOR CONTRIBUTIONS

DL wrote, edited, and revised the manuscript. FM, FC, MG, GF, LB, JA, AA, and IM contributed to the writing and editing of the manuscript. AV, CR, NF, and GR revised the manuscript. AC supervised the project, revised the manuscript, and generated the figures.

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