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Molecular and Cellular Basis of Misfolded Proteins in Neurodegenerative Diseases

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Abstract

Background: Neurodegeneration is characterized by a progressive loss of nerve structure and function which lead to cognitive impairment such as dementia. Neurodegenerative diseases (NDs) are partially caused by neuronal cell death and glial homeostasis. NDs such as Alzheimer's disease (AD) and Parkinson's disease (PD) can develop with aging. As well, in Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), genetic mutations can affect CNS cell function. NDs occur through important processes including, protein misfolding and aggregation of misfolded proteins. These processes cause neurofibrillary tangles and plaques that result in neuronal cytotoxicity. Here, our intention is to shed light on some of the key roles of protein misfolding and aggregation in NDs. This review focuses specifically on understanding the molecular and cell-based mechanisms of protein misfolding and aggregation involved in the development of NDs.

Keywords: Neurodegenerative diseases; Protein aggregation; Mutation; Posttranslational modifications

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Introduction

Neurodegenerative diseases (NDs) including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are involved with progressive decrease in motor and/or cognitive function. These diseases are associated with selective neuronal susceptibility with degeneration in specific brain regions and abnormal protein deposition in neurons. Convincing evidence from genetic, neuropathological, cellular and biochemical studies and experiments with animal models shows that misfolding, oligomerization and accumulation of proteins in the brain is the cause of the disease. It is the main event that causes the pathological abnormality.[1-3] Many proteins fold back into their original and biologically functional structure immediately after being produced. Intrinsically disordered proteins (IDPs), also referred to as natively unfolded proteins, lack inherently stable tertiary conformation.[4] The ability of misfolded proteins to replicate and proliferate in large numbers plays an important role in the progression of brain disease. Although protein aggregation is distinct in different NDs, the process of misfolding proteins and their functions are remarkably similar.[5] In general, protein aggregation forms a special structure called amyloid. It is characterized by a β-sheet structure that can aggregate into long fibrils, as well as convert proteins that have not yet been misfolded.[6] Most proteins form amyloid fibrils under unfavorable biochemical conditions.[7] Following formation, higher amyloid aggregates assembly are very resistant to degradation. The thermodynamics stability of amyloid formation also involves their ability to convert intrinsic proteins to amyloid morphology.[8] In AD, misfolded proteins cause plaques and tangles. In PD and Lewy body dementia, they form Lewy bodies (LBs). Misfolded proteins are soluble nanoparticles that have the ability to spread to unaffected cells.[9] They interfere with normal protein synthesis and degradation of nerve cells and appear to lead to cell death. At high concentrations, misfolded proteins tend to form large insoluble proteins. Protein aggregates have a toxic effect when they accumulate in cells above a certain level. Abnormal protein accumulation leads to progressive loss of neuronal structure and/or function, including neuronal cell death.[10]

Common molecular and cellular processes that lead to NDs include protein misfolding and aggregation, mitochondrial dysfunction and oxidative stress, inadequate protein clearance, axonal transport disturbance, neuroinflammation, and RNA-mediated toxicity.[11,12] Today, mechanisms involved in protein aggregation and the development of NDs are not clear at the molecular level. The purpose of this review is to evaluate the role of the misfolded proteins in NDs from a

molecular and cell-based perspective.

Some Factors Involved in Aggregation Behavior of Proteins in ND

Mutations

Several genetic and environmental factors could promote proteins misfolding and aggregation in various ND.[13] These include gene mutations and promoter polymorphisms that can affect levels and conformation of protein. In fact, the inheritance of pathological genetic mutations is involved in onset and development of ND. For example, mutation in the MAPT gene encoding tau protein or other genes, such as C9ORF72 or GRN cause FTD.[14] Mutations in genes encoding APP or presenilin (PSEN) resulting in early-onset familial forms of AD.[15]

Patients with early-onset PD have mutations in the gene encoding Parkin, DJ-1, or PINK1.[16] Mutations in the SOD1, FUS or TARDBP (encoding TDP-43) genes are known to cause rare early-onset familial forms of ALS (fALS).[17] Moreover, polymorphisms in the promoter region of disease-related genes may result in enhanced gene transcription or alternative splicing, protein levels and aggregation-prone transcript variant.[18]

The proposed molecular mechanism for NDs should always strive to explain how cumulative damage from hereditary/germline mutations manifests itself in highly specific neuronal loss after decades.[19] The brain has been shown to undergo particularly high alternative splicing compared to other human tissues and also tends to follow clearer patterns.[20] The results of alternative splicing may have important biological relevance in the brain. For example, pattern detection of receptor and channel isoform expression that is important for neurotransmission.[21] Mutations play an important role in protein aggregation and can markedly alter protein stability, solubility, and aggregation tendencies.[22] Further aggregation lead to amyloid fibrils, which deposit in tissues and are related with NDs.[23] Alpha-synuclein (140 amino acid) encoded by the SNCA gene on chromosome 4q21. Although widely expressed within neurons, it is abundant at presynaptic terminals, indicative of a role in synaptic signaling. Rare point mutations of SNCA trigger dominant familial forms (early-onset) of PD. Fibrillar forms of α-synuclein have been identified within LBs that accumulate in hereditary and sporadic forms of PD.[24]

Tauopathy is a neurodegenerative disease in which the microtubule-associated protein tau is associated with numerous filamentous inclusion bodies in some neurons or both neurons and glial cells. MAPT (tau gene) mutations lead to hereditary cases of FTD characterized by abundant filamentous tau inclusion bodies. This evidence suggest that tau dysfunction is sufficient to trigger neurodegeneration and dementia. Orderly placement of tau on filaments may indicate disease-causing toxic functions.[25]

In summary, genetic and molecular alteration occur at the subcellular level in most ND, as follows: mutations in DNA lead to various changes at the level of RNA processing and cryptic splicing suppression, formation of hairpin structures that trigger RNA silencing pathways and sequester proteins, formation of stable G-quadruplex (G-Q) structures that can form aggregates with RNA-binding protein (RBPs), mutations in RBPs that affect their RNA processing functions, and formation of aggregation-prone polyglutamine (polyQ) and dipeptide repeat (DPR) proteins.[19]

Posttranslational Modifications

After protein synthesis, post-translational modifications (PTMs) of amino acids can increase protein diversity through additional functional groups (acetates, phosphates, various proteins, etc) and structural changes.[26] Especially, phosphorylation has an important role in ND and seems necessary for protein aggregation and misfolding in ND.

Development of AD is associated with extracellular plaque deposition of aggregated amyloid beta peptide (Aβ) and tauopathy due to intracellular neurofibrillary tangles composed mainly of hyperphosphorylated fibrils of the microtubule-associated protein tau.[27] Tau protein in brain neurons contains rich phosphorylation sites that are targeted by various kinases. When tau is highly phosphorylated, its binding to microtubules is broken and the release of tau from microtubules promotes self-association and aggregate formation.[28] Aβ is thought to play many physiological roles, including synaptic activity regulation,[29,30] but in AD it acquires toxic function, causes oligomerization and aggregation, and ultimately leads to formation of insoluble plaques.[31,32] Furthermore, other PTMs including polyamination, glycation, truncation, and nitration are associated with the disease of protein misfolding.[33] Cohen and colleagues have confirmed that tau acetylation as a PTM may regulate normal tau function suggesting the pathological role for tau aggregation in AD. They showed that tau acetylation at K280 could impair tau- interactions with micro-tubule and increase cytosolic tau pool availability for pathological paired helical filaments aggregation.[34]

A pathological feature of PD is the progressive loss of dopaminergic neurons in the basal ganglia, especially in the substantia nigra pars compacta.[35,36] In addition, the main pathological features of PD are presence of intraneuronal proteinaceous inclusions called LBs, which are composed primarily of α-synuclein.[37] α-Syn influence by PTMs, including phosphorylation, nitration, ubiquitination, acetylation, truncation, SUMOylation, and O-GlcNAcylation, which can lead to changes in protein structure, size or charge.[38]

Among the α-syn PTM, phosphorylation is the most studied subtype.[39] Anderson et la showed that less than 4%

of α-syn was phosphorylated in the normal brain, while about 90% of α-syn is found to be phosphorylated at serine 129 and 87 (S129 and S187) in LBs.[40] Additionally, it has been also confirmed that α-syn could be phosphorylated at tyrosine 39, 125, 133, and 136 (Y39, Y125, Y133, and Y136).[41]

Several studies have demonstrated a potential role for ubiquitinated α-syn in the LB-like ubiquitin-positive formation in PD.[42,43] Both in vivo and in vitro experiments revealed that α-syn ubiquitination with the E3 ubiquitin ligase SIAH (seven in absentia homologue) may enhance α-syn aggregation.[44,45] Moreover, mass spectrometry analysis showed SIAH monoubiquitinates α-syn at different lysine residues (K12, 21, and 23) which were previously found to be ubiquitinated in LBs.[46]

Acetylation is another PTM that regulates gene expression, where acetyl groups co-bind to N-terminal amino or lysine residues, generally resulting in changes in protein stability. The level of acetylation is the result of a balance of activity between histone acetyltransferase (HAT) and histone deacetylase (HDAC). Maintaining optimal HAT/HDAC balance is critical for neuronal survival. The alteration of neuron protein acetylation and deacetylation homeostasis cause several pathological cellular processes which lead to NDs.[47,48]

For example, the α-syn amino acid sequence contains a significant amount of lysine in patients with PD, which can be a target for N-terminal acetylation. A previous study has shown α-syn with acetylated N-terminus in the temporal and prefrontal cortex of patients with PD.[49] Although, other studies have also suggested the protective effect of acetylation on the α-syn pathogenesis.[50]

Other Factors

In addition to the critical role of PTMs in proper folding and function of proteins, molecular chaperones also support conformal folding or unfolding of large or macromolecular proteins.[51] Although molecular chaperones are essential for the cellular homeostasis and survival maintenance under stress and optimal conditions, most are activated by several stressors such as high temperature or changes in pH value or salt concentration.[52] In response to cellular stress such as heat, higher level of protein misfolding may result in to protein aggregation. For instance, heat shock protein 70 (Hsp70) contains a large ubiquitous family of ATP-dependent molecular chaperones known to suppress the aggregation of several neuropathic proteins and their consequent toxicity in response to neuronal stressors such as NDs and stroke.[53,54]

Concentration is another important parameter for protein aggregation. At higher the protein concentration, the possibility of aggregation increase. Protein-protein and intramolecular interactions, particularly hydrophobic interaction, can produce aberrant protein structure. Above certain concentrations, some misfolded protein aggregates can represent ND.[33,55]

Conclusion

In this article, we collectively reviewed the important role of protein misfolding and aggregation in NDs. Here, we focused specifically for understanding the molecular and cellular mechanisms of protein misfolding and aggregation involved in NDs. Enhancing understanding of these underlying mechanisms can lead to the development of effective therapeutic strategy.

Author Contributions

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Conflict of Interest Disclosures

There are no conflicts of interest to declare.

Ethical Statement

Not applicable.

References

1. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004;10 Suppl:S10-7. doi: 10.1038/nm1066.
2. Soto C. Unfolding the role of protein misfolding in neurodegenerative diseases. Nat Rev Neurosci. 2003;4(1):49-60. doi: 10.1038/nrn1007.
3. Zare Mehrjerdi F, Niknazar S, Yadegari M, Akbari FA, Pirmoradi Z, Khaksari M. Carvacrol reduces hippocampal cell death and improves learning and memory deficits following lead-induced neurotoxicity via antioxidant activity. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(7):1229-37. doi: 10.1007/s00210-020-01866-6.
4. Dunker AK, Silman I, Uversky VN, Sussman JL. Function and structure of inherently disordered proteins. Curr Opin Struct Biol. 2008;18(6):756-64. doi: 10.1016/j.sbi.2008.10.002.
5. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat Neurosci. 2018;21(10):1332-40. doi: 10.1038/s41593-018-0235-9.
6. Sorg C, Grothe MJ. The complex link between amyloid and neuronal dysfunction in Alzheimer's disease. Brain. 2015;138(Pt 12):3472-5. doi: 10.1093/brain/awv302.
7. Guijarro JI, Sunde M, Jones JA, Campbell ID, Dobson CM. Amyloid fibril formation by an SH3 domain. Proc Natl Acad Sci U S A. 1998;95(8):4224-8. doi: 10.1073/pnas.95.8.4224.
8. Finley D. Recognition and processing of ubiquitin-protein conjugates by the proteasome. Annu Rev Biochem. 2009;78:477-513. doi: 10.1146/annurev.biochem.78.081507.101607.
9. Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004;55(2):164-73. doi: 10.1002/ana.10795.

10. Gorman AM. Neuronal cell death in neurodegenerative diseases: recurring themes around protein handling. J Cell Mol Med. 2008;12(6a):2263-80. doi: 10.1111/j.1582-4934.2008.00402.x.
11. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015;16(6):358-72. doi: 10.1038/nrn3880.
12. Decker H, Lo KY, Unger SM, Ferreira ST, Silverman MA. Amyloid-beta peptide oligomers disrupt axonal transport through an NMDA receptor-dependent mechanism that is mediated by glycogen synthase kinase 3beta in primary cultured hippocampal neurons. J Neurosci. 2010;30(27):9166-71. doi: 10.1523/jneurosci.1074-10.2010.
13. Takalo M, Salminen A, Soininen H, Hiltunen M, Haapasalo A. Protein aggregation and degradation mechanisms in neurodegenerative diseases. Am J Neurodegener Dis. 2013;2(1):1-14.
14. Goedert M, Ghetti B, Spillantini MG. Frontotemporal dementia: implications for understanding Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(2):a006254. doi: 10.1101/cshperspect.a006254.
15. Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(10):a006296. doi: 10.1101/cshperspect.a006296.
16. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998;392(6676):605-8. doi: 10.1038/33416.
17. Liscic RM, Breljak D. Molecular basis of amyotrophic lateral sclerosis. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(2):370-2. doi: 10.1016/j.pnpbp.2010.07.017.
18. Singleton A, Myers A, Hardy J. The law of mass action applied to neurodegenerative disease: a hypothesis concerning the etiology and pathogenesis of complex diseases. Hum Mol Genet. 2004;13 Spec No 1:R123-6. doi: 10.1093/hmg/ddh093.
19. Conlon EG, Manley JL. RNA-binding proteins in neurodegeneration: mechanisms in aggregate. Genes Dev. 2017;31(15):1509-28. doi: 10.1101/gad.304055.117.
20. Yeo G, Holste D, Kreiman G, Burge CB. Variation in alternative splicing across human tissues. Genome Biol. 2004;5(10):R74. doi: 10.1186/gb-2004-5-10-r74.
21. Grabowski PJ, Black DL. Alternative RNA splicing in the nervous system. Prog Neurobiol. 2001;65(3):289-308. doi: 10.1016/s0301-0082(01)00007-7.
22. Guthertz N, van der Kant R, Martinez RM, Xu Y, Trinh C, Iorga BI, et al. The effect of mutation on an aggregation-prone protein: an in vivo, in vitro, and in silico analysis. Proc Natl Acad Sci U S A. 2022;119(22):e2200468119. doi: 10.1073/pnas.2200468119.
23. Stroo E, Koopman M, Nollen EA, Mata-Cabana A. Cellular regulation of amyloid formation in aging and disease. Front Neurosci. 2017;11:64. doi: 10.3389/fnins.2017.00064.
24. Venda LL, Cragg SJ, Buchman VL, Wade-Martins R. α-Synuclein and dopamine at the crossroads of Parkinson's disease. Trends Neurosci. 2010;33(12):559-68. doi: 10.1016/j.tins.2010.09.004.
25. Chang E, Kim S, Yin H, Nagaraja HN, Kuret J. Pathogenic missense MAPT mutations differentially modulate tau aggregation propensity at nucleation and extension steps. J Neurochem. 2008;107(4):1113-23. doi: 10.1111/j.1471-4159.2008.05692.x.
26. Schaffert LN, Carter WG. Do post-translational modifications influence protein aggregation in neurodegenerative diseases: a systematic review. Brain Sci. 2020;10(4):232. doi: 10.3390/brainsci10040232.
27. Gouras GK, Olsson TT, Hansson O. β-Amyloid peptides and amyloid plaques in Alzheimer's disease. Neurotherapeutics. 2015;12(1):3-11. doi: 10.1007/s13311-014-0313-y.
28. Alonso AD, Cohen LS, Corbo C, Morozova V, Elldrissi A, Phillips G, et al. Hyperphosphorylation of tau associates with changes in its function beyond microtubule stability. Front Cell Neurosci. 2018;12:338. doi: 10.3389/fncel.2018.00338.
29. Brothers HM, Gosztyla ML, Robinson SR. The physiological roles of amyloid-β peptide hint at new ways to treat Alzheimer's disease. Front Aging Neurosci. 2018;10:118. doi: 10.3389/fnagi.2018.00118.
30. Morley JE, Farr SA, Nguyen AD, Xu F. What is the physiological function of amyloid-beta protein? J Nutr Health Aging. 2019;23(3):225-6. doi: 10.1007/s12603-019-1162-5.
31. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239-59. doi: 10.1007/bf00308809.
32. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. Cold Spring Harb Perspect Biol. 2017;9(7):a028035. doi: 10.1101/cshperspect.a028035.
33. Tutar Y, Özgür A, Tutar L. Role of protein aggregation in neurodegenerative diseases. In: Kishore U, ed. Neurodegenerative Diseases. Rijeka, Croatia: IntechOpen; 2013. p. 55-76.
34. Cohen TJ, Guo JL, Hurtado DE, Kwong LK, Mills IP, Trojanowski JQ, et al. The acetylation of tau inhibits its function and promotes pathological tau aggregation. Nat Commun. 2011;2:252. doi: 10.1038/ncomms1255.
35. Singh A. Oscillatory activity in the cortico-basal ganglia-thalamic neural circuits in Parkinson's disease. Eur J Neurosci. 2018;48(8):2869-78. doi: 10.1111/ejn.13853.
36. Asaadi S, Hojjati M, Zali A, Ashrafi F. Effect of HU-308 in mice models of Parkinson's disease. J Neurol Sci. 2013;333(Suppl 1):e65. doi: 10.1016/j.jns.2013.07.505.
37. Choong CJ, Mochizuki H. Neuropathology of α-synuclein in Parkinson's disease. Neuropathology. 2022;42(2):93-103. doi: 10.1111/neup.12812.
38. Beyer K. Alpha-synuclein structure, posttranslational modification and alternative splicing as aggregation enhancers. Acta Neuropathol. 2006;112(3):237-51. doi: 10.1007/s00401-006-0104-6.
39. Erskine D, Patterson L, Alexandris A, Hanson PS, McKeith IG, Attems J, et al. Regional levels of physiological α-synuclein are directly associated with Lewy body pathology. Acta Neuropathol. 2018;135(1):153-4. doi: 10.1007/s00401-017-1787-6.
40. Anderson JP, Walker DE, Goldstein JM, de Laat R, Banducci K, Caccavello RJ, et al. Phosphorylation of Ser-129 is the dominant pathological modification of alpha-synuclein in familial and sporadic Lewy body disease. J Biol Chem. 2006;281(40):29739-52. doi: 10.1074/jbc.M600933200.
41. Zheng W, Zhang Z, Ye Y, Wu Q, Liu M, Li C. Phosphorylation dependent α-synuclein degradation monitored by in-cell NMR. Chem Commun (Camb). 2019;55(75):11215-8. doi: 10.1039/c9cc05662a.
42. Gómez-Tortosa E, Newell K, Irizarry MC, Sanders JL, Hyman BT. alpha-Synuclein immunoreactivity in dementia with Lewy bodies: morphological staging and comparison with ubiquitin immunostaining. Acta Neuropathol. 2000;99(4):352-7. doi: 10.1007/s004010051135.
43. Puschmann A, Englund E, Ross OA, Vilariño-Güell C, Lincoln SJ, Kachergus JM, et al. First neuropathological description of a patient with Parkinson's disease and LRRK2 p.N1437H mutation. Parkinsonism Relat Disord. 2012;18(4):332-8. doi:

10.1016/j.parkreldis.2011.11.019.
44. Rott R, Szargel R, Haskin J, Shani V, Shainskaya A, Manov I, et al. Monoubiquitylation of alpha-synuclein by seven in absentia homolog (SIAH) promotes its aggregation in dopaminergic cells. J Biol Chem. 2008;283(6):3316-28. doi: 10.1074/jbc.M704809200.
45. Oueslati A, Fournier M, Lashuel HA. Role of post-translational modifications in modulating the structure, function and toxicity of alpha-synuclein: implications for Parkinson's disease pathogenesis and therapies. Prog Brain Res. 2010;183:115-45. doi: 10.1016/s0079-6123(10)83007-9.
46. Nonaka T, Iwatsubo T, Hasegawa M. Ubiquitination of alpha-synuclein. Biochemistry. 2005;44(1):361-8. doi: 10.1021/bi0485528.
47. Saha RN, Pahan K. HATs and HDACs in neurodegeneration: a tale of disconcerted acetylation homeostasis. Cell Death Differ. 2006;13(4):539-50. doi: 10.1038/sj.cdd.4401769.
48. Shukla S, Tekwani BL. Histone deacetylases inhibitors in neurodegenerative diseases, neuroprotection and neuronal differentiation. Front Pharmacol. 2020;11:537. doi: 10.3389/fphar.2020.00537.
49. Öhrfelt A, Zetterberg H, Andersson K, Persson R, Secic D, Brinkmalm G, et al. Identification of novel α-synuclein isoforms in human brain tissue by using an online nanoLC-ESI-FTICR-MS method. Neurochem Res. 2011;36(11):2029-42. doi: 10.1007/s11064-011-0527-x.
50. Iyer A, Roeters SJ, Schilderink N, Hommersom B, Heeren RM, Woutersen S, et al. The impact of N-terminal acetylation of α-synuclein on phospholipid membrane binding and fibril structure. J Biol Chem. 2016;291(40):21110-22. doi: 10.1074/jbc.M116.726612.
51. Kim YE, Hipp MS, Bracher A, Hayer-Hartl M, Hartl FU. Molecular chaperone functions in protein folding and proteostasis. Annu Rev Biochem. 2013;82:323-55. doi: 10.1146/annurev-biochem-060208-092442.
52. Mayer MP, Bukau B. Hsp70 chaperones: cellular functions and molecular mechanism. Cell Mol Life Sci. 2005;62(6):670-84. doi: 10.1007/s00018-004-4464-6.
53. Chittoor-Vinod VG, Lee S, Judge SM, Notterpek L. Inducible HSP70 is critical in preventing the aggregation and enhancing the processing of PMP22. ASN Neuro. 2015;7(1):1759091415569909. doi: 10.1177/1759091415569909.
54. Falsone A, Falsone SF. Legal but lethal: functional protein aggregation at the verge of toxicity. Front Cell Neurosci. 2015;9:45. doi: 10.3389/fncel.2015.00045.
55. Wang W. Protein aggregation and its inhibition in biopharmaceutics. Int J Pharm. 2005;289(1-2):1-30. doi: 10.1016/j.ijpharm.2004.11.014.