Blood Proteomics in Relation to Alzheimer's Disease and Dementia: Potential Biomarkers and Systemic Implications

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Abstract

Dementia is a decline in cognitive abilities that impairs an individual's ability to engage in everyday activities, commonly caused by Alzheimer's disease (60-70% of cases). Current biomarkers are usually derived using neuroimaging or from cerebrospinal fluid (CSF) and include a decrease in amyloid beta 42 fragment (Aß42) and an increase in phosphorylated tau (p-tau). Blood-based biomarkers are an attractive alternative due to lower invasiveness and cost, yet accurate interpretation remains a significant challenge in reflecting AD pathology. This review aims to assess the plasma proteomic changes in AD and dementia by examining the replicability of blood plasma biomarkers and identifying shared pathways and distinctive AD-specific markers. After excluding 307 records from a total of 316, fourteen articles were included in the literature review, reporting 33 association studies with 7931, 8687, and 145 AD, dementia, and Mild Cognitive Impairment (MCI) subjects, respectively. We identified 1579 unique proteins associated with the conditions, with the majority (80.7%) originating from AD vs control studies.To ensure reliable results for subsequent analyses, we applied replicability filters based on the number of proteins that met the threshold. In the overlap of 215 proteins between AD and dementia, enriched biological functions implicated blood coagulation, hemostasis, cell secretion, organization, and adhesion. Specific genes, such as *SERPINF2*, associated with the plasmin cascade and neurodegeneration, emerged as potential indicators of AD-related vascular changes. AD-specific proteins revealed enriched biological functions related to magnesium ion response, neuromuscular junction development, and postsynapse organization. *APP* and *LRRK2*, associated with early onset AD and dementia, were replicated in our review. Comparisons with a recent proteomics study using brain cortex tissue underscored the need for a multi-tissue approach in biomarker discovery for AD. While overlaps in some genes (e.g., *APP*, *GFAP*) suggested shared molecular mechanisms across tissues, distinctive sets of genes indicated tissue-specific responses to AD.

Despite challenges in consistency and heterogeneity, the findings encourage further exploration of blood-based biomarkers. Recognizing the complexity in identifying these markers and their interplay with central nervous system processes is crucial for advancing our understanding of the mechanisms associated with AD and dementia.

Keywords: Dementia; Alzheimer's Disease; Neurodegenerative disorder; Blood-based biomarkers

Introduction

Dementia is a categorical term denoting a decline in cognitive abilities that impairs an individual's capacity to engage in everyday activities. This decline typically manifests as challenges in memory, thinking, and behavior[1,2]. In addition to memory issues and disruptions in thought patterns, common symptoms encompass emotional difficulties, language challenges, and decreased motivation. Dementia can arise from various sources, including vascular diseases and brain injuries such as strokes. However, the neurodegenerative Alzheimer's disease (AD) accounts for 60-70% of all cases and stands out as the most prevalent cause[3]. Diagnosing dementia involves a multifaceted including a cognitive assessment, history evaluation and collaborative evaluation of clinicians and close associates, with confirmation through neuropsychological testing, physical examination, and neuroimaging[4]. Alzheimer's disease diagnosis follows criteria such as the NINCDS-ADRDA, relying on clinical features and, when feasible, histopathologic confirmation via autopsy for a definitive diagnosis[5].

The pathophysiology of AD is known to begin years before the brain develops abnormalities – raising the need for early detection[6,7]. Current biomarkers are usually derived using neuroimaging or from cerebrospinal fluid (CSF)[8,9]. Validated biomarkers in CSF encompass a decrease in amyloid beta 42 fragment (Aß42) and an increase in phosphorylated tau (p-tau). Additionally, potential imaging biomarkers proposed for AD include glial inflammation, epigenomic alterations, structural and functional changes, as well as synaptic and cellular degeneration[10]. These markers can be assessed through techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI).

Despite their sensitivity and specificity in diagnosing AD at an early stage, the practical application of these biomarkers in clinical settings is hindered by vari-

ous limitations. These include the invasive nature of the procedures, financial constraints, and the lack of availability in most clinics. A more accessible and pragmatic approach would be blood-based biomarkers, which is feasible due to the disrupted blood-brain barrier in AD – enabling small molecules and proteins to leak into the blood circulation[11,12]. Proteomics allows investigation for proteins associated with AD on a large scale with techniques like mass spectrometry, electrophoresis, and immunoassays. However, there are some general considerations for using blood-based biomarkers, such as the low concentration of CNS proteins, dual expression in peripheral tissue, interference from other proteins, endogenous antibodies, and proteolytic degradation[13,14].

There are numerous methods for profiling proteomics. Proteomic profiling methods can be broadly categorized into two types: gel-based and gel-freetechniques. Gel-based techniques, such as two-dimensional electrophoresis (2-DE), have been traditionally used for protein separation and quantification. However, these techniques are limited by their inability to detect low-abundance proteins due to the high dynamic range of protein abundances, and those with extreme isoelectric points or molecular weights[15]. On the other hand, gel-free techniques, including liquid chromatography-tandem mass spectrometry (LC-MS/MS), overcome these limitations and offer higher sensitivity and throughput. LC-MS/MS allows for the simultaneous identification and quantification of thousands of proteins, making it particularly suitable for large-scale proteomic studies. However, performing plasma proteomics using MS poses several challenges, primarily due to the exceptionally wide dynamic range of protein abundance and need for sophisticated equipment and expertise, which may not be readily available in all laboratories [16–18].

In recent years, targeted proteomics platforms such as Olink and SomaScan have emerged as promising methods for protein profiling. These platforms offer a more targeted approach, focusing on specific proteins of interest with great sensitivity. This makes it particularly suitable for detecting low-abundance proteins that may be missed by other techniques[19]. However, the correlation between levels of proteins targeted by Olink and SomaScan and other platforms is modest, indicating that it may not always accurately target the intended proteins[20,21]. Additionally, many proteins altered in AD cerebrospinal fluid (CSF) were found to be altered in the opposite direction in plasma, which shows that

these platforms may not always provide consistent results across different biofluids[19].

Proteomic studies using MS and targeted proteomics with Olink and SomaScan have shown limited overlap in results, indicating that these technologies target different fractions of the proteome, and they meet in the high-abundance proteins region[22]. Both targeted and untargeted proteomics-based technologies have their own strengths and weaknesses, emphasizing the importance of a multi-faceted approach to improve overall performance.

Blood-based biomarkers present a less invasive and potentially cost-effective avenue for diagnosing and classifying AD processes. Over the past several decades, numerous studies have explored plasma biomarkers relevant to AD, marking significant progress in the field. For instance, recent research has demonstrated the predictive accuracy of AD hallmarks in plasma, such as Aβ42/40, p-tau 181, and 217, for brain pathology, suggesting their potential as non-invasive tools for diagnosing and prognosticating AD[23–26]. However, despite these advancements, there is notable variability in the reliability of blood biomarkers observed across individual studies. A recent meta-analysis highlighted the crucial role of analytical assays in assessing the accuracy of detecting AD hallmarks in blood[27], emphasizing the necessity for additional research to validate their effectiveness as screening tools.

This review aims to find the robustness of plasma proteomic changes in AD and dementia by assessing the replicability of blood plasma biomarkers. Beyond individual biomarkers, we aim to identify shared pathways and distinctive AD-specific markers, contributing to a comprehensive understanding of these neurodegenerative disorders.

Methods

A comprehensive search was conducted on Embase for papers published between 2019-2023. The keywords used for the search included “Alzheimer’s,” “proteomics,” and “blood”, focusing on human organisms and excluding preprints. Additional records were identified through manual search, for example based on the references of the papers. The resulting records were screened based on title and abstract. Records that passed the screening were assessed for eligibility criteria. The exclusion criteria involved studies not centered on blood

or using techniques other than mass spectrometry, Olink, or SomaScan. By combining these proteomic techniques, the analysis included of a broader spectrum of proteins than could be captured by any single method. Exclusion also applied to studies not sharing detailed results or a focus on core biomarkers such as amyloid beta 42 or phosphorylated tau. Finally, articles meeting all criteria were included in the literature review.

Significant results – as determined by the authors - were gathered, and when available, we collected the complete datasets for extra information on the proteins. The identified proteins from the studies were categorized based on the classifications from the authors; Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD) and dementia. Missing UniProt IDs were complemented using UniProt ID mapping[28]. Descriptive statistics, such as mapping overlapping proteins and testing replicability, were created in R version 4.2.2[29]. To refine for the more robust results, replicability filters for downstream analysis were applied based on the number of proteins that pass the threshold. For proteins identified in AD as well as dementia, this threshold was set to greater than two. Proteins that were AD specific in our results were included if they were identified more than once. GO biological functions for these proteins were retrieved using the ShinyGO app v.0.77[30] with a false discovery rate (FDR) below 10%. We assessed robustness of the direction of effect for the proteins, with robust proteins exhibiting consistent directional effects across all studies in which they were identified as significant. Protein-protein interaction plots were made using STRING v12.0 for consistently up- or downregulated proteins.

Results

Selected Papers and Study Characteristics

The literature research commenced with an Embase search resulting in a total of 316 records (Supplementary file s1). An additional five records, that were not included in the Embase results, were identified through manual searches. This led to a total of 321 records subjected to screening. After applying our exclusion criteria, fourteen articles were included in this literature review (Figure 1). Several articles performed multiple association tests, for example on a different dataset, which resulted in 33 association studies. The total amount of Alzheimer's

disease (AD), dementia and Mild Cognitive Impairment (MCI) subjects add up to 7931, 8687, and 145, respectively (Table 1). Aggregating the number of significantly altered proteins per study resulted in a total of 1718 hits for AD, 1339 hits for hits and 51 hits for MCI.

Biomarkers in Alzheimer's Disease and Dementia

In total, the included studies focusing on Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), and dementia collectively revealed 1579 unique proteins associated with these conditions, as identified by the respective authors. Noteworthy is the inclusion of multiple association tests conducted by some authors, for instance on AD and dementia separately, to enrich the dataset. The predominant focus of the studies was on Alzheimer's Disease versus controls (AD vs CTRL), with 18 studies making up the majority (Figure 2A). Unsurprisingly, this design yielded the most significant results (Figure 2B). AD vs CTRL studies

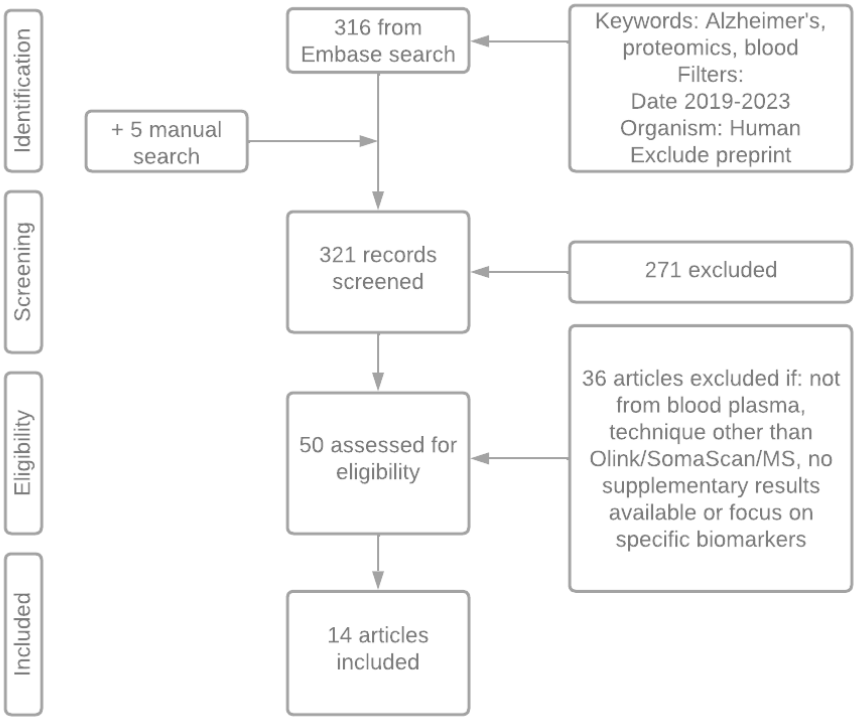

Figure 1 Flowchart illustrating the systematic review process for articles related to Alzheimer's and blood proteomics. The diagram depicts the stages of identification, screening, eligibility assessment, and inclusion of records from a comprehensive search on Embase and a manual search. The inclusion criteria involve data availability, specific focus on blood plasma and the use of Olink, SomaScan, or mass spectrometry techniques. A total of 14 articles passed the rigorous screening and eligibility criteria.

Table 1: Summary of included papers.

Reference	Cohort	Subjects				Blood fraction	Proteomic platform	# Significant hits			Significance cutoff by author
		Control	MCI	AD	Dementia			MCI	AD	Dementia	
Jiang et al. 2022[31]	180 Hong Kong Chinese people ≥ 60 years old	74	0	106	0	Plasma	Olink	-	429	-	Q < 0.05
Whelan et al. 2019[32]	Swedish BioFINDER study	415	75	161	0	Plasma	Olink	23	33	-	Q < 0.05
Walker et al. 2023[33]	ARIC	9078	0	161	1903	Plasma	SomaScan	-	9	26	P < 1.03 × 10-5
Lindbohm et al. 2021[34]	Whitehall II	2242	0	0	106	Plasma	SomaScan	-	-	21	x**
Ferkingstad et al. 2021[35]	35,559 Icelanders	3075 - 25601*	0	825-1549*	2106-3588*	Plasma	SomaScan	-	15-129*	471-615*	P < 2.7 × 10−8
Eldjarn et al. 2023[20]	35,559 Icelanders + 1514 Icelanders	39197	0	132-1958*	60-268*	Plasma	SomaScan + Olink	-	4-605*	5-23*	P < 1.0 × 10−5 / 1.7 × 10−5
Walker et al. 2021[36]	ARIC	x**	0	0	428	Plasma	SomaScan	-	-	38-44*	P < 1.0 × 10-5
Ehtewish et al. 2023[37]	122 particicipants from Doha, Qatar	32	0	0	22	Plasma	Olink	-	-	60	Q < 0.05
Kim et al. 2022[38]	GARD	46	50	136	0	Plasma	MS	19	18	-	
Dey et al. 2019[39]	Brain and Body Donation Program	5	0	6	0	Serum	LC-LC/MS-MS	-	30	-	P < 0.05
Park et al. 2019[40]	KBASE	79	0	40	0	Plasma	LC−MS/MS-MS	-	19	-	
Chen et al. 2023[41]	Framingham Heart Study Offspring	380 - 359*	0	64	85	Plasma	Olink	-	2	3	Q < 0.1
Francois et al. 2022[42]	SAND	40	20	20	0	Plasma	GC-MS /LC-MS	9	9	-	x**
Ashton et al. 2019[43]	AIBL and KARVIAH	100	0	44	0	Plasma	LC-MS/MS	-	6-8*	-	Q < 0.05
Total		**191368**	**145**	**7931**	**8687**			**51**	**1718**	**1339**	

Abbreviations: MCI: Mild Cognitive Impairment, AD: Alzheimer's Disease. Significant threshold was determined by the author of the paper based on the P value or corrected P value (Q). More details on the papers can be found in the Supplementary file S2.
**Multiple association studies, for instance on a different dataset, were performed, **Not defined*

identified 1273 distinct significant proteins, accounting for approximately 80.7% of the total unique proteins. Dementia vs CTRL studies identified 751 proteins, constituting around 47.6%, and MCI vs CTRL studies found 42 proteins, making up about 2.7% of the total. 792 (50.2%) of the identified proteins were exclusively found in AD studies. Similarly, dementia studies identified 285 (18.1%) proteins exclusively and 453 (28.7%) proteins overlapping in dementia and AD.

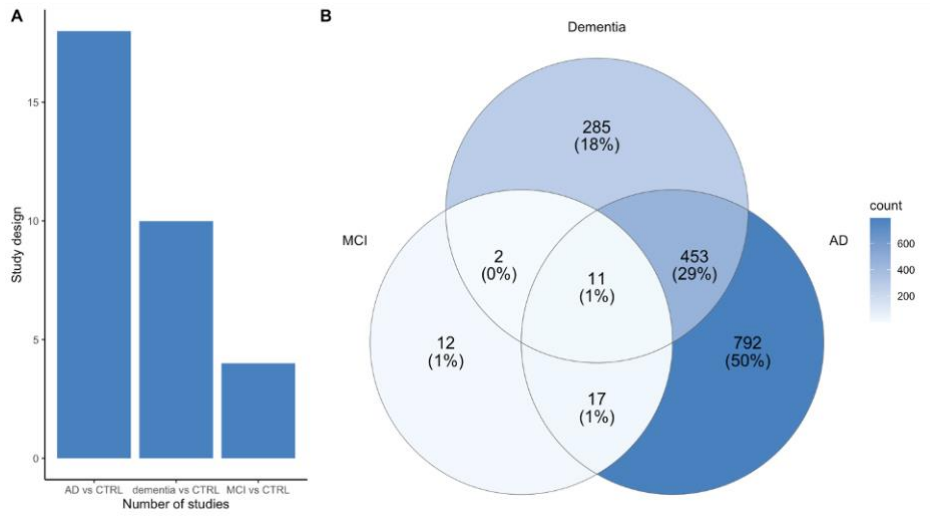

Figure 2: *illustration of the distribution of studies across different designs (A) and the overlap of proteins identified in association with Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), and dementia (B). The figure provides a visual representation of the prevalence of study designs and the distinctive protein landscapes associated with each condition.*

In the intersection of AD and dementia, zero proteins were identified uniquely (count of one) (Table 2). This observation suggests that the proteins in this category may originate from studies by the same authors that focus on proteomics in both conditions, ensuring technical and biological consistency. To ensure robust results for subsequent analyses, we used proteins identified in at least three studies in the AD + dementia comparison and at least two studies in AD specific. This approach resulted in 215 proteins in the first category and 92 in the second.

Table 2: Overview of the counts of identified proteins in the context of Alzheimer's Disease (AD) and dementia, differentiating between proteins specific to AD and those overlapping with dementia.

Count identified/ Threshold value	AD + Dementia		AD specific	
	Proteins	**Robust direction**	**Proteins**	**Robust direction**
14	1	0	0	0
9	1	0	0	0
7	9	4	0	0
6	4	0	2	2
5	14	7	3	2
4	54	9	3	3
3	132	38	16	13
2	238	44	68	52
1	0	0	700	700

The 'Count Identified' columns represent the number of times proteins were identified in the specified category and the 'Robust direction' columns indicates the robustness of the direction (up/down regulated) between the studies.

The identified biomarkers display inconsistencies in regulation patterns, with a significant portion exhibiting varied directional effects (Table 2). These discrepancies can be attributed to a combination of technical and biological variations. Firstly, the diversity in sample cohorts and ancestry among different studies may lead to variations in genetic backgrounds, influencing regulation patterns. The inclusion of diverse case classification methods further contributes to the heterogeneity across studies. Various classification systems, such as the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-AD&DA) criteria, Diagnostic and Statistical Manual of Mental Disorder–Fifth Edition (DSM-5) criteria, ATN (Amyloid, Tau, Neurodegeneration) criteria, and neuropshycological assessments, introduce different diagnostic frameworks. Additionally, variations in sample size, disease stage, sample preparation techniques, sequencing platforms, and statistical models further contribute to the observed inconsistencies.

Proteins that were AD specific showed higher robustness in direction of effect between studies than proteins in the AD and dementia category. This may stem from the higher biological homogeneity within the AD-specific subset, as these proteins could represent a more unified molecular profile. In contrast, the

proteins identified in the intersection of AD and dementia show lower robustness, reflecting a broader range of biological variation influenced by the heterogeneous nature of dementia. Additionally, the likelihood that AD-specific proteins originate from studies conducted by the same authors implies a level of author consistency in experimental design and analysis.

Overlap between proteomic platforms

The majority of the results originated from studies employing the SomaScan technique (Figure 3). One gene was found significant in both dementia and AD in studies across all three platforms, which is *NEFL* - a known biomarker in AD and dementia[37,44]. Similarly, the AD specific results identified one gene, namely *IGFBP3*, across the three platforms. This gene has been linked to AD in serum, but not in cerebrospinal fluid (CSF)[45,46].The consistent detection of *NEFL* and *IGFBP3* affirms their reliability as a marker, emphasizing its significance across different proteomic methodologies.

The limited overlap in results among the three platforms implies their unique focus on distinct fractions of the proteome. Each platform has its own strengths and limitations, and the absence of certain proteins in the results may be attributed to either their lack of significance or their non-measurement (or inaccurate measurement) in the respective platforms [20,21].

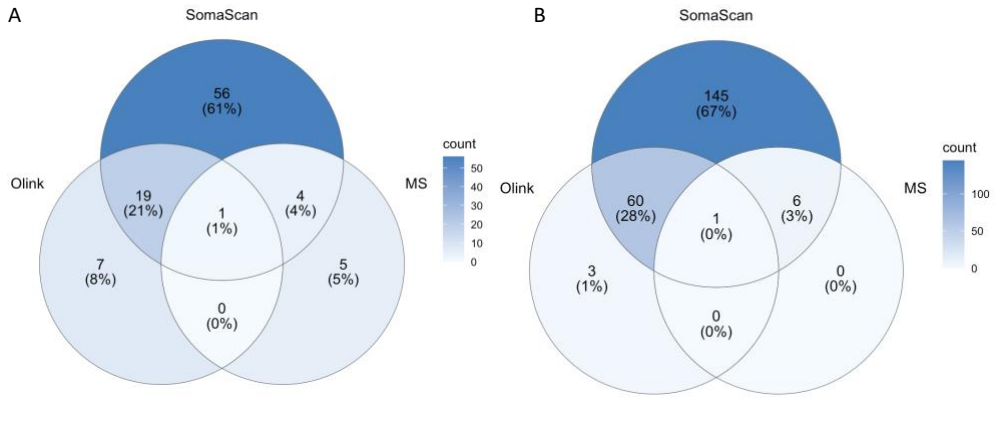

Figure 3: *: Illustration of the distribution of robust study results across proteomic platforms. Left (A) displays results specific to Alzheimer's (AD) and right (B) are shared results between AD and dementia.*

Shared biomarkers and enriched biological functions for AD and dementia

In the overlap of 215 selected proteins between dementia and Alzheimer's Disease (AD), a predominant inconsistency in the regulation pattern across studies was observed, with 73.0% displaying variability (Figure 4A). The enriched Gene Ontology (GO) biological functions of these proteins were associated with blood coagulation and hemostasis (Figure 4B). Additional processes were linked to cell secretion, organization, and adhesion. The 58 proteins that exhibited robust and consistent up- or downregulation showed several interactions (Figure 4C). The most enriched GO biological function among these proteins is collagen fibril organization, with the involved genes (*SERPINF2, COL11A2, TLL1, BMP1, ACAN,* and *FMOD)* highlighted in red. One of the highlighted genes, *SERPINF2*, known as α2-antiplasmin, has been recognized for its intricate interplay with the plasmin cascade and neurodegeneration[47,48]. While ongoing investigations explore the specific role of *SERPINF2* in AD, its differential expression in blood proteomics positions it as a promising peripheral biomarker for AD, improving our understanding of the molecular landscape associated with these neurodegenerative conditions.

AD-specific biomarkers and enriched biological functions

Contrastingly, AD-specific proteins demonstrated a higher degree of consistency in their regulation types across studies. The analysis revealed 60 downregulated, 20 upregulated, and 12 inconsistently regulated proteins (Figure 5A). Response to magnesium ion and neuromuscular junction development GO biological processes showed the highest fold enrichment (Figure 5B). 71 proteins showed robust direction between studies, with numerous interactions (Figure 5C). The most enriched biological function of these proteins is regulation of postsynapse organization. Genes involved in this process (*APP*, *LRRK2*, *BAIAP2*, *EGNL1* and *NTRK3*) are indicated in red. This finding gains significance when considering the interaction between *LRRK2* and the AD risk gene *APP*. Additionally, *LRRK2*'s association with dementia and AD, especially in the context of early onset[49,50], confirms the potential relevance of these proteins in the molecular mechanisms underlying AD and dementia.

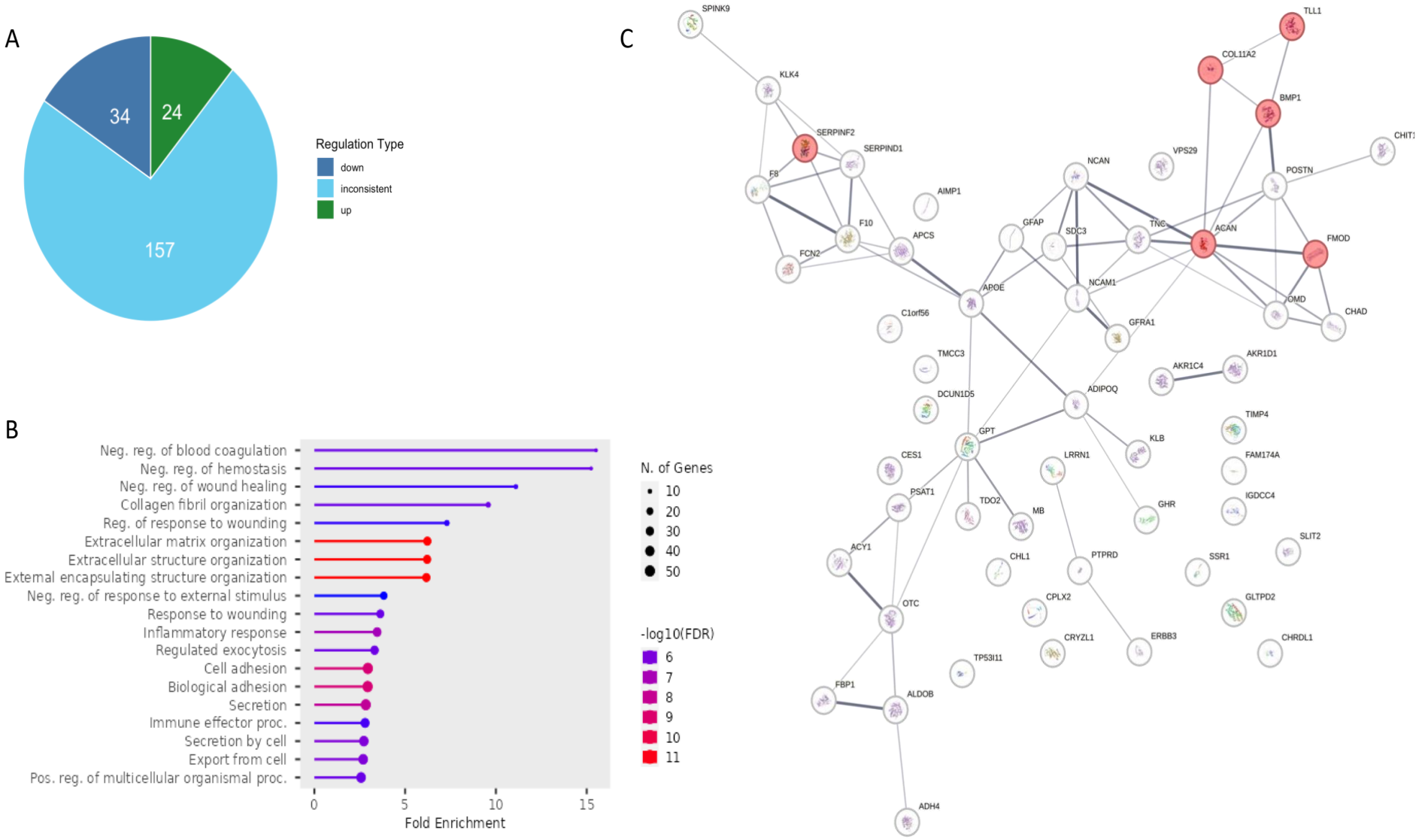

Figure 4: *Graphical overview of shared blood proteomics in Alzheimer's Disease (AD) and dementia. Graph A: Pie chart displays regulation type between studies of 157 replicated overlapping proteins. Graph B: Bar graph highlights biological processes of the 157 replicated proteins with -log10(FDR) values. Graph C: Protein-Protein interaction network of consistently up- and downregulated proteins. The most enriched biological GO function (collagen fibril organization) is highlighted in red.*

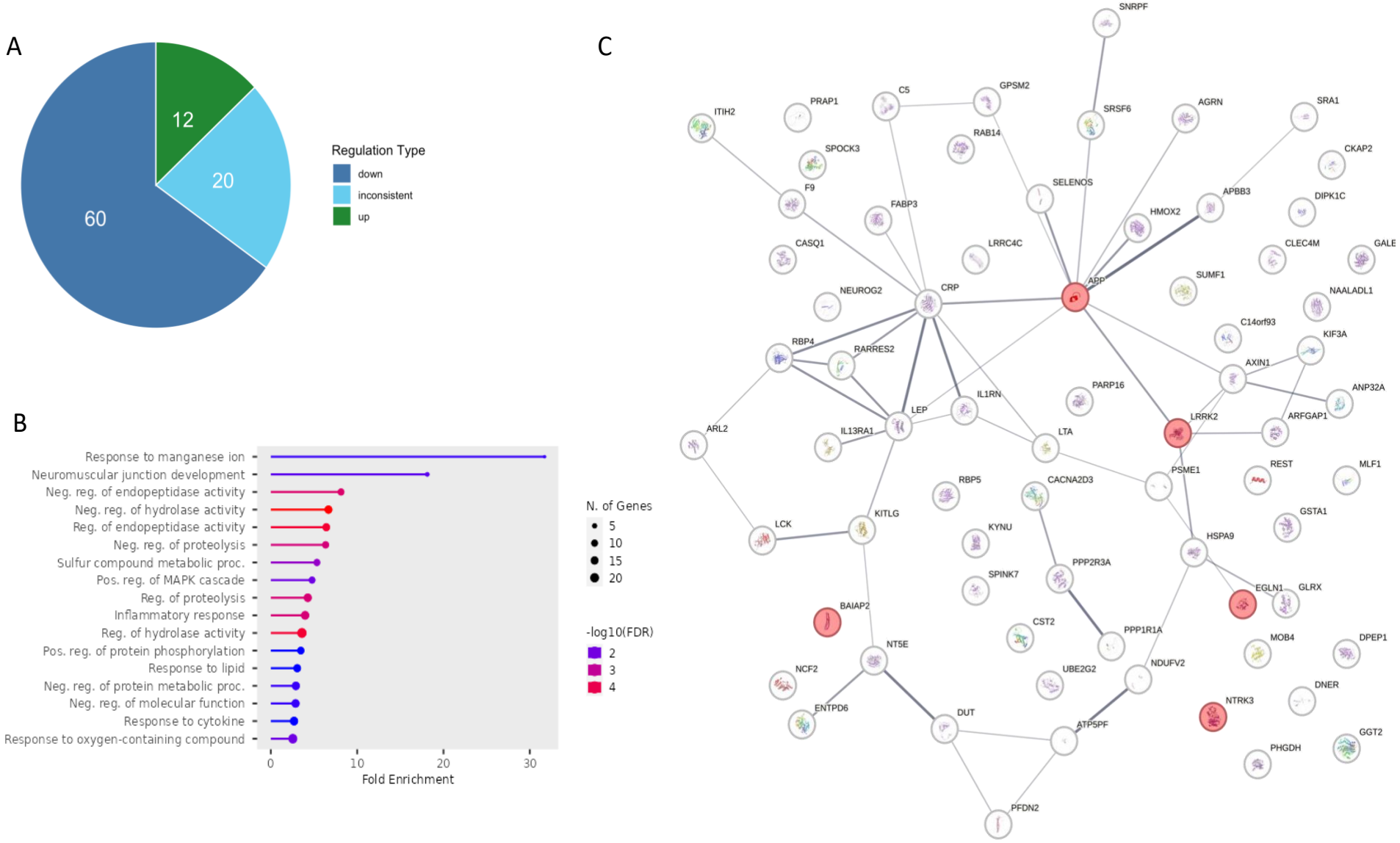

Figure 5: *Graphical overview of blood proteomics specific to Alzheimer's Disease (AD). Graph A: Pie chart displays regulation type between studies of the 92 replicated proteins. Graph B: Bar graph highlights biological processes of the 92 replicated proteins with -log10(FDR) values. Graph C: Protein-Protein interaction network of consistently up- and downregulated proteins. The most enriched biological GO function (regulation of post synapse organization) is highlighted in red.*

Comparison of blood and brain proteomics

The comparison of blood-based AD proteomics with other tissues, such as brain cortex tissue, holds relevance in understanding the systemic implications of the disease. While the blood provides a readily accessible and non-invasive source for biomarker discovery, it may not fully capture the molecular processes occurring within the central nervous system. The brain, being the primary site of AD pathology, offers a more direct insight into the molecular landscape of the disease. By comparing blood proteomics with brain tissue findings, we gain a perspective on the shared and distinct molecular elements between systemic and central nervous system processes. This analysis not only enhances our understanding of AD but also guides the development of blood-based biomarkers.

We compared our blood proteomics study on AD with a recent systemic review on AD proteomics in brain cortex tissue, both employing a similar approach—literature review, data collection, and identification of robust results[51]. Notably, there were overlaps in some genes, such as *APP* and *GFAP*, indicating shared molecular mechanisms across different tissues. However, distinctive sets of genes were also observed, reflecting tissue-specific responses to AD. The brain cortex tissue study highlighted distinct genes such as *HSPB1, CD44*, and *CLU*. Enriched biological functions in the brain study pointed towards synaptic signaling, vesicle-mediated transport, neurotransmitter transport, and neuron projection organization, suggesting the importance of synaptic dysfunction.

In terms of enriched biological functions, our blood study pointed towards processes related to blood coagulation, hemostasis, and neuromuscular junction development. This suggests that blood-based biomarkers may provide insights into AD-related vascular and muscular changes, potentially offering a unique perspective on disease progression. Conversely, the brain cortex tissue study emphasized synaptic signaling, vesicle-mediated transport, neurotransmitter transport, and neuron projection organization. These findings underscore the importance of synaptic dysfunction and neurodegeneration in the central nervous system during AD, which may not be fully reflected in blood proteomics.

The identification of distinct genes and enriched processes in blood versus brain cortex tissue signifies the need for a multi-tissue approach in biomarker

discovery for AD. Combining insights from different tissues could enhance the specificity and sensitivity of diagnostic tools, providing a more comprehensive understanding of AD pathology and potentially laying the groundwork for more effective interventions.

Discussion

This review compared several blood proteomics studies in the context of Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), and dementia. Beyond assessing individual biomarkers and their replicability, we aimed to identify shared pathways and distinctive AD-specific pathways in order to gain understanding of the mechanisms underlying these neurodegenerative disorders and compare these with known AD processes in the brain.

The study selection process led to the inclusion of 14 relevant articles, each employing distinct cohorts, subjects, proteomic platforms and blood fractions. The selected cohorts represented a spectrum of populations, including Chinese individuals from Hong Kong and participants from large-scale studies like the ARIC and Whitehall II cohorts. As evidenced by previous studies, it is evident to consider ethnicity when analyzing blood proteomics in AD and dementia[52–54]. Differences in case classification methodologies added an additional layer of complexity to the study selection process. Variations in how AD, MCI, and dementia were defined and classified across the diverse studies (Supplementary file s2) highlights the importance of considering these discrepancies in the interpretation of findings. Furthermore, the review considered disparities in the proteomic platforms employed by the included studies. Distinct techniques such as mass spectrometry, Olink, and SomaScan were used, each providing unique insights on the identification and characterization of blood proteomic signatures.

One notable strength lies in the integration of data from multiple proteomic platforms. This approach enhances the breadth and depth of our analysis, providing a more holistic view of the proteomic landscape associated with AD and dementia. The inclusion of various platforms enriches the dataset, capturing a diverse array of proteins and their potential implications. Another strength is our emphasis on replicability. By prioritizing the identification of robust biomarkers through multiple studies, we aim to enhance the reliability and credibility of the identified proteins. An additional strength is the comparative

analysis with brain tissue. This comparative aspect adds a layer of context to our findings, highlighting both shared and distinctive elements between blood-based biomarkers and brain-specific markers.

However, our study has certain limitations that should be acknowledged. Firstly, our review did not include all available proteomic platforms. The exclusion of platforms like 2D gel may result in missing potential proteins or regulatory patterns that could contribute to a more comprehensive understanding of AD and dementia. Despite our efforts to address heterogeneity, there remains a substantial level that we could not fully account for. The inherent variability in study designs, participant characteristics, and analytical methods across different studies may introduce confounding factors that influence the interpretation of our results.

The observed heterogeneity in results and the intricate interplay between systemic and central nervous system processes call for a multi-faceted approach in future investigations. Recognizing the limitations of individual studies and incorporating diverse methodologies will be crucial for gaining a more nuanced understanding of the molecular landscape associated with these neurodegenerative conditions.

This review investigated the blood proteome of Alzheimer's Disease (AD) and dementia. The analysis of candidate biomarkers shows challenges in establishing consistent regulatory patterns and the heterogeneity of blood proteomics studies. Enriched biological functions, particularly in blood coagulation and hemostasis, suggest systemic implications beyond the central nervous system, emphasizing the need for a holistic perspective. Comparative analysis with brain cortex tissue showed both shared and distinctive elements, underscoring the unique nature of blood-based biomarkers. Recognizing the interplay between systemic and central nervous system processes is crucial in advancing our comprehension of blood proteomics in AD and dementia. Acknowledging the complexity and heterogeneity of blood-based biomarkers, the findings encourage further exploration to bridge the gap between systemic markers and the pathology of AD and dementia.

Supplementary material

Details on the studies and proteins included in this review can be found in the Supplementary file.

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