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Are Microbes Implicated in the Etiology of Alzheimer's Disease?

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Abstract

Humans live in an evolutionary association with the plethora of microbes that reside within them. Since birth, humans and microbes are engaged in a state of long-term symbiosis; both entities benefit from it. Although microbial communities are found in almost every niche of the human body, the gut microbiome attracts all the attention of the scientific research. It's unfamiliar the fact that many forms of neurodegenerative disorders are now being related with gut dysbiotic states (disruption of a balanced composition of the gut microbiome), the microbes' detrimental activities and gut-derived metabolites. The complex interplay between the host and its indigenous bacteria is a topic of great interest; research though is still in its infancy. Alzheimer's disease (AD), the most common cause of dementia, involves the accumulation and self-propagation of Aβ amyloids, brain aggregates that display prion-like properties. Although heavily studied, the true etiologic mechanisms of the disease remain obscure. Recent publications, however, have demonstrated a modulatory influence of the gut microbes on the central nervous system and have proposed a few pathogenetic models for many neurodegenerative diseases. In this review we will be probing into the association between the microbes and the AD.

Keywords: *Gut microbiome; Microbiota; Alzheimer's disease; Aβ amyloid; Infection*

Abbreviations: Aβ: amyloid β peptide; AD: Alzheimer's disease; APP mice: animals with the human Amyloid beta Precursor Protein transgene; CNS: Central Nervous System; GF: germ-free; GI: gastrointestinal; HSV-1: Herpes Simplex Virus 1; LPS: Lipopolysaccharide; PSEN1: human gene of the presenilin 1, subunit of the γ-secretase complex that processes the amyloid precursor protein

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Introduction

A Brief Introduction to Our Microbiome

A prosperous, symbiotic relationship between humans and their microbes has been forming since time immemorial. Scientific progress has shown us that the human being isn't a sole organism but a living ecosystem with a ratio of indigenous cells to microbes approximately 1:1 [1]. Microbes inhabit every niche of the human body; yet the ecosystem with the most complexity lies in the gut. The gut microbiome, by its very definition, represents the collective genome material of all microbes that inhabit our intestines [2]. It is considered as an essential component of the host's physiology; it holds tremendous capacities since it is able to affect the host in terms of health and disease.

The extensive surface of the GI tract serves as a communication window between the body and the environment. Microbes dwelling in it are not mere bystanders; they are engaged in a reciprocal connection with the host [3]. The vast variety of its biochemical activities, the communication between its parts (the microbes) and the human body cells, and the entanglement of the microbiome in human health and development have led to its description as ''a forgotten organ''[4].

It's intriguing the fact that the gut microbes are engaged not only in local events, but may influence remote tissues and organs as well. One example of this is the ability to guide the maturation and functionality of the host's immune system [5]. GF mice (germ free mice, sterile animals which are born and raised within germ free isolators) show extensive defects at structural levels of the immune system (defective lymphoid tissue of the gut, fewer and smaller Peyer's patches and impaired development of isolated lymphoid follicles), as well as at cellular levels including reduced presence of local immune cells and defects in antibody production [6]. These flaws seem to be restored to normal levels following the introduction of gut bacteria. This observation suggests that commensal microbes are required for programming and maturation of the immune system.

Alterations in the composition of the gut microbiota, a term called dysbiosis, has emerged as a major risk factor for many local diseases in the gut such as colorectal cancer [7], inflammatory bowel disease [8] and irritable bowel syndrome [9]. Emerging evidence, however, point to the involvement of the gut microbes in the pathogenesis of diseases in remote organs, notably the CNS. Via the gut-brain axis, a multichannel system of pathways connecting the two organs, microbes can affect mood, behavior and cognition and have been associated with the pathogenesis of many neuropsychological disorders [10].

How microbes communicate with the brain – the Gut Brain axis

The Gut-Brain axis is a concept of connection between the two major systems, the gut and the brain. It consists of a range of multichannel pathways that integrate and relay the brain signals to the intestines and vice versa [11]. For years it was believed that the communication between the gut and the brain was one-directional, top-down, from brain to the intestines. However, emerging evidence suggests that the axis be bidirectional, mediating the fundamental functions of these two complex systems [10-12]. Critical mediators of this communication include the neural avenue (vagal afferent neurons, spinal sympathetic neurons) [11,13], immune pathways [11,12], the regulation of the Hypothalamic-Pituitary-Adrenal axis [12,14,15] and metabolic mechanisms, primarily microbial products and their metabolites [14,15].

With the unanticipated importance of the gut microbiome in CNS development [14] and the rising number of neuroimmune [16] and neuropsychiatric diseases [10] that are now being related with gut dysbiotic states, a new concept of microbiome-gut-brain axis has emerged, underlining the importance of the microbes on CNS physiology.

Alzheimer's disease and microbes

AD is a chronic neurodegenerative disorder that affects primarily people over 65 years of age, although 4–5% of cases may begin earlier [17]. Brain findings in this disease involve degenerative changes such as the loss of neurons and synapses in selected brain regions, including the temporal and parietal lobes and restricted regions within the frontal cortex and cingulate gyrus [18]. Key pathological markers of the disease is the extracellular accumulation of amyloid plaques (Aβ amyloid) and the presence of neurofibrillary tangles, hyper phosphorylated tau proteins that are mostly intracellular, but may be found outside the cells as ghost tangles (when the neuron has died) [19,20].

AD comes with great emotional and physical burden to sufferers and their carriers. As the disease progresses, cognitive decline becomes more prominent. Individuals eventually lose the ability to communicate or respond to their environment, and require complete assistance with activities of daily living [21]. Currently there is no cure, only treatment that alleviates the symptoms of the disease. A crucial problem of AD research is that despite the number of pathogenetic models about the disease that have been developed, none of them is able to fully explain the origin of the histopathological findings, neither the true etiologic factor of the disease.

Recently, it has been suggested that changes in the population of gut microbes may be an environmental risk factor for many diseases [22]. Given that an association between microbes and the brain has been well established [14, 15], it has been proposed that they may be the missing link that could trigger or even cause the disease in predisposed individuals. Mounting evidence support this notion. In this review we will be studying the pathogenesis of AD through the prism of microbial interaction with the brain.

Amyloid Beta in Alzheimer's disease

The physiological role of amyloid-beta peptide

The hallmark of AD is the accumulation and deposition of misfolded proteins in the brain [23]. These proteins adopt a polymer structure with biophysical properties resembling prion disease; they can transmit between hosts and from one brain region to another [24]. This mechanism has been heavily studied, but the primary event that leads to the formation of the first folded molecule remains obscure [23]. Many scientists in this field have suggested that the initial event of misfolding may emerge randomly, but the hypothesis that the first amyloid in the brain is instigated by other environmental amyloids is becoming more appealing.

The Amyloid beta (Aβ), a peptide crucially involved in AD, has been postulated to be a part of the innate immunity and its physiologic role is to form cocoon-like structures in order to entrap pathogenic substances and isolate them from the surrounding brain [25]. The polymerization of Aβ is an essential property that is necessary for the antimicrobial activities of the peptide. Kumar D., *et al*. [26] showed that Aβ expression protects against fungal or bacterial infections in mouse and cell culture models of AD. When transgenic mice (animals with genes expressing Aβ in their brain at high levels but lack the features of Neuroinflammation) where infected with Salmonella Typhimurium in their brains, they found accelerated Aβ deposition that inhibits infection.

In another study, mice infected with Chlamydia pneumoniae via the intranasal route exhibited amyloid deposits in their brains, with the number and the size of these deposits increasing as the infection progressed [27]. These aggregations resembled the plaques found in AD. Aβ amyloid has also antiviral activity. In vitro cultures of neoplasmatic brain cells secrete Aβ in response to HSV-1 infection [28]. Exogenous administration of HSV1 and Aβ induced the production of pro-inflammatory cytokines. Transfer experiments of media in the same study showed that Aβ production inhibits secondary replication of the virus.

Zhao Y., *et al*. [29], provided evidence that LPS of the gram-negative *E. Coli* (a microbe abundant in the GI tract) is found in higher concentrations (up to 26-fold) in neocortical and hippocampal extracts from human AD brain; regions that develop the most profound neuropathology. LPS in known to attract immune cells, activates microglial cells and induces inflammation, leading to loss of synapses and cell death [30]. Zhan X., *et al*. [31] also detected *E.coli* proteins and LPS in greater proportions in AD human brains as compared with control. These bacterial products colocalized with the Aβ in the amyloid plaques. The intriguing fact is how bacterial LPS managed to translocate through at least two major barriers, the GI tract and the BBB in order to access the CNS compartment. Leblhuber F., *et al*. [32] detected increased concentrations of fecal calprotectin in the blood of AD patients. This biomarker indicates a disruption of intestinal barrier function, an important step that facilitates the translocation of bacteria and LPS across the epithelial barrier, gaining access to the periphery.

Can an infection be the initial event of AD? Are the Aβ plaques and the neurofibrillary tangles an attempt of the host's immune system to confine the pathogenic factor? This hypothesis, though peculiar, is not unfounded; there is evidence that suggests a chronic infection as an etiology of many neurodegenerative disorders. Among the most studied microorganisms, HSV attracts all the attention of the scientific community.

Amyloids in the microbial kingdom

Apart from the immune cells, microbes are also capable of producing amyloids. Bacteria in our gut are known to secrete proteins that share structural and biophysical properties with amyloids. Species of *E.coli*, Streptococcus, Salmonella, Pseudomonas, Citrobacter, and Bacillus excrete extracellular protein fibrils that may assemble into formations resembling amyloids [33,34]. Lundmark K., *et al.* [35] found that these protein fibrils exert amyloid-accelerating properties in the murine experimental AA amyloidosis, suggesting that

the gut environment may be an important risk factor in amyloidogenesis. Another access to the brain is offered by the olfactory bulb. Oral and nasal bacteria may also excrete amyloid proteins. Oli MW., *et al*. [36] showed that amyloid is present in human dental plaque. Adhesin P1 produced by Streptococcus mutans (a bacterium commonly found in human oral cavity) is an amyloid-forming protein.

Another pathogenetic model emerges. Bacterial fibrlis may act as a template for the formation of proteins with amyloidic properties. These amyloids may cross-seed amyloid formation in vivo by neuronal proteins [37]. The propagation of these proteins to the CNS may involve the Gut-Brain axis in a manner similar to that of prion disease. The axis may act as a portal for the misfolded proteins to gain access to the brain tissue. This hypothesis sheds light on the pathogenesis of bovine spongiform encephalopathy [38] and Kuru disease [39], which are caused by the ingestion of abnormally folded proteins (prions).

Studies have proposed that bacteria population in the gut may be an important risk factor in the formation of Aβ in the brain. Harach., *et al*. [40] found that APPPS1 transgenic mice bear a remarkable different gut microbiome as compared to non-transgenic wild-type mice. APPPS1 mice are animals that contain both APP and PSEN1 mutated human genes. In these mice, expression of the human APP transgene is approximately 3-fold higher than endogenous murine APP) [41] When they developed germ-free APP transgenic mice they found that cerebral Aβ amyloid accumulation was drastically reduced when compared to the conventionally raised APP mice. Subsequently, when they transferred the gut microbiota from the conventionally raised APP mice to germ-free APP mice, they found increased cerebral Aβ pathology. This effect was ''milder'' when colonization with microbes from wild-type mice occurred. This research indicates that the gut microbiota is involved in Ab deposits in the brain.

Immune system and Alzheimer's disease

Inflammatory response towards the brain amyloids dominates the pathogenesis of neurodegenerative disorders [23]. Interestingly, inflammatory changes in the brain seem to occur prior to the deposition of Aβ [42]. Local activation of the innate immune system in the gut may trigger or exacerbate the neuroinflammation. Immune cells trafficking through the body may be stimulated in the gut by bacterial antigens or metabolites and cast a systemic effect through the mechanism of molecular mimicry [43]. Misfolded proteins secreted by the gut bacteria may induce inflammatory response against their neural counterparts [37].

Responses involve TLR 2 and 1, CD14, iNOS and NFκB inflammatory pathways [37]. The same responses are found in the CNS upon recognition of misfolded Aβ [44]. We know that expression of CD14 on the surface of microglial cells is involved in Aβ clearance [45]. Chen SG., *et al*. [46] tested this idea on murine models. They exposed aged rats to *E.coli* producing the extracellular bacterial amyloid protein curli. The specimens displayed increased neuronal amyloid deposition in both gut and brain and a more prominent inflammatory response in comparison with rats exposed to mutant bacteria unable to produce the amyloid.

Neuroinflammation acts as a disease-promoting factor. The incessant formation and accumulation of Aβ deposits causes chronic activation of the immune system and disturbance of neuronal and microglial functions [23]. Microglia and astrocytes play a role in the progression of AD. Upon activation, these cells contribute to neuroinflammation, cell death and blood brain barrier dysfunction [47]. Activated microglia secrete pro-inflammatory cytokines such as IL-1, IL-6, TNF-a, and TGF-b [48].

Acute and chronic peripheral inflammations are correlated with cognitive decline in AD. Cattaneo A., *et al*. [49] detected an increase in the numbers of a pro-inflammatory and a concurrent reduction of anti-inflammatory microbes in elderly people with cognitive impairment and brain amyloidosis, pointing to a peripheral inflammatory state in these patients. Acute systemic inflammation is known to contribute to the exacerbation of neurodegeneration by activating microglial cells in the brain [50]. Villarán R., *et al*. have shown that inflammation in the colon of rats may worsen LPS-induced neuroinflammation in certain regions of the brain [51]. Even in rats with no LPS injected, inflammatory markers in the midbrain were prominent. In a study of Holmes C., *et al*. [50], it was shown that increased baseline levels of serum TNF-a were associated with a 4-fold increase in the rate of cognitive dysfunction over a 6-month period.

Brain infection in Alzheimer's disease

A great many studies, mainly on humans, implicate some infectious agents in the brain, notably herpes simplex virus type 1 (HSV1) [52], influenza virus [53], Chlamydia pneumonia [54], and several types of spirochaete [55], in the etiology of AD. Fungal infection of AD brain has also been described [56]. These microbes can remain latent in the body with the potential of reactivation. Pathogens interact with genetic and environmental factors to initiate brain inflammation, accumulation of Aβ and hyper phosphorylation of tau proteins, all of which are hallmarks of AD pathogenesis [57].

Accumulating evidence point to the significance of HSV infection in the pathogenesis of AD. Some authors propose that this virus may be the most common etiologic agent of AD [52]. There are some facts that point to this suggestion. First of all, infection with HSV is significantly associated with the development of AD as is revealed retrospectively by seropositivity of IgM and IgG antibodies [58]. In this study, IgM-positive patients showed a significant higher risk of developing AD, although no significant increased risk was observed in IgG-positive subjects (indicator of life-long infection) [58]. In another recent nationwide population-based study from Taiwan [59], it was shown that HSV-infected patients have an almost 3-fold increased risk of developing any type of dementia. They also found that anti-herpetic medication could lower the risk of developing dementia.

HSV DNA has been found in the brain of AD patients [57]. Wozniak MA., *et al*. showed that in vitro infection with HSV1 of cultured neuronal and glial cells resulted in accumulation of intracellular Aβ amyloid 1-40 and 1-42 and tau abnormalities [60]. In a later study, they discovered deposits of Aβ in mouse brain after they have been infected with HSV1 and also, HSV1-DNA by PCR in Aβ amyloid plaques [61].

HSV-1 DNA has been detected by PCR in olfactory bulb samples of the human brain [57,62]. Olfactory receptor neurons project to the entorhinal cortex (with the mediation of mitral cells) and then to amygdala and hippocampus [63]. It is known that the olfactory bulb and the entorhinal cortex demonstrate neurodegenerative pathology early in the development of AD [64]. The olfactory nerve is a likely portal of entry of HSV1.

Lastly, it is interesting the fact that HSV encephalitis may damage specific regions of the CNS related to the limbic system, the same system affected in AD [65]. Infections of the central nervous system, especially those characterized by a chronic progressive course, may produce multiple damage in infected and neighboring cells [52]. They also produce molecular hallmarks of neurodegeneration, such as deposition of protein aggregates, oxidative stress, deficient autophagic processes, synaptopathies and neuronal death [52].

It seems that some infectious agents can reach the CNS and remain there in a dormant state. Upon reactivation (the trigger is unknown) brain inflammation occurs leading to neuronal damage and loss, progressive synaptic dysfunction and eventually AD. Aβ is initially produced by the innate immune system. It has shown to have antimicrobial properties and may serve as a protective mechanism against the reactivated microbes [66]. As the disease progresses, the prion-like properties of the Aβ peptide become more significant in the pathogenesis of the disease; the accumulation and dissemination of these structures may worsen the cognitive function even in the absence of the primary cause [24].

Probiotics and Metabolites

Owing to the fact that the connection between microbes and brain disorders is now indubitable, a great interest aroused. Can altering the microenvironment of our gut microbes lead to changes in the bidirectional communication between the gut and the brain? And if so, is there any therapeutic value in this? Probiotics are live microorganisms intended to provide health benefits to the host when consumed in sufficient amounts [67]. The use of probiotics has been suggested that may possibly prevent or ameliorate AD symptoms.

In light of this fact, Kobayashi Y., *et al*. [68] showed that administration of bifidobacterium breve A1 to AD mice reversed cognitive impairment in a series of tests. Interestingly enough, non-viable components of the bacterium partially attenuated the cognitive

decline in AD mice. Further analysis of the brain of the involved mice revealed that the consumption of this strain reshaped gene expression in the hippocampus suppressing the immune-reactive and inflammation genes that are induced by Aβ.

Compellingly, the expression of bdnf, a gene with a crucial role in learning and memory function, was up regulated to normal level after the administration of B. breve A1. These findings illustrate the notion that probiotics confer beneficial effects not only in the gut, but also in the brain. Akbari., *et al*. [69] in a randomized, double blind clinical trial demonstrated that a 12-week administration of probiotics lead to an increase in cognitive function in patients with Alzheimer's disease, as was shown by the significant improvement in the mini mental state examination.

How do microbes confer a beneficial effect on the host? The gut microbiome, being a very complex and intricate system, comprises a vast array of metabolic pathways and a continuous communication with the host's cells. Among the numerous metabolites being produced by the microbiota population, Short-chain fatty acids (SCFAs) are the most studied of them. They originate from fibers and undigested carbohydrates from our diet in the colonic lumen as fermentation by-products [70]. They have substantial influence on the brain since they regulate the gut–brain axis and systemic immunity [12,14]. Butyrate, one of the SCFAs, is shown to have beneficial effects in the gut and systemic influences, including the brain [15]. Govindarajan N., *et al*. [71], found that treatment with sodium butyrate improved memory function in APPPS1 mice. Butyrate serves as histone deacetylase (HDAC) inhibitor.

The augmented memory function correlated with elevated hippocampal histone acetylation and elevated gene expression implicated in associative learning. Changes in the gut microbiota population may sufficiently improve cognitive function and thus, in the near future, probiotics may be an effective therapeutic measure in patients with AD. However, more clinical trials are required to truly determine their extent of efficacy in treating CNS disorders.

Conclusion

The human body consists of trillions of cells. Not until very recently we came to understand that it hosts an equivalent amount of foreign microbial cells that live in a symbiotic relationship with it. We have yet to unravel the precise nature of this relationship, but we do know that these microbes affect us in the most significant way, in terms of health and disease. In recent years, a link between microbes and brain disorders has started to emerge. Alzheimer's disease, the most common cause of dementia, puzzles the scientific community since the initial events of its pathogenesis remain recondite.

In this review we developed some of the most plausible hypotheses regarding the role of the microbial population in the development of AD. Microbes may promote the occurrence of AD either via CNS infection or via the production of foreign amyloids that induce the propagation and accumulation of similar structures in regions of the CNS in a prion-like manner. The precise mechanism by which this happens is far from elucidated. One thing is clear though: the current pathophysiology of AD warrants re-evaluation.

References

1. Sender Ron., *et al*. "Revised Estimates for the Number of Human and Bacteria Cells in the Body". *PLoS Biology* 14.8 (2016).
2. Joy Yang. "The Human Microbiome Project: Extending the definition of what constitutes a human". *Genome Advance NIH* (2012).
3. Marchesi Julian R., *et al*. "The gut microbiota and host health: a new clinical frontier". *Gut* 65.2 (2015): 330-339.
4. Lam Yan Y., *et al*. "Are the Gut Bacteria Telling Us to Eat or Not to Eat? Reviewing the Role of Gut Microbiota in the Etiology, Disease Progression and Treatment of Eating Disorders". *Nutrients* 9.6 (2017) 602.
5. Chang H Kim. "Immune regulation by microbiome metabolites". *Immunology* 154.2 (2018): 220-229.
6. June L Round and Sarkis K Mazmanian. "The gut microbiome shapes intestinal immune responses during health and disease". *Nature Reviews Immunology* 9.5 (2009): 313–323.
7. Dahmus Jessica D., *et al*. "The gut microbiome and colorectal cancer: a review of bacterial pathogenesis". *Journal of Gastrointestinal Oncology* 9.4 (2018): 769-777.

8. Linda Chia-Hui Yu. "Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis". *Journal of Biomedical Science* 25 (2018): 79.
9. Matthew J Bull and Nigel T Plummer. "Part 1: The Human Gut Microbiome in Health and Disease." *Integrative Medicine (Encinitas)* 13.6 (2014): 17-22.
10. Lefas Iraklis. "The intriguing role of the Gut Microbiome in the etiology and pathogenesis of Neuropsychiatric Disorders". *Dialogues in Clinical Neuroscience & Mental Health* 1.2 (2018).
11. Tillisch Kirsten. "The effects of gut microbiota on CNS function in humans". *Gut Microbes* 5.3 (2014): 404-410.
12. Zhu Xiqun., *et al*. "Microbiota-gut-brain axis and the central nervous system." *Oncotarget* 8.32 (2017): 53829-53838.
13. Yan Wang and Lloyd H. Kasper. "The role of microbiome in central nervous system disorders". *Brain, Behavior, and Immunity* 38 (2014): 1–12.
14. Rogers GB *et al*. "From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways". *Molecular Psychiatry* 21.6 (2016): 738-748.
15. Lerner Aaron., *et al*. "The Gut Microbiome Feelings of the Brain: A Perspective for Non-Microbiologists." *Microorganisms* 5.4 (2017): 66.
16. Dinan Timothy G and John F Cryan. "Microbes, Immunity, and Behavior: Psychoneuroimmunology Meets the Microbiome'' *Neuropsychopharmacology* 42.1 (2016): 178-192.
17. Mario F. Mendez. "Early-onset Alzheimer's Disease: Nonamnestic Subtypes and Type 2 AD". *Archives of Medical Research* 43.8 (2012): 677–685.
18. Gary L Wenk. "Neuropathologic changes in Alzheimer's disease'' *The Journal of Clinical Psychiatry* 64 (2003): 7-10.
19. Tiraboschi P., *et al*. "The importance of neuritic plaques and tangles to the development and evolution of AD". *Neurology* 62.11 (2004):1984-1989.
20. Bancher C. et al. "Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease". *Brain Research* 477.1-2 (1989): 90-99.
21. Hannah Nichols. "What are the stages of Alzheimer's disease?'' (2018).
22. Zhi Ying Kho and Sunil Kumal Lal. "The Human Gut Microbiome – A Potential Controller of Wellness and Disease". *Frontiers Microbiology* (2018).
23. Robert P Friedland and Matthew R Chapman. "The role of microbial amyloid in neurodegeneration" *PLoS Pathogens* 13.12 (2017): e1006654.
24. Lary C Walker., *et al*. "The Prion-Like Properties of Amyloid-b Assemblies: Implications for Alzheimer's disease". *Cold Spring Harbor Perspectives in Medicine* 6.7 (2016)
25. Holly M Brothers., *et al*. "The Physiological Roles of Amyloid-b Peptide Hint at New Ways to Treat Alzheimer's disease". *Frontiers in Aging Neuroscience* 10 (2018):118.
26. Deepak Kumar., *et al*. "Amyloid-β Peptide Protects against Microbial Infection in Mouse and Worm Models of Alzheimer's Disease". *Science Translational Medicine* 8.340 (2016): 340ra72.
27. Little CS., *et al*. "Chlamydia pneumoniae induces Alzheimer-like amyloid plaques in brains of BALB/c mice". *Neurobiology of Aging* 25.4 (2004):419-429.
28. Bourgade K., *et al*. "Protective Effect of Amyloid-β Peptides against Herpes Simplex Virus-1 Infection in a Neuronal Cell Culture Model". *Journal of Alzheimer's disease* 50.4 (2016): 1227-1241.
29. Zhao Yuhai., *et al*. "Secretory Products of the Human GI Tract Microbiome and Their Potential Impact on Alzheimer's disease (AD): Detection of Lipopolysaccharide (LPS) in AD Hippocampus". *Frontiers in Cellular and Infection Microbiology* 7 (2017): 318.
30. Jiayi Zhao., *et al*. "Neuroinflammation induced by lipopolysaccharide causes cognitive impairment in mice". *Scientific Reports* 9 (2019): 5790.
31. Xinhua Zhan., *et al*. "Gram-negative bacterial molecules associate with Alzheimer disease pathology". *Neurology* 87 (2016): 2324-2332.

32. Leblhuber Friedrich., *et al*. "Elevated fecal calprotectin in patients with Alzheimer's dementia indicates leaky gut". *Journal of Neural Transmission* 122 (2015): 1319-1322.
33. Matthew R. Chapman., *et al*. "Role of Escherichia coli Curli Operons in Directing Amyloid Fiber Formation". *Science* 295.5556 (2002): 851–855.
34. Yizhou Zhou., *et al*. "Promiscuous Cross-seeding between Bacterial Amyloids Promotes Interspecies Biofilms". *Journal of Biological Chemistry* 287.42 (2012): 35092–35103.
35. Lundmark Katarzyna., *et al*. "Protein fibrils in nature can enhance amyloid protein A amyloidosis in mice: Cross-seeding as a disease mechanism." *Proc Natl Acad Sci U S A*. (2005) Apr 26;102(17):6098-102.
36. Oli M W., *et al*. "Functional amyloid formation by Streptococcus mutans." *Microbiology* (Reading, England) (2012). vol. 158,Pt 12 2903-16.
37. Friedland Robert P. ''Mechanisms of Molecular Mimicry Involving the Microbiota in Neurodegeneration'' *Journal of Alzheimer's Disease* (2015). vol. 45, no. 2, pp. 349-362.
38. Cristina Casalone and James Hope. ''Atypical and classic bovine spongiform encephalopathy'' *Handbook of Clinical Neurology* (2018) Volume 153, Pages 121-134
39. Imran Muhammad and Saqib Mahmood. "An overview of human prion diseases." *Virology journal* (2011) vol. 8 559.
40. Harach T *et al*. "Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota." *Scientific reports* (2017) vol. 7 41802.
41. Research Models. "APPPS1."
42. Sherri Dudal., *et al*. '' Inflammation occurs early during the Aβ deposition process in TgCRND8 mice'' *Neurobiology of Aging* (2004). Vol. 25. Pages 861-871.
43. Wei Cao and Hui Zheng. "Peripheral immune system in aging and Alzheimer's disease'' *Molecular Neurodegeneration* (2018) 13:51.
44. Carmen Venegas and Michael T. Heneka. "Danger-associated molecular patterns in Alzheimer's disease.'' *Journal of leukocyte biology* (2017) vol. 101. Pages 87-98.
45. Nick Powell., *et al*. "The mucosal immune system: master regulator of bidirectional gut–brain communications'' *Nat Rev Gastroenterol Hepatol.* (2017) Mar 14(3): 143-159.
46. Shu G. Chen., *et al*. "Exposure to the Functional Bacterial Amyloid Protein Curli Enhances Alpha-Synuclein Aggregation in Aged Fischer 344 Rats and Caenorhabditis elegans'' *Scientific Reports* (2016). Vol. 6, Article number: 34477.
47. Kiran Bhaskar., *et al*. "Microglial Derived Tumor Necrosis Factor-α Drives Alzheimer's Disease-Related Neuronal Cell Cycle Events'' *Neurobiol Dis*. (2014).
48. Veit Rothhammer., *et al*. "Microglial control of astrocytes in response to microbial metabolites". *Nature* (2018) May 557(7707): 724-728.
49. Annamaria Cattaneo., *et al*. "Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly.'' *Neurobiology of Aging* (2017) Jan;49:60-68.
50. Holmes Clive., *et al*. "Systemic inflammation and disease progression in Alzheimer disease." *Neurology* (2009) vol. 73,10: 768-74.
51. Ruth F. Villarán., *et al*. "Ulcerative colitis exacerbates lipopolysaccharide-induced damage to the nigral dopaminergic system: potential risk factor in Parkinson`s disease'' *J Neurochem*. (2010) Sep;114(6):1687-700.
52. Itzhaki Ruth F., *et al*. "Microbes and Alzheimer's Disease." *Journal of Alzheimer's disease* (2016) vol. 51,4 979-84.
53. Jang Haeman., *et al*. "Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration." *Proc Natl Acad Sci U S A*. (2009) Aug 18;106(33):14063-8.
54. Brian J. Blain., *et al*. "Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain'' *Med Microbiol Immunol.* (1998) Jun;187(1):23-42.
55. Miklossy Judith. "Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease." *Frontiers in aging neuroscience* (2015) vol. 7 46. 16.
56. Alonso Ruth., *et al*. "Fungal Infection in Patients with Alzheimer's Disease''. *Journal of Alzheimer's Disease* (2014), vol. 41, no. 1, pp. 301-311.

57. Steven A. Harris and Elizabeth A. Harris "Molecular Mechanisms for Herpes Simplex Virus Type 1 Pathogenesis in Alzheimer's Disease.'' *Front. Aging Neurosci.* (2018) 10:48.
58. Letenneur Luc., *et al*. "Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study." *PloS One* (2008). vol. 3,11 e3637.
59. Tzeng Nian-Sheng *et al*. "Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan." *Neurotherapeutics*. (2018) Apr;15(2):417-429.
60. Wozniak MA., *et al*. "Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation.'' *Neurosci Lett*. (2007) Dec 18;429(2-3):95-100.
61. Wozniak MA., *et al*. "Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques." *J Pathol*. (2009) Jan;217(1):131-8.
62. Baringer J. Richard and Pisani Pamela. "Herpes simplex virus genomes in human nervous system tissue analyzed by polymerase chain reaction." *Ann Neurol.* (1994) Dec;36(6): 823-9.
63. Price JL. "Olfactory Higher Centers Anatomy." *Encyclopedia of Neuroscience* (2009) P:129-136.
64. Zou Yong- ming., *et al*. "Olfactory dysfunction in Alzheimer's disease." Neuropsychiatr Dis Treat. (2016) Apr 15;12:869-75.
65. Bradshaw Michael J. and Arun Venkatesan. "Herpes Simplex Virus-1 Encephalitis in Adults: Pathophysiology, Diagnosis, and Management." *Neurotherapeutics*. (2016) Jul;13(3):493-508.
66. Soscia, J. Stephanie., *et al*. "The Alzheimer's Disease-Associated Amyloid b-Protein Is an Antimicrobial Peptide." *PLoS One* (2010) 5(3): e9505
67. Hill Colin., *et al*. "Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic." *Nat Rev Gastroenterol Hepatol*. (2014) Aug;11(8):506-14.
68. Kobayashi Yodai., *et al*. "Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease." *Sci Rep*. (2017) Oct 18;7(1):13510.
69. Akbari Elmira., *et al*. "Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial." *Front Aging Neurosci.* (2016) Nov 10;8:256.
70. Tan Jian., *et al*. "The role of short-chain fatty acids in health and disease." *Adv Immunol.* (2014);121:91-119.
71. Govindarajan Nambirajan., *et al*. "Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression." *J Alzheimers Dis*. (2011): 26.1: 187-97.