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Regulation of Neurodegenerative Diseases by Classic Interplay of RNA Binding Proteins and Hsp40 Chaperones

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Abstract

Neurodegenerative diseases are a class of diseases involving a gradual loss of neurons and cognitive impairments. Protein depositions in the brain is another hallmark of these conditions. Along with clinical manifestations of neurodegenerative diseases, this review focuses on the use of heat shock proteins to combat the toxicity related to these conditions, especially Huntington's Disease (HD). This includes screening of Hsp40 and related chaperones to look for suppressors of Huntington's disease-related phenotypes. Crosstalk amongst Huntingtin aggregates and RNA binding proteins is explored shedding light on prion-like protein Orb2A and another Hsp40 chaperone Mrj being rescuers of HD-related toxicity. Some of these chaperones show conserved protein sequences across species of yeast, flies, and humans making them potential targets for treating HD-related pathophysiologies.

Keywords: Neurodegenerative Diseases; Huntington's Disease; Chaperones; Protein Aggregation; RNA Binding Proteins

Abbreviations

HD: Huntington's disease; Htt: Huntingtin; UPS: ubiquitin-proteasome system; HSP: Heat shock proteins; TDP: Transactive DNA Binding protein; ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal Dementia; FUS: Fused in sarcoma; Mrj: mammalian relative of DnaJ; LGMD1: limb girdle muscular dystrophy type 1; CPEB: cytoplasmic polyadenylation element binding; SDD-AGE: Semi-denaturing detergent agarose gel electrophoresis; SCA: Spinocerebellar ataxia; GFP: green fluorescent protein; RFP: Red fluorescent protein

Introduction

Neurodegenerative diseases are commonly characterized by loss of neurons and progressive degeneration of the brain. Protein deposits in the human brain is also a fundamental characteristic of most neurodegenerative disorders [1]. These diseases are the fourth biggest cause of mortality in developed countries and are growing more common in developing countries [2]. A slow continuous loss of neural cells causes neurodegenerative diseases that lead to dysfunction of the nervous system [3]. These diseases have diverse pathophysiologies ranging from cognitive defects to difficulties in performing day-to-day tasks [4]. The main reasons for the development of neurodegeneration are aging and autophagy defects (for example, tauopathies like Alzheimer's disease and synucleopathies like Parkinson's disease), mutations (like trinucleotide repeat expansions seen in Huntington's disease and Spinocerebellar ataxia type 1,2,3,6,7, and 17), inflammations in the nervous system, and adverse

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environmental factors. This review focuses on Huntington's disease and sheds light on Hsp40 chaperones that ameliorate the phenotype related to HD. Slow growth and protein aggregation are two primary phenotypes of Htt-103Q HD mutants as seen in yeasts. Screening of Hsp40 and related chaperones led to the suppression of these phenotypes by some of the chaperones in yeast.

A Crosstalk amongst Htt aggregates and RNA binding proteins is explored with respect to different RNA binding proteins such as Orb2, a prion like translation regulator protein, and Mrj, a Drosophila Hsp40 chaperone, both of which also rescue HD related toxicity.

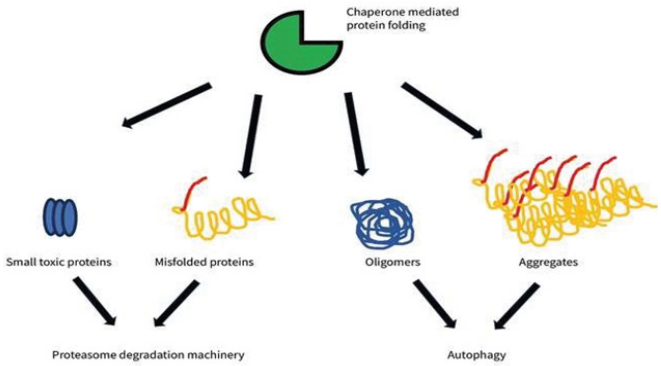

Figure 1: Mechanisms to combat proteostatic stress with the help of chaperone-assisted protein folding. The aggregated toxic proteins are subjected to either autophagy or proteasome degradation machinery.

Huntington's Disease

Huntington's disease (HD) is caused due to an autosomal dominant mutation resulting in trinucleotide repeat expansion on chromosome four is the cause of this condition. A mutant form of Huntingtin (HTT) has this sequence repeated more than 35 times which results in an abnormal protein that increases the decay rate of neurons. Huntington's disease symptomized by involuntary movements, psychological abnormalities, cognitive dysfunction, death of brain cells, problems with mental abilities, lack of coordination, dementia, etc. Insomnia and circadian rhythm issues in Huntington's disease might be associated with depression, mania, involuntary movements, and motor activities during sleep [5]. Other neuropsychiatric symptoms of the disease may include mood disorders, bipolar syndromes, paranoid hallucinations, and delusions, and frontal dysexecutive syndrome [6]. A peculiar characteristic of the disease is the selective loss of medium spiny neurons in the striatum of HD patients [7]. Several imaging studies have supported the finding of cortical atrophy in parietal and occipital regions of the brain in Huntington's disease [8,9]. Significant patterns of cortical thinning and reduction of grey matter volume are associated with severe cognitive degradation of Huntington's disease [10]. Apart from mutant Huntingtin aggregation, other mechanisms like inflammation, autoimmunity, and TAU pathology have been speculated to play an important role in neurodegeneration and expression of Huntington's disease [11].

On a cellular level, protein aggregation and aberrant translational repression has emerged to be a common feature of neurodegenerative diseases [12]. Aberrant sequestration of ubiquitin-proteasome system (UPS) components inhibits the delivery of misfolded proteins to the nuclear proteasome in HD and related disorders [13]. Failure of UPS might lead to upregulation of autophagy. Biopsies of the brains of Huntington's disease patients report abnormalities in the vesicular-endocytic pathway, disruption of the Golgi apparatus, and disorganization of the endoplasmic reticulum. [14] HTT Staining of striatal neurons from the brains of HD patients also reported dramatic increases in endosome-lysosome-like organelles [15]. The presence of cytosolic or empty autophagosomes is a result of autophagy defects caused by Huntington mutant. It disturbs the recognition of cargo by SQSTM1/p62 which is a selective autophagy receptor [16]. Autophagic vacuoles and autophagy markers p62 and LC3-II have been found to be increased in mouse models of Huntington's disease [17,18]. Work from various groups over a period of time showed that HD mutants show protein aggregation [19,20] and growth defects [21]. The role of these aggregates seen in the HD mutant has been in debate. Findings from other groups reveal that aggregates sequester essential proteins including transcription factors [22,23] and ubiquitin protease system components [24,25]. These aggregates were also seen to reduce the viability of cells [26] and in some cases led to cell death [27].

Heat Shock Proteins (HSPs) and their role in neurodegenerative diseases

Heat shock proteins are chaperones with the ability to inhibit proteostatic stress [28]. They aid in disassembly of protein aggregates or target proteins for degradation. They thus act as a backbone of protein quality control checks. Most of the neurodegenerative disease conditions have disturbed protein homeostasis accompanied by oligomerization or aggregation of misfolded proteins. They can also degrade these aggregates into toxic filaments causing neurotoxicity. Chaperones in the cells regulate the folding and maturation of newly made as well as partially folded proteins of the cell. Figure 1 shows the mechanism by which chaperones combat proteostatic stress. They also help in resolving the aggregated misfolded proteins [29]. Hsps can be characterized based on their structure, functions, and molecular weights. Hsp10, Hsp40, Hsp60, Hsp70, Hsp90 and Hsp110 are some examples of the same [30]. Small molecular weight Hsps can be classified based on the pattern of their expression i.e., ubiquitous or tissue specific [31]. Hsp104, Hsp16, Hsp40, and Hsp70 are a part of/required for protein aggregate centers in yeast.

HspB8 associates with the misfolded RNA recognition motif of FUS (fused in sarcoma) and partitions into FUS

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condensates which prevents their hardening [32]. While analyzing the effect of mild heat shock on protein quality control in fission yeast, researchers observed that proteins conjugated to Rho1.C17R-GFP (Green fluorescent protein), a fluorescent protein with cytosolic or nuclear localization, (or any other soluble reporters) form reversible aggregate-like structures at 37oC, which they termed as protein aggregate canters. The chaperones in these canters reverse the aggregated reporter to its original native conformation [33]. Hsp40 is a class of proteins having a presence of the J domain making them members of the DnaJ domain chaperone family. J domain assists in the activation of the Hsp70 ATPase in the chaperone cycle [34]. It transfers the substrate protein to the substrate binding domain of Hsp70. This causes substrate protein folding. J protein then dissociates from Hsp70 and the substrate protein is released. This is shown schematically in Figure 2.

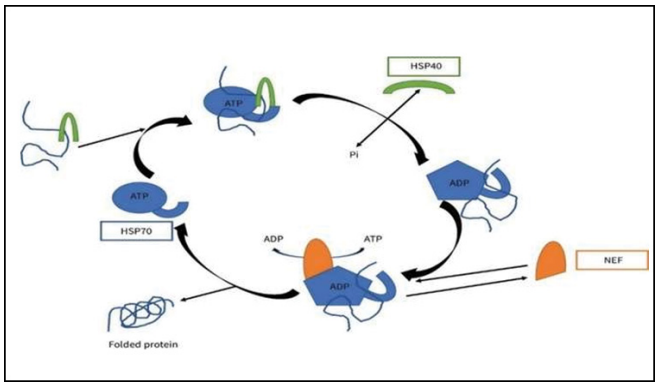

Figure 2: Graphical representation of the chaperone cycle. J protein of DNAJ chaperones (Hsp40) activates the Hsp70 ATPase in the chaperone cycle. It transfers the substrate protein to the substrate binding domain of Hsp70. This leads to the folding of the substrate protein. Then J protein dissociates from Hsp70 and the substrate protein is released

Members of this Hsp40 protein family play a role in numerous processes involving protein folding and refolding. Liberek et al had first established that DnaJ assists Dnak (bacterial Hsp70) in increasing its ATPase activity. This was found in vitro by purification of DnaJ from E. coli [35]. It is known previously that DnaJ helps Hsp70 and its DnaK in the disaggregation of proteins in vitro [36,37]. A study by Acebron et al. [38] also reports DnaJ working with DnaK and GrpE, a nucleotide exchange factor to prevent protein aggregation. It also helps in solubilizing the aggregates alone or with the help of E. coli Hsp100 representative ClpB [38]. DnaJ chaperones act as the first blockade against protein aggregation as Hsp40 recruits Hsp70 in stress conditions. This led researchers to manage toxicity caused due to protein aggregation diseases by using DnaJ and other chaperones. Cytosolic members of DnaJA and DnaJB subfamilies have been found to inhibit parkin C289G aggregation in an Hsp70-dependent fashion [39].

Hsp40 class actively works against disease toxicity in different models as well. E. coli, Drosophila melanogaster, Saccharomyces cerevisiae, Mus musculus, and human cell line HEK293 are a few of them [40,41]. Full-length DnaJB14 and DnaJB12 have protective properties against mutant FUS aggregation. These properties are in an Hsp70-dependent manner. Overexpression of Drosophila DnaJ1 which encodes a protein homologous to human chaperone HDJ1 reduces poly Q toxicity in a fly model of spinocerebellar ataxia type-1 [42]. Yeast strains exhibiting prion domains are also used to study the effects of chaperones on protein aggregations. Metabolomic analysis of Huntington's disease patients and yeast model of Huntington's disease shows a substantial overlap of unregulated metabolic pathways. These pathways are common to human, mice, and yeast model systems. The unregulated pathways include autophagy, mitophagy, longevity, metabolism of amino acids, and glutathione [43].

Earlier work has shown that Sis1, an HSP40 chaperone, involved in protein folding, transport of misfolded protein, and catabolism of ubiquitin-dependent misfolded proteins reduces the toxicity of TDP-43 (Transactive response DNA binding protein) when overexpressed in TDP-43 overexpressed cells. Its mammalian homolog DNAJB1 also reduces TDP-43 toxicity when overexpressed in rodent primary cortical neurons [44]. TDP-43 aggregation was decreased in cell culture experiments when another Hsp40 chaperone, DNAJB2 was co-transfected and TDP-43 folding levels simultaneously increased. These studies suggest that HSPs work in reducing protein misfolding and aggregation in ALS (Amyotrophic lateral sclerosis) and FTD (Frontotemporal dementia).

A study on Hsp40 chaperones in yeast reports that excess of the Hsp40 chaperone sis1, decreases polyglutamine related aggregation size and toxicity of Huntington's model in yeast [45]. Overexpression of another yeast Hsp40 chaperone Ydj1 was reported to modulate the physical properties of the Huntington diseased (HD) exon 1 aggregates by decreasing the formation of SDS insoluble HD aggregates [46]. Chaperone Hsp104 was found to neutralize poly Q toxicity in mammalian neuronal cultures as well as in Huntington's models of rats and mice [47–49]. A study from Drosophila sheds light on suppression of large detergent insoluble poly Q HTT aggregates by Hsp70 and its co-chaperone Hsp40. This results in detergent soluble inclusions accumulation. Thus, these chaperones have an ability to shield toxic forms of poly Q proteins and direct them into non-toxic aggregates [46]. HDJ1, the human DnaJ protein form of DnaJB1, reduces the neurotoxicity in the fly model of Huntington's disease [50]

There has been work done on chaperone screens of DnaJ isoforms to find their role in the modulation of poly-Q aggregation in HD using cell lines [51]. Poly Q mediated neurodegeneration was suppressed by molecular chaperone Hsp70 in Drosophila [52]. Another molecular chaperone Mrj,

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when overexpressed, suppressed poly Q dependent protein aggregation, caspase activity, and cellular toxicity in vitro [53].

Screening Hsp40 chaperones for modifiers of HD related phenotype-

Work from different research groups in the past few years has focussed on screening of Hsp40 and related chaperones and expressing them in different model systems including S.cerevisiae and Drosophila. The neurodegenerative diseases model mutant strain showed reduced growth and clusters of protein aggregates visible as bright green fluorescent punctae under the confocal microscope. Screening led to shortlisting of different chaperones which could be categorised either as enhancers or suppressors. These chaperones when overexpressed in the neurodegenerative diseased mutant strain, rescued the slow growth phenotype and reduced the protein aggregation levels where they were classified as suppressors (Figure 3A, B). On further validation, these chaperones reduced protein aggregation levels even in higher groups of organisms (Figure 3C). Multiple sequence alignment of these chaperone proteins hints towards some of these chaperones having protein sequences conserved across the species of yeast, flies, and humans. As a further extension of this study, these chaperones could be used for the treatment in other neurodegenerative disease model, such as ALS, with mutants of TDP-43 and FUS. These chaperones can possibly be used for managing the phenotypes related to other neurodegenerative diseases.

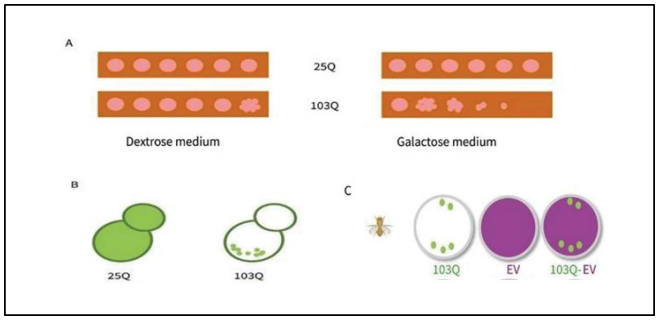

Figure 3: Effect of HD mutation on yeast and S2 cells. A. HD mutant (103Q) showed reduced growth as compared to 25Q in serial dilution assay in the presence of galactose medium. B. 103Q mutant shows protein aggregation seen as bright green fluorescent punctae in yeast cells as compared to control 25Q which shows diffused cytoplasm phenotype C. Effect of chaperones on HD mutant (Htt103Q-GFP) of S2 cells seen by immunostaining

Drosophila Hsp40 chaperone Mrj suppresses HD toxicity

Mrj (mammalian relative of DnaJ) is a Hsp40 chaperone, highly enriched in the nervous system. DnaJB6 is the human ortholog of Mrj. Mutations in DnaJB6 result in limb girdle muscular dystrophy type 1 (LGMD1) [54]. In cell models of Huntington's disease, Mrj inhibits Huntingtin aggregation, caspase activity and cellular toxicity[53]. Proteins with expanded polyglutamine tract form nuclear and cytoplasmic inclusions. This produces cytotoxicity seen as loss of eye pigmentation and structural integrity in Drosophila eye. Transgenic Mrj suppressed polyglutamine toxicity and colocalized with its inclusions in retina and other neurons. It also increased monomeric detergent soluble Poly-Q expanded protein levels [55]. The preventive effect of Drosophila Mrj on Htt oligomers and aggregates was seen via biochemical and imaging assays with a decrease in the number of Htt 103Q aggregates (Figure 4 A,B) and oligomeric smear of 103Q in respectively S2 cells [56].

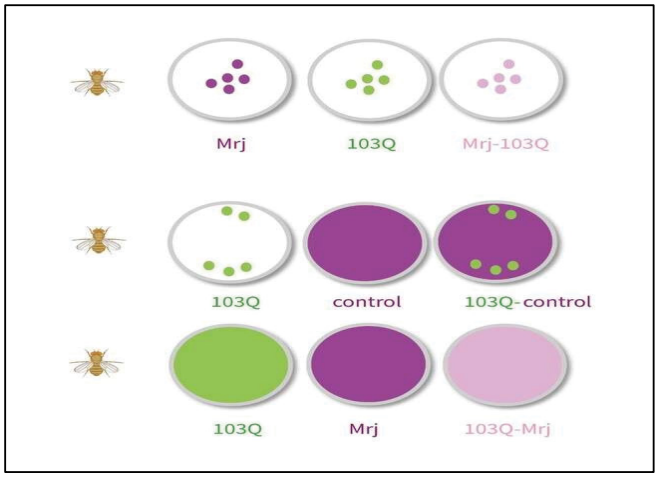

Figure 4: Interaction of Mrj with Huntingtin aggregates. A. Colocalization of Htt103Q aggregates (GFP) and Mrj (RFP, shows as magenta). B. Effect of Mrj (RFP, shown as magenta) as seen on the level of Htt aggregates (GFP) with the help of confocal microscopy

Crosstalk amongst Huntingtin aggregates and RNA Binding Proteins

A class of RNA binding proteins was found to be enriched in Huntington's background of mouse neural crest-derived N2a cell line [57]. Significant ones among them were proteins PAT1, EDC3, DHH1, DCP2, PAN3, and CAF40. PAT1 is a part of the P body (processing body) assembly. EDC3 (enhancer of decapping 3) is a member of Sm (named in honor of Stephanie Smith) [58] proteins and is a P body component. EDC3 interacts with multiple components of decapping machinery using its modular architecture consisting of an N-terminal LSm (Sm-like) domain, a central FDF domain, and a C terminal Yjef-N domain [59]. DHH1 is a member of a highly conserved family of DEAD-box proteins. DCP2 in humans has an enzyme containing intrinsic decapping activity [60]. PAN3 encodes a subunit of Pab1p, poly(A) binding protein-dependent Poly(A) nuclease in Saccharomyces cerevisiae [61]. CAF40 is the component of the CCR4-NOT complex.

Another RNA binding protein which has been studied earlier, that an interactor of Huntingtin aggregates, was prion

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like Orb2 [62]. Orb2 is a translational regulator and Drosophila CPEB (cytoplasmic polyadenylation element binding) protein [63]. CPEB proteins mediate polyadenylation or deadenylation of transcripts, activating or repressing protein synthesis. CPEB proteins are involved in cell division, neural development, learning, and memory [64]. Long-term conditioning of male courtship behavior in Drosophila suggests that Orb2 is crucial for long-term memory [65]. Orb2 was found to be sequestered by Htt aggregates in S2 Drosophila cells (Figure 5A).

Co-expression of Orb2 partially rescued the lethality associated with poly Q expanded Htt [62]. Taking cues from these findings, we checked the association of these RNA-binding proteins with Huntington aggregates. They all showed colocalization up to a certain extent. CAF40 and Orb2 overexpression rescued the slow growth phenotype of the Huntington's mutant in yeast. Orb2 has two isoforms, namely Orb2A and Orb2B based on position of prion like domain, enrichment in the brain and aggregation propensity. Orb2A and Orb2B respectively have 8 and 162 amino acids in front of prion like domain. Orb2B is more abundant in the brain but Orb2A has higher propensity to aggregate [62].

Interaction of Orb2 and Hsp40 chaperones

Previous work on Drosophila Hsp40 and Hsp70 chaperones for interaction with Orb2A showed a few chaperones like, CG4164, CG9828, Droj2, CG7130, Tpr2, Mrj, Hsc70-1, Hsc70-4, Hsc70-Cb, and Hsp70Aa which emerged as interactors of Orb2A [56]. Mrj was seen sequestering with Orb2A in S2 cells.

To check the effect of these interactors on the oligomerization of Orb2, a heterologous yeast sup35 based chimeric system was used. Sup35 is a translation terminator protein that exists in prion and nonprion states. Several new prions could be previously identified by replacing prion like the NM domain of Sup35 with putative prion like domains

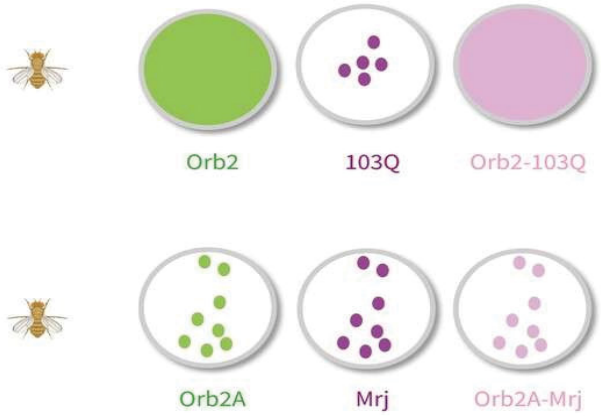

Figure 5: Interaction of Orb2 and Htt. A. Effect of Orb2 (GFP) expression on Htt 103Q (RFP, shown as magenta) aggregates as seen with confocal microscopy. B. Co-expression of Orb2A (GFP) and Mrj (RFP, shown as magenta) as seen with confocal microscopy.

of other proteins [66,67]. On replacing the NM domain of Sup35 with N terminal 162 amino acid of Orb2A, prion like behaviour was seen using red (non-prion) or white (prion) colony colour on dextrose medium. Red non prion colonies could not grow on adenine lacking medium whereas white prion colonies were able to grow on it. Galactose inducible constructs of Hsp40 and related chaperones were transformed into Orb2A-PrD-C-Sup35 red strain. They could not grow on adenine lacking medium. These transformants were independently grown and induced with galactose. Mrj co-expression changed red colony colour to white and cells on galactose medium and they were able to grow on adenine lacking medium. Mrj could convert non prion form of Orb2A to prion like state shown in Fig.6

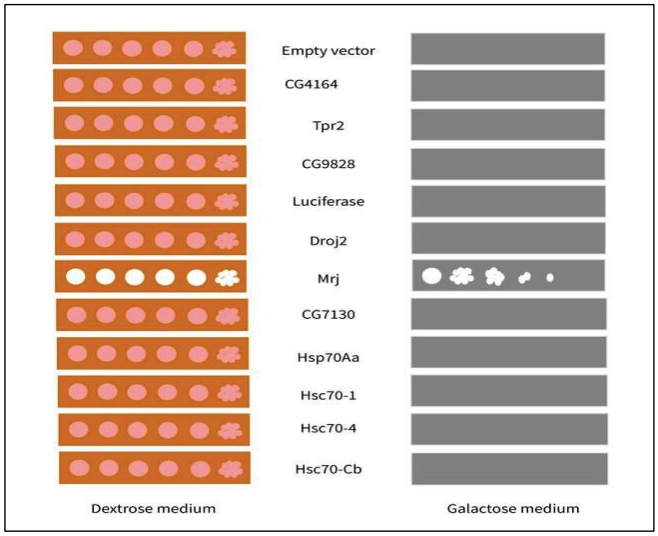

Figure 6: Mrj encourages Sup35 conversion from non-prion to prion state. Nonprion form of Orb2A-PrD-Sup35C, when coexpressed with Mrj, converts into prion form, thus making it appear white on dextrose medium and can grow on adenine lacking medium.

This non prion to prion conversion of Orb2A suggested an increase in its oligomeric state. The oligomeric smear of Orb2A was increased significantly in presence of Mrj. The preventive effect of Drosophila Mrj on Htt oligomers and aggregates characterized via biochemical and imaging assays showed a decrease in the number of Htt 103Q aggregates and oligomeric smear of the 103Q HTT construct in S2 cells of Drosophila.

Conclusion

Numerous factors are interacting with and affecting different facets of the HD mutation at different times under different conditions. Q-rich proteins, heat shock proteins, chemical and natural compounds, fluorescent tags, Poly Q stretch flanking sequences, and cellular mechanisms like autophagy and mitochondrial functions are only a few of them. Although there have been many screens involving chaperones like Hsp40, the candidate hits of this screen have

been validated in 3 different model systems using yeast and Drosophila. These chaperones or their human orthologs have not been studied previously in this aspect.

Multiple sequence alignment of protein sequences of these DnaJ domain chaperones and co-chaperones reveal that a lot of these chaperones have protein sequences conserved across species of yeast, Drosophila, and humans (Figure 7).

This makes these chaperones a potential target for ameliorating phenotypes related to such diseases. It would be insightful to study the exact domain sequence of chaperones that is responsible for the rescue by techniques like site-directed mutagenesis. The exact mechanistic pathway of chaperone action can be deduced. These chaperones should be explored further for their ability to manage the effects of other neurodegenerative diseases like ALS, Parkinson's, Spinocerebellar ataxia (SCA), and other toxic poly Q mutations.

Revisiting the interaction between a prion like RNA binding protein and translational regulator Drosophila Orb2A and Drosophila Hsp40 chaperone Mrj coupled with the suppression of HD related phenotype by both along with sequestration of Huntingtin aggregates with these and other RNA binding proteins hints towards a crosstalk amongst RNA binding proteins and Huntingtin aggregates which should be explored further.

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Conflict of Interest

The authors declare no conflict of interest

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