

Misfolded Proteins in Neurodegenerative Dementias: Molecular Mechanisms

Hyun Duk Yang, M.D.,
Dong-Hwan Ho, M.S.,
Myoung-Jea Yi, M.D.,
Wongi Seol, Ph.D.,
SangYun Kim, M.D.*

Inam Neuroscience Research Center,
Department of Neurology, Sanbon Medical
Center, Wonkwang University College of
Medicine, Gunpo; Department of Neurology*,
Seoul National University College of
Medicine & Seoul National University
Bundang Hospital, Seoul, Korea

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Address for correspondence

Hyun Duk Yang, M.D.
Inam Neuroscience Research Center, Department
of Neurology, Sanbon Medical Center, Wonkwang
University College of Medicine, 1142 Sanbon-dong,
Gunpo 435-040, Korea
Tel: +82-31-390-2422
Fax: +82-31-390-2422
E-mail: hyundyang@gmail.com

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During recent years, there has been remarkable progress with respect to the identification of molecular mechanisms and underlying pathology of neurodegenerative dementias. The latest evidence indicates that a common cause and pathological mechanism of diverse neurodegenerative dementias can be found in the increased production, misfolding, aggregation, and accumulation of specific proteins such as β -amyloid, tau protein, α -synuclein, prion protein, polyglutamine, transactive response DNA-binding protein (TARDBP or TDP-43), or fused in sarcoma (FUS). The conformational variants of these proteins range from small oligomers to the characteristic pathologic inclusions. However, it is noteworthy that a certain pathology can be a hallmark of a certain dementia, but there is a substantial overlap between different pathologies and different types of dementias. In this review, molecular mechanisms and pathologies of different neurodegenerative dementias will be summarized from the perspective of proteins rather than from the viewpoint of individual dementias. We will also review recent evidence surrounding these protein misfolding disorders, the role of toxic oligomers, cell-to-cell transmission, and the links between the misfolded proteins, along with the general therapeutic strategies for the protein misfolding disorders.

Key Words: Neurodegenerative disorders, Protein misfolding disorders, Dementia

INTRODUCTION

In the last several years, noticeable progress has been made in regard to the identification of underlying molecular and pathologic mechanisms of neurodegenerative disorders in which dementias are the major clinical presentation. Although the exact causes of most dementias have not been fully understood, studies suggest that the increased production, misfolding, aggregation, and accumulation of proteins are a common factor in the development of many neurodegenerative dementias [1-4].

This diverse group includes Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease with de-

mentia (PDD), multiple system atrophies (MSAs), frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Huntington's disease (HD) and related polyglutamine diseases, and prion diseases.

The proteins which are overproduced, misfolded, and pathologically aggregate include β -amyloid (A β), tau protein, α -synuclein, prion protein, polyglutamine, transactive response DNA-binding protein (TARDBP or TDP-43), and fused in sarcoma (FUS) protein. Molecular classification based on these proteins comprises β -amyloidopathies, tauopathies, α -synucleinopathies, prionopathies, polyglutaminopathies, TDP-43 proteinopathies, and FUS proteinopathies (Table 1).

Table 1. Misfolded proteins and neuropathologic changes

Misfolded proteins	Neuropathologic changes	Cellular location of aggregates
A β	Senile plaques, dystrophic neuritic plaques, diffuse plaques, amyloid angiopathy	Extracellular
α -synuclein	Lewy bodies, Lewy neurites, oligodendroglial inclusions	Cytoplasmic
FUS	FUS-positive inclusions	Cytoplasmic and nuclear
Huntingtin	Neuronal intranuclear inclusions	Nuclear
Prion proteins	Prion protein amyloid plaques	Extracellular
Tau	Neurofibrillary tangles, neurofibrillary pretangle, dystrophic neurites, neuropil threads, Pick bodies	Cytoplasmic
TDP-43	TDP-43 inclusions, TDP-43 preinclusions	Cytoplasmic and nuclear

A β , β -amyloid; FUS, fused in sarcoma; TDP-43, transactive response (TAR)-DNA-binding protein or TARDBP.

These are collectively called protein conformational disorders, protein misfolding disorders, proteinopathies, or proteopathies.

Although some protein aggregations are hallmarks of certain dementias, for example, extracellular senile plaques and intracellular neurofibrillary tangles in AD, they are not exclusively found in any singular type of dementia. One type of dementia may have multiple types of protein aggregations and one type of protein aggregation may be found through various dementias.

In this review, we attempted to determine the roles of misfolded proteins in order to understand the pathologic origin of neurodegenerative dementias, and demonstrated the interconnectedness of misfolded proteins and neurodegenerative dementias.

1. General principles

1) The mechanisms of misfolding and aggregation

The canonical features of these neurodegenerative disorders is that a specific protein can enfold into an alternative conformation which is stable, precipitates its aggregation, and is deposited in tissues in a fibrillar form [1-3]. These fibrillar deposits share similar morphological and tinctorial characteristics with amyloids. In general, the naïve protein consists of α -helices and random coils, whereas the misfolded protein is composed of rich β -structures which are insoluble and implicated in diseases [5, 6]. During misfolding and aggregation, a large conformational change in the proteins takes place, forming a misfolded intermediate with exposed hydrophobic fragments. This intermediate has a tendency to aggregate and stabilize, giving rise to the formation of oligomers, protofibrils, fibrils, and finally aggregates or inclusions (Fig. 1). The expo-

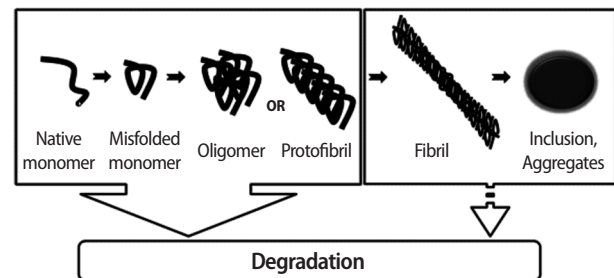


Fig. 1. Pathogenesis of protein misfolding diseases. Naïve proteins are misfolded, self-accumulate, and form oligomers, protofibrils, fibrils, and eventually aggregates or inclusions. An imbalance between production, aggregation, and clearance of proteins brings about accumulation of misfolded proteins. The mature forms are more resistant to degradation than the intermediate species. The common toxic effects of the misfolded proteins may include oxidative stress, neuroinflammatory damage, and disturbed neurotransmitter, synaptic, and mitochondrial functions.

sure of hydrophobic sequences of the misfolded proteins to the surface is considered critical for protein aggregation [2, 3, 6-8]. The aggregation of proteins follows nucleation-dependent polymerization, in which the critical event is oligomer formation that is soluble but serves as a nucleus to direct further elongation of aggregates. This process is characterized by a slow lag phase which is followed by a rapid growth to form polymers [9-11]. An imbalance between production, aggregation, and clearance of proteins brings about accumulation of misfolded proteins. In general, the accumulation of these misfolded proteins causes oxidative and neuroinflammatory damage leading to subsequent neurotransmitter, synaptic, and mitochondrial dysfunctions.

2) Selective neuronal vulnerability

The diverse phenotypes of different protein misfolding disorders may come from the selective vulnerability of neurons or glial cells to the specific misfolded proteins. The relation-

ship between the phenotypes and the brain regions affected is more pronounced in the early stage of the diseases than in the later stages in which there are more extensive and diverse manifestations.

Postmortem analyses of human brains have revealed a characteristic pathological pattern of the deposition of specific proteins. A β plaques appear first in the neocortex, followed by the allocortex and the subcortical structures in AD [12-15]. Tau pathologies first appear in the locus coeruleus and transentorhinal area including the entorhinal cortex, and then spread to the amygdala and interconnected neocortical areas in AD [15, 16]. The mutant polyglutamines also have their own specific groups of neurons showing selective vulnerability to each protein in polyglutaminopathies [17]. Huntingtin (HTT) begins to appear in the striatum in HD. α -Synuclein initially accumulates in the lower brainstem centers and ascends to the limbic and cortical association areas in PD [18, 19], while in contrast, α -synuclein first appears in the cortex in DLB [20]. Although why different proteins are prone to accumulate in specific brain areas is still unknown, it has been speculated that local changes in expression or post-translational modifications of the specific proteins may account for the regional selectivity of early involvement [4].

In addition to the regional selectivity, these protein deposits may have different pathological and clinical features, depending on whether the aggregates accumulate predominantly in neurons or in glial cells, or intracellularly or extracellularly (Table 1). Unlike other α -synucleinopathies or protein misfolding disorders, the pathological deposition of α -synuclein in MSA is predominant in oligodendrocytes, forming oligodendroglial inclusions [21]. A β and prion proteins accumulate extracellularly, tau and α -synuclein aggregate in the cytoplasm, HTT assembles in the nucleus, and TDP-43 and FUS proteins accumulate primarily in the cytoplasm but are also found in the nucleus [22-24].

2. Basic pathologies of neurodegenerative dementias

1) β -Amyloid (A β) and β -amyloidopathies

Under physiological conditions, A β may attenuate excitatory transmission at the synapse and suppress neuronal hyperactivity [25]. A β peptides are produced by proteolysis of

the neuronal transmembrane amyloid precursor protein (APP) through sequential cleavage by β - and γ -secretases, by way of the amyloidogenic pathway. Monomers of A β_{40} are more prevalent than the highly toxic and aggregation-prone A β_{42} species [26-28]. However, the predominant pathway of amyloid metabolism is through the non-amyloidogenic pathway, in which APP is processed by α - and γ -secretases forming a soluble fragment of APP (sAPP) which may have protective and neurotrophic effects [29]. Multiple genetic and environmental factors may shift this equilibrium toward the increased formation of A β_{42} species which is followed by oligomerization, aggregation, and deposition as insoluble fibers of amyloid plaques. Nonetheless, A β also makes up diffuse plaques that contain nonfibrillar deposits of peptides. Neprilysin and insulin-degrading-enzyme (IDE) degrade A β monomers and oligomers to maintain the steady-state levels of A β [30-32]. Among the various forms of A β , soluble oligomers and intermediate fibrils are known to be the most toxic [33].

Although A β deposits are one of the pathological hallmarks of AD, amyloid plaques are also found in other dementias including DLB [34, 35], PDD [36], Down syndrome [37-39], Creutzfeldt-Jakob disease (CJD) and Gerstmann-Sträussler-Scheinker disease (GSS) [40-42] (Table 2).

2) Tau and tauopathies

Tau protein, one of the microtubule-associated proteins (MAPs), is abundant in axons and promotes the assembly and stabilization of microtubule and intracellular transport. Hyperphosphorylated tau, which is caused by a combination of excessive kinase and decreased phosphatase activities, becomes insoluble, is detached from microtubules, and self-aggregates into pair helical filaments (PHFs) and straight filaments [43]. Similar to A β oligomers, intermediate aggregates are toxic [44]. PHFs sequester toxic intermediate species and are considered to be protective [45, 46].

Neurofibrillary lesions contain aggregated filaments which are formed by abnormal phosphorylation of tau protein. Neurofibrillary lesions include not only neurofibrillary tangles (NFTs), but also neuropil threads and dystrophic neurites. NFTs accumulate around the nuclei and dystrophic neurites and neuropil threads accumulate in axons and dendrites. Dystrophic neurites are usually associated with amyloid plaque

Table 2. Misfolded proteins and dementias

Misfolded proteins	A β	α -synuclein	FUS	Huntingtin	Prion proteins	Tau	TDP-43
AD	√√	√				√√	
ALS/PDC*						√√	√√
CBD						√√	
DLB	√	√√				√	
DM	√					√	
Down's syndrome	√√					√√	
FTLD							
BIBD			√√				
bvFTD*			√√			√√	√√
c9FTD/ALS							√√
FTD/ALS*			√√				√√
FTDP-17						√√	
IBMPFD							√√
NIFID			√√				
Pick's disease						√√	
PNFA*						√√	√√
SD*						√	√√
HD				√√			
MSA		√√				√	
NBIA		√√				√√	
PDD	√	√√				√	
CJD	√				√√	√	
PSP						√√	

√√, major component; √, minor component.

*For ALS/PDC, bvFTD, FTD/ALS, PNFA, and SD, these may have one of the different pathologies depending on each case. It does not mean that different pathologies shown in the table are found simultaneously.

A β , β -amyloid; AD, Alzheimer's disease; ALS/PDC, amyotrophic lateral sclerosis-Parkinsonism-dementia complex of Guam; BIBD, bvFTD, behavioral variant FTD; c9FTD/ALS, chromosome 9p-linked frontotemporal dementia and amyotrophic lateral sclerosis; CBD, corticobasal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; DM, Dystrophia myotonica; FFI, fatal familial insomnia; FTD/ALS, frontotemporal dementia and amyotrophic lateral sclerosis; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; FTLD, Frontotemporal lobar degeneration; FUS, fused in sarcoma; GSS, Gerstmann-Sträussler-Scheinker disease; HD, Huntington's disease; IBMPFD, Inclusion body myopathy, Paget's disease of the bone and frontotemporal dementia; MSA, Multiple system atrophy; NBIA, neurodegeneration with brain iron accumulation; NIFID, neuronal intermediate filament inclusion disease; basophilic inclusion body disease; PDD, Parkinson disease with dementia; PNFA, progressive nonfluent aphasia; PSP, progressive supranuclear palsy; SD, semantic dementia; TDP-43, transactive response (TAR)-DNA-binding protein or TARDBP.

cores to form neuritic plaques.

Although there has been a poor correlation between the severity of neuronal loss, dementia, and the distribution of amyloid plaques, several studies supported that NFTs parallel with the severity of AD dementia [15, 47-49].

Neurofibrillary lesions are also characteristically part of the main pathology in several neurodegenerative dementias other than AD, which are termed tauopathies. Some tauopathies also show the combined amyloid plaques, while other tauopathies show only abundant neurofibrillary lesions without amyloid plaques. The former group includes Down syndrome [37-39] and some cases of CJD and Gerstmann-Sträussler-Scheinker disease (GSS) [40-42], while the latter encompasses CBD [50-53], PSP [54-56], MSA [57], neurodegeneration with brain iron accumulation (NBIA, formerly known as Hallervorden-Spatz disease) [58], Pick's disease [59-61], and

FTDP-17 [62, 63]. However, MSA, NBIA, some subtypes of AD also have prominent α -synuclein lesions. In AD, tau pathology is largely limited to neurons, whereas some other tauopathies such as MSA, PSP, CBD, and FTDP-17 demonstrate both neuronal and glial inclusions [64-67].

3) α -Synuclein and α -synucleinopathies

α -Synuclein is a 140-residue neuronal protein which is found mostly in the neuronal presynaptic terminal in an unfolded form under normal physiological conditions. This protein was first identified as the precursor protein for non-amyloid constituents of senile plaques in AD [68]. It is presumed to support the regulation of the release of synaptic vesicles and the stabilization of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) family proteins including synaptobrevin-2 and vesicle-associated

membrane protein 2 (VAMP2) [69, 70]. Genome-wide association studies (GWASs) have shown that *SNCA* gene which encodes α -synuclein is linked to sporadic PD [71] and the missense point mutations in the *SNCA* gene and the multiplications of the gene loci have been found in *SNCA* in families with autosomal dominant PD [72]. Pathological deposits of α -synuclein have been identified within aggregates in the forms of Lewy bodies and Lewy neurites in patients with PD and DLB, and oligodendroglial inclusions in MSA patients, collectively termed α -synucleinopathies [73]. However, AD and neurodegeneration with brain iron accumulation (NBIA, formerly known as Hallervorden-Spatz disease) are known to have abnormal deposition of α -synuclein [74, 75]. The pathogenic mechanisms underlying the aberrant functions of α -synuclein still remain poorly understood, but some possibilities including alteration of neurotransmitter release, lysosomal dysfunction, calcium homeostasis, cytoskeletal effects, and mitochondrial dysfunction have been suggested [76].

4) Prion protein and prionopathies

PrP^C (normal cellular prion protein isoform) is the natural prion protein encoded by the *PRNP* gene. PrP^C is a glycoprotein which is expressed in the cells in the central nervous system (CNS) and the immune system [77]. In the brain, the expression of PrP^C is notably observed in neuronal synaptic membranes and is also expressed in astrocytes [78]. PrP^C has been shown to be involved in signal transduction and to interact with several intracellular signaling proteins [79]. Although the understanding of the biologic functions of PrP^C remains elusive, it is known to not be essential for cell survival [80]. However, the conversion of PrP^C to the pathogenic PrP^{Sc} (PrP scrapie) ends up resulting in neurodegeneration [81, 82]. PrP^C acts as the raw material for conversion to PrP^{Sc} [83]. Thus, these corrupted molecules easily self-aggregate and elicit neuronal injury. Although the exact mechanism of transmission remains uncertain, it is believed that prions can spread to other cells by synaptic transport [84].

In humans, a variety of prion diseases (prionopathies or transmissible spongiform encephalopathies) are present, including CJD, GSS, fatal familial insomnia, and kuru [83, 85], although the diseases are uncommon. Prion diseases are unique in that the same disease can have genetic, sporadic, and

infectious (transmissible) origins and in that prion disease is the only infectious cerebral proteopathy [83, 84]. However, several studies implicated prion-like transmission of protein aggregates or inclusions in the initiation and spread of various neurodegenerative disorders [84, 86-90].

5) Huntingtin and polyglutaminopathies

Huntingtin (HTT) is a cytoplasmic protein which is found to be associated with synaptic vesicles and microtubules. In Huntington's disease (HD), the CAG repeats in the *HD* gene are suggested to be expanded by dynamic mutation as other trinucleotide repeat expansion disorders [91] and mutant HTT proteins with an expanded polyglutamine tract are produced. Mutant proteins are prone to toxic conformational changes and accumulate into insoluble aggregates as neuronal intranuclear inclusions (NIIs) [92-94]. These processes are common features among polyglutamine diseases which include HD, spinocerebellar ataxia 1, 2, 3, 6, 7, and 17 (SCA1/2/3/6/7/17), dentatorubral-pallidoluysian atrophy (DRPLA), and spinal and bulbar muscular atrophy (SBMA, also known as Kennedy's disease). Among them, SCA17 and DRPLA include dementia as one of the cardinal manifestations, similar to HD [95-97]. The counterparts of HTT are TATA-binding protein gene (TBP) and atrophin 1 in SCA17 and DRPLA, respectively [98-100].

6) Transactive response DNA-binding protein of 43kDa (TDP-43) and TDP-43 proteinopathies

TDP-43 is a ubiquitously expressed 414-residue protein which is mainly localized inside the nucleus under physiological conditions and is able to shuttle between the nucleus and the cytoplasm in a transcription-dependent manner by virtue of the presence of a nuclear localization sequence (NLS) and nuclear export sequence (NES) [101]. It regulates diverse processes of gene expression including transcription and splicing through RNA and DNA binding. It contains two RNA recognition motifs (RRMs) that allow for binding to nucleic acids and a C-terminal glycine-rich domain (GRD) which is important for protein-protein interactions and essential for solubility and cellular localization. Disruption of the RRM changes nuclear distribution by decreasing the level of TDP-43 in the nucleoplasm. Deletion of the C-terminal GRD elicits the

formation of nuclear and cytoplasmic aggregates.

TDP-43 pathology is, along with tau pathology, also the main cause for some clinical subtypes of FTLD such as behavioral variant FTD (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA) [102, 103] and amyotrophic lateral sclerosis-Parkinsonism-dementia complex of Guam (ALS/PDC) [104].

TDP-43 has been identified as the major protein aggregation in frontotemporal dementia and amyotrophic lateral sclerosis (FDT/ALS), one of the subtypes of frontotemporal lobar degeneration with ubiquitin inclusions (FTLD-U) [105]. Pathologic TDP-43 is ubiquitinated, hyperphosphorylated, and cleaved to produce C-terminal fragments. Remarkably, it is consistently observed that normal nuclear localization of TDP-43 is lacking in inclusion-bearing neurons. In addition to the TDP-43 inclusions, TDP-43 preinclusions, which are observed cell bodies without inclusions, are a common neuropathologic finding. They show diffuse or granular cytoplasmic TDP-43 staining and do not colocalize with ubiquitin [106].

In FTLD, TDP-43 positive aggregates are found in most sporadic cases as well as in familial forms. Familial forms are caused by mutations in the *TAR-DNA binding protein* (*TAR-DBP*) gene [107], *progranulin* (*GRN*) genes [105, 108], and *valosin containing protein* (*VCP*) genes [109]. Recently, it has been found that an expanded hexanucleotide repeat in chromosome 9 open reading frame 72 (*C9ORF72*) is the most common mutation in FTD/ALS families with TDP-43 pathology [110, 111]. However, the causative relationship between TDP-43 pathology and the mutation remains unclear at this time.

7) Fused in sarcoma (FUS) and FUS proteinopathies

FUS, also known as translocated in liposarcoma (TLS) or heterogeneous ribonucleoprotein (hnRNP) P2, is a 526-residue protein identified as a proto-oncogene that causes liposarcoma via chromosomal translocation [112]. FUS is an RNA-binding protein like TDP-43 and comprises the RRM domain, GRD, and NLS/NES, which are arranged differently in various proteins from TDP-43. The FUS protein is a nuclear protein and is involved in DNA repair and RNA splicing regulation [113, 114].

Mutations within the *FUS* gene in the GRD and the C-ter-

minus of FUS protein impair nuclear import and lead to redistribution to the cytoplasm, consequently affecting FUS-dependent RNA metabolism.

FUS pathology is observed in the majority of FTLD cases with ubiquitin-positive, and TDP-43 negative pathology (FTLD-FUS) [115-117]. FTLD-FUS cases are characterized by negative family history, disease onset at young age, presence of bvFTD, and caudate atrophy. FUS-positive inclusions are also found in basophilic inclusion body disease [118] and neuronal intermediate filament inclusion disease [24].

FUS has been identified to misfold and aggregate in distinct subtypes of FTLD-U (FTD/ALS), similar to TDP-43 but with TDP-43 negative pathology [116, 119]. Contrary to TDP-43, no association of post-translational modifications such as ubiquitination, phosphorylation, or truncation has been identified.

3. Links between proteins

Some of the protein misfolding diseases have more than one pathology, as some proteins are commonly found in more than one disease (Table 2). The understanding of the interaction between the misfolded proteins will help elucidate in part the complexity of the protein misfolding disorders.

1) β -amyloid (A β) and tau

Several experimental studies support that the accumulation of A β precedes and trigger the aggregation of tau [120-123], which is consistent with the amyloid cascade hypothesis. Furthermore, A β -induced neuronal dysfunction was prevented by tau reduction [124], and morphological analysis showed that tau-depleted neurons revealed no evidence of degeneration in the presence of A β [125]. These results are supported by prior evidence that A β promotes the activation of glycogen synthase kinase-3 β (GSK3 β) through the insulin and Wnt signaling pathways, with subsequent tau phosphorylation [126-129].

2) β -amyloid (A β) and α -synuclein

AD patients develop features of PD and vice versa. Moreover, A β pathology and α -synuclein pathology can be found in both AD and DLB/PDD. It has been found that A β and

α -synuclein synergistically interact to cause neurodegeneration in the transgenic mouse model [130]. A β promoted the aggregation and intraneuronal accumulation of α -synuclein and the development of motor deficits, supporting that A β may contribute to the development of DLB or PDD by promoting α -synuclein aggregation. Although α -synuclein did not affect A β pathology, it aggravated the cognitive deficits, suggesting that α -synuclein may augment the A β -independent neurotoxicity of A β [131, 132].

3) β -amyloid (A β) and prion protein

It has been reported that prion protein which A β binds is required for the impairment of synaptic plasticity mediated by A β oligomers [133]. It has also been found that the region of importance for the interaction between prion proteins and A β resides at the extreme amino-terminus of prion protein [134]. The role of prion protein in A β -induced toxicity was confirmed by a recent study showing that prion protein is required for disrupting hippocampal synaptic plasticity by A β peptides [135].

4) α -Synuclein and tau

GWASs have shown that there are strong associations with PD for *SNCA*, *LRRK2*, and *MAPT* [71], suggesting functional links among these proteins that affect the cytoskeleton. Oligomeric α -synuclein indirectly augments the phosphorylation of tau presumably via GSK-3 β or other kinases and destabilizes the microtubules, which in turn may promote the formation of α -synuclein oligomers and cause further disruption of microtubules [136-139]. Additionally, leucine-rich repeat kinase 2 (LRRK2, also known as dardarin) which is encoded by *LRRK2*, an autosomal dominant inherited PD gene, can increase the phosphorylation of tau through GSK-3 β and Ste20 kinase [140-142]. These findings suggest a synergistic interaction between α -synuclein and LRRK2 that involve tau.

5) Transactive response DNA-binding protein (TARDBP or TDP-43) and fused in sarcoma (FUS) protein

Both TDP-43 and FUS are the cytoplasmic RNA-binding proteins which play critical roles in the development of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLU-U) and ALS. These proteins are transported to

the nucleus via import receptors and also contribute to stress granule formation. Although the exact mechanisms for the accumulation of TDP-43 and FUS and the resultant neurodegeneration are currently unclear [119], it has been proposed that excessive mislocation of the proteins along with ataxin-2 into the cytoplasm causes dysfunction of the RNA quarantine system, inducing a joined cascade of neurodegeneration which is promoted by ataxin-2 [143].

4. Some issues under debate

1) The relationship between soluble oligomers and insoluble inclusions

Determining which particular species of the misfolded proteins are neurotoxic has been under debate. Several experiments are in favor of the toxicity of soluble oligomeric species [33, 44-46, 144]. However, this oligomeric species-induced toxicity does not indicate that the insoluble inclusions are innocent. There has still been evidence that these inclusions are toxic [145, 146], but other data support that the insoluble inclusions may be neuroprotective [45, 46, 147, 148].

Considering that oligomers are found around and within the amyloid plaques and are toxic to adjacent neurons [149-151], it has been suggested that inclusions serve as reservoirs for oligomers that can diffuse away from the inclusions and cause synaptic or neuronal toxicity [152]. The inclusions may initially sequester toxic soluble oligomers, but, eventually the reservoirs are overwhelmed and can no longer be protective. Mass effect of the inclusions on surrounding neurons seems to be plausible but it has been shown that senile plaques did not exert any mass lesion effects on neighboring cells [153]. Nonetheless, whether it can be the case for other protein misfolding disorders needs to be further investigated.

2) Cell-to-cell disease transmission

Pathological similarities between prion diseases and AD suggest that the prion-like formation and seeding of proteinaceous lesions may be involved in the pathogenesis of disease [154-157].

The deposition of A β deposits were found in axonally interconnected areas following the injection of A β aggregates into the brain, suggesting it spreads through neuronal path-

ways [157-159]. The accumulation of abnormal tau starts in the entorhinal cortex (ERC) in the earliest stage of AD, and then spreads to the hippocampus followed by the neocortical regions [15]. However, it has been poorly explored whether tau pathology in the ERC initiates spreading to other structures, or that the pathology in the extrahippocampal areas begins independently. Using a transgenic mouse model expressing the pathological human tau protein primarily in the ERC, it has been demonstrated that tau pathology which began in the ERC spreads out from one neuron to other neurons outside of the ERC across synapses [160]. This study result confirms observations from previous studies suggesting the trans-synaptic cell-to-cell spread hypothesis for AD [161, 162].

α -Synuclein pathology in PD starts in the anterior olfactory nucleus and the lower brainstem centers and ultimately ascends to the cortex [18, 19]. A recent study showed that purified α -synuclein fibrils are internalized into primary mouse hippocampal cells by endocytosis, recruit soluble endogenous α -synuclein, and promote the formation of insoluble Lewy bodies or neurites [163]. In this study, the aggregates of α -synuclein appeared early in the axon terminals and later in the cell body, suggesting propagation along the axon and eventually to other cells. The report reinforces the earlier conclusions suggesting α -synuclein pathology from dying neurons is conveyed to neighboring neurons through cell-to-cell transmission [19, 164, 165], which is similar to the transmission of misfolded prion proteins in CJD [166].

Furthermore, the prion-like cell-to-cell transmission of the lesions has also been demonstrated in polyglutamine and TDP-43 aggregates [167, 168]. However, the mode of cell-to-cell transmission for these proteins remains unclear.

5. General therapeutic strategies for protein misfolding disorders

Despite remarkable progress in the understanding of the pathomechanisms of protein misfolding disorders, there has been no successful disease-modifying therapy for them as this has been the case in AD. Therapeutic strategies targeted for the misfolded and aggregated proteins have been proposed: 1) stabilization of the normal protein conformation; 2) inhi-

bition of the protein misfolding by interfering with post-translational modification; 3) unfolding the misfolded proteins; 4) inhibition of protein oligomerization by compounds binding to monomers; 5) inhibition of protein aggregation with small molecules that bind to aggregates and further interfere with the recruitment of monomers; 6) upregulating molecular chaperones; 7) enhancing the clearance mechanisms by immunization; and 8) gene therapy [4, 169, 170]. The combinations of more than one strategy, particularly in the earliest stages of the diseases are expected to be the most effective treatments for patients with disorders in the near future.

CONCLUSIONS

The misfolding and aggregation of proteins have been regarded as central events in the development of various neurodegenerative dementias. The common pathological mechanisms of these disorders are increased production, misfolding, aggregation, and accumulation of specific proteins, with the conformational variants ranging from small oligomers to the characteristic inclusions. However, there is a substantial overlap between different pathologies and different dementias evidenced by the existence of the interactions between the misfolded proteins, although certain pathologies can be a hallmark of certain dementias. There has been remarkable progress in understanding the role of toxic oligomers and cell-to-cell transmission. The understanding of the pathomechanistic roles of misfolded proteins will be the fundamental basis for the identification of biomarkers in the earliest stage of dementia, and should facilitate the development of effective treatments which can modify the natural course of the dementia.

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