Journal of Neurological Disorders
ISSN: 2329-6895

Sengupta and Bhattacharya, J Neurol Disord 2016, 4:1
DOI: 10.4172/2329-6895.1000252

Review Article Open Access

Polyglutamine Diseases-Understanding the Mechanism of Pathogenesis

Sonali Sengupta[1*] **and Saurabh Bhattacharya**[2]

[1]*Division of Biomolecules and Genetics, School of Biosciences and Technology (SBST), VIT University, India*

[2]*Cytogenetics Department, Dr. Lal Path Labs Pvt. Ltd, National Research Laboratory, New Delhi, India*

[*]**Corresponding author:** Sonali Sengupta, Division of Biomolecules and Genetics, School of Biosciences and Technology (SBST), VIT University, Tamil Nadu, India, Tel: +919566812955; E-mail: sonalisengupta@vit.ac.in

Received date: January 05, 2016; **Accepted date:** February 18, 2016; **Published date:** February 22, 2016

Abstract

Protein misfolding has been implicated in a large number of diseases, which are now grouped under the name of Protein conformational disorders (PCDs). Few examples of diseases that fall in this group are Alzheimer's disease, Parkinson's disease and Huntington's disease. All these disorders are characterized by sets of protein that misfold and aggregate in specific tissues. In order to identify and develop possible routes of therapeutic strategies, scientists have discovered several modifiers for these fatal diseases. These modifiers, primarily identified using models systems, include heat shock proteins, components of UPS pathway and autophagy, transcription factors, detoxifying enzymes, several RNA binding proteins, and RNA species, among other examples. These reviews will focus primarily on cellular processes that are affected in Polyglutamine disorders.

Keywords: Polyglutamine disease; Neurodegeneration; Aggregates/ Inclusion; Huntington`s disease; Spinocerebellar ataxia

Introduction

Expansion of CAG trinucleotide repeat sequences has been associated with a number of inherited human disorders [1-3]. These neurodegenerative diseases include Huntington's disease (HD), Spinocerebellar ataxias, type 1 (SCA-1), type 2 (SCA-2), type 3 (SCA-3, also known as Machado-Joseph disease), type 6 (SCA-6), type 7 (SCA-7), Dentatorubropallidoluysian atrophy (DRPLA) and Spinobulbar muscular atrophy (SBMA) [4-9]. With the exception of SBMA, all these neurodegenerative diseases are inherited in an autosomal dominant manner. The CAG repeat expansion occurs in the translated region of the gene that encodes a stretch of polyglutamines. In SCA-2, SCA-3, HD, and SBMA, repeats are found in the first exon, while those in the SCA-1, SCA-7 and DRPLA are located in the eighth, third and fifth exons, respectively [2,4-6,8-10]. The expansion of CAG repeats in all these cases has been classified as "dynamic mutation" in which the repeat number changes during intergenerational transmission. Polyglutamine expansion disorders are characterized by "*genetic anticipation*", i.e. there is a progressively earlier onset and increased severity in successive generations in a family [11-13]. Anticipation has a sex bias and is most pronounced on paternal transmission [14]. A common feature of these diseases is that they become clinically evident only late in life. These diseases are also characterized by selective vulnerability of neurons despite widespread expression of the diseased protein in brain and other tissues [15]. It is important to note that the genes causing these diseases show no homology to each other, except in the highly polymorphic CAG tract but pathogenicity results when the CAG tract in the disease causing allele expands beyond a threshold of 35-40 CAG repeats [16-20] (Figure 1).

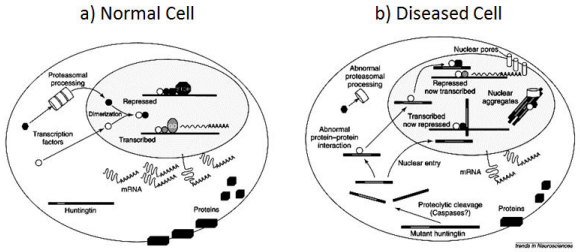

Figure 1: Mechanism of cellular pathogenesis in Poly-Q expansion diseases. a) Normal cell showing normal transcription and protein turnover. b) Diseased cell expressing expanded hunting tin protein that undergoes proteolytic cleavage and interacts with transcriptional and Proteasomal machinery inside the cell. This aberrant interaction leads to transcriptional dysregulation and proteasomal blockage. (Image adapted from Jhang Ho Cha, Trends in Neurosciences, 2000).

Aggregates and PolyQ Toxicity

A morphological feature that characterizes these polyQ expansion disorders is the presence of intracellular aggregates in neurons of affected patients, *in vitro* cell culture studies and also in mouse and fly models [21-25]. These aggregates are truncated polyglutamine fragments. Aggregates are found both in cytoplasm and nucleus and are often referred to as cytoplasmic and nuclear inclusion bodies, respectively. Whether inclusion bodies are pathogenic or are protective to a cell is still debated [14,26]. But their presence in neuronal cells that later undergo degeneration and death intrinsically links them to pathogenecity [21-23]. Furthermore studies have shown that mice expressing full length huntingtin [27] and mice expressing ataxin-1 lacking the self association domain of the protein develop specific neuronal loss characteristic of the disease in the absence of aggregates

[17]. Thus aggregates may not be required for neuronal loss but may be representative markers of neurotoxicity.

Cellular Processes Affected in Polyglutamine Diseases

All the CAG-repeat diseases share common features like adult onset, progressive neurodegeneration, generational anticipation and a remarkable threshold-expansion length which suggests that these diseases may share a common pathogenetic mechanism [14]. Genetic data suggests new gain of function acquired by these expanded proteins to be important in manifestation of the disease phenotype [19].

As discussed below, studies in cell culture and in model organisms have implicated several cellular processes to be affected in these diseases [28].

Transcription

The possibility that the mutant polyQ proteins may affect nuclear functions arose when it was noted that nuclear localization of the protein increases toxicity. Transcriptional dysregultion may be a primary pathogenic process affected in polyglutamine diseases [17,29-31]. Many transcription factors contain glutamine rich regions. Other proteins that contain significant polyglutamine stretches include transcriptionally active molecules like N-Oct-3 (a nervous system specific POU domain transcription factor) [32,33], TATA binding protein (TBP), a transcriptional co-activator with intrinsic histone acetyltransferase activity, [34-36], CREB-binding protein (CBP), a transcriptional co-activator with histone acetylase function [37,38] etc. Interaction of polyQ aggregates with transcriptional factors can be mediated via the polyglutamine-tract present in the other proteins. Several studies have shown that nuclear inclusions of mutant Htt contain transcriptional co-activators such as CBP, an acetyl transferase (AT) etc. [38]. CBP and other histone acetyl transferases act as co-activators of transcription by modifying histones and other proteins to increase transcription. Whether sequestration of transcriptional factors is relevant to neuropathology *in vivo* was examined in *Drosophila* models. Using *Drosophila* model of Huntington's disease, a direct relevance of reduced acetylation activity and/or enhanced deacetylation was established. Histone deacetylases (HDACs) work in concert with histone acetyl transferases (HATs) to modify chromatin and regulate transcription [39]. In *Drosophila* model of Huntington's disease, genetic reduction of Sin 3A co-repressor activity or introducing inhibitors of histone deacetylases like SAHA have been shown to rescue the neurodegenerative phenotype associated with Huntington's disease [38]. Following the promising finding in *Drosophila*, the therapeutic potential of SAHA (Suberoylanilide hydroxamic acid) and another HDAC inhibitor, phenylbutyrate was tested in HD transgenic mouse models. Two mice models, R6/2 and HD-N171-82Q, expressing truncated portions of Htt was used in the study [40,41]. SAHA dramatically improved the motor impairment in R6/2 mice and phenylbutyrate revealed an overall improvement in the condition of HD-N171-82Q transgenic mice which showed decreased striatal atrophy [40,41] .These study validated this class of compounds as HD therapeutics [41].

Further work with a poly-Q *Drosophila* model showed complete rescue of neurodegenerative phenotype by over expression of a endogeneous *Drosophila* CBP (dCBP) [42]. Rescue of phenotype was also associated with eradication of polyglutamine aggregates, recovery of histone acetylation level and normalization of transcription profile [42]. It is important to note that this was the first report of rescue of neurodegenerative phenotype which was associated with lessening of burden of mutant polyQ aggregates in cells. This finding is in contrast to other findings where previously known suppressors of polyglutamine toxicity such as *Drosophila* heat shock protein 70 (dHSP70), *Drosophila* heat shock protein Hdj1 (dHDJ1), *Drosophila* tetratrico repeat protein (dTPR2) and *Drosophila* myeloid leukemia factor (dMLF) rescued phenotype but did not have any effect on formation of aggregates in diseased cells [24,43,44]. Thus the transcriptional dysregulation seems to be an important component of pathogenesis in polyglutmine induced neurodegeneration.

Protein folding and turnover

The mutational mechanism associated with the neurodegenerative diseases is a dominant toxic gain of function attained by the expanded proteins rather than loss of function [14]. The different CAG repeat disease proteins do not share any homology except in the polyglutamine tract. PolyQ expansion confers a dominant toxic property on the protein that leads to neuronal dysfunction and degeneration [16,18-20]. Evidence suggests that polyglutamine expansion increases the probability that the protein will attain an abnormal conformation. *In vitro* studies have shown that PolyQ self associates to form amyloid like fibrils and several studies in diseased tissue, transfected cells and in animal models have demonstrated expanded polyQ protein to form intracellular inclusions [45-47]. These inclusion bodies have been shown to be associated with various molecular chaperones and proteasome components [14]. The association of inclusion bodies with proteasome components impairs the function of Ubiquitin-Proteasome system (UPS) [48,49]. Since the UPS normally controls the quality of proteins by degradation, a blockage of UPS might result in accumulation of misfolded proteins that are produced during normal protein turnover. Thus it appears that cells recognize aggregated disease protein as abnormal protein and recruitment of chaperone and proteasome to the inclusion bodies is for refolding and or degradation of the mutant protein [14]. Recently, it has been reported ataxin 3 physically interacts with VCP and regulates proteasomal degradation of substartes derived from ER [50]. Ataxin-3, is a 42 Kda cytoplasmic protein and expansion of poly-Q repeat in ataxin -3 causes the most common form of autosomal dominant SCA, also known as SCA-3 or Machado-Joseph disease [51]. Using a *Drosophila* melanogaster model of SCA 3, it was shown that over-expression of molecular chaperones results in suppression of the neurotoxicity associated with these diseases [52,53].

Concluding Remarks

Understanding the molecular basis of neurological diseases will help us to find drugs that can prevent or to some extent delay the onset of these fatal disorders. With the advent of animal models it has been possible to establish the sequence of pathological changes that characterizes these diseases. Transgenic mice expressing diseased genes have allowed studies of the early phenotypic changes as patient material for such a kind of analysis is seldom available. These animal models also provide an opportunity to test several potential therapies, which can be aimed to block or slow down the progressive neuro-pathological phenotype [14,52].

Therapeutic Strategies/Future Directions

As described in the sections above, transcriptional dysregulation is the primary cause of pathogenesis in *Drosophila* and mouse models of Huntington`s disease. Mutant huntingtin has been shown to disrupt the activity of transcriptional factors with acetyltransferase activity. HDAC inhibitos like suberoylanilide hydroxamic acid, sodium butyrate, and phenylbutyrate have been shown to rescue neurodegenerative phenotype in various animal models of HD diseases [40,41,53,54]. Activation of cellular protein clearance pathway helps to target the misfolded/aggregated disease protein. Geldenamycin and Geranylgeranyla that stimulates the production of molecular chaperone, Hsp70, has been a focus of therapeutic strategy for several years [55]. Interestingly, mTOR inhibitior rapamycin that stimulates autophagy and helps in clearance of aggregated proteins has been proved to beneficial in cell, *Drosophila* and mouse model of poly Q expanded diseases [56].

Acknowledgement

The authors would like to thank VIT management and core group members for providing help and support for all academic activities and always being a source of inspiration.

References

1. Fu Y-H, Kuhl DPA, Pizzuti A, Pieretti M, Sutcliffe JS, et al. (1991) Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 67: 1047-58.
2. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 352: 77-79.
3. Zoghbi HY, Orr HT (2000) Glutamine repeats and neurodegeneration. Annu Rev Neurosci 23: 217-247.
4. Orr HT, Chung MY, Banfi S, Kwiatkowski TJ Jr, Servadio A, et al. (1993) Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet 4: 221-226.
5. Imbert G, Saudou F, Yvert G, Devys D, Trottier Y, et al. (1996) Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. Nat Genet 14: 285-291.
6. Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, et al. (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 8: 221-228.
7. Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, et al. (1997) Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage dependent calcium channel. Nat Genet 15: 62-69.
8. David G, Abbas N, Stevanin G, Durr A, Yvert G, et al. (1997) Cloning of the SCA 7 gene reveals a high unstable CAG repeat expression. Nat Genet 17: 65-70.
9. Koide R, Ikeuchi T, Onodera O, Tanaka H, Igarashi S, et al. (1994) Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat Genet 6: 9-13.
10. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, et al. (1985) Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 44: 559-577.
11. [No authors listed] (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 72: 971-983.
12. Rubinsztein DC, Leggo J, Coles R, Almqvist E, Biancalana V, et al. (1996) Phenotypic characterisation of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. Am J Hum Genet 59: 16-22.
13. Vonsattel JP, DiFiglia M (1998) Huntington disease. J Neuropathol Exp Neurol 57: 369-384.
14. Shao J, Diamond MI (2007) Polyglutamine diseases: emerging concepts in pathogenesis and therapy. Hum Mol Genet 16 Spec No.
15. Ross CA (1995) When more is less: pathogenesis of glutamine repeat neurodegenerative diseases. Neuron 15: 493-496.
16. Servadio A, Koshy B, Armstrong D, Antalffy B, Orr HT, et al. (1995) Expression analysis of the ataxin-1 protein in tissues from normal and spinocerebellar ataxia type 1 individuals. Nat Genet 10: 94-98.
17. Klement IA, Skinner PJ, Kaytor MD, Yi H, Hersch SM, et al. (1998) Ataxin-1 nuclear localization and aggregation: role in polyglutamine-induced disease in SCA1 transgenic mice. Cell 95: 41-53.
18. Tait D, Riccio M, Sittler A, Scherzinger E, Santi S, et al. (1998) Ataxin-3 is transported into the nucleus and associates with the nuclear matrix. Hum Mol Genet 7: 991-997.
19. Trottier Y, Cancel G, An-Gourfinkel I, Lutz Y, Weber C, et al. (1998) Heterogeneous intracellular localization and expression of ataxin-3. Neurobiol Dis 5: 335-347.
20. Paulson HL (1999) Protein fate in neurodegenerative proteinopathies: polyglutamine diseases join the (mis)fold. Am J Hum Genet 64: 339-345.
21. DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, et al. (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 277: 1990-1993.
22. Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, et al. (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 90: 537-548.
23. Skinner PJ, Koshy BT, Cummings CJ, Klement IA, Helin K, et al. (1997) Ataxin-1 with an expanded glutamine tract alters nuclear matrix-associated structures. Nature 389: 971-974.
24. Warrick JM, Paulson HL, Gray-Board GL, Bui QT, Fischbeck KH, et al. (1998) Expanded polyglutamine protein forms nuclear inclusions and causes neural degeneration in Drosophila. Cell 93: 939-949.
25. Kim S, Nollen EA, Kitagawa K, Bindokas VP, Morimoto RI (2002) Polyglutamine protein aggregates are dynamic. Nat Cell Biol 4: 826-831.
26. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 431: 805-810.
27. Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, et al. (1999) A YAC mouse model for Huntigton's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. Neuron 23: 181-192.
28. Marsh JL, Thompson LM (2004) Can flies help humans treat neurodegenerative diseases? Bioessays 26: 485-496.
29. Saudou F, Finkbeiner S, Devys D, Greenberg ME (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell 95: 55-66.
30. Lin X, Antalffy B, Kang D, Orr HT, Zoghbi HY (2000) Polyglutamine expansion down-regulates specific neuronal genes before pathologic changes in SCA1. Nat Neurosci 3: 157-163.
31. Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, et al. (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Hum Mol Genet 9: 1259-1271.
32. Millevoi S, Thion L, Joseph G, Vossen C, Ghisolfi-Nieto L, et al. (2001) A typical binding of the neuronal POU protein N- Oct3 to noncanonical DNA targets. Implications for heterodimerization with HNF-3 beta. Eur J Biochem 268: 781-791.
33. Blaud M, Vossen C, Joseph G, Alazard R, Erard M, et al. (2004) Characteristic patterns of N Oct-3 binding to a set of neuronal promoters. J Mol Biol 339: 1049-1058.
34. Sharp PA (1992) TATA-binding protein is a classless factor. Cell 68: 819-821.
35. Gostout B, Liu Q, Sommer SS (1993) "Cryptic" repeating triplets of purines and pyrimidines (cRRY(i)) are frequent and polymorphic:

analysis of coding cRRY(i) in the proopiomelanocortin (POMC) and TATA-binding protein (TBP) genes. Am J Hum Genet 52: 1182-1190.

36. Martinez E, Zhou Q, L'Etoile ND, Oelgeschläger T, Berk AJ, et al. (1995) Core promoter-specific function of a mutant transcription factor TFIID defective in TATA-box binding. Proc Natl Acad Sci U S A 92: 11864-11868.
37. Goodman RH, Smolik S (2000) CBP/p300 in cell growth, transformation, and development. Genes Dev 14: 1553-1577.
38. Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, et al. (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 413: 739-743.
39. Ng HH, Bird A (2000) Histone deacetylases: silencers for hire. Trends Biochem Sci 25: 121-126.
40. Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, et al. (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc Natl Acad Sci U S A 100: 2041-2046.
41. Gardian G, Browne SE, Choi DK, Klivenyi P, Gregorio J et al. (2005) Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. J Biol Chem 280: 556–563.
42. Taylor JP, Taye AA, Campbell C, Kazemi-Esfarjani P, Fischbeck KH et al. (2003) Aberrant histone acetylation, altered transcription and retinal degeneration in a Drosophila model of polyglutamine diseases are rescued by CREB-binding protein. Genes Dev 17: 1463-1468.
43. Kazemi-Esfarjani P, Benzer S (2000) Genetic suppression of polyglutamine toxicity in Drosophila. Science 287: 1837-1840.
44. Kazemi-Esfarjani P, Benzer S (2002) Suppression of polyglutamine toxicity by a Drosophila homolog of myeloid leukemia factor 1. Hum Mol Genet 11: 2657-2672.
45. Perutz MF, Johnson T, Suzuki M, Finch JT (1994) Glutamine repeats as polar zippers: their possible role in inherited neurodegenerative diseases. Proc Natl Acad Sci USA 91: 5355-5358.
46. Scherzinger E, Lurz R, Turmaine M, Mangiarini L, Hollenbach B, et al. (1997) Huntingtin-encoded polyglutamine expansions form amyloid-like protein aggregates in vitro and in vivo. Cell 90: 549-558.
47. Temussi PA, Masino L, Pastore A (2003) From Alzheimer to Huntington: why is a structural understanding so difficult? EMBO J 22: 355-361.
48. Bence NF, Sampat RM, Kopito RR (2001) Impairment of the ubiquitin-proteasome system by protein aggregation. Science 292: 1552-1555.
49. Jana NR, Zemskov EA, Wang G, Nukina N (2001) Altered proteasomal function due to the expression of polyglutamine-expanded truncated N-terminal huntingtin induces apoptosis by caspase activation through mitochondrial cytochrome release, Hum Mol Genet 10: 1049-1059.
50. Wang Q, Li L, Ye Y (2006) Regulation of retrotranslocation by p97-associated deubiquitinating enzyme ataxin-3. J Cell Biol 174: 963-971.
51. Maciel P, Gaspar C, DeStefano AL, Silveira I, Coutinho P, et al. (1995) Correlation between CAG repeat length and clinical features in Machado-Joseph disease. Am J Hum Genet 57: 54-61.
52. Warrick JM, Chan HY, Gray-Board GL, Chai Y, Paulson HL, et al. (1999) Suppression of polyglutamine-mediated neurodegeneration in Drosophila by the molecular chaperone HSP70. Nat Genet 23: 425-428.
53. Cummings CJ, Sun Y, Opal P, Antalffy B, Mestril R, et al. (2001) Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice. Hum Mol Genet 10: 1511-1518.
54. Sengupta S, Ganesh S (2008) Non-coding RNAs in polyglutamine disorders: friend or foe? J Biosci 33: 303-306.
55. Dantuma NP, Bott LC (2014) The ubiquitin-proteasome system in neuro degenerative diseases :precipitating factor, yet part of the solution Frontiers in Molecular Neurosciences 7: 70.
56. Rubinsztein DC, Gestwicki JE, Murphy LO, Klionsky DJ (2007) Potential therapeutic applications of autophagy. Nat Rev Drug Discov 6: 304-312.