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Protein aggregation in cell biology: An aggregomics perspective of health and disease

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1. Abstract

Maintaining protein homeostasis (proteostasis) is essential for cellular health and is governed by a network of quality control machinery comprising over 800 genes. When proteostasis becomes imbalanced, proteins can abnormally aggregate or become mislocalized. Inappropriate protein aggregation and proteostasis imbalance are two of the central pathological features of common neurodegenerative diseases including Alzheimer, Parkinson, Huntington, and motor neuron diseases. How aggregation contributes to the pathogenic mechanisms of disease remains incompletely understood. Here, we integrate some of the key and emerging ideas as to how protein aggregation relates to imbalanced proteostasis with an emphasis on Huntington Disease as our area of main expertise. We propose the term "aggregomics" be coined in reference to how aggregation of particular proteins concomitantly influences the spatial organization and protein-protein interactions of the surrounding proteome. Meta-analysis of aggregated interactomes from various published datasets reveals chaperones and RNA-binding proteins are common components across various disease contexts. We conclude with an examination of therapeutic avenues targeting proteostasis mechanisms.

2. Keywords

Protein aggregation, misfolding, interactome, chaperone, therapeutics

3. Introduction

Along with nucleic acids, polysaccharides and lipids, proteins constitute the major class of building blocks of cells. Proteins comprise the organellar and sub-organellar macromolecular structures, mediate enzymatic activity, drive signalling cascades, drive transcription and translation, constitute transport mechanisms and are fundamental components of most, if not all, other basic operations involved in life. Most proteins require a complex folding process after they are synthesized, a process which distinguishes them from the other classes of biomolecules in terms of the sheer complexity involved. The management of the folding process (proteostasis) requires extensive guidance from a quality control network, which comprises about 800 proteins in humans (reviewed in [1]). When proteostasis becomes imbalanced, protein folding can become impaired, which leads to abnormal aggregation and/or protein mislocalisation (reviewed in [2]). In turn, this can impair protein activity or cause other proteins to aggregate *in trans*, which may be a contributing factor to neurodegenerative diseases characterized by extensive protein aggregation [3-9]. Other protein domains such as polyglutamine (polyQ), which in the soluble state lacks regular secondary structure, become highly aggregation prone upon mutations that expand the polyQ sequence [10-13]. Hence aggregation of polyQ does not involve "misfolding" in the classic sense. However, the aggregation of polyQ can imbalance proteostasis and lead to co-aggregation *in trans* of other proteins in the proteome [8, 14].

Protein quality control networks are dynamic in their capacity to respond to acute challenges on proteome foldedness, such as through heat shock and oxidative stress [15]. However, the dynamism may decline with age [16, 17], and this may increase the susceptibility for proteostasis imbalance and therefore account for the accumulation of protein aggregates [6, 18-20]. One of the remaining challenges is in understanding how the proteome changes in solubility and foldedness in relation to proteostasis balance and neurodegenerative disease settings. In this review, we attempt to bring together some of the key and emerging ideas on this theme. We consider protein aggregation in a variety of disease contexts, including polyQ expansion disorders and amyotrophic lateral sclerosis (ALS). We consider how protein aggregation of particular proteins concomitantly influences the spatial organization and protein-protein interactions of the surrounding broader proteome (Fig 1). We suggest the term "aggregomics" can be used to define how aggregation state of the proteome impacts cellular mechanisms. Thereby aggregomics has particular utility in understanding the contrast of a healthy state of proteostasis from an imbalanced state. A noteworthy example that illustrates the importance of aggregomics is the case of TDP-43 in ALS. TDP-43 normally is nuclear localized but becomes aggregated and trapped in the cytoplasm in patient neurons of most forms of motor neuron disease [21]. Loss of nuclear TDP-43 levels lead to lethality and hence cytoplasmic mislocalisation

appears to be an important mechanism contributing to pathology [22]. We discuss other examples in the following sections.

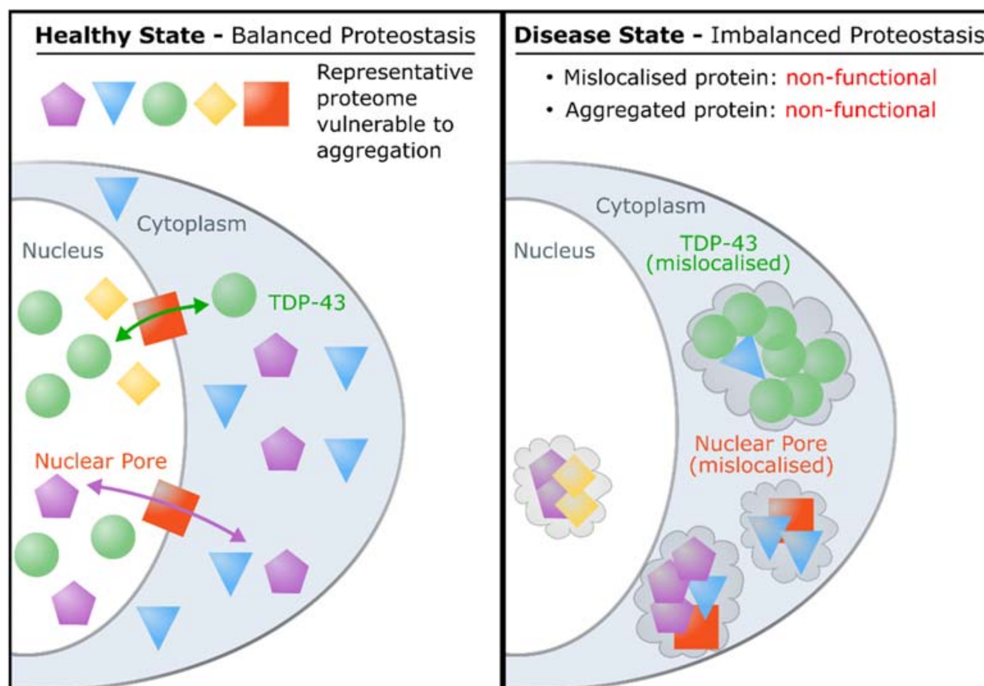

Fig 1: Imbalanced proteostasis leads to proteome mislocalisation and aggregation in neurodegenerative disease. A. Illustration of how proteins can mis-aggregate and interfere with cellular activities. For example, TDP-43 (mislocalized in cytosol in motor neuron disease) and the nuclear pore complex (mislocalized or aggregated in Alzheimer, Huntington and motor neuron disease contexts)[21, 23-26].

4. Aggregomics: does size matter?

Non-native protein aggregates can adopt many different structural configurations and sizes. Classically, the following broad groupings have been ascribed: soluble oligomers, amorphous aggregates, protofibrils, amyloid fibrils, and other superstructural variants thereof including spherulites and particulates [27, 28]. The amyloid fibril structure is a classic signature of many diseases (i.e. the amyloid diseases [29]), which forms by a nucleation dependent mechanism. In essence, β-sheet rich fibrils rapidly assemble from an energetically unfavourable primary nucleus comprising a small number of the misfolded protein entity. Secondary nucleation can also proceed whereby new fibrils are formed from breakages of established fibrils [30, 31]. Excellent reviews have been published on the fundamental principles of amyloid kinetics and hence will not be covered further here (e.g. [32, 33]). In addition, recent evidence indicates protein aggregates can also arise (including amyloid structures) by a phase separation mechanism from solution into liquid droplets, gels and fibrillar states [34, 35]. The phase separation mechanism appears to be critical to both normal and pathological cellular events, and hence is discussed in further detail in section 4.3.

4.1. Soluble oligomers

How aggregates contribute to the pathogenic mechanisms and cascade of dysfunction remains incompletely understood, although size and morphology appear important in certain contexts. A long-established hypothesis is that protein aggregates, and in particular the soluble oligomer class, have a general capacity to exert a gain of toxic property. The toxicity arising from the soluble oligomers class has been extensively reviewed by others [36-40] and hence will only briefly be covered here. The main evidence underpinning this hypothesis is that cytotoxicity for a range of model proteins correlates with the appearance of submicroscopic soluble aggregates, and often occurs in the absence of detectable inclusion formation [41-44]. The mechanisms for how soluble oligomers exert their toxicity seems to involve broadly non-specific impairment of the activity of essential cellular machinery, including chaperones [14, 45], degradation machinery [46], transcription factors [47] and nucleocytoplasmic transport machinery [26] or plasma membrane integrity [48, 49].

Even within a classic subgroup, such as oligomers, there is evidence of finer structural heterogeneity governing distinct functional consequences. For example, two different oligomer subtypes of α-synuclein (associated with Parkinson's disease), which while similar in size and morphology display different abilities to penetrate membranes [50]. The mechanism to account for the differences in membrane perturbation was explained by the formation of α-helix and a lipophilic β-sheet unique to the more toxic oligomer form upon association with lipids. Other examples also indicate the ability of oligomers to interact with membranes depends on subtle differences in oligomer structural composition, including two subclasses of oligomers of HypF-N which are otherwise similar in size and shape yet exert differing abilities to engage with membranes [51]. The more toxic variant had a more porous, less well packed hydrophobic core [51]. Addition of various chaperones to oligomers of amyloid-β (Aβ) and HypF-N that were toxic alleviated the toxicity [52]. This appeared to arise by chaperones shielding the oligomers and preventing their interaction with membranes.

4.2. Macroscopic aggregates

Larger-sized aggregates (i.e. macroscopic inclusions greater than about 100 nm – 1 µm in size) that form intracellularly have been suggested to arise in some instances from adaptive strategies to sequester soluble proteins into discrete depots for storage or processing [4, 43, 53]. Various models have been described to account for different types of macroscopic aggregates including the aggresome, Q-bodies, IPOD and JUNQ [44, 54, 55]. Details of the mechanisms that describe these structures have been reviewed elsewhere and hence will not be covered here [5, 53, 56]. One challenge with these models is that they don't properly account for the proteotoxicity associated with large scale aggregation (which is covered in more detail in the sections below).

4.3. Protein aggregation mediated by phase separation

One of the more interesting developments in the last decade is the discovery that proteins phase separate into membrane-less compartments [34, 57-61]. It is becoming apparent that phase separation is a widespread phenomenon in normal cellular functioning and pathology. Notable examples of physiological liquid-liquid phase separation include the formation of nuclear pore complex, nucleoli, spliceosomes and cytoplasmic ribonucleoprotein granules (for a recent review, see [62]).

The phase separation of macromolecules is mediated by multivalent protein-protein or protein-RNA interactions, which cause 'demixing' of the solution to produce a dense, protein enriched phase (liquid droplet) surrounded by a dilute phase [63-65]. The resulting non-membrane bound compartments are multicomponent viscous liquid droplets which undergo dynamic fusion, wetting and shearing [66]. While the physics explaining phase separation is well-established, the mechanisms governing demixing, mixing and selective recruitment of other components into the droplets in the complex cellular environment remain largely to be determined [62]. Clues come from parameters known to regulate assembly, including the local concentration of protein and/or RNA, modulated through changes in transcription, translation, degradation and trafficking, or ionic strength. Increasing concentrations of RNA promote liquid-liquid phase separation of proteins containing intrinsically disordered regions such as tau, FUS, hnRNPA1, Lsm4, Tia1 and TDP-43 proteins, while increasing salt concentration destabilises the liquid droplets [67-71] . Post-translational modifications including phosphorylation and methylation, appear to be a key 'switch' for assembly or disassembly of liquid droplets [72]. For example, methylation of arginine residues in DDX4 have been shown to inhibit phase separation, an effect which is attributed to a decrease in the number of cation-phosphate interactions [73]. Phosphorylation can promote [74-76] or reverse [72] phase separation depending on the proteins involved.

The key protein domains promoting liquid-liquid phase separation are low complexity, often intrinsically disordered, regions common to many RNA-binding proteins. Low complexity domains have been shown to be both necessary and sufficient for liquid-liquid phase separation of a range of proteins [70], and many disease-related aggregating proteins also possess intrinsically disordered regions. The disease associated proteins may lead to aberrant phase separation mechanisms, such as shifting the phase boundaries, and therefore detrimentally alter the dynamics of complexes that rely on phase separation for function. For example, disease causing mutants of phase separating proteins FUS and TIA1 form liquid droplets that become less dynamic over time than the wild-type protein counterparts, and mature abnormally into hydrogels and fibres [35, 70, 71, 77-79]. Hence, the

pathological aggregates of these proteins may originate from a dysfunctional phase separation process.

5. Functional consequences of protein aggregation

Heterotypic co-aggregation patterns, as illustrated in Fig 1, are likely crucial to the mechanisms of toxicity. Many proteins can co-aggregate with macroscopic aggregates of aggregation-prone proteins [80]. Particular classes of proteins enriched in aggregates of other proteins include those associated with protein quality control, intracellular transport, and RNA granules [81, 82]. The co-aggregation, and any secondary effects that lead to aggregation of other proteins *in trans*, form important signatures of disease. For example, TDP-43 aggregation and mislocalisation in the cytoplasm is now one of the key immunohistochemical markers for ALS [21, 83]. In ALS cases associated with *C9ORF72* mutations (but not necessarily other cases) nuclear protein hnRNPA3 is also, like TDP-43, trapped in cytosolic aggregates [84]. In other ALS cases as well as Alzheimer and Huntington diseases, proteins in the nuclear pore complex become aggregated and/or mislocalized [23-26]. Below we discuss some of the functional consequences of co-aggregation.

5.1. Hierarchical patterns of heterotypic interactions and functional consequences as aggregates change size

The impact of co-aggregation on toxicity can depend on the aggregation state. We recently discovered that toxicity caused by polyQ-expanded mutant Huntingtin exon 1 (mHttex1) involves two distinct phases [85]. The soluble state (monomers and-or small oligomers) triggers apoptosis. While the mechanisms of the apoptotic trigger remain to be determined, the soluble mHttex1 correlates to deactivation of cAMP response element-binding protein (CREB) signalling and activation of autophagy gene expression [86]. The second phase arises when inclusions form and mature. In this state, the trigger for apoptosis wanes and the cell enters a metabolically inactive state culminating in a slow(er) death by necrosis [85]. The evolution of the inclusions involves a progressive change in the co-aggregated proteome, which may explain a progressive loss of function that leads to quiescence [85].

Recent studies have dissected the progressive change in heterotypic interactions with mHttex1 aggregates as the mHttex1 aggregates evolve from oligomers to inclusions [81, 85]. Kim et al found about 900 proteins enriched with the oligomers [81]. A notable feature of these proteins was that about 200 of them contained low complexity sequences, which as discussed above can be important domains driving phase separation. There was also an enrichment for proteins associated with RNA-binding, ribosome biogenesis, transcription and translation. By contrast, larger aggregates of mHttex1 featured a far less complex interactome consisting of only 85 identified proteins, and which included protein quality control machineries, chaperones and members of the ubiquitin-proteasome system

[81, 87]. Once the inclusions had formed, they initially lack amyloid structure and contain structurally disordered proteins, which suggests that they may form by a phase-separation mechanism [85]. Older, more mature inclusions are rich in β-sheet amyloid structure and contain other proteins with predicted prion-domains in them [85].

5.2. Loss of function from heterotypic co-aggregation

Protein aggregation (either heterotypic or *in trans*) clearly has a role in depleting the function of proteins. As indicated above, a loss of the nuclear pool of TDP-43 is lethal [22]. In the case of Huntington Disease, the CREB binding protein (CBP), becomes trapped in the aggregates formed by mutant Huntingtin, and this correlates with a reduction in CREB signalling activity [88]. This appears to be important pathologically because toxicity in Huntington cell models can be rescued by pharmacological stimulants of CREB signalling pathways and normal healthy cells rapidly lose viability when CREB signalling is inhibited [86].

Other examples of heterotypic co-aggregation causing a loss of function include poly(glycine-alanine) (poly-GA) protein associated with aberrant translation from the CCCCGG hexanucleotide repeat expansion in *C9ORF72* transcripts, which can coaggregate the transport factor Unc119 and deplete its cytosolic availability [89]. Another example is Munc18-1 (associated with early infantile epileptic encephalopathy (EIEE)), which upon harbouring a disease-associated mutation that confers aggregation, sequesters α-synuclein [90]. Conversely, mutant α-synuclein can sequester wildtype Munc18-1 [90], and although the functional consequence of sequestration of both proteins remains to be fully defined, it is likely to significantly impact the ability of Munc18-1 to facilitate neurotransmitter release [91]. In other examples, the SOD1 copper chaperone CCS colocalises with aggregates formed by five SOD1 mutant isoforms [92]. The membrane repair protein dysferlin, which normally interacts with Aβ precursor protein, is sequestered into immune-reactive Aβ42 aggregates [93]. Indeed, up to 60% of the proteins found to coaggregate with TDP-43 are normal interactors of soluble TDP-43 [94].

This mechanism of recruitment is not limited to protein-protein interactions, since aggregating proteins may also sequester other cellular components such as lipids in the case of α-synuclein [95], or RNA in the case of *C9ORF72*-related polydipeptide repeat proteins [96]. Abnormal aggregates of mRNA can also sequester proteins. For example, RNA transcribed from pathogenic CTG repeat expansions cluster into nuclear foci and coaggregate RNA-binding proteins such as muscleblind-like MBNL1 protein [97]. Sequestration of these macromolecules via heterotypic interactions with aggregating proteins forms the basis of a popular theory, which posits that the gain of toxic function

of aggregating proteins is rooted in the functional depletion of crucial cellular proteins and other macromolecules from their normal roles, thereby manifesting toxicity.

5.3. Template driven recruitment into aggregates

Proteins that have similar primary or secondary structure, or are themselves amyloidogenic, can be captured by aggregating proteins via templated or seeded coaggregation. Mutation, fragmentation or post-translational modification commonly increases the amyloidogenicity of a protein [98]. During seeded coaggregation, conformational differences in the aggregating protein are propagated through structural conversion of newly added monomers. This process can recruit wildtype isoforms to aggregates of mutant proteins. For example, mHttex1 sequesters wildtype (non-expanded) isoforms [99], and mutant isoforms of Munc18-1 form large oligomers that sequester wildtype Munc18-1 [90]. Seeded aggregation can also contribute to the cell-to-cell transmission of aggregates of Aβ [100], tau [101] (both associated with Alzheimer's disease), and α-synuclein [102-104]. Such a cell-to-cell mechanism of transmission has been suggested to be akin to a prion infection. This has been demonstrated in transgenic tau mice inoculated with different tau strains which resulted in the strains conferring different pathologies in distinct brain regions and cell types [105]. Co-aggregation effects of this type are not restricted to amyloid-related neurodegenerative diseases. Recently, the pathological mechanism underlying malignant tumors characterised by misfolded p53, a tumor-suppressor protein, has also been linked with coaggregation. In this case, some mutations in p53 confer a pro-aggregation property which allows it to hijack wildtype p53, resulting in the loss of its tumor-suppressor function [106].

Other pseudo-homotypic and heterotypic interactions can also lead to the recruitment of structurally related proteins to the fibril elongation process. Soluble and macroscopic aggregates of polyQ-containing proteins such as mHttex1 sequester other proteins that also contain polyQ domains [107, 108]. For example, several transcription factors are known to be co-aggregated and functionally affected by this mechanism [109]. This phenomenon has been extensively documented for CBP and TATA box-binding protein (TBP) *in vitro* and *in vivo* [88, 99, 110-115]. Interestingly, five out of 9 genes that were upregulated in mRNA levels by more than 2-fold by soluble mHttex1 contain endogenous polyQ sequences [86], and four of these are involved in CREB signalling (*NCOA3*, *MAML2*, *MN1* and *RUNX2*), which may explain why CREB signalling is profoundly affected by mHttex1. These data suggest that soluble aggregation and sequestration of polyQ proteins leads to a cellular response to compensate by upregulation of these genes that encode polyQ domains.

Template-mediated aggregation has also been observed in other amyloid contexts such Islet amyloid polypeptide (IAPP) seeding the aggregation of α-synuclein *in vitro* [116]. Coaggregates of α-synuclein

and tau have been detected *in vitro* and in post-mortem patient-derived tissue [117, 118]. Similarly, tau pathology was also induced by aggregated Aβ, both *in vivo* and in functionally connected brain areas of preclinical models [119, 120]. Aβ also shares 50% sequence similarity with Islet amyloid polypeptide (IAPP), and cross-reactivity has been demonstrated in aggregates co-formed *in vitro* [121] and deposits *in vivo* [122]. Of note are that diseases associated with these proteins (Alzheimer's disease and Type II diabetes mellitus respectively) show a clinical correlation, raising the prospect that co-aggregation could mechanistically promote comorbidity [123].

5.4. Protein quality control at the aggregates

Imbalances in proteostasis in neurodegenerative diseases are evident by markers of autophagy, ER stress, chaperones, stress granules, heat-shock response factor (HSF-1), and ubiquitin-proteasome system being altered [4, 124-127]. Quality control systems, including chaperone machinery, the ubiquitin-proteasome system and autophagy markers, have been commonly observed in macroscopic protein aggregates of mHttex1, mutant SOD1 and proline-arginine polydipeptide repeats [81, 82, 128]. Chaperones are particularly abundant, and found associated with at least 28 amyloid-forming proteins *in vivo* or *in vitro* [87]. Three of the nine chaperones identified in this network, Hsc70, BAG6 and Hsp90 co-chaperone Cdc37, represent either hub or bottleneck nodes in the aggregate interactome, underscoring the importance of chaperones in the formation, evolution and potential remediation of a diverse range of aggregates.

The presence of chaperones within inclusions may represent a slow (but potentially ineffective) adaptive strategy aimed at dissolving the aggregates. There is increasing evidence that chaperones have a specific activity for dissociating amyloids and other aggregates. This activity is attributed to disaggregases (Hsp104, Hsp110) in cooperation with holdase/foldase chaperones (Hsp70 and Hsp90) [129-133]. Disaggregation is primarily mediated by an ATP-dependent disaggregase chaperone (Hsp104, Hsp110), and facilitated by the functional cooperation of the other chaperone networks for substrate delivery and refolding. For example, the Hsp70/40 system directs Hsp104 disaggregases to aggregates and prions *in vivo* [134], activates the ATP-driven motor [135-138], and assists in the recovery of clients that depend on Hsp70 for folding [130, 138, 139]. This system is finely tuned by individual (and often client-specific) Hsp40 (DNAJ) cochaperones and nucleotide exchange factors (NEFs), and several DNAJ proteins have specific functions in inhibiting aggregation or directing clients towards degradation. For example, DNAJB6 and DNAJB8 were both identified as potent inhibitors of polyQ aggregation and toxicity [140-143]. Similarly, a combination of Hsc70, DNAJB1, and an Hsp110 family NEF was demonstrated to dissassemble α-synuclein aggregates via fibril fragmentation and depolymerization [19]. Small heat shock molecular chaperone proteins (sHsps) may also facilitate

disaggregation, either in conjuction with Hsp40/70 and Hsp104 machinery [144, 145], or independently by mediating the disocciation of monomers from fibrillar aggregates *in vitro* [146]. Little is known about the precise mechanism given their lack of ATPase activity.

Chaperones may also mediate clustering of dispersed aggregates. The sHsps αB-crystallin and Hsp27 bind amyloid fibrils *in vitro* with micromolar affinity [146-149] and can promote tangling of aggregates [146-148, 150]. These sHsps can also suppress fibril elongation and fragmentation [151], and hence the activity of these holdase chaperones may be multifunctional in reducing aggregate burden on the cell [146-148, 150]. The recruitment of chaperones to inclusions may also act as a sensor of proteostasis imbalance. For example, the ribosome-bound chaperone nascent polypeptide-associated complex (NAC), which is normally required for translation, becomes bound to protein aggregates under conditions of proteostasis imbalance [152]. This reduces NAC at the ribosome, and therefore acts as a mechanism to reduce translational activity.

Defects in protein clearance mechanisms such as autophagy and the ubiquitin-proteasome system are well-established sources of proteostasis imbalance and disease [6]. This is illustrated most pertinently by the observation that mutations in many of the genes involved in these pathways cause neurodegenerative disease. This includes Parkinson Disease (PD) mutations in PINK-1, Parkin, Ubiquitin carboxy terminal hydrogenase L1 and LRRK2, and ALS mutations in p62, Ubqln2 and Optineurin [153, 154]. In turn, mutant proteins that misfold or aggregate may themselves impair or stress the clearance mechanisms. This includes disease-associated mutant α-synuclein [155-157], tau [158, 159], Htt [160, 161], SOD1 and TDP-43 [162-164]. In some cases, the physiological function of the aggregation-prone protein also lies within the degradation pathways, such as the role of mHtt in regulating retrograde transport of autophagosomes along the axon [165]. Thus, mHtt aggregation impacts autophagy both directly (through loss of function) and indirectly (through overloading the degradation capacity with aggregates).

5.5. Impairment of intracellular transport

The nuclear pore complex appears to be particularly susceptible to co-aggregating with aggregation-prone proteins (Figure 1) [23, 166-169]. This may be mediated by nuclear pore complex subunits THOC2 and Ran-GAP, which engage with amyloid-forming proteins, and appears to be sufficient to impair nuclear-cytoplasmic transport [25, 26]. Impairment leads to protein aggregation or mislocalisation of nuclear proteins, notably TDP-43 and FUS in the cytosol [26, 170-172]. Other examples include LIR-3, which is mislocalized in the cytosol upon polyQ aggregation [173].

Failure of nucleo-cytoplasmic transport may also be attributed to disrupted phase separation dynamics. Nucleoporins, the primary building blocks of the nuclear pore complex, consist of intrinsically disordered FG-rich domains that undergo phase separation [174, 175]. In contrast to typical intrinsically disordered regions, the FG domains are comparatively hydrophobic and less charged [176], and form a more solid hydrogel on timescales in which liquid droplets are typically dynamic [175, 176]. Hydrogel formation by these domains is proposed to constitute the nuclear pore complex permeability barrier, known as the 'selective phase model' [177]. Thus, disruption of nucleoporin phase separation is likely to significantly impact the transit of a diverse range of molecules across the nuclear pore complex. Some proteins, such as the arginine-rich polydipeptide repeats associated with *C9ORF72* transcripts, interact with nucleoporins and can mediate toxicity [178].

One consequence of a defective nucleo-cytoplasmic transport system is that quality control systems that rely on nuclear translocation break down and hence compromise cell viability. Notably, misfolded proteins can be transported to the nucleus by the nuclear pore complex for degradation by Hsp40 protein Sis1p in association with the nuclear E3 ubiquitin ligase San1p [14, 179, 180]. In cells with cytosolic polyQ aggregates, Sis1p, becomes sequestered into the aggregates which reduces the capacity of nuclear quality control machinery [14].

Transport mechanisms may also be perturbed in the mitochondria and contribute to mitochondrial dysfunction [181]. While it remains to be determined whether the import machinery in the mitochondria operates a phase separation mechanism for selective filtering, several lines of data point to this conclusion or to having similar blocks in quality control arising from a disrupted transport process. For example, several aggregation-prone proteins including mHttex1 and α-synuclein, interact with subunits of the translocases of the (inner and outer) membrane and can detrimentally affect import [181, 182]. Such effects can interfere with quality control in that mitochondria can no longer import misfolded proteins, including mutant TDP-43, for degradation via the TIM/TOM complexes [183].

5.6. Metanalysis-based discovery of heterotypic interactions from aggregation

Because most studies looking at the interactome of protein aggregates have been done using a single mutant model protein, we investigated whether further insight could be gleaned on common underlying mechanisms associated with protein aggregation more generally by completing a metanalysis of published data sets. To do this, we identified papers in PubMed with the search terms "interactome" and "neurodegenerative disease" (06/06/17). The publications were filtered using the following criteria: (i) data is reported from an immunoprecipitation experiment with the protein of interest; (ii) article contains or has made available the complete raw and processed interactome

dataset; and (iii) article was published within the last 10 years (Supplementary Information). From this list, four independent proteomic studies of sufficient quantitative quality were chosen for analysis [78, 81, 82, 158]. No proteins were found in common across all studies, which may reflect one of two outcomes. Either the depth of proteome coverage was insufficient to yield commonalities, or there are no authentically overlapping commonalties that can describe protein aggregation in terms of heterotypic interactions. This is supported by the observation that proteins of different types can partition into mutually exclusive foci in cells, which may represent distinct phase transition patterns [184, 185]. However, 138 proteins were found as common interactors to two or more misfolded proteins (Figure 2A).

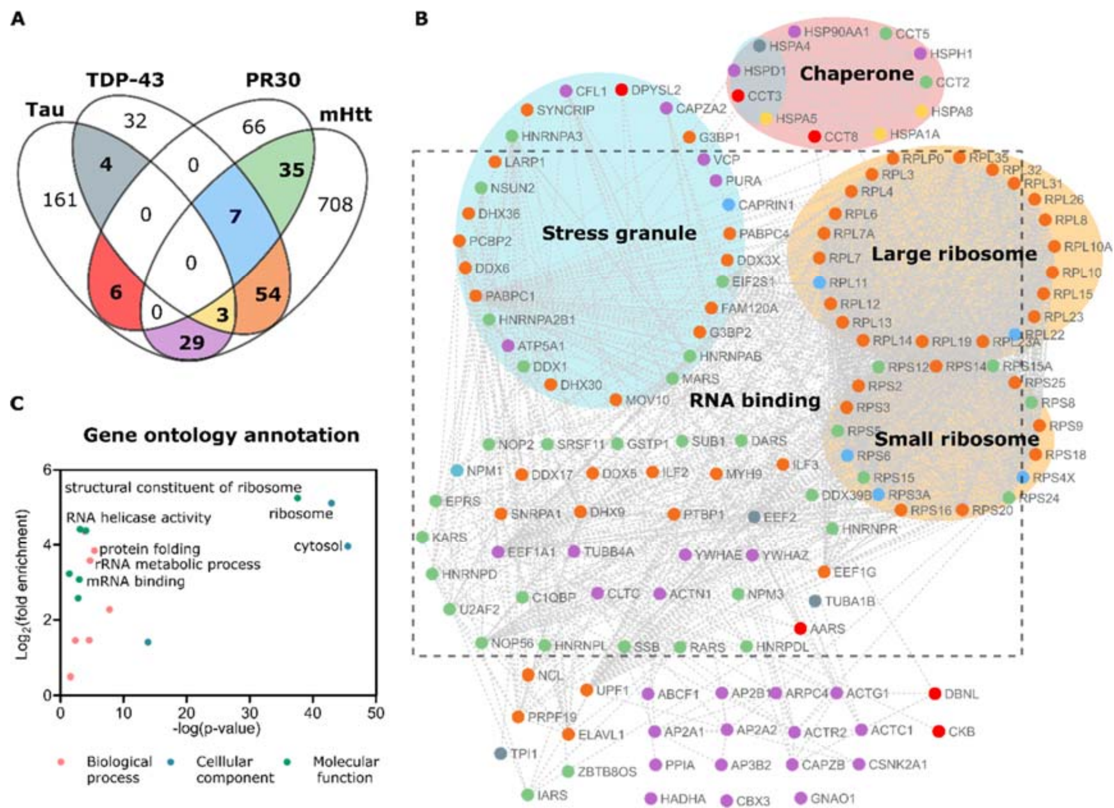

Figure 2. The misfolded protein interactome. (A) Intersection of protein-protein interactions derived from proteomic studies of misfolded or aggregation-prone proteins. Protein interactors gathered from raw datasets were manually compared and the number of common interactors is shown. Sectors containing proteins common to two or more diseases are colored. (B) Common interactors of two or more disease-relevant proteins were subjected to STRING analysis and the resulting network was shown. Each protein was represented as a circle with the same color scheme as Figure 1A. (C) Gene ontology (GO) terms enriched in common interactors of at least two misfolded proteins. Significantly affected functional categories among the common interactors are displayed. The logarithm of fold enrichment of GO-Slim terms is plotted against the logarithm of p-value derived from binomial statistic tests. Each term is represented by a circle. Only categories with $p<0.05$ and at least 4 proteins are shown. Selected categories are indicated.

Analysis of the interactions between these proteins by GO-Slim [186] reveals RNA binding proteins and protein folding machinery as among the most enriched gene ontology terms (Figure 2B-C). It is noteworthy that more than 70% of common interactors are RNA binding proteins, which is consistent with interruptions in RNA granule biology being a general molecular mechanism for neurodegenerative diseases [78, 79, 187]. Of the chaperone pool, the Hsp70 family proteins and chaperonins appear as the central hubs. This may relate to the function of Hsp70 in preventing the accumulation of misfolded proteins in stress granules and in promoting stress granule disassembly [187].

Our data also indicate that the ribosome and ribosome-associated proteins are common, and in fact the most enriched cellular component. This may arise from newly synthesized proteins being more susceptible to aggregating and hence sequestering the translational machinery into the aggregates. Xu et al found that up to 5-10% of newly synthesized proteins aggregate under proteostasis stress in HEK293 cells [188]. We discovered recently that inclusions of mHttex1 appear to arise from clustering of disordered mHttex1 proteins and ribosomes [85]. The inclusions then converted into an amyloid conformation which correlated with further co-recruitment of predicted prion domain-containing proteins [85]. Hence the initial steps of protein aggregation in the cell may be mediated more directly from co-translational faults than the stochastic self-association events of free chains that are examined in test tube conditions.

This raises the question as to what the major driver of aggregation is in the cellular context. Prematurely translated proteins (also known as Defective ribosomal products (DRiPs) [189] are predicted to constitute up to a third of the production pipeline [190]. These proteins are typically degraded with a half-life of 10 min by the proteasome [191]. This therefore suggests that protein quality control efforts are disproportionately invested in managing the earliest steps of protein synthesis. It follows that proteostasis imbalance may disproportionately affect the translation machinery. Support for this idea comes from recent studies indicating that nascent chains contribute most of the aggregate load under proteotoxic stress [188, 192]. Importantly, aggregates could be alleviated by inhibition of protein synthesis prior to stress [188]. Furthermore, DRiPs appear to be recruited into newly forming stress granules under oxidative, heat shock or proteasome-inhibition stresses [187, 193]. These stress granule-DRiPs complexes can be disassembled by the HSPB8-BAG3-HSP70 chaperone complex, suggesting chaperones are central to this as well [193].

6. Targeting therapeutics via the interactome

Diseases involving abnormal protein aggregation remain stubborn to effectively treat. Many of the drugs in clinical development have failed at mid-late clinical trial stages [194]. No drugs currently approved for market by the FDA have been shown conclusively to modify disease for Alzheimer, Huntington or Parkinson diseases [195]. Until recently riluzole was the only disease modifying drug that had successfully passed clinical trials for ALS, offering a lifespan extension of around 2-3 months (see Table 1). One of the great challenges has been a lack of diagnostics at a sufficiently early stage of disease. By the time symptoms present neuronal damage is widespread and may well be largely irreversible, which leaves a very narrow window for treatments to exert a positive influence [196-198].

With that in mind, what are the current therapeutic strategies in trials? (Table 1). Some of the therapeutics focus on reducing levels of the 'toxic' protein, on targeting key enzymes involved in their generation or reducing oxidative stress and inflammation of the brain (Table 1). In Alzheimer disease, the sequential cleavage of Amyloid Precursor Protein (APP) by β- and γ-secretase yields Aβ, which assembles into oligomers and aggregates that may contribute to the pathology [199, 200]. Strategies that inhibit APP cleavage into Aβ products are well developed (Table 1). This includes principally β-site amyloid precursor protein cleaving enzyme 1 (BACE-1), a primary β-secretase in the brain which increases in quantity and activity in Alzheimer disease patients [199-201]. Several BACE-1 inhibitors have been demonstrated to reduce Aβ production and build up in the brain (Table 1). However further research continues to uncover additional neuronal substrates of BACE-1, and targeting this enzyme may result in a range of neurological and cognitive abnormalities such as those observed in BACE-1 knockout mice [202]. Despite these shortcomings, several BACE-1 inhibitors have made it to later stages of development, are generally well tolerated.

Other strategies such as vaccination/monoclonal antibody targeting of Aβ to prevent aggregation and stimulate immunogenic clearance, as well as those that target dysfunctional calcium homeostasis associated with the disease, are also progressing through the pharmaceutical pipeline. Treatments that target different aspects of the disease have scope to be included in combinatorial therapeutics such as ALZT-OP1, which contains an agent to reduce neural inflammation and a small molecule that interferes with Aβ oligomerisation.

Unlike Alzheimer, comparatively few therapeutics are in late stages of development for Parkinson, Huntington and motor neuron diseases. Key mechanisms of action for these strategies include employing anti-oxidants and anti-inflammatory agents to mitigate damage done in the brain, and targeting ion channels to reduce excitotoxicity and restore ion homeostasis (Table 1). ALS now has a second treatment approved for clinical use, the free radical scavenger endaravone, and the tyrosine kinase inhibitor masitinib has successfully completed phase III trials (Table 1).

Oligonucleotide-based therapies have also been used to silence genes, affect RNA splicing, introduce steric hindrance for transcriptional control or block microRNAs gene regulatory control [203]. While administration across the blood brain barrier has remained a challenge, methods such as lumbar puncture have helped circumvent this hurdle. Such approaches have been used for anti-sense oligonucleotide nusinersen, the first treatment for Spinal Muscular Atrophy, which recently made it to market [204, 205]. The anti-sense oligonucleotide therapy eteplirsen has also recently been approved for Duchenne Muscular Dystrophy [205], and small interfering RNA patisiran is currently in phase III for Amyloid Polyneuropathy. Other oligonucleotide-based approaches being implemented include IONIS HTTRx, which reduced mutant huntingtin load in mice and is now in early clinical trials [206, 207]. Similar approaches have been used to reduce RNA foci and toxicity in the context of ALS *C9ORF72* repeat expansions [208].

Manipulation of the proteostasis network or protein foldedness has emerged as an area of active interest. At present, there are three main strategies currently in the therapeutic pipeline for which examples are explored here. The first is the development of pharmacological chaperones to alter the aggregation propensity or structural ensembles accessible to problematic proteins. Pharmacological chaperones are small molecules that mimic the behaviour of biological chaperones or aid in stabilizing the folded state to prevent protein aggregation. One of the most successful examples of this approach is tafamidis to treat transthyretin amyloidoses [209]. Tafamidis binds to the thyroxine binding site of wild-type and mutant forms of transthyretin to stabilize the native tetramer state, suppressing levels of the monomer which are otherwise prone to aggregation [209]. Migalastat is another pharmacological chaperone currently in the final stages of the FDA approval process for treatment of the lysosomal storage disease Fabry-Anderson [210]. Fabry-Anderson disease arises from mutant α-galactosidase A being degraded by protein quality control in the ER, resulting in the pathological accumulation of its substrates [211]. Migalastat binds to mutant α-galactosidase A, enabling folding and restoring delivery to the lysosome where the enzyme can function to degrade its substrates [211].

Other approaches rely on more non-specific effects on protein structure. One example is the small sugar trehalose, a chemical chaperone which can bind to and stabilise partially misfolded proteins to inhibit misfolding and maintain substrates in a folding-competent state [212]. Trehalose is a disaccharide found in bacteria, fungi, plants and invertebrates (but not in vertebrates) which acts as an energy storage molecule, as well as having a key role in desiccation and stress resistance [213]. Theories to its general mechanism of action relate to its ability to act as a kosmotrope (“order making”), generating a water-trehalose matrix around proteins that stabilise the protein by reducing proximal entropy, or by direct interaction via hydrogen bonding of hydroxyl groups on the molecule

and the protein of interest [214, 215], thus preventing their aggregation and holding them in a folding-competent state. The sugar also promotes mTOR-independent induction of autophagy [214], and neuroprotective effects of trehalose have been demonstrated in multiple disease models, however the specific mechanism of action differs for each system [216, 217]. In a mouse model of Huntington's disease, oral administration of trehalose was able to alleviate polyQ toxicity, potentially by directly binding polyQ expansions and preventing inter-and intramolecular interactions and protein aggregation [218]. Similar mechanisms have been proposed to explain the alleviation of toxicity in prion [219] and Aβ models [220]. In a rat model of Parkinson disease, higher doses of orally administered trehalose were effective in rescuing cognitive and neurophysiological defects associated with mutant α-synuclein [221]. A point of note for the order-making nature of trehalose is its ability to impose order on intrinsically disordered proteins, which can create nucleation sites to drive aggregation, and has also been observed for α-synuclein [222]. Presently, trehalose has been demonstrated to be well tolerated in clinical trials with no adverse effects even at high intravenous doses [223], and has passed clinical trial stage II for use in Spinocerebellar Ataxia (SCA3) and Oculopharyngeal Muscular Dystrophy (OPMD)[224, 225].

The second strategy targets downregulation of endogenous proteostasis machinery to inhibit overzealous degradation of destabilised but functional proteins, such as in the case of Cystic Fibrosis. Cystic Fibrosis is caused by mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein, thereby leading to premature degradation of the protein and hence dysfunctional ion and fluid transport across the membrane [226]. In the case of the most common mutation, a phenylalanine deletion at residue 508 (ΔF508), the protein is improperly, but able to be, folded and function can be restored by impairing quality control surveillance and degradation. For example, knockdown of the Hsp90 co-chaperone Aha1 reduces CFTR ΔF508 degradation in the ER and restores levels at the cell membrane [227]. Agents that promote evasion of protein quality control mechanisms from degrading proteins (so called "correctors" such as lumacaftor or tezacaftor) and agents that help restore mutant protein function ("potentiators" such as ivacaftor) have also proven successful strategies against the disease and received FDA marketing approval, as has the corrector-potentiator combinatorial treatment Orkambi [226].

Finally, strategies that target upregulation of endogenous components of the proteostasis network such as chaperones, autophagy and the UPS, are also in development. It has been demonstrated that NRF2 (Nuclear Factor (erythroid-derived 2)-like 2) can potently suppress Aβ toxicity by stimulating key proteostasis pathways involved in the unfolded protein response, autophagy and ubiquitin-proteasome system, offering a potential Alzheimer treatment strategy focusing on enhanced

clearance of misfolded proteins [228, 229]. In another example, enhanced expression of the Hsc70 co-chaperone CHIP (carboxyl terminus of Hsc70-interacting protein), was stimulated by Lanosterol which reduced aggregation in cell models expressing SOD1 (G37R), α- synuclein (S87A) and polyQ-expanded ataxin-3 (84Q) [230]. Lanosterol has now been licensed for the treatment of cataracts involving protein aggregation in the lens [231]. One challenge that remains with targeting proteostasis is that strategies that promote proteasomal-mediated degradation of misfolded proteins can also promote oncogenic transformation [232]. In cancer cell culture models, it was demonstrated that cells undergoing oncogenic transformation had increased capacity to clear misfolded proteins [232].

<u>Table 1:</u> Current disease modifying therapeutics for diseases associated with protein aggregation.
Therapeutics which are currently considered mid- to late-pipeline or approved for the treatment of AD, PD HD and ALS by the FDA.

Disease	Drug name	Alternative names	Drug type	Putative target/mechanism	Pipeline phase	NCT/NDA identifier
AD	Aducanumab	BART; BIIB 037; NI-10	Monoclonal antibody	Binds aggregated Aβ and promotes microglial recruitment and phagocytotic clearance from the brain[233]	3	NCT02484547 NCT02477800
	ALZT OP1	ALZTOP1a + ALZTOP1b; Ibuprofen + cromolyn; Sodium cromoglicate + ibuprofen combination regimen	Small molecule	ALZT OP1a binds to Aβ and prevents oligomerisation; ALZT OP1b is a NSAID that reduces inflammation [234, 235]	3	NCT02547818
	Amilomotide	CAD 106	Virus-like particle vaccine	Vaccine against N-terminal $A\beta_{1-6}$ peptide fragment[236]	2/3	NCT02565511
	Azeliragon	PF-04494700; PF-4494700; TTP-488	Small molecule	Inhibitor of RAGE-ligand interactions which reduces formation of amyloid plaques and reduces RAGE upregulation [237]	3	NCT02916056 NCT02080364
	CNP520	AMG 520	Small molecule	BACE inhibitor that stops Aβ deposition. Three times more selective for BACE-1 than BACE-2[237]	2/3	NCT03131453 NCT02565511
	Crenezumab	MABT5102A; R 5490245; RG 7412; RO 5490245	Monoclonal antibody	Passive immunisation strategy against $A\beta_{1-42}$ which reduces Aβ-induced neuronal death and promotes microglial engulfment and degradation of oligomeric Aβ [238]	3	NCT03114657 NCT02670083
	Elenbecestat	[14C]E2609; E-2609	Small molecule	BACE-1 inhibitor demonstrated to prevents build-up of $A\beta_{40}$ and $A\beta_{42}$ in the brain [239]	3	NCT03036280 NCT02956486
	Epigallocatechin Gallate	EGCG; Sunphenon EGCg; green tea extract	Small molecule	Neuroprotective flavonoid antioxidant with anti-inflammatory and vasodilation properties [240]	2/3	NCT00951834
	Gantenerumab	R-1450; RG-1450; RO-4909832	Monoclonal antibody	Passive immunisation strategy specifically against Aβ plaques and promotes clearance [241]	3	NCT01224106 NCT02051608 NCT01760005
	Isradipine	Dynacirc; Prescal	Small molecule	Selectively binds hippocampal calcium channel L-type $Ca_v1.2$. Supresses calcium influx to cytoplasm and modulates aberrant APP processing, hyperphosphorylation of tau and autophagy [242]	3	NCT02585934 NCT02586909
	JNJ-54861911	none	Small molecule	BACE-1 inhibitor demonstrated to reduce $A\beta_{1-40}$ in CSF [243]	2/3	NCT02569398 NCT01760005
	Lanabecestat	AZD3293; LY 3314814	Small molecule	BACE-1 inhibitor demonstrated to reduce $A\beta_{40}$ and $A\beta_{42}$ peptides in plasma and CSF[244]	3	NCT02972658 NCT02783573 NCT02245737
	Nilvadipine	Nilvad; Nivadil; ARC029	Small molecule	Calcium channel antagonists that blocks vasoconstriction associated with Aβ. Inhibits Syk to reduce Aβ production and neuroinflammation by antagonising STAT3 and NFκB signalling. Propose Syk also reduces tau hyperphosphorylation by interfering at GSK3β and Y18 epitopes [245, 246]	3	NCT02017340
	Masitinib	AB-1010; Masican; Masitinib mesilate; Masitinib mesylate; Masiviera; Masivet; Kinavet	Small molecule	Prevents inflammation by modulating mast cell-glia axis and inhibiting c-Kit and Lyn, two tyrosine kinases involved in abnormal mast cell recruitment. Also blocks Fyn kinase, potentially preventing tau phosphorylation [247]	3	NCT01872598
	Pioglitazone	Actos; AD-4833; Glustin; PGZ; Piozone; U 72107; U 72107A; U 72107E; Zactos	Small molecule	PPAR-γ agonist that promotes microglial clearance of Aβ, ApoE/LXR-dependent degradation of soluble Aβ and reduces neuroinflammation. Regulates insulin sensitivity [248, 249]	3	NCT02284906 NCT01931566
	Solanezumab	LY-2062430	Monoclonal antibody	Passive immunisation strategy that targets central portion of β-amyloid peptide, preventing formation of β deposits [250]	3	NCT02008357 NCT01760005
	Verubecestat	MK-8931; SCH-900931	Small molecule	BACE-1 inhibitor that reduces $A\beta_{40}$ and $A\beta_{42}$ and sAPPβ concentrations in brain, plasma and CSF [251]	3	NCT01953601

PD	Inosine	Urate; hypoxanthine 9-β-D-ribofuranoside	Small molecule	Neuroprotection conferred by antioxidant and metal chelation properties of urate [252]	3	NCT02642393
	Isradipine	Dynacirc; Prescal	Small molecule	Antagonism of L-type calcium channels conferring neuroprotection [253]	3	NCT02168842
HD	Resveratrol	none	Small molecule	Antioxidant flavonoid that enhances ERK phosphorylation, Nrf2 induction and enhances proteasome activity resulting in neuroprotection [253]	3	NCT02336633
ALS	Edaravone	MCI-186; Norphenazone; Radicava; Radicut; Radicut Bag	Small molecule	Free radical scavenger that protects cells against oxidative stress [253]	Approved	NDA 209176
	Masitinib	AB-1010; Masican; Masitinib mesilate; Masitinib mesylate; Masiviera	Small molecule	Tyrosine kinase inhibitor that reduces glial cell activation and neuroinflammation [254]	3	NCT03127267 NCT02588677
	Mecobalamin	E 0302; Methylcobalamin; Vitamin B12 analogue	Vitamin	Prevents SOD1-associated motor neuron death [255, 256]	2/3	NCT00445172
	Riluzole	PK 26124; Rilutek; RP 54274	Small molecules	Inhibits glutamate release, normalises cortical hyperexcitability and modulates sodium channel activity [257]	Approved	NDA 20599

Abbreviations: Aβ (amyloid beta); ALS (Amyotrophic Lateral Sclerosis); APP (amyloid precursor protein); AD (Alzheimer's Disease); CSF (cerebrospinal fluid); FDA (Food and Drug Administration); HD (Huntington's Disease); NCT (National Clinical Trial); NDA (New Drug Application); PD (Parkinson's Disease); NSAID (non-steroidal anti-inflammatory drug; RAGE (Receptor for Advanced Glycation End-products); BACE (Beta-secretase); Syk (spleen tyrosine kinase); STAT3 (Signal transducer and activator of transcription 3); sAPPβ (soluble amyloid precursor protein β); PPAR-γ (peroxisome proliferators activated receptor-gamma); LXR (Liver X Receptors); ApoE (apolipoprotein E); ERK (Ras-extracellular signal-regulated kinase); GSK3β (Glycogen synthase kinase 3 beta); NFκB (Nuclear factor kappa B)

7. Conclusions

Recent advances in our ability to map protein-protein interactions, and the application of systems biology networking approaches, has led to increasingly rich protein interactomes which allow us to view disease-associated genes within the context of their biologically relevant molecular interactions. It is becoming increasingly clear that many protein misfolding and aggregation diseases share common interactome features, as well as many unique patterns to diseases. Collectively, these maps are aiding our ability to determine the underlying molecular mechanisms of disease. We believe the term "aggregomics" provides a useful framework to define how these maps intersect with the protein quality control systems that regulate proteostasis and the biological pathways involved in pathogenesis. Moreover, understanding how the proteome misfolds and aggregates, especially in the case where such effects lead to loss of function, may provide new opportunities for therapeutic development in efforts to either supplement the proteins or prevent them from aggregating (e.g. with pharmacological chaperones). Evidence for this being a possible route to therapeutics is a recent study showing that certain proteins depleted in transgenic Huntington-disease mouse model brain (compared to a non-transgenic control littermate) can alleviate toxicity when overexpressed in a cell model of Huntington disease [258].

One remaining challenge is defining how proteome aggregation differs across cell types. The common theme among neurodegenerative diseases is a preferential degeneration of neurons. Hence, are neurons more predisposed to collapses in proteostasis? Are neurons more vulnerable to the consequences of proteome aggregation? One line of evidence to support this role is provided by a mutant alanyl tRNA synthetase that leads to a loss of editing fidelity and occasional misincorporation of serine in place of alanine codons [259]. This leads to a systemic defect in proteome foldedness. The mutant mouse line is viable, but characterized by a phenotype of cerebellar Purkinje cell loss and ataxia – indicative of a preferential vulnerability of neurons to proteostasis stress [259]. Another line of evidence, albeit controversial, is that the non-protein amino acid, β-N-methylamino-L-alanine (BMAA), which occurs as an environmental toxin for inducing ALS, can be misincorporated in place of l-serine into human proteins to cause a global proteostasis stress response [260-262]. Hence, these data point to a generic systemic alteration of proteostasis leading to preferential damage to neurons.

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11. Abbreviations

αB-c	αB-crystallin
HSR	Heat Shock Response
UPR	Unfolded Protein Response
Y2H	yeast two-hybrid
AD	Alzheimer’s Disease
ALS	amyotrophic lateral sclerosis
PD	Parkinson’s Disease
HD	Huntington’s Disease
TDP-43	TAR DNA-binding protein 43
FUS	Fused in sarcoma
polyQ	polyglutamine
SOD1	superoxide dismutase 1
mHtt	mutant huntingtin
UPS	ubiquitin-proteasome system
FTD	frontal temporal dementia
DPR	polydipeptide repeat proteins
TBP	TATA box-bonding protein
CBP	CREB-binding protein
IAPP	Islet amyloid polypeptide
DLB	dementia with Lewy bodies
APP	amyloid precursor protein
EIEE	early infantile epileptic encephalopathy
Hsp	Heat shock protein
NAC	nascent polypeptide-associated complex
SCA3	spinocerebellar ataxia
OPMD	oculopharyngeal muscular dystrophy
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
CHIP	carboxyl terminus of Hsc70-interacting protein
HRD1	HMG-CoA reductase degradation protein 1
sHsps	small Heat shock proteins
NEF	Nucleotide Exchange Factor
AAA+	ATPases Associated with diverse cellular Activities
GNDF	glial cell line-derived neurotrophic factor (GDNF)