Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(6): 53859
https://doi.org/10.31083/FBL53859

Opinion

Beyond Amyloid: Evolutionary and Immune-Metabolic Perspectives on Alzheimer's Disease

George B. Stefano[1,2,*]

[1]Department of Psychiatry, First Faculty of Medicine, Charles University and General University Hospital, 116 36 Prague, Czech Republic
[2]Mind-Cell LLC, Baltimore, MD 21230, USA
*Correspondence: gstefano@sunynri.org (George B. Stefano)
Academic Editor: Antoni Camins
Submitted: 26 March 2026 Revised: 14 May 2026 Accepted: 27 May 2026 Published: 16 June 2026

Abstract

Alzheimer's disease (AD) is increasingly recognized as a multifactorial and systems-level disorder that extends beyond the classical amyloid cascade hypothesis. Rather than dismissing established concepts such as tau pathology, synaptic dysfunction, vascular compromise, mitochondrial abnormalities, and impaired proteostasis, emerging evidence suggests that these processes may interact dynamically with chronic immune activation, microbial signaling, and systemic metabolic stress. Recent studies examining the microbiome-gut-brain axis, chronic infection, innate immunity, and systemic immune-metabolic dysfunction have broadened the conceptual framework of AD pathogenesis. Importantly, amyloid-β (Aβ) is now understood to possess evolutionarily conserved antimicrobial and immunomodulatory properties, suggesting that amyloid deposition may initially represent a protective host-defense response rather than solely a toxic pathological event. This perspective does not overturn the amyloid cascade model but instead reframes amyloid biology within a broader adaptive evolutionary context in which chronic or dysregulated activation becomes maladaptive during aging. The present opinion article integrates these converging concepts into a unified framework in which AD emerges from the prolonged interaction among immune responses, microbial exposures, metabolic disturbances, mitochondrial dysfunction, vascular injury, and age-associated failures in proteostatic resilience. This integrative interpretation seeks to humanize the disease process by viewing neurodegeneration not simply as isolated protein accumulation, but as the gradual exhaustion of ancient host-defense and energy-regulatory systems that were originally evolutionarily advantageous for survival.

Keywords: Alzheimer's disease; amyloid-β; innate immunity; microbiome-gut-brain axis; neuroinflammation; mitochondrial dysfunction

1. Microbiome-Gut-Brain Axis Dysregulation Theory (Systems-Metabolic + Neuroimmune Model)

According to the theory of microbiome-gut-brain axis dysregulation, alterations in microbial composition may contribute to the onset and progression of Alzheimer's disease (AD). This concept proposes that intestinal microbial ecosystems influence systemic immune signaling, metabolic homeostasis, vascular integrity, and neuroinflammatory pathways that are relevant to neurodegeneration (Fig. 1) [1,2,3]. The microbiota generates metabolites, including short-chain fatty acids, bile acids, and neurotransmitter precursors, that can modulate neural and immune function [2,4]. In addition, gut microbial products influence blood-brain barrier integrity, microglial maturation, and inflammatory signaling pathways [4,5].

Importantly, this relationship should not be interpreted as a direct causal mechanism proving that microbiome alterations alone produce AD. Rather, current evidence supports the interpretation that microbiome dysregulation may function as a contributing systems-level stressor capable of amplifying neuroinflammatory and metabolic vulnerabilities that already exist in susceptible aging individuals. This distinction between association and causation is critical because AD is likely multifactorial, involving interacting genetic, vascular, inflammatory, metabolic, and proteostatic Open components.

Neuroinflammation remains one of the central pathways implicated in AD [6,7]. Within this framework, amyloid-β may also function as an antimicrobial peptide [8,9], suggesting that microbial exposure and innate immune activation may influence amyloidogenesis [10,11,12]. However, this interpretation should not be viewed as evidence that microbial exposure universally initiates AD pathology. Instead, microbial signaling may represent one of several interacting biological stressors that influence the intensity and duration of immune activation within the aging brain.

The evidence supporting microbiome involvement in AD includes experimental study showing that germ-free conditions in animal models can reduce amyloid pathology, whereas reintroduction of dysbiotic microbiota can restore AD-like phenotypes [13]. Nonetheless, the translational relevance of these findings to human disease remains incomplete, and controlled longitudinal human studies are

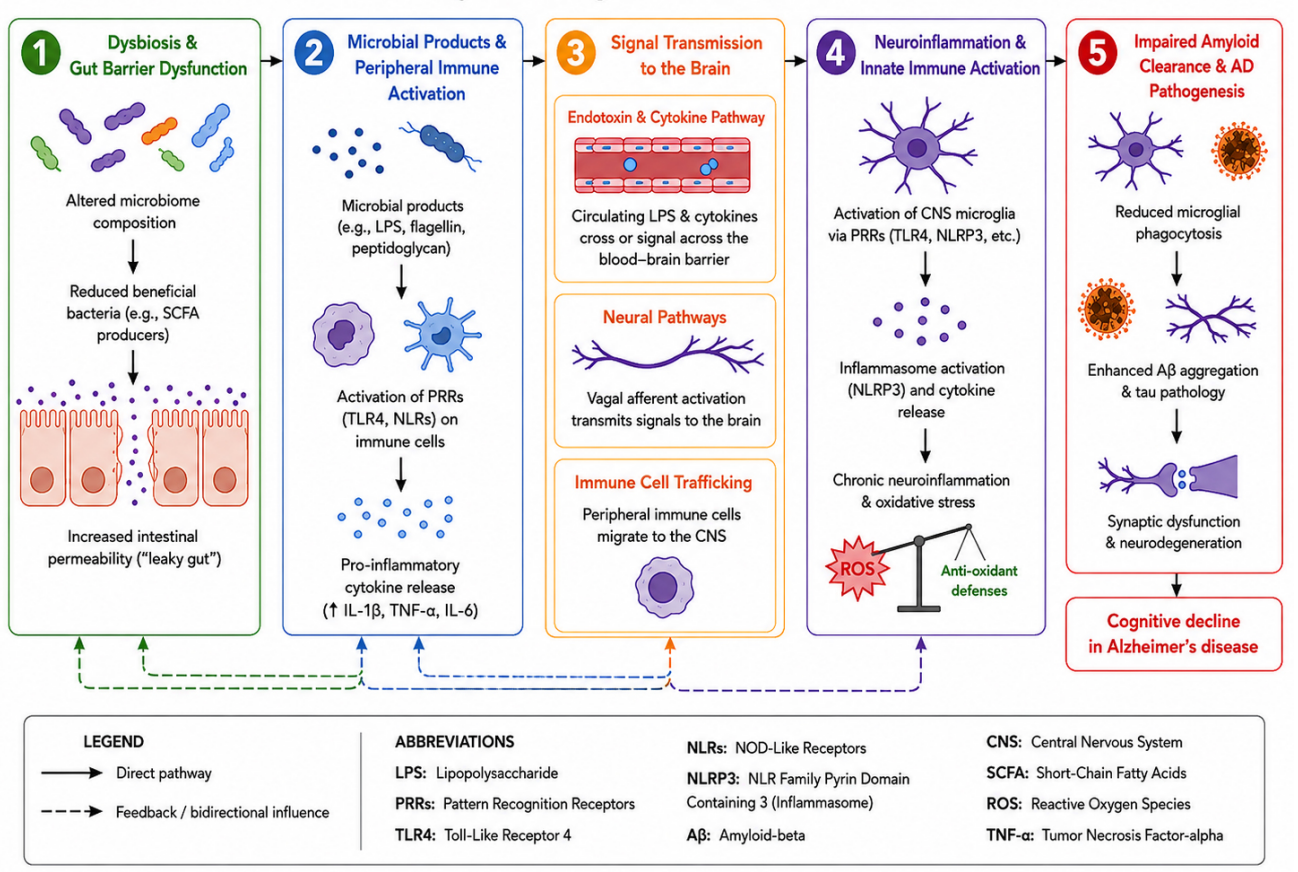

Fig. 1. Integrated systems-level model linking innate immune amyloid biology with inflammatory, metabolic, mitochondrial, vascular, and microbial contributions to Alzheimer's disease. Established pathological mechanisms in Alzheimer's disease - including amyloid aggregation, neuroinflammation, mitochondrial dysfunction, oxidative stress, vascular/barrier impairment, and proteostatic failure - are integrated with emerging evidence involving microbial signaling and systemic immune-metabolic dysregulation. Amyloid-β (Aβ) is illustrated not solely as a pathogenic aggregate but also as a potentially evolutionarily conserved innate immune effector capable of responding to infectious or inflammatory stimuli. Upon chronic or dysregulated activation, adaptive host-defense responses may progressively transition into maladaptive neuroinflammatory and proteotoxic states. Solid mechanistic interactions in the figure reflect relatively established biological processes, whereas dashed interactions represent emerging integrative systems-level associations requiring further experimental validation. Therapeutic interventions are depicted as acting across multiple interacting nodes rather than targeting a single isolated pathway. This figure was generated by ChatGPT-4 (OpenAI).

still required before definitive causal conclusions can be established.

Furthermore, concerns regarding bacterial species differences are also important. Gram-negative bacteria may be particularly relevant because they release lipopolysaccharides (LPS), potent inflammatory endotoxins capable of inducing systemic immune activation, oxidative stress, endothelial dysfunction, and neuronal injury. Elevated LPS signaling has been associated with amyloid aggregation, microglial activation, and disruption of amyloid homeostasis [14,15]. In contrast, some gram-positive bacterial populations may exert protective effects through production of anti-inflammatory metabolites and maintenance of intestinal barrier integrity. Thus, the balance between protective and pro-inflammatory microbial populations may influence whether immune signaling remains adaptive or becomes chronically pathological. Recent human microbiome studies further demonstrate compositional alterations in Alzheimer's disease involving inflammatory microbial signatures and altered metabolic pathways, thereby supporting the interpretation that microbiome-associated immune signaling may contribute to disease vulnerability at a systems level rather than through direct deterministic causation alone [14,15].

In addition, natural aging demonstrates that cognitive decline varies considerably among individuals. Recent evidence indicates that gut-derived immune and metabolic signaling pathways may contribute to these differences [16]. Age-related microbial changes, including increases in bacterial species such as Parabacteroides goldsteinii,

may activate peripheral immune pathways through GPR84-mediated signaling, resulting in inflammatory disruption of vagal afferent communication and impaired hippocampal function [16,17]. These findings are particularly compelling because they suggest that age-associated cognitive decline may not solely arise from intrinsic neuronal aging but also from systemic alterations in peripheral signaling networks that continuously communicate with the brain.

2. Microbial/Infectious Hypothesis (Chronic Infection + Host-Defense Model)

The microbial or infectious hypothesis of AD proposes that chronic infections or repeated microbial exposures may contribute to sustained immune activation associated with neurodegeneration. Neurotropic pathogens, including herpes simplex virus type-1 (HSV-1), Porphyromonas gingivalis, and Borrelia burgdorferi, have been associated with amyloid deposition, neuroinflammation, and tau-related abnormalities in some AD studies (Fig. 1) [10,11,12].

Importantly, the available evidence does not support the conclusion that chronic infection alone directly causes Alzheimer's disease. Rather, infections may represent biologically relevant contributors capable of interacting with aging, genetic susceptibility, vascular dysfunction, mitochondrial stress, and impaired proteostasis. In this context, it can be surmised, infections may serve as chronic inflammatory triggers that repeatedly stimulate innate immune pathways over prolonged periods. For example, HSV-1 infection in apolipoprotein E epsilon 4 (APOE ε4) carriers has been associated with increased amyloid deposition and tau phosphorylation. Likewise, oral pathogens such as P. gingivalis may contribute to inflammatory signaling and amyloidogenic responses through gingipain-mediated tissue injury [11]. However, these observations remain associative and should not be interpreted as evidence that infection supersedes protein misfolding as the singular explanation for AD pathogenesis. Instead, microbial factors may operate alongside established mechanisms such as tau aggregation, synaptic degeneration, cerebrovascular dysfunction, mitochondrial impairment, and age-related failures in protein homeostasis.

This broader interpretation may be more biologically realistic because evolution rarely favors single-cause explanations for complex chronic diseases. Rather, AD likely emerges from cumulative interactions among multiple adaptive systems that progressively lose resilience during aging.

3. Amyloid-β as an Evolutionarily Conserved Innate Immune Effector

One of the most significant conceptual developments in AD research is the recognition that amyloid-β possesses antimicrobial and innate immune properties [8,9]. This observation introduces the possibility that amyloid formation initially evolved as a protective biological response rather than solely as a pathological event. Experimental study demonstrate that Aβ can bind microbial organisms, aggregate around pathogens, and exhibit antimicrobial activity comparable to classical antimicrobial peptides such as LL-37 and defensins [8]. This evolutionary perspective suggests that amyloidogenesis may represent an ancient host-defense mechanism designed to sequester infectious or inflammatory threats.

The novel insight emerging from this interpretation is not merely that amyloid possesses antimicrobial properties, but that the evolutionary persistence of amyloid biology may reflect selective survival advantages throughout human evolution. In early biological systems, rapid peptide aggregation around pathogens may have enhanced host survival by limiting microbial spread and modulating innate immune responses. Under modern conditions of prolonged lifespan, chronic inflammation, metabolic disease, vascular dysfunction, and repeated immune activation, this once-protective process may become maladaptive and self-perpetuating. Accordingly, amyloid may be viewed less as a biological error and more as an example of antagonistic pleiotropy: a conserved defense mechanism beneficial earlier in life but potentially harmful during aging when regulatory clearance systems fail. The conceptual novelty of the present framework does not arise from proposing a single new pathogenic mechanism, but rather from integrating immune, microbial, metabolic, vascular, mitochondrial, and proteostatic theories into a unified evolutionary interpretation of Alzheimer's disease. Within this model, amyloid-β is viewed not exclusively as a pathological byproduct, but as an evolutionarily conserved host-defense effector whose persistence across biological evolution may have provided selective survival advantages under infectious and inflammatory pressures. Accordingly, the manuscript proposes that Alzheimer's disease may partly represent the chronic dysregulation and exhaustion of adaptive survival systems that originally evolved to preserve organismal resilience.

This interpretation also helps reconcile competing hypotheses. Rather than overturning the amyloid cascade hypothesis, the immune-defense framework broadens it by asking why amyloid production evolved and under what circumstances protective responses become pathological. Chronic activation of Aβ production due to inflammation, microbial signaling, oxidative stress, vascular compromise, or mitochondrial dysfunction may overwhelm clearance mechanisms, leading to persistent amyloid accumulation, proteotoxicity, and neurodegeneration. Importantly, tau pathology, synaptic dysfunction, vascular injury, mitochondrial impairment, and failures in proteostasis remain central components of AD biology. The present framework proposes that these processes interact dynamically with chronic innate immune activation rather than functioning as isolated pathological pathways.

4. Systemic Immune-Metabolic Failure and Peripheral Contributions

The systemic immune-metabolic model of AD proposes that neurodegeneration may partly arise from disturbances occurring outside the central nervous system. Chronic inflammatory activation involving macrophages, adipose tissue, cytokine signaling, and metabolic dysfunction may influence the brain through blood-brain barrier signaling pathways and vascular interactions [6,7]. Elevated inflammatory mediators, including IL-6, TNF-α, and complement-associated pathways, have been implicated in AD-related pathology [6].

In addition, several genes associated with AD risk, including TREM2 and CD33, are linked to immune system regulation rather than exclusively to protein processing pathways [18]. Metabolic disturbances involving glucose utilization, mitochondrial dysfunction, oxidative stress, and impaired NAD homeostasis are also increasingly recognized as important contributors to AD vulnerability [17].

Importantly, this systems-level interpretation does not diminish the importance of classical neuropathological findings. Instead, it suggests that protein aggregation, synaptic injury, and neurodegeneration may represent downstream manifestations of prolonged failures in immune-metabolic resilience. From a human perspective, this framework may also help explain why AD frequently coexists with aging-associated systemic disorders such as obesity, insulin resistance, cardiovascular disease, chronic inflammation, frailty, and impaired energy metabolism. The aging brain does not exist in isolation but continuously responds to signals generated throughout the body.

5. Integrated Interpretation: Convergent Systems Architecture of Alzheimer's Disease

Despite their differences, the microbiome-gut-brain axis model, microbial/infectious hypothesis, innate immune interpretation of amyloid biology, and systemic immune-metabolic framework converge upon several shared biological principles. This convergence model is additionally supported by emerging evidence demonstrating that innate immune activation, microbial signaling, vascular dysfunction, and metabolic stress interact bidirectionally across systemic and central nervous system compartments, thereby reinforcing the concept that Alzheimer's disease may arise from network-level failures in biological resilience rather than from a single isolated initiating event [19,20].

First, innate immunity appears central to AD pathophysiology. Microglial activation, cytokine signaling, and Aβ production may all initially represent adaptive defense responses [6,21]. Second, microbial and metabolic processes are deeply interconnected. The microbiota influences mitochondrial function, redox balance, vascular signaling, and energy homeostasis [2]. Third, amyloid may represent a reactive and context-dependent biological molecule rather than solely a constitutively toxic species. Emerging evidence further indicates that innate immune signaling pathways may function as central integrative nodes connecting microbial exposure, inflammatory activation, vascular dysfunction, and neurodegeneration [19,20].

Most importantly, the convergence of these models suggests that Alzheimer's disease may represent the chronic exhaustion of evolutionarily conserved survival systems. Mechanisms that originally protected organisms against infection, metabolic instability, tissue injury, and environmental stress may gradually lose regulatory precision during aging. The resulting persistent activation of inflammatory, proteostatic, vascular, and metabolic pathways may ultimately produce neurodegeneration.

This interpretation also provides a more balanced framework than purely reductionist models because it incorporates established mechanisms including tau pathology, vascular compromise, synaptic dysfunction, mitochondrial impairment, oxidative stress, and proteostatic failure within a broader systems-level architecture. Furthermore, the present framework attempts to humanize AD by emphasizing that the disease may not simply represent abnormal protein accumulation, but rather the long-term biological cost of adaptive survival systems functioning beyond their evolutionary design limits during extended human lifespan. Importantly, the present synthesis differs from reductionist interpretations by proposing that classical pathological findings, including amyloid deposition, tau aggregation, neuroinflammation, vascular dysfunction, mitochondrial impairment, and failures in proteostasis, and should not necessarily be viewed as isolated parallel abnormalities, but rather as dynamically interacting components within an evolutionarily conserved systems architecture of host defense and energy regulation.

6. Conclusion and Summary

Current evidence supports a continuing transition in AD research toward integrative and systems-level models that extend beyond purely neuron-centric or protein-centric interpretations of disease. The microbiome-gut-brain axis, chronic infection-associated immune activation, the innate immune properties of amyloid-β, vascular dysfunction, mitochondrial abnormalities, and systemic immune-metabolic dysregulation all contribute to a more comprehensive understanding of AD biology. Importantly, the present interpretation does not reject classical amyloid or tau-based mechanisms. Rather, it integrates these established findings into a broader evolutionary and immunological framework in which amyloid biology may initially represent an adaptive host-defense response that becomes maladaptive during chronic aging-associated stress.

The evolutionary persistence of amyloid may therefore provide one of the most important conceptual insights emerging from modern AD research. Amyloid formation

may have been conserved because it once enhanced survival under infectious and inflammatory pressures. However, under conditions of prolonged lifespan, chronic systemic inflammation, impaired mitochondrial energetics, vascular dysfunction, and reduced proteostatic clearance, this protective mechanism may transition into a chronic pathological state. Accordingly, AD may be more accurately conceptualized as a disorder arising from the interaction of immune, metabolic, vascular, microbial, mitochondrial, and proteostatic systems rather than from a single isolated pathological pathway. Such a perspective may help guide future therapeutic strategies toward restoring systemic resilience rather than exclusively targeting amyloid deposition alone.

The principal conceptual contribution of the present opinion article is the proposal that Alzheimer's disease may represent the long-term biological consequence of evolutionarily conserved adaptive mechanisms functioning beyond their regulatory limits during aging. This systems-level interpretation attempts to unify traditionally separate pathological frameworks into a coherent model linking immune activation, microbial signaling, mitochondrial energetics, vascular dysfunction, proteostatic failure, and innate host-defense biology within a shared evolutionary context. Future progress in Alzheimer's disease research may increasingly depend upon integrative models capable of bridging molecular pathology with systemic biology, evolutionary adaptation, immune signaling, and metabolic resilience. Rather than viewing amyloid, tau, inflammation, mitochondrial dysfunction, vascular compromise, and microbial influences as competing explanations, the present framework proposes that these processes may represent interconnected manifestations of progressive regulatory failure across ancient adaptive host-defense systems.

Abbreviations

AD, Alzheimer's disease; Aβ, amyloid-β; APOE ε4, apolipoprotein E epsilon 4; FMT, fecal microbiota transplantation; LPS, lipopolysaccharide; NAD, nicotinamide adenine dinucleotide; ROS, reactive oxygen species.

Author Contributions

The single author was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The author is an employee of Mind-Cell LLC. The author declares that this relationship did not influence the research findings or the interpretation of the data, and that the work was conducted independently of any commercial interests.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author used ChatGPT to generate Fig. 1. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the integrity of the figure.

References

[1] Stefano GB, Pilonis N, Ptacek R, Raboch J, Vnukova M, Kream RM. Gut, Microbiome, and Brain Regulatory Axis: Relevance to Neurodegenerative and Psychiatric Disorders. Cellular and Molecular Neurobiology. 2018; 38: 1197–1206. https://doi.org/10.1007/s10571-018-0589-2

[2] Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. Physiological Reviews. 2019; 99: 1877–2013. https://doi.org/10.1152/physrev.00018.2018

[3] Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009; 73: 768–774. https://doi.org/10.1212/WNL.0b013e3181b6bb95

[4] Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nature Neuroscience. 2015; 18: 965–977. https://doi.org/10.1038/nn.4030

[5] de la Torre JC, Stefano GB. Evidence that Alzheimer's disease is a microvascular disorder: the role of constitutive nitric oxide. Brain Research. Brain Research Reviews. 2000; 34: 119–136. https://doi.org/10.1016/s0165-0173(00)00043-6

[6] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. The Lancet. Neurology. 2015; 14: 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5

[7] Perry VH, Nicoll JAR, Holmes C. Microglia in neurodegenerative disease. Nature Reviews. Neurology. 2010; 6: 193–201. https://doi.org/10.1038/nrneurol.2010.17

[8] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, et al. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PloS One. 2010; 5: e9505. https://doi.org/10.1371/journal.pone.0009505

[9] Kumar DKV, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, et al. Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Science Translational Medicine. 2016; 8: 340ra72. https://doi.org/10.1126/scitranslmed.aaf1059

[10] Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, et al. Microbes and Alzheimer's Disease. Journal of Alzheimer's Disease : JAD. 2016; 51: 979–984. https://doi.org/10.3233/JAD-160152

[11] Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, et al. *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Science Advances. 2019; 5: eaau3333. https://doi.org/10.1126/sciadv.aau3333

[12] Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shan-

non P, Haroutunian V, et al. Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus. Neuron. 2018; 99: 64–82.e7. https://doi.org/10.1016/j.neuron.2018.05.023

[13] Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Scientific Reports. 2017; 7: 41802. https://doi.org/10.1038/srep41802

[14] Kowalski K, Mulak A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. Journal of Neurogastroenterology and Motility. 2009; 25: 48–60. https://doi.org/10.5056/jnm18087

[15] Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nature Immunology. 2015; 16: 229–236. https://doi.org/10.1038/ni.3102

[16] Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Scientific Reports. 2017; 7: 13537. https://doi.org/10.1038/s41598-017-13601-y

[17] Cox TO, Devason AS, de Araujo A, Mason S, Subramanian M, Salvador AFM, et al. Intestinal interoceptive dysfunction drives age-associated cognitive decline. Nature. 2026; 652: 442–450. https://doi.org/10.1038/s41586-026-10191-6

[18] Zhan X, Stamova B, Sharp FR. Lipopolysaccharide Associates with Amyloid Plaques, Neurons and Oligodendrocytes in Alzheimer's Disease Brain: A Review. Frontiers in Aging Neuroscience. 2018; 10: 42. https://doi.org/10.3389/fnagi.2018.00042

[19] Finch CE, Kulminski AM. The Alzheimer's Disease Exposome. Alzheimer's & Dementia : the Journal of the Alzheimer's Association. 2019; 15: 1123–1132. https://doi.org/10.1016/j.jalz.2019.06.3914

[20] Stefano GB, Esch T, Ptacek R, Kream RM. Dysregulation of Nitric Oxide Signaling in Microglia: Multiple Points of Functional Convergence in the Complex Pathophysiology of Alzheimer Disease. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research. 2020; 26: e927739. https://doi.org/10.12659/MSM.927739

[21] Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biological Psychiatry. 2015; 77: 43–51. https://doi.org/10.1016/j.biopsych.2014.05.006