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Misfolding and aggregation of protein in progressive neurodegenerative diseases: novel biomarkers and intervention strategies

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Abstract: This review aims to examine the role of protein misfolding and aggregation in the pathogenesis of neurodegenerative diseases (NDDs) and to evaluate emerging biomarkers and therapeutic strategies. A comprehensive literature-based approach was adopted to synthesize recent advances in molecular mechanisms, diagnostic tools, and intervention methods related to major NDDs, including Alzheimer's, Parkinson's, and Huntington's diseases. The findings indicate that protein misfolding leads to the formation of toxic aggregates that disrupt neuronal function and drive disease progression. While traditional biomarkers such as amyloid-beta and alpha-synuclein remain important, they are limited in detecting early-stage disease; in contrast, emerging biomarkers, including tau oligomers and blood-based indicators, demonstrate improved sensitivity for preclinical diagnosis. Regarding treatment, approaches such as immunotherapy, molecular chaperones, aggregation inhibitors, and gene-based therapies show promising potential, although challenges related to delivery, specificity, and long-term safety persist. Overall, advances in biomarker development and targeted therapies offer new opportunities for early diagnosis and disease modification. Continued optimization may enhance diagnostic accuracy, enable timely intervention, and support personalized treatment strategies for patients with NDDs.

Keywords: *Aggregation, Biomarkers, Neurodegenerative diseases, Protein misfolding, Therapeutic strategies.*

1. Introduction

Neurodegenerative diseases (NDDs) refer to disorders that cause the gradual degeneration of nerve cells in the brain and spinal cord. NDDs (Alzheimer's disease, Parkinson's disease, or Huntington's disease) are becoming more common in this era. People with NDDs often experience a decline in memory, movement problems, and difficulties with coordination, all of which might affect their quality of life [1]. As these diseases progress, they lead to irreversible brain damage, making them a major health concern worldwide.

One key feature of NDDs is the misfolding and buildup of proteins. Normally, proteins fold into specific shapes that allow them to function properly. However, in NDDs, some proteins fold incorrectly, leading to abnormal shapes that cause them to stick together and form clumps [2]. These protein clumps, or aggregates, can disrupt the normal function of brain cells and contribute to the symptoms of these diseases. For example, in AD, the amyloid-beta protein forms sticky plaques accumulating between nerve cells, while in Parkinson's disease, alpha-synuclein protein forms clumps, "Lewy bodies".

Protein misfolding and aggregation are believed to significantly impact the development and progression of neurodegenerative diseases (NDDs). When proteins misfold, they often become toxic to cells, causing damage. The accumulation of these toxic proteins can lead to inflammation and brain damage, worsening disease symptoms [3]. Understanding how and why proteins misfold in these diseases is essential for developing diagnostic, preventive, and therapeutic strategies.

Currently, there are a few methods used to detect protein misfolding in patients with NDDs. In Alzheimer's disease, for example, doctors can measure amyloid-beta and tau proteins in the

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cerebrospinal fluid to help diagnose the disease. Imaging techniques, such as PET scans, can also be used to visualize protein plaques in the brain. However, there is still a need for more reliable and accessible biomarkers that can detect protein misfolding in the early stages of disease, before symptoms appear.

Treatment for neurodegenerative diseases mainly focuses on managing symptoms, as there are no cures yet. For Alzheimer's disease, drugs like cholinesterase inhibitors can help improve memory and thinking skills, but they do not address the root of the disease. Similarly, in Parkinson's disease, medications can help control movement symptoms but do not stop the disease progression. Researchers are exploring new treatments that target the misfolding and aggregation of proteins, slowing or even stopping progression. Some potential therapies include using antibodies to clear protein clumps from the brain or developing small molecules that can prevent proteins from misfolding in the first place.

This review explains the effect of protein misfolding and aggregation in neurodegenerative diseases, focusing on how these processes contribute to disease development. It also examines some new biomarkers used to detect protein misfolding and discusses potential treatment strategies targeting harmful protein aggregates. By understanding these mechanisms, we aim to improve comprehension of how protein misfolding links to neurodegenerative diseases and to inform future research and treatment approaches.

2. Biomarkers in Protein Misfolding and Aggregation

2.1. Traditional Biomarkers

Biomarkers could help diagnose NDDs. Traditional biomarkers, such as amyloid-beta plaques for AD or alpha-synuclein aggregates for PD, have been essential in understanding the pathologies of these diseases.

In Alzheimer's, amyloid-beta plaques accumulate in the brain, disrupting cell function and contributing to neurodegeneration. These plaques can be detected using imaging techniques like positron emission tomography (PET), which uses radioactive tracers that bind to amyloid plaques [4]. Additionally, cerebrospinal fluid (CSF) analysis measures amyloid-beta and tau proteins to aid diagnosis. High levels of amyloid-beta in the brain, combined with low levels in the CSF, are strong indicators of Alzheimer's, especially when observed with clinical symptoms.

In Parkinson's disease, the accumulation of alpha-synuclein aggregates, known as Lewy bodies, is a key feature. Although these aggregates are challenging to detect in living patients, post-mortem studies and emerging imaging techniques aim to identify them more effectively [5]. However, clinical diagnosis of PD still relies largely on symptom progression rather than biomarkers, though research is ongoing to enhance early detection.

While these traditional biomarkers have been instrumental in understanding disease mechanisms, they have limitations, particularly in detecting diseases at early stages.

2.2. Emerging Biomarkers

Emerging biomarkers offer promise for earlier and more specific detection of neurodegenerative diseases. For instance, tau oligomers, small soluble aggregates, are more neurotoxic than larger tau tangles and appear in blood or CSF prior to tangle formation [6]. Detecting these oligomers enables earlier intervention, potentially slowing Alzheimer's disease progression before significant neuronal damage occurs. Similarly, misfolded proteins like mutant huntingtin in Huntington's disease are being investigated in biofluids to enhance diagnostic accuracy.

Together, traditional and emerging biomarkers provide complementary insights into disease onset. Crucially, fluid biomarkers typically rise in the preclinical stage, followed by structural changes detectable by imaging, and finally, clinical symptoms. This temporal trajectory is illustrated in Figure 1. A detailed comparison of these biomarkers is provided in Table 1.

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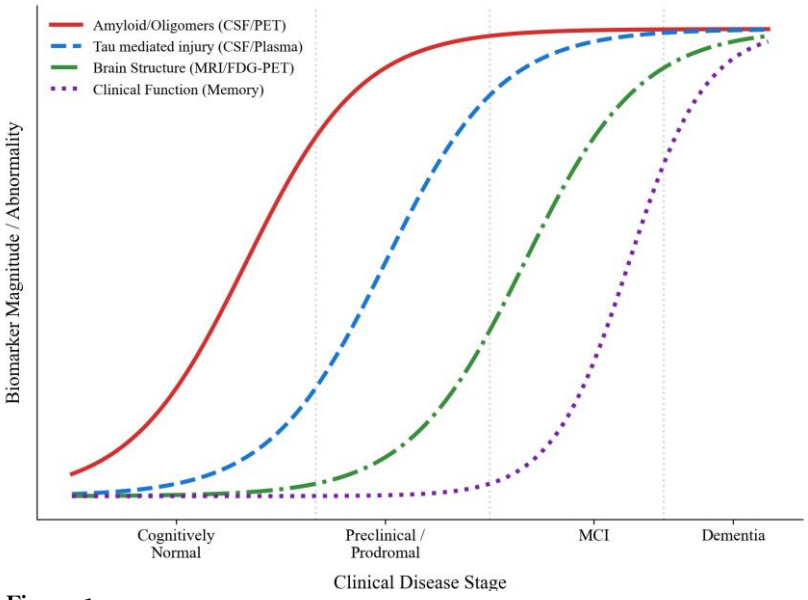

Figure 1.
Biomarkers in the progression of AD.

Table 1.
Comparison of Traditional and Emerging Biomarkers in Major Neurodegenerative Diseases.

Disease	Biomarker	Sample Source	Detection Method	Stage of Appearance	Key Advantages	Major Limitations
Alzheimer's disease (AD)	Amyloid-beta (Aβ42) plaques	Brain (PET), CSF	PET imaging, ELISA	Mid–late (plaques); CSF changes early	Well-validated; core diagnostic criterion	Invasive (CSF); expensive (PET); poor correlation with symptoms
	Total tau / Phospho-tau (p-tau)	CSF, blood (emerging)	ELISA, mass spectrometry	Early–mid	Reflects neuronal injury & tangle pathology	Limited specificity across NDDs
	Tau oligomers	CSF, blood	Ultrasensitive immunoassays (e.g., SIMOA)	Very early (pre-tangle)	High neurotoxicity is a better predictor of cognitive decline	Low abundance; assay standardization lacking
	Plasma p-tau217 / p-tau181	Blood	Mass spectrometry, SIMOA	Early	Minimally invasive; high AD specificity	Still under clinical validation
Parkinson's disease (PD)	α-Synuclein aggregates (Lewy bodies)	Brain (post-mortem)	Histopathology	Late	Pathognomonic for PD	Not detectable in living patients (until recently)
	α-Synuclein seed amplification assays (SAA)	CSF, skin, saliva	RT-QuIC, PMCA	Early / prodromal	High sensitivity/specificity (>90%); detects misfolded conformers	Requires specialized labs; not yet routine
Huntington's disease (HD)	CAG repeat expansion in HTT gene	Blood (DNA)	PCR, genetic testing	Lifelong (genetic)	Definitive diagnosis	Does not reflect protein aggregation dynamics or disease stage
	Mutant huntingtin (mHTT) protein	CSF, blood	Immunoassays (e.g., mHTT ELISA)	Pre-symptomatic to symptomatic	Direct measure of pathogenic protein; tracks therapeutic response	Low concentration; limited commercial assays

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2.3. Detection Methods

Several advanced methods are used to detect protein misfolding and aggregation, with imaging and fluid-based assays being the most common, focusing on accuracy and efficiency.

PET is used to detect amyloid-beta plaques and tau tangles in Alzheimer's patients. PET employs radiolabeled tracers that bind to specific misfolded proteins, enabling in vivo visualization of protein aggregates [7]. Although PET is highly sensitive, its high cost and limited availability restrict widespread use. Magnetic resonance imaging also helps assess structural brain changes due to neurodegeneration, but cannot directly visualize protein aggregates like PET.

Blood and CSF are valuable sources for detecting biomarkers of misfolding and aggregation. CSF analysis, which measures levels of amyloid-beta, tau, and other proteins, has been used for diagnosing Alzheimer's disease. Newer research focuses on biomarkers in blood, offering a safer and more feasible alternative to CSF analysis. Techniques like enzyme-linked immunosorbent assays and mass spectrometry are used to measure these biomarkers. Although blood tests for amyloid-beta and tau are still being validated, they hold promise for early detection of AD.

2.4. Challenges in Biomarker Discovery

Despite the progress made in identifying biomarkers, several challenges remain in their clinical application.

One of the primary challenges is improving the sensitivity and specificity of biomarkers. Some biomarkers, such as tau oligomers, are difficult to measure accurately due to their low concentration and transient nature. This limits their ability to detect diseases at early stages when treatment could be most beneficial.

Ensuring that biomarker measurements are reproducible across different labs and testing conditions is a challenge. Variations in testing methods and reagents can lead to inconsistencies in results. Standardizing protocols and validating assays are crucial steps toward making biomarkers more reliable for clinical use.

The ultimate goal of biomarker research is to identify misfolded proteins in the earliest stages of disease. While biomarkers are useful for monitoring disease progression, they are not sensitive enough to detect subtle changes before clinical symptoms emerge. Developing biomarkers that can identify these early-stage changes is critical for improving treatment outcomes.

3. Mechanisms of Protein Misfolding and Aggregation

3.1. Protein Folding and Misfolding

Proteins are essential molecules that perform various functions in cells, and their proper function depends on their ability to fold into specific three-dimensional shapes. The amino acid sequence guides this folding process, determining how the protein interacts with other molecules to achieve its native structure [8]. Protein folding is typically spontaneous and occurs in an aqueous environment, assisted by molecular chaperones and enzymes that ensure proper conformation.

When proteins fold correctly, they adopt a stable structure, allowing them to carry out their biological functions. However, misfolding occurs when a protein fails to achieve this correct structure. This can result from factors such as genetic mutations, errors in folding, or environmental changes like heat or pH shifts. Misfolded proteins expose hydrophobic regions that are usually hidden inside the protein, which can lead to interactions with other misfolded proteins, causing aggregation.

Aggregation refers to the clumping of misfolded proteins into larger complexes. While some aggregates are non-toxic, in neurodegenerative diseases, these aggregates often become harmful to cells [9]. They can form small, soluble oligomers or large, insoluble fibrils, disrupting normal cellular functions. These aggregated proteins are connected to several different NDDs. The pathway from protein misfolding to neuronal dysfunction is summarized in Figure 2.

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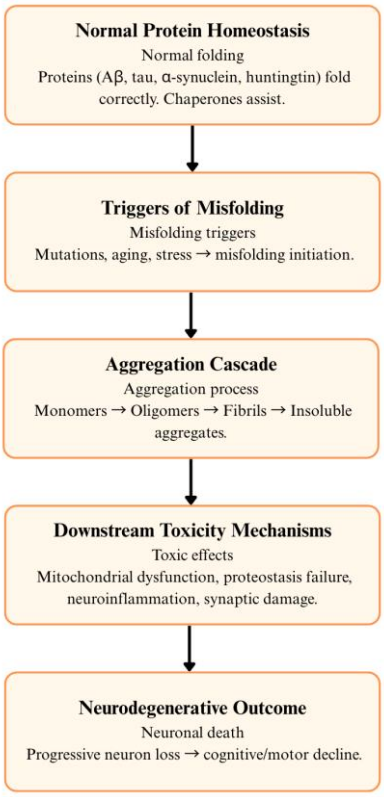

Figure 2.
From protein misfolding to neurodegeneration: a schematic overview of the pathogenic cascade in neurodegenerative diseases.

3.2. Pathological Aggregates

In NDDs, the accumulation of pathological aggregates is a key feature. These aggregates often form amyloid fibrils, tau tangles, and alpha-synuclein fibrils, each linked to specific diseases.

In AD, amyloid-beta peptides misfold and aggregate into fibrils, forming plaques between neurons. These plaques disrupt communication and function, playing a central role in disease progression [10]. While relatively stable and detectable via imaging like PET scans, amyloid plaques are toxic, promoting inflammation and oxidative stress, leading to neuronal death.

Tau, a protein that stabilizes microtubules in neurons, becomes hyperphosphorylated in AD and other tauopathies. This may generate insoluble tangles, impairing microtubule stability and intracellular transport, leading to neuronal dysfunction and death [11]. Tau tangles often co-occur with amyloid plaques, both contributing to cognitive decline.

In Parkinson's, alpha-synuclein aggregates into fibrils called Lewy bodies, disrupting synaptic vesicle release and neurotransmitter signaling. These aggregates are toxic, particularly in the substantia nigra, and trigger inflammation and oxidative stress, exacerbating neuronal damage. Similarly, in Huntington's disease, mutant huntingtin protein forms intranuclear inclusion bodies, which interfere with gene transcription and mitochondrial function. A summary of these pathological aggregates and their mechanisms is provided in Table 2.

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Table 2.
Characteristics of Pathological Protein Aggregates in Major Neurodegenerative Diseases.

Disease	Misfolded Protein	Aggregate Form	Primary Location	Key Pathological Mechanisms
Alzheimer's Disease (AD)	Amyloid-beta (Aβ)	Amyloid plaques (Fibrils)	Extracellular (between neurons)	Disrupts neuronal communication, promotes inflammation and oxidative stress, leading to neuronal death [10].
	Tau (Hyperphosphorylated)	Neurofibrillary tangles (NFTs)	Intracellular (inside neurons)	Impairs microtubule stability and intracellular transport; causes neuronal dysfunction; correlates with cognitive decline [11].
Parkinson's Disease (PD)	Alpha-synuclein	Lewy bodies (Fibrils)	Intracellular (synaptic terminals, substantia nigra)	Disrupts synaptic vesicle release and neurotransmitter signaling; triggers inflammation and oxidative stress.
Huntington's Disease (HD)*	Mutant Huntingtin (mHTT)	Intranuclear inclusion bodies	Intracellular (nucleus and cytoplasm)	Disrupts gene transcription and mitochondrial function; leads to preferential loss of striatal neurons.

***Note:** HD is included for comparison based on the broader context of neurodegenerative proteinopathies.

3.3. Toxicity of Aggregates

Protein aggregates are a major mechanism driving neurodegenerative diseases, causing cell damage through multiple pathways. Aggregates generate reactive oxygen species (ROS), causing oxidative stress. ROS oxidize lipids, proteins, and DNA, damaging cellular structures and disrupting function. Neurons, with limited repair capacity, are especially vulnerable to this damage [12]. ROS accumulation leads to mitochondrial dysfunction, further amplifying damage.

Mitochondria are critical targets; aggregates disrupt their function, reducing ATP production and causing apoptotic cell death in diseases like Parkinson's and Alzheimer's. Additionally, the buildup of aggregates exceeds the cell's protein quality control capacity, particularly the proteasome and autophagy pathways. When these clearance mechanisms fail, toxic proteins accumulate, resulting in irreversible neuronal damage. The interaction of these toxic mechanisms, mitochondrial impairment, oxidative stress, and proteostatic failure, is depicted in Figure 3.

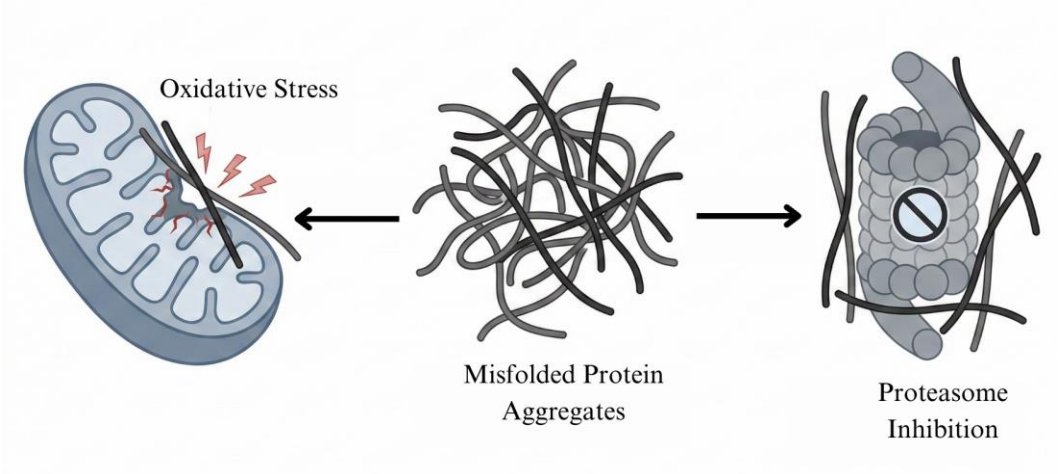

Figure 3.
Cellular mechanisms of toxicity induced by protein aggregates.

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3.4. Genetic and Environmental Factors

Genetic mutations and environmental factors both influence protein misfolding and aggregation. Mutations in genes encoding specific proteins can lead to the production of mutant forms that are more likely to misfold.

In AD, mutations of the amyloid precursor protein (APP) gene and in the presenilin-1 and presenilin-2 genes result in the overproduction of amyloid-beta peptides, which are more likely to aggregate. These mutations are typically found in rare, early-onset familial forms of Alzheimer's. In Parkinson's disease, mutations in the alpha-synuclein (SNCA) gene cause the production of mutant alpha-synuclein, which is more likely to aggregate into toxic fibrils [13]. In Huntington's disease, an expanded CAG repeat in the huntingtin gene leads to a mutant protein that aggregates and causes neurodegeneration.

Environmental elements such as toxins, oxidative stress, and aging can also contribute to protein misfolding. For instance, exposure to certain chemicals or pesticides might be related to an increased risk of Parkinson's disease, possibly due to their impact on protein aggregation. Aging itself is a significant risk factor for neurodegenerative diseases, as the ability of cells to maintain proteostasis diminishes over time.

Genetic mutations and environmental factors interact to influence the development of neurodegenerative diseases. Understanding how these factors impact protein misfolding and aggregation is important for developing effective therapeutic strategies to prevent or reverse these processes.

4. Intervention Strategies

4.1. Current Therapeutic Approaches

Currently, therapies for NDDs primarily aim at symptom management, as there are no cures to reverse disease progression. AD and PD treatments focus on modulating neurotransmitter activity rather than addressing the underlying protein misfolding and aggregation.

In AD, cholinesterase inhibitors like donepezil help improve cognition by increasing acetylcholine levels. However, these drugs do not target amyloid plaques or tau tangles, the disease's core pathology [14]. Similarly, in PD, levodopa and dopamine agonists control motor symptoms, but they don't prevent alpha-synuclein aggregation or halt neurodegeneration.

Immunotherapy has emerged as a promising strategy targeting protein aggregation directly. Immunotherapies aim to improve the immune system's ability to discover and clear toxic protein aggregates, like amyloid-beta in AD. Aducanumab, an FDA-approved antibody, targets amyloid plaques, though its clinical benefits are still debated. In PD, antibody-based therapies targeting alpha-synuclein are being tested, though challenges remain, such as ensuring these therapies can cross the blood-brain barrier and minimizing side effects. A comparison of these current therapeutic approaches and their limitations is presented in Table 3.

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Table 3.
Comparison of Symptomatic Treatments and Immunotherapeutic Strategies in Neurodegenerative Diseases.

Therapeutic Approach	Target Disease	Example Agents	Mechanism of Action	Current Limitations & Challenges
Symptom Management	Alzheimer's Disease (AD)	Cholinesterase inhibitors (e.g., Donepezil)	Increases acetylcholine levels to improve cognition.	Does not target amyloid plaques or tau tangles; it cannot reverse disease progression [14].
	Parkinson's Disease (PD)	Levodopa, Dopamine agonists	Modulates neurotransmitter activity to control motor symptoms.	Does not prevent alpha-synuclein aggregation or halt neurodegeneration.
Immunotherapy (Disease-Modifying)	Alzheimer's Disease (AD)	Anti-amyloid antibodies (e.g., Aducanumab)	Enhances immune clearance of toxic amyloid plaques.	Clinical benefits are debated; high cost; potential side effects (e.g., ARIA).
	Parkinson's Disease (PD)	Anti-α-synuclein antibodies	Targets and clears alpha-synuclein aggregates.	Difficulty crossing the blood-brain barrier (BBB); safety concerns; efficacy still under testing.

4.2. Chaperone Proteins and Heat Shock Proteins

Molecular chaperones and heat shock proteins assist in protein folding and prevent misfolded proteins from aggregating. These proteins are crucial for maintaining cellular protein homeostasis. Under stress conditions, cells increase the expression of HSPs like HSP70 and HSP90, which help refold damaged proteins or direct them for degradation.

Treatment strategies to boost HSP activity could help prevent protein misfolding in NDDs. Small molecules activating HSPs are being explored for AD and PD, showing promise in reducing amyloid-beta and alpha-synuclein aggregation in cell models [15]. While these therapies show potential, challenges remain in ensuring HSP activation targets only misfolded proteins without disrupting normal cellular processes.

4.3. Inhibition of Aggregation

Preventing the aggregation of misfolded proteins is a key therapeutic approach for NDDs. Small molecules and peptides are actively explored to block or reverse this process by stabilizing proteins in their native conformation. In AD, agents targeting amyloid-beta aim to prevent toxic plaque formation, while in PD, inhibitors focus on stopping alpha-synuclein aggregation into Lewy bodies. Additionally, peptides mimicking aggregation-prone sequences compete with misfolded proteins to prevent clumping. The specific intervention points for these strategies along the protein aggregation pathway, from monomer stabilization to fibril inhibition, are illustrated in Figure 4. While promising, effective brain delivery and long-term efficacy remain significant challenges.

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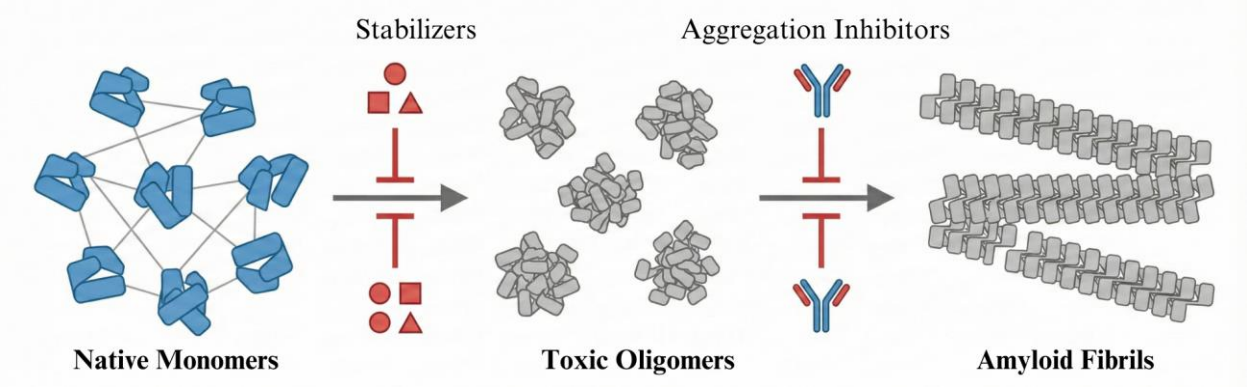

Figure 4.
Therapeutic intervention points in the protein aggregation pathway.

4.4. Enhancing Protein Clearance Mechanisms

Another strategy is to enhance the brain's natural protein clearance ability, such as autophagy and proteasomal degradation. The failure of these systems contributes to the accumulation of protein aggregates in neurodegenerative diseases (NDDs).

Several compounds, such as rapamycin, have been identified that induce autophagy, enhancing the clearance of amyloid-beta and alpha-synuclein aggregates. These compounds show promise in biological models of AD and PD, though their clinical application is still in early stages. Gene therapies designed to upregulate autophagic or proteasomal proteins could further help clear protein aggregates, offering a potential avenue for slowing or halting disease progression. However, manipulation of these pathways must be done carefully to avoid disrupting normal cellular functions.

4.5. Gene Editing and RNA-based Therapies

Gene editing technologies like CRISPR/Cas9 can directly modify genes responsible for producing misfolded proteins. For example, in Huntington's disease, CRISPR/Cas9 reduces mutant huntingtin expression, preventing aggregation. Similar strategies could target mutations in genes like APP (Alzheimer's) or SNCA (Parkinson's), which lead to misfolded protein production.

RNA-based therapies, such as antisense oligonucleotides (ASOs) and RNA interference (RNAi), are promising approaches. ASOs can bind to specific mRNA molecules, preventing the production of harmful proteins. For instance, ASOs targeting alpha-synuclein mRNA are under clinical investigation for Parkinson's disease, aiming to reduce toxic aggregates. RNAi-based therapies also aim to silence specific genes contributing to protein misfolding. These approaches offer hope for genetic neurodegenerative diseases, but challenges like delivery to the brain and long-term effects require further research.

5. Conclusion

This review highlighted the significant role of protein misfolding and aggregation in the pathogenesis of neurodegenerative diseases (NDDs) such as Alzheimer's, Parkinson's, and Huntington's diseases. Traditional biomarkers, including amyloid-beta plaques in Alzheimer's and alpha-synuclein aggregates in Parkinson's, have provided valuable diagnostic insights but are limited by their inability to detect early-stage disease and lack of specificity across different NDDs. Emerging biomarkers, such as tau oligomers and mutant protein forms in blood and cerebrospinal fluid, show promise for early detection and more accurate disease monitoring. Advances in imaging techniques, especially PET scans, and fluid-based assays are improving biomarker precision, although challenges in sensitivity, reproducibility, and validation remain.

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Regarding therapeutic strategies, current approaches largely focus on symptom management, with immunotherapy, small molecules, and molecular chaperones showing promise in addressing the root causes of protein aggregation. Efforts to enhance protein clearance through autophagy and proteasomal degradation pathways, as well as gene-editing techniques like CRISPR/Cas9, hold significant potential for disease-modifying treatments. However, delivery challenges and long-term safety concerns must be solved before these therapies are widely implemented.

The findings from this review underscore the importance of biomarkers in the early diagnosis and monitoring of NDDs. The development of more sensitive and specific biomarkers will enhance the ability to detect diseases in their earliest stages, improving patient outcomes by enabling timely intervention. Therapeutic approaches targeting protein misfolding and aggregation, if proven effective, could revolutionize treatment strategies by addressing the key causes of neurodegeneration.

Future research could validate and standardize emerging biomarkers to improve diagnostic accuracy and reliability. Further research on the molecular mechanisms driving protein misfolding and aggregation will facilitate the development of more targeted and personalized therapies. Additionally, exploring the role of neuroinflammation, epigenetic modifications, and the microbiome could open new avenues for preventing or slowing disease progression. With continued innovation and collaboration, the future of neurodegenerative disease treatment looks promising, with the potential for transformative breakthroughs.

Transparency:

The author confirms that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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