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996 *Current Neuropharmacology*, **2017**, *15*, **996-1009**

REVIEW ARTICLE

The Infectious Etiology of Alzheimer's Disease

Marta Sochocka[1,*], Katarzyna Zwolińska[1] and Jerzy Leszek[2]

[1]*Laboratory of Virology, Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland;* [2]*Department of Psychiatry, Wroclaw Medical University, Wroclaw, Poland*

ARTICLE HISTORY

Received: October 02, 2016
Revised: March 06, 2017
Accepted: March 09, 2017

DOI:
10.2174/1570159X15666170313122937

Abstract: ***Background*:** Inflammation is a part of the first line of defense of the body against invasive pathogens, and plays a crucial role in tissue regeneration and repair. A proper inflammatory response ensures the suitable resolution of inflammation and elimination of harmful stimuli, but when the inflammatory reactions are inappropriate it can lead to damage of the surrounding normal cells. The relationship between infections and Alzheimer's Disease (AD) etiology, especially late-onset AD (LOAD) has been continuously debated over the past three decades.

***Methods*:** This review discusses whether infections could be a causative factor that promotes the progression of AD and summarizes recent investigations associating infectious agents and chronic inflammation with AD. Preventive and therapeutic approaches to AD in the context of an infectious etiology of the disease are also discussed.

***Results*:** Emerging evidence supports the hypothesis of the role of neurotropic viruses from the *Herpesviridae* family, especially *Human herpesvirus 1* (HHV-1), *Cytomegalovirus* (CMV), and *Human herpesvirus 2* (HHV-2), in AD neuropathology. Recent investigations also indicate the association between *Hepatitis C virus* (HCV) infection and dementia. Among bacteria special attention is focused on spirochetes family and on periodontal pathogens such as *Porphyromonas gingivalis* or *Treponema denticola* that could cause chronic periodontitis and possibly contribute to the clinical onset of AD.

***Conclusion*:** Chronic viral, bacterial and fungal infections might be causative factors for the inflammatory pathway in AD.

Keywords: Alzheimer's Disease, neuroinflammation, chronic bacterial infections, chronic viral infections, neuroinfection, neurotropic viruses.

1. INTRODUCTION

Neurodegenerative disorders are defined as hereditary, sporadic and age-related conditions which are characterized by cognitive decline, especially in learning and memory. These disorders are often associated with problems with movement (ataxias), or mental functioning (dementias). Alzheimer's disease (AD) and other dementias, brain cancer, encephalitis, epilepsy, Parkinson's disease (PD), stroke, Huntington's disease, multiple sclerosis (MS), and prion diseases, are the most common and problematic neuro-degenerative disorders in the elderly.

According to an Alzheimer's Association report, AD constitutes 50 to 75% of cases of dementia in elderly persons above 60 years old. Individuals affected by AD number more than 35 million worldwide and more than 10 million in Europe [1]. AD is multifactorial and characterized by early neuronal loss. In AD brains, two pathological characteristics are observed: extracellular insoluble senile plaques formed by amyloid-β (Aβ) peptide and intraneuronal neurofibrillary tangles (NFT) formed by tau protein [2]. Interestingly, Aβ plaques and NFT are not unique to AD. Other central nervous system (CNS) conditions, including chronic infections, develop with the production of those specific histopathologic hallmarks [3]. Moreover, recent findings show antimicrobial activity of Aβ, thus suggesting that infections may induce the Aβ production and deposition in the brain. Bourgade and colleagues established that H4 neuroglioma cells produced Aβ-42 in response to HHV-1 infection thus inhibiting secondary replication of the virus [4]. As discussed by White and colleagues, Aβ may inhibit replication of the H3N2 and H1N1 influenza A virus (IAV) *in vitro*. These investigations showed that Aβ has antiviral properties and modulates viral interactions with phagocytes [5]. Current data suggest that vascular factors, oxidative stress and a neuroinflammatory process in the brain are primary contributors to AD pathogenesis [6, 7]. Among many critical components of AD, the most important are immune response and inflammation.

*Address correspondence to this author at the Laboratory of Virology, Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Rudolfa Weigla 12, 53-114 Wroclaw, Poland;
Tel. +48 713709924; Fax: +48-71-337 2171; E-mail: mars@iitd.pan.wroc.pl

1570-159X/17 $58.00+.00

There are no doubts that an inappropriate immune response in the brain may be engaged in the neurodestructive process [8]. Increasing pathological Aβ deposits activate glial cells (microglia and astrocytes), lymphocytes and macrophages which in turn release large amounts of inflammatory mediators such as cytokines, chemokines, neurotransmitters and reactive oxygen species (ROS) [9]. Reactive microglia and astrocytes induce neuronal apoptosis and blood brain barrier (BBB) dysfunction. BBB is important for the integrity and correct functioning of the CNS. Next, this process leads to the recruitment of peripheral blood leukocytes (PBL) through the BBB and their active participation in local inflammation in the brain tissue. Leukocytes release more inflammatory factors (cytokines), escalate the inflammatory state, and exacerbate other AD pathologies [8, 10, 11].

To modify or prevent neurodegenerative diseases, further environmental risk factors are investigated. Recent studies show the possibility that accumulative infections may be associated with AD and indicate the crucial role of neuroinflammation in the etiopathogenesis of AD. The inflammatory response is a typical reaction of most infectious diseases but could be triggered by several other harmful stimuli. It is believed that the infectious factors could stimulate activation of microglia and astrocytes, thus induce the inflammation in the brain. Therefore, neuropathological changes observed in AD might be a manifestation of an infection in the brain or elsewhere [3, 10]. In the present review, we discussed the existing data for infections and chronic inflammation as possible risk factors for AD.

2. NEUROINFLAMMATION IN AD PATHOGENESIS

Inflammation is a biological response of the body to different types of damages within the cells and tissues caused by chemical, physical and biological factors [12]. An acute inflammatory response can be beneficial as an immune response to tissue injury or infections, and the proper inflammatory reactions are characterized by an advantage of processes of restoring homeostasis over the destructive processes. However, these reactions might be impaired during aging, thus resulting in increased susceptibility to infection. If the activity of stimulating factors and the mechanisms of the proper development of inflammation are dysregulated, the body still receives a signal of health hazard and switches from the acute to a chronic inflammatory state [13, 14]. Chronic inflammation results in a response that leads to tissue degeneration and development of autoimmune or circulatory system diseases, arthritis and CNS disorders [15]. The "inflammation hypothesis of AD" proposed more recently by Krstic and Knuesel [16] is one of three important hypotheses on the etiopathogenesis of AD along with the "cholinergic hypothesis" by Bartus and colleagues [17] then "amyloid cascade hypothesis" by Hardy and Allsop [18].

Neuroinflammation is an inflammatory response in the CNS as a reaction to injury or infection, with the accumulation of glial cells. In this process, cytokines, chemokines, complement and pattern-recognition receptors (PRRs), cellular and molecular immune factors, may activate microglia and astrocytes, which produce pro-inflammatory cytokines, especially IL-1β, IL-6, TNF-α, and additional Aβ production [19, 20]. Stimulated microglia in turn activate other microglia and astrocytes. Liddelow and co-workers described a subtype of reactive astrocytes (A1), which is induced by classically activated neuroinflammatory microglia. They showed that activated microglia induce A1 astrocytes by secreting Il-1α, TNF and C1q. As a result, A1 astrocytes are not able to promote neuronal survival, outgrowth, synaptogenesis and phagocytosis, but induce the death of neurons and oligodendrocytes [21].

An acute inflammatory response in the brain induced by activated glial cells leads to repair of the damaged area of the brain, but chronic inflammatory reactions, which are usually of low grade and persistent in time, result in a response that supports the neurodestructive processes. Moreover, chronic inflammation impairs the mechanism for clearing abnormal proteins in aging brains that lead to tau-associated impairments of axonal integrity and transport, accumulation of amyloid precursor protein (APP), formation of paired helical filaments, and synaptic dysfunction. All these events precede and cause prominent neurodegeneration and result in cognitive decline [10, 20]. Importantly, it is well known that matrix metalloproteinases (MMPs), a branch of the large family of metalloproteinases, play an important role in the neuroinflammatory processes, and might be involved in the pathology of several neurodegenerative disorders, including AD [22, 23]. MMPs are zinc- and calcium-dependent endopeptidases, which are activated by inflammatory mediators or abnormal peptides (*e.g*., peptide aggregates). Their activity must be strictly controlled, because any dysregulation might be detrimental and leads to various disorders. Four types of proteins called tissue inhibitors of metalloproteinases (TIMPs) can modulate MMPs activity [24]. MMPs participate in tissue repair by promoting angiogenesis and neurogenesis and in the formation and clearance of Aβ in AD. MMPs are induced endogenously by the amyloid molecules in blood vessels, astrocytes and microglia [25, 26]. Astrocytes exposed to Aβ 1-40 secrete MMP2, MMP3 and MMP9 [27], which contribute to neuronal death. Thus, the increase in the expression of MMPs in the brain tissue and blood of patients with AD is a part of inflammatory response. In AD, MMP-3 and MMP9 are located around neurofibrillary tangles and amyloid plaques [24]. Their activity might be associated with the metabolism of Aβ because Aβ has been found to induce the expression of MMPs by both astrocytes and neurons [28]. According to some authors, MMP9 expression in the hippocampus is involved in Aβ induced cognitive dysfunction [29]. Plasma concentration of MMP9 is increased in AD, however there is no increase in MMP9 concentration in the CSF in AD. This discrepancy remains to be resolved. Studies indicate that cognitively healthy elderly individuals, with increased risk of developing AD in the future, have elevated CSF MMP3 and MMP9 levels, indicating that MMP3 and MMP9 might be involved in early pathogenesis of AD, and could be associated with neuronal degeneration and formation of neurofibrillary tangles even prior to development of overt cognitive dysfunction [23].

3. INFECTIONS AND AD

The importance of inflammatory processes in the pathogenesis of AD has also initiated research on the role of infectious agents in these reactions in the CNS. In recent

Table 1. Pathogens that are the key causes of AD.

Pathogens	Refs.
Viruses	
Human herpesvirus 1 (HHV-1)	[3, 32]
Human herpesvirus 2 (HHV-2)	[32, 33]
Cytomegalovirus (CMV), (HHV-3)	[3, 32]
Epstein-Barr virus (EBV), (HHV-4)	[3, 32]
Varicella-zoster virus (VZV), (HHV-5)	[3, 34]
Human herpesvirus 6 (HHV-6)	[3, 32]
Hepatitis C virus (HCV)	[35]
Bacteria	
Chlamydia pneumoniae	[36, 37]
Helicobacter pylori	[3, 36, 37]
Borelia burgdorferi	[36, 37]
Treponema pallidum	[38, 39]
Porphyromonas gingivalis	[32, 36, 40]
Fusobacterium nucleatum	[40]
Prevotella intermedia and other periodontal bacteria	[40]
Fungi	
Candida albicans	[41, 42]
Protozoa	
Toxoplasma gondii	[37]

years, numerous studies have confirmed the relationship between different microbial infections, cognitive decline and AD. Systemic bacterial and viral infections, such as human herpesviruses, spirochetes, *Chlamydia pneumoniae* or *Borrelia burgdorferi*, may increase the inflammatory state and the susceptibility to development of AD [10, 30, 31]. Pathogens possibly associated with the development of AD are presented in Table **1**.

The CNS is highly protected by the BBB system, consisting of microvascular endothelial cells, astrocytes and pericytes, which controls the passage of molecules into and out of the brain. However, a large spectrum of pathogens, such as viruses, bacteria, fungi, and protozoa can gain access and cause many serious illnesses. Bacteria can cross the BBB through different mechanisms including transcellular traversal, paracellular traversal and Trojan-horse. On the other hand, viruses can directly infect endothelial cells to cross the BBB into the CNS. As pathogens replicate, they release their component molecules, called pathogen-associated molecular patterns (PAMPs), that can be identified by PRRs, expressed on antigen-presenting cells (APCs). Examples of PRRs include toll-like receptors (TLRs), RIG-I-like receptors (RLRs), receptors for advanced glycation end products (RAGEs), c-type lectin receptors (CLRs), nucleotide binding oligomerization domain (NOD)-like receptors (NLRs) and intra-cytosolic DNA sensors [43]. Damage to the CNS during infection triggers the release of inflammatory mediators and activation of the innate immune response necessary to eliminate the invasive pathogens. Infectious factors are responsible for the activation of glial cells that produce several inflammatory molecules (cytokines such as TNF-α, IFN-γ, IL-1β, IL-6 IL-18, chemokines, and ROS) which in turn leads to exacerbation of other AD pathologies. The most important mediators of the inflammatory and innate immune response in the CNS are microglia, which express various PRR receptors. Moreover, a strong inflammatory response in the periphery from bacterial or viral infections leads to the peripheral leukocyte's (T-cells, macrophages and neutrophils) infiltration to the CNS, which share several functional features with microglia. Leukocytes express TLRs and are able to be activated by abnormal proteins or PAMPs. Therefore, an acute neuroinflammatory response is beneficial, and leads to repair of the damaged area of the brain and helps to restore brain homeostasis. However, if the inflammatory response is uncontrolled and chronic, characterized by long-lasting activation of microglia that release pro-inflammatory mediators, and increase oxidative and nitrosative stress, it consequently perpetuates the inflammatory cycle, which is detrimental for neuro-degenerative diseases such as AD [44].

3.1. Viral Infections

One hypothesis about the development of AD blames the reactivation of latent infection of herpes simplex virus (HHV-1, *Human herpesvirus* 1). The concept of the viral, especially HHV-1, role in AD was proposed for the first time in 1982 by Ball [45] and in 1986 by Gannicliffe and colleagues [46]. It was noted that damage of the brain tissue in the early stages of the disease includes the same areas, that are affected by the inflammation of the brain caused by HHV-1 [32, 45]. Based on the presence of antibodies in the blood, it is estimated that about 80% of the population is infected with HHV-1. After the primary infection the virus turns into a latent state, and exists in the trigeminal ganglia. Periodic reactivation of HHV-1 can be asymptomatic, unless the immune system is weakened, for example because of aging, stress, immunosuppression or peripheral infections [47]. In these circumstances, the virus is propagated freely, taking up several nerve cells, which involves a cascade of intracellular changes leading to cell death and neuro-degeneration of other areas of the brain [48]. HHV-1 acts directly, causing the cell machinery to produce viral proteins and indirectly via an inflammatory process. Moreover, the virus might be a risk factor for AD when it occurs concomitantly with the type 4 allele of the apolipoprotein E gene (APOE ε4). When the virus acts with (APOE ε4), it causes accumulation of Aβ and an increase in the formation of amyloid plaques. Moreover, there is accumulation of hyperphosphorylated tau characteristic for NFT [49-51]. It is worth mentioning that (APOE ε4) has been found to modulate the severity of disease of microbial cause or susceptibility to infection, including HHV-1 and HHV-2 (*Human herpesvirus* 2) [47]. Reactivation of HHV-1 infection may induce AD-relevant cellular changes *i.e*., formation of Aβ plaques and accumulation of tau protein (NFT), which has been demonstrated in studies with neural cells infected with this virus [47, 52]. Additionally, studies on the distribution of HHV-1 DNA in human brains revealed that viral DNA was found within senile plaques. Moreover, HHV-1 DNA was present with high frequency in elderly brains in contrast to the brains of young people and

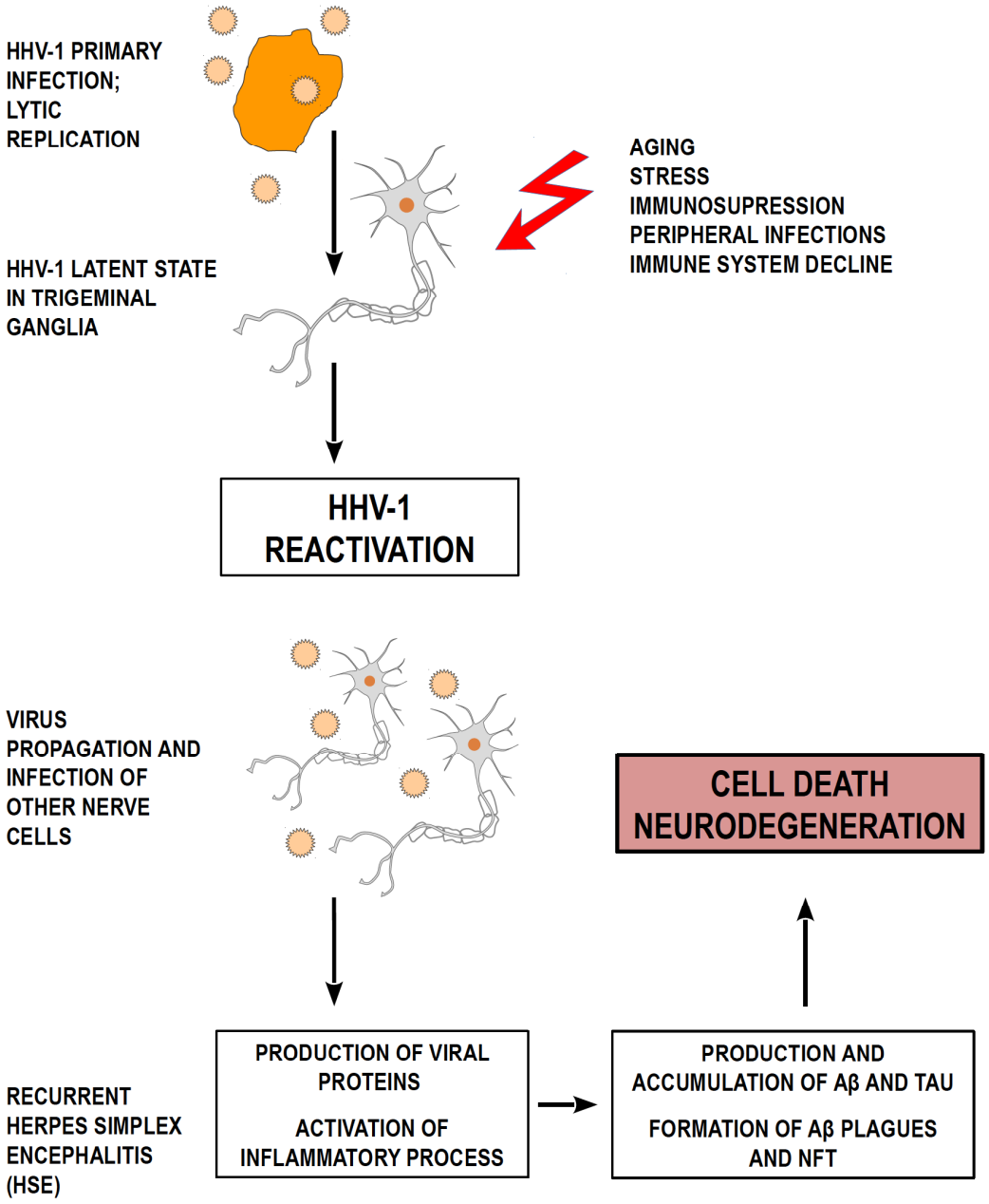

Fig. (1). HHV-1 CNS reactivation and AD-associated neurodegenerative processes.

children [53]. Probably, the virus easily enters the brain in older age because of the impaired immune response with age. Also, because of higher permeability of BBB in elderly individuals. During long-term studies on an elderly population it was found that there was a significant association between presence of anti-HHV-1 IgG antibodies and AD [54]. Prospective studies with over 3000 participants showed that positivity for anti-HHV-1 IgM, a sign of reactivated infection, increase to almost double the risk for AD [55]. Investigations of Hu and colleagues concerning the mechanisms of the viral infection showed that in primary murine microglia intracellular ROS were highly elevated following infection with HHV-1. Moreover, they reported that pro-inflammatory cytokines and chemokines production induced by viral replication decreased with the inhibition of NADPH oxidase [56]. The major uncertainty concerning the suggested role of HHV-1 in AD is that herpes simplex encephalitis (HSE) causes serious brain damage in a short period of time whereas the neurodegenerative changes seen in AD are gradual, accumulating over several years. Thus, HHV-1 reactivation events must presumably produce a milder and a recurrent disease. These limited and asymptomatic reactivations has been described in recurrent HSE [50, 57, 58]. It was proposed that AD might be caused by incidents of mild HSE. However, survivors of mild as well as full-blown HSE experience memory loss, the primary neurological symptom of AD, thus indicating HHV-1 as the main cause of this decline. The possible role of HHV-1 in AD pathogenesis is presented in Fig. (**1**).

It is also worth to noticing that other viruses of the *Herpesviridae* family, such as HHV-2, cytomegalovirus (HHV-5, *Cytomegalovirus*, CMV) and varicella zoster (HHV-3, *Varicella zoster virus*, VZV) can also infect nerve cells, and pass into latent infection [32]. Studies focused on the viruses from this family in the context of age-related diseases are very limited. Recent publications suggest that there is an association between CMV infection and risk of AD and the relationship between infection with VZV and risk of MS [58]. Prospective studies with 849 participants over 75 years old, without vascular dementia and vascular diseases, performed by Barnes and colleagues showed the relationship between CMV seropositivity and increased risk of AD and cognitive decline [59]. Nimgaonkar and co-workers confirmed that infection with CMV, HSV-2, or *Toxoplasma gondii* (TOX) exacerbate cognitive decline in older individuals [60]. Direct and indirect links between CMV and AD pathology were also confirmed by Lurain and colleagues [61]. They found a significant association between CMV-specific serum IgG antibody levels and NFT. Moreover, they noted that only CD4+ T-cells responded to the CMV pp65 antigen and it was associated with the elevation of several AD markers. Interestingly, studies with human foreskin fibroblast (HFF) confirmed that CMV, but not HHV-1, induced Aβ production. Shingles (zoster) is a disease caused by reactivation of latent infection and the development of inflammation in the intervertebral ganglia or cranial nerve ganglia. Primary infection with VZV, usually at a young age, causes the development of chicken pox. In older people, because of the natural immune system dysfunction and other chronic diseases (diabetes, cancers, immunosuppressive therapy), VZV reactivation is relatively frequent [62]. Data from the Center for Disease Control and Prevention in Atlanta (CDC) indicate that in the United States one in three people aged over 60 suffers or will suffer from shingles, which indicates the growing health problem, mainly because of recurrent nerve pain. For this reason, shingles is an extremely troublesome disease including in patients with AD. It is a growing health problem also in Europe and Asia. HHV-2, HHV-6 and HHV-4 (*Epstein-Bar virus*, EBV) have also been examined for their potential role in AD pathogenesis. The evidence linking AD to these viruses is incomplete. As discussed by Kristen and colleagues human SK-N-MC neuroblastoma cells infection with HHV-2 results in the accumulation of tau protein and the Aβ peptides Ab40 and Ab42 [33]. They claimed that HHV-2 infection also leads to a reduction in the amount of Aβ40 and APP. Moreover, Carbone and colleagues analyzed DNA isolated from PBL and brain samples for the presence of EBV, HHV-6 and CMV [63]. DNA of EBV and HHV-6, but not CMV, has been found. In this prospective studies, increase in EBV-positive or HHV-6-positive PBL has been noted in patients who developed clinical AD. Moreover, the authors determined that IgG levels for CMV and EBV antigens were significantly elevated in those patients.

Recent investigations also suggest that there is a relationship between *Hepatitis C virus* (HCV) infection and risk of dementia. The first significant investigations which linked HCV infection and cerebral function abnormalities was reported over a decade ago. Since that time several published studies have investigated cognitive abilities in patients with HCV infection and hepatic impairment [64]. Current findings suggest that HCV may be a risk factor for dementia and for the subtypes of dementia in HCV-infected patients [35]. Prospective studies of Chiu and colleagues showed that HCV was related to increased risk for AD and vascular dementia and did not interact with other medical illnesses, but the mechanisms by which HCV infection increases the risk of dementia should be clarified. The authors proposed that: (*) the virus may infect the brain and have a direct neurotoxic effect; or (**) the virus is indirectly neurotoxic via cerebral and/or systemic inflammation [35]. It is noted that the HCV infection causes the activation of the immune system, and it is postulated that chronic activation of the immune system could relate to the cerebral abnormalities via the exacerbation of systemic and/or local inflammation [64]. Fletcher and McKeating confirmed that HCV RNA is associated with CNS tissue. Viral sequence diversity between brain and liver tissue indicate the independent viral evolution in the CNS and liver [65]. HCV can infect monocytes/macrophages and cross the BBB. These immune cells may next secrete large amount of cytokines (TNF-α, IL-6) and cause excitotoxicity in the brain tissue. Grover and colleagues confirm that in patients with mild hepatitis C, activation of microglia cells is positively correlated with HCV viremia and with altered cerebral metabolism [66].

Standard antiviral drugs inhibit pathological changes observed in AD caused by viral infections. The main anti-HHV-1 antiviral agent is acyclovir (ACV), which targets infected cells and viral DNA replication. Acyclovir does not affect uninfected cells or the normal metabolism of infected cells, so it has no harmful side-effects, unlike many other treatments. There are promising results from studies involving valaciclovir (VCV), which is characterized by high bioavailability and does not cause any obvious adverse effects [47]. However, it should be noted that all antiviral preparations have limited effectiveness against certain viruses. Moreover, the side effects often limit application of these drugs especially in the elderly population. New effective antiviral therapies and a vaccine to prevent viral infections, especially CMV infection, are needed. Preventive and therapeutic approaches to AD in the context of an infectious etiology of the disease will be discussed in detail below.

3.2. Bacterial Infections

More than a century ago, Alzheimer and his colleagues discussed the possibility that microorganisms may be involved in the formation of senile plaques [67]. Currently the important role of infections in AD etiology is postulated by many research teams [68]. Chronic spirochetal infections are responsible for syphilitic dementia in the atrophic form of general paresis, and it was noted in the past that clinical and pathological hallmarks of the disease are similar to those observed in AD. It is well known that spirochetes are neurotropic pathogens [38, 39]. These bacteria infect the brain and pass into latent infection. In addition to hematogenous dissemination, spirochetes can spread via the lymphatics and along nerve fiber tracts; *e.g.*, periodontal invasive spirochetes can invade and transmit along the trigeminal

nerve and trigeminal ganglia. Bacteria might also spread along the fila olfactoria and tractus olfactorius, which confirmed the olfactory hypothesis and investigations indicating that in the early stages of the degenerative process in AD the olfactory tract and bulb are infected with spirochetes [40, 69]. In this aspect, the innate immune system plays an important role in the recognition of spirochetes via PRRs, executes pro-inflammatory reactions, and initiates adaptive immune responses. After infection spirochetes initiate the host defense and pass into latent chronic infection. Since chronic bacterial infections can lead to amyloid deposition, it is postulated that amyloidogenic proteins, which are an integral part of spirochetes, could contribute to Aβ deposition in AD [39]. Bacterial amyloids are very important for the bacteria life cycle contributing to bacterial virulence and invasion of host cells [70]. Noguchi and Moore reported that *Treponema pallidum* (*Spirochaetaceae*) might infect the cerebral cortex [71]. Moreover they determined that *T. pallidum* infection causes slowly progressive dementia, cortical atrophy and local amyloidosis in the atrophic form of this chronic bacterial infection. Based on the growing body of evidence it is considered that spirochetes might be responsible for AD progression [36, 38, 72]. Lyme disease (borreliosis), caused by *Borrelia burgdorferi*, another pathogen from spirochetes, is often related to dementia associated with cortical atrophy and microgliosis, especially in the late stages of the disease. It means that various types of spirochetes might cause dementia and brain damage (such as that observed in AD) similarly to *T. pallidum* [39]. *B. burgdorferi* was first isolated from the brain of AD patients by McDonald and colleagues and Miklossy [73, 74]. Currently, many investigations obtained from several research teams show that spirochetes can invade the brain in AD. Moreover, co-infection with several types of spirochetes was observed. In recent years there has been increased incidence of borreliosis in European countries [75]. According to recent proposed hypothesis *B. burgdorferi* causes neuro-degenerative changes through the induction of intracellular inflammation in neurons. In consequence, the inflammatory state leads to abnormal tau phosphorylation, microtubular dysfunction, and NFT generation. An expanding inflammatory process in the brain next leads to the disruption of enzymatic homeostasis [76]. Thus, the role of *B. burgdorferi* in the pathogenesis of AD is that in AD patients who suffered from neuroborreliosis, *B. burgdorferi* antigens in NFT and Aβ are detected as well as extensive neurodegenerative changes in brain tissue [39].

Apart from above-mentioned bacteria other spirochetes, probably involved in the pathogenesis of AD, are described. *Treponema denticola*, the most readily cultivable oral spirochete, can cause periodontal disease (periodontitis), a peripheral chronic infection that elicits a significant systemic inflammatory response [77]. Numerous other pathogens of periodontitis such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Tannerella forsythensis*, and *Eikenella corrodens* are implicated in the development of several inflammatory diseases at remote organ sites like AD [78]. Periodontitis can be characterized as a "low-grade systemic disease" with elevation of C-reactive protein (CRP) and release of pro-inflammatory cytokines into the systemic circulation [79]. Periodontal disease may in turn stimulate recurrent chronic oral infections, and the periodontal pathogens contribute to the destruction of soft and hard tissues supporting the teeth [79, 80]. Moreover, bacterial lipopolysaccharide (LPS) also leads to tissue destruction by inducing the immune response and production of pro-inflammatory molecules, such as TNF-α, IL-1β, and IL-6. It is well known that inflammation play a pivotal role in periodontitis and AD, while being a connecting link between the two diseases [40, 81]. Two different pathways by which pathogens can enter the brain structures from the mouth are possible. First, the periodontal inflammatory process can expand to the brain through the circulatory system with pro-inflammatory cytokines but without the contact of the bacteria with the brain tissue. Secondly, periodontal bacteria or bacterial molecules can penetrate to the CNS either through the blood stream or via peripheral nerves [82]. The hypothesis that there is an association between oral health status and cognitive decline in AD [83] suggests that chronic oral infection promotes inflammation, and several pro-inflammatory cytokines enhance the pool of inflammatory mediators in the brain, and lead to confusion and dementia [40, 81]. Therefore, periodontal disease may be an important source of systemic inflammatory molecules, which was also confirmed by our team [84, 85]. Kamer and colleagues showed that AD patients with periodontitis have an increased level of periodontal bacteria-specific antibodies and TNF-α [86]. Similar results, showing a higher level of TNF-α in serum of AD patients with periodontal disease were reported by Farhad and colleagues [87]. Thus, spirochetes are the most neurotropic bacteria, and have been detected in the trigeminal nerve and trigeminal ganglia [88]. Spirochetes and their DNA have been found associated with AD and are strongly suspected to be the causative agents leading to dementia [39, 79]. Indeed, infections with spirochetes can cause serious brain disturbance *i.e.*, cerebral hypoperfusion, cerebrovascular lesions, and a severely disturbed capillary network [40]. Additionally, Poole and colleagues tried to determine the link between periodontal disease and AD. They investigated the major periodontal disease bacteria and/or bacterial components in brain tissue from 12 h postmortem delay. It was confirmed that LPS from periodontal bacteria can access the AD brain during life. Identification of a known chronic oral-pathogen-related virulence factor reaching the human brains suggests an inflammatory role in AD pathology [89]. Moreover, Wu and colleagues claim that the leptomeningeal cells are involved in the transmission of systemic inflammatory signals between macrophages and brain-resident microglia by secreting inflammatory mediators during periodontitis. Pro-inflammatory macrophages and cellular components of periodontal bacteria (*e.g.*, LPS or flagellin) activate the receptors presented on the surface of leptomeninges. This process leads to the activation of brain-resident microglia which in turn induce neuroinflammation. The excessive neuroinflammatory reactions evoked by senescent-type microglia may lead to AD initiation and progression, resulting in the cognitive decline [90]. The relationship between periodontal disease and AD is presented in Fig. (**2**).

According to Shima and colleagues, *Chlamydia pneumoniae* is currently the most plausible of all infectious

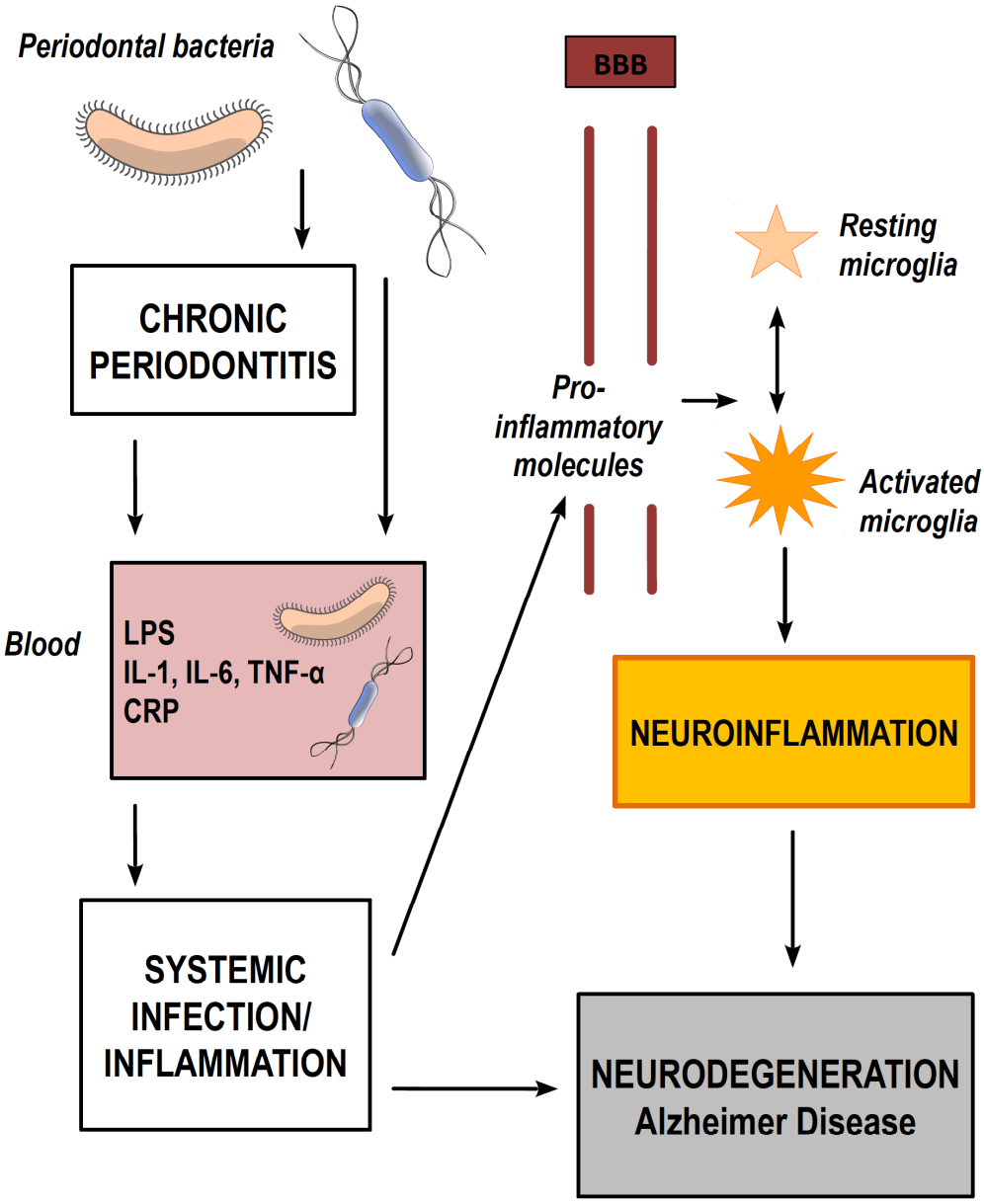

Fig. (2). Association between chronic periodontitis and AD.

bacterial agents proposed to be involved in AD [91]. Various cell types found in the brain may be infected by *C. pneumoniae*, including endothelial cells, astrocytes, microglia and neurons [92]. *C. pneumoniae* may reside in an intracellular inclusion that resists lysosomal fusion and immune recognition. These bacteria require energy and nutrients (sphingomyelin and cholesterol) which are gathered from the host; therefore *C. pneumoniae* interacts with and manipulates the host cells [93]. It is postulated that *C. pneumoniae* and related antigens may interact with extracellular proteins and lipids in the brain. Chlamydial antigens may interact with soluble oligomeric forms of amyloid, such as ADDLs, although these molecules usually do not occur in mature plaques due their soluble nature. This interesting relationship between amyloid and *Chlamydia* (between pathology and infection) in the same cortical regions of the brain of AD patients requires further investigations. However, it is difficult to establish an association between *C. pneumoniae* infections and AD pathogenesis, due to the complexity of AD and this bacterial infection. Currently, anti-chlamydia antibodies on frontal and temporal cortical sections of AD brains are used to provide more a valuable insight into the association between infection and AD pathology [92]. Takeda and colleagues suggested that Aβ plaques and NFT leads to neurodegenerative changes in the brain, which in turn causes progressive cognitive decline. However, agitation, aggression and psychosis, non-cognitive symptoms observed in AD patients, can be triggered by an infection elsewhere. It suggests a contribution of peripheral inflammation in AD pathogenesis [94]. The relationship between pneumonia complications and prognosis of patients with varying types of dementia was also described by Manabe and co-workers [95].

Recently, a growing body of evidence implicates *Helicobacter pylori* in AD pathogenesis. Many investigations suggest that *H. pylori* may be associated with neuro-degenerative, respiratory, and other miscellaneous disorders. *H. pylori*-specific IgG antibody levels were analyzed in CSF and serum of AD patients. These antibody levels were significantly increased [96]. The occurrence of molecular mimicry mechanisms, or induction of a low-grade inflammatory state has been hypothesized as a possible pathogenic mechanisms. Most important investigations of the last year are summarized in the review by Franchesi and colleagues [97]. The evidence compiled from the literature linking AD to *H. pylori* is also discussed by Mawanda [3].

The oral cavity, lungs, and the gastrointestinal and urinary tracts are the most important sources of brain microorganisms. Thus, bacteria and their toxic products present in brain tissue of AD patients and experimental animals are the key perpetrators of the inflammatory state. Bacteria activate several pathways that include TLR signaling and the complement cascade [98]. Next, activation of the NF-kB signaling pathway leads to pro-inflammatory cytokine/ chemokine release, production of free radicals, nitric oxide and activation of apoptosis which collectively contribute to the capacity for enhancing neuroinflammation.

3.3. Fungal Infections

Recently, fungal infections in AD patients have gained much attention [99]. Alonso and colleagues detected fungal proteins in CSF from AD patients by using different anti-fungal antibodies [99]. Fungal DNA and proteins were also found in frozen brain tissue from AD patients, but not from control patient tissue. Fungal material was detected both intra-and extracellularly using specific antibodies against several fungi: *Candida famata*, *C. albicans*, *C. glabrata*, *Phoma betae*, and *Syncephalastrum racemosum*. Fungal material was found in particular brain regions including the external frontal cortex, entorhinal cortex/hippocampus, cerebellar hemisphere, and choroid plexus. Detailed analysis of brain sections derived from AD patients showed that all were infected with fungi [42].

4. PREVENTIVE AND THERAPEUTIC APPROACHES TO AD

The accumulating evidences presented above suggest that infectious agents might be important etiological factors in AD. The hypothesis of infection with HHV-1 may indicate that antiviral drugs and vaccination against HHV-1 can prevent an increase of the disease [100, 101]. According to some authors, it is necessary to prepare clinical trials using antiherpetics such as acyclovir (ACV, a drug used for the treatment of MS patients) and its bio-drug valaciclovir (VCV, which is metabolized to ACV) in the group of AD patients. Importantly, ACV crosses the BBB and causes only a few side-effects [101]. Intravenous immunoglobulin (IVIG), which acts by a different way than that of ACV or other anti-HHV-1 agents, raises hopes for using it in the treatment of AD. IVIG has the property of neutralizing any extracellular virus and also helps to destroy cells affected by HHV-1 [102]. At present, the usage of IVIG in HHV-1 disorders such as HSE, where IVIG was found to reduce the number of trigeminal ganglia with latent, chronic HHV-1 infection, is successful [103]. Treatment with IVIG in a few AD patients showed that the preparation was well tolerated, and neuropsychiatric tests indicated stabilization or trends toward improvement in some aspects [102]. It was observed that anti-Aβ antibodies in AD patients increased proportionately to IVIG dose; no improvement of cognitive functions was determined when monoclonal anti-Aβ antibodies were used, thus suggesting that IVIG acts in some different way [102, 104]. Moreover, recent investigation showed a significant improvement in some cognitive functions in patients with early AD treated for twenty eight weeks with interferon beta-1 [105]. According to our opinion, and based on the above mentioned investigations, a rapidly growing body of evidence indicates that antiviral drugs would be a completely new way of inhibiting one of the risk factors of the disease but unfortunately not the consequences.

Recent findings reinforced the notion that brain inflammation, as assessed by CSF markers such as Aβ42, sAPPβ, β-secretase, total-tau [t-tau], phospho-tau [p-tau], and chitinase-3-like protein 1 (CHI3L1) known as YKL-40, increased in normal aging and was associated with markers of neurodegeneration in the preclinical stages of AD [106]. As we have suggested in our paper, not only viral infections but also chronic and persistent bacterial infections play an important role in the induction and amplification of chronic neuroinflammation in AD. Successful treatment of chronic infections is a great challenge. As many authors have showed and epidemiological evidence indicated, using non-steroidal anti-inflammatory drugs (NSAIDs) can lower the risk of AD, because NSAIDs inhibit the production of prostaglandin inflammatory mediators [107]. The treatment of patients with NSAIDs prior to the development of AD reduces the possibility of developing the disease, because – as clinical trials suggested - these drugs act as inhibitors of the immune response. Therefore, therapeutic strategies that induce an immunological response may be viewed as potential treatments. Theoretically, this kind of treatment should decrease infiltration of senile plaques by immune cells and inhibit the release of cytokines and other inflammatory factors [107]. Steroids are unsuitable candidates for immuno-suppressive therapy of AD because of significant changes in cytosolic glucocorticoid receptors in peripheral blood mononuclear cells (PBMCs) such as lymphocytes and monocytes and changes in the hypothalamic – pituitary - adrenal axis [108, 109]. More recent data show that NSAIDs, which attenuate the inflammatory processes in the brain, may decrease the production of Aβ peptides and might reduce the risk of developing the disease [107]. According to other authors NSAIDs do not act in patients with clinically developed AD. Moreover, it was previously determined that treatment with a COX-2 inhibitor may increase Aβ deposits in the brain. Additionally, laboratory evidence suggests that NSAIDs might prevent the onset of AD [108]. However, those pieces of evidence remain controversial. On the other hand, several studies in humans provide evidence that treatment with NSAIDs may lower the risk of developing AD. Once again, however, randomized trials have suggested that NSAIDs are ineffective in patients with clinically established disease or do not have the ability to prevent the onset of dementia in cognitively normal and/or those with

only mild cognitive impairment [108]. Thus, the hypothesis that NSAIDs have a beneficial effect on the pathophysiology of AD seems uncertain. However examination (meta-analyses) of the studies, performed by Wang and colleagues, reinforced the therapeutic role of cholinoesterase inhibitors (ChEIs) in AD. Based on their results we can conclude that combination of the glutamatergic inhibitor, memantine, with ChEIs is effective in ameliorating AD progression and occurrence [110]. Contradicting the observational studies, therapeutic role of NSAIDs in AD are intriguing but unproven [111]. These failures may be the result of patients selection, drug selection and dose, and duration of therapy, According to some authors initiation of therapy before any symptoms, or at the stage of mild cognitive impairment may be necessary [112]. Further debate on this subject leads to the quite limiting conclusion that immunosuppressive therapy can be useful but should not be prolonged and should be stopped after obtaining optimal improvement of AD. In this situation it is necessary to search for new generation of immunosuppressors, possibly from a natural origin. Several reports have assessed the efficacy of natural immuno-suppressive drugs for AD treatment [108, 113]. Currently, plant natural preparations, such as *Ginkgo biloba* extracts, are intensively investigated due to their potential anti-inflammatory and anti-HHV-1 activity [our unpublished data].

We have tested Colostrinin, a proline-rich polypeptide (PRP) complex that is a natural product isolated from bovine colostrum. This agent has immunomodulatory properties in experimental animals such as mice, rats, and chicken because it induces maturation of thymocytes, and in humans with mild to moderate AD, it improves the cognitive functions [114, 115]. This context led us to explore anti-inflammatory activity of acetylcholinesterase (AChE) inhibitors such as donepezil [116]. Donepezil revealed anti-inflammatory activity in experimental animal models [117, 118]. It is possible that donepezil and other cholinesterase inhibitors exert their anti-inflammatory activity by elevation of the level of acetylcholine, and acetylcholine-activated cholinergic receptors on glial cells. For example, acetylcholine is perceived as an important modulator of the neuroimmune-endocrine axis [119], astrocytes and microglia carry cholinergic receptors and adrenergic receptors and activation of adrenergic receptors leads to release of pro-inflammatory cytokines, whereas activation of cholinergic receptors decreases the cytokine deliverance from glial cells [120, 121]. Elevation of acetylcholine (ACh) level in the brain induced by donepezil increases the activation of cholinergic (nicotinic) receptors on microglia, thus leading to decrease of the release of cytokines [121]. After treatment of our patients with donepezil for one month, we noted marked attenuation of the release of cytokines from PBMC [122]. Also, donepezil was able to directly inhibit inflammatory NF-kB signaling, causing a decrease of TNF-α, and suppressed the gene expression that play an important role in the synthesis of nitric oxide synthase (iNOS), TNF-β, and IL-1 in purified cultures of microglia [123]. These effects were independent of ACh receptors, but well pronounced when the donepezil dose was significantly higher than the therapeutic dose of the drug, demonstrating a potential and novel therapeutic strategy against AD [124, 125]. According to our observations, the mechanism of neuroprotection of donepezil may be related to the histamine signaling through H1R and H2R receptors. We have found that donepezil probably restores the proper balance between H1R and H2R expression [126]. In the brain tissue, both neurons and glial cells produce histamine as well as responding to it by paracrine mechanisms [127]. A normal physiological balance of histamine receptor expression is an important factor in the prevention of neuronal autoimmune inflammatory reactions in the brain tissue [128, 129]. Some evidence suggests an anti-inflammatory role for AChE inhibitors because of their activity against free radical generation and through decreasing the cytokine release from activated microglia mostly by enhancement of ACh action on cholinergic receptors on glial cells. Donepezil for instance prevented depletion of reduced glutathione (GSH) and precluded an increase of malondialdehyde (MDA) in experimental oxidative stress in mice [130]; it also blocked lipid peroxidation and showed an efficient neuroprotective effect [131].

These observations are supported by evidence of a role played by ACh in the inhibition of the cytokine release through the cholinergic, anti-inflammatory pathway [131]. According to the mentioned data we hypothesize that it is important to gain a better understanding of the role of neuroinflammation in the development of AD before assessing therapeutic strategies aimed at improving neuronal survival.

CONCLUDING REMARKS

AD etiology has not been completely established. A rapidly growing body of evidence indicates that neuro-inflammation has emerged as an important component of AD pathology, and a vast amount of experimental and clinical data indicates the crucial role of activation of the innate immune system in the disease promotion and symptoms progression. Persistent formation and deposition of Aβ aggregates give rise to chronic activation of the immune system. Interactions between activated glia and neurons around Aβ plaques maintain a chronic self-sustaining inflammatory state in the affected brain. Some authors suggest that infectious factors such as viruses or bacteria can lead to cytokine dysregulation and brain injury through a variety of mechanisms, including altered neurotransmission, apoptosis and activation of microglia and astrocytes. Because postmortem study of AD brains demonstrated the presence of acute-phase inflammatory reactants, many investigators suggest that AD is an infectious disease or infectious agents constitute a risk factor for AD. It is worth mentioning that the concept of the infectious nature of AD is still controversial because – as yet - no specific pathogen has been linked conclusively to the causation of AD in humans. However, data from many laboratories are interesting and lead to a renewed interest in the role played by pathogens such as bacteria, viruses or fungi in the etiology of late-onset AD. Future confirmation that infectious agents can play an important role in the pathogenesis of AD provides new opportunities for anti-inflammatory therapy against AD. The accumulating evidence of common causative factors of AD suggests that understanding of the associations between AD

and infections opened new ways to control this highly prevalent and debilitating disease. In the latest review, Itzhaki and colleagues presented evidence for an infectious/ immune component in AD pathogenesis, and for causation of infection and AD [132]. Moreover, McNamara and Murray compared the last findings of the role of neuropathological viruses in the progression of AD [133]. There are also more and more investigations that link HHV-1 infection and modulation of host autophagy [134].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The project was supported by Wroclaw Centre of Biotechnology, The Leading National Research Centre (KNOW) program for the years 2014-2018.

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