

Editorial

Microbes and Alzheimer's Disease

Ruth F. Itzhaki^{a,*}, Richard Lathe^{b,*}, Brian J. Balin^c, Melvyn J. Ball^d, Elaine L. Bearer^e, Heiko Braak^f, Maria J. Bullido^g, Chris Carter^h, Mario Clericiⁱ, S. Louise Cosby^j, Kelly Del Tredici^f, Hugh Field^k, Tamas Fulop^l, Claudio Grassi^m, W. Sue T. Griffinⁿ, Jürgen Haas^b, Alan P. Hudson^o, Angela R. Kamer^p, Douglas B. Kell^q, Federico Licastro^r, Luc Letenneur^s, Hugo Lövhelm^t, Roberta Mancuso^u, Judith Miklossy^v, Carola Otth^w, Anna Teresa Palamara^x, George Perry^y, Christopher Preston^z, Etheresia Pretorius^{aa}, Timo Strandberg^{bb}, Naji Tabet^{cc}, Simon D. Taylor-Robinson^{dd} and Judith A. Whittum-Hudson^{ee}

^aFaculty of Life Sciences, University of Manchester, Oxford Road, Manchester, UK

^bDivision of Infection and Pathway Medicine, University of Edinburgh, Little France, Edinburgh, UK

^cCenter for Chronic Disorders of Aging, Philadelphia College of Osteopathic Medicine, Philadelphia, USA

^dDepartment of Pathology (Neuropathology), Oregon Health and Science University, Portland, Oregon, USA

^eDepartment of Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

^fClinical Neuroanatomy Section, Department of Neurology, Center for Biomedical Research, University of Ulm, Ulm, Germany

^gCentro de Biología Molecular 'Severo Ochoa' (CSIC-UAM), Universidad Autónoma de Madrid, and Centro de Investigación en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

^hPolygenic Pathways, Hastings, East Sussex, UK

ⁱUniversity of Milano and IRCCS SM Nascente, Don C Gnocchi Foundation, Milan, Italy

^jCentre for Infection and Immunity, Medical Biology Centre, Queen's University, Belfast, UK

^kQueens' College, Cambridge, UK

^lDepartment of Medicine, Division of Geriatrics, Université de Sherbrooke, Sherbrooke, Québec, Canada

^mInstitute of Human Physiology, Medical School, Università Cattolica, Rome; San Raffaele Pisana Scientific Institute for Research, Hospitalization, and Health Care, Rome, Italy

ⁿDepartment of Geriatrics, University of Arkansas for Medical Sciences, and Geriatric Research, Education, and Clinical Center, Little Rock, Arkansas, USA

^oDepartment of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan, USA

^pNYU College of Dentistry, Department of Periodontology and Implant Dentistry, New York, New York, USA

^qSchool of Chemistry, Manchester Institute of Biotechnology, University of Manchester, Manchester, UK

^rDepartment of Experimental, Diagnostic, and Specialty Medicine, School of Medicine, University of Bologna, Bologna, Italy

^sINSERM, Université de Bordeaux, Bordeaux, France

^tDepartment of Community Medicine and Rehabilitation, Geriatric Medicine, Umeå University, Umeå, Sweden

^uDon Gnocchi Foundation ONLUS, Milan, Italy

*Correspondence to: Current address: Prof. Ruth F. Itzhaki, Nuffield Department of Clinical Neurosciences, University of Oxford, Level 6, West Wing, John Radcliffe Hospital, Oxford, UK. Tel.: +44 01865 250853; E-mail: ruth.itzhaki@manchester.ac.uk

and Richard Lathe, Division of Infection and Pathway Medicine, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, UK. E-mail: richardlathe@ed.ac.uk

^v*Prevention Alzheimer International Foundation, International Alzheimer Research Center, Martigny-Croix, Switzerland*

^w*Institute of Clinical Microbiology, Faculty of Medicine, Austral University of Chile, Valdivia, Chile*

^x*Department of Public Health and Infectious Diseases, Institute Pasteur Cenci Bolognetti Foundation, Sapienza University of Rome; San Raffaele Pisana Scientific Institute for Research, Hospitalization, and Health Care, Rome, Italy*

^y*College of Sciences, University of Texas at San Antonio, San Antonio, Texas, USA*

^z*Institute of Virology, Glasgow, UK*

^{aa}*Applied Morphology Research Centre, Department of Physiology, Faculty of Health Sciences, University of Pretoria, Arcadia, South Africa*

^{bb}*Helsinki University Hospital and University of Helsinki; University of Oulu, Centre of Life Course Health Research, Oulu, Finland*

^{cc}*Division of Old Age Psychiatry, Brighton and Sussex Medical School, Brighton, UK*

^{dd}*St Mary's Hospital, Imperial College London, London, UK*

^{ee}*Departments of Immunology and Microbiology, Internal Medicine (Rheumatology), and Ophthalmology, Wayne State University School of Medicine, Detroit, Michigan, USA*

Accepted 9 February 2016

We are researchers and clinicians working on Alzheimer's disease (AD) or related topics, and we write to express our concern that one particular aspect of the disease has been neglected, even though treatment based on it might slow or arrest AD progression. We refer to the many studies, mainly on humans, implicating specific microbes in the elderly brain, notably herpes simplex virus type 1 (HSV1), *Chlamydia pneumoniae*, and several types of spirochaete, in the etiology of AD [1–4]. Fungal infection of AD brain [5, 6] has also been described, as well as abnormal microbiota in AD patient blood [7]. The first observations of HSV1 in AD brain were reported almost three decades ago [8]. The ever-increasing number of these studies (now about 100 on HSV1 alone) warrants re-evaluation of the infection and AD concept.

AD is associated with neuronal loss and progressive synaptic dysfunction, accompanied by the deposition of amyloid- β (A β) peptide, a cleavage product of the amyloid- β protein precursor (A β PP), and abnormal forms of tau protein, markers that have been used as diagnostic criteria for the disease [9, 10]. These constitute the hallmarks of AD, but whether they are causes of AD or consequences is unknown. We suggest that these are indicators of an infectious etiology. In the case of AD, it is often not realized that microbes can cause chronic as well as acute diseases; that some microbes can remain latent in the body with the potential for reactivation, the effects of which might occur years after initial infection; and that people can be infected but not necessarily

affected, such that 'controls', even if infected, are asymptomatic [2].

EVIDENCE FOR AN INFECTIOUS/IMMUNE COMPONENT

- (i) Viruses and other microbes are present in the brain of most elderly people [11–13]. Although usually dormant, reactivation can occur after stress and immunosuppression; for example, HSV1 DNA is amplified in the brain of immunosuppressed patients [14].
- (ii) Herpes simplex encephalitis (HSE) produces damage in localized regions of the CNS related to the limbic system, which are associated with memory, cognitive and affective processes [15], as well as personality (the same as those affected in AD).
- (iii) In brain of AD patients, pathogen signatures (e.g., HSV1 DNA) specifically colocalize with AD pathology [13, 16, 17].
- (iv) HSV infection, as revealed by seropositivity, is significantly associated with development of AD [18–21].
- (v) AD has long been known to have a prominent inflammatory component characteristic of infection (reviewed in [22, 23]).
- (vi) Polymorphisms in the apolipoprotein E gene, *APOE*, that modulate immune function and susceptibility to infectious disease [24], also govern AD risk (reviewed in [25, 26]).

Genome-wide association studies reveal that other immune system components, including virus receptor genes, are further AD risk factors [27–32].

- (vii) Features of AD pathology are transmissible by inoculation of AD brain to primates [33, 34] and mice [35, 36].

EVIDENCE FOR CAUSATION

- (i) In humans, brain infection (e.g., by HIV, herpesvirus, measles) is known to be associated with AD-like pathology [37–42]. Historical evidence shows that the clinical and pathological hallmarks of AD occur also in syphilitic dementia, caused by a spirochaete [4].
- (ii) In mice and in cell culture, A β deposition and tau abnormalities typical of AD are observed after infection with HSV1 [43–52] or bacteria [16, 53–55]; a direct interaction between A β PP and HSV1 has been reported [56]. Antivirals, including acyclovir, *in vitro* block HSV1-induced A β and tau pathology [57].
- (iii) Olfactory dysfunction is an early symptom of AD [58]. The olfactory nerve, which leads to the lateral entorhinal cortex, the initial site from where characteristic AD pathology subsequently spreads through the brain [59, 60], is a likely portal of entry of HSV1 [61] and other viruses [62], as well as *Chlamydia pneumoniae*, into the brain [63], implicating such agents in damage to this region. Further, brainstem areas that harbor latent HSV directly irrigate these brain regions: brainstem virus reactivation would thus disrupt the same tissues as those affected in AD [64].

GROWING EVIDENCE FOR MECHANISM: ROLE OF A β

- (i) The gene encoding cholesterol 25-hydroxylase (CH25H) is selectively upregulated by virus infection, and its enzymatic product (25-hydroxycholesterol, 25OHC) induces innate antiviral immunity [65, 66].
- (ii) Polymorphisms in human *CH25H* govern both AD susceptibility and A β deposition [67], arguing that A β induction is likely to be among the targets of 25OHC, providing a potential mechanistic link between infection and A β production [68].

(iii) A β is an antimicrobial peptide with potent activity against multiple bacteria and yeast [69]. A β also has antiviral activity [70–72].

(iv) Another antimicrobial peptide (β -defensin 1) is upregulated in AD brain [73].

Regarding HSV1, about 100 publications by many groups indicate directly or indirectly that this virus is a major factor in the disease. They include studies suggesting that the virus confers risk of the disease when present in brain of carriers of the $\epsilon 4$ allele of *APOE* [74], an established susceptibility factor for AD (*APOE* $\epsilon 4$ determines susceptibility in several disorders of infectious origin [75], including herpes labialis, caused usually by HSV1). The only opposing reports, two not detecting HSV1 DNA in elderly brains and another not finding an HSV1–*APOE* association, were published over a decade ago [76–78]. However, despite all the supportive evidence, the topic is often dismissed as ‘controversial’. One recalls the widespread opposition initially to data showing that viruses cause some types of cancer, and that a bacterium causes stomach ulcers.

In summary, we propose that infectious agents, including HSV1, *Chlamydia pneumoniae*, and spirochetes, reach the CNS and remain there in latent form. These agents can undergo reactivation in the brain during aging, as the immune system declines, and during different types of stress (which similarly reactivate HSV1 in the periphery). The consequent neuronal damage—caused by direct viral action and by virus-induced inflammation—occurs recurrently, leading to (or acting as a cofactor for) progressive synaptic dysfunction, neuronal loss, and ultimately AD. Such damage includes the induction of A β which, initially, appears to be only a defense mechanism.

AD causes great emotional and physical harm to sufferers and their carers, as well as having enormously damaging economic consequences. Given the failure of the 413 trials of other types of therapy for AD carried out in the period 2002–2012 [79], antiviral/antimicrobial treatment of AD patients, notably those who are *APOE* $\epsilon 4$ carriers, could rectify the ‘no drug works’ impasse. We propose that further research on the role of infectious agents in AD causation, including prospective trials of antimicrobial therapy, is now justified.

DISCLOSURE STATEMENT

Authors’ disclosures available online (<http://j-alz.com/manuscript-disclosures/16-0152>).

REFERENCES

- [1] De Chiara G, Marcocci ME, Sgarbanti R, Civitelli L, Ripoli C, Piacentini R, Garaci E, Grassi C, Palamara AT (2012) Infectious agents and neurodegeneration. *Mol Neurobiol* **46**, 614-638.
- [2] Itzhaki RF (2014) Herpes simplex virus type 1 and Alzheimer's disease: Increasing evidence for a major role of the virus. *Front Aging Neurosci* **6**, 202.
- [3] Balin BJ, Hudson AP (2014) Etiology and pathogenesis of late-onset Alzheimer's disease. *Curr Allergy Asthma Rep* **14**, 417.
- [4] Miklossy J (2015) Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease. *Front Aging Neurosci* **7**, 46.
- [5] Alonso R, Pisa D, Marina AI, Morato E, Rabano A, Carrasco L (2014) Fungal infection in patients with Alzheimer's disease. *J Alzheimers Dis* **41**, 301-311.
- [6] Pisa D, Alonso R, Rabano A, Rodal I, Carrasco L (2015) Different brain regions are infected with fungi in Alzheimer's disease. *Sci Rep* **5**, 15015.
- [7] Potgieter M, Bester J, Kell DB, Pretorius E (2015) The dormant blood microbiome in chronic, inflammatory diseases. *FEMS Microbiol Rev* **39**, 567-591.
- [8] Jamieson GA, Maitland NJ, Wilcock GK, Craske J, Itzhaki RF (1991) Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *J Med Virol* **33**, 224-227.
- [9] Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van BG, Berg L (1991) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* **41**, 479-486.
- [10] Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)* **82**, 239-259.
- [11] Jamieson GA, Maitland NJ, Wilcock GK, Craske J, Itzhaki RF (1991) Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *J Med Virol* **33**, 224-227.
- [12] Miklossy J (1993) Alzheimer's disease – a spirochetosis? *Neuroreport* **4**, 841-848.
- [13] Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP (1998) Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. *Med Microbiol Immunol* **187**, 23-42.
- [14] Saldanha J, Sutton RN, Gannicliffe A, Farragher B, Itzhaki RF (1986) Detection of HSV1 DNA by in situ hybridisation in human brain after immunosuppression. *J Neurol Neurosurg Psychiatry* **49**, 613-619.
- [15] Roos KL (2014) Encephalitis. *Handb Clin Neurol* **121**, 1377-1381.
- [16] Miklossy J, Khalili K, Gern L, Ericson RL, Darekar P, Bolle L, Hurlimann J, Paster BJ (2004) Borrelia burgdorferi persists in the brain in chronic lyme neuroborreliosis and may be associated with Alzheimer disease. *J Alzheimers Dis* **6**, 639-649.
- [17] Wozniak MA, Mee AP, Itzhaki RF (2009) Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. *J Pathol* **217**, 131-138.
- [18] Letenneur L, Peres K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, Orgogozo JM, Gauthier S, Dartigues JF (2008) Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: A population-based cohort study. *PLoS One* **3**, e3637.
- [19] Mancuso R, Baglio F, Cabinio M, Calabrese E, Hernis A, Nemni R, Clerici M (2014) Titers of herpes simplex virus type 1 antibodies positively correlate with grey matter volumes in Alzheimer's disease. *J Alzheimers Dis* **38**, 741-745.
- [20] Lövheim H, Gilthorpe J, Johansson A, Eriksson S, Hallmans G, Elgh F (2015) Herpes simplex infection and the risk of Alzheimer's disease: A nested case-control study. *Alzheimers Dement* **11**, 587-592.
- [21] Lövheim H, Gilthorpe J, Adolfsson R, Nilsson LG, Elgh F (2015) Reactivated herpes simplex infection increases the risk of Alzheimer's disease. *Alzheimers Dement* **11**, 593-599.
- [22] Wyss-Coray T, Rogers J (2012) Inflammation in Alzheimer disease – a brief review of the basic science and clinical literature. *Cold Spring Harb Perspect Med* **2**, a006346.
- [23] Stefaniak J, O'Brien J (2015) Imaging of neuroinflammation in dementia: A review. *J Neurol Neurosurg Psychiatry* **87**, 21-28.
- [24] Mahley RW, Weisgraber KH, Huang Y (2009) Apolipoprotein E: Structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *J Lipid Res* **50**(Suppl), S183-S188.
- [25] Verghese PB, Castellano JM, Holtzman DM (2011) Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurol* **10**, 241-252.
- [26] Yu JT, Tan L, Hardy J (2014) Apolipoprotein E in Alzheimer's disease: An update. *Annu Rev Neurosci* **37**, 79-100.
- [27] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De DP, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanche H, Dartigues JF, Tzourio C, Gut I, Van BC, Alperovitch A, Lathrop M, Amouyel P (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* **41**, 1094-1099.
- [28] Porcellini E, Carbone I, Ianni M, Licastro F (2010) Alzheimer's disease gene signature says: Beware of brain viral infections. *Immun Ageing* **7**, 16.
- [29] Carter CJ (2010) APP, APOE, complement receptor 1, clusterin and PICALM and their involvement in the herpes simplex life cycle. *Neurosci Lett* **483**, 96-100.
- [30] Lambert JC, Zelenika D, Hiltunen M, Chouraki V, Combarros O, Bullido MJ, Tognoni G, Fievet N, Boland A, Arosio B, Coto E, Del ZM, Mateo I, Frank-Garcia A, Helisalmi S, Porcellini E, Pilotto A, Forti P, Ferri R, Delepine M, Scarpini E, Siciliano G, Solfrizzi V, Sorbi S, Spalletta G, Ravaglia G, Valdivieso F, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Licastro F, Lathrop M, Soininen H, Amouyel P (2011) Evidence of the association of BIN1 and PICALM with the AD risk in contrasting European populations. *Neurobiol Aging* **32**, 756.e11-e15.
- [31] Licastro F, Carbone I, Ianni M, Porcellini E (2011) Gene signature in Alzheimer's disease and environmental factors: The virus chronicle. *J Alzheimers Dis* **27**, 809-817.
- [32] Carter CJ (2013) Susceptibility genes are enriched in those of the herpes simplex virus 1/host interactome in psychiatric and neurological disorders. *Pathog Dis* **69**, 240-261.

- [33] Baker HF, Ridley RM, Duchon LW, Crow TJ, Bruton CJ (1994) Induction of beta (A4)-amyloid in primates by injection of Alzheimer's disease brain homogenate. Comparison with transmission of spongiform encephalopathy. *Mol Neurobiol* **8**, 25-39.
- [34] Ridley RM, Baker HF, Windle CP, Cummings RM (2006) Very long term studies of the seeding of beta-amyloidosis in primates. *J Neural Transm* **113**, 1243-1251.
- [35] Kane MD, Lipinski WJ, Callahan MJ, Bian F, Durham RA, Schwarz RD, Roher AE, Walker LC (2000) Evidence for seeding of beta-amyloid by intracerebral infusion of Alzheimer brain extracts in beta-amyloid precursor protein-transgenic mice. *J Neurosci* **20**, 3606-3611.
- [36] Meyer-Luehmann M, Coomaraswamy J, Bolmont T, Kaeser S, Schaefer C, Kilger E, Neuenschwander A, Abramowski D, Frey P, Jaton AL, Vigouret JM, Paganetti P, Walsh DM, Mathews PM, Ghiso J, Staufenbiel M, Walker LC, Jucker M (2006) Exogenous induction of cerebral beta-amyloidogenesis is governed by agent and host. *Science* **313**, 1781-1784.
- [37] Stanley LC, Mrak RE, Woody RC, Perrot LJ, Zhang S, Marshak DR, Nelson SJ, Griffin WS (1994) Glial cytokines as neuropathogenic factors in HIV infection: Pathogenic similarities to Alzheimer's disease. *J Neuropathol Exp Neurol* **53**, 231-238.
- [38] Esiri MM, Biddolph SC, Morris CS (1998) Prevalence of Alzheimer plaques in AIDS. *J Neurol Neurosurg Psychiatry* **65**, 29-33.
- [39] Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL (2005) Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS* **19**, 407-411.
- [40] Bearer EL, Woltjer R, Donahue JE, Kilpatrick K (2013) Herpes encephalitis and Abeta plaques. *FASEB J* **27**, 873-16.
- [41] Smith DB, Simmonds P, Bell JE (2014) Brain viral burden, neuroinflammation and neurodegeneration in HAART-treated HIV positive injecting drug users. *J Neurovirol* **20**, 28-38.
- [42] McQuaid S, Allen IV, McMahon J, Kirk J (1994) Association of measles virus with neurofibrillary tangles in subacute sclerosing panencephalitis: A combined in situ hybridization and immunocytochemical investigation. *Neuropathol Appl Neurobiol* **20**, 103-110.
- [43] Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB (2007) Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. *Neurosci Lett* **429**, 95-100.
- [44] Wozniak MA, Frost AL, Itzhaki RF (2009) Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. *J Alzheimers Dis* **16**, 341-350.
- [45] Zambrano A, Solis L, Salvadores N, Cortes M, Lerchundi R, Oth C (2008) Neuronal cytoskeletal dynamic modification and neurodegeneration induced by infection with herpes simplex virus type 1. *J Alzheimers Dis* **14**, 259-269.
- [46] De Chiara G, Marcocci ME, Civitelli L, Argnani R, Piacentini R, Ripoli C, Manservigi R, Grassi C, Garaci E, Palamara AT (2010) APP processing induced by herpes simplex virus type 1 (HSV-1) yields several APP fragments in human and rat neuronal cells. *PLoS One* **5**, e13989.
- [47] Lerchundi R, Neira R, Valdivia S, Vio K, Concha MI, Zambrano A, Oth C (2011) Tau cleavage at D421 by caspase-3 is induced in neurons and astrocytes infected with herpes simplex virus type 1. *J Alzheimers Dis* **23**, 513-520.
- [48] Ill-Raga G, Palomer E, Wozniak MA, Ramos-Fernandez E, Bosch-Morato M, Tajés M, Guix FX, Galan JJ, Clarimon J, Antunez C, Real LM, Boada M, Itzhaki RF, Fandos C, Munoz FJ (2011) Activation of PKR causes amyloid beta-peptide accumulation via de-repression of BACE1 expression. *PLoS One* **6**, e21456.
- [49] Santana S, Recuero M, Bullido MJ, Valdivieso F, Aldudo J (2012) Herpes simplex virus type I induces the accumulation of intracellular beta-amyloid in autophagic compartments and the inhibition of the non-amyloidogenic pathway in human neuroblastoma cells. *Neurobiol Aging* **33**, 430-433.
- [50] Martin C, Aguila B, Araya P, Vio K, Valdivia S, Zambrano A, Concha MI, Oth C (2014) Inflammatory and neurodegeneration markers during asymptomatic HSV-1 reactivation. *J Alzheimers Dis* **39**, 849-859.
- [51] Civitelli L, Marcocci ME, Celestino I, Piacentini R, Garaci E, Grassi C, De Chiara G, Palamara AT (2015) Herpes simplex virus type 1 infection in neurons leads to production and nuclear localization of APP intracellular domain (AICD): Implications for Alzheimer's disease pathogenesis. *J Neurovirol* **21**, 480-490.
- [52] Piacentini R, Li Puma DD, Ripoli C, Marcocci ME, De Chiara G, Garaci E, Palamara AT, Grassi C (2015) Herpes simplex virus type-1 infection induces synaptic dysfunction in cultured cortical neurons via GSK-3 activation and intraneuronal amyloid-beta protein accumulation. *Sci Rep* **5**, 15444.
- [53] Little CS, Hammond CJ, MacIntyre A, Balin BJ, Appelt DM (2004) Chlamydia pneumoniae induces Alzheimer-like amyloid plaques in brains of BALB/c mice. *Neurobiol Aging* **25**, 419-429.
- [54] Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, Reiss K, Darbinian N, Darekar P, Mihaly L, Khalili K (2006) Beta-amyloid deposition and Alzheimer's type changes induced by Borrelia spirochetes. *Neurobiol Aging* **27**, 228-236.
- [55] Boelen E, Stassen FR, van der Ven AJ, Lemmens MA, Steinbusch HP, Bruggeman CA, Schmitz C, Steinbusch HW (2007) Detection of amyloid beta aggregates in the brain of BALB/c mice after Chlamydia pneumoniae infection. *Acta Neuropathol* **114**, 255-261.
- [56] Cheng SB, Ferland P, Webster P, Bearer EL (2011) Herpes simplex virus dances with amyloid precursor protein while exiting the cell. *PLoS One* **6**, e17966.
- [57] Wozniak MA, Frost AL, Preston CM, Itzhaki RF (2011) Antivirals reduce the formation of key Alzheimer's disease molecules in cell cultures acutely infected with herpes simplex virus type 1. *PLoS One* **6**, e25152.
- [58] Velayudhan L, Gasper A, Pritchard M, Baillon S, Messer C, Proitsi P (2015) Pattern of smell identification impairment in Alzheimer's disease. *J Alzheimers Dis* **46**, 381-387.
- [59] Braak H, Braak E, Bohl J (1993) Staging of Alzheimer-related cortical destruction. *Eur Neurol* **33**, 403-408.
- [60] Ball MJ, Lukiw WJ, Kammerman EM, Hill JM (2013) Intracerebral propagation of Alzheimer's disease: Strengthening evidence of a herpes simplex virus etiology. *Alzheimers Dement* **9**, 169-175.
- [61] Mori I, Nishiyama Y, Yokochi T, Kimura Y (2005) Olfactory transmission of neurotropic viruses. *J Neurovirol* **11**, 129-137.
- [62] Gillet L, Frederico B, Stevenson PG (2015) Host entry by gamma-herpesviruses – lessons from animal viruses? *Curr Opin Virol* **15**, 34-40.

- [63] Little CS, Bowe A, Lin R, Litsky J, Fogel RM, Balin BJ, Fresa-Dillon KL (2005) Age alterations in extent and severity of experimental intranasal infection with *Chlamydomypha pneumoniae* in BALB/c mice. *Infect Immun* **73**, 1723-1734.
- [64] Braak H, Del Tredici K (2015) The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain* **138**, 2814-2833.
- [65] Blanc M, Hsieh WY, Robertson KA, Kropp KA, Forster T, Shui G, Lacaze P, Watterson S, Griffiths SJ, Spann NJ, Meljon A, Talbot S, Krishnan K, Covey DF, Wenk MR, Craigmiles M, Ruzsics Z, Haas J, Angulo A, Griffiths WJ, Glass CK, Wang Y, Ghazal P (2013) The transcription factor STAT-1 couples macrophage synthesis of 25-hydroxycholesterol to the interferon antiviral response. *Immunity* **38**, 106-118.
- [66] Liu SY, Aliyari R, Chikere K, Li G, Marsden MD, Smith JK, Pernet O, Guo H, Nusbaum R, Zack JA, Freiberg AN, Su L, Lee B, Cheng G (2013) Interferon-inducible cholesterol-25-hydroxylase broadly inhibits viral entry by production of 25-hydroxycholesterol. *Immunity* **38**, 92-105.
- [67] Papassotiropoulos A, Lambert JC, Wavrant-De Vrieze F, Wollmer MA, von der KH, Streffer JR, Maddalena A, Huynh KD, Wolleb S, Lutjohann D, Schneider B, Thal DR, Grimaldi LM, Tzolaki M, Kapaki E, Ravid R, Konietzko U, Hegi T, Pasch T, Jung H, Braak H, Amouyel P, Rogaeve EI, Hardy J, Hock C, Nitsch RM (2005) Cholesterol 25-hydroxylase on chromosome 10q is a susceptibility gene for sporadic Alzheimer's disease. *Neurodegener Dis* **2**, 233-241.
- [68] Lathe R, Saponova S, Kotelevtsev Y (2014) Atherosclerosis and Alzheimer – diseases with a common cause? Inflammation, oxysterols, vasculature. *BMC Geriatrics* **14**, 36.
- [69] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, Moir RD (2010) The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* **5**, e9505.
- [70] White MR, Kandel R, Tripathi S, Condon D, Qi L, Taubenberger J, Hartshorn KL (2014) Alzheimer's associated beta-amyloid protein inhibits influenza A virus and modulates viral interactions with phagocytes. *PLoS One* **9**, e101364.
- [71] Bourgade K, Garneau H, Giroux G, Le Page AY, Bocti C, Dupuis G, Frost EH, Fulop T Jr (2015) Beta-amyloid peptides display protective activity against the human Alzheimer's disease-associated herpes simplex virus-1. *Biogerontology* **16**, 85-98.
- [72] Bourgade K, Le PA, Bocti C, Witkowski JM, Dupuis G, Frost EH, Fulop T Jr (2016) Protective effect of amyloid-beta peptides against herpes simplex virus-1 infection in a neuronal cell culture model. *J Alzheimers Dis* **50**, 1227-1241.
- [73] Williams WM, Torres S, Siedlak SL, Castellani RJ, Perry G, Smith MA, Zhu X (2013) Antimicrobial peptide beta-defensin-1 expression is upregulated in Alzheimer's brain. *J Neuroinflammation* **10**, 127.
- [74] Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA (1997) Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* **349**, 241-244.
- [75] Itzhaki RF, Wozniak MA (2009) Apolipoprotein E: Microbial friend or foe? In *Apoprotein Research*, Penfield LR, Nelson RT, Eds, Nova Biomedical, New York, pp. 99-112.
- [76] Marques AR, Straus SE, Fahle G, Weir S, Csako G, Fischer SH (2001) Lack of association between HSV-1 DNA in the brain, Alzheimer's disease and apolipoprotein E4. *J Neurovirol* **7**, 82-83.
- [77] Hemling N, Roytta M, Rinne J, Pollanen P, Broberg E, Tapio V, Vahlberg T, Hukkanen V (2003) Herpesviruses in brains in Alzheimer's and Parkinson's diseases. *Ann Neurol* **54**, 267-271.
- [78] Beffert U, Bertrand P, Champagne D, Gauthier S, Poirier J (1998) HSV-1 in brain and risk of Alzheimer's disease. *Lancet* **351**, 1330-1331.
- [79] Cummings JL, Morstorf T, Zhong K (2014) Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimers Res Ther* **6**, 37.