WHITE PAPER

Emerging Insights into Neurodegeneration: A Proteomic Perspective

- Understand the key molecular mechanisms driving neurodegenerative diseases
- Explore how therapies are evolving to target root causes rather than just symptoms
- See how high-dimensional proteomics is uncovering new biological insights in Alzheimer's and Parkinson's diseases

Introduction

Neurodegenerative diseases affect over 15% of the world's population, with chronic cases predicted to double over the next two decades[1]. They are defined by the progressive loss of neuronal structure and function, ultimately leading to cell death[2]. Although the underlying causes vary, these disorders result in the irreversible breakdown of the nervous system, impairing cognition, movement or both. To date, no effective treatments exist, and early diagnosis remains a challenge due to gradual onset, overlapping symptoms and a lack of validated, non-invasive biomarkers capable of detecting pathology before significant neuronal loss occurs.

Major disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are primarily driven by intrinsic cellular dysfunction triggered by the accumulation of misfolded proteins (Table 1)[2]. These aberrant proteins not only accumulate into toxic aggregates but also interfere with neighboring cellular systems, amplifying dysfunction across affected tissues.

In contrast, in some neurodegenerative disorders, such as multiple sclerosis (MS), immune-mediated damage is the primary driver while neurodegeneration emerges as a secondary but significant contributor to long-term disability (Figure 1)[3]. Chronic inflammation and demyelination gradually lead to axonal loss and neuronal degeneration, particularly in progressive forms of the disease. Despite differences in their etiologies, neurodegenerative disorders converge on a common endpoint: progressive loss of neurons that underlies the clinical symptoms and functional decline observed across the neurodegenerative spectrum[2,3].

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In addition to environmental and age-related influences, genetic mutations significantly contribute to disease susceptibility and progression. In AD, for example, hundreds of genetic mutations have been linked to increased risk[4]. Among these, the APOE4 variant allele is the strongest known genetic risk factor: individuals homozygous for the variant have a 50–70% lifetime risk of developing sporadic AD, representing a three- to eight-fold increase compared with those without the variant (Figure 2)[4–6]. Yet, notably, around 40% of individuals who are homozygous for the APOE4 variant remain unaffected, while 35–60% of AD patients do not carry a single copy of the variant[4]. This underscores the complexity of neurodegeneration and **the importance of understanding how non-genetic factors contribute to disease trajectories**.

Within this context, the identification of protein biomarkers is particularly vital. These molecular indicators can reveal neurodegenerative changes up to 20 years before clinical symptoms appear, offering valuable tools for early diagnosis, monitoring disease progression and guiding timely therapeutic intervention[2].

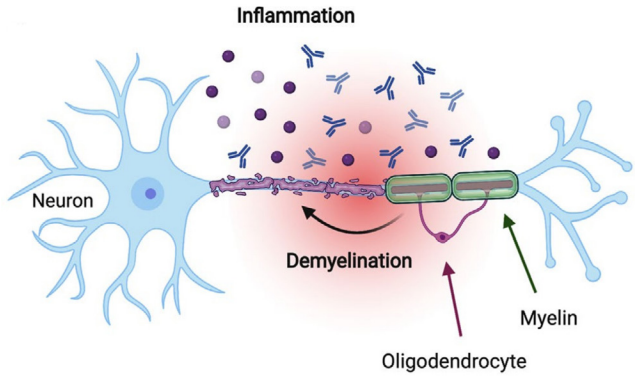

Figure 1. Demyelination in MS, leading to neuronal damage. Figure from Martinsen (2022) under the terms of the Creative Commons Attribution License (CC BY).

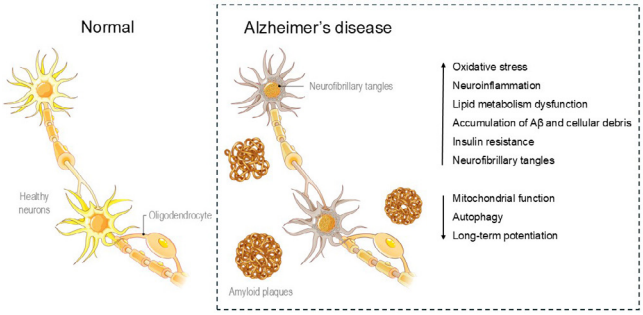

Figure 2. APOE4's impact on AD pathology. Figure adapted from designua – stock.adobe.com.

Table 1. Key proteins and their roles in five common neurodegenerative diseases

Disease	Disease-Associated Proteins	Mechanism of Action in Disease
AD	Amyloid-beta (Aβ) peptide	Forms plaques outside cells, with smaller plaques interfering with synaptic function
	Tau	Forms tangled filaments within neurons upon hyperphosphorylation, weakening neuronal structure and propagating further Tau tangles
	APOE4*	Unable to mediate lipid efflux from astrocytes effectively or clear Aβ peptide plaques, resulting in disruption of cellular homeostasis and the progression of neurodegeneration
ALS	TDP-43	Forms toxic aggregates in neurons, leading to motor neuron degeneration
	SOD1*	Unable to convert reactive oxygen species into less harmful molecules, resulting in mitochondrial dysfunction and oxidative damage
HD	HTT*	Forms aggregates in neuron, which bind to several transcription factors, ultimately altering widespread gene expression
MS	MBP	Targeted by the immune system in an autoimmune response, leading to demyelination and secondary axonal loss
PD	Alpha-synuclein	Forms aggregates called Lewy bodies inside neurons, affecting neuronal communication and propagating further Lewy bodies
	PINK1*, Parkin*	Unable to clear damaged mitochondria, leading to increased oxidative stress and reduced neuronal survival

* Protein dysfunction associated with or resulting from genetic mutation.

This white paper first examines therapeutic advances in the treatment of neurodegenerative diseases, including drugs approved by the United States Food and Drug Administration (FDA) and promising candidates currently in clinical trials. It then reviews a broad range of studies that have expanded our understanding of AD and PD through the use of advanced proteomic approaches, enabling the development of more personalized and targeted therapeutic strategies. These studies applied high-plex protein profiling, autoantibody (AAb) detection, single-cell proteomics and spatial protein mapping (Table 2).

Therapeutic advances in the treatment of neurodegenerative diseases

Recent advances in neurodegenerative disease therapy reflect a growing shift from symptomatic management toward precision medicine approaches that target the underlying mechanisms of disease. The integration of proteomics into therapeutic research is accelerating this transition by enabling the identification of molecular subtypes, predictive biomarkers and treatment-responsive pathways (Table 3)[2,7]. However, the mechanisms of action for some agents, such as edaravone and interferon beta-1a, remain only partially understood, highlighting the need for continued mechanistic research alongside therapeutic development.

This growing emphasis on targeting disease mechanisms is also evident in the clinical trial landscape (Table 4)[8]. In 2025, AD trials addressed 15 basic disease processes, with 73% employing disease-targeted therapies[9]. The pipeline reflects expanding therapeutic diversity for neurodegenerative diseases, including small molecules, stem cells, antibodies, polypeptides and gene therapies designed to reduce toxic protein accumulation, modulate immune responses, restore cellular function or even reprogram gut–brain interactions. Together, these emerging approaches – supported by proteomic insights – are laying the foundation for disease-modifying interventions.

Proteomic insights, from plasma to tissue

Recent insights into neurodegeneration have been made possible through the application of four proteomic technologies from Standard BioTools: the SomaScan™ Assay, KREX™ microarrays, CyTOF™ technology and the Hyperion™ Imaging system (Table 2). These approaches offer complementary views of the neurodegenerative process, capturing molecular and cellular changes across sample types, from peripheral blood to brain tissue (Tables 5, 6). This section highlights how each technology has contributed to a deeper understanding of disease mechanisms in AD and PD, revealing new opportunities for biomarker discovery, disease monitoring and therapeutic targeting.

Table 2. Proteomic technologies at Standard BioTools

Technology	Analytical Focus	Sample Type	Description
SomaScan Assay	Protein profiling	Biological fluid*	Quantifies up to 11,000 unique human proteins with approximately 5% coefficient of variation (CV)
KREX microarrays	Antibody profiling	Biological fluid*	Profiles 1,800-plus antibodies with a false discovery rate (FDR) below 1%
CyTOF technology	Single-cell proteomics	Cells**	Measures 50-plus surface and intracellular proteins per cell, the highest multiplexing capability on the market
Hyperion Imaging System/Imaging Mass Cytometry™ (IMC™)	Spatial proteomics	Tissue	Analyzes 40-plus protein markers in any tissue with high spatial resolution and no autofluorescence interference

* Pre-validated biological fluids include plasma and serum. Cerebrospinal fluid (CSF) is also validated for use with the SomaScan 11K and 7K Assays. For information on additional compatible sample types, please **contact us**.

** Includes the analysis of cells in whole blood.

Table 3. Examples of FDA-approved drugs for neurodegenerative disorders

Disease	Approved Drug(s)	Therapeutic Class	Mechanism(s) of Action
AD	Donanemab-azbt (Kisunla), Lecanemab-irmb (Leqembi)	Antibody	Targets beta-amyloid, stimulating the immune system to clear plaques
	Donepezil (Aricept), rivastigmine (Exelon), galantamine (Razdyne/Reminyl)	Small molecule	Inhibits acetylcholinesterase, increasing the concentration of acetylcholine to improve cognition
	Memantine (Namenda)	Small molecule	Blocks NMDA receptors from binding to glutamate, protecting neuronal damage
ALS	Edaravone (Radicava ORS)	Small molecule	Suppresses free radicals and inhibits glutamate signaling, protecting neuronal damage
	Riluzole	Small molecule	Blocks glutamate-dependent signaling through several ways, protecting neuronal damage
HD	Deutetrabenazine (Austedo), tetrabenazine (Xenazine), valbenazine tosylate (Ingrezza)	Small molecule	Inhibits vesicular monoamine transporter 2 (VMAT), reducing involuntary muscle movements associated with HD
MS	Cladribine (Mavenclad)	Nucleoside analog	Leads to programmed cell death of lymphocytes, disabling their ability to attack the myelin sheath
	Glatiramer acetate	Polypeptide mixture	Inhibits T cell response to several myelin antigens, reducing inflammation and protecting the destruction of myelin
	Interferon beta-1a (Avonex)	Protein	Modulates the immune system, reducing inflammation
	Natalizumab-sztn (Tyruko)	Antibody	Blocks interaction between VCAM1 and α4β1-integrin, reducing inflammation and preventing lesions
	Ocrelizumab (Ocrevus)	Antibody	Targets CD20-expressing B cells, reducing MS-associated pathology
PD	Amantadine	Small molecule	Blocks NMDA receptors, releases dopamine from central neurons and delays dopamine uptake, improving motor function and protecting neurons
	Levodopa* (Rytary)	Small molecule	Converted into dopamine in the brain, improving motor function

* Administered with carbidopa, which inhibits its breakdown before it reaches the brain.

Table 4. Examples of investigational drugs for neurodegenerative disorders in clinical trials

Disease	Drug(s)	Therapeutic Class	Phase	Mechanism(s) of Action*
AD	CB-AC-02	Stem cell	Phase 1/2 (NCT02899091)	Reduces plaque formation and inflammation
	GV1001	Stem cell	Phase 2 (NCT05189210)	Inhibits neurotoxicity, apoptosis and the production of reactive oxygen species induced by Aβ in neural stem cells, improving cognitive function and reducing Aβ and Tau proteins
	ALZ-801 (valiltramiprosate)	Small molecule	Phase 2 (NCT04693520)	Stabilizes Aβ peptide, inhibiting plaque formation
	Semaglutide	Polypeptide	Phase 3 (NCT05891496)	May have neuroprotective and anti-inflammatory effects
	ONO-2020	Small molecule	Phase 2 (NCT06881836)	Regulates epigenetics, improving cognitive functions
	LHP588	Small molecule	Phase 2 (NCT06847321)	Targets the bacteria *Porphyromonas gingivalis*, slowing or halting disease progression
ALS	RAPA-501-ALS	Stem cell	Phase 2/3 (NCT04220190)	Reduces inflammation as a hybrid TREG/Th2 stem cell
	Lenzumestrocel (Neuronata-R)	Stem cell	Phase 3 (NCT04745299)	Reduces inflammation as a bone marrow-derived mesenchymal stem cell
	Nicotinamide riboside	Small molecule	Phase 2 (NCT05589766)	Increases NAD+ levels for cellular energy production and stress response, protecting from neuronal damage
HD	SPK-10001, AMT-130	Gene therapy	Phase 1/2 (NCT06826612 NCT05243017)	Inhibits the production of the HTT protein, slowing disease progression
MS	Autologous hematopoietic stem cell transplantation	Stem cell	Phase 2/3 (NCT04220190)	Reduces inflammation as a hybrid TREG/Th2 stem cell
	Frexalimab (Freviva)	Antibody	Phase 3 (NCT06141486)	Binds to CD40L, inhibiting the activation of specific immune cells
PD	DNL151	Stem cell	Phase 2/3 (NCT04220190)	Reduces inflammation as a hybrid TREG/Th2 stem cell
	A9-DPC, HB-adMSCs, pluripotent adipose stem cells	Stem cell	Phase 1/2 (NCT05887466, NCT04995081, NCT06141317)	Delays, stops or induces recovery of neurodegeneration
	NouvNeu001	Progenitor cell	Phase 1/2 (NCT06167681)	Releases dopamine, slowing disease progression
	Ambroxol	Small molecule	Phase 2 (NCT05287503)	Acts as a protein chaperone to fold glucocerebrosidase correctly, reducing plaque formation
	Resistant maltodextrin	Fiber	Phase 2 (NCT03667404)	Alters the gut microbiome, improving motor function

* Based on current research; the exact mechanisms are still being investigated.

Alzheimer's disease

Proteomic profiling uncovers AD biomarkers decades before symptoms

While the APOE4 variant is the strongest genetic risk factor for AD, the molecular pathways through which it influences disease remain unclear. In a study by Dammer et al., the SomaScan 7K Assay was used to profile over 4,500 proteins in CSF from 300 individuals with and without AD, revealing three clusters of proteins with common expression variation across individuals that were significantly associated with APOE4 variant status as well as cognitive function, Aβ peptide and/or Tau levels (p <10^{-5})[10]. These clusters were further validated through module quantitative trait loci (QTL) analysis, which confirmed a strong genetic link to APOE4 status (p <10^{-8}). Notably, these associations were not clearly captured using mass spectrometry, underscoring the sensitivity of the SomaScan Assay.

Longitudinal data from over 11,000 individuals showed that these APOE4-associated protein signatures were predictive of dementia onset up to 21 years in advance. Moreover, protein levels in one cluster were reduced following treatment with the norepinephrine reuptake inhibitor atomoxetine in a Phase 2 clinical trial. These findings illustrate how high-plex proteomics can uncover AD subtypes and treatment-responsive pathways beyond classical amyloid and Tau pathology, offering direct applications in early diagnosis, disease monitoring and drug development.

AAb profiling reveals novel serum biomarkers of AD

Early and specific diagnosis of AD remains a major clinical challenge. To explore immune-related biomarkers, Wang et al. applied the KREX i-Ome™ Discovery microarray to profile serum AAbs in patients with mild AD or non-AD dementia, classified by CSF levels of Aβ and Tau[11]. Six AAbs were uniquely elevated in the AD group. Their target antigens (NAP1L3, MAP4, PANK3, PIK3R1, PTP4A1, SOX15) are involved in transcription, cell cycle, metabolism and cytoskeletal regulation, with some linked to cognitive dysfunction and Tau phosphorylation pathways. As the first study to identify these AAbs in biomarker-confirmed AD, the findings underscore the potential of AAb profiling to uncover previously unrecognized disease mechanisms. These AAbs also represent promising candidates for earlier and more precise diagnostic strategies.

Adaptive immune changes measured by CyTOF track with AD progression

The role of peripheral immunity in AD remains poorly defined, particularly across disease stages. Van Olst et al. used a 33-marker CyTOF panel to characterize peripheral immune changes across the AD continuum[12]. Patients with mild cognitive impairment (MCI) or AD dementia exhibited increased levels of senescent CD57+ CD8+ T effector memory cells re-expressing CD45RA (TEMRA), which are known for their pro-inflammatory and cytotoxic functions. Within this subset, the expression of a marker related

Table 5. Proteomic insights into AD and their clinical applications

Biological level	Technology	Key Insight	Potential Application	Representative Study
Molecular	SomaScan	APOE4-associated proteomic networks	Predictive and treatment-response biomarkers; stratification by genetic risk	Dammer (2024)
	KREX	Autoantibodies distinguish biomarker-confirmed AD	Diagnostic biomarker for early-onset AD; immune mechanism discovery	Wang (2020)
Cellular	CyTOF	Adaptive immune alterations track with disease progression	Prognostic tool for disease staging and progression; potential immunotherapy markers	Van Olst (2024)
Spatial	Hyperion	Glial senescence correlates with Aβ burden	Therapeutic target discovery; supports development of glial senolytics	Fancy (2024)

to suppressed T cell activity, PD-1, was elevated in MCI-AD patients. Lower PD-1 expression in AD dementia patients correlated with reduced CSF Aβ (p = 0.022) and elevated phosphorylated Tau (p = 0.049), aligning with increased AD pathology (Table 1). These associations were stage-dependent: Aβ-related immune changes predominated in MCI, while Tau correlations were more prominent in dementia. The study suggests that peripheral immune dysregulation evolves alongside AD pathology and may offer the potential of peripheral immune profiling as a prognostic or therapeutic tool in AD.

Spatial proteomics reveals senescence in microglia

Glial dysfunction is increasingly recognized as a driver of AD, but the extent and spatial organization of glial senescence are not well characterized. Fancy et al. mapped cellular senescence in brains from control and AD donors (n=69) using the Hyperion Imaging System[13]. Senescence markers (GLB1, p16, p21, γH2AX) were significantly elevated in microglia, which were also enriched in Aβ. RNA sequencing confirmed a senescence-associated transcriptional profile marked by inflammation and impaired Aβ clearance. These findings implicate glial senescence in AD progression and suggest senolytic therapies as a potential disease-modifying strategy.

Parkinson's disease

Protein profiling discovers proteins with potential causal roles in PD

PD lacks disease-modifying treatments, largely due to gaps in understanding which proteins are causally involved in its onset and progression. To address this, Gao et al. performed a comprehensive proteome-wide association study (PWAS), integrating protein quantitative trait loci (pQTL) data from plasma and brain with PD genome-wide association studies (GWAS; n=449,296)[14]. Plasma protein levels were measured using the SomaScan Assay, capturing over 4,900 proteins from 35,559 Icelandic participants, while brain proteomic data was obtained via mass spectrometry. The study assessed protein associations with PD onset and three progression phenotypes (cognitive, motor, composite) using multiple causal inference methods. Additional analyses included phenome-wide Mendelian randomization (PheW-MR) to predict off-target effects, cell-type–specific gene expression clustering, protein–protein interaction mapping and evaluation of druggability using existing pharmacological databases.

The study identified 25 proteins with potential causal roles in PD (p <0.05): 16 related to progression and nine to onset, with GPNMB uniquely implicated in both plasma and brain for disease onset. PheW-MR indicated that 83.7% of potential off-target effects from modulating these proteins were beneficial. Many targets showed distinct brain cell expression patterns and formed key interaction clusters relevant to PD pathology. Importantly, 15 of these proteins are already targeted by existing drugs, highlighting opportunities for drug repurposing. These findings deepen our mechanistic understanding of PD and lay the groundwork for developing more effective, personalized interventions.

AAb signatures link bacterial exposure to greater PD severity

Helicobacter pylori (*H. pylori*) infection has been epidemiologically associated with worsened motor symptoms in PD, suggesting a potential role in disease progression. To explore whether this link might be mediated by autoimmune mechanisms, Suwarnalata et al. used the KREX i-Ome Discovery microarray to profile serum AAbs in *H. pylori*-seropositive and -seronegative PD patients (n=60)[15]. They identified eight AAbs significantly elevated in the seropositive group (p <0.04), targeting proteins involved in neuroprotection, growth factor signaling and memory (NFIA, PDGFB, EIF4A3, FKBP4, TSPY3, PTGER3, CXCR6, MLKL). These findings support the hypothesis that microbial triggers, potentially through molecular mimicry (see gray box on next page), may exacerbate PD pathology via immune dysregulation, and further underscore the importance of the gut–brain–immune axis in neurodegenerative disease.

CyTOF analysis indicates immune dysfunction in early PD

Emerging research indicates that peripheral immune cells, particularly T lymphocytes and NK cells, may contribute to PD pathogenesis. Yet, the mechanisms by which these cells influence disease progression remain poorly defined, constraining efforts to harness immune alterations for diagnostic or therapeutic purposes. In this study, Jiang et al. employed CyTOF analysis to profile cytokine and chemokine expression in CD8+ T cell and NK cell subsets from drug-naïve individuals with early- and late-onset PD, compared with age-matched healthy controls[16].

The results revealed a marked reduction in intracellular pro-inflammatory cytokines and chemokines, including TNFα, IFNγ and CCL17, across several immune cell subpopulations in PD patients. Notably, these altered expression profiles correlated with motor and cognitive function, implicating immune dysfunction in symptom severity. This work is significant because it moves beyond phenotypic immune profiling to functional characterization, suggesting that early PD may involve a state of peripheral immune hypoactivity. These insights position immune cell secretory capacity as a promising biomarker for disease monitoring and a potential avenue for novel therapeutic interventions.

Spatial proteomics reveals complex mitochondrial dysfunction in PD

Mitochondrial dysfunction is implicated in the selective loss of dopaminergic neurons in PD, but deficits vary across cells and individuals. To resolve this heterogeneity, Chen et al. applied the Hyperion Imaging System to profile oxidative phosphorylation (OxPhos) complexes I–V within individual dopaminergic neurons from postmortem midbrain tissue of idiopathic PD, POLG-mutant PD and control donors[17]. Their analysis confirmed known patterns – such as age-related increases in OxPhos deficiency and frequent complex I loss in POLG PD – but also uncovered new layers of complexity. POLG-mutant neurons showed more severe loss of complex I and IV MTCO1 marker, while idiopathic PD presented a more heterogeneous pattern, often with co-loss of complexes I, III and IV. Interestingly, neurons with these deficiencies exhibited increased mitochondrial mass, suggesting compensatory biogenesis.

The same group extended their analysis to astrocytes, which are key neuronal support cells, in tissue from healthy and sporadic PD patients[18]. Although astrocytes rely less on OxPhos than neurons, mitochondrial dysfunction in astrocytes can disrupt glutamate and calcium homeostasis, potentially contributing to neuroinflammation and neuronal damage. Chen et al. found widespread deficiencies across all OxPhos complexes except complex III, with the most significant increases in complex I- and IV-deficient astrocytes in PD (p <0.05). Notably, complex IV-deficient astrocytes adjacent to neurons showed elevated mitochondrial mass (p = 0.02), while other astrocytes showed reduced mass compared with controls (p = 0.02), suggesting possible uptake of damaged neuronal mitochondria by astrocytes. These studies reveal previously unrecognized metabolic impairments in neurons and astrocytes and highlight astrocytic mitochondrial dysfunction as a novel therapeutic target in PD.

> “Compared to [immunofluorescence], these images [from the Hyperion Imaging System] have the added advantage of an increased signal-to-noise ratio in highly auto-fluorescent tissues.” – Chen et al. (2021)

Table 6. Proteomic insights into PD and their clinical applications

Biological Level	Technology	Key Insight	Potential Application	Representative Study
Molecular	SomaScan	Identified 25 proteins with potential causal roles in PD; GPNMB linked to both onset and progression	Target discovery; drug repurposing; genetic risk stratification	Gao (2025)
	KREX	AAb signatures differ by *H. pylori* exposure status, implicating microbial triggers in PD severity	Biomarker discovery; immune-targeted interventions; gut–brain axis research	Suwarnalata (2016)
Cellular	CyTOF	Reduced TNFα, IFNγ and CCL17 in CD8+ T and NK cells; immune hypoactivity correlates with motor and cognitive symptoms	Functional immune profiling; biomarker development; early diagnostic tools	Jiang (2023)
Spatial	Hyperion	Neuronal OxPhos deficits show distinct patterns in idiopathic and genetic PD; astrocytes also exhibit mitochondrial dysfunction	Therapeutic targeting of metabolic pathways in neurons and glia	Chen (2021, 2022)

Conclusion

High-dimensional proteomics is transforming our understanding of neurodegenerative diseases by uncovering biomarkers and mechanisms across molecular, cellular and spatial levels. These insights go beyond traditional pathology, offering a more comprehensive view of disease biology.

Several key themes emerge from the case studies in Alzheimer's and Parkinson's diseases presented in this white paper. First, both diseases exhibit strong immune system involvement, although in different forms. In AD, peripheral immune changes such as increases in senescent T cells and altered PD-1 expression track with disease stage, while in PD, immune dysfunction appears earlier and is marked by hypoactive cytokine and chemokine signaling in T and NK cells. Additionally, both diseases demonstrate links between autoimmunity and disease mechanisms: AAb profiles distinguish early-stage AD and connect *H. pylori* exposure to increased PD severity, highlighting systemic immune contributors and the gut–brain axis.

Second, both diseases are shaped by metabolic and cellular stress responses. In AD, spatial proteomics revealed glial senescence in amyloid-laden brain regions, implicating senescent microglia in disease progression. In PD, complex mitochondrial impairments were mapped in neurons and astrocytes, with evidence of compensatory biogenesis and potential neuron-to-astrocyte mitochondrial transfer.

Finally, both conditions exhibit molecular heterogeneity: AD through APOE4-associated proteomic networks, and PD through diverse patterns of mitochondrial dysfunction tied to genetic and idiopathic forms. These findings highlight the value of proteomics in defining disease subtypes, identifying early biomarkers and informing drug development strategies.

Collectively, these studies illustrate how advanced proteomic platforms like the SomaScan Assay, KREX microarrays, CyTOF technology and Hyperion systems can generate actionable insights to accelerate precision medicine in neurodegenerative disease.

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