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Advancements in Alzheimer's Disease Biomarkers: Emerging Protein Targets for Early Diagnosis and Therapeutic Intervention

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and neuronal loss. The identification of reliable biomarkers is crucial for early diagnosis and therapeutic intervention. This study explores an insight into current strategies and future approaches for improvement of the treatment, diagnosis, or prevention of AD. AD relevant data were collected from databases like PubMed, Google Scholar, and ScienceDirect. Our study findings reveal that traditional biomarkers such as amyloid-beta (Aβ) and tau proteins remain central to AD pathology, but emerging targets, including neurofilament light chain (NfL), triggering receptor expressed on myeloid cells 2 (TREM2), and synaptic proteins, are gaining attention for their diagnostic and prognostic value. Additionally, lipid peroxidation markers (4-HNE, MDA) and Cytokines (IL-6, TNF-α, and IL-1β) analyses have provided an invasive alternatives for disease monitoring. These advancements facilitate the development of precision medicine approaches, including targeted therapies aimed at modulating key pathological proteins.

Keywords: Alzheimer's disease; Biomarker; Astrocyte; Neurodegeneration; Pathophysiology

1. Introduction

Alzheimer's disease (AD) is a progressive, unremitting, neurodegenerative disease that damages large portions of the hippocampus and cerebral cortex. It is characterized by the accumulation of insoluble forms of toxic amyloid-beta (Aβ) plaques in extracellular spaces and blood vessel walls, and the microtubule protein tau aggregates in neurofibrillary tangles and causes neuroinflammation in the brain, which ultimately leads to irreversible neuronal loss (Botella Lucena et al., 2024; Thakur et al., 2018; Kumar et al., 2015; Masters et al., 2015). The accumulation of Aβ peptide in the brain, known as amyloid plaques, is an early occurrence in AD that may lead to neurodegeneration, cognitive, and functional impairment (Mintun et al., 2021). AD is an age-related disease that increases around 5% of those aged 65 to 74, 13.1% of those aged 75 to 84, and 33.3% of those aged 85 or older. Global population aging predicted the present significant rise in the number of people with this condition and predicts a future spike in the number of affected individuals. Between 2015 and 2050, the proportion of the global population over 60 will almost double, from 12% to 22%, or 2.1 billion people (Cummings et al., 2024). The worldwide burden of AD is anticipated to increase from 26.6 million cases in 2006 to 106.8 million by 2050 (Thakur et al., 2018). The abnormal amyloid plaque triggers the phosphorylation of tau protein, which subsequently spreads nearly infectiously by microtubule transport to adjacent neurons, causing neuronal death (Pooler et al., 2013). Therefore, targeted Aβ and phosphorylated tau (p-tau) are considered potential treatments in AD. However, cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers, in conjunction with several relatively recent clinical criteria, can help diagnose AD in live individuals, although the assessment of brain tissue is still the primary method of diagnosis (Bateman et al., 2020; Budson et al., 2012). Disease-modifying treatments for AD are still being researched extensively. Currently, treatment focuses on symptomatic therapy, gene therapy, immunotherapy, probiotics, peptidomimetics, metal chelators, and quantum dots as breakthroughs in existing AD management strategies (Khan et al., 2020; Yiannopoulou et al., 2020). Although attempts are now underway to lessen the generation and overall burden of disease in the brain.

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Based on available data, monoclonal antibodies, also known as passive immunotherapy, are used to treat AD by injecting an antibody that targets abnormal Aβ and makes it easier for the brain to eliminate it (Weller et al., 2018). Several specialists believe that combining a monoclonal antibody and a beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor to remove Aβ will lead to success in treating AD (Jacobsen et al., 2014; Perry et al., 2015). For the diagnosis of AD, phosphorylated tau 181 (P-tau181) can be utilized as a predictive and confirmatory biomarker that placed in the brain and released in CSF, which crosses the blood-brain barrier and reaches the bloodstream to function as an AD biomarker (Janelidze et al., 2020; Thijssen et al., 2020). In treating AD, many tau vaccinations have demonstrated both safety and effectiveness in animal studies (Rosenmann et al., 2013; Panza et al., 2016). In human patients, an anti-tau medication showed a notable safety profile and even boosted a beneficial immunological response (Novak et al., 2017). There are now some further early-phase trials of drugs that target the tau protein, but the findings have not yet been released (Weller et al., 2018; Panza et al., 2016). This study aims to give an insight into current strategies and future approaches for improvement of the treatment, diagnosis, or prevention of AD.

2. Methodology

A systematic and in-depth search was conducted across premier scientific databases (current as of January 10, 2025), including PubMed, ScienceDirect, Web of Science, and Google Scholar, using the keywords "Alzheimer," "Protein," and "Biomarker" to uncover relevant research.

2.1. Inclusion criteria

Specific criteria were established to select studies for this review, focusing on key biomarkers associated with Alzheimer's disease. Research conducted *in vivo*, *in vitro*, or *ex vivo*, with or without the use of experimental animals, was considered. Additionally, studies were included regardless of whether they detailed the underlying mechanism of action.

2.2. Exclusion criteria

The exclusion criteria for this review were clearly defined to maintain the relevance of the included studies. Studies were excluded if their titles or abstracts did not meet the inclusion criteria or if they contained duplicate data. Additionally, research focusing on neurological diseases was excluded if the findings were not directly related to the primary objectives of the current study.

3. Results and discussion

3.1. Pathophysiology of Alzheimer's disease

AD is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment (Chen et al., 2022). It's pathophysiology involves multiple interrelated mechanisms, including Aβ accumulation, tau pathology, neuroinflammation, and synaptic dysfunction, ultimately leading to neuronal loss (Long & Holtzman, 2019). The pathophysiology of Alzheimer's disease depicted in **Fig. 1**.

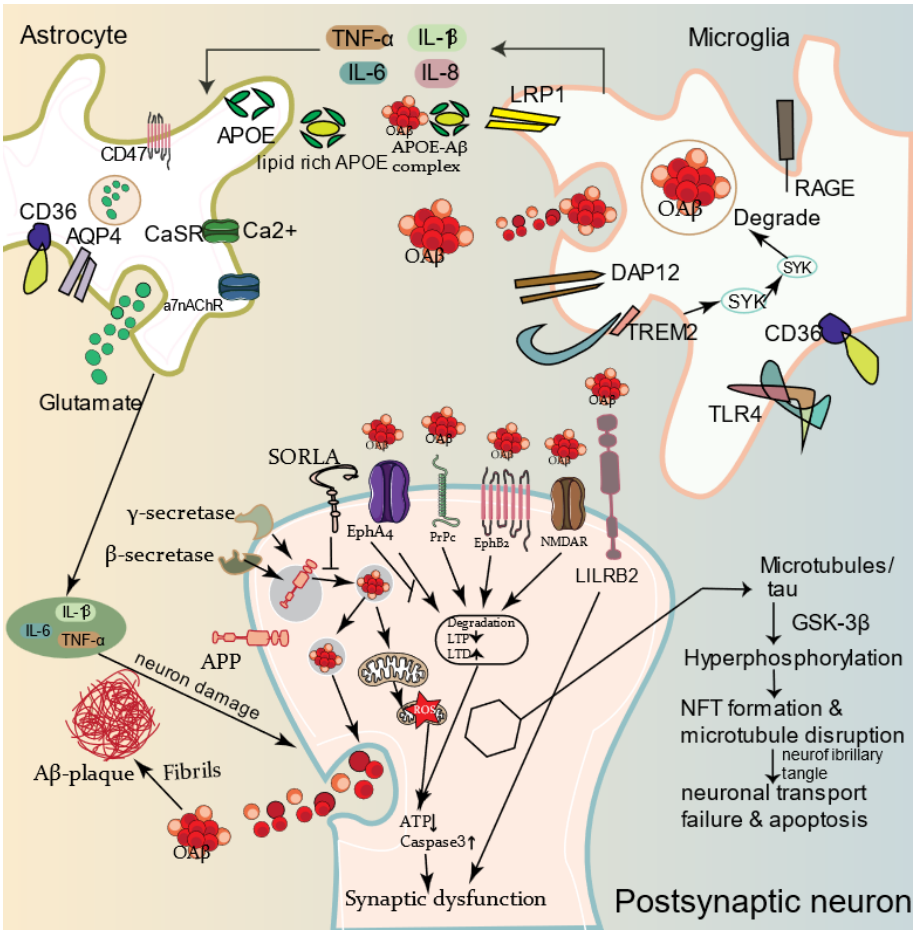

Fig. 1. The pathophysiology of Alzheimer's disease via amyloid-beta plaque and neurofibrillary tangles formation. Microglia uptake amyloid-beta plaque degrade it, release pro-inflammatory cytokines, and attract astrocytes to response. [IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alpha; IL-1β: Interleukin-1 Beta; Aβ: Amyloid-beta]

The amyloid cascade hypothesis posits that the accumulation of Aβ, generated from amyloid precursor protein (APP) via β- and γ-secretase cleavage, plays a central role in AD pathology (Hardy & Higgins, 1992; Selkoe & Hardy, 2016). Aβ deposition disrupts neuronal function and initiates downstream pathological events, including Tau hyperphosphorylation and microglial activation (Knopman et al., 2021). Tau hyperphosphorylation leads to the formation of neurofibrillary tangles (NFTs) by destabilizing microtubules and promoting aggregation into toxic forms, with GSK-3β and other kinases contributing to this process (Shi & Zhao, 2024; Shareena & Kumar, 2023). Chronic neuroinflammation in AD is driven by activated microglia and astrocytes, which release proinflammatory cytokines and reactive oxygen species (ROS) in response to Aβ and tau aggregates, further exacerbating neuronal damage and synaptic dysfunction (Agostinho et al., 2010). Synaptic impairment is amplified by soluble Aβ oligomers, which disrupt synaptic plasticity and cause excitotoxicity through N-Methyl-D-Aspartate/ α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (NMDA/AMPA) receptors, while tau pathology impairs microtubule stability. These processes ultimately lead to neuronal loss and cognitive decline (Meftah & Gan, 2023; Bukke et al., 2020).

3.2. Role of Proteins in Alzheimer's disease and therapeutic approach

Chen et al. (2017) highlighted the neurotoxic role of Aβ in AD, emphasizing its aggregation into oligomers, protofibrils, and fibrils. Advances in structural studies reveal Aβ fibril formation, guiding therapeutic strategies such as inhibiting oligomerization, immunotherapy, and targeting microglia to reduce inflammation. Despite ongoing efforts, current treatments remain symptomatic, while Aβ inhibitors and antibodies are under clinical investigation. Identifying key Aβ receptors and their structures is crucial for developing effective therapies (Chen et al., 2017). Monteiro et al. (2023) and Medina et al. (2014) demonstrated that neurofibrillary tangles, composed of hyperphosphorylated tau protein, represent a key hallmark of AD. Tau, a microtubule-associated protein, regulates axonal transport and dendritic structure, but abnormal hyperphosphorylation disrupts its function, leading to aggregation, synaptic loss, and neuronal death. Key factors driving Tau toxicity include conformational changes favoring phosphorylation and an imbalance between kinases (e.g., GSK-3β, cdk5) and phosphatases (PP1, PP2A). GSK-3β, a major contributor to tau hyperphosphorylation, is a promising therapeutic target for AD treatment (Monteiro et al., 2023; Medina et al., 2014). Monteiro et al. (2023) also find that oxidative stress in AD arises from an imbalance between reactive oxygen/nitrogen species and antioxidant defenses, leading to lipid, protein, and DNA damage. It contributes to AD progression through Aβ accumulation, microglial activation, redox-active metal dysregulation, and mitochondrial dysfunction. Aβ enhances oxidative stress by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, while microglia and astrocytes exacerbate neuroinflammation, releasing proinflammatory cytokines. Redox-active metals like Cu and Fe further amplify ROS production, promoting neurotoxicity. Mitochondrial dysfunction, characterized by impaired bioenergetics and increased ROS, accelerates neuronal damage. Targeting oxidative stress, metal homeostasis, and mitochondrial health holds promise for AD therapeutics (Monteiro et al., 2023). Established biomarkers and proteins associated with Alzheimer's disease are displayed in **Table 1.**

3.3. Emerging protein and biomarkers: novel targets and future directions

3.3.1. Inflammatory and immune biomarkers

3.3.1.1. Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is a key protein expressed by astrocytes and serves as a marker of astrocyte activation. It is upregulated during reactive gliosis, which occurs in response to brain injury, inflammation, or neurodegenerative diseases (Pekny & Nilsson, 2005). Increased GFAP expression indicates astrocyte activation, often associated with neuroinflammation in conditions like AD, multiple sclerosis, and traumatic brain injury (TBI). Elevated levels of GFAP are considered biomarkers of neurodegeneration and injury (Kim et al., 2023; Rauf et al., 2022) (**Fig. 2**).

3.3.1.2. Triggering receptor expressed on myeloid cells 2

Triggering receptor expressed on myeloid cells 2 (TREM2) is a cell surface receptor predominantly expressed on microglia, the resident immune cells of the central nervous system (CNS). TREM2 plays a crucial role in microglial function, including regulating their response to injury, inflammation, and neurodegeneration (Jay et al., 2017). It is involved in the recognition and clearance of cellular debris, as well as modulating immune responses in the brain. Mutations in TREM2 have been linked to neurodegenerative diseases such as AD, where they impair microglial function, leading to an inadequate immune response and exacerbating disease progression (Gratuze et al., 2018; Carmona et al., 2018) (**Fig. 2**).

Table 1. Established biomarkers and proteins for Alzheimer's disease

Key proteins Involved	Role of the protein	Therapeutic approaches	Key findings	References
Amyloid-beta oligomers (AβOs)	Forms amyloid plaques in the brain	Immunotherapy, small molecule inhibitors	Reduce Aβ plaques	Chen et al., 2017
Tau	Formation of neurofibrillary tangles and neuronal loss	Immunotherapy, multi-target small molecules	Reduce or clear tau from the brain	Monteiro et al., 2023; Medina et al., 2014
Oxidative stress	Formation of senile plaques in the brain	Antioxidant therapy, multi-target small molecules	Protect against oxidative stress and decrease ROS production	Monteiro et al., 2023
ROS: Reactive Oxygen Species; Aβ: Amyloid-beta				

3.3.1.3. Cytokines (IL-6, TNF-α, IL-1β)

Cytokines such as Interleukin-6 (IL-6), Tumor Necrosis Factor Alpha (TNF-α), and Interleukin-1 Beta (IL-1β) play pivotal roles in neuroinflammation, a key factor in neurodegenerative diseases like Alzheimer's, Parkinson's, and multiple sclerosis (Heneka et al., 2015; Cacquevel et al., 2004). These pro-inflammatory cytokines activate glial cells, enhance the production of other inflammatory mediators, and contribute to neuronal damage. IL-6 promotes glial activation, TNF-α triggers cell death and disrupts the blood-brain barrier, while IL-1β induces further inflammation and neurodegeneration by activating microglia and astrocytes, driving disease progression (Ng et al., 2018; Zheng et al., 2016) (**Fig. 2**).

3.3.2. Synaptic and neuronal biomarkers

3.3.2.1. Synaptosomal-associated protein 25: Synaptic integrity

SNAP-25 is a crucial protein involved in synaptic vesicle fusion and neurotransmitter release, playing an essential role in maintaining synaptic integrity (Li et al., 2024). SNAP-25 is part of the SNARE complex, which facilitates the docking and fusion of synaptic vesicles with the presynaptic membrane (Antonucci et al., 2016). Alterations in SNAP-25 expression or function can lead to disruptions in synaptic transmission, contributing to neurodegenerative diseases and neurological disorders, such as AD and schizophrenia (Mazzucchi et al., 2020) (**Fig. 2**).

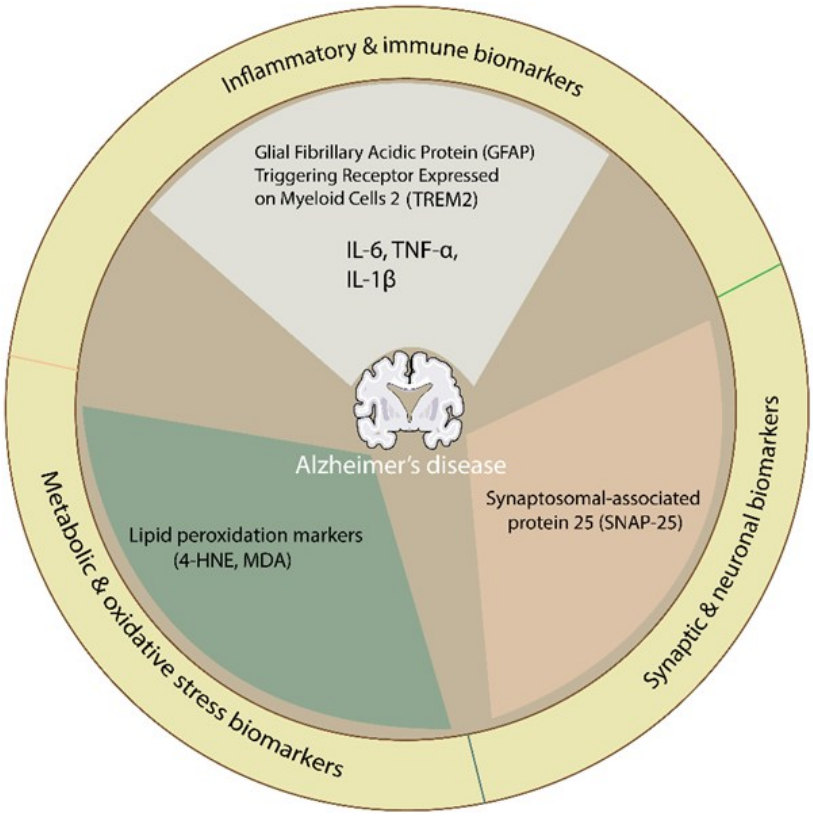

Fig. 2. Emerging Protein and Biomarkers. IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alpha; IL-1β: Interleukin-1 Beta; 4-HNE: 4 -hydroxy-2-nonenal; MDA: Malondialdehyde; Synaptosomal-associated protein 25 (SNAP-25)

3.3.3. Metabolic and Oxidative Stress Biomarkers

3.3.3.1. Lipid peroxidation markers

Lipid peroxidation markers, such as 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA), are products of oxidative stress that occur when polyunsaturated fatty acids in cell membranes are degraded (Breitzig et al., 2016). These markers are commonly elevated in neurological diseases, reflecting neuronal damage and oxidative injury. Increased levels of 4-HNE and MDA have been associated with various neurodegenerative conditions, including AD, Parkinson's disease, and multiple sclerosis. These markers contribute to neuroinflammation and are used as biomarkers to assess the extent of oxidative damage in the brain (Žarković et al., 2024) (**Fig. 2**).

4. Conclusion

In conclusion, the identification and development of novel biomarkers in AD have significantly advanced, offering promising avenues for early diagnosis and therapeutic intervention. Traditional biomarkers, such as amyloid-beta and tau proteins, continue to play a central role in understanding AD pathology, while emerging protein targets like neurofilament light chain (NfL), TREM2, and synaptic proteins show great potential for improving diagnostic accuracy and monitoring disease progression. minimally invasive methods, such as blood-based biomarkers and cerebrospinal fluid analyses, paves the way for more accessible and efficient disease tracking. These advancements in biomarker research hold the promise of personalized treatment strategies, ultimately leading to more effective therapies and improved patient outcomes in the fight against AD.

Conflict of interest

The authors declared no conflict

Data availability

Data will be made available on request.

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Author's contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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