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Beyond the brain: How does Alzheimer's disease affect the body?

Ye-Jin Park, Hongjie Li*

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the pathological accumulation of extracellular amyloid-β (Aβ) peptides and intracellular neurofibrillary tangles composed of hyperphosphorylated Tau. Since AD is the most common cause of dementia and is predominantly considered a disorder of memory and cognition, current research has largely focused on the brain. However, the brain, the primary site of AD pathology, interacts dynamically with peripheral organs to maintain systemic homeostasis, implying that alterations in brain function will extend their impact to the whole body.

Increasing evidence indicates that AD is associated not only with the brain but also with multiple peripheral systems, underscoring the need to view AD as a systemic disease. Several recent reviews have provided insightful overviews of recent advances in this area (Yin et al., 2024; Sönmez et al., 2025). However, most have focused on peripheral contributions to the brain, including inflammatory cytokines, gut microbiota-derived metabolites and toxins, adipose-derived adipokines, impaired hepatic Aβ clearance, and bone-derived factors. While such work has been invaluable in highlighting systemic contributions, the directionality of these interactions often remains unclear. Many peripheral changes could either be causal factors or consequences of AD brain pathology. Indeed, the reviews themselves frequently acknowledge this ambiguity, yet with limited attention to how AD brain pathology may influence peripheral systems.

Moreover, most prior analyses have examined individual organ- or tissue-specific axes, such as the gut–brain or immune–brain axis. While these analyses have gradually built our knowledge of specific interactions, a comprehensive view of how AD brain pathology affects multiple peripheral systems across the organism remains limited, pointing to the need for integrative, whole-organism approaches to study systemic effects (**Figure 1**). This perspective aims to address these gaps by first reviewing evidence from mouse and human studies on brain-to-periphery interactions in AD, and then by introducing our recent work using Drosophila AD models and whole-organism single-nucleus RNA sequencing to provide a comprehensive view of systemic effects (Park et al., 2025).

Brain to body studies in mouse and human: AD pathology in the brain can propagate its effects to peripheral systems (Yin et al., 2024). Mechanistic and correlative evidence now indicates that neuronal Aβ and Tau influence gastrointestinal, neuromuscular, metabolic, immune, and physiological processes beyond the central nervous system.

Among peripheral targets, the gastrointestinal system provides the most consistent and mechanistically supported evidence for brain-to-body propagation. In humans, elevated markers of intestinal inflammation have been associated with greater cortical Amyloid burden and cognitive decline, suggesting that gut inflammatory status may mirror or even influence AD pathology (Heston et al., 2023). Consistent with clinical observations, AD mouse models display gut abnormalities characterized by enteric Amyloid and Tau accumulation, neuronal loss, epithelial barrier disruption, and inflammatory transcriptomic and microbial signatures (Han et al., 2017; He et al., 2023). More recently, direct mechanistic evidence from both *in vivo* AD mouse models and an *in vitro* colon-on-a-chip system has demonstrated that brain-derived Tau pathology can propagate to the gut via the vagal efferent pathway, resulting in enteric Tau accumulation and intestinal dysfunction (Choi et al., 2025).

Besides the gut, the links between central AD pathology and peripheral tissue alterations have been reported. In 5×FAD mice, a transgenic AD mouse model, early neuromuscular deficits and neuromuscular junction alterations have been observed, with neuron-derived factors implicated in muscle atrophy and dysfunction (Brisendine et al., 2023). Correspondingly, in humans, reduced skeletal muscle mitochondrial function and altered metabolic signatures correlate with cognitive impairment and cortical AD biomarkers, suggesting that peripheral bioenergetic measures may reflect central disease burden (Tian et al., 2023). Notably, a recent study found that individuals with a neuropathologic diagnosis of AD exhibited downregulation of oxidative phosphorylation pathways in skeletal muscle, with the most pronounced effects observed in apolipoprotein E ε4 carriers (Johnson et al., 2025). In AD patients, alterations in hepatic lipid metabolism have been observed, correlating with disrupted brain lipid homeostasis and disease progression (Zhou et al., 2024), and changes in liver enzyme levels, such as the aspartate transaminase/alanine aminotransferase ratio, have been linked to cognitive decline (Lu et al., 2024), highlighting systemic metabolic dysregulation associated with AD. Supporting these clinical observations, recent studies have demonstrated that AD mouse models exhibit hepatic metabolic alterations, suggesting that liver dysfunction may contribute to or reflect the systemic manifestations of AD pathology (Zheng et al., 2019). Systemic immune alterations have also been reported. In humans with mild cognitive impairment, large Aβ aggregates in plasma associate with altered monocyte subsets and markers of integrin activation, and *ex vivo* assays suggest these aggregates engage monocytes and trigger phagocytic/lysosomal responses (Juul-Madsen et al., 2024). Consistent with this, a recent study has reported broader adaptive immune alterations in AD, reflecting systemic immune dysregulation linked to disease progression (van Olst et al., 2024).

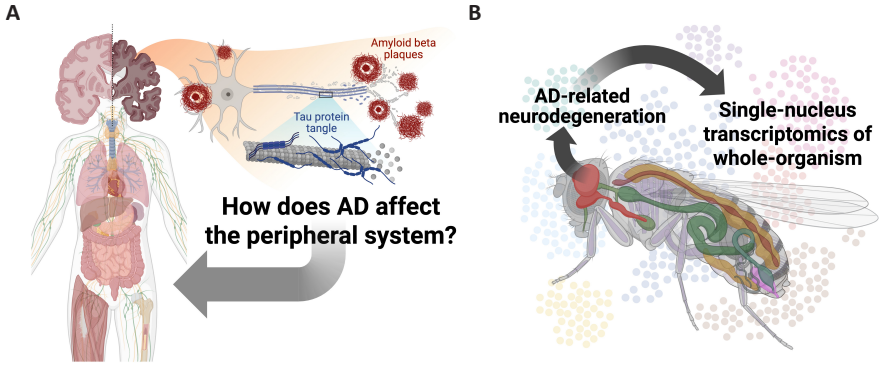

Figure 1 | **Alzheimer's disease (AD) beyond the brain: toward a systemic understanding.**
(A) AD research has largely focused on brain pathology, where Amyloid plaques and Tau tangles are key hallmarks. However, increasing evidence indicates that AD also affects peripheral systems, underscoring the need for a comprehensive investigation beyond the brain. (B) To explore organism-wide effects, Alzheimer's Disease Fly Cell Atlas profiles single-nucleus transcriptomes from whole flies expressing neuronal amyloid-β 42 or human Tau, providing a framework to study systemic responses to neurodegeneration. Created with BioRender.com.

Together, these studies provide converging evidence that AD pathology in the brain can exert diverse effects across peripheral systems. While these findings have been invaluable in demonstrating the impacts of AD on the periphery, most investigations have focused on individual organ systems, leaving organism-wide consequences largely unexplored. Next, we will focus the discussion on our recent study where we surveyed the systematic impact of AD-related toxic proteins on different cell types across the whole organism (Park et al., 2025).

Alzheimer's Disease Fly Cell Atlas — a systemic view of brain to body: We used two fly models in which the representative human AD pathological proteins, $A\beta_{42}$ or Tau, are expressed specifically in adult neurons, and developed the Alzheimer's Disease Fly Cell Atlas (AD-FCA) using whole-organism single-nucleus RNA sequencing. Comprising 219 distinct cell types, AD-FCA provides a platform to comprehensively investigate the systemic impact of neuronal pathology to the whole organism.

Distinct systemic effects of amyloid-β 42 and Tau as revealed by Alzheimer's Disease Fly Cell Atlas: One key finding of the AD-FCA is that $A\beta_{42}$ and Tau, when expressed in neurons, drive distinct systemic consequences throughout the organism, despite both representing core features of AD pathology. Notably, their mechanisms of action diverge at the organismal level, highlighting the contrasting pathways through which these proteins influence systemic function. Neuronal $A\beta_{42}$ primarily disrupts the nervous system, with the sensory system being particularly vulnerable, and induces a conserved lactate dehydrogenase (LDH)-high neuronal state. In contrast, neuronal Tau promotes accelerated aging phenotypes in peripheral tissues, including alterations in fat metabolism, gut homeostasis, and reproductive capacity, while also affecting brain-body communication. In what follows, we highlight several specific findings from the AD-FCA that illustrate these contrasting mechanisms and discuss their broader implications for how AD pathology should be conceptualized and studied.

Amyloid-β 42–induced lactate dehydrogenase-high neuronal cluster as a conserved stress signature: A notable finding was the identification of a neuronal cluster enriched for LDH expression in $A\beta_{42}$ flies. Rather than representing a single neuronal subtype, this LDH-high cluster emerged from multiple types of neurons that converged into a common transcriptional state under $A\beta_{42}$ toxicity. Importantly, similar LDH-high clusters were observed in both 5×FAD mice and human AD cortical samples, displaying upregulation of unfolded protein response and endoplasmic reticulum stress-related genes. The conservation of this cluster across species underscores its significance as a molecular signature of neuronal stress and vulnerability, reflecting a fundamental response to amyloid pathology that bridges metabolic stress and neurodegeneration. Notably, in human AD cortical samples, many genes enriched in this cluster overlapped with established plasma and cerebrospinal fluid biomarkers, providing a framework for linking neuronal state transitions in the brain to measurable indicators in the periphery. These findings suggest that transcriptional changes in vulnerable neurons may ultimately guide biomarker discovery and enable earlier diagnosis.

We want to point out that the biological meaning of the LDH-high state remains unresolved, even with its strong conservation across species. It could represent neurons undergoing metabolic reprogramming as part of an adaptive stress response to resist degeneration, or a terminal trajectory preceding neuronal death. Distinguishing between these possibilities will be critical, as it will determine whether this state represents a neuroprotective response or the terminal phase of degeneration. Future studies will be essential to resolve the mechanisms driving this state and to evaluate its potential as both a therapeutic target and an early biomarker.

Sensory neuron vulnerability of Alzheimer's disease: While AD research has historically focused on hippocampal and cortical regions, sensory deficits remain relatively less explored, despite sensory decline preceding cognitive symptoms in patients. The AD-FCA revealed that sensory systems, including olfactory, auditory, and visual circuits, show pronounced susceptibility to $A\beta_{42}$ compared to other neuronal populations. The olfactory receptor neurons showed greater vulnerability than their downstream projection neurons, despite comparable $A\beta_{42}$ expression levels across all neurons. This finding suggests that AD pathology is not restricted to higher-order cognitive circuits but extends to, and may even preferentially affect, peripheral sensory systems.

Moreover, the atlas adds cellular resolution by identifying specific olfactory receptor neuron subtypes that are particularly vulnerable, which indicates that not all neurons are equally affected by Amyloid pathology, even within the same cell class. This raises the possibility that analogous vulnerabilities may exist in human patients, where selective loss of specific sensory modalities could provide an opportunity for non-invasive sensory-based assessments as predictive tools for AD, long before cognitive symptoms emerge. Such insights could guide future research to map these vulnerabilities and develop functional assays of sensory decline, enabling early biomarker discovery and therapeutic interventions in AD.

Neuronal Tau drives accelerated peripheral aging: By contrast to $A\beta_{42}$, Tau expression in neurons drives systemic alterations that mimic accelerated aging. At the transcriptomic level, younger (20-day-old) Tau flies already resembled older (30-day-old) controls, and this premature molecular aging was mirrored in peripheral tissues, with hallmarks such as gut dysplasia, disruption of lipid metabolism in the fat body, and reduced reproductive capacity. These organism-wide phenotypes indicate that neuronal Tau is not merely a local neuronal stressor but a driver of systemic aging-like changes. Conceptually, this observation reframes AD as both a neurodegenerative and an organismal aging disorder, positioning Tau as a molecular bridge between neuronal dysfunction and peripheral decline. From a broader perspective, this raises several opportunities for future work: whether peripheral "aging signatures" can be exploited as early, non-invasive indicators of Tau pathology in the brain; whether Tau accelerates canonical aging pathways or establishes a distinct aging-like program; and whether interventions that target aging-related pathways, for example, agents such as metformin or rapamycin that modulate metabolic and longevity pathways, or senolytics that eliminate senescent cells, could mitigate both neural degeneration and systemic manifestations in peripheral tissues.

Conserved lipid metabolism defects in peripheral adipose tissue: Tau-induced disruption of lipid metabolism exemplifies how brain pathology can impact peripheral tissues. In Tau fly fat body cells, lipid droplets initially enlarge but later become fragmented, reflecting dynamic fluctuations in lipid metabolism that were conserved in the adipose tissue of PS19 tauopathy mice. The mechanisms underlying these changes remain unclear. One possibility is that the broad upregulation of poly(ADP-ribose) polymerase in Tau-expressing neurons (internal preliminary observation) leads to NAD^+ depletion, which contributes to the disruption of energy homeostasis [poly(ADP-ribose) polymerase is one of the main enzymes in the cell to consume NAD^+]. These findings highlight a bidirectional relationship: while metabolic dysfunction has traditionally been viewed as a risk factor for AD, Tau pathology in the brain can itself reshape peripheral metabolism. The cross-species conservation of these effects underscores their translational relevance, suggesting that adipose-derived transcriptomic or lipidomic signatures could serve as accessible biomarkers of brain Tau pathology, and pointing toward metabolic interventions as potential therapeutic strategies. Moreover, given that apolipoprotein E is a well-established genetic risk factor for AD and plays key roles in lipid transport and metabolism, it is possible that apolipoprotein E isoforms could modulate the systemic lipid metabolism changes induced by neuronal Tau pathology. Further studies are needed to unravel the mechanisms driving these dynamic metabolic changes, which could clarify how neuronal Tau contributes to systemic energy alterations and guide the development of early biomarkers and targeted interventions.

Tau rewires systemic brain-to-body networks: The AD-FCA revealed that neuronal Tau alters brain-to-periphery communication, potentially contributing to functional changes in peripheral tissues. Cell-cell communication analysis identified broad alterations in brain-to-body communication in Tau compared with controls. Peripheral cell types involved in fat metabolism, digestion, and reproduction exhibited the most pronounced communication changes. Complementing these molecular insights, structural remodeling of neuronal circuits, such as altered synaptic connectivity in the hindgut, may further influence peripheral tissue function and metabolic homeostasis. Taken together, these findings indicate that neuronal Tau acts not only as a local neurotoxin but also as a driver of systemic changes that reshape brain-body communication at both molecular and structural levels. These results further extend the perspective beyond a single organ axis, such as the brain-gut connection, highlighting the need to examine additional brain-periphery connections within a whole-organism network view.

Future outlook: Collectively, the AD-FCA provides a comprehensive view of AD pathology, showing that $A\beta_{42}$ and Tau extend their influence beyond the brain through distinct systemic pathways: $A\beta_{42}$ predominantly disrupts peripheral sensory circuits, whereas Tau induces accelerated aging across multiple peripheral systems. By profiling how neuronal pathology impacts the whole organism, the AD-FCA establishes a foundation for exploring systemic effects and identifying potential biomarkers or therapeutic targets. It also highlights the importance of viewing AD not merely as a brain disorder, but as a condition with organism-wide consequences. From this perspective, several important questions arise for future research.

First, what are the precise molecular and cellular mechanisms by which neurodegenerative stress propagates from the brain to peripheral tissues? Understanding these mechanisms may also inform the discovery of compartment-specific biomarkers, such as changes in peripheral sensory neurons, cerebrospinal fluid, blood, or other peripheral signals. For example, our AD-FCA data showed that specific types of olfactory receptor neurons are particularly vulnerable to AD-related toxicity. Is such specificity conserved in human AD? If so, olfactory function-based biomarkers can be potentially developed for clinical diagnosis.

Second, it is critical to clarify the role of brain-body communication: do peripheral changes arise solely as downstream consequences of neuronal dysfunction, act as intermediaries that transmit neuronal effects, or form bidirectional feedback loops that amplify systemic decline? Addressing these challenges will require integrative approaches that combine omics, systems biology, and computational modeling to map and manipulate brain-body networks.

Third, it is also essential to assess the reversibility of peripheral alterations and to test whether interventions at the level of peripheral tissues can attenuate not only local dysfunction but also neuronal pathology and organism-wide decline.

Finally, while the AD-FCA highlights that $A\beta_{42}$ and Tau exert distinct systemic effects, AD in patients involves both pathologies. Determining how $A\beta_{42}$- and Tau-driven changes intersect or synergize across tissues will be critical for clarifying the temporal progression from early Amyloid pathology to later Tau-driven decline, and for understanding how their combined effects shape the systemic manifestations of disease.

Addressing these questions will clarify the mechanisms by which neuronal pathology drives systemic dysfunction and will guide the development of biomarkers and therapeutic strategies aimed at preserving brain-body homeostasis and mitigating the broader impact of AD.

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Ye-Jin Park, Hongjie Li*

Huffington Center on Aging, Baylor College of Medicine, Houston, TX, USA (Park YJ, Li H)
Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA (Park YJ, Li H)
Program in Development, Disease Models & Therapeutics, Baylor College of Medicine, Houston, TX, USA (Park YJ)
***Correspondence to:** Hongjie Li, PhD, hongjie.li@bcm.edu.
https://orcid.org/0000-0002-8066-4194 (Ye-Jin Park)
https://orcid.org/0000-0002-7332-7122 (Hongjie Li)

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