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The Possible Role of Chronic Periodontal Disease in Neurodegenerative Diseases and Glioblastoma Pathogenesis- An Essential Review

Chrysanthakopoulos NA[1,*] and Vryzaki E[2]

[1]Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Greece
[2]MD, PhD, Department of Dermatology, Rio University Hospital of Patras, Greece

[*]Corresponding author: Chrysanthakopoulos NA, Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Athens, Greece; E-mail: nikolaos_c@hotmail.com

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Abstract

Chronic periodontal disease (PD), and especially periodontitis is a multifactorial disease caused by dental plaque accumulation, which formed by pathogenic bacteria that are able to trigger an immune response in susceptible hosts. Pathogenic bacteria in oral cavity are a source of chronic immunological reaction which can result in local and peripheral production of pro-inflammatory cytokines such as IL-1ß, IL-6 and TNF-α, inflammatory mediators, and bacterial products such as lipopolysaccaride endotoxin. Similarly, viruses, such as herpes and Epstein-Barr, have also been detected in periodontal pockets. In a similar way, a chronic systemic inflammation has been linked with an increased risk of brain pathological conditions such as cerebrovascular diseases, abscesses, etc. Therefore, it is reasonable, that a chronic infection and inflammation disease, such as periodontitis, may affect theāa central nervous system (CNS). It is well evidenced that oral pathogenic bacteria may cause systemic infection by transient or persistent bacteraemia, and in-filtrate distal locations and organs. It has also been suggested that in susceptible populations and under certain circumstances, bacterial and viral infections may enter the brain from the blood circulation. After entering the brain periodontal bacteria and their products may affect brain's vascular integrity. Therefore, a potential role of chronic periodontitis in the development and progression of cerebral infection and inflammation could be suggested. No direct evidence has been revealed regarding a possible causal association between periodontal pathogens and brain diseases, however several researches have detected periodontal bacteria survived in the brain. It is possible that both inflammatory conditions may share a causal association with common risk factors and complex multifactorial aetiologies. Nevertheless, the possibility that pathogenic oral bacteria spread to the blood circulation and reach the brain, initiating or exacerbating existing cerebral diseases, could not be ignored. Moreover, the pro-inflammatory factors, and biomarkers induced systemically by a chronic periodontal inflammation, may play a role in CNS pathological conditions, such as Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, etc. Systemic infection and/or inflammation, and especially chronic inflammation has also been associated with an increased risk of diverse types of cancer in organs such as liver, colorectal, pancreatic, lung, etc. Gliomas, and especially Glioblastoma Multiforme (GBM) is the most common type of primary malignant brain tumor, which currently has no effective treatments. The etiology of GBM has not been fully elucidated and it still remains unclear. Genetic influences in combination with environmental risk factors have been suggested as pathogenic factors of GBM. Viruses, such as Human Cytomegalovirus (HCMV), is also considered to be among the etiologic factors for gliomas development as exhibits tropism for glial cells. Human studies have recorded that oral pathogens are closely associated with cancers, however, whether those pathogens play a role in gliomas development remains unclear. The current review highlights the possible role of chronic periodontitis in brain, and especially in GBM development, focused on the role of chronic inflammation in carcinogenesis, in the light of recent literature.

Keywords: Periodontal disease; Tumorigenesis; Cancer; Fusobacterium nucleatum; Porphyromonas gingivalis; Neurodegenerative Diseases; Immune Response

Introduction

Glioma is the most conventional form of brain malignant tumors, accounting for 25.1% of the primary tumors in the central nervous system (CNS) [1], and are categorized into 4 histological grades according to the malignancy level. WHO grades I-II gliomas (low-grade gliomas, LGG) exhibit low aggressive tendencies and have a better prognosis, whereas WHO grades III-IV gliomas (high-grade gliomas, HGG) show a high rate of deterioration and a poor prognosis [2]. Glioma patients with the isocitrate dehydrogenase 1(IDH1) mutation have a more favourable prognosis, and the mutation is frequently expressed in LGG patients but rarely observed in WHO grade IV glioma patients [3]. The LGG, WHO grades II and III, could progress in Glioblastoma Multiforme (GBM), WHO grade IV, along with the progression of the tumor [4]. GBM is the most frequent and malignant glioma type, with an extremely poor prognosis because of its histopathological characteristics [5]. GBM, also known as diffuse astrocytoma, shows a great morphological and genetical heterogeneity. GBM's incidence is about 5-6 cases/100,000 population and its frequency varies between 12.0%-15.0% of all intracranial tumors [6,7]. The mean survival is under 15 months and the five-year rate is under 10%. The poor prognosis of GBM could be attributed to a highly abnormal vascularization, resistant to the common chemotherapy and radiotherapy and to the fact that general is difficult to be completely removed surgi-cally [8]. GBM is mainly diagnosed at advanced ages, with a mean age on diagnosis of 64 years [9]. Its etiology still remains unclear, however, genetic influences in combination with environmental risk factors have been suggested as GBM pathogenic factors [10]. It has also been suggested that is associated with constant exposure to ionizing radiation or chemical agents such as polycyclic aromatic hydrocarbons (PAH), electromagnetic fields and certain metals [11-13]. Viruses infe-ctions with human cytomegalovirus (CMV), genetic diseases such as tuberous sclerosis, multiple endocrine neoplasia (MEN) type IIA, Turcot syndrome, and neurofibromatos is type I, NF1 [14-16]. Moreover, acquired head traumas, which occurred as a result of a brain contusion, may predispose to the GBM development [17]. GBM is classified as a primary or as a secondary tumor as a result of a malignant transformation from a lower grade brain tumor and/or with mutation in the IDH gene and is classified in diverse histopathological types such as Classical, Proneural, Neural and Mesenchymal according to the gene expression profile [18]. Periodontitis, is a chronic inflammatory condition characterized by the disruption of tissues surrounding and supporting the teeth [19]. Periodontal Disease (PD) in Europe affects 5-20% of adults aged 35-44 years old and 40% of the elderly aged 65-74 [20,21] whereas chronic periodontitis affects approximately 50% of the adult individuals and its incidence and severity increase with age, showing a prevalence of 70% of over-65 years-old in the USA [22]. PD or periodontitis is caused by the host's immunological response to periodontal pathogens [23], and leads to local inflammation, ultimately contributing to chronic systemic inflammation. Periodontal infection individuals exhibit increased circulating inflammatory biomarkers levels indicating the systemic implications of periodontal infection [23,24]. PD is significantly associated with other pathological conditions such as cardiovascular disease, rheumatoid arthritis, pneumonia, chronic obstructive pulmonary disease, metabolic syndrome, obesity, chronic kidney disease, and cancer [25]. Individuals with chronic inflammatory diseases such as the mentioned may be at greater risk of cancer [26].The controversial differences between the association of PD and systemic diseases in different studies could be attributed to the heterogeneity in the definitions. The susceptibility to PD is individual, as it depends on possible dysbiosis and immune response to the bacteria accumulation, genetics, oral hygiene and the chronic disease [27]. Gram-negative bacteria are responsible for the dysbiosis in PD [28]. In PD the most conventional species are Porphyromonas gingivalis, Treponema dent cola, and Tanneralla forsythia, also known as the red-complex [28]. Moreover, P. gingivalis, Aggregatibacter actionmycetemcomitans, Fusobacterium spp., and Prevotella intermedia/nigrescens, have been described as the most common subgingival pathogens detected in chronic PD patients [29, 30]. PD also results in the development of more diverse microbiota population, potentially caused by an increase of different nutrients available to microorganisms due to ongoing inflammation and weakened immune response, not sufficient to control bacterial proliferation [28]. Chronic inflammation has been suggested to be implicated in tumor initiation and progression [13]. For more than five decades the relationship between PD and increased cancer risk has been investigated, however, findings to date have limited practical significance as cancer prevention indices, despite the fact that useful knowledge have been acquired regarding the role of PD treatment in reducing the risk of different types of cancer [31]. Recently, an increasing interest exists in examining the possible association between PD variables, and cancer risk, in several organs and systems. Epidemiological studies have suggested significant associations between periodontitis indices, tooth loss and cancer risk of diverse organs and locations such as head and neck region, lungsupper gastro-intestinal system, pancreas, etc. [25,32-35]. During the PD active phase P. gingivalis partially

disrupts the periodontal tissue, enters the blood circulation, and causes bacteremia, which leads to a great number of inflammatory mediators release, eventually inducing a prolonged low-grade inflammatory response in distant organs [36]. P.gingivalis is the most conventional periopathogenic bacteria associated with periodontitis [24,37], and it plays a crucial role in tumor initiation and progression. Significantly increased numbers of P.gingivalis have been detected in oral squamous cell carcinoma [38], orodigestive [34], and pancreatic cancer [39]. The substances produced by oral microbiota may be carcinogenic [40,41]. Chronic periodontitis exposes organs to bacterial endotoxins, enzymes, metabolic by-products and continuously stimulates the immune response and production of cytokines, chemokines, prostaglandins, and other inflammatory biomarkers [42]. Chronic inflammation lengthens the cell cycle, stimulates proliferation, angiogenesis and migration, and inhibits apoptosis. Oxidative stress destroys the mucosa making it more susceptible to other carcinogens such as tobacco, alcohol, HPV and EBV [43]. All of the mentioned factors may predispose individuals to the development of diverse types of cancer [44]. Recent reports have recorded that PD may affect the development and progression of some brain disorders. Examining the association between periodontitis and cancer, it is interesting to identify whether periodontal infections are potentially associated with glioma. Evidence from human studies has indicated that oral microbiota is closely related to cancers [45,46], however, whether oral microbiota is involved in glioma malignancy remains unclear P. gingival is has been detected in the brains of patients with Alzheimer's disease and intracranial aneurysm [47-49]. P. gingival is lipopolysaccharide (LPS) has been identified in brain tissue using immunofluorescence labeling [50], whereas is frequently used to examine how PD affects cancers [47-50] and CNS diseases [51,52]. Experimental studies have shown that P. gingival is or its LPS is able to cross the blood-brain barrier, enter brain tissue, and stimulate the proliferation and migration of glioma cells at diverse concentrations [36]. P. gingival is associated with glioma grading and also shows a significant association with IDH1 mutations in gliomas [53]. Those observations suggest that periodontal pathogens may have a significant role in glioma development. However, the precise mechanisms through which PD contributes to the initiation and progression of GBM remain incompletely understood. No previous studies have specifically investigated the possible association between PD and GBM. However, recently PD and GBM have been associated with an increased activity of CMV [54,55], leading to a possible relationship between both. The mentioned increased activity of CMV has been also detected in others inflammatory diseases such as cardiovascular disease, rheumatoid arthritis, and diabetes mellitus [55,56].

The aim of the current review was to explore the common pathogenesis of Neurodegenerative Diseases and GBM, in an effort to detect the possible role of PD as an etiologic or risk factor for their development.

P. gingivalis andF. nucleatum Molecular Mechanisms in Cancer Pathogenesis

Recent epidemiological researches have suggested an increase in the risk of cancer incidence and /or mortality in PD individuals [42]. Dysbiosis in chronic periodontitis is attributed to oral pathogens [57], and Porphyromonas gingivalis and Fusobacterium nucleatum are the main microbial pathogens in its pathogenesis [58]. Those bacteria also play an essential role in initiation and promotion of carcinogenesis [59]. Resent interest has focused on the role of P. gingivalis in cancer due to its ability to evade the immune system whereas maintains a persisting chronic inflammation condition in the surrounding environment [60]. In a similar way, but to a lesser extent, the role of F. nucleatum in carcinogenesis has been a central point due to its ability to coaggregate with oral biofilm colonizers and to regulate other bacteria's crossing of the host's epithelial and endothelial cells barrier [61-63].

Role of P. gingivalis in Mediating Cellular Transformation

Long-term infections of P. gingivalis in human immortalized oral epithelial cells [64] showed that the infected cells ultrastructure was indicated by aberrant nucleoli and heterochromatin and weakened cellular junctions highlighted by desmosomes scarcity, known morphological characteristics of cancer cells. In P. gingivalis infected cells the plakophilin 1 (PKP1), which stabilizes desmosomes, was decreased [65]. The following biomarkers, Colony-Stimulating Factor 1 (CSF1), Friend Leukemia Virus Integration 1 (FLI1), Growth Arrest Specific 6 (GAS6), Programmed Cell Death 1 Ligand 2 (PDCD1LG2), CD274, Colon-Cancer-Associated Transcript 1 (CCAT1) and Nicotinamide N-Methyltransferase (NNMT), which are tumorigenesis markers, were up-regulated in P. gingivalis infected cells. In addition, proMMP9 and activated MMP9, which are involved in cellular invasion, were increased in P. gingivalis infected cells [64]. GroEL, a Heat Shock Protein (HSP) 60 family member, is considered one of the virulent factors released by P. gingivalis [66]. That member is responsible for induction neo-angiogenesis in epithelial progenitor cells and promotes their migration and progression by up-regulating E-selectin via activation of the SAPK/JNK, PI3K, and p38MAPK signaling pathways and also to a lesser extent through the NOS-related pathways [67]. P. gingivalis activates the PI3K/Akt and JAK/STAT signaling pathways and inhibits the apoptotic intrinsic pathway by preventing mitochondrial membrane depolarization and blocking cytochrome C release followed by pro-apoptotic down-regulation (caspase 3, caspase 9, Bad and Bax) and anti-apoptotic genes up-

regulation (survivin, Bcl-2, bcl-XL and Bfl-1) in gingival epithelial cells [68-71]. P. gingivalis also up-regulates Cyclin A, CDK4 and CDK6 expression and activates CDK2, down-regulates the Cyclin D and INK4 expression, decreases p53's concentrations and activation, and also decreases the levels of the following kinases Chk2, CK1delta,CK1 epsilon and Aurora A. Moreover, it increases the levels of PI3K, PDK1, p70S6K and p90RSK whereas inactivates PTEN by phosphorylation at s370 [72]. P. gingivalis induces the inflammatory cytokines IL-6, IL-8, sICAM-1 and MCP-1 production and their increase may be in part dependent on RgpA-Kgp activity, whereas the MIP-1α and IL1α post-infection secretion were found to be independent of RgpA-Kgp proteinase-adhesin complex [73,74]. Those events are responsible for an inflammatory environment which promotes tumor development. P. gingivalis also increases Toll-Like Receptor 2 (TLR2) signaling in gingival epithelial cells through the miR-105 down-regulation. TLR2 increased levels lead to IL-6 and TNF-α production and the NF-kB activation, which promotes pro-inflammation, contributing to an adequate tumor microenvironment [75]. Infected gingival epithelial cells by P. gingivalis upregulate the mi RNA-203 expression which applies its silencing effect on the cytokine signaling 3 (SOCS3) and SOCS6 suppressor, which leads to an increase in STAT3 and results in increased inflammation, a perfect tumorigenic microenvironment [76]. A P. gingivalis post-infection increase in Cyclin D1 and Cyclin E, which are implicated in promoting the transition from the G1 to S phase, simultaneously with a decrease in p21has been detected [73,77].

Role of P. gingivalis and F. nucleatum in Exacerbating Malignancy

P. gingivalis and F. nucleatum co-infection leads to an inflammatory response reflected by an increase in TNF-α and IL-1β [78]. The same co-infection led to tumor growth, invasion and proliferation in oral carcinoma in mouse model. TLR2 and TLR4, induce the IL-6 increase which is possible to activate STAT3 and NF-kB. STAT3 leads to Cyclin D1transcription, which promotes cellular proliferation [59]. F. nucleatum promotes tumor development and proliferation in vivo and in vitro in colorectal cancer cases, via FadA-binding to E-cadherin and the β-catenin pathway signaling activation [79]. FadA binds to region 3 of the E-cadherin extracellular domain 5 (EC5), which is activated and internalized by clathrin and activates the β-catenin which is translocated to the nucleus, and activates inflammatory genes NF-kB1 and NF-kB2, IL-6, IL-8 and IL18, Cyclin D1 and Myc oncogenes, transcription factors LEF/TCF and Wnt genes WNT7a, WNT7b and WNT9a [79].

Central Nervous System Cells Functions

Astrocytes, the glia dominant neural type in the CNS, and microglial cells, originating from the hematopoietic lineage with monocyte/macrophage precursors are distributed uniformly throughout the CNS parenchyma [74]. Those CNS cells cooperate with one another in normal and pathological conditions. Astrocytes are not immune cells, however their morphology allow them to perform diverse important functions, such as providing metabolic support to neurons, regulazing neuronal activity, maintaining the extracellular fluids balance, and isolating excitable cells electrically [76]. Astrocytes also undergo proliferation and secrete matrix ingredients, resulting in a "glial scar" formation which surrounds the affected location. Moreover, they secrete proinflammatory and chemotactic mediators [75]. The neurons contribute to the processes implicated in neuro-inflammation, through constant communication with microglia, endothelial cells and the CNS blood vessels pericytes [80]. Microglia are the permanent mononuclear phagocyte population in the CNS, which shares phenotypical and functional features with macrophages, and are essential to the brain's immune and inflammatory response [81,82]. Upon exogenous stimulation or micro-environment alterations, microglia are activated, release pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α and cytotoxic agents such as Reactive Oxidative Species (ROS) [74]. The increased level of ROS can cause neurotoxicity that affects diverse cellular proteins and homeostasis in the cells [83]. Microglia are also critical for phagocytosis of pathogens and debris [84-86], functions which are regulated by CD68, CD14, CX3CR1, and toll-like receptors (TLRs) [82,87,88]. TLRs are associated with microglial recognition of patterns on bacterial pathogens, where CD14 acts as a co-receptor for transmembrane TLR2 and TLR4, presenting antigens to them [82,89]. In microglial cells downstream signaling is mediated by NF-κB activation and the pro-inflammatory genes transcription such as, TNF-α,IL-1α, IL-6 [88]. Thus, microglia are the multi-tasking first line of defense in the brain, contributing to the inflammatory response upon detecting any danger signals presented by infectious stimuli or debris. Microglial cells in an activated state undergo morphological alterations and exhibit increased proliferation, acquire migration capacity, and display increased phagocytic activity [82].

Chronic Neuro-inflammation and Neurodegenerative Disorders Pathogenesis

Until now, the exact cause of the most prevalent neurodegenerative disorders, such as Alzheimer's Disease (AD) and Parkinson's Disease (PSD), is still unknown. However, chronic neuro inflammation seems to be a potentially significant risk factor for those diseases. Moreover, evidence indicates that systemic inflammation may potentially trigger the neuro-inflammation

appearance [81]. Microglial cells are crucial for the neuro-inflammatory process within the brain [81,90,91]. In neurodegenerative diseases, such as AD, where neuro-inflammation is a part of the pathogenesis, microglial cells become chronically activated, release pro-inflammatory cytokines and display abnormal phagocytic ability of proteins, such as Aβ peptides, leading to further microglial activation [81,90,92]. Microbial ingredients are also able to trigger microglial activation and initiate the neuro-inflammatory response. Recent reports have suggested that oral microbes and/ or their virulence factors may contribute to this process [93-95], thus linking oral health status with neuro-inflammation risk.

Periodontitis is linked with neurodegenerative diseases and neuro-inflammatory processes through circulating mediators or the oral microbes direct access to the CNS via systemic circulation [96-98]. Treponema different species associated with periodontitis were revealed in AD cases brains [99]. Animal studies have indicated its migration from the oral cavity to the CNS, and post-mortem human studies in human AD have confirmed its presence intra-cerebrally [48, 100]. P. gingivalis, LPS and gingipains were also detected in AD patients brains [48,50,81,101,102]. P. gingivalis has unique abilities as is able to escape from the immune system, displays invasive properties, proteolytic nature and aggressive virulence factors, such as LPS and gingipains. The bacteria and its gingipains can directly invade astrocytes, microglia and neurons and mediate their neuro-inflammatory activity [103]. Moreover, gingipains is able to initiate physical injury to the cerebral microvasculature with degeneration of endothelial tight junctions and blood-brain barrier (BBB) increased permeability [103-105]. Neuro-inflammation and amyloid plaque formation developed after repeated oral infection of P. gingivalis in mice [93], indicating that infectious and inflammatory mechanisms are reasonable in the association between PD and neurodegenerative processes. However, it remains unclear whether PD-associated pathogens can directly activate the microglial function. In addition to P. gingivalis, other periodontal pathogens, such as T. denticola, A. actinomycetem- comitans), and F. nucleatum, might have a potential role in neuro-inflammation, especially in AD [106]. Animals studies have revealed that Treponema species have the ability to invade CNS and produce amyloid, A. actinomycetemcomitans serotype b triggers pro-inflammatory cytokines secretion by microglia and F. nucleatum-induced periodontitis can result in the worsening of AD symptoms in mice [107]. Neuro-inflammation is considered to be essential in PSD pathogenesis. It is suggested that an inflammatory response in the intestine may be responsible for initiating the disease. It has been supposed that bacteria form the intestine could access the brain via the vagus nerve, subsequently resulting in brain inflammation, especially in the substantia nigra region which disrupts the dopamine production, which is a hallmark element of PSD [101,102]. Neuro-inflammation is also thought to play a critical role in the appearance and progression of Multiple Sclerosis (MS). It has been found that inflammatory cytokines disrupt the blood-brain barrier, allowing B and plasma cells to enter the CNS, which then damage the myelin sheath, resulting in demyelination, a primary symptom of the disease [101,102].

Pathogenesis of Periodontitis and Its Role in Neuro-inflammation

In susceptible individuals with periodontitis, oral microbial dysbiosis triggers exaggerated chro-nic inflammation [108]. Possible direct and indirect mechanisms through which periodontitis may contribute to the appearance and progression of neuro-degeneration diseases have been recorded in the literature. It has been suggested that humoral, neuronal and cellular pathway are e low-grade systemic inflammation or locally released in periodontitis can enter the brain via the blood circularesponsible for the possible role of periodontitis in neuro-inflammation. Pro-inflammatory cytokines induced by thtion. Periodontal pathogens can reach the intestine by swallowing or via the blood circulation, are able to disrupt the intestine microbiota. The infected intestine epithelial cells release pro-inflammatory mediators that enter the brain, i.e., “oral-gut-brain axis” through the blood circulation. Another way to enter the brain is via the vagus nerve, whereas periodontal pathogens can reach the brain through the trigeminal nerve. Those pathogens might trigger trained myelopoiesis (trained immunity) which might induce hyper-inflammatory response that could affect the brain [80].

Molecular Mechanisms between Periodontitis and Glioblastoma

A previous survey has suggested a strong association between GBM and PD [36]. However, the specific pathogenic mechanism and crosstalk genes remain unclear. Another recent study [109] revealed that Chemokine (C-X-Cmotif) Receptor 4(CXCR4), Lymphocyte antigen 96 (LY96), and C3 genes play a crucial role in the co-pathogenesis of both diseases. CXCR4, a G protein-coupled receptor, binds its typical ligand Stromal cell-Derived Factor 1 (SDF-1). Although CXCR4 signaling is crucial for individual development and organ repair [110], high CXCR4 expression has been associated with an increased risk of cancer [111]. It was also found that CXCR4 was overexpressed in GBM and was associated with a poorer prognosis [112], consistent with previous findings [109]. In GBM, ligand binding to CXCR4 leads to conformational alterations which activate PI3K-AKT, JAK/STAT, and MEK1/2-Erk1/2 signaling pathways, resulting in the STAT3 activation, an oncogenic transcription factor implicated in GBM development [113]. MEK-ERK1/2 signaling inhibition

amplifies the glioma cells adhesion to the extracellular matrix and reduces cell proliferation and migration [114]. Moreover, CXCR4 was found to be overexpressed in periodontitis gingival tissue [115]. CXCR4 activation by P. gingivalis results in crosstalk with TLR2, which disrupts the monocytes or macrophages killing function by inhibiting NO production and increasing cAMP-dependent protein kinase A (PKA) signaling [116]. In addition, PI3K-dependent adhesion pathway activation via CXCR4 in macrophages and monocytes results in CR3 activation, which is used by P. gingivalis and other pathogens as a safe entry portal to increase their intracellular survival [117]. Lymphocyte antigen 96 (LY96, MD2) is a critical component required for the TLR4 activation by LPS in the outer wall of P. gingivalis. It acts as the first defense line against bacterial infection [118]. LY96 expression is significantly increased in gingival tissues in periodontitis patients [119], leading to the TLR4-LY96-CD14 complexes formation which trigger the MyD88 signaling pathway, resulting in the production of TNF-α, IL-6, IL-8, and IL-2 [120]. Recent reports have detected that LY96 is closely associated with tumorigenesis and progression in diverse types of cancer, such as colon cancer [121], and GBM [122], with the highest expression being observed in GBM [123,124]. In GBM, TLR4 is commonly expressed on glioma tissues and microglia/macrophages [125]. The TLR4/MD2 complex signalling stimulation by LPS may involve tumour suppressor PTEN [126] loss or mutation, which can have a significant impact on cancer susceptibility and tumorigenesis. Complement C3 is an essential ingredient where classical, lectin, and alternative pathways connect, producing effector molecules such as C3a and C5a that activate C3aR and C5aR, respectively, resulting in leukocyte mobilization and activation [127]. Histological findings indicated that C3-activated complement fragments are in abundance in the periodontitis gingival crevices and significantly associated with inflammatory indices. After periodontitis treatment, levels of complement C3 significantly decrease (Top 5% genes), whereas they are present at lower levels or absent in healthy individuals [127]. Mechanistically, C3 activation may promote periodontal inflammation commonly by increasing vascular permeability and inflammatory cells chemotactic recruitment through C5aR activation, increasing vascular permeability and inflammatory exudates flow and inflammatory cells [128] chemotactic recruitment, however it is not able to control the infection [129]. Consequently, C3 is currently identified as one of the 21 most promising candidate genes for treatment of periodontitis [130]. Complement-activating proteins high levels may be beneficial for tumors [131]. It has been observed that C3 deposition was revealed in GBM tissues, suggesting local activation of complement in GBM, and confirmed the complement C3 protective effect on GBM development and progression [132]. It is important to highlight that glioma stem cells (GCS) may activate C3 with the alternative pathways assist and activate STAT-3, ERK2/1, and PI3K/Akt/mTOR signaling pathways to retain their pluripotent status [132]. Moreover, hypoxic conditions contribute to C3 activation and amplify C3a-C3aR effects [133], generating an additional effector mechanism for GSC survival, self-renewal, and tumour growth. A recent report analysed the immune characteristics of GBM and PD using immune infiltration, and showed decreased macrophage M2 polarization in PD, which negatively associated with key crosstalk gene expression and was consistent with a PD pro-inflammatory demonstration [134]. Increased macrophage M2 polarization in GBM positively associated with key cross-talk gene expression and was consistent with an immunosuppressive tumour microenvironment in GBM [135].The discrepancies in gene effects may primarily be attributed to the separate cells in which interacting genes function and the diverse inflammatory factors secretion. For instance, in GBM cells, the CXCR4 up-regulation recruit's glioma-associated microglia/macrophages (GAMs) and leads to macrophages M2 polarization [136]. On the contrary, in periodontal inflammation, the CXCR4 up-regulation inhibits TLR4-induced NF-κB activation through the LPS-CXCR4 axis, thereby suppressing macrophages M2 polarization [137]. Moreover, it is also associated with the lack of other immune cell types, such as insufficiently activated CD8+ T cells and functionally impaired microglia in GBM [138,139]. Those observations indicate that these shared differentially expressed genes may bridge the common pathogenesis of GBM and PD by affecting immune cells. The exploration of the mechanism of crosstalk between PD and GBM [109] showed that P. gin-givalis, the primary causative factor of PD, activates complement C3 or CXCR4, deteriorate the killing capacity of macrophages and neutrophils and fail to control the infection [127,129,140]. Therefore P. gingivalis proliferates excessively in an inflammatory environment. Moreover, P. gingivalis spreads distantly with the blood circulation. Thereafter, LPS binding to LY96 leads to the blood-brain barrier disruption, triggering chronic and insidious inflammation in the brain, promoting glial cell carcinogenesis and exacerbating tumor development [141]. Although glioma-associated microglia and macrophages (GAMs) and MDSC are recruited into the glioma microenvironment and release diverse growth factors and cytokines, CXCR4 and C3 abnormal expression results in immunosuppression [142], leading to cancer cells limited clearance.

Conclusions

PD may are responsible for production of pro-inflammatory cytokines and bacterial products in the brain. Those products affect the brain as are able to increase the BBB permeability directly or

indirectly by inducing the recruitment of other inflammatory cells. Chronic neuro-inflammation is triggered by systemic inflammation as a consequence of PD. AD is the most common reported neurodegenerative disease which has been associated with periodontitis, and that association is overall significant. For PSD and MS, those association appear to be weak. The possible role of PD in GBM pathogenesis remains unclear, whereas in one study only was recorded that three genes may play a role in the crosstalk between those diseases through immune pathways and provided new perspective data regarding the co-pathogenesis of PD and GBM.

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