REVIEW

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Misfolding and aggregation in neurodegenerative diseases: protein quality control machinery as potential therapeutic clearance pathways

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Abstract

The primary challenge in today's world of neuroscience is the search for new therapeutic possibilities for neurodegenerative disease. Central to these disorders lies among other factors, the aberrant folding, aggregation, and accumulation of proteins, resulting in the formation of toxic entities that contribute to neuronal degeneration. This review concentrates on the key proteins such as β-amyloid (Aβ), tau, and α-synuclein, elucidating the intricate molecular events underlying their misfolding and aggregation. We critically evaluate the molecular mechanisms governing the elimination of misfolded proteins, shedding light on potential therapeutic strategies. We specifically examine pathways such as the endoplasmic reticulum (ER) and unfolded protein response (UPR), chaperones, chaperone-mediated autophagy (CMA), and the intersecting signaling of Keap1-Nrf2-ARE, along with autophagy connected through p62. Above all, we emphasize the significance of these pathways as protein quality control mechanisms, encompassing interventions targeting protein aggregation, regulation of post-translational modifications, and enhancement of molecular chaperones and clearance. Additionally, we focus on current therapeutic possibilities and new, multi-target approaches. In conclusion, this review systematically consolidates insights into emerging therapeutic strategies predicated on protein aggregates clearance.

Keywords α-synuclein, β-amyloid, Aggregates, Chaperones, Misfolded proteins, Neurodegenerative disease, Tau
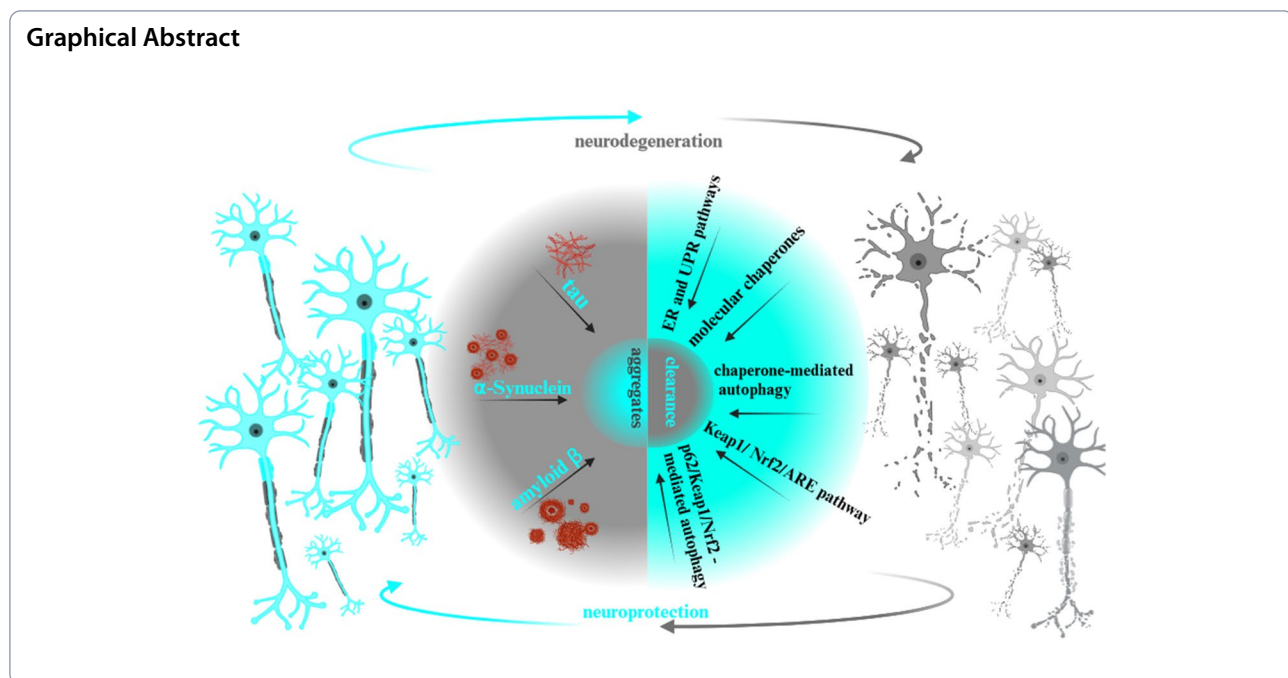
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Graphical Abstract

Neurodegenerative disease

Neurodegenerative diseases (ND) pose an unparalleled challenge in the realm of global clinical exigencies, covering a spectrum of disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and Alexander disease (AxD). These conditions manifest with discernible impairments in both motor and cognitive functions, frequently coupled with psychiatric disturbances. Moreover, an onset of neurological symptoms tends to manifest during the middle-age phase and progressively intensifies over the course of the disease. The limited regenerative capacity of the human brain significantly contributes to the marked depletion of neuronal populations, principally attributed to processes of protein misfolding and aggregation, thereby engendering the formation of more potent neurotoxic forms [1].

Despite numerous scientific studies in this field, there are currently significant gaps in our knowledge regarding the fundamental mechanisms of the pathogenesis of these disorders. A myriad of hypotheses has been proffered by the scientific community in the context of neurodegeneration, yet a predominant reliance on speculative postulations remains evident. Therapeutic and pathomechanistic paradigms seem to converge notably on the intricacies of protein misfolding and the resultant formation of toxic aggregates [2, 3].

In light of the above, this review aims to systematically gather pertinent and reliable information on neurodegenerative diseases, focusing on potential mechanisms for aggregated protein clearance and new multi-target therapeutic approaches. To realize that objective, our

description started with a brief delineation of selected diseases intricately associated with the overarching phenomenon of neurodegeneration.

This review systematically integrates the mechanisms underlying the clearance of misfolded proteins in neurodegenerative diseases. We emphasize potential strategies, highlighting the roles of the endoplasmic reticulum (ER) and unfolded protein response (UPR), chaperones, chaperone-mediated autophagy (CMA), and the intersecting signaling pathways of Keap1-Nrf2-ARE, as well as the connection between autophagy and p62. While these pathways hold promise, the review acknowledges that further research, regarding the mentioned mechanisms is essential for advancing therapeutic strategies.

Alzheimer's disease

Alzheimer's disease (AD) stands as the predominant form of dementia, representing 60–70% of documented cases [4]. The current global impact is staggering, with an estimated 46.8 million individuals affected, a figure projected to escalate to 131.5 million by 2050 [5]. AD is characterized by an inexorable and irreversible progression, marked by cerebral atrophy and the consequential loss of cognitive functions. This pathophysiological cascade manifests across a spectrum of symptoms, intricately complicating daily activities. Communication disorders, disorientation, impaired swallowing and motor functions, as well as the emergence of apathy and depression, collectively underscore the multifaceted challenges posed by this debilitating disorder. Remarkably, the insidious trajectory of pathological alterations within the brain

commences long before clinically observable symptoms manifest [6], and according to data, cholinergic and glutamatergic neurons are the most affected.

Presently, the most widely accepted conceptualization of AD pathogenesis revolves around a sequence of events initiated by the accumulation of β-amyloid (Aβ) and tau proteins, culminating in neurodegeneration and the manifestation of the disease [7]. Misfolding of these proteins leads to the formation of toxic aggregates in specific brain regions, which allows them to spread to connected areas [8]. Numerous studies indicate that fibrillar Aβ deposits form senile plaques, and the concomitant emergence of neurofibrillary tangles, constituting neurofibrillary degeneration. These pathological entities preferentially manifest in brain regions involved in memory and emotional processing, including the entorhinal cortex, hippocampus, and amygdala [9].

The discernible shortcomings in the clinical efficacy of anti-Aβ pharmaceutical interventions have instigated a critical reassessment of the entrenched "amyloid cascade hypothesis". Despite the discordant nature of empirical findings, that theoretical framework remains a focal point of rigorous scrutiny to validate its foundational tenets [5].

At the molecular level, the aberrant accumulation of Aβ and tau proteins disrupts neuronal homeostasis, triggering inflammatory responses and oxidative stress. The interaction between Aβ and synaptic proteins interferes with neurotransmission, contributing to synaptic dysfunction and neuronal loss. Tau protein, on the other hand, forms intracellular tangles that disrupt cellular transport mechanisms and induce neuronal death. The intricate interplay of these molecular events elucidates the complexities underlying AD pathogenesis and highlights the need for targeted interventions at the molecular level to impede the progression of this devastating neurodegenerative disorder. General characteristics of Alzheimer's disease are included in Table 1.

Table 1 General characteristics of selected neurodegenerative diseases

Disease	common symptoms	population of affected cells of CNS	brain areas first affected	proteins agreggates
Alzheimer's disease	communication disorders, disorientation, dementia, apathy, depression	cholinergic neurons, glutamatergic neurons	entorhinal cortex, hippocampus, amygdala	β-amyloid, tau
Parkinson's disease	resting tremors, slow movement, sleep disorders, depression, rigidity of muscles	dopaminergic neurons	striatum	α-synuclein
Dementia with Lewy Bodies	dementia, psychosis, numerous features of parkinsonism, visual hallucinations	dopaminergic neurons	striatum	α-synuclein
Alexander disease	seizures, macrocephaly, encephalopathy, motor delay, eye movement abnormalities, ataxia, dysphagia	astrocytes	white matter	rosenthal fibers

Parkinson's disease

Parkinson's disease (PD) is a complex neurodegenerative disorder ranking second in prevalence, following Alzheimer's disease. Originally denoted as "shaking palsy", PD predominantly manifests with motor disturbances including resting tremors, muscle rigidity, and bradykinesia, complemented by non-motor symptoms such as sleep disruptions and depression [10]. Additionally, with disease progression, some patients experience postural instability. Motor symptoms correlate with the loss of approximately 50% to 80% of dopaminergic neurons in the substantia nigra. It is recognized that pathophysiological changes in the brain occur well before the onset of motor symptoms [11]. A pivotal advancement in comprehending PD lies in the identification of pathological hallmarks, namely Lewy bodies (LB), observed in PD patients. These bodies principally harbor abnormal accumulations of α-synuclein aggregates. The pathogenesis of α-synuclein in Parkinson's disease unfolds as a multistep process, initiating with protein misfolding. This process leads to the formation of increasingly intricate oligomers, soluble intermediates, and eventually insoluble fibrils and aggregates [12]. As a consequence, the scientific community has proposed the synucleinopathy hypothesis to illuminate the nuanced development of PD. The aggregates of α-synuclein have the potential to induce atrophy through diverse mechanisms, encompassing lysosomal impairment, mitochondrial dysfunction, endoplasmic reticulum stress, and dysfunction in synaptic transmission. Despite scientific efforts, the precise molecular mechanisms instigating neuronal toxicity and demise remain elusive [13]. Notably, oxidative stress emerges as a contributing factor associated with a heightened risk of Parkinson's disease, and experimental evidence corroborates that an imbalance in redox equilibrium may contribute to the aggregation of α-synuclein [14]. Preclinical investigations into therapeutic approaches targeting α-synuclein have yielded promising evidence, focusing on inhibiting synthesis, aggregation, and the removal of improperly folded synuclein. The current state of understanding, however, remains incomplete regarding whether α-synuclein aggregation constitutes a pivotal feature in the intricate PD development and progression [15].

At the molecular level, the involvement of various cellular processes such as autophagy, chaperone-mediated autophagy, and the ubiquitin-proteasome system in the clearance and degradation of α-synuclein aggregates is under intense investigation. A comprehensive understanding of these intricate molecular pathways holds promise for the development of targeted therapies that could impede or halt the progression of Parkinson's disease at its molecular roots. General characteristics of Parkinson's disease are included in Table 1.

Dementia with Lewy bodies

Dementia with Lewy Bodies (DLB) stands among the neurodegenerative disorders associated with ageing, ranking as the third most prevalent form of dementia following Alzheimer's disease and Vascular dementia. This degenerative brain disorder is characterized by progressive dementia, psychosis, and numerous parkinsonian features [16, 17]. Clinical diagnosis of DLB poses a formidable challenge due to symptom overlap with other dementias, substantial inter-individual variability, and temporal dynamics. Consequently, DLB can be classified into two clinical entities: (1) dementia with Lewy bodies and (2) dementia due to Parkinson's disease (PDD). To distinguish between these diagnoses, clinicians often employ the "1-year rule". This rule suggests that if parkinsonism emerges and persists for less than 12 months before cognitive impairment, the diagnosis is DLB. Conversely, if parkinsonism precedes dementia by 12 months or more, it qualifies as PDD [18]. In diagnostic considerations, recurrent visual hallucinations and rapid eye movement REM sleep behavior disorder (RBD) characterized by swift eye movements are pivotal features in DLB patients. While these traits are crucial for individual diagnosis, the neurobiological identification of the disorder remains challenging. Both Parkinson's disease and DLB share the hallmark of dopaminergic neuron loss in the substantia nigra. Furthermore, similar to PD, the neuropathological features are associated with the presence of α-synuclein aggregates in Lewy bodies and Lewy neurites [16–18]. The molecular intricacies of α-synuclein aggregation in DLB are complex. Extensive research on α-synuclein aggregates has revealed their potential to spread between neurons akin to prions. This intriguing hypothesis may elucidate the clinical heterogeneity observed in DLB.

In summary, DLB engenders numerous brain changes for which effective therapeutic methods are currently lacking. Advancements in research are impeded by the observed heterogeneity of this disorder. The lack of a detailed understanding of the molecular underpinnings of DLB significantly constrains the development of pharmacotherapies [17]. A short characteristic of the disease is included in Table 1.

Alexander disease

Alexander's Disease (AxD) emerges as an exceedingly rare and fatal neurodegenerative disorder, typically presenting in infancy, although other varieties also occur. Falling within the spectrum of neurodegenerative leukodystrophies, AxD constitutes a group of rare genetic diseases primarily affecting the white matter of the central nervous system (CNS), often extending to the peripheral nervous system [19, 20]. Beyond its rarity, the disorder

is distinguished by aberrant development or destruction of the myelin sheath. AxD significantly impacts the astrocyte functions. The identified culprit behind AxD is a dominant mutation within the GFAP gene situated in the chromosomal region 17q21. This gene encodes a glial fibrillary acid protein (GFAP), a key player in regulating the morphology and mobility of astrocytes and in intercellular signaling between astrocytes and oligodendrocytes. Aberrations in GFAP induce the development of protein aggregates, known as Rosenthal fibers, within the cytoplasm of astrocytes. The resultant astrocyte damage sets the stage for numerous deleterious changes in neuronal cells and other types of glial cells [19]. Furthermore, the disease's pathogenesis may involve other mechanisms linked to proteasome dysfunction and accumulated aggregates impaired degradation. Despite the autosomal dominant inheritance pattern, the precise pathomechanism of AxD remains incompletely elucidated. Research indicates highly variable symptoms, leading to the classification of two subtypes based on lesion localization. Type 1 of the disease is severe, with an average life expectancy of around 14 years. Toxic changes predominantly affect the forebrain. Typical symptoms encompass seizures, macrocephaly, encephalopathy, delayed motor and cognitive development, and developmental disorders. Type 2 represents a milder form of the disease, with an average life expectancy of approximately 25 years. Changes mainly involve the hindbrain and characteristic symptoms for this type are associated with autonomic dysfunction, ataxia, oculomotor disturbances, and dysphagia [19]. Molecularly, ongoing investigations delve into the specific pathways involved in the aggregation of GFAP, elucidating genetic modifiers influencing AxD susceptibility, and unraveling potential neuroprotective strategies targeting the distinctive molecular signatures of this complex disorder. The aggregation of GFAP, leading to the formation of Rosenthal fibers, involves intricate processes of protein misfolding, oligomerization, and fibrillogenesis.

Despite the intricate challenges in diagnosis, the current treatment landscape relies solely on supportive therapy, aiming to control seizures and motor symptoms. The imperative for research in this field cannot be overstated, given the disease's high mortality and the limited life expectancy post-diagnosis [19, 20]. The general characteristics of Alexander's disease are included in Table 1.

Selected neurodegenerative diseases are presented above, however, the number of all ND is quite extensive. The molecular classification of these diseases is mainly based on proteins. The basic classes include: amyloidoses, tauopathies, α-synucleinopathies, prion protein accumulation (PrP), and transactivation response DNA binding protein 43 (TDP-43) proteinopathies [21, 22]. Table 2 shows the classification of neurodegenerative diseases based on neuropathologies associated with protein aggregates.

Protein misfolding and aggregation

It is recognized that neurodegenerative diseases are characterized mainly by the aberrant folding, aggregation, and accumulation of proteins, leading to the formation of toxic proteinaceous entities. These pathogenic proteins disrupt cellular function, cause loss of synaptic connections, and ultimately contribute to brain atrophy. Generally, the resulting proteinaceous interferes with the process of neurogenesis and deposits manifest in various cellular compartments, including the nucleus, cytoplasm, cell membrane, and extracellular spaces. Key proteins implicated in the genesis of these aggregates include among others β-amyloid, tau, and α-synuclein. Despite distinct functionalities, sizes, structures, and expression levels, these proteins share remarkably similar processes of misfolding and aggregation. In general, proteins undergo misfolding from their native state, forming intermolecular structures rich in β-sheets. This cascade leads to the production of oligomers, protofibrils and fibril aggregates (Fig. 1) [1, 43]. These β-sheet-rich structures are formed through hydrogen bonding and hydrophobic interactions. Consequently, protein molecules associate with the resulting sticky ends, forcing them into a misfolded conformation to match the cross-β polymer structure [44].

The mechanism underlying the misfolding and aggregation of proteins follows the "seeding-nucleation" model, initially described by Lansbury and colleagues [45]. This process involves two kinetic phases. The first, unfavorable thermodynamically, termed the nucleation phase, proceeds slowly until the formation of an oligomeric unit. This stage is often referred to as the lag phase, with the formation of a stable nucleus or polymerized protein nucleus determining its speed. Subsequently, the elongation phase ensues exponentially. The lag phase generates a minute amount of oligomeric and misfolded structures, serving as seeds for the subsequent phase. Once these seeds are formed, the elongation phase witnesses rapid growth by incorporating monomeric proteins into the polymer. Additionally, an acceleration of the exponential phase may be associated with an excess of preformed seeds, shortening the lag phase. Notably, excess seeding can also result from large polymers fragmentation. The oligomers formed during the initial phase are crucial for exponential misfolding. However, fibrils also play a significant role due to their high resistance to clearance compared to smaller aggregates [46, 47].

Table 2 Overview of neurodegenerative diseases [23–42]

Disease	proteins agreggates	brain areas first affected	references
Amyotrophic lateral sclerosis	TDP-43	cerebral cortex, spinal cord	[23,24]
Frontotemporal disorders	TDP-43	frontal lobes, temporal lobes	[25–27]
Progressive muscular atrophy	TDP-43	brainstem motor neurons, spinal cord motor neurons	[28–30]
Creutzfeldt–Jakob disease	PrP	cerebral cortex, neostriatum, thalamus, cerebellum	[31,32]
Gerstmann–Sträussler–Scheinker disease	PrP	cerebral cortex, cerebellum	[33,34]
Multiple-system atrophy	α-synuclein	striatonigral and olivopontocerebellar systems	[35–37]
Progressive supranuclear palsy	4R-tau	ubthalamic nucleus, pallidum, striatum, red nucleus, substantia nigra, pontine tegmentum, oculomotor nucleus, medulla, and dentate nucleus	[38–40]
Pick's disease	3R tau	basal forebrain, frontal lobes, temporal lobes, limbic structures, striatum	[41,42]

Recent breakthroughs in the field propose that misfolded aggregates may propagate between cells akin to prions. This revolutionary theory suggests that disease progression involves the intercellular transfer of pathogenic proteins, inducing severe neuropathology. This bears immense therapeutic significance for neurodegenerative diseases. However, the exact mechanism of aggregate propagation remains unclear. It is hypothesized that protein aggregates may be released from neurons during cell death or exocytosis. Furthermore, aggregates may be captured by axon terminals and subsequently transported to the soma of the cell. Data also suggests that, through axonal transport, aggregates may spread to neighbouring brain regions [48].

In Parkinson's disease, evidence of the intercellular transfer of α-synuclein aggregates was observed in cerebrospinal fluid. Notably, an increase in α-synuclein occurred temporally and spatially with the advancing stages of Parkinson's disease. The pathology related to α-synuclein was noted in the early stages in the enteric nervous system and
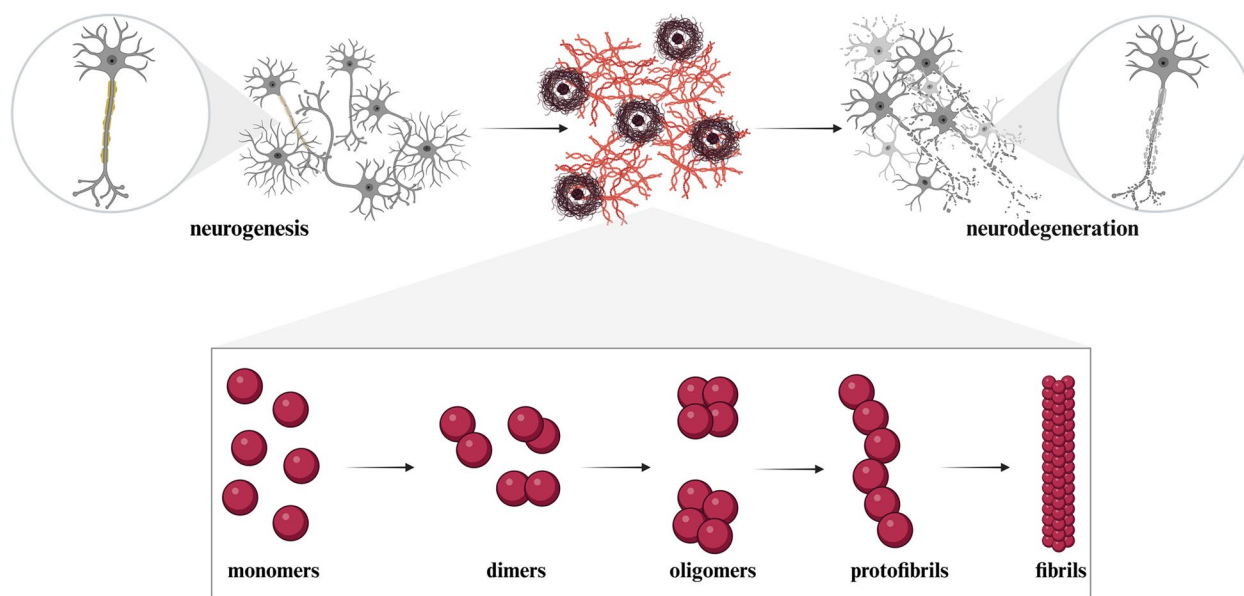
Fig. 1 The process of protein aggregation in neurodegeneration. Monomeric proteins can misfold and aggregate to form dimers, oligomers, protofibrils and mature fibrils. Created with BioRender.com

olfactory bulb. In further stages, the pathology extended to limbic areas, cortical regions, and the brainstem. The degradation of these regions correlated with observations of motor, cognitive, and psychiatric symptoms. The precise mechanism of pathological protein spread is not fully understood. Nevertheless, it is suggested that occurs through exocytosis and endocytosis mechanisms. Alternative studies propose that α-synuclein is transmitted via synaptic pathways through axon-dendrite connections or cytoskeletal elements like nanotubes [48–50].

In Alzheimer's disease, the propagation of prion-like Aβ aggregates in the brain is crucial. Aggregates appearing in specific brain regions induce protein aggregation in axonally connected regions. This process involves a mechanism reminiscent of neuronal transport and trans-synaptic spreading of prions. Studies confirm that Aβ aggregates first manifest in the hippocampus and, through axonal transport, move to closely associated structures and further to the brainstem and basal nuclei. Furthermore, transport may also occur via passive diffusion through cerebrospinal fluid or interstitial fluid. Studies do not rule out vascular transport, as Aβ deposits also move from the periphery to the brain [51, 52].

Similarly, like α-synuclein and Aβ, tau can self-organize and propagate in a prion-like mechanism. Tau pathology initiates in the entorhinal cortex and then spreads to axonally connected areas, such as the hippocampus, frontal cortex, and isocortical areas. Notably, the cerebellum remains unaffected by the progressive changes related to tau toxicity. Unfortunately, the mechanism underlying the susceptibility of various structures to tauopathy remains unknown. Additionally, the discussion remains open regarding whether the presence of Aβ is essential for the permanent spread of tau or whether their coexistence is associated with the spontaneous propagation of tau aggregates [51, 53].

The prion hypothesis, proposed by Braak et al., provides a theoretical framework for understanding the progression of Parkinson's and Alzheimer's diseases through a predictable topographic sequence of neurodegenerative changes. This hypothesis posits that the disease process begins when a pathogenic agent, introduced into the body via the nasal or gastrointestinal tract, is subsequently transported to the central nervous system (CNS). Supporting evidence includes the detection of Lewy bodies in both the intestinal and peripheral nervous systems. Additionally, early olfactory disturbances in Parkinson's disease correlate with Lewy pathology in the anterior olfactory nucleus and mitral cells of the olfactory bulb. Braak et al. also suggest a gastrointestinal route for pathogen entry, where pathogens may access the brain through the vagus nerve. Similar to olfactory disturbances, gastrointestinal dysfunctions appear early in the disease progression and can be observed in the gastrointestinal tract. To delineate the disease progression, Braak and colleagues proposed a six-stage grading system [54, 55]. In the initial stage, pathology originates in the structures of the lower brainstem and olfactory system, specifically starting in the dorsal motor nucleus of the vagus nerve in the medulla oblongata and the anterior olfactory

nucleus. In the subsequent stage, pathological changes extend to the raphe nuclei and the giant cell reticular nuclei of the medulla oblongata, with progression to the top of the brainstem and migration to the locus coeruleus in the pontine tegmentum. The third stage involves the substantia nigra and the nucleus basalis of Meynert. The fourth stage is characterized by widespread dopaminergic cell degeneration and the propagation of Lewy bodies to the amygdala and subnuclei of the thalamus. In the fifth stage, pathology affects the neocortex and extends to the temporal, frontal, and parietal lobes, with continued cell degradation in the substantia nigra, gigantocellular reticular nucleus, locus coeruleus, and dorsal motor nucleus of the vagus nerve. Finally, in the sixth stage, the disease encompasses the entire neocortex, leading to the most severe manifestations of the disorder [54, 56].

The abnormal protein folding and the resultant formation of aggregates constitute a central theme in the realm of neuroscience. Despite the extensive body of research dedicated to this phenomenon, persistent inquiries linger concerning the underlying pathomechanisms and the effectiveness of therapeutic interventions for neurodegenerative diseases.

Potential mechanistic strategies for protein clearance

The pathology underlying neurodegenerative diseases remain incompletely elucidated, yet the common thread among many of these conditions appears to involve the presence of abnormal folded proteins and their aggregates [57]. In the pursuit of innovative therapeutic strategies, three fundamental approaches can be identified. The first therapeutic strategy encompasses interventions aimed at inhibiting protein aggregation, employing peptides and small molecules identified through screening studies. The second equally significant therapeutic avenue involves the disruption of post-translational modifications designed to regulate misfolded proteins and their aggregates. The final and arguably most consequential therapeutic strategy involves the development of methodologies to augment the levels of molecular chaperones and diverse mechanisms that initiate the aggregates clearance, thereby alleviating the toxic effects associated with misfolded proteins [58]. In this chapter, we present a systematic description of the key pathways involved in the clearance of aggregates, due to their mechanism. Therapeutic methods based on these strategies have the potential to prevent and treat neurodegenerative diseases. In the context of therapeutic synergy, particularly through the application of drugs with diverse mechanisms of action, represents a prospective trajectory in the therapeutic landscape for individuals afflicted by neurodegenerative diseases [57].

Protein quality-control-related ER and UPR pathways

The endoplasmic reticulum (ER) serves as a central hub for protein biosynthesis, cholesterol, and lipid production, as well as an intracellular Ca^{2+} reservoir [59]. Calcium signaling also transpires within the ER [60], and its dysregulation has been implicated in neurodegenerative diseases [61]. However, the ER is a crucial site for protein folding, playing a pivotal role in monitoring the synthesis, assembly, and transport of secretory and membrane proteins. Notably, the ER also plays a significant role in distinguishing normal proteins from abnormal folded ones. Additionally, it is a membranous complex that is highly sensitive to changes that affect its function, integrity, and, above all, structure [62]. Proper ER function is indispensable for cell survival. In cases where the equilibrium between the demand for protein folding and the capacity of the folding mechanism is disrupted, the accumulation of improperly folded proteins in the ER occurs. The excess of aggregates leads to the generation of cellular toxicity, ultimately resulting in ER stress. The ER stress response occurs regardless of whether misfolded proteins are located directly in the ER, in the cytosol or nucleus. In such instances, cells activate an intracellular signaling cascade known as the quality control system to prevent ER stress. Upon excessive generation of improperly folded proteins, associated with compromised defense mechanisms, ensues organelle dysfunction and cell death. These mechanisms have been associated with the pathogenesis of neurodegenerative diseases [59].

ER stress can activate cellular response mechanisms collectively referred to as the Unfolded Protein Response (UPR) (Fig. 2). UPR detects and transmits the ER stress signal to cellular organelles such as the nucleus or cytosol. Activation of UPR cellular responses results in the reduction of protein synthesis rates, upregulation of chaperone and other protein expression, and the degradation of improperly folded proteins located in the ER. These three pathways contribute to the reduction of protein aggregates, concurrently reinforcing the entire ER machinery for proper folding and degradation [63].

UPR comprises three signaling cascades, regulated by transmembrane proteins (1) inositol-requiring protein 1 (IRE1), (2) protein kinase RNA-like ER kinase (PERK), and (3) activating transcription factor 6 (ATF6) (Fig. 2). The intricate process through which transmembrane proteins recognize endoplasmic reticulum stress remains incompletely elucidated. Nonetheless, it is hypothesized that this phenomenon is linked to the chaperone protein GRP78, known as Bip. Research indicates that Bip preserves the inactive conformation of IRE1, PERK, and ATF6 by engaging with them through its peptide-binding domains. Additionally, this domain serves as the binding site for improperly folded proteins [59].

IRE1 pathway

The activation of IRE1 is initiated during ER stress. IRE1 is characterized by three distinct domains: the N-terminal transmembrane domain (1) responsible for sensing ER stress, the subsequent transmembrane domain (2), and the C-terminal effector domain (3), which is located outside the ER membrane and possesses endoribonuclease (RNase) activity. The N-terminal domain associates with Bip, which disengages from IRE1 upon the detection of ER stress. The activated transmembrane protein facilitates dimerization, trans-autophosphorylation, and activation of the C-terminal domain, leading to cleavage at two sites of the preformed mRNA substrate. The endoribonuclease activity results in the excision of a 26-nucleotide intron from the target mRNA. Following cleavage, tRNA ligase ligates the two ends of the mRNA. The splicing of mRNA by IRE1 enables the generation of the active form XBP-1, known as spliced XBP-1 (XBP1s). XBP1s is a unique transcription factor with a basic leucine zipper (bZIP) domain, and acts as a transcription factor, modulating gene expression and cellular responses to stress by inducing chaperone proteins (Fig. 2) [59, 64].

PERK pathway

PERK is a kinase protein localized on the membrane of the endoplasmic reticulum (ER). Similar to IRE1, PERK associates with Bip and undergoes activation in response to ER stress. The dissociation of Bip from PERK triggers its dimerization and autophosphorylation. The activated PERK phosphorylates the eukaryotic initiation factor 2α (eIF2α), leading to its inactivation and the subsequent inhibition of protein translation. The phosphorylated eIF2α, in turn, activates the transcription factor ATF4 [64]. ATF4 functions as a heterodimer and, as data suggests, can form complexes with members of the ATF, FOS/JUN, and CCAAT enhancer-binding protein (C/EBP) transcription factor families. In conjunction with these factors, ATF4 binds to DNA sequences known as cAMP-responsive elements (CREs) or C/EBP-ATF response elements (CAREs). This binding regulates the expression of target genes associated with the cellular stress response or apoptosis. Notably, C/EBP homologous protein 10 (CHOP) emerges as a highly characterized target gene of ATF4. Signaling pathways initiated through the CHOP mechanism propels stress-affected cells towards apoptosis. Despite the
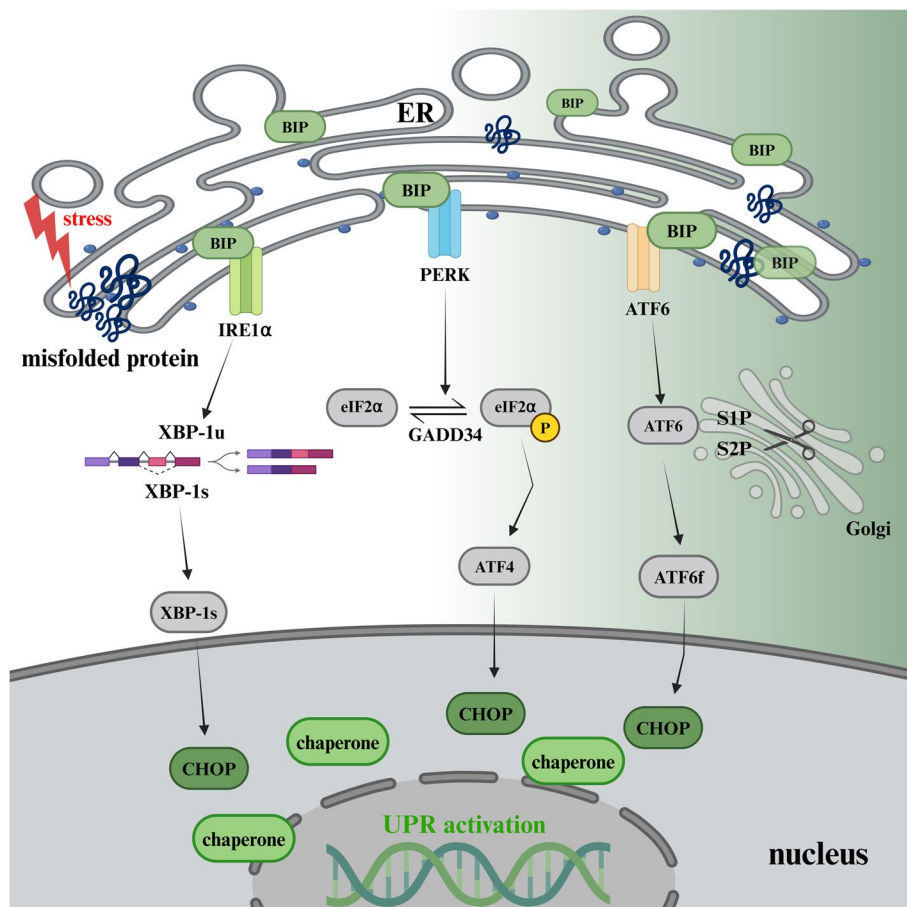

Fig. 2 Protein quality-control-related ER and UPR signaling pathways. IRE1, PERK, and ATF6 proteins activate three separate UPR pathways in response to ER stress. Created with BioRender.com

capability of all three UPR signaling cascades to activate CHOP, ATF4 stands out as the principal factor inducing its transcription (Fig. 2) [65].

ATF6 pathway

Under homeostatic conditions, ATF6 is situated on the ER membrane and, like the previous proteins, forms a complex with Bip. ATF6 comprises two isoforms, ATF-6α and ATF-6β, serving as ER membrane-associated transcription factors. Upon initiation of ER stress, ATF6 perceives the signaling event, undergoes dissociation from Bip, and translocates to the Golgi apparatus. Subsequent proteolytic processing takes place at this cellular site. ATF6 is processed by site-1 (S1P) and site-2 (S2P) proteases, cleaving peptide bonds and releasing the cytoplasmic domain ATF6f. Finally, the cytoplasmic domain is transported to the nucleus, where it binds to ATF/cAMP response elements and ER stress response elements (ERSE I and II). The presence of nuclear factor-Y (NF-Y) and CCAAT binding factor (CBF) is pivotal for the binding process. This binding results in CHOP, XBP1, and Bip upregulation (Fig. 2) [64, 66].

Molecular chaperones activity

The protein quality control system encompasses molecular chaperones, known as heat shock proteins (Hsps), owing to their ability to respond to cellular stress (Fig. 3). They are also designated with numerical notations reflecting their molecular weights. These proteins play a crucial role in the regulation of highly specific processes associated with the folding and unfolding of cellular proteins. Their capacity to mitigate protein aggregates results from continuous interactions with other proteins, leading to subsequent release from these complexes [67]. Notably, heat shock proteins stabilize the conformation of other proteins through binding interactions (Fig. 3). In the context of proper protein folding, chaperones assume a pivotal role, participating in de novo polypeptide synthesis, membrane transport, protein refolding, and even degradation. Mechanisms involving molecular chaperones confer fundamental significance to these proteins in diverse cellular processes. Endoplasmic reticulum stress is one such process that activates chaperones to safeguard against the formation of improperly folded proteins and aggregates. Detailed information regarding the interactions between chaperones and substrate proteins is currently limited, primarily due to the disordered specificity of improperly folded proteins, which are partially folded or unfolded [68]. The classification of molecular chaperones can be primarily based on their mode of energy dependence. This category includes (1) ATP-dependent and (2) ATP-independent chaperones. ATP-dependent chaperones, primarily foldases, utilize cycles of ATP hydrolysis to drive conformational changes necessary for their function. These chaperones facilitate the recognition of misfolded proteins, their refolding, and subsequent release through regulated interactions with substrate proteins [69]. Translocase chaperones facilitate the transport of proteins across cellular membranes, primarily through the SEC pathway utilizing the SecA motor
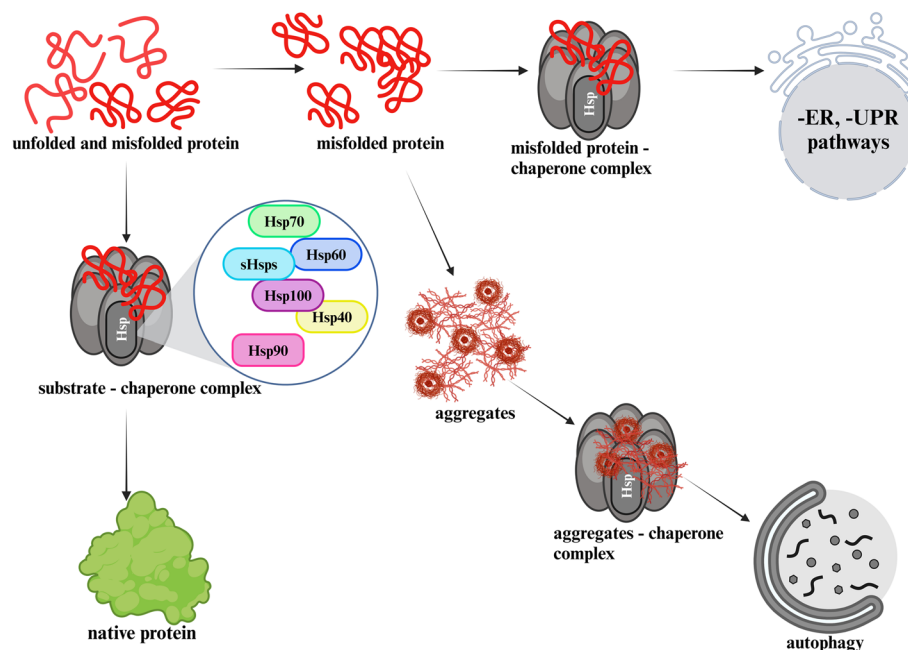

Fig. 3 Molecular chaperones interact with misfolded proteins and direct them to specific pathways preventing protein degradation and assisting with maintaining cellular homeostasis. Created with BioRender.com

protein. SecA functions by converting chemical energy into mechanical force, essential for translocating nascent and unfolded proteins through the SecYEG membrane channel while maintaining their unfolded state. Proteins destined for this pathway can be directed to SecA via SecB and Trigger Factor (TF) or directly transported to the motor protein. SecA then associates with ribosomes, enabling interaction with the emerging polypeptides, ensuring their proper translocation across the membrane [70]. ATP-independent chaperones, primarily holdases, function to prevent protein aggregation without the need for energy. They operate through the reversible formation of complexes with substrate proteins, effectively stabilizing them in a non-aggregated state. This process is not associated with the cleavage of any exergonic covalent bonds [71]. However major families of chaperone proteins encompass Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, as well as small Hsps (sHsps).

Hsp40
Members of the Hsp40 protein family are categorized into three distinct types – I, II, and III, primarily delineated by the inclusion of a J domain consisting of approximately 70 amino acids. In types I and II, this domain is exclusively located at the N-terminus. Both types I and II have a peptide-binding fragment at the C-terminus, connected to the N-terminal J domain via a G/F-rich linker. Type I Hsp40s, such as human Hdj2 or E. coli DnaJ, contain two zinc-finger motifs positioned between the J domain and the C-terminal peptide-binding fragment. In contrast, type II Hsp40s, such as human Hdj1 and yeast Sis1, lack these zinc-finger motifs, exhibiting structural differences. Type III Hsp40s have modified J domains or other structures that perform similar functions to the classic J domain, differentiating them significantly from types I and II [72]. Additionally, Hsp40 proteins belonging to these types exhibit a peptide-binding domain at the C-terminus. In type III, the J domain can be positioned at any location within the protein sequence. Numerous scientific investigations have reported on the collaborative relationship between Hsp40 and Hsp70, which contributes to the facilitation of proper protein folding, transport, and degradation. Hsp40 proteins primarily function as holdases, recognizing and binding to misfolded proteins to prevent their aggregation. In contrast, Hsp70 proteins serve as foldases, facilitating the refolding of these misfolded proteins back to their native conformations [73]. The presence of the J domain enables specific interactions with the N-terminal ATPase domain in Hsp70, thereby playing a regulatory role in stimulating the ATPase activity of Hsp70. The role of Hsp40, along with its complex with Hsp70, extends to interactions with the Hsp90 family of chaperones, which are essential for the binding and release of client proteins. This mechanism operates under the premise that client proteins initially bind to Hsp70. ATP hydrolysis by Hsp40 stabilizes the Hsp70/Hsp40/HOP complex, facilitating its interaction with Hsp90 in an open conformation bound to ADP. The subsequent exchange of ADP for ATP in Hsp90 leads to the dissociation of the Hsp70/Hsp40/HOP complex and the formation of a mature complex with CDC37 and p23, resulting in the activation of the client protein [74]. Additionally, Hsp40, in complexes with Hsp70 and Hsp100, supports protein disaggregation and refolding. This process begins with the recognition of misfolded proteins by the JPD/Hsp40 complex, whose J domain interacts with the nucleotide-binding domain of Hsp70. ATP hydrolysis is induced, which closes the substrate-binding domain of Hsp70. Subsequently, Hsp70 bound to the aggregate interacts with the Hsp100 disaggregase. This allosteric interaction activates Hsp100, enabling it to bind to the aggregate. In an ATP-dependent process, Hsp100 disentangles polypeptides from the aggregates, leading to their refolding [75]. To summarize, Hsp40 exhibits the capability to bind non-native polypeptides through its C-terminal peptide-binding domain and subsequently transfer them to Hsp70 [68, 72].

Hsp60
The family of molecular chaperones, designated as Hsp60 or chaperonins, is predominantly localized in the mitochondria of eukaryotic cells. Chaperonins play a pivotal role in the de novo assembly and folding of proteins, particularly participating in the assembly of oligomeric proteins. Additionally, they facilitate the importation of protein substrates into mitochondria, addressing the refolding of proteins that have undergone denaturation due to stress. It is noteworthy that the Hsp60 family is instrumental in the folding and maintenance of the proper conformation of approximately 15–30% of all proteins within the cell. The structural features of Hsp60 have been extensively documented in the scientific literature. Hsp60 proteins are structured as two interconnected ring complexes. These rings exhibit a total subunit content ranging from 14 to 18. Subunits are characterized by three domains: (1) equatorial, (2) intermediate, and (3) apical. The first domain of Hsp60 exhibits ATPase activity, with the ATP-binding pocket located in its apical region. The intermediate domain functions as a hinge, facilitating conformational changes of Hsp60 during polypeptide folding. The apical domain hosts a polypeptide-binding site and a cofactor, identified as Hsp10. In the bacterial context, there are homologs of Hsp60, such as GroEL, and cochaperone Hsp10, referred to as GroES. They are called chaperonins group I. The GroEL/GroES mechanism involves the binding of polypeptide chains,

concomitantly facilitating proper folding [76, 77]. GroEL consists of two heptameric rings arranged with a 2-fold inter-ring symmetry axis, creating a chamber where client proteins are encapsulated. GroES binds to GroEL in an ATP-dependent manner, preventing the escape of the substrate protein. Group II chaperonins, found in eukaryotes, include the TRiC/CCT complex. Unlike group I chaperonins, group II chaperonins consist of eight subunits, each with a molecular weight of 50–60 kDa. They do not require an obligatory co-chaperone like Hsp10; instead, they possess an inherent lid mechanism that closes the folding chamber, enabling substrate folding without additional proteins. The TRiC/CCT complex primarily facilitates the folding of various eukaryotic proteins, ensuring their proper functional conformation [78, 79].

Hsp70

The molecular chaperone Hsp70 plays a pivotal role in various essential cellular processes, mainly involved in the expansive folding mechanism, encompassing fundamental folding processes, refolding and the restoration of misfolded proteins. Activation of Hsp70 occurs in response to cellular stress conditions, wherein the chaperone interacts with substrate proteins, providing stability until cellular conditions ameliorate. The Hsp70 chaperone family comprises two domains: (1) the N-terminal nucleotide-binding domain (NBD) and (2) the C-terminal substrate-binding domain (SBD), interconnected by a flexible linker. The NBD exhibits a V-shaped structure, encompassing two subdomains, I and II, further divided into regions a and b. Through the nucleotide-binding cassette, subdomains Ia and IIa engage with ATP. The SBD features two subdomains: the beta-sheet domain (SBDβ) or basic domain and the alpha-helical domain (SBDα) or Lid domain. Conformational changes are requisite during the ATPase cycle in the chaperone mechanism of other proteins. When the NBD is bound to ATP, the SBD adopts an open conformation, facilitating rapid substrate binding and dissociation. Conversely, when the NBD is bound to ADP, the SBD undergoes a conformational change to a closed state, involving the substrate-binding pocket. Subsequently, upon ADP release and ATP rebinding, Hsp70 reverts to its open conformation, enabling substrate release. As previously mentioned, Hsp40 acts as an obligatory regulatory partner, modulating the Hsp70 activity [80–82].

Hsp90

The Hsp90 protein family represents one of the most abundant protein families within the cell, comprising approximately 1–2% of the entire cellular proteome. This percentage escalates to 4–6% under cellular stress. Hsp90 proteins are discernible in various cellular compartments, including mitochondria, the endoplasmic reticulum (ER), and the cytosol. Their functional role is intricately associated with participating in the intricate mechanism governing proper protein folding. Hsp90 exists in a homodimer form, wherein each monomer is comprised of three distinct domains: (1) N-terminal domain (NTD), (2) middle domain (MD), and (3) C-terminal domain (CTD). The NTD houses an ATP-binding pocket, which is crucial for its function. The middle domain, where protein-protein interactions occur, is also involved in ATP hydrolysis. The CTD plays a role in homodimerization and features a nucleotide-binding site that regulates ATPase activity within the NTD. Notably, the CTD terminates with a (MEEVD) sequence, facilitating interactions with co-chaperones, many of which possess the tetratricopeptide-containing repeats (TPR) domain. This TPR domain facilitates interactions with co-chaperones, thereby regulating various cellular functions, prominently including proper protein folding. Additionally, a highly charged linker region mediates the binding between the NTD and MD in the cytoplasmic and ER compartments. The dynamic processes of ATP binding, hydrolysis, and ADP release induce conformational changes in Hsp90, accompanied by the formation of open, semi-open, and closed conformations, intricately linked with the association and dissociation of co-chaperones [83–85]. For the proper function and coordination of Hsp90 or Hsp70, co-chaperones are essential. These co-chaperones include HOP, PP5, p23, Sgt1, FKBP51/52, Cyp40, and Cdc37 [86]. One of the most critical co-chaperones for these proteins is HOP. HOP contains three tetratricopeptide repeat domains that have binding sites for the conserved C-terminal - EEVD of Hsp70 and Hsp90. Misfolded proteins are initially recognized by Hsp40 and Hsp70. Subsequently, the transfer of the client protein is facilitated by the HOP co-chaperone, which simultaneously interacts with Hsp70 and Hsp90 through their conserved C-terminal amino acid motifs. The protein then binds to Hsp90, and through ATP hydrolysis, the client protein is released, and the chaperone complex dissociates [87, 88]. ATP hydrolysis induces the formation of a stable substrate complex. Both hydrolysis and substrate binding are further regulated by two co-chaperones: the J-domain protein and the nucleotide exchange factor (NEF). The J-domain protein stimulates ATP hydrolysis, while NEF accelerates nucleotide exchange by promoting ADP release and ATP binding, thereby facilitating substrate release [89–91].

Hsp100

The Hsp100 protein family comprises a set of large chaperone proteins whose functionality relies on the presence of ATP. In contrast to most chaperones that utilize

ATP for protein folding processes, Hsp100, as part of a bipartite chaperone system with other proteins, utilizes energy to induce the reverse process. This involvement leads to active participation in disaggregation processes, encompassing the unfolding of improperly folded proteins. Structurally, Hsp100 proteins consist of an N-terminal domain (NTD) and two ATP-binding domains (AAA domains). Despite their engagement in diverse cellular processes, a shared characteristic of this protein family lies in their oligomeric structure and the existence of a homologous Walker-type (A,B) nucleotide-binding domain, essential for ATP binding and hydrolysis. The mechanism of disaggregation involving Hsp100 is not fully understood, but fundamental insights propose a preceding role of Hsp70 in the cellular context. In the initial stage, Hsp70 controls protein aggregates to which it binds and further facilitates the Hsp100 recruitment. Interactions between Hsp100 proteins and the ATPase domain of Hsp70 are evident. It is crucial to underscore that the Hsp70 and Hsp100 complex assumes a pivotal role in cellular survival. Persistent activation of Hsp100 proves detrimental to the cell, underscoring the regulatory importance of co-chaperones in restricting Hsp100 activity on the surface of aggregates [71, 92, 93].

sHsps

The family of small heat shock proteins (sHsps) serves as integral components within the intricate protein quality control system. These petite holdase proteins function as a primary defense line under cellular stress. Their characteristic feature is low molecular weight, typically ranging from approximately 14 to 43 kDa. sHsps consist of an N-terminal domain, a C-terminal domain, and a unique central region termed the alpha-crystallin domain (ACD). Notably, their dynamic structure allows them to exist in various forms, including monomers, dimers, and large oligomers. All domains play a pivotal role in the intricate process of oligomer formation, which can encompass 4 to 40 monomers. ACD predominantly governs the dimerization process, while both CTD and NTD domains contribute to the formation of dimeric and oligomeric structures. The monomers assemble into larger complexes and the disassembly of sizable complexes into dimers or monomers undergo modulation through post-translational modifications, including phosphorylation. That regulation significantly impacts the multifaceted functions of sHsps, empowering them to prevent protein aggregation, assist in protein refolding, participate in autophagy by directing proteins toward apoptotic pathways, promote the UPR, and play a pivotal role in the cellular response to oxidative stress [94, 95].

Chaperone-mediated autophagy (CMA)

Three principal categories can be delineated within the realm of the catabolic process termed autophagy. (1) Macroautophagy initiates with the sequestration of a portion of the cytoplasm by a membranous structure referred to as the phagophore. Further, the phagophore transforms into an autophagosome, encapsulating a portion of the cytoplasm along with proteins earmarked for degradation. This event culminates in the fusion of the autophagosome membrane with the lysosome, resulting in the formation of an autophagolysosome. The establishment of this complex constitutes a pivotal step in the degradation of its contents facilitated by lysosomal enzymes (Fig. 4A). (2) Microautophagy, a mechanism predicated on the direct degradation of proteins by the lysosome, involves the engulfment of components through the invagination of the lysosomal membrane, leaving aside autophagosome formation (Fig. 4C). The third and particularly important type of autophagy is (3) chaperone-mediated autophagy (CMA) (Fig. 4B).

CMA serves as a quality control mechanism leading to the degradation of damaged or misfolded proteins [96]. It selectively degrades cytosolic proteins within lysosomes, based on the KFERQ motif (pentapeptide sequence) in proteins, which directs them through the lysosomal membrane. Activation of CMA occurs in response to cellular stress, notably oxidative stress, which may induce substantial protein damage. This mechanism is controlled by molecular chaperone proteins. In the first stage, CMA substrates are recognized in the cytoplasm by the Hsp70 protein. Upon reaching the lysosomal surface, the resulting complex (substrate-chaperone) binds to lysosome-associated type-2A membrane protein (LAMP-2A). LAMP-2A functions as a receptor for CMA and encompasses a C-terminal domain, exposed on the lysosomal surface, facilitating the binding of substrate proteins. After substrate binding, it undergoes unfolding and traverses the lysosomal membrane, where degradation occurs. This transmembrane passage necessitates the support of the lysosomal isoform of Hsp70 and an energy source in the form of ATP [97, 98]. Activation of the CMA pathway does not require de novo LAMP-2A synthesis, as the lysosomal membrane contains additional regulators to control CMA activity. Primarily, Hsp90 contributes to maintaining the LAMP-2A stability. Furthermore, all these processes are regulated by proteins associated with lysosomes. The primary regulatory pair comprises GFAP/EF1α. Their presence modulates the translocation complex LAMP-2A in a GTP-dependent manner. Two forms of GFAP are discernible: (1) Unmodified, which binds to LAMP-2A and maintains
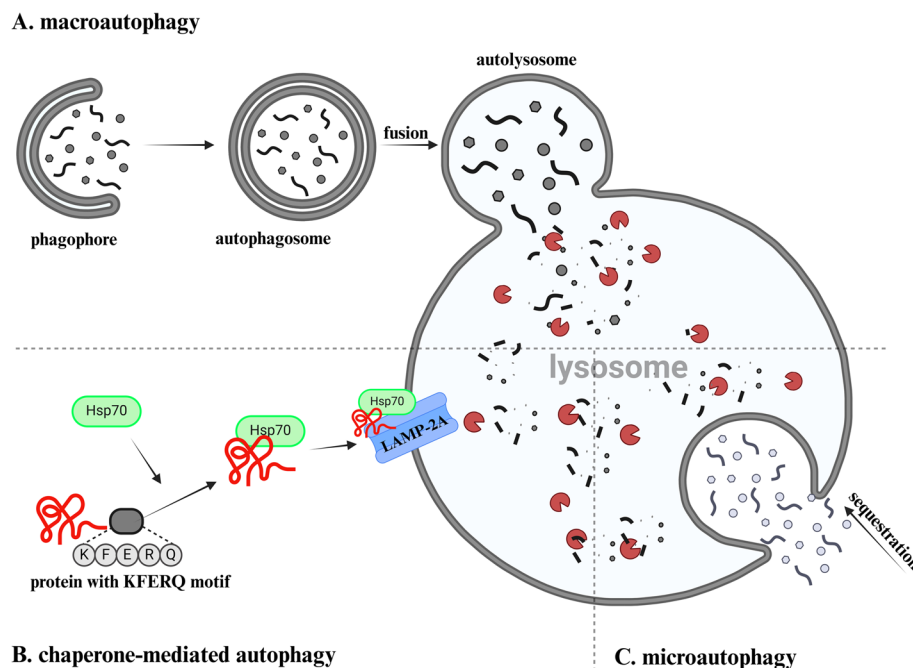
Fig. 4 Three main types of autophagy mechanisms. **A** macroautophagy, **B** chaperone-mediated autophagy, **C** microautophagy. Created with BioRender.com

the stability of the translocation complex. (2) Phosphorylated (pGFAP) – inactivated by EF1α. EF1α is released from the membrane under GTP control only. Consequently, unmodified GFAP can bind to pGFAP. Nonetheless, GFAP exhibits a higher affinity for pGFAP than for LAMP-2A, prompting the formation of a GFAP-pGFAP dimer and resulting in the translocation complex breakdown (Fig. 5A). Another regulatory mechanism of the translocation complex is the mTORC2/AKT1/PHLPP1 pathway. mTORC2 negatively impacts CMA by phosphorylating AKT, the kinase of GFAP. Overphosphorylation of GFAP disrupts the formation of the translocation complex, significantly decelerating the process. Activation of CMA necessitates the attachment of PHLPP1 to the lysosomal membrane, where it dephosphorylates AKT. This results in an acceleration of LAMP-2A assembly and disassembly (Fig. 5B) [99]. Numerous studies have associated the CMA mechanism with neurodegenerative diseases. Similar sequences to KFERQ have been identified in proteins linked to neurodegenerative conditions, such as synuclein, tau, and APP. The aggregates of these proteins can be cleared through the CMA pathway, underscoring its potential therapeutic utility [98].

Keap1/ Nrf2/ARE pathway

Disturbances in redox homeostasis, particularly the excessive generation of reactive oxygen and nitrogen species (ROS/RNS), have been linked to neurodegenerative disorders pathogenesis characterized by aberrantly folded proteins and aggregates. This perturbation adversely affects the levels of nuclear factor-erythroid 2-related factor 2 (Nrf2), including the Keap/Nrf2/ARE antioxidant pathway's functionality (Fig. 6). Cells, in response to oxidative stress and the presence of improperly folded proteins, engage a mechanism associated with Nrf2. The Keap1/Nrf2/ARE pathway assumes a pivotal role as a regulatory system for redox balance and a sensor for detecting elevated oxidative stress. It comprises three primary components: (1) Kelch-like ECH-associated protein 1 (Keap1), (2) nuclear factor erythroid 2-related factor 2 (Nrf2), and (3) antioxidant response element (ARE). Within cellular contexts, Nrf2 activity is subject to stringent control and regulation. Under normal physiological conditions, Nrf2 is maintained at a low level due to continuous ubiquitin-proteasome degradation. Keap1 exerts inhibitory control over Nrf2 activity. Upon exposure to oxidative or nitrosative stress, Keap1 undergoes modifications, disrupting its binding with Nrf2. This enables the accumulation and translocation of newly synthesized Nrf2 to the cell nucleus, where it associates with the small protein Maf and the antioxidant response element ARE. ARE functions as an enhancer element in the cis-regulatory system, resulting in antioxidants and phase II enzymes increased expression. The response secures a cell from oxidative and
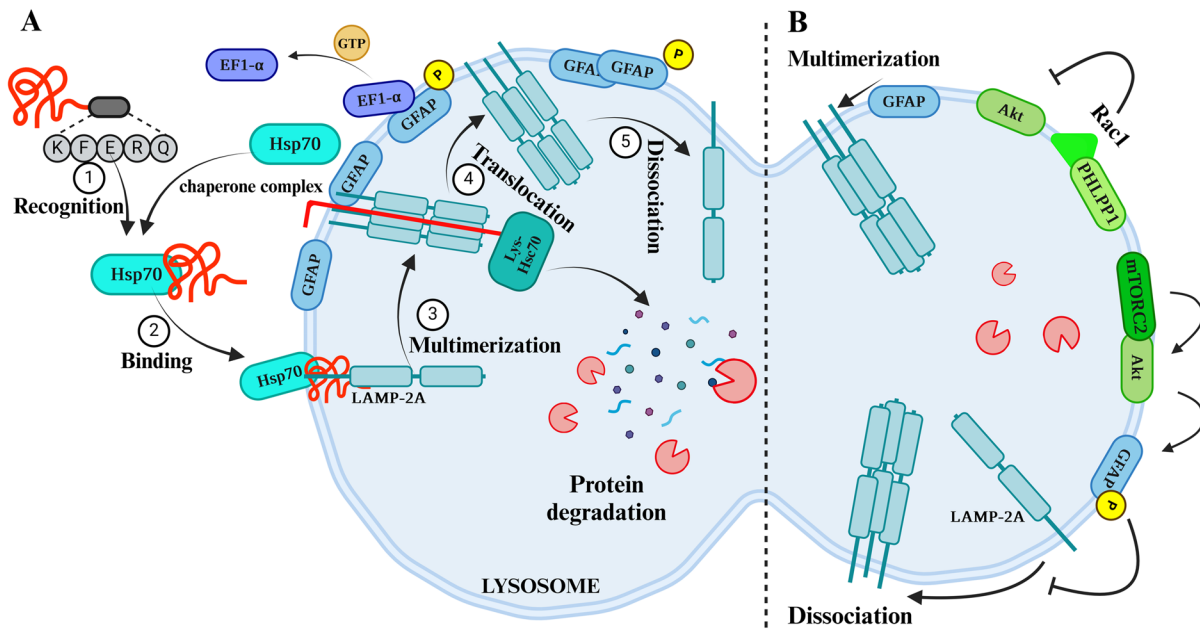
Fig. 5 Chaperone-mediated autophagy (CMA) mechanism (**A**) and regulation (**B**). Created with BioRender.com
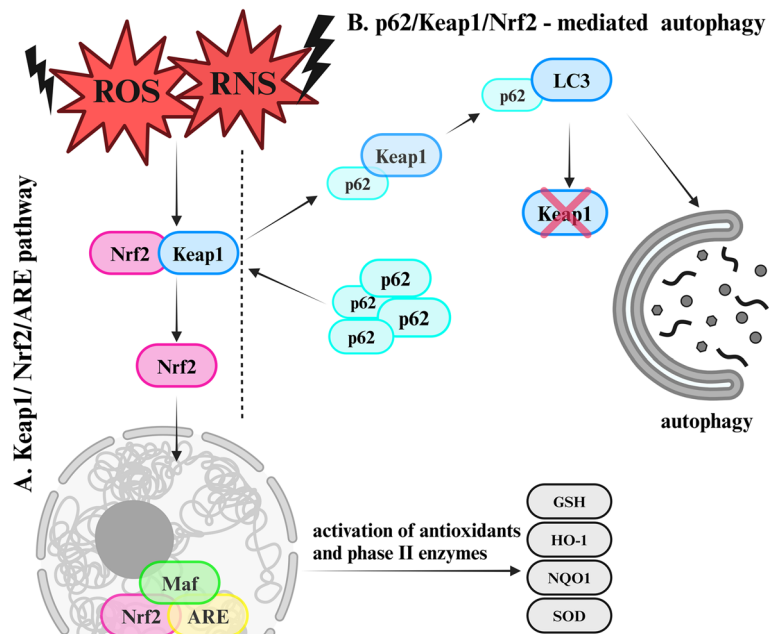

Fig. 6 Intersection of the p62-Keap1-NRF2-ARE signaling pathways and autophagy. Created with BioRender.com

nitrosative damage. Phase II enzymes that are antioxidants include, among others heme oxygenase-1 (HO-1), glutathione (GSH), NAD(P)H quinone oxidoreductase 1 (NQO1), and superoxide dismutase (SOD) (Fig. 6). The described Nrf2 signaling is commonly referred to as the canonical pathway [100, 101]. Data indicate a decrease in Nrf2 levels with advancing age. Loss of Nrf2 function is associated with increased neurodegenerative pathology. Noteby, studies suggest that Nrf2 deficiency may contribute to proteinopathies development. Therefore, the proper Keap1/Nrf2/ARE pathway function is essential for improperly folded protein clearance and degradation [102].

p62/Keap1/Nrf2 - mediated autophagy

Autophagy represents a highly regulated cellular protein quality control machinery responsible for the degradation of damaged or misfolded proteins and organelles. As previously outlined, a spectrum of autophagy types exists. This complicated cellular process is regulated not only by the chaperone proteins but also by p62/sequestosome 1 (SQSTM1). Of notable significance, the p62 protein plays a complex role in the Nrf2 pathway modulation in a Keap1-dependent manner (Fig. 6). This unique regulatory mechanism has been designated the non-canonical pathway. The interaction of p62 with Keap1 results in a competitive binding way against NRF2, facilitating the sequestration of Keap1 into the autophagosome by p62. It prevents the degradation of NRF2 through Keap1. The p62-Keap1-NRF2 axis is implicated in the induction of autophagy through interaction with LC3. Beyond its participation in the non-canonical Nrf2 pathway, p62 is recognized for its role as an adaptor protein binding protein aggregates targeted for degradation within autophagosomes. Characterized by multiple domains, p62 engages with various binding partners, resulting in a spectrum of cellular events of diverse nature. These findings underscore the intricate interplay between autophagic and Nrf2 pathways, mediated through the pivotal participation of the p62 protein. The interactions within the Nrf2/Keap1/ARE axis and autophagy hold promise for the exploration of innovative therapeutic strategies in the realm of neurodegenerative diseases [103, 104].

Innovative approaches to multi-target treatment of neurodegenerative disease

At present, the majority of neurodegenerative conditions lack a cure. Extensive research endeavors focus on therapies aimed at alleviating symptoms and slowing disease progression. Nevertheless, achieving a treatment capable of halting or reversing neurodegenerative processes entirely remains a significant challenge. After many years of intensive research, great progress has recently been made in developing therapies that modify

the course of the disease or symptomatic treatment of neuropsychiatric syndromes [105]. Levodopa stands as the foremost pharmacological intervention for individuals suffering from Parkinson's disease. This naturally occurring compound undergoes conversion into dopamine upon reaching the brain. Despite the significant scientific advancements surrounding levodopa's development, prolonged use has been associated with diminishing efficacy over time. As levodopa's effectiveness wanes, dyskinesias, characterized by hyperkinetic movements, may manifest. In such instances, amantadine, a medication commonly employed in PD treatment, emerges as a viable option, offering relative efficacy in mitigating dyskinesia [106, 107]. In 2023, a novel medication named produodopa entered the pharmaceutical landscape. It is a combination of two substances - foslevodopa and foscarbidopa. This medicine works by converting foslevodopa into the dopamine, thereby facilitating intercommunication among brain regions governing movement [108, 109]. In 2024, there are significant opportunities for the approval of four novel drugs for Parkinson's disease in the United States. First, the subcutaneous continuous infusion of apomorphine, administered via a pump, is critical for managing motor fluctuations that are inadequately controlled by oral or transdermal medications. Second, the infusion of levodopa/carbidopa using a pump-like device ensures regular and precise delivery of the medication, representing another promising option. Additionally, the subcutaneous levodopa/carbidopa infusion delivered through a pump patch is a notable development with potential for Food and Drug Administration (FDA) approval, joining existing therapies such as the transdermal rotigotine patch and the rivastigmine patch. The fourth method under FDA evaluation is a reformulated levodopa/carbidopa pill designed to provide lower doses with extended effects. A decision on these therapies is anticipated by the end of August 2024 [110–112]. Moreover, recent research published in Nature Medicine offers hope for slowing neurodegeneration and improving patient outcomes. Prasinezumab, an experimental therapeutic monoclonal antibody, is the first to specifically target aggregated alpha-synuclein for degradation. Its mechanism aims to protect neurons, prevent the cell-to-cell transmission of pathological alpha-synuclein aggregates, and slow disease progression [113]. Also in 2023, the approval of two monoclonal antibodies targeting amyloid marked significant progress in Alzheimer's disease treatment. Aducanumab and lecanemab demonstrate the capacity to retard cognitive decline. Furthermore, brexpiprazole has already secured approval for effectively managing agitation in dementia [114]. This year, donanemab, marketed under the brand name Kisunla, was approved as a new drug for Alzheimer's

disease. Similar to Leqembi, which was approved last year, both medications are administered via intravenous infusion. Leqembi is given every 2 weeks, while Kisunla is administered monthly [115]. A notable drawback of current amyloid-targeted therapies is the requirement for regular intravenous infusions. However, ALZ-801, the first oral drug aimed at modifying the course of Alzheimer's disease, is currently in phase III clinical trials. ALZ-801 targets an earlier form of amyloid and presents a lower risk of side effects, with the oral form facilitating easier access to treatment [116]. Additionally, the modified antidepressant drug AXS-05 is in phase III trials and has shown positive effects in treating Sundowner Syndrome in Alzheimer's patients [117]. The completion of phase III clinical trials for the drug simufilam, scheduled for 2024, is of significant importance. Simufilam functions by inhibiting filamin A, a biological agent implicated in the formation of amyloid plaques and tau tangles [118]. Treatment for Dementia with Lewy Bodies draws upon substances utilized in AD and PD therapy [119]. In the case of AxD, until now there were no effective treatments, only anticonvulsants were used to relieve symptoms. However, recent reports indicate that zilganersen sodium is currently undergoing phase III clinical trials. As an inhibitor of glial fibrillary acidic protein, this substance holds promise for enhancing the efficacy of AxD treatment [120, 121]. The list of available drugs currently used to treat ND is presented in Table 3.

Despite significant strides in developing symptomatic treatments in recent years, effective solutions for neurodegenerative diseases remain elusive. The latest data suggests a reduction in drug trials related to these conditions in the 2024 schedule. This shift is attributed to the observation that therapies aimed at modifying disease progression and alleviating symptoms do not necessarily advance the treatment of neurodegenerative diseases [114].

Therefore, there is a great need to develop effective therapies for neurodegenerative diseases. It's widely acknowledged that a single drug may not attain comparable therapeutic outcomes as a combination of drugs, particularly those demonstrating hyperadditive synergism. Consequently, neuroscientists are directing their efforts towards implementing multi-target therapy utilizing primarily natural substances. For instance, in studies, levodopa, renowned for its efficacy but burdened with numerous side effects, was amalgamated with resveratrol [122] and herbal remedies [123]. These studies confirmed the increased effectiveness of levodopa along with the elimination of side effects. Notably, resveratrol, possessing potent antioxidant properties, operates through the Nrf2 pathway [124]. Other studies have delved into assessing synergistic effects not only among existing neurodegenerative disease medications but also

within compositions of natural products. Collectively, these studies corroborate the augmented effectiveness of combination therapy [125–127]. Moreover, various combination therapies for neurodegenerative diseases have progressed to clinical trials. One such combination involves FDA-approved medications, specifically dasatinib, an anticancer drug and quercetin, a naturally occurring flavonoid with antioxidant and anti-inflammatory properties. This combination therapy is currently in phase I/II clinical trials. Research indicates that dasatinib and quercetin work synergistically to eliminate senescent cells associated with numerous age-related chronic diseases. Additionally, this combination reduces inflammation linked to Aβ plaques and mitigates cognitive decline. Clinical trial data show that the therapy has produced positive results in terms of target engagement [128]. Another promising combination therapy in phase III clinical trials is ALZT-OP1, which combines two established drugs: ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), and cromolyn, currently used to treat asthma. Preliminary results suggest that ALZT-OP1 is effective in reducing amyloid production and inflammation [129]. Recent developments also highlight JM-010 as an innovative treatment for Parkinson's disease dyskinesia. JM-010 is a proprietary formulation that combines immediate-release buspirone and extended-release zolmitriptan. This combination has shown a synergistic anti-dyskinetic effect. Co-treatment with JM-010 has demonstrated clinical efficacy and safety in phase I trials and clinical proof of concept in phase II trials. Currently, JM-010 is undergoing phase II clinical trials in both Europe and the USA [130].

In conclusion, the multi-target therapy paradigm emerges as highly significant in the quest for effective treatments. This model posits that drugs employed in combination operate independently, avoiding interference, with distinct mechanisms of action and uptake points. Considering the molecular mechanisms elucidated in this review concerning the clearance of protein aggregates, prioritizing the development of co-treatments utilizing multiple substances targeting these pathways becomes imperative.

Future perspectives

Neurodegenerative diseases represent a formidable challenge to unravel their intricate pathophysiology and develop effective therapeutic strategies. The complexities surrounding Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies or Alexander disease demand a comprehensive approach to address existing gaps in their understanding. Unraveling the intricate mechanisms underlying misfolded proteins and aggregate clearance provides a promising avenue for future therapeutic interventions. In this review we highlight potential mechanistic strategies, emphasizing protein

Table 3 Agent/drugs in neurodegenerative diseases developmental

Mechanism of action	Drugs
Parkinson's disease	
Precursor action of dopamine	Carbidopa/levodopa
Dopamine agonists	Pramipexole Ropinirole Rotigotine
MAO-B inhibitors	Rasagiline Selegiline Safinamide
COMT inhibitors	Entacapone Co-careldopa and entacapone Tolcapone Opicapone
Anticholinergics	Procyclidine Trihexyphenidyl
Dopamine agonists	Pramipexole Ropinirole Rotigotine Apomorphine
Glutamate antagonist	Amantadine
Binds and reduction α-synuclein	Prasinezumab
Alzheimer's disease	
AChEIs inhibitors	Tarcine Galantamine Rivastigmine Donepezil
NMDA receptor antagonist	Memantine
Agonist 5-HT$_{1A}$, antagonist 5-HT$_{2A}$	Brexpiprazole
Binds and reduction β- amyloid	Aducanumab Lecanemab Donanemab
Blocking filamin A	Simufilam
Dementia with Lewy Bodies	
AChEIs inhibitors	Galantamine Donepezil Rivastigmine
Precursor action of dopamine	Carbidopa/levodopa
Alexander disease	
GFAP inhibitors/Anticonvulsants	Zilganersen sodium

quality control pathways shedding light on their implications for neurodegenerative diseases. Advancements in molecular techniques are essential to decipher the intricate molecular landscapes underlying NDs. Additionally, a deeper understanding of the misfolding processes, aggregation kinetics, and intercellular propagation of pathogenic proteins, will pave the way for targeted therapeutic interventions.

Finally, given the complexity of NDs, ongoing research should critically reassess entrenched pathomechanistic paradigms. Rigorous investigations into the intricacies of Aβ, tau, and α-synuclein interactions, their role in neurodegeneration, and the limitations of current therapeutic strategies will redefine our understanding and guide future therapeutic developments. Tailoring therapeutic strategies based on an individual's genetic and molecular profile could enhance treatment efficacy and reduce adverse effects, thus precision therapeutics targeting specific molecular vulnerabilities may represent a paradigm shift in ND management. The future of ND research lies in the integration of diverse approaches, from advanced molecular characterization to translational research and precision therapeutics.

Therefore, future research should focus not only on the development of oral drugs but also on alternative drug delivery methods. Currently, many therapies are being developed in capsule form, but their effectiveness is limited by the challenges of bypassing the gastrointestinal barrier and the blood-brain barrier (BBB). For individuals unable to take oral medications, subcutaneous infusions administered via pumps or patches present a superior alternative, as they bypass gastrointestinal absorption. However, crossing the BBB remains a significant challenge. Recent breakthrough reports highlight the development of nasal spray therapies, opening new avenues for future research on medicinal substances. This innovative approach allows for the non-invasive delivery of therapeutic antibodies directly to the brain. The drug is administered through the nasal cavity, leveraging the direct connection to the brain and bypassing both the gastrointestinal barrier and the BBB. This method of administration offers a unique strategy to enhance drug bioavailability in the brain, representing a promising advancement in neurodegenerative disease treatment [131]. Unraveling the complexities of protein misfolding, aggregation, and intercellular propagation will redefine our understanding of ND pathophysiology and inspire innovative therapeutic strategies.

Therefore, current research should focus on preventing protein aggregation by activating various mechanistic pathways, such as protein quality-control-related ER and UPR pathways, molecular chaperones activity, chaperone-mediated autophagy, Keap1/ Nrf2/ARE pathway and p62/Keap1/Nrf2 - mediated autophagy. However, it remains a conceptual question whether a single agent aimed at increasing the clearance process will have a lasting neuroprotective effect, given the presence of many other disease pathways. Therefore, it is believed that approaches that use combination therapy, especially those using substances with different mechanisms of action, will be highly effective in the treatment of people suffering from neurodegenerative diseases. An innovative clinical trial set to commence in 2024 aims to evaluate the efficacy of a novel drug that slows the progression of Alzheimer's disease when used in combination with two other drugs targeting the pathogenic proteins associated with the disease. This trial represents the first instance of simultaneously testing drugs that act on both tau proteins and amyloid, including lecanemab (Leqembi), which was approved in January 2023. This study holds the potential to pioneer more effective treatment strategies for neurodegenerative diseases by employing a combination of therapies that may exhibit additive or synergistic effects. The enhancement of therapeutic outcomes through co-treatment offers innovative and groundbreaking perspectives for the advancement of neurodegenerative disease therapy.

To summarize, collaborative efforts across disciplines, coupled with advancements in technology, will undoubtedly shape the landscape of neurodegenerative disease research in the years to come.

Conclusions

1. Neurodegenerative diseases (NDs) are inherently complex, necessitating a multifaceted approach to both understanding and treatment. This involves examining protein misfolding, aggregation, and clearance mechanisms, alongside exploring diverse therapeutic strategies.
2. Future research should prioritize the investigation and manipulation of protein quality control pathways, such as ER and UPR pathways, molecular chaperones, and autophagy-related pathways, including the intersecting p62-Keap1-Nrf2-ARE pathway. Targeting these mechanisms could offer new avenues for therapeutic intervention.
3. Personalized treatment approaches, tailored to individual genetic and molecular profiles, show promise in enhancing efficacy and minimizing adverse effects in ND management. Innovative drug delivery methods, such as oral medications, subcutaneous infusions via pumps or patches, and nasal sprays, hold the potential for revolutionizing personalized treatment paradigms.

4. Given the complexity of NDs and the involvement of multiple disease pathways, combination therapy using substances with different mechanisms of action is proposed as a highly effective strategy. This approach could address various aspects of the disease pathology simultaneously, specifically, if targeting two different target proteins that cause the disease.

5. The future of ND research hinges on collaborative efforts across disciplines and the integration of advanced technologies. These collaborations, alongside technological advancements, will shape the research landscape, facilitating innovative discoveries and therapeutic developments in the years ahead.

Abbreviations

Aβ	β-Amyloid
ACD	Alpha-crystallin domain
AD	Alzheimer's disease
ARE	Antioxidant response element
ATF6	Activating transcription factor 6
AxD	Alexander disease
BBB	Blood-brain barrier
CHOP	C/EBP homologous protein
CMA	Chaperone-mediated autophagy
CNS	Central nervous system
CREs	CAMP responsive elements
CTD	C-terminal domain
DLB	Dementia with Lewy bodies
ER	Endoplasmic reticulum
GFAP	Glial fibrillary acidc protein
GSH	Glutathione
HO-1	Heme oxygenase-1
Hsps	Heat shock proteins
IRE1	Inositol-requiring protein 1
Keap1	Kelch-like ECH-associated protein 1
LAMP-2A	Lysosome-associated type-2A membrane protein
LB	Lewy bodies
MD	Middle domain
NBD	Nucleotide-binding domain
ND	Neurodegenerative diseases
NF-Y	Nuclear factor-Y
Nrf2	Nuclear factor-erythroid 2-related factor 2
NTD	N-terminal domain
NQO1	NAD(P)H quinone oxidoreductase 1
PD	Parkinson's disease
PERK	Protein kinase RNA-like ER kinase
RBD	REM sleep behavior disorder
SBD	Substrate-binding domain
sHsps	Small heat shock proteins
SOD	Superoxide dismutase
UPR	Unfolded protein response

Authors' contributions
O.K.: developed and planned the idea presented, designed figures, wrote the manuscript; P.S.: wrote the manuscript, provided critical advice and guidance. All authors have read and agreed to the published version of the manuscript.

Authors' information
Not applicable.

Availability of data and materials
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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