Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 383 - 384 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.185
Short communication

The emerging role of proteomics in Alzheimer's disease: Moving beyond single biomarkers

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Introduction

Alzheimer's disease is a progressive neurodegenerative disorder and a leading cause of dementia worldwide, representing a significant clinical and societal burden. Current diagnostic and monitoring approaches rely on few established biomarkers such as amyloid-β and tau proteins. While these markers have significantly advanced the management of Alzheimer's disease, they do not fully capture its complex and heterogeneous nature. In addition, their performance is limited, particularly in the early, preclinical stages of the disease and their assessment currently depends on invasive cerebrospinal fluid sampling, which restricts routine clinical application (Blennow and Zetterberg, 2018).

These limitations highlight the need for introducing integrative, scalable biomarker strategies capable of elucidating the multifactorial pathology of Alzheimer's disease.

Proteomic biomarker discovery in Alzheimer's disease

Because of disease-associated changes in protein expression and abundance, proteomics is a powerful tool for identifying biomarker panels for Alzheimer's disease. It offers more comprehensive insight than conventional single markers such as amyloid-β and tau by capturing alterations across multiple biological pathways (Magnelli et al., 2025).

The main pathways involved in AD, investigated using cerebrospinal fluid (CSF) samples, are neuroinflammation and immune dysregulation, with key proteins such as TREM2 and C1QA (Ali et al., 2026). In addition, proteins from the humoral immune system such as IGHG2, IGHV2-70, and IGHV3-72 have also been identified and associated with the disease (Wingo et al., 2025). These proteins are involved in distinct immune-related pathways, and the complexity is further increased with involvement of synaptic dysfunction as another feature of the disease, reflected by changes in proteins such as NRGN and NPTX2. Enrichment of apoptosis-related pathways, involving TP53 and YWHAH, indicates intensive cell death and neuronal loss in AD (Ali et al., 2026), while metabolic and mitochondrial dysfunction are also early pathological changes in AD progression, involving proteins such as SOD2 and PRDX3 (Ryu et al., 2025). Overall, CSF proteomics reveals the involvement of multiple biological pathways, underscoring the complex and multifactorial nature of Alzheimer's disease (Ryu et al., 2025).

Beyond the presence of distinct biological pathways, an important observation is that proteins, such as TREM2 while primarily associated with immune dysregulation and microglial activation, are also implicated in other biological processes. This

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further supports the idea that AD is not driven by isolated processes, but rather by interconnected biological alterations (Ali et al., 2026).

Different biofluids provide complementary perspectives on Alzheimer's disease. While some biological pathways overlap with those observed in CSF, blood-based proteomics predominantly reflects systemic and vascular processes. Although multiple plasma protein panels have been identified across studies, a reproducible core signature including APOE, C3, clusterin, α2-macroglobulin, α1-antitrypsin, and TNF-α consistently emerges. Individually these proteins lack disease specificity, but collectively they provide a strong molecular reflection of Alzheimer's disease pathology. Similarly, serum-based studies reveal biomarker panels overlapping with those in plasma, mainly involving inflammatory and coagulation pathways, though with inter-study variability requiring further validation (Dong et al., 2024).

Blood/plasma-based proteomics provides an advantage through minimally invasive sampling, yet it is challenged by the wide dynamic range of circulating proteins, where high-abundance proteins can obscure low-abundance signals, and by the presence of comorbidities that further complicate the interpretation of complex molecular profiles (Ali et al., 2026).

Conclusion

Accumulating evidence indicates that single biomarkers are insufficient to capture the complexity of Alzheimer's disease, highlighting the need for multi-protein panels. AD is a heterogeneous and multifactorial disorder driven by overlapping pathological processes, including neuroinflammation, synaptic dysfunction, metabolic and vascular alterations, which cannot be fully captured by a single molecular readout. In contrast, multi-protein panels provide a more comprehensive representation of disease biology by integrating complementary pathological pathways, thereby improving diagnostic accuracy and more accurately reflecting disease complexity.

Despite their strong potential, proteomics-based biomarker discovery is largely limited by inter-study variability, a lack of standardization of the research methodology, high analytical complexity, and relatively high cost of these technologies.

This warrants further efforts to design interdisciplinary research studies that address current challenges and facilitate the identification of relevant biomarker panels with the potential for early diagnosis, patient stratification, and disease monitoring. Such advances would also support the emerging framework of precision medicine by enabling a more precise characterization of AD biology and the development of personalized therapeutic strategies.

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