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Role of Protein Aggregation in Neurodegenerative Diseases

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1. Introduction

Proteins and peptides are essential complex macromolecules of organisms and participate in actually every process within cells. Three dimensional structures of proteins play a critical role for biological functions. Therefore, they must be properly folded for performing these functions. Three dimensional structures are determined by composition of amino acid sequence. In addition to hydrophobic forces, covalent and weak interactions direct the formation of native protein conformation [1].

Proteins can be exposed to internal and external forces such as protein-protein interactions, various stresses, mutations etc. Since these forces alternates protein conformation, the biological activity of the protein decreases. However, newly synthesized proteins may not fold correctly, or properly folded proteins cannot spontaneously fold. In this case, proteins have a strong tendency to aggregate [1-3]. Especially, heat shock proteins (chaperones) play a key role in correcting protein folding and prevention of protein aggregation [1, 4, 5].

Protein aggregates has toxic effects when accumulated over a certain amount in the cell. The accumulation of abnormal proteins leads to progressive loss of structure and/or function of neurons, including the death of neurons. Many diseases associate with protein aggregation such as prion, Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases (HD). Thus, dysmnesia, mental retardation, and also cancer are seen in these diseases. Many of the neurodegenerative disorders likely occur due to environmental and genetic factors. Especially, probability of AD and PD occurrence rise with increasing age. Briefly, neurodegenerative diseases have similar pathogenesis and cellular mechanisms [6-10].

Nowadays, mechanisms of protein aggregations and generation of neurodegenerative diseases with misfolded proteins are not clear at the molecular level. Thus, protein aggregation is a bone to pick for biotechnology and pharmaceutical industries. The aim of this chapter is to bring a perspective to the role of misfolded proteins in neurodegenerative diseases in terms of molecular and cellular basis.

2. Overview of protein aggregation

Formation of neurodegenerative diseases has not been elucidated for many years. To date, a variety of mechanisms have been suggested for explaining protein misfolding and protein aggregation, however we cannot understand the mechanism clearly at the molecular and cellular basis.

Functional proteins must pass a quality control process in terms of folding to perform catalysis, cellular transport, signal transmission and regulation. However, variety of structural and environmental factors influence this process negatively [1-3]. In this section, we will focus on aggregation behavior of proteins and these factors.

2.1. Factors affecting protein aggregation in neurodegenerative diseases

2.1.1. Protein structures

The first critical factor is protein structure. Especially, primary and secondary structures of a protein are two of the most important factors for physical and chemical features.

Encoded information in amino acid sequence of a protein determines the three dimensional structure. Position and number of different characteristic amino acid residues in primary structure may lead to an increase or a decrease in aggregation behavior. Number of hydrophobic amino acids in proteins is proportional to tendency of aggregation [2].

Secondary structures of proteins involve in protein misfolding as well as stability. Proteins often fold locally into stable structures that include α -helix and β -sheet. Generally, some β -sheet-rich proteins (such as scrapie infected prion protein) associate with pathological states. During protein aggregation, the secondary structure is converted from α -helix to β -sheet. Thus, protein gets strictness and wide surface area [1, 11, 12].

2.1.2. Mutations

Mutations play determinative role in protein aggregation and they may dramatically alter solubility, stability, and aggregation tendency of proteins [13].

Thermally stable proteins may change its stability even with a point mutation in its structure. For example, a human lysozyme I56T and D67H mutants greatly decreases the lysozyme stability and as a result the lysozyme aggregates easily upon heating. Further aggregation cause amyloid fibrils and these fibrils are deposited in tissues and are associated with neurodegenerative diseases [2].

Recently, scientists have been suggested a new protein for understanding of ALS (amyotrophic lateral sclerosis), AD, cystic fibrosis (CF) and frontotemporal lobar degeneration (FTLD) mechanisms. The transactive response DNA binding protein 43 (TDP-43) is expressed by all mammalian tissues, conformational changes in this protein cause aggregation and loss of function. TDP-43 has been shown to bind to DNA and mRNA and participate in regulation of transcription and translation. TDP-43 has a glycine rich C-terminal tail and mutation occurs from this region. Consequently, TDP-43 is converted to aggregated form which is accumulated in tissues [14].

2.1.3. *Post-translational modifications*

After a protein is synthesized, the posttranslational modifications (PTM) of amino acids may increase the diversity of proteins by additional functional groups (acetate, phosphate, various proteins etc.) and structural changes [15]. In particular, phosphorylation plays a significant role in neurodegenerative diseases. It is also known that, occurrence of AD is associated with tauopathy due to aggregation of the tau protein. In brain, tau protein is found in neurons and it can be phosphorylated with kinase enzymes. Thus, aberrant tau aggregates are formed and they can be accumulated in neurons, thereby their toxic effects are caused neuronal loss and synaptic alteration [16, 17].

Glycosylation is an important PTM for protein stability and aggregation potential. Human prion protein has two potential *N*-glycosylation sites (Asn181 and Asn197). However, in prion pathology, conversion of PrP^c to PrP^{sc} occurs easily if the PrP^c is glycosylated. In AD patients, hyperglycosylated tau protein is found in brains [18, 19].

Hyperphosphorylation and hyperglycosylation are seemed to be required for protein aggregation and misfolding in neurodegenerative diseases. Moreover, the other PTMs such as glycation, nitration, truncation, polyamination etc. involve in protein misfolding diseases [17].

2.1.4. *Oxidative stress*

Oxidative stress leads to protein oxidation which is a biomarker for many neurodegenerative diseases. In particular, free radicals and ROS (reactive oxygen species) cause protein oxidation. A variety of oxidants can be occurred in normal aerobic metabolism [20]. Also, lack of antioxidants, excess of oxygen and lipid and metal ions can generate free radicals.

The oxidation of proteins extremely depends on their amino acid compositions. Generally; lysine, histidine, arginine, methionine, cysteine, phenylalanine, tryptophan, threonine, glutamic acid, and proline residues incline oxidation. Some proteins have metal binding regions on its own structure. Metal ions such as copper, zinc, and iron, are capable of redox reactions and electrons are transferred from ions to oxidizing compounds. Therefore, toxic free radicals are formed and proteins can be converted into aggregation forms or proteins can be aggregated by conformational changes [20, 22].

2.1.5. Protein concentration

Protein concentration is an important parameter in protein aggregation. High protein concentration can increase the likelihood of aggregation. Protein-protein interactions and intermolecular interactions (especially interactions among hydrophobic amino acids) may generate abnormal protein structures. Some misfolded protein aggregates can be constituted neurodegenerative diseases above a certain concentration. Moreover, proteins are refolded at low concentrations spontaneously. For example, lysozyme and immunoglobulin G refold itself at low protein concentration however, refolding yield decreases with increasing protein concentration. Therefore, the optimum spontaneous protein concentration range is accepted as 10-50 $\mu\text{g/ml}$. [2, 23].

2.1.6. pH

Environmental pH is to be critical for protein aggregation due to changes in net charge on protein. Protonation state of ionizable sites of protein and positive net charge are increased in acidic conditions. Especially, organization of salt bridges is changed in parallel with composed new secondary structures [2,20]. In prion diseases, acidic pH facilitates generation of PrP^{Sc} . At low pH, PrP^{c} gains β -sheet structures and shows aggregation tendency [24]. According to the Finl (2006), α -Syn incubated at different temperature and pH values, and the best formation conditions were determined as pH 7.4 and 37°C [25]. α -Syn can be lost its native structures and PD is accelerated in these conditions.

3. Neurodegenerative diseases

In the world, millions of elder people suffer from neurodegenerative diseases and diagnosis and treatment of these diseases costs millions of dollars per year. Unfortunately, the mechanisms of these diseases are still unclear and we don't have effective treatment methods. Neurodegenerative diseases are identified as protein misfolding diseases, proteopathies and protein conformational disorders. All diseases (prion, AD, PD, and HD) show typical symptoms: loss and deterioration of neurons and synaptic alterations.

Protein misfolding leads to protein aggregation and accumulation of these aggregates is implicated as the main reason of neurodegenerative diseases. In brain, some native proteins (prion, tau, β -amyloid, α -synuclein, and huntington) undergo conformational changes via genetic and environmental factors. Therefore, secondary structures of protein convert from α -helix/random coil to β -sheet (Table 1.). Consequently, neurotoxic misfolded protein aggregates are deposited in central nervous systems and brain damage and neurodegenerative diseases are formed. In this section, we will analyse the most important four neurodegenerative diseases; prion diseases, AD, PD, and HD, on the basis of protein aggregation and its molecular and cellular mechanisms [6, 8-10].

| Neurodegenerative Diseases | Respective Proteins | Mechanism | Conformation in Aggregates | Inclusion |
|----------------------------|----------------------|---------------------|----------------------------|---|
| Prion Diseases | Prion | Protein aggregation | β -sheet | Spongiosis |
| Alzheimer's Diseases | Tau β -amyloid | Protein aggregation | β -sheet | Neurofibrillary Tangles Senile Plaques |
| Parkinson's Diseases | α -Synuclein | Protein aggregation | β -sheet | Lewy Bodies |
| Huntington's Diseases | Huntington | Protein aggregation | β -sheet | Huntington Inclusion |

Table 1. Properties of neurodegenerative diseases.

3.1. Prion diseases

The group of prion diseases, including Creutzfeldt-Jakob (CJD), fatal familial insomnia (FFI), Kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS) are seen in humans, and in similar fashion scrapie, bovine spongiform encephalopathy (mad cow disease), chronic wasting diseases (CWD), transmissible mink encephalopathy (TME), feline spongiform encephalopathy (FSE) diseases are observed in animals. All of these diseases give similar neurological symptoms such as dysmnnesia, depression, sense disturbances, and psychosis [26].

3.1.1. Structure of PrP^c and PrP^{Sc}

In 1982, prion term coined by Stanley Prusiner and co-workers from “proteinaceous infectious particle”. Prion protein is found in two different forms: a cellular form of prion protein (PrP^c) and scrapie isoform of prion protein (PrP^{Sc}). Properly folded form is denoted as PrP^c while misfolded form is denoted as PrP^{Sc} [27].

The PrP^c is an α -helix-rich glycoprotein that is approximately 250 amino acids in length. It is encoded by the *prion protein gene (Prpn)* which is located on chromosome 20. PrP^c is commonly found on neuronal cell membrane by a glycosyl phosphatidylinositol (GPI), however it is also expressed on other cells such as leukocytes and dendritic cells. PrP^c has been assumed a variety of functions including cell adhesion, intracellular signaling, copper metabolism, and protective antioxidant activity [8, 12, 28].

PrP^c is highly conserved protein among mammals during evolution (Fig.1.). When we examine the primary structure of the protein, PrP^c consist of a signal peptide (1-22), five octapeptide repeats (PHGGGWGQ) (51-91), a highly conserved hydrophobic domain (106-126), and a GPI (glyco-sylphosphatidylinositol) anchor. Furthermore, PrP^c contains two N-linked glycosylation sites (¹⁸¹Asn-Ile-Thr and ¹⁹⁷Asn-Phe-Thr). Thus, they get dynamic and flexible properties and the glycan covers prevent intermolecular and intramolecular interactions. His96 and His111 are found in metal binding domains of PrP^c and they compose coordination sites with metal ions (Cu⁺², Zn⁺², Mn⁺², Ni⁺²). A disulfide bond between Cys179 and Cys214 play a significant role for proper folding of PrP^c [9, 18-20, 24, 27].

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Rabbit  --MAHLGYWMLLLFVATWSDVGLCKKRPKPGGGWNTGGSRYPGQSSPGGN
Bovine  MVKSHIGSWILVLFVAMWSDVGLCKKRPKPGGGWNTGGSRYPGQSSPGGN
Human   --MANLGCWMLVLFVATWSDLGLCKKRPKPGG--WNTGGSRYPGQSSPGGN
Mouse   --MANLGYWLLALFVTMWTDVGLCKKRPKPGG--WNTGGSRYPGQSSPGGN

Rabbit  RYPPQGGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQ-----
Bovine  RYPPQGGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGG
Human   RYPPQGGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQ-----
Mouse   RYPPQGG--TWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQPHGGGWGQ-----

Rabbit  --GGGTHNQWGKPSKPKTSMKHVAGAAAAGAVVGGGLGGYMLGSMSRPLI
Bovine  WGQGGTHGQWNKPSKPKTNMKHVAGAAAAGAVVGGGLGGYMLGSMSRPLI
Human   --GGGTHSQWNKPSKPKTNMKHMAGAAAAGAVVGGGLGGYMLGSMSRPII
Mouse   --GGGTHNQWNKPSKPKTNLKHVAGAAAAGAVVGGGLGGYMLGSMSRPMI

Rabbit  HFGNDYEDRYRENMYRYPNQVYRYPVDQYSNQNSFVHDCVNIITVKQHTV
Bovine  HFGSDYEDRYRENMHRYPNQVYRYPVDQYSNQNNFVHDCVNIITVKEHTV
Human   HFGSDYEDRYRENMHRYPNQVYRPMDEYSNQNNFVHDCVNIITIKQHTV
Mouse   HFGNDWEDRYRENMYRYPNQVYRYPVDQYSNQNNFVHDCVNIITIKQHTV

Rabbit  TTTTKGENFTETDIKIMERVVEQMCITQYQRESQAYYQ--RAAGVLLFSS
Bovine  TTTTKGENFTETDIKMMERVVEQMCITQYQRESQAYYQ--RGASVILFSS
Human   TTTTKGENFTETDVKMMERVVEQMCITQYERESQAYYQ--RGSSMVLFSS
Mouse   TTTTKGENFTETDVKMMERVVEQMCVITQYQRESQAYYDGRSSSTVLFSS

Rabbit  PPVILLISFLIFLIVG
Bovine  PPVILLISFLIFLIVG
Human   PPVILLISFLIFLIVG
Mouse   PPVILLISFLIFLIVG

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Figure 1. Multiple protein sequence alignment of prion proteins. Full length amino acid sequences of rabbit (NP_001075490.1), bovine (GenBank: CAA39368.1), human (UniProtKB/Swiss-Prot: P04156.1), and mouse (NP_035300.1) were aligned using the program Clustal W. PHGGGWGQ repeats are shaded in red. Metal binding sites, His96, and His111 are shaded in blue. Glycosylation sites, ¹⁸¹NIT and ¹⁹⁷NFT, are shaded in pink. Finally, Cys179 and Cys214 (disulfide bond sites) are shaded in black.

PrP^{Sc} can be defined as an infectious isoform of PrP^c and causes fatal prion diseases. PrP^{Sc} is formed by misfolding of PrP^c with a lost in α -helical content. PrP^{Sc} has same amino acid sequence with PrP^c, but their secondary, tertiary, and quaternary structures are different. Approximately, PrP^c includes 3% β -structure and 47% α -helix structure, but nonetheless PrP^{Sc} is composed of 43% β -structure and 30% α -helix structure [24, 29]. It becomes non-soluble and resists to proteolytic degradation with conformational changes, whereas PrP^c is soluble and protease sensitive. This insoluble protein accumulates in brain and causes a variety of prion diseases in human and animals.

3.1.2. Molecular pathology of Prion diseases

Previous studies suggested a variety of mechanisms for explaining prion pathology. Oxidative stress and lipid peroxidation are the major factors in prion diseases [20, 30]. In central nervous systems, a variety of oxidative stresses including high level of oxygen and lipid, metal ions, and inadequate antioxidants produce free radicals. In PrP^{Sc} infected mice, superoxide anion (O₂⁻) is extremely increased in brain. Therefore, high levels of heme oxygenase-1 and malondialdehyde are observed as oxidative stress markers in brain. Cytochrome c oxidase is a large transmembrane protein in mitochondria and it shows antioxidant activity in mitochondria [12, 31]. The level of lipid peroxidation is increased while Cytochrome c oxi-

dase activities are reduced in scrapie infected animal models. Phospholipase D catalyzes the hydrolysis of phosphatidylcholine to generate choline and phosphatidic acid, and its expression level is induced by H_2O_2 [12]. According to the studies, activity of phospholipase D is increased in the brains of scrapie infected animals. As a result, PrP^c transforms into PrP^{Sc} because of the formation of these free radicals.

As we discussed the effect of metal ions on protein misfolding in section 2.1.4, the metal ions also play key roles in prion formation. Cu^{2+} ions play a critical role in prion diseases. PrP^c has five conserved octapeptide repeats (PHGGGWGQ) which have an affinity for Cu^{2+} ions. In contrast, affinity of other metal ions (Mg^{2+} , Mn^{2+} , Ni^{2+} etc.) is weak or nonexistent. The binding of Cu^{2+} provides formation of protease resistant form: PrP^{Sc} . It is also suggested that, PrP^c protects cells from harmful redox activities. Especially, in copper-rich environment, PrP^c acts as a “copper buffer” that means it inhibits toxic effects of Cu^{2+} ions for central nervous system and helps maintaining neurons in high level of copper ions. Thus, redox damage of PrP^c has been involved in prion diseases. In brief, copper can convert the cellular prion protein into a protease-resistant species with conformational changes [31-35].

Glycosylation is a stability-enhancing post translational modification in proteins. PrP^c contains two potential glycosylation sites which are Asn181 and Asn197 in human PrP^c [36]. Generally, binding of carbohydrates can protect protein surface from proteases and undesired protein-protein interactions. Moreover, N-glycosylated prion protein is anchored to the lipid membranes via GPI [18, 19].

Interaction of PrP^c with membrane lipid layers play a significant role in conversion of PrP^c to PrP^{Sc} . PrP^c is localized in cholesterol and sphingomyelin rich area on cell surface (known as lipid raft). PrP^c is bound to lipid membranes through its GPI anchor. While leaving PrP^c from the membranes by catalysis of phosphatidylinositol phospholipase C (PIPLC), PrP^{Sc} show resistance to PIPLC. When binding of PrP^c to the lipid membranes, PrP^c is degraded or converted into PrP^{Sc} form [37-40].

3.2. Alzheimer's diseases

Alzheimer's disease (AD) is the most frequent type of neurodegenerative disorder in the world. AD is composed of accumulation of aberrant folded tau protein and beta-amyloid protein ($A\beta$ protein) in brain. In 1906, AD was first described by psychiatrist and pathologist Dr. Alois Alzheimer and then the disease was named with his surname [8-10].

To date, there are no effective treatment methods for AD, but some nuclear medicine applications (MRI and PET) are applied in diagnosis of AD. Dramatically, symptoms of AD rise with increasing age and the first sign is memory lapse. Cellular and molecular mechanisms of AD are not well understood yet. Researchers have been reported that AD is associated with genetic and environmental factors and life-style.

3.2.1. Structure of Tau gene and proteins

A microtubule associated protein, Tau, is a biggest component of AD. In 1975, tau proteins were first discovered by Marc Kirschner in Princeton University. Tau was derived from

“tubulin associated unit” as a term. It is highly expressed in brain, but other organs such as lung, hearth, and kidney have trace amounts. Many animals (bovine, goat, monkey, goldfish etc.) also have tau proteins [41].

The human *tau* gene is located on chromosome 17q21 and contains 16 exons. Among these exons of the tau gene, exon 2, 3, and 10 are alternatively spliced and these exons allow six combinations (2-3-10-; 2+3-10-; 2+3+10-; 2-3-10+; 2+3-10+; 2+3+10+). Thus, human brain contains six isoforms of tau proteins which range from 352 to 441 amino acids length and approximate molecular weights are between 60 and 70 kDa (Fig. 2.) [16, 17].

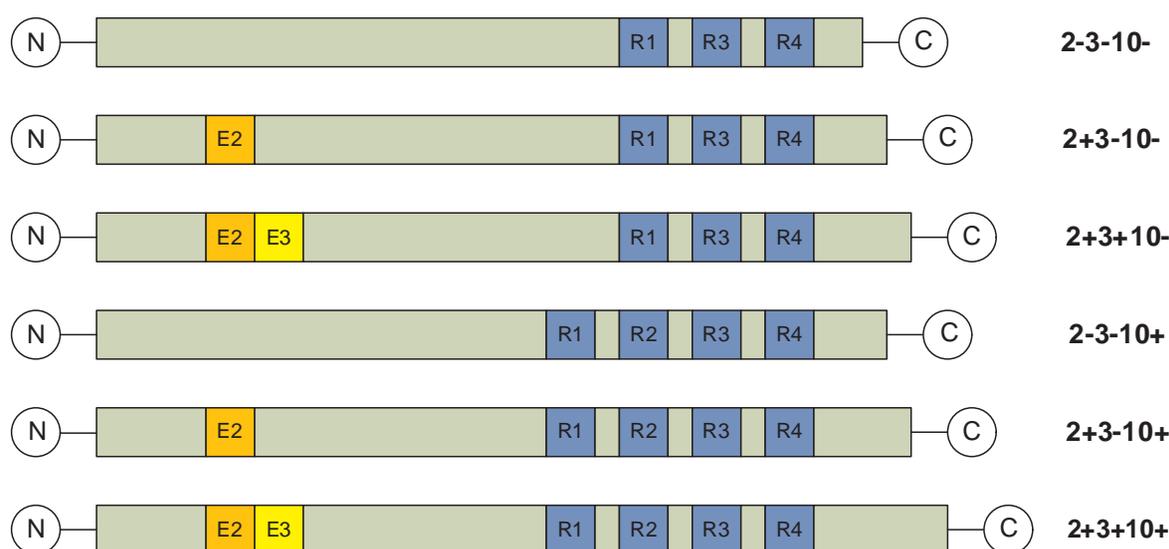


Figure 2. Schematic representation of six human tau isoforms. R1, R2, R3, and R4 (blue boxes) indicate repeat regions. E2 and E3 (orange and yellow box) indicate Exon 2 and Exon 3 respectively (Redrawn from Buee et al., 2000).

Tau protein has four main regions in its primary structures. Acidic region is located in the N-terminal part and it is encoded by exon 2 and exon 3. Prolin-rich region located in the middle of the protein, is encoded by exon 7 and exon 9 and contains several PXXP motifs which can interact with tyrosine kinase. Prolin-rich region works together with acidic region, therefore these two regions are called projection domain which interacts with neural plasma membrane and cytoskeletal elements [16, 17, 41-43].

Tau protein has three to four highly conserved repeats in the C-terminal part for binding to microtubules. Therefore, these repetitive regions are called microtubule binding domains (MBDs) which is encoded by exons 9-12. ²⁷⁵VQIINK²⁸⁰ and ³⁰⁶VQJVK³¹¹ are conserved hexapeptides which are located at the beginning of the second and third MBDs. These peptides involve in the generation of β -sheet structure during tauopathy [44].

3.2.2. Aggregation of Tau protein

Microtubules are major proteins of the cytoskeleton. They have hollow and cylindrical structure and participate in intracellular transport, protection cell structure, and continuity of cell viability. The main function of the tau protein is to stabilize microtubules with binding to microtubules and to other proteins [16, 41]. To perform these functions, tau proteins must be phosphorylated at normal level. However, if tau protein hyperphosphorylate, its biological activity can be lost. Moreover, hyperphosphorylation causes conformational changes and aggregation of tau proteins. Other post-translational modifications such as glycosylation, glycation, polyamination, and nitration may play essential roles in AD [17].

The longest isoform of tau protein (441 amino acids) has seventy nine Ser or Thr phosphorylation sites which are mainly found on prolin-rich regions. Also, Ser²⁶², Ser²⁹³, Ser³²⁴, and Ser³⁵⁶ are located in KXGS motif of R1, R2, R3, and R4 domains. Many of kinases and phosphatases (glycogen synthase kinase-3 β (GSK3 β), mitogen activated protein kinase (MAPK), tau tubulin kinase 1-2 (TTBK1/2), cyclin dependent kinase 5 (CDK5), microtubule affinity regulating kinase (MARK), and stress activated protein kinase (SAP) are affected in tau phosphorylation [17, 45, 46].

Frontotemporal dementia with parkinsonism-17 (FTDP-17) is a progressive neurodegenerative disease which is caused by mutations in the tau gene. The tau gene is mutated in familial FTDP-17 and this mutation accelerates formation of neurofibrillary tangles (NFTs) in the brain. Furthermore, hyperphosphorylation is promoted by this mutation [47,49].

Excess of NFTs and senile plaques (SPs) are important markers in AD. NFTs are aggregates of hyperphosphorylated tau protein that are most commonly known as a primary marker of AD [50]. NFTs are originated from abnormally hyperphosphorylated tau protein. Normally, tau is a microtubule binding protein that stabilizes and assembles microtubules. However, in AD, tau protein undergoes biochemical changes because it twists into pairs of helical filaments and they twist into tangles. Also, tau is generally located in axons, but in tauopathy, it is located in dendrites. Thus, neuron's transport system may be disintegrated and microtubule cannot function correctly [16, 50].

3.2.3. Structure of A β protein and gene

A β is a relatively small peptide of 4 to 4.4 kDa that is the major component of amyloid deposits. Intracellular A β protein is widely found in neurons and it is associated with inflammatory and antioxidant activity, regulation of cholesterol transport, and activation of kinase enzyme. However, A β is one of the best known components in formation of neurodegenerative diseases including AD.

A β is approximately composed of 36-43 amino acids and it originates from amyloid precursor protein (APP). In human, *APP gene* is encoded on chromosome 21 and contains at least 18 exons. APP is a glycoprotein of 695-770 amino acids which has three main regions: an extracellular N-terminal region, a hydrophobic transmembrane region, and cytoplasmic C-terminal region. Mutations in APP gene cause familial susceptibility to AD. Furthermore, mutations in other three genes, including apoE, PS1, and PS2 are associated with AD and

increased production of A β protein and amyloidogenicity. In contrast, a coding mutation (A673T) in APP gene shows protective effects for AD [51-53].

APP can be cleaved into fragments by α , β , and γ secretases and A β protein is formed by the action of the β and γ secretases. A β protein contains two important regions which play a major role in the formation insoluble amyloid fibrils. C-terminal regions (residues 32 to 42) and internal hydrophobic regions (residues 16 to 23) may enhance increasing β -sheet conformation and A β protein misfolding [53].

3.2.4. Aggregation mechanisms of A β protein

In normal brain, A β proteins contain mixture of β -sheet and random coil structures. However, a number of β -sheet structures are increased at high protein concentration. A β protein constitutes SPs which are important markers in AD. The formation of SPs is a problem of protein folding because of misfolded and aggregated form of A β accumulates and shows toxicity in brain [54].

Genetically, three genes: *APP*, *PS1*, and *PS2* are associated with AD. More than 50 different mutations in the APP gene can cause AD. The most frequent APP mutation is a single mutation in the APP at position 717. As a result of this single mutation, a valine residue is replaced by an isoleucine, or phenylalanine, or glycine. *APP* mutations lead to an increased amount of the A β proteins which are deposited in neuritic plaques [50, 54].

3.3. Parkinson's diseases

Parkinson's disease (PD) is neurodegenerative movement disorder of the central nervous systems. In 1817, Dr. James Parkinson published "*An Essay on the Shaking Palsy*" in which he first described paralysis agitans and then this disorder was entitled as a Parkinson's disease by Dr. Jean Martin Charcot. The occurrence of an illness is characterized by accumulation of misfolded α -synuclein protein in brain. Generally; anxiety, tremor, rigidity, depression, bradykinesia, and postural abnormalities are the most common symptoms in Parkinson's disease. Also, α -Syn related neurodegenerative diseases are known as "Synucleinopathies" [55].

3.3.1. Structure of α -synuclein

Natively unfolded α -synuclein (α -Syn) is a 14 kDa and highly conserved protein that localize different regions of the brain. The name of protein was preferred as " α -synuclein" because of it shows **syn**aptic and **nuc**lear localization. α -Syn regulates dopamine neurotransmission by modulation of vesicular dopamine storage. It interacts with tubulin and can function like tau protein. Also, α -Syn shows a molecular chaperon activity in folding of SNARE (soluble N-ethylmaleimide-sensitive-factor attachment protein receptor) proteins [56].

Natively, α -Syn is an unfolded protein, but obtains its conformation with biological interactions. In cytoplasm, α -Syn is a soluble and in an unfolded state, but it can be found in α -helical conformation for binding to lipid membranes. Also, α -Syn can be in the form of β -sheet for composing Lewy bodies as explained below [56-58].

α -Syn is encoded with *SNCA gene* which is located on chromosome 4q21. Human α -Syn has 140 amino acids and three main domains: (i) an amphipathic N-terminal region (residues 1-60), (ii) a central hydrophobic region (residues 61-95) and (iii) a highly acidic C-terminal region (residues 96-140) (Fig. 3.). Amphipathic N-terminal region contains imperfect six hexamer motif repeats (KTKEGV) which involve in binding of micelles and liposomes.



Figure 3. Primary structure of human α -Syn (Gen Bank: AAL15443.1). Imperfect KTKEGV repeats are colored in blue. Acidic residues are colored in red. Phosphorylation sites (Ser87 and Ser129) are colored in yellow.

Central hydrophobic region contains non-amyloid beta component (NAC) sequences from residue 61 to 95. This region is highly hydrophobic, and it can promote formation of β -sheet structure. The less conserved C-terminal region consists of a large number of acidic amino acids and several prolines [56-60].

3.3.2. Structures of Lewy bodies

At present, biological role and pathogenic processes of Lewy bodies are still unclear. As far as we know, Lewy bodies are aberrant protein aggregates and their deposits cause PD. Lewy bodies are localized not only in PD brains, but also in other neurodegenerative disorders such as AD brains. According to the electron microscopy images, Lewy bodies are 8-30 μ m which are consisted of approximately 10 nm amyloidogenic fibrils such as fibrillary α -Syn and neurofilaments. Lewy bodies contain a variety of proteins including α -Syn, neurofilaments, ubiquitinated proteins, and heat shock proteins (Hsp70 and Hsp90). Oxidative stress, mitochondrial dysfunction, inflammation, ubiquitin proteasome system, pH, protein concentration, and high temperature may be affected negatively by Lewy bodies. Therefore, these factors induce misfolding and aggregation of proteins in the Lewy bodies [57, 61].

3.3.3. Mechanisms of α -Syn misfolding and aggregation

α -Syn plays crucial role in PD because α -Syn is a major fibrillary component for Lewy bodies. There are many adjuvant and disincentive factors available in α -Synfibrillogenesis. Two mutations, A53T and A30P, in the α -Syn gene and overexpression of wild type α -Syn are increased misfolding processes and aggregation. Also, accumulation of abnormal form of α -Syn can inhibit proteasomal functions [9, 61, 62].

It is known that, α -Syn is natively unfolded as well as predominantly non-phosphorylated *in vivo*. In PD brains, α -Syn is found to be phosphorylated at Ser87 and Ser129 in aggregates. These serine residues are phosphorylated with casein kinase 1 (CK1) and casein kinase 2 (CK2). Several studies reported that accumulation of phosphorylated α -Syn was observed in animal models of synucleinopathies. Therefore, this post translational modification has a pathological role in fibrillation of α -Syn [63, 64].

As known, oxidative stress is one of the major factors in many diseases as well as the formation of PD [9, 20]. As a result of oxidation, formed free radicals react rapidly with proteins thus, misfolding and aggregation are generated inside the cells. Among twenty amino acids, methionine and cysteine are capable of being easily oxidized. α -Syn doesn't have cysteine residues, but high content of methionine residues oxidize to methionine sulfoxide. Thus, due to methionine content of α -Syn, the protein is readily aggregates at oxidation conditions. On the other hand, α -Syn phosphorylation can be increased with oxidative stresses as well [65].

3.4. Huntington's diseases

Huntington's disease (HD) is a genetic neurodegenerative disorder and the disease is caused by autosomal dominant inheritance. In 1872, HD was first described as a genetic disease by Dr. George Huntington. Involuntary muscle contractions, movement, and mental disorders are progressed in HD. The disease is inherited as an autosomal dominant and effects brain and nervous systems. Huntington protein undergoes conformational changes with mutation and it shows aggregation tendency [66].

3.4.1. Structure of Huntington protein and genes

Huntington (Htt) is a large size protein of 350 kDa that is generally composed of 3144 amino acids. Normal protein is highly expressed in peripheral tissues and brain, and it is involved in endocytosis, cytoskeletal functions, vesicle trafficking, cellular signal transduction, and membrane recycling. In brains, Htt protein leads to cell damage and toxicity through deposition of misfolded aggregate form of Htt protein [8, 9].

The gene for HD is located on the tip of chromosome 4, and is called the *IT-15 gene*. This part of DNA contains cytosine-adenine-guanine (CAG) repeats which are called trinucleotide repeats. Number of trinucleotide repeats is determined as risk of HD development. The CAG repeats are translated into polyglutamine (polyQ) residues which are located in the N-terminal region [66-68].

Htt proteins interact with a variety of peptides including huntington associated protein 1 (HAP1), huntington interacting protein 1 and 2 (HIP1 and HIP2) and huntington yeast partners A, B, and C (HYPA, HYPB, and HYPC). These peptides are functioned in cell signaling, transport, and transcription processes [67, 69].

3.4.2. Mechanisms of Huntington misfolding and aggregation

In HD, the neuropathology is characterized with accumulation of Htt protein aggregates. HD is caused by a number of CAG repeats in the gene. To date, many theories have been suggested in HD, but functions of CAG repeats and mechanisms of HD cannot be understood yet. However, common opinion is long CAG repeats (polyQ) are the most important promoter for toxicity of Htt protein aggregates. The polyQ region starts at residue 18 and the number of glutamine residues are the most important marker in HD. Surprisingly, 40 or more CAG repeats are always generated neuropathy, while 35 or few-

er CAG repeats are never generated neuropathy. However, in childhood, CAG repeats from 27 to 35 can develop neuropathy [66, 70-72].

In 1994, Max Perutz put forward a “**polar zipper**” hypothesis about HD pathology. In this model, many polar glutamine residues can generate anti parallel β -sheet structures with hydrogen bonds. Therefore, aggregation tendency of Htt protein is increased and this state lead to cell death [73-75]. Furthermore, aggregation of Htt protein induces oxidative stress, mitochondria dysfunction, lipid peroxidation etc.

4. Prevention of neurodegenerative diseases and molecular chaperones

Until this section, neurodegenerative diseases have been discussed on the basis of protein aggregation and misfolding. In healthy organisms, a variety of mechanisms work efficiently for prevention of preteopathies. Molecular chaperones are known to be critical for protein folding processes and neurodegenerative diseases. Heat shock proteins (Hsps) are well-known molecular chaperons in living organisms [1, 76-78].

4.1. The Hsp chaperons

Hsps are highly conserved proteins among living organisms. Hsps are an important class of molecular chaperons and they are located in different parts of the cells such as endoplasmic reticulum, cytosol, and mitochondria. Mainly, Hsps are related with formation of proper protein conformation, and also prevention protein aggregation, misfolding, and oligomerization. Proteins can be exposed a number of cellular and environmental factors including high temperature, inflammation, growth factors, oxidative stress etc. which can cause misfolding and protein aggregation. Overexpression of Hsps has been observed under these stress conditions. Several studies have focused on the neuroprotective role of Hsps. Therefore, the expression levels of Hsps are decreased and misfolded protein accumulation can be occurred in brain [1, 76-78].

Generally, Hsps are divided into six groups on the basis of molecular mass. In this section; Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, and small Hsp (sHsp) have been examined and characterized for association with neurodegenerative diseases and protein folding processes [1].

Hsp70 is a highly conserved protein in all living organisms. It makes complex with unfolded or partially denatured proteins. Hsp70 has two functional domains: ATPase domain and substrate binding domain (SBD). The operation of these domains is controlled with hydrolysis of ATP. ATPase domain binds to ATP and hydrolyzes it to ADP. This energy drives the protein folding function of the Hsp70. Similarly, Hsp70 binding to misfolded peptides, increases the ATP hydrolysis. Also, Hsp70 interacts with Hsp40 and Hsp90 to perform protein folding process. Hsp70 serves a neuroprotective role in all of neurodegenerative diseases [79-81]. Auluck and co-workers indicated that, expression of Hsp70 reduced α -Syn aggregation, accumulation, and toxicity in PD animal models [82]. In HD models, Hsp70 shows protective assignment in polyglutamine-induced toxicity [83]. Also, Hsp70 is involved in the

folding and functional maintenance of tau protein. In prion diseases, Hsp70 binds aggregate form of prion proteins and it mediates their degradation by the proteasome [81].

Hsp40 is expressed in variety of organisms in different isoforms. It associates with unfolded polypeptides and prevents protein aggregation. Hsp40 can be found in a cell in three different types. All types of Hsp40 contain highly conserved J domain which interacts with Hsp70 ATPase domain. Thus, ATPase activity of Hsp70 is regulated by this interaction. Hsp40 transmits substrate towards Hsp70 SBD domain with an appropriate conformation. Thus, Hsp70 help substrate peptide in its hydrophobic SBD region and assists the peptide to come to a state of proper three-dimensional structure [1, 84]. Hsp40 is extensively found in neurodegenerated brains due to its association with Hsp70 as a co-chaperon [83].

Hsp100 participates in counteraction of protein aggregation with Hsp70 and Hsp40. This hexameric 100 kDa protein has substrate and ATP binding regions. Large protein aggregates are broken by Hsp100 and formed small aggregates are carried forward by Hsp70-Hsp40 complex. In yeast, overexpression of Hsp100 leads to disassemble of large prion aggregates and generate the small prion seeds for new rounds of prion propagation [1, 83].

Hsp90 is a highly expressed cellular molecular chaperon and also stabilizes certain proteins and aids protein degradation. Hsp90 is a dimeric protein which has a highly conserved N-terminal domain and a C-terminal domain. Hsp90 is one of the main cytosolic molecular chaperons which is activated with Hsp40 and Hsp70 [1, 85]. Uryu and co-workers demonstrated that expression of Hsp90 is increased in transgenic mouse model of PD. Inhibition of Hsp90 lead to generation of tauopathies because of protein hyperphosphorylation and abnormal neuronal activity can be increased in AD [86].

Hsp60 is a heptameric 60 kDa protein which is located particularly in mitochondria. Hsp60 works with Hsp70 coordinately for protein folding. Furthermore, it plays key roles in mitochondrial protein transport, replication and transmission of mitochondrial DNA, and apoptosis. For actin and tubulin, Hsp60 is a specific chaperon which is decreased in AD. In AD effected neurons, aggregated and misfolded tau protein is increased in contrast with expression of Hsp60 is decreased [1, 83].

sHsp has a molecular mass between 12 and 30 kDa [87]. As a molecular chaperone, sHsp are located at different compartments in the cell and they can protect protein structures and activities. Also, overexpression of sHsp have reported in many studies [87-90]. In HD, the expression level of Hsp27 is increased and it prevents polyglutamine induced toxicity in neurons. Furthermore, Hsp27 reduces α -syn-induced toxicity in PD patient brain [82, 88]. The other sHsps including Hsp10, Hsp12, Hsp20, Hsp26 are associated with protein folding diseases [89].

5. Conclusion

More than 600 diseases such as Alzheimer's disease, Huntington's disease, prion diseases, Parkinson's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and others

are characterized by progressive nervous system dysfunction. In the world, millions of people are affected from these diseases. For example, five million people suffer from Alzheimer's disease, one million people from Parkinson's disease and 30.000 people from Huntington's diseases in USA. US government spends approximately 50-100 billions of dollars for diagnosis and therapies [91]. Today, we are using effective methods (PET, MRI, SPECT etc.) for diagnosis of neurodegenerative diseases, but we cannot treat the diseases easily as we diagnose them.

All of neurodegenerative diseases are related with protein misfolding and aggregation. Different native proteins lead to formation of diseases, but practically same factors involve in these diseases. Structurally, β -sheet conformation plays a key role in neuropathies. Furthermore, oxidative stress, pH, mutations, post translational modifications etc. lead to protein folding diseases.

New innovations in biochemical and medicinal fields lead to development of a number of mechanisms for protein aggregation and neurodegenerative diseases. Moreover, a variety of analytical techniques such as IR (infrared spectroscopy), NMR (nuclear magnetic resonance), CD (circular dichroism), calorimeters, and electron microscopy have been used for detection of aggregation process. Nevertheless, we cannot identified cellular mechanisms of protein misfolding and related diseases clearly yet. In the future, scientists will concentrate on design of practical and fast methods for detection of protein aggregation in cells.

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