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Review

Amyloid cross-seeding raises new dimensions to understanding of amyloidogenesis mechanism

Paramita Chaudhuri, Kailash P. Prajapati, Bibin G. Anand, Kriti Dubey, Karunakar Kar*

Biophysical and Biomaterials Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, 110067, India

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ABSTRACT

Hallmarks of most of the amyloid pathologies are surprisingly found to be heterocomponent entities such as inclusions and plaques which contain diverse essential proteins and metabolites. Experimental studies have already revealed the occurrence of coaggregation and cross-seeding during amyloid formation of several proteins and peptides, yielding multicomponent assemblies of amyloid nature. Further, research reports on the co-occurrence of more than one type of amyloid-linked pathologies in the same individual suggest the possible cross-talk among the disease related amyloidogenic protein species during their amyloid growth. In this review paper, we have tried to gain more insight into the process of coaggregation and cross-seeding during amyloid aggregation of proteins, particularly focusing on their relevance to the pathogenesis of the protein misfolding diseases. Revelation of amyloid cross-seeding and coaggregation seems to open new dimensions in our mechanistic understanding of amyloidogenesis and such knowledge may possibly inspire better designing of anti-amyloid therapeutics.

1. Introduction

Proteins are vital to almost every metabolic process manifested in living systems and they possess inherent ability to specifically interact with other proteins and metabolites present in the huge crowd of various cellular components (Phillip and Schreiber, 2013; Piazza et al., 2018). The intrinsic intermolecular forces that drive protein-protein interaction and protein complex formation can sometimes promote the self-assembly of protein molecules, yielding higher order cytotoxic aggregates (McManus et al., 2016). Self-assembly of proteins and peptides into toxic supramolecular conformers such as amyloid deposits has been recognized as one of the most important reasons for the onset of many pathologies including a series of neurodegenerative diseases such as Alzheimer's disease(AD), Parkinson's disease (PD), Polyglutamine diseases (Huntington's disease or HD), Amyotrophic lateral sclerosis (ALS) and Prion diseases (Ebrahim-Habibi et al., 2010; Ross and Poirier, 2004; Dobson, 2003). The process of protein aggregation also shows its imprint on non-neuronal pathologies including type II diabetes, cancer and systemic amyloidosis (Ejazul et al., 2017; Yang-Hartwich et al., 2015; Benson, 2013). The issue of what effects the aggregation process of one type of protein would have on the aggregation propensity of other proteins and metabolites present in its surrounding environment becomes an important area of investigation, because the process of co-aggregation and amyloid cross-seeding has been identified as fundamental events in biology (Dubey et al., 2014; Anand et al., 2017, 2018a; Tavassoly et al., 2018; Sarell et al., 2013). Recent research reports reveal the co-occurrence of different amyloid linked diseases in the same individual, with higher rate of aggression and progression of the disease (Table 2) (Moss et al., 1988; Tsuchiya et al., 2004; Miyazono et al., 1992; Janson et al., 2004; Sims-Robinson et al., 2010; Izumi et al., 2015; Panegyres et al., 2013; Rubio et al., 1996; Tada et al., 2012; Bereznai et al., 2010; Kapur and Goldman, 2012; Ikeda et al., 1996; Singh et al., 2017; Park et al., 2015; Brenowitz et al., 2015; Ezrin-Waters et al., 1985; Rajput et al., 1993). More importantly, pathological hallmarks of these diseases, for example, Aβ-linked plaques, tau-linked neurofibrillary tangles, α-synuclein-linked lewy bodies and huntingtin-linked neuronal intranuclear inclusions (NIIs) have been considered as multicomponent systems containing several other proteins (Liao et al., 2004; Mesulam and Asuncion Moran, 1987; Anand and Singh, 2013; Kondratick and Vandre, 1996; Perry et al., 1987, 1991; Wakabayashi et al., 2007; Wear et al., 2015) (Table 1). All these evidences indicate the possible molecular cross-talk among these disease-linked amyloidogenic proteins and peptides. Though amyloid related pathologies have been thought to be originated from the self-assembly process of the specific proteins or peptides, it is certainly surprising that the resultant hallmarks of amyloid growth such as plaques, lewy bodies and

* Corresponding author at: School of Life Sciences, Jawaharlal Nehru University, Room 310, New Delhi, 110067, India.
E-mail address: kkar@mail.jnu.ac.in (K. Kar).

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Table 1
Heterogeneity of the pathological hallmarks of amyloid linked diseases.

Amyloid Hallmark	Major protein constituent	Total proteins in aggregated structure	Example of other proteins apart from the major protein
Alzheimer's disease linked Amyloid plaque	Aβ peptide	488	Adhesion molecules-Fibrinogen; Cytoskeletal components- Actin, Tubulin; Actin binding protein- Coronin; Microtubule-associated protein- Tau; Membrane trafficking Protein- Clathrin heavy chain, Dynamin; Chaperones-HSP90; Constituents of glial intermediate filaments- Glial fibrillary acidic protein, Vimentin; Cysteine proteinase inhibitor- Cystatin C; Kinases/Phosphatases- 14-3-3 protein isoforms; Proteins of Ubiquitin Proteasome system-Ubiquitin-activating enzyme E1 (Liao et al., 2004)
Alzheimer's disease linked neurofibrillary tangles	Tau	Data not available	Kinases/Phosphatases-14-3-3 proteins, Cholinesterases-Acetylcholinesterase(AChE), Butrylcholinesterase (BuChE); Proteins of Ubiquitin Proteasome system- Ubiquitin; Component of cell surface/extracellular matrix- Heparin sulfate proteoglycan; Mitosis-specific phosphoepitopes (Mesulam and Asuncion Moran, 1987; Anand and Singh, 2013; Kondratick and Vandre, 1996; Perry et al., 1987, 1991)
Parkinson's disease linked Lewy body	α-Synuclein, Synphilin-1	~550	Structural elements- α-Synuclein, Neurofilament; α-Synuclein-binding protein- Agrin, 14-3-3 protein, Synphilin-1, Tau; Synphilin-1-binding proteins- α-Synuclein, Dorfin, Parkin Elements of ubiquitin proteasome system- Ubiquitin,Ubiquitin activating enzyme(E1), Ubiquitin-conjugating enzyme (E2); Proteins involved in different cellular responses-Heat-shock proteins, TorsinA; Proteins associated with signal transduction and phosphorylation-Calcium/calmodulin-dependent protein kinase II; Cytoskeletal components-Microtubule Associated protein 1B, Tubulin; Cell cycle proteins- Cyclin B; Cytoplasmic proteins that diffuse into LBs passively- Chromogranin A, Amyloid precursor protein; Mitochondrial protein-Cytochrome c (Wakabayashi et al., 2007; Xia, 2008)
Huntington's disease linked neuronal intranuclear inclusions (NIIs)	Huntingtin	~85	Chaperone/ Protein quality control- Proteasomal ubiquitin receptor, DNA damage-inducible 1 homolog 2, DnaJ homolog subfamily A member 2, Heat shock cognate 71 kDa protein; DNA/RNA binding protein- TBP or TATA-binding protein, Translocated-in-liposarcoma (TLS), CBP or CREB-binding protein, Alanine-tRNA ligase; Mitochondrial protein-Alanine-tRNA ligase, Acad9 protein, Acyl-CoA synthetase family member 2, Electron transfer flavoprotein, Glutaminase; Proteins involved in Vesicle mediated transport, Cytoskeletal transport and endocytosis-AP2-associated protein kinase 1, Clathrin interactor 1, Calponin, NSFL1 cofactor p47, SCY1-like pseudokinase 2; Others-Keratinocyte proline-rich protein, L-lactate dehydrogenase A chain (Wear et al., 2015; Busch et al., 2003; Nucifora, 2001; Huang et al., 1998; Kim et al., 2016; Doi et al., 2008)
Prion linked amyloid plaque	Prion protein	Data not available	Proteinaceous component- Heterogeneous prion variants or strain; Nonproteinaceous component- polysaccharides, nucleic acids and lipids like cholesterol and sphingolipid (Wickner, 2018; Panza et al., 2008)
Amyotrophic Lateral Sclerosis linked inclusions	SOD1, FUS/TLS, TDP-43 etc.	More than 80	Transcriptional modulator-SMAD3; RNA binding proteins-XRN1, Ataxin-2; Proteins involved in stress granule formation-TIA-1; Protein associated with m-RNA transport-Staufen; Translation initiation factors-eIF3, eIF4G; Cytoskeletal components- α-tubulin, β-tubulin, Vimentin; Metal binding proteins- S-100, Calmodulin; Endoplasmic Reticulum Stress-related protein-PDI; Proteins which mediate vesicle transport-VCP; Antioxidant proteins-Metallothionein, Peroxiredoxin2 (Ciryam et al., 2017; Bergemalm et al., 2010)
IAPP-amyloid plaque	IAPP	Data not available	Serum amyloid P component, Apolipoprotein E, Heparan sulfate proteoglycans (Chargé et al., 1996; Westermark et al., 1975; Young et al., 1992)

Table 2
Coexistence of different amyloid diseases in the same individual.

Amyloid pathology #1	Amyloid pathology #2
Alzheimer's disease	Huntington's disease (Moss et al., 1988)
	Sporadic Creutzfeldt-Jakob disease (Tsuchiya et al., 2004)
	Idiopathic Parkinson's disease (Rajput et al., 1993)
	Gerstmann-Sträussler Syndrome (Miyazono et al., 1992)
	Impairment in glucose tolerance or frank diabetes, type 2 diabetes (Janson et al., 2004; Sims-Robinson et al., 2010)
	Cerebral Amyloid Angiopathy (Brenowitz et al., 2015)
Parkinson's disease	Creutzfeldt-Jakob disease (Ezrin-Waters et al., 1985)
	Amyotrophic lateral sclerosis (Izumi et al., 2015)
	Diabetes (Yang et al., 2017; Sun et al., 2012)
Creutzfeldt-Jakob disease	Amyotrophy (Panegyres et al., 2013)
Huntington's disease	Familial amyotrophic lateral sclerosis (Rubio et al., 1996)
	Sporadic amyotrophic lateral sclerosis (Tada et al., 2012)
	Spinocerebellar ataxia type 8 (Bereznai et al., 2010)
	Diabetes (Montojo et al., 2017)
Spinocerebellar ataxia type 2	Amyotrophic lateral sclerosis (Singh et al., 2017)
	Spinocerebellar Ataxia type 10 (Kapur and Goldman, 2012)
	Parkinsonism (Kapur and Goldman, 2012)
Spinocerebellar ataxia type I	Type I familial amyloid polyneuropathy (Ikeda et al., 1996)

inclusions are heterocomponent entities (Table 1). Creation of such heterocomponent higher order structures originating from the amyloid formation of one type of protein validates the possible occurrence of amyloid cross-seeding or co-assembly during the growth of the pathological amyloid structures. Such fundamental concepts on the biological events involving coaggregation and cross-seeding have also been suggested in recent studies where the aggregation process of one type of protein or peptide was shown to induce amyloid aggregation process in other proteins and metabolites, irrespective of their sequence similarities (Dubey et al., 2014; Anand et al., 2018a, b). Also, amyloid structures made up of biologically relevant single metabolites have been shown to induce aggressive amyloid cross-seeding in other proteins or peptide types (Anand et al., 2017; Tavassoly et al., 2018; Anand et al., 2018b). What are the driving forces behind the occurrence of amyloid cross-seeding and co-assembly? Is the process of amyloid cross-seeding or co-assembly/co-oligomerization fundamentally important to the molecular mechanism of growth of such heterocomponent amyloid entities found in different neurodegenerative disorders? Does the onset of co-recruitment/co-assembly during amyloid growth directly or indirectly lead to multitude of diverse metabolic defects seen in individuals suffering from amyloid-linked pathologies? Fundamental answers to these questions are essential not only for understanding the mechanism of amyloidogenesis but also for the development of effective anti-amyloid agents.

In this review paper, we have tried to explore reported research investigations on amyloid cross-seeding, co-aggregation and co-occurrence of amyloidogenesis. This review also discusses various aspects of cross-seeding events observed in both *in vitro* and *in vivo* systems while the main attempt is to understand their relevance to the mechanism of different amyloid-linked diseases.

2. Coaggregation and cross-seeding in amyloid pathologies

2.1. Coaggregation and cross-seeding in Alzheimer's disease(AD)

AD is characterised by the presence of extracellular amyloid plaques with Aβ peptide as a major component and intracellular tangles with tau protein as major constituent in brain leading to degeneration of neurons and pathological symptoms of dementia (Ross and Poirier, 2004; Aguzzi and O'Connor, 2010).

2.1.1. Diversity of Aβ peptides and their coaggregation

One of the crucial components of the plaque is Aβ peptide which is known to be synthesized from Amyloid Precursor Protein (APP) by sequential cleavage of β- and γ-secretase (Murphy and LeVine, 2010). The cleavage of γ-secretase is somewhat indefinite, thus giving rise to numerous heterogeneous population of Aβ peptide (Murphy and LeVine, 2010). Two Aβ peptides viz. $A\beta_{40}$ and $A\beta_{42}$ are relatively abundant in brain than other Aβ fragments (Murphy and LeVine, 2010; Mori et al., 1992) (Table 3). Though the relative abundance of $A\beta_{40}$ (˜80-90%) is much greater than that of $A\beta_{42}$ (˜5-10%) in the brain, the $A\beta_{42}$ peptide acquires more hydrophobicity and constitutes the major proportion of the resultant plaques (Murphy and LeVine, 2010; Selkoe, 2001). Several experiments based on both *in vitro* and *in vivo* systems have already revealed the interaction between different versions of Aβ peptides (Szczepankiewicz et al., 2015; Tran et al., 2017; Kim et al., 2007; Sowade and Jahn, 2017). Occurrence of cross-seeding and coaggregation between the $A\beta_{42}$ peptide and the $A\beta_{40}$ peptide has been reported under *in vitro* conditions (Tran et al., 2017). Additionally, $A\beta_{42}$ and N-terminally extended forms of Aβ (NTE-Aβ) follow co-aggregation pathway and cause formation of mixed fibrils, in which either of the two can serve as the catalytic molecule for the aggregation reaction (Szczepankiewicz et al., 2015). The coexistence of several extended and truncated forms of Aβ peptides in nature implies the possibility of coaggregation under *in vivo* condition (Szczepankiewicz et al., 2015).

2.1.2. Heterogenic nature of Aβ plaques

Apart from Aβ peptides, plaque comprises different other functional cellular proteins (Liao et al., 2004)(Table 1). Analysis of plaques has indicated the presence of more than 488 components in the amyloid entities (Table 1). Interestingly, as evident from Fig. 1, AD patients also show wide range of medical symptoms including both neuronal and non-neuronal complications. Further, AD post-mortem plaques show adhesion molecules like fibrinogen; cytoskeletal components like actin, tubulin, neurofilament; actin-binding protein, coronin (Liao et al., 2004). Microtubule-associated protein tau, known to be major component of neurofibrillary tangles is also found to be present in plaques (Liao et al., 2004). Existence of proteins involved in diverse functions including sorting and membrane trafficking proteins (i.e. clathrin heavy chain, dynamin, dynein heavy chain), heat shock proteins (such as HSP90), constituents of glial intermediate filaments (glial fibrillary acidic protein and vimentin) has also been reported in Aβ plaque (Liao et al., 2004). Proteins associated with degradation (i.e. ubiquitin-activating enzymes, subunits of lysosomal ATPase), cysteine proteinase inhibition (such as cystatin C) are also found to occur in plaque (Liao et al., 2004). Polymorphism of Cystatin C, one of the significant component of plaque in AD patients was previously linked to elevation of risk of AD (Levy et al., 2001; Deng et al., 2001) but later on it was proved that this protein also coexists with Aβ amyloids in the brain of aged normal individuals (Kaur and Levy, 2012).

Table 3
Selected list of protein isoforms of major pathological constituents of aggregated structures in various protein misfolding diseases.

Diseases	Aggregated structure as pathological hallmark	Major protein constituents	Major isoforms		
Alzheimer's disease	Amyloid plaque	Aβ peptide (Murphy and LeVine, 2010)	Aβ40 Aβ42		
	Neurofibrillary tangles	Tau (Kolarova et al., 2012; Espinoza et al., 2008; Adams et al., 2010)	Total isoforms 6	Major isoforms Tau protein with three repeats (3R) Tau protein with four repeats (4R)	
Lewy body diseases	Lewy body	α-Synuclein (Bungeroth et al., 2014; Cardo et al., 2014; Lee et al., 2002)	Isoform type Isoforms generated through alternative splicing Structural isoforms	Isoforms SNCA140 (full length transcript) SNCA126 (lacking exon 3) SNCA112 (lacking exon 5) SNCA98 (lacking exon 3 and 5) Helix rich membrane bound form Disordered cytosolic form	
		Synphilin-1 (Beyer et al., 2008b)	Total isoforms At least 8	Major isoform SNCAIP1 SNCAIP1A SNCAIP1B SNCAIP1C	
		Parkin (Beyer et al., 2008b)	Total isoforms 7	Isoforms PARK2 (TV = Transcript variant)	 TV1 TV2 TV3 TV6 TV7 TV11 TV12
Huntington's Disease	Neuronal Intranuclear inclusions	Huntingtin (Lee et al., 2018)	Highly polymorphic, Poly Q repeats range 10 to 35 in normal population, more than 39 in HD patients		

2.1.3. Heterogenic nature of neurofibrillary tangles

Deposition of neurofibrillary tangles is another pathological hallmark of AD which mainly contain Tau proteins (Kolarova et al., 2012).Tau proteins have been found to be associated with several other proteins in the neurofibrillary tangles (Mesulam and Asuncion Moran, 1987; Anand and Singh, 2013; Kondratick and Vandre, 1996; Perry et al., 1987, 1991) (Table 1). 14-3-3 proteins, majorly known for MAP kinase signalling are known to co-exist with tau protein which is related to phosphorylation of tau in neurofibrillary tangles (Layfield et al., 1996). Catalytic cholinesterases such as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are also found within the neurofibrillary tangles and these proteins are known to play a critical role in the amyloid aggregation during initial stages of plaque formation (Anand and Singh, 2013; Mesulam and Asuncion Moran, 1987). Presence of ubiquitin, heparin sulphate proteoglycan and mitosis-specific phosphoepitopes in neurofibrillary tangles also suggests the possible co-assembly events during aggregation of tau species (Kondratick and Vandre, 1996; Perry, 1991; Perry et al., 1987).

2.1.4. Interaction between plaques and tangles

Although plaques exist extracellularly and neurofibrillary tangles occur intracellularly (Ross and Poirier, 2004), there are certain evidence in literature which indicate possible interaction between these two aggregated structures. Some of the components present in plaque such as isoforms of 14-3-3 proteins are also found to occur in tau-linked neurofibrillary tangles (Liao et al., 2004). Cholinesterases and ubiquitins are also found to be associated with both plaques and neurofibrillary tangles (Anand and Singh, 2013; Perry et al., 1987). Occurrence of these common protein molecules in these different forms of amyloid aggregates related to AD suggests connection between two structurally different pathological assemblies of common protein misfolding diseases. An *in vivo* investigation has also revealed that Aβ fibrils can effectively accelerate the formation of neurofibrillary tangles (Gotz, 2001). Besides, tau species are also found to form stable complexes with Aβ species (Guo et al., 2006).

2.1.5. Evidence of interrelationship between AD and other protein misfolding diseases (PMDs)

AD patients often suffer from other PMDs or symptoms related to other metabolic disorders (Moss et al., 1988; Tsuchiya et al., 2004; Miyazono et al., 1992; Janson et al., 2004; Sims-Robinson et al., 2010; Rajput et al., 1993), (Table 2). Previous reports have already revealed the co-existence of both HD and AD pathologies in the same patient (Moss et al., 1988). Further, idiopathic Parkinson's disease (IPD) becomes more damaging when it occurs in AD patients, reducing the life expectancy of the individuals (Rajput et al., 1993). Lethal protein misfolding diseases such as prion diseases and AD are also found to coexist in the same patient (Tsuchiya et al., 2004). A case report based on an autopsy of an individual has shown the presence of senile plaques in the final stage of sporadic Creutzfeldt–Jakob disease (Tsuchiya et al., 2004). Investigations using double immunolabeling tools have also proved the occurrence of β protein in the plaques obtained from brain sections of patients diagnosed with Gerstmann-Sträussler Syndrome or GSS (Miyazono et al., 1992). Direct link between Type II diabetes and AD has been suggested in numerous studies (Sims-Robinson et al., 2010). Research studies conducted by Mayo Clinic Alzheimer Disease Patient Registry (ADPR) has also shown that type II diabetes appears in a large number of AD patients (Janson et al., 2004). Occurrence of more than one protein-misfolding diseases in single individuals (Table 2) suggests the possibility of molecular cross-talk between these disease-related proteins which has been further proposed by recent *in vitro* and *in vivo* experiments (Ono et al., 2012; O'Nuallain et al., 2004; Oskarsson et al., 2015; Masliah et al., 2001; Moreno-Gonzalez et al., 2017). Aβ aggregates are found to be facilitating the amyloid aggregation of amylin and α-synuclein, pathological hallmark of type II diabetes and parkinson's disease respectively, both under *in vitro* (Ono et al., 2012; O'Nuallain et al., 2004) and *in vivo* (Oskarsson et al., 2015; Masliah et al., 2001)conditions. Conversely, amylin seeds were also found to have the potential to trigger the aggregation of Aβ peptides, resulting in fibrils that contain both the peptides (Moreno-Gonzalez et al., 2017). Additionally, when pancreatic amylin aggregates were introduced into the brain of transgenic mice, it showed severity of pathological

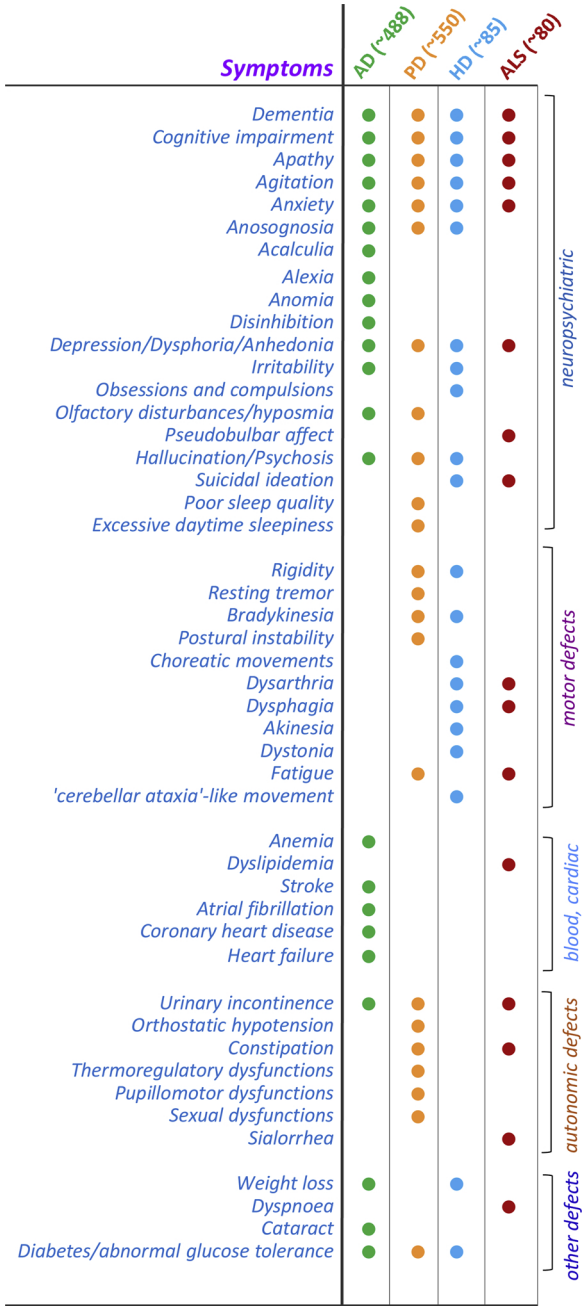


Fig. 1. List of diverse medical complication including neuronal and non-neuronal pathologies observed in different neurodegenerative diseases: Alzheimer's disease (AD) (●) (Janson et al., 2004; Sims-Robinson et al., 2010; Bature et al., 2017; Faux, 2014; Goldstein et al., 2003; de Bruijn and Ikram, 2014; Lee et al., 2014), Parkinson's disease (PD) (●) (Poewe, 2008; Tibar et al., 2018; Thanvi et al., 2003; Orfei et al., 2018; Yang et al., 2017; Sun et al., 2012) Huntington's disease (●) (Roos, 2010; Dale and van Duijn, 2015; Montojo et al., 2017) and Amyotrophic lateral sclerosis (ALS)(●) (Hardiman et al., 2011; Fang et al., 2017; Santangelo et al., 2017; Grossman et al., 2007). The corresponding number given in the parenthesis beside the disease names indicate the approximate number of different protein components reported in literature (as listed in Table 1).

symptom of AD (Moreno-Gonzalez et al., 2017). Recently, our research group has shown that under physiological mimicked condition, $A\beta_{40}$ fibrils can induce the aggregation of globular proteins like lysozyme, bovine serum albumin, insulin, cytochrome c and myoglobin (Anand et al., 2018a). Lethality of cerebral amyloid angiopathy, a symptom often observed in AD patients, is known to increase with the progression of the deposition of Aβ amyloids (Veerbeek et al., 2009; Alonzo et al., 1998). Again, cerebrospinal fluid of AD patients exhibits abundance of soluble $A\beta_{40}$ oligomers (Gao et al., 2010; Hölttä et al., 2013). Moreover, different globular proteins like insulin, neuroglobin, extramitochondrial cytochrome c, lysozyme and albumins are found to occur in the circulating cerebrospinal fluid (Plata-Salamán, 1991; Casado et al., 2005; Satchell et al., 2005; Hansen et al., 1977). Furthermore, examination of proteomic contents of plaques from post-mortem brain samples has revealed the presence of mitochondrial cytochrome c, albumin precursors, globin subunits and lysozyme precursor (Liao et al., 2004). Hence, the interaction between several globular proteins with $A\beta_{40}$ -linked fibrillar and oligomeric entities may have direct relevance to the disease pathology, as evident from three important revelations: (i) the *in vitro* cross-seeding efficacy of $A\beta_{40}$ fibrils to drive aggregation of globular proteins (Anand et al., 2018a) (ii) evidence of the coexistence of multiple proteins in plaque components present in AD patients (Liao et al., 2004) and (iii) the co-occurrence of diverse globular proteins with $A\beta_{40}$ oligomers (in case of AD) and with $A\beta_{40}$ fibrils (in case of cerebral amyloid angiopathy) in cerebrospinal fluid (Veerbeek et al., 2009; Casado et al., 2005; Satchell et al., 2005; Hansen et al., 1977). Another autopsy study has showed the deposition of both isolated and combined transthyretin amyloids (pathological hallmark of cerebral amyloid angiopathy) and Aβ amyloids in the cortical and leptomeningeal blood vessel walls (Sakai et al., 2017), suggesting viable interaction of Aβ.

2.2. Coaggregation and cross-seeding in Lewy body diseases (LBDs)

Lewy body diseases are specified by the presence of lewy body (LB) in the brain. LBD is a broader term used for several neurological disorders including Parkinson's disease (PD), Lewy bodies in its pure form with dementia (pDLB) and common Lewy body disease (cLBD). The term cLBD denotes both pDLB and AD due to occurrence of both LBs and plaque in the brain (Beyer et al., 2008a). Death of dopaminergic neurons and existence of lewy bodies mostly in the substantia nigra pars compacta are the characteristic features of PD which result in symptoms like tremor, rigidity in patients where as in other two LBDs, LBs are widely distributed in almost all parts of the brain resulting in dementia (Ross and Poirier, 2004; Beyer et al., 2008a; Szargel et al., 2008; Beyer et al., 2008b).

2.2.1. Amyloid cross-seeding in α-synuclein, synphilin-1 and parkin

The vital component of lewy body, α-synuclein protein, is encoded by SNCA gene. This gene can give rise to four different isoforms by alternative splicing mechanism (Bungeroth et al., 2014). These isoforms are SNCA140 (full length transcript), SNCA126 (lacking exon 3), SNCA112 (lacking exon 5) and SNCA98 (lacking exon 3 and 5) (Bungeroth et al., 2014; Cardo et al., 2014) (Table 3). An *in vitro* experiment shows that carboxy truncated α-synuclein proteins with an expanded region of 1–102 and 1–110 but not 1–120 stretches can efficiently seed full length α-synuclein aggregation (Bungeroth et al., 2014; Murray et al., 2003). Differential expression level of α-synuclein isoforms during diseased condition (Bungeroth et al., 2014; Cardo et al., 2014), their dissimilar aggregation properties (Beyer et al., 2008a; Beyer, 2006) and the *in vitro* experiment showing capability of the carboxy truncated forms of α-synuclein seeding the full length form suggest possibility of cross-interaction of those isoforms which may be related to lewy body formation. This hypothesis is further supported by another investigation which showed that reducing the levels of SNCA-112 and SNCA-98 isoforms can protect the dopaminergic neurons against harmful effect of neurotoxic agents like rotenone (Cardo et al., 2014; Ma et al., 2013). Likewise, mitochondrial inhibitor rotenone is found to be associated with PD pathophysiology (Tanner et al., 2011). Lewy body related α-synuclein protein is also known to interact with synphilin-1 (Kawamata et al., 2001). Co-expression of α-synuclein and synphilin-1 in cell culture has been shown to result in the formation of

lewy body-like aggregates (Engelender et al., 1999). Additionally, synphilin-1 protein is also susceptible to interaction with different proteins like parkin, SIAH, Dorfin, LRRK2 etc., which certainly indicates its ability to assemble these proteins into a larger complex (Szargel et al., 2008). Parkin protein normally occurs in multiple areas of brain (Beyer et al., 2008b) and being an E3 ubiquitin ligase, it becomes a part of ubiquitin proteasome system and can act on synphilin-1 (Beyer et al., 2008b). Occurrence of seven parkin isoforms and at least eight transcript variants of synphilin-1 have been reported (Beyer et al., 2008b) (Table 3) and it has been suggested that altered expression levels of parkin and synphilin-1 isoforms might be involved in the pathogenesis of LBDs (Humbert et al., 2007). Shorter versions of isoforms of synphilin-1 and parkin might undergo stronger protein-protein interaction than full length protein versions and the non-dissociative nature of synphilin-1-parkin or synphilin1-α-synuclein complexes might play significant role in the preceding steps of LB formation (Beyer et al., 2008b). It has been suggested that synphilin-1 itself may possess the potential to begin the nucleation events during lewy body formation because it is an integral constituent of various synucleinopathy lesions and it has the ability to induce lewy body-like inclusion formation in presence of α-synuclein within cells (Szargel et al., 2008; Engelender et al., 1999; Wakabayashi et al., 2002). A splice variant of synphilin-1, known as synphilin-1A, is also vulnerable to amyloid aggregation (Szargel et al., 2008). Synphilin-1A is also found to be present in lewy bodies of PD patients (Szargel et al., 2008; Eyal et al., 2006). Also, it has been proposed that synphilin-1A can interact with α-synuclein and synphilin-1, recruiting them into aggregates (Szargel et al., 2008). All these studies suggest that synphilin-1A isoform might influence the formation of lewy bodies (Szargel et al., 2008).

2.2.2. Heterogenic nature of Lewy body(LB)

Lewy body entity is known to contain more than 500 other biomolecules (Table 1) of different kinds (Wakabayashi et al., 2007; Xia, 2008). Also, multiple medical severities are observed in PD patients (Fig. 1). These molecules are grouped into different classes which include: (i) LB fibril forming structural elements i.e. α-synuclein and neurofilaments; (ii) Specific proteins that bind to α-synuclein such as agrin, 14-3-3 protein, microtubule-associated protein (MAP)1B, synphilin-1 and tau species; (iii) Synphilin-1-binding proteins, viz. dorfin, parkin, and NUB1; (iv) Elements of ubiquitin proteasome system which contain ubiquitin, ubiquitin activating enzyme (E1), ubiquitin-conjugating enzyme (E2), parkin and dorfin; (v) Proteins involved in different cellular responses like heat-shock proteins, clusterin or apolipoprotein J, torsin A; (vi) Proteins that take part in signal transduction and phosphorylation events, for example, calcium/calmodulin-dependent protein kinase II and cyclin dependent kinase 5; (vii) Cytoskeletal components including microtubule associated protein or MAP1, tubulin and neurofilaments; (viii) Cyclin B and retinoblastoma proteins which are involved in cell cycle process; (ix) Cytoplasmic proteins that diffuse into LBs passively, namely, chromogranin A, tyrosine hydroxylase, amyloid precursor protein and (x) Others non-proteinaceous compounds like lipids (Wakabayashi et al., 2007).

2.2.3. Co-occurrence of Parkinson's disease and other amyloid pathologies

Incidence of other protein misfolding diseases in PD patients is not that uncommon (Izumi et al., 2015; Ezrin-Waters et al., 1985; Rajput et al., 1993) (Table 2). Literature study reveals that PD is also found to co-exist with other amyloid-linked diseases (Izumi et al., 2015; Ezrin-Waters et al., 1985) (Table 2). Cross-interaction between AD and PD is further supported by the fact that the extremely hydrophobic central region of α-synuclein (61–95 amino acid residue) was detected in AD senile plaque before this protein was identified as the major constituent of LB (Beyer et al., 2008a; Ueda et al., 1993). Then it was named as the precursor of non-Aβ component of AD amyloid or NACP (Ueda et al., 1993). Further, AD-linked tau protein is also found to occur in the LB along with α-synuclein and experimental evidence has indicated that both tau and α-synuclein can accelerate polymerization of each other (Wakabayashi et al., 2007; Giasson et al., 2003). An *in vivo* study has also shown the occurrence of α-synuclein in polyQ inclusions in samples collected from HD post-mortem brains and R6/1 mouse model of HD (Chánez-Cárdenas and Vázquez-Contreras, 2012; Tomás-Zapico et al., 2012). Bimolecular fluorescence complementation assay revealed that at the initial steps of coaggregation of huntingtin (Htt, exon 1) and α-synuclein, Htt gets oligomerized with α-synuclein triggering its sequestration in the cytosol (Chánez-Cárdenas and Vázquez-Contreras, 2012; Tomás-Zapico et al., 2012). There are reports in literature which show that patients with diabetes mellitus exhibit risk of incidence of Parkinson's disease (Yang et al., 2017; Sun et al., 2012) (Table 2). In yet another study, viable interaction between amylin and α-synuclein in the β-cells of pancreas has been reported which further links diabetes mellitus with Parkinson's disease or other lewy body diseases (Martinez-Valbuena et al., 2018). All these reports suggest the process of coaggregation as one of the foundational reasons behind the existence of other protein-misfolding diseases in PD patients.

2.3. Coaggregation and cross-seeding in Polyglutamine (Poly Q) diseases

Expansion of cytosine-adenine-guanine(CAG) repeats in translated portion of the related protein results in a series of neurodegenerative pathologies, broadly known as polyglutamine (PolyQ) diseases (Fan et al., 2014), leading to dysfunction and degeneration of neurons with formation of inclusion bodies as characteristic pathological hallmark. PolyQ diseases include nine disorders, namely Huntington's disease (HD); six spinocerebellar ataxias (SCA) types 1, 2, 3, 6, 7 and 17; Spinal and bulbar muscular atrophy (SBMA) and Dentatorubral-pallidoluysianatrophy (DRPLA) (Fan et al., 2014).

2.3.1. Coaggregation and cross-seeding among polyQ proteins

The polyglutamine repeats in normal individuals mostly range from 10 to 35 residues, however, in HD patients the repeat-length becomes more than ˜40 glutamine residues (Lee et al., 2018) (Table 3). An investigation based on mammalian cell lines has revealed that mutant huntingtin protein can trigger the aggregation of wild type huntingtin protein and results in formation of mixed fibrils (Busch et al., 2003). This process was shown to depend on both the polyQ stretch and the flanking amino acid sequence (Busch et al., 2003). These heterologous aggregates of wild-type and mutant huntingtin show more stability and have distinguishable biochemical and morphological characteristics than that of the homologous aggregates produced by only mutant huntingtin (Busch et al., 2003). It is also suggested that this type of coaggregation can also occur in brain of HD patients and can cause pathogenesis due to loss of wild type huntingtin function as it is eliminated from its native environment and trapped in aggregates (Busch et al., 2003). Another interesting *in vitro* experiment has shown that D-polyQ amyloid fibrils can seed aggregation of monomers of L-polyQ proteins and the reverse is also true (Kar et al., 2014). It has been demonstrated that RNA binding proteins are preferentially recruited into polyQ amyloids (Wear et al., 2015). A recent study, based on discrete molecular dynamics simulations, has proposed the molecular mechanism of heterogeneous oligomerization of huntingtin proteins containing shorter and larger polyglutamine tracts (Bonfanti et al., 2019).

2.3.2. Multicomponent nature of huntingtin inclusion bodies

Neuronal intranuclear inclusions (NIIs) contain various proteins apart from the huntingtin proteins (Busch et al., 2003) (Table 1). The inclusion bodies related to HD contain proteins like molecular chaperones, polyQ containing transcription factors like TBP or TATA-binding protein, CBP or CREB-binding protein, ubiquitin and RNA binding protein translocated in liposarcoma (TLS) (Busch et al., 2003; Nucifora, 2001; Huang et al., 1998; Doi et al., 2008; Juenemann et al., 2018). CBP is also found to be sequestered in inclusion bodies in other

polyglutamine diseases like SBMA and SCA3 (McCampbell et al., 2000). Soluble oligomers of huntingtin exon-1 (Httex1) are found to interact with hundreds of different proteins including RNA binding proteins, proteins linked to ribosome biogenesis, transcription and translation related proteins, vesicular transport mediators and cytoskeletal components (Kim et al., 2016). A common character was observed in these interacting proteins is the presence of extended low-complexity sequences (Kim et al., 2016). Some proteins were found to have prion-like domains and have potential for undergoing aggregation in other neurodegenerative diseases (Kim et al., 2016). The insoluble Httex1 inclusion bodies were found to consist of about 85 diverse proteins (Kim et al., 2016).

2.4. Coaggregation and cross-seeding in prion diseases

Prion diseases or transmissible spongiform encephalopathies are one of the deadliest neurodegenerative diseases with clinical features of motor and cognitive malfunctioning caused by infectious proteinaceous particles named as 'prions' (Aguzzi and Calella, 2009; Prusiner, 1982). Human and various other animals acquire this disease through environmental transmission of prion molecules or genetic mutation in the prion gene or in sporadic manner (Ros and Poirier 2004; Aguzzi and Calella, 2009). Conformational changes in the cellular form of prion protein PrP^{C} lead to formation of a protease-resistant and insoluble isoform PrP^{Sc} which can further interact with the normal cellular form and can convert it into PrP^{Sc} leading to its own propagation (Aguzzi and Calella, 2009). Creutzfeldt-Jakob disease (CJD), kuru, fatal familial insomnia (FFI) and Gerstmann-Sträussler-Scheinker (GSS) syndrome are human prion diseases whereas Scrapie, Bovine spongiform encephalopathy, chronic wasting disease etc. are those prion diseases which affect other animals (Aguzzi and Calella, 2009). Pathological hallmark of prion diseases are amyloid plaques labelled with prion antibodies (Ross and Poirier, 2004). Prion amyloids related to diseases are proposed to be heterogeneous in nature consisting of different prion strains or variants (Wickner, 2018).

2.4.1. Cross-seeding and coaggregation phenomenon in prion proteins with protein components

Protein aggregates which belong to protein misfolding diseases other than prion diseases, for example, tau aggregates and polyglutamine aggregates are reported to be internalized by cells in culture (Aguzzi and Calella, 2009; Ren, 2009; Frost et al., 2009). Selective recruitment and misfolding of soluble cytosolic proteins induced by the internalized aggregates possibly suggests that amyloid aggregates of all protein misfolding diseases may act as infectious particles similar to prion molecules, executing as a template for misfolding and recruitment of other native proteins (Aguzzi and Calella, 2009).

Components of cholinergic system are also known to induce aggregation of prion protein *in vitro* and gets recruited into the prion protein fibril, losing its enzymatic property (Torrent et al., 2015). The aggregated form of human prion protein and $A\beta_{42}$ has been extracted from Alzheimer's brain which suggests cross-interactions among these two protein-misfolding diseases (Zou et al., 2011). This is further supported by the presence of Alzheimer's disease and Creutzfeldt-Jakob disease in the same patient (Tsuchiya et al., 2004). Creutzfeldt-Jakob disease is also found to coexist in patients with Parkinson's disease (Ezrin-Waters et al., 1985) (Table 2). Studies also suggest the PrP^{C} protein-mediated uptake of α-synuclein amyloid inside the cell (Aulić et al., 2017) which further indicate possible intermolecular interaction between components of two protein-misfolding diseases.

2.4.2. Coaggregation of prion proteins with non-proteinaceous components

Prion aggregates also contain non-proteinaceous components apart from misfolded prion protein, for example, polysaccharides, nucleic acids and lipids like cholesterol and sphingolipid in small amount (Panza et al., 2008). One study has proved that glycogen can trigger amorphous aggregation of prion protein and can form coaggregates (Panza et al., 2008). Various non-proteinaceous components of prion aggregates are also predicted to behave as molecular scaffold which might facilitate conversion of PrP^{C} to PrP^{Sc} by allowing addition of new PrP^{Sc} molecules in ordered manner (Choi and Priola, 2013; Appel et al., 1999; Dumpitak et al., 2005)

2.5. Coaggregation and cross-seeding in Amyotrophic Lateral Sclerosis (ALS)

ALS is another severe neurodegenerative disease that causes neuromuscular defects due to degeneration of upper and lower motor neurons (Ciryam et al., 2017). Familial ALS is associated with mutation in multiple genes such as SOD1(Superoxide dismutase 1), Alsin and Senataxin which results in different neuropathological subtypes (Ciryam et al., 2017). Each subtype is again related to diverse histologically distinct inclusions consisting of various proteins (Ciryam et al., 2017). These inclusion inhabiting proteins are found to be not related to each other with respect to structure, function, sequence and localization (Ciryam et al., 2017). Numerous protein constituents of inclusion are not even the regular interacting partners of the proteins which are primarily associated with ALS inclusion formation (Ciryam et al., 2017).

2.5.1. Interaction of protein aggregates of ALS and its relation with other diseases

Among various inclusions of ALS related to different mutant proteins, SOD1 aggregates are the one which is thoroughly studied (Ciryam et al., 2017). α-tubulin is known to surround mutant SOD1 aggregates near microtubule organizing centre (unpublished observation as mentioned) (Matsumoto et al., 2005). An *in vivo* study also shows that tubulin acetylation can promote aggregation of mutant SOD1 (Gal et al., 2013). SOD1 mutants are also reported to get accumulated along with the polyalanines (37A) in the same juxtanuclear quality control (JUNQ)-like inclusion (Polling et al., 2014). At least nine human diseases are associated with the proteins containing expanded polyalanine tracts (Shoubridge and Gecz, 2012). However, their aggregation in *in vivo* model is not reported with exception of one protein PABPN1 (Shoubridge and Gecz, 2012). Association of SOD1 mutants and polyalanine tracts in the same inclusion further points towards a probable link between ALS and polyalanine diseases. TDP-43 positive inclusions are also well-known pathological hallmark of ALS. These inclusions are generally characterized as tau-negative (Takeda, 2018). An autopsy study reveals the presence of tau proteins in these inclusions (Takeda, 2018). Further, TDP-43 accumulation is also observed during AD pathogenesis (McAleese et al., 2017). A post-mortem examination of an ALS patient also shows axonal spheroids exhibiting positive result for α-synuclein antibody (McCluskey et al., 2009). There were reports of autopsy cases which prove coexistence of ALS with Parkinson's disease (Izumi et al., 2015). All these reports link ALS with other diseases which may be important for understanding the pathological mechanism of these neurodegenerative diseases.

2.5.2. Heterogenic nature of ALS inclusion bodies

ALS inclusion bodies are proved to be complex heterogeneous entities (Table 1) rather than homogeneous protein aggregates (Bergemalm et al., 2010). Many of these proteins are associated with fundamental processes of cell like transcriptional regulation (e.g. SMAD3) (Ciryam et al., 2017; Nakamura et al., 2008), initiation of translation (e.g. eIF3, eIF4G) (Ciryam et al., 2017; Liu-Yesucevitz et al., 2010; Dormann et al., 2010) and m-RNA transport (e.g. staufen) (Ciryam et al., 2017; Volkening et al., 2009). Proteins involved in other cellular physiological activities like stress granule formation (e.g. TIA1) (Ciryam et al., 2017; Liu-Yesucevitz et al., 2010), endoplasmic reticulum stress (e.g. PDI) (Ciryam et al., 2017; Honjo et al., 2011), vesicle transport (e.g.VCP) (Ciryam et al., 2017; Weisberg et al., 2012)

and antioxidant activity (e.g. Metallothionein, Peroxiredoxin 2) (Ciryam et al., 2017; Kato et al., 1997, 2004) also get recruited within ALS inclusions. Other proteins which are found to be present in ALS aggregates are RNA-binding proteins (e.g. XRN1, ataxin-2) (Ciryam et al., 2017; Volkening et al., 2009; Elden et al., 2010), structural cytoskeletal proteins (e.g.α-tubulin, β-tubulin, vimentin) (Ciryam et al., 2017; Bergemalm et al., 2010; Kato et al., 1997) and metal binding proteins (e.g. S-100, calmodulin) (Ciryam et al., 2017; Kato et al., 1997; Chou et al., 1996).

2.6. Amyloid cross-seeding and coaggregation in oncopathology

Loss of function of the tumour suppressor protein p53 is a characteristic feature of many cancers (Yang-Hartwich et al., 2015). p53 protein is known to regulate apoptosis and its inactivation is considered as one of the foundational reasons for the onset of cancer development (Brown and Attardi, 2005). Formation of both oligomeric and fibrillar structures of amyloid nature has been observed in misfolded p53 proteins (Yang-Hartwich et al., 2015). Coaggregation phenomenon has also been reported in case of p53 molecules (Wang and Fersht, 2015; Forget et al., 2013). In cancer cell lines, oncogenic mutant p53 molecules show coaggregation with wild type p53 and its homologs p63 and p73 (Wang and Fersht, 2015). This type of coaggregation follows trapping mechanism rather than seeding method and may lead to gain of oncogenic function as the functional wild type p53 molecules are trapped in the aggregates (Wang and Fersht, 2015). The mutant and wild type molecules simultaneously unfold and cross react in this process (Wang and Fersht, 2015). Another study has reported the 'Prionoid' character of p53 i.e. aggregated full length and N-terminally truncated form of p53 can penetrate into the cell using macropinocytosis (a pathway for non-specific entrance) and these aggregates show coaggregation with endogenous p53 molecules (Forget et al., 2013). Previous research reports, based on cell model studies, have also shown that in cell culture amino-terminal region of huntingtin can recruit p53 molecules during formation of inclusions (Steffan et al., 2000).

3. Understanding the possible mechanism of amyloid cross-seeding and coaggregation

3.1. Role of intermolecular interactions for driving amyloid cross-seeding

Fundamentally, cross-seeding is considered as a biological event in which amyloid structures made up of one type of protein (homogenous amyloids) can efficiently trigger aggregation of heterogeneous protein species resulting in the formation of heterocomponent amyloids. However, the process of coaggregation of proteins is believed to be an aggregation trap that preferably allows diverse proteins to attach to the sticky amyloid structures, resulting in a coaggregated structure without necessarily refolding into an amyloid structure. Coaggregation process is similar to spontaneous aggregation of single protein in terms of following a "nucleation dependent aggregation" pathway with nucleation or lag phase and polymerization or growth phase (Slepko et al., 2006; Wood et al., 1999; Morales et al., 2013). Fundamental mechanism of cross-seeding process is explained by template assisted growth or oligomer-nucleated conformational induction model (Farmer et al., 2017). Nucleation phase can be defined as the accumulation phase of aggregation initiators like proteins with mutated monomeric form or in partially denatured state and various small sized oligomers during which high energy barrier is overcome, whereas during growth phase seeds recruit similar or dissimilar protein monomers in wild type or mutated form and proceed in a fast and exponential reaction yielding large aggregated deposits (Morales et al., 2013; Farmer et al., 2017). However, the lag phase is reduced in both cross-seeded and self-seeded reactions which make them distinct from the spontaneous aggregation (Morales et al., 2013). Further, in some cases, cross-seeded aggregation reaction shows faster kinetics as observed for the self-seeded aggregation reaction (Dubey et al., 2014). This distinguishable feature of coaggregation reaction is the outcome of the intermolecular interactions between the dissimilar protein molecules which has been studied in oppositely charged coaggregating partners (Oki et al., 2018). In a homegeneous protein solution, aggregation may be restrained by electrostatic repulsion among the protein molecules, however, in a heterogeneous solution, oppositely charged proteins may attract each other by electrostatic interactions which results in partial unfolding of protein species. Exposed hydrophobic surfaces in partially unfolded proptein species is known to promote hydrophobic interaction which facilitates the nucleation and growth phases during protein aggregation (Oki et al., 2018). Mechanism of cross-seeding phenomenon in dissimilar proteins has been proposed by examining the circular dichroism and molecular docking data of cross-seeding potential of $A\beta_{40}$ in triggering aggregation of diverse globular proteins and aromatic amino acids under mimicked physiological conditions (37 °C, pH7.4) (Anand et al., 2018a). Globular proteins exhibit native conformation with exposed charged groups on the surface under such physiological temperature and pH (Anand et al., 2018a). Viable non-covalent interactions between those charged side chains of proteins and β-sheet structures of Aβ amyloids might induce amyloid promoting β-conformation in the interacting proteins (Anand et al., 2018a). Trapping of proteins in their native states may also occur by electrostatic interaction between charged residues of dissimilar interacting partners exposed to the solvent at a higher degree than the buried hydrophobic residues (Anand et al., 2017). It is also possible that preferable trapping of proteins at various fibril growth sites may increase the local concentration of bound proteins which may lead to their molecular self-assembly (Anand et al., 2018a). Further, long intrinsically-disordered segments (≥100 amino acid stretch) of proteins are found to play a significant role in amyloid cross-seeding of polyQ aggregates (Wear et al., 2015). An *in silico* study shows that the intrinsically disordered stretches of the coaggregating globular proteins are mostly found to contain the major residues interacting with β-sheet framework of seeds or aggregates of Aβ peptide. Such information further indicates the importance of the unstructured segments of any protein in determining its ability for co-assembly/coaggregation (Anand et al., 2018a). When intrinsically disordered domain of a protein is recruited into the aggregated structures, such interaction can cause undesirable temporal and spatial functioning of that protein, leading to toxic gain of function (Wear et al., 2015). Increase in the magnitude of both gain of toxic function and loss of essential function due to recruitment of proteins into aggregates would lead to overall cytotoxicity (Wear et al., 2015). Sometimes N-terminal and C-terminal sequences of amyloid proteins are found to be more consistent than other portions of the amyloid proteins (Luo et al., 2016). So, it has been proposed that these regions might have the capability of inducing cross-interaction for many amyloid proteins (Luo et al., 2016). Also, in solution, most of the amyloid proteins exhibit heterogeneous conformations often with a remarkable flexible loop considered as promiscuous binding site and an important conformational feature for their cross-interaction property (Luo et al., 2016).

Examination of the molecular interaction between the amylin and cross-β structure of the $A\beta_{42}$ shows strong non-covalent interactions between them (Fig. 3). Further, the interacting residues of the amylin protein were found to occur mostly within the disordered stretches of its sequence, suggesting that intrinsically disordered regions of a protein may possibly drive the initiation of the recruiting of proteins into the β-amyloid aggregates. *In vitro* study on the cross-seeding ability of the $A\beta_{40}$ has revealed that $A\beta_{40}$ fibrils can trigger aggregation of diverse globular proteins including insulin (Anand et al., 2018a). The docking analysis of Aβ aggregates and a diabetes linked protein amylin also shows feasible molecular interactions between them (Fig. 3). All these reports suggest a possible link between type II diabetes and the pathophysiology of AD and PD. It is further justified by the literature survey which shows co-occurrence of these diseases within the same patients (Table 2). As discussed in the previous section, aggregates of

IAPP is also found to be associated with a number of proteins such as apolipoprotein E, heparan sulfate proteoglycans, serum amyloid p component (Table 1). Again, a recent study shows formation of the multicomponent 'protein corona' formed by association of heterogeneous proteins with the aggregates of the IAPP amyloids (Pilkington et al., 2018).

3.2. Relevance of the sequence and the conformation of proteins during heterogeneous amyloid formation

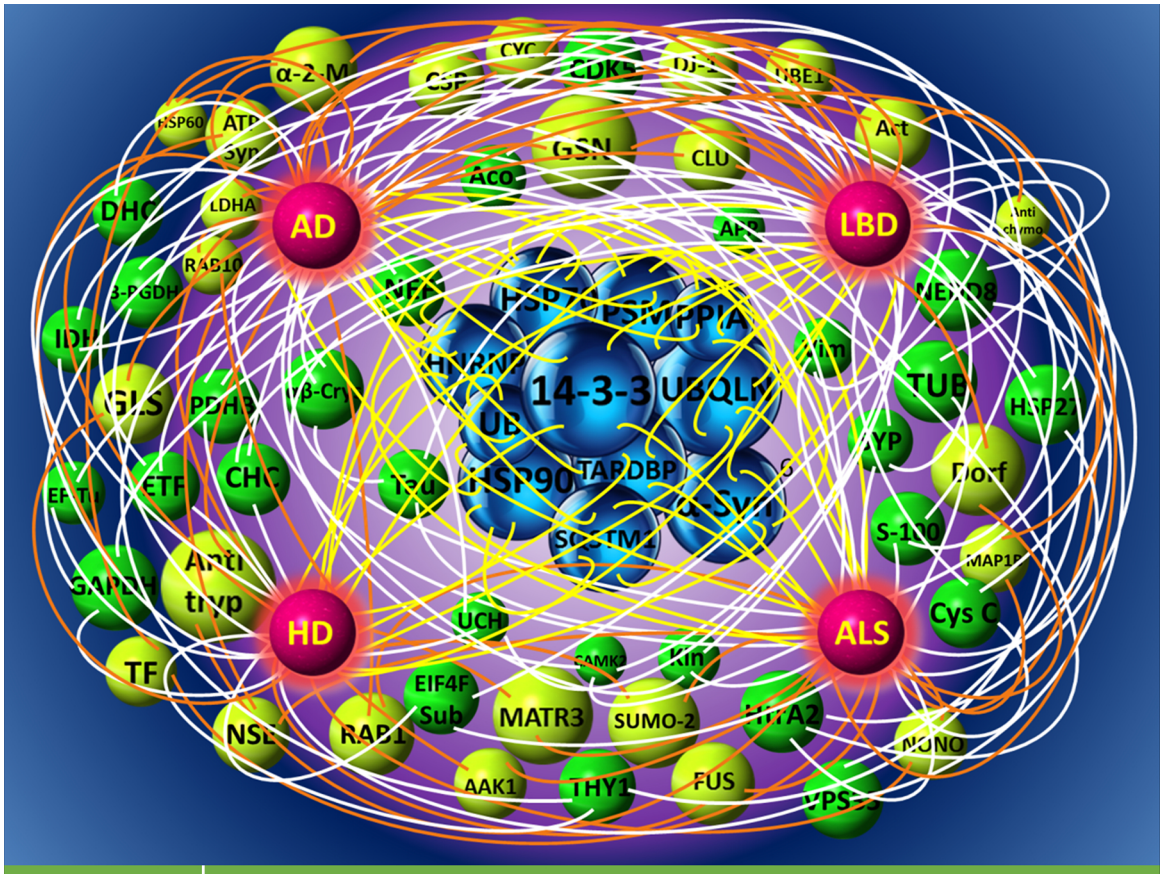
Fundamentally, the nature of the amino acid sequence of proteins has been considered as one of the criteria to determine their ability to coaggregate or to induce amyloid cross-seeding (Dubey et al., 2014; Wright et al., 2005). Aggregation studies on immunoglobin domains has shown that coaggregating partners with higher sequence similarity (more than about 70%) have been recognized as more efficacious cross-seeding or co-polymerizing pairs than those having less (30–40%) or no sequence similarity (Wright et al., 2005). However, there are plenty of examples of coaggregation experiments which prove that proteins with negligible sequence similarity can undergo rapid coaggregation and can trigger amyloid cross-seeding efficiently than that of the self-seeding (Dubey et al., 2014; Anand et al., 2018a). Cross-seeding study conducted at physiological temperature and pH has shown more efficient aggregation of globular proteins in the presence of Aβ-fibril than in its absence (Anand et al., 2018a) suggesting the ability of Aβ-fibrils to trap diverse proteins and to trigger coaggregation/cross-seeding reactions efficiently. Recent studies have also revealed favourable co-oligomerization of $A\beta_{42}$ and α-synuclein (Iljina et al., 2018), however, these interacting species show lower sequence similarity. Cross-seeding mechanism may also be important in case of transmission of pathological molecules related to protein-misfolding diseases. A recent study has proved that Aβ pathology can be transmitted to human during neurosurgery and can develop cerebral amyloid angiopathy even if those individuals do not carry the pathogenic mutation associated with early development of Aβ pathology (Jaunmuktane et al., 2018). This again suggests that cross-seeding event may be a probable transmission mechanism of Aβ pathology in patients (Jaunmuktane et al., 2018). Likewise, cross-seeding can be bidirectional i.e. both the aggregates can influence aggregation of each other or unidirectional (Farmer et al., 2017). Baskakov and Makarava (Makarava and Baskakov, 2012) have proposed a "deformed templating" mechanism, where amyloid structures with one type of cross-β arrangement can initiate the formation of the amyloid structures having a different pattern of cross-β structure. It has also been suggested that this conformational switching can yield hybrid fibrils (Makarava and Baskakov, 2012). Such proposed "deformed templating" mechanism predicts that abnormal PrP conformers can trigger the onset of PrP^{Sc} formation de novo (Makarava and Baskakov, 2012). More importantly, this process involves alteration of the cross-β folding pattern from PrP type to PrP^{Sc} specific folding pattern (Makarava and Baskakov, 2012). Usually, seeding or cross-seeding event during amyloid aggregation is believed to be driven by the interaction between H-bond acceptors and donors located on the fibril growth sites (Kar et al., 2014). Wetzel's group has shown the ability of L-polyQ fibrils to cross-seed amyloid formation by D-polyQ peptides both in cell and *in vitro* systems (Kar et al., 2014). It was proposed that the geometric feasibility of a D, L antiparallel β-sheet motif exists despite fundamentally altered side chain topologies (Kar et al., 2014). Recent research reports have revealed that metabolite generated amyloid-like nanostructures can induce amyloid cross-seeding, leading to aggregation of diverse proteins (Anand et al., 2017, 2018b; Anand, 2019). Such studies have proposed that protein monomers may bind to lateral sites on the amyloid-like fibrillar entities and such binding event may possibly enhance the ability of the docked proteins to initiate the formation of new amyloid structures (Anand, 2019). In a recent study by Davis's group (Pilkington et al., 2018), it is hypothesized that amyloid aggregates might be forming a protein corona similar to surface-corona observed in chemically synthesized nanoparticles. The same study has proposed the existence of both outer "soft corona" and inner "hard corona" (Pilkington et al., 2018). Proteins having lower binding affinity are predicted to form the outer layer and the set of proteins having higher binding affinity are expected to remain in the inner hard-corona (Pilkington et al., 2018).

Understanding the energetic associated with the process of amyloid cross-seeding or coaggregation demands extensive research works involving both computational and experimental approaches. In an *in vitro* study, it has been shown that the coaggregation process of mixed protein monomers was found to be faster than the kinetics of the individual protein aggregation reactions (Dubey et al., 2014). Such data suggest that heterogenous amyloid formation may be thermodynamically more favourable than the process of homogenous amyloid formation. A recent review by Mezzenga et al. have discussed both permissible and prohibited morphological transitions among different amyloid polymorphs like twisted ribbon, helical ribbon, nanotube and crystals (Adamcik and Mezzenga, 2018). It is believed that the funnel of the energy landscape for off-pathway folding may possibly split into comparative minima where amyloid crystals occupy the lowest energy states (Adamcik and Mezzenga, 2018). Structural diversity at the mesoscopic level as well as molecular polymorphism at the atomic level have been discussed in various research reports (Adamcik and Mezzenga, 2018). Structural examination of two pathogenic amyloids extracted from the patients suffering from systemic amyloidosis has revealed both the structural polymorphism and structural similarity in the amyloid samples (Adamcik and Mezzenga, 2018). However, future investigations using high-resolution X-ray or NMR techniques on amyloid fibrils consisting of multiple proteins would be necessary for the mechanistic understanding of heterocomponent amyloid formation and its biological relevance.

4. Conclusions

In this review we attempted to figure out the pathological significance of heterocomponent nature of amyloid deposits observed in different protein misfolding diseases and to understand its relevance to amyloid cross-seeding and co-recruitment. Our analysis has revealed the occurrence of amyloid cross-seeding or coaggregation as a fundamental common event during the growth of amyloid structures irrespective of the disease types (as schematically proposed in Fig. 4). We compared the protein constituents of the aggregates of four major protein misfolding diseases, viz. AD, PD, HD and ALS and found that at least eleven proteins are there which are found to be present in the aggregates of all the four devastating neurodegenerative diseases (Fig. 2, Table 4). Further, we were interested to see if the loss of function or the direct pathogenicity linked to these recruited proteins is also observed in the pathological symptoms of amyloid diseases. Interestingly, examination of various symptoms observed for each protein showed a direct correlation with the primary as well as secondary symptoms seen in amyloid diseases (Table 4). Hence, all those loss of functions were likely to cause pathology in patients when these proteins are trapped inside the aggregates. Furthermore, examination of the diverse symptoms found in these neurodegenerative disorders, as listed in Fig. 1 certainly points to the possible correlation between heterogeneity of amyloid hallmarks and the magnitude of diverse disease symptoms. It may also be concluded that the direct aggregation promoting functions of these proteins could be one of the reasons behind the formation of those pathological aggregates. Hence, we propose that the onset of multitude of diverse severities observed in patients suffering from neurodegenerative diseases may possibly be related to the co-recruited proteins apart from the major hallmark amyloidogenic proteins (Table 4, Fig. 2, Fig. 4).

This review also revealed the possible susceptibility of patients of one protein-misfolding disease to other protein misfolding diseases. Effect of monomeric, oligomeric or higher order aggregated species of



Disease combination*	Common protein constituents of pathological aggregates **
AD+LBD+HD+ALS	14-3-3 Protein (14-3-3), Heat-shock protein 90 (HSP90), α-Synuclein (α-Syn), Heat-shock protein 70 (HSP70), Proteasome (PSM), Ubiquitin (UB), Heterogeneous nuclear ribonucleoprotein (HNRNP), Peptidylprolyl isomerase A (PPIA), TAR DNA-binding protein-43 (TARDBP), Sequestosome 1 (SQSTM1), Ubiquilin (UBQLN)
AD+LBD+HD	Ubiquitin C-terminal hydrolase (UCH), Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Clathrin heavy chain (CHC), Dynein heavy chain (DHC), Electron transfer flavoprotein (ETF), Isocitrate dehydrogenase [NADP] mitochondrial (IDH), Pyruvate dehydrogenase E1 component subunit beta mitochondrial (PDHB), D-3-phosphoglycerate dehydrogenase (3-PGDH), Vacuolar protein sorting-associated protein 35 (VPS35), Tu translation elongation factor mitochondrial (EF-Tu),Thy-1 cell surface antigen (THY1)
AD+LBD+ALS	αβ-Crystallin (αβ-Crys), Amyloid precursor protein (APP), Heat-shock protein 27 (HSP27), Neurofilaments (NEF), Synaptophysin (SYP), Tau, Tubulin (TUB), Calcium/calmodulin-dependent protein kinase II (CAMK2), Aconitase (Aco), Cystatin C (Cys C), Kinesin (Kin), S-100, Vimentin (Vim), Cyclin-dependent kinase 5 (CDK5), NEDD8, Omi/HtrA2
AD+HD+ALS	Subunit of the eIF4F complex (EIF4F sub)
AD+LBD	α2-Macroglobulin (α-2-M), Chondroitin sulfate proteoglycans (CSP), Clusterin (CLU), Cytochrome c (CYC), DJ-1, Gelsolin-related amyloid protein Finnish type (GSN), Heat-shock protein 60 (HSP60), Ubiquitin activating enzyme E1 (UBE1)
AD+HD	ATP synthase subunit alpha mitochondrial (ATP Syn), Glutaminase kidney isoform (GLS), L-Lactate dehydrogenase A (LDHA), Ras-related protein Rab-10 (RAB10)
AD+ALS	α-Actin (Act), Neuron-specific enolase (NSE), Ras-related protein Rab-1 (RAB1), Antitrypsin (Anti tryp), α1-Antichymotrypsin (Anti chymo), Transferrin (TF)
LBD+ALS	Dorfin (Dorf), Microtubule-associated protein 1B (MAP1B), Superoxide dismutase 1 (SOD1)
HD+ALS	RNA-binding protein FUS (FUS), AP2-associated protein kinase 1 (AAK1), Matrin-3 isoform (MATR3), Non-POU domain-containing octamer-binding protein (NONO), Small ubiquitin-related modifier 2 (SUMO-2)

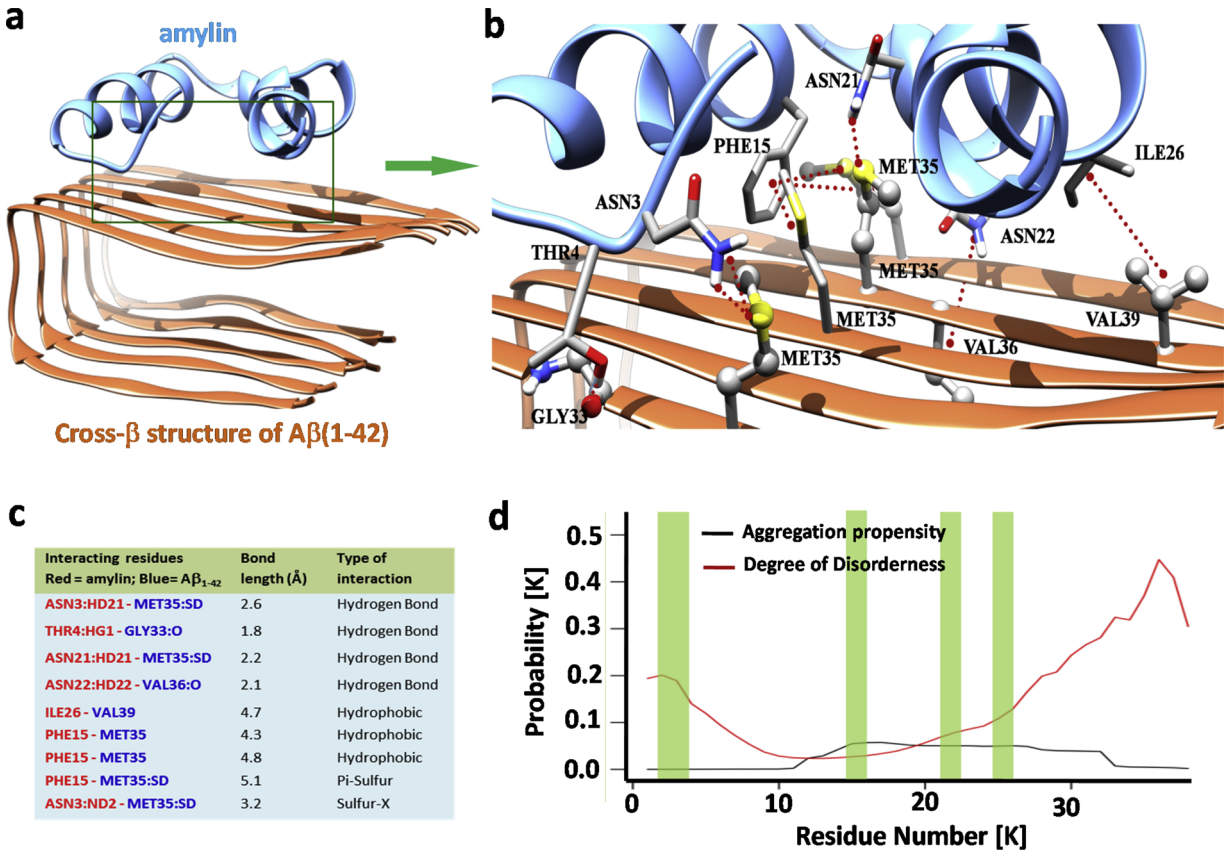
(caption on next page)

Fig. 2. Schematic representation of the interlinked protein components of amyloid entities of different neurodegenerative diseases:*Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS). Lower panel displays the list of common proteins found in the above mentioned diseases. ** Short names used for the common protein constituents in the diagram are mentioned within the parentheses. The blue colored spheres are denoting the proteins present in the aggregates of four neurodegenerative diseases [AD + LBD + HD + ALS] (Alves-Rodrigues et al., 1998; Carra et al., 2005; Ciryam et al., 2017; Kuusisto et al., 2002; Liao et al., 2004; Mah et al., 2000; Tomás-Zapico et al., 2011; Wakabayashi et al., 2007; Wear et al., 2015; Wyttenbach et al., 2000; Xia, 2008). The green colored spheres are denoting the proteins present in the aggregates of three neurodegenerative diseases: [AD + LBD + HD] (Liao et al., 2004; Wakabayashi et al., 2007; Wear et al., 2015; Wu et al., 2007; Xia, 2008); [AD + LBD + ALS] (Bergemalm et al., 2010; Ciryam et al., 2017; Furuta et al., 1995; Iwatsubo et al., 1991; Kawamoto et al., 2010; Liao et al., 2004; Mori et al., 2005; Wakabayashi et al., 2007; Westerlund et al., 2011; Xia, 2008); [AD + HD + ALS] (Ciryam et al., 2017; Liao et al., 2004; Wear et al., 2015). The yellow colored spheres indicate the proteins present in the aggregates of two neurodegenerative diseases: [AD + LBD] (Liao et al., 2004; Wakabayashi et al., 2007); [AD + HD] (Liao et al., 2004; Wear et al., 2015); [AD + ALS] (Bergemalm et al., 2010; Ciryam et al., 2017; Liao et al., 2004); [LBD + ALS] (Bergemalm et al., 2010; Ciryam et al., 2017; Wakabayashi et al., 2007); [HD + ALS] (Bergemalm et al., 2010; Ciryam et al., 2017; Wear et al., 2015).

one type of protein on the aggregation propensity of other protein types seems to be an important factor in the mechanism of amyloid growth. Hence, aggregates accumulating in one type of protein misfolding disease may trigger aggregation of other amyloidogenic proteins or peptides. This assumption is further supported by co-existence of more than one protein misfolding diseases in the same individual (Moss et al., 1988; Tsuchiya et al., 2004; Miyazono et al., 1992; Janson et al., 2004; Sims-Robinson et al., 2010; Izumi et al., 2015; Panegyres et al., 2013; Rubio et al., 1996; Tada et al., 2012; Bereznai et al., 2010; Kapur and Goldman, 2012; Ikeda et al., 1996; Singh et al., 2017; Park et al., 2015; Brenowitz et al., 2015; Ezrin-Waters et al., 1985; Rajput et al., 1993). Even an autopsy case study of a 79 years old sporadic Creutzfeldt–Jakob disease patient reports co-occurrence of Alzheimer pathology and inclusion bodies of α-Synuclein which links minimum three protein misfolding diseases together (Vital et al., 2007). In case of polyQ aggregates, there is evidence of recruitment of proteins related to other neurodegenerative diseases among which the biasedness towards proteins associated with amyotrophic lateral sclerosis (ALS) is more pronounced (Wear et al., 2015).

Regarding the biological relevance of amyloid cross-seeding, it has been revealed that the consumption of amyloid-like nanostructures could result in severe health consequences (Solomon et al., 2007; Raynes et al., 2014; Cao and Mezzenga, 2019). Interestingly, Solomon et al. (2007), based on mouse-model experiments, have revealed that consumption of Foie gras (amyloid containing food) can efficiently promote the protein amyloidosis in the mouse population (Solomon et al., 2007).

Moreover, multiple pathological symptoms are found to be associated with these neurodegenerative diseases, for example, oxidative stress, mitochondrial dysfunction etc. (Bhat et al., 2015; Zhang et al., 2009). Pathological hallmarks of these diseases such as plaques, lewy bodies or inclusions show diverse cellular proteins within their higher



Interacting residues Red = amylin; Blue= $A\beta_{1-42}$	Bond length (Å)	Type of interaction
ASN3:HD21 - MET35:SD	2.6	Hydrogen Bond
THR4:HG1 - GLY33:O	1.8	Hydrogen Bond
ASN21:HD21 - MET35:SD	2.2	Hydrogen Bond
ASN22:HD22 - VAL36:O	2.1	Hydrogen Bond
ILE26 - VAL39	4.7	Hydrophobic
PHE15 - MET35	4.3	Hydrophobic
PHE15 - MET35	4.8	Hydrophobic
PHE15 - MET35:SD	5.1	Pi-Sulfur
ASN3:ND2 - MET35:SD	3.2	Sulfur-X

Fig. 3. Rigid body protein-protein docking data between $A\beta_{1-42}$ fibril and the native structure of human amylin protein performed by ClusPro web server (Kozakov et al., 2017). (a) The docked complex of Human amylin (PDB ID: 2L86) (Nanga et al., 2011) with β-sheet structure of $A\beta_{1-42}$ (PDB ID:2BEG) (Lührs et al., 2005). Binding affinity energy = -8.83 kcal/mol^{-1}. (b) List of viable contacts between of Human amylin (PDB ID: 2L86) and β-sheet structure of $A\beta_{1-42}$ (PDB ID:2BEG). (c) Sequence analysis of human amylin using PASTA 2.0 (Walsh et al., 2014). Red colored curves indicate the disorderness profile for human amylin and the green shaded regions indicate the residues interacting with β-sheet structure of $A\beta_{1-42}$ (PDB ID: 2BEG).

Table 4
Selected list of pathogenicity and metabolic defects related to diverse proteins found in the aggregated deposits of four major neurodegenerative diseases*.

Proteins	Related pathogenicity, metabolic defects	Diseases
14-3-3 protein	Its loss of function leads to learning and memory impairment (Steinacker et al., 2011; Philip et al., 2001; Skoulakis and Davis, 1996)	Alzheimer's Disease (AD) (Jahn, 2013; Hyman et al., 1984), Parkinson's Disease (PD) (Reitan and Boll, 1971; Frank et al., 2004), Huntington's Disease (HD) (Hodges et al., 1990; Heindel et al., 1988), Amyotrophic Lateral Sclerosis (ALS) (Phukan et al., 2012)
	Involved in axonal transport (Steinacker et al., 2011; Erickson and Moore, 1980)	Alzheimer's Disease (AD) (Vicario-Orri et al., 2015), Parkinson's Disease (PD) (Chu et al., 2012), Huntington's Disease (HD) (Sinadinos et al., 2009), Amyotrophic Lateral Sclerosis (ALS) (Ikenaka et al., 2012)
	Plays role in protection against oxidative stress (Steinacker et al., 2011)	Alzheimer's Disease (AD) (Huang et al., 2016), Parkinson's Disease (PD) (Hwang, 2013), Huntington's Disease (HD)(Kumar and Ratan, 2016), Amyotrophic Lateral Sclerosis (ALS) (Barber et al., 2006)
	Promotes protein aggregation	Alzheimer's Disease (AD) (Steinacker et al., 2011; Hernández et al., 2004)
	Regulatory role in seizures (Steinacker et al., 2011; Schindler et al., 2006)	Alzheimer's Disease (AD) (Pandis and Scarmeas, 2012), Parkinson's Disease (PD) (Gruntz et al., 2018), Huntington's Disease (HD) (Cloud et al., 2012)
α-Synuclein	Toxic oligomers, oxidative stress, lysosome impairment, mitochondrial dysfunction	Alzheimer's Disease (AD) (Crews et al., 2009), Parkinson's Disease (PD) (Ingelsson, 2016; Dias et al., 2013; Bourdenx et al., 2014; Cho et al., 2010)
	Worsening of disease phenotype, onset of tremors, weight loss, autophagy impairment, inducing Huntingtin aggregation, early motor phenotype of HD	Huntington's Disease (HD) (Corrochano et al., 2011; Furlong et al., 2000; Tomás-Zapico et al., 2011; Corrochano et al., 2012)
	Promotion of oligomerization	Amyotrophic Lateral Sclerosis (ALS) (Helferich et al., 2015), Parkinson's Disease (PD) (Ingelsson, 2016)
Heat-shock protein 90	Loss of memory and synaptic dysfunction	Alzheimer's Disease (AD) (Wang et al., 2017)
	Improvement of cognitive deficiency	Alzheimer's Disease (AD) (Zhang et al., 2018)
	Prevention of TDP-43 clearance	Amyotrophic Lateral Sclerosis (ALS) (Jinwal et al., 2012)
	Promoting protein aggregation	Alzheimer's Disease (AD) (Tortosa et al., 2009; Luo et al., 2010), Parkinson's Disease (PD) (Falsone et al., 2009)
	Prevention of mutant huntingtin degradation by proteasome	Huntington's Disease (HD) (Baldo et al., 2012)
Heat-shock protein 70	Prevention of apoptosis and dopaminergic neuronal loss	Parkinson's Disease (PD) (Auluck et al., 2002; Turturici et al., 2011; Dong et al., 2005; Nagel et al., 2008)
	Protection from α-Synuclein induced cellular toxicity	Parkinson's Disease (PD) (Klucken et al., 2004)
	Reduce the effect of seizures (Hu et al., 2018)	Alzheimer's Disease (AD) (Pandis and Scarmeas, 2012), Parkinson's Disease (PD) (Gruntz et al., 2018), Huntington's Disease (HD) (Cloud et al., 2012)
	Protection of motoneurons	Amyotrophic Lateral Sclerosis (ALS) (Gifondorwa et al., 2007)
	Inhibition of protein aggregation	Alzheimer's Disease (AD) (Evans et al., 2006), Parkinson's Disease (PD) (Roodveldt et al., 2009), Amyotrophic Lateral Sclerosis (ALS) (Bruening et al., 1999), Huntington's Disease (HD) (Guzhova et al., 2011)
	Delayed loss of body weight	Huntington's Disease (HD) (Hansson et al., 2003)
Ubiquitin-Proteasome	Degradation of misfolded proteins (Ciechanover and Brundin, 2003; Dantuma and Bott, 2014)	Alzheimer's Disease (AD) (Morawe et al., 2012), Parkinson's Disease (PD) (Cook et al., 2012), Huntington's Disease (HD) (Koyuncu et al., 2017), Amyotrophic Lateral Sclerosis (ALS) (Webster et al., 2017)
	DNA repair (Dantuma and Bott, 2014; Vlachostergios et al., 2009)	Alzheimer's Disease (AD) (Coppedè and Migliore, 2009), Parkinson's Disease (PD) (Sepe et al., 2016), Huntington's Disease (HD) (Shiwaku and Okazawa, 2015), Amyotrophic Lateral Sclerosis (ALS) (Coppedè, 2011)
	Autophagy (Dantuma and Bott, 2014; Kraft et al., 2010)	Alzheimer's Disease (AD) (Zare-shahabadi et al., 2015), Parkinson's Disease (PD) (Lynch-Day et al., 2012), Huntington's Disease (HD) (Martin et al., 2015), Amyotrophic Lateral Sclerosis (ALS) (Ramesh and Pandey, 2017)
Heterogeneous nuclear ribonucleoprotein	Loss of function results into increased level of secreted Aβ, impaired primary neuron with loss of dendrites, loss of memory, learning impairment	Alzheimer's Disease (AD) (Donev et al., 2007; Berson et al., 2012)
	Induction of mitochondrial dysfunction (Park et al., 2015b)	Alzheimer's Disease (AD) (Cho et al., 2010; Knott et al., 2008), Parkinson's Disease (PD) (Cho et al., 2010; Knott et al., 2008), Huntington's Disease (HD) (Cho et al., 2010; Knott et al., 2008), Amyotrophic Lateral Sclerosis (ALS) (Knott et al., 2008)
Peptidylprolyl isomerase A	Plays role in the dysfunction of Blood-brain barrier with the help of apolipoprotein E4 (Bell, 2012)	Alzheimer's Disease (AD) (Zipser et al., 2007; Zlokovic, 2011)
	Motoneuronal cell death	Amyotrophic Lateral Sclerosis (ALS) (Tanaka et al., 2011)
TAR DNA-binding protein-43	Inclusion formation	Alzheimer's Disease (AD) (Josephs et al., 2014; Gao et al., 2018; Josephs et al., 2016), Amyotrophic Lateral Sclerosis (ALS) (Gao et al., 2018)
	Regulates cell death	Huntington's Disease (HD) (Tauffenberger et al., 2012)
	Axonal transport disruption (Gao et al., 2018)	Alzheimer's Disease (AD) (Vicario-Orri et al., 2015), Parkinson's Disease (PD) (Chu et al., 2012), Huntington's Disease (HD) (Sinadinos et al., 2009), Amyotrophic Lateral Sclerosis (ALS) (Ikenaka et al., 2012)
	Dysfunction of mitochondria (Gao et al., 2018)	Alzheimer's Disease (AD) (Cho et al., 2010; Knott et al., 2008), Parkinson's Disease (PD)(Cho et al., 2010; Knott et al., 2008), Huntington's Disease (HD) (Cho et al., 2010; Knott et al., 2008), Amyotrophic Lateral Sclerosis (ALS) (Knott et al., 2008)
	Neuronal loss	Parkinson's Disease (PD) (Gao et al., 2018; Markopoulou et al., 2008)
	Increases disease duration in a significant manner	Alzheimer's Disease (AD) (Uryu et al., 2008)

(*continued on next page*)

Table 4 (*continued*)

Proteins	Related pathogenicity, metabolic defects	Diseases
Sequestosome 1	Regulates ubiquitin-proteasome mediated protein degradation (Wooten et al., 2006)	Alzheimer's Disease (AD) (Morawe et al., 2012), Parkinson's Disease (PD) (Cook et al., 2012), Huntington's Disease (HD) (Koyuncu et al., 2017), Amyotrophic Lateral Sclerosis (ALS) (Webster et al., 2017)
	Modulates autophagy (Wooten et al., 2006)	Alzheimer's Disease (AD) (Zare-shahabadi et al., 2015), Parkinson's Disease (PD) (Lynch-Day et al., 2012), Huntington's Disease (HD) (Martin et al., 2015), Amyotrophic Lateral Sclerosis (ALS) (Ramesh and Pandey, 2017)
	Absence of its expression induces tau pathology	Alzheimer's Disease (AD) (Salminen et al., 2012)
	Direct genetic role in degeneration of motor neuron	Amyotrophic Lateral Sclerosis (ALS) (Fecto et al., 2011)
Ubiquilin**	Loss of function related to juvenile and adult onset of neurodegenerative disease	Amyotrophic Lateral Sclerosis (ALS) (Williams et al., 2012; Deng, 2011)
	Autophagy (Zhang et al., 2014)	Huntington's Disease (HD) (Martin et al., 2015), Amyotrophic Lateral Sclerosis (ALS) (Ramesh and Pandey, 2017), Alzheimer's Disease (AD) (Zare-shahabadi et al., 2015), Parkinson's Disease (PD) (Lynch-Day et al., 2012)
	Regulation of presenilin protein linked to early-onset of neurodegenerative disease	Alzheimer's Disease (AD) (Mah et al., 2000)
	Modulation of ubiquitin-proteasome mediated protein degradation	Amyotrophic Lateral Sclerosis (ALS) (Deng, 2011)

*The pathogenicity described here is based on the loss of function of these proteins in mutant studies in different animal/cell models which are found to be similar to the pathological characteristics of these neurodegenerative diseases. These proteins are also found to have different physiological functions some of which are found to be hampered in these amyloid linked diseases in patients or in the animal models.
Direct pathophysiological properties of these proteins related to protein aggregation diseases. Indication of pathologies when these proteins are overexpressed, downregulated or deleted in the neurodegenerative disease animal models. Neurodegenerative pathological symptoms rescued when inhibitors against these proteins are used. Pathologies observed in animal model system when inducers of these proteins are used.
** Although Ubiquilins are related to the ubiquitin-proteasome system (Zhang et al., 2014; Marín, 2014), they are markedly found to be present in the aggregates of all the major type of amyloid linked neurodegenerative diseases (Mah et al., 2000; Wear et al., 2015; Ciryam et al., 2017). So we have mentioned its functional significance separately.

order entities which might explain the appearance of secondary pathological symptoms. Hence, it seems there exists a direct correlation between multiple pathological symptoms and diverse cellular proteins in the aggregates of protein misfolding diseases. Coaggregation phenomenon can also be utilized as an inhibition strategy as recently shown by Gallardo et al. (Gallardo, 2016). This study designed a short amyloidogenic protein fragment which triggered the aggregation of VEGFR2 which is not an amyloidogenic protein, thus inhibiting the function of VEGFR2 and reducing VEGFR2 associated tumour growth in mice (Gallardo, 2016) . Further, if coaggregation process is found to be associated with any disease pathology then inhibitory strategies should be designed to nullify the effect of coaggregation or cross-seeding. Coaggregation inhibition of oppositely charged proteins is studied in case of globular proteins (Oki et al., 2018). Though these coaggregation

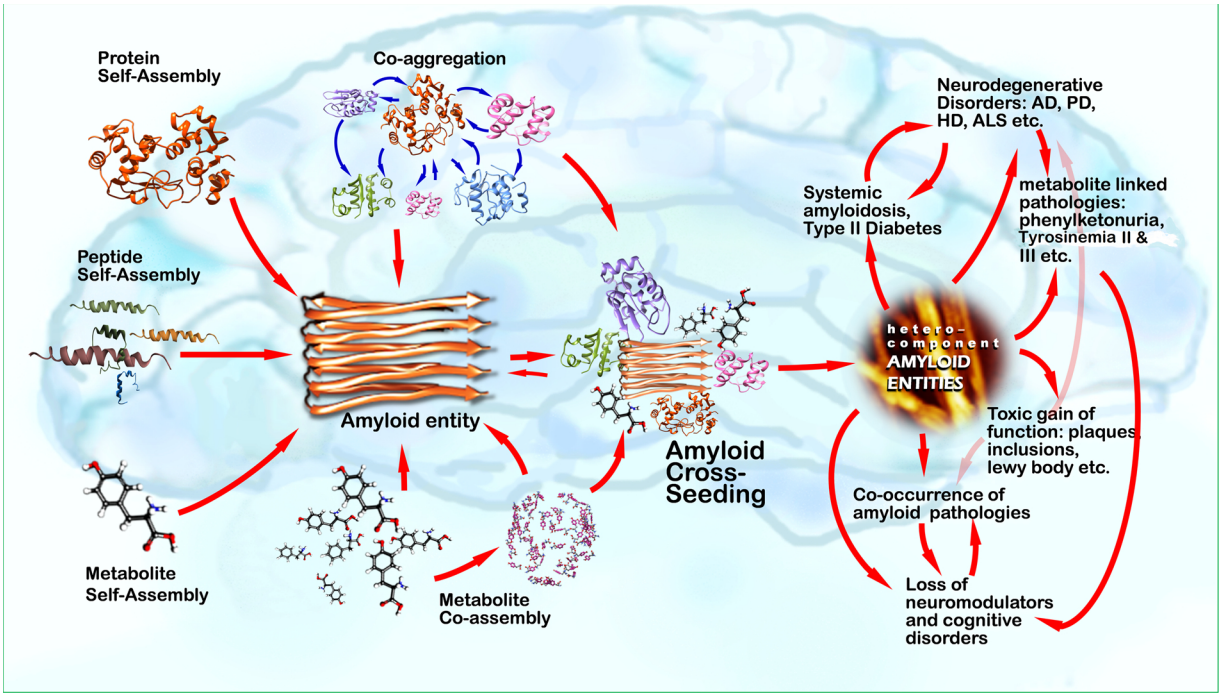


Fig. 4. Schematic representation of the occurrence of amyloid cross-seeding and coaggregation and its relevance to both amyloid formation and possible diverse consequences. The representative protein structures of proteins and metabolites shown here are of lysozyme (PDB ID: 193 L), insulin (PDB ID:1TRZ), Myoglobin (PDB ID: 1DWR), $A\beta_{1\text{-}42}$ (PDB ID:2BEG) and tyrosine (PubChem CID:6057).

inhibitors are mostly validated for food proteins (Oki et al., 2018), such inhibitors or discovery of other molecules with similar properties inspire future investigation to strategically prevent coaggregation/co-assembly events of disease associated proteins. Extensive *in vitro* and *in vivo* studies may help us to identify the major proteomic components of the pathological aggregates apart from hallmark proteins and such information may be relevant to diverse pathologies of the patients at different clinical stages. For aggregation related diseases, much attention is focused on aggregates of single marker protein. However, it seems that knowledge on the presence of other protein constituents in the amyloid hallmarks including plaques, tangles and inclusions is important for both diagnosis and therapeutic approaches. Mechanistic understanding of the nature of heterocomponent amyloid formation seems to be important for the future research on the development of therapeutic strategies against amyloid-linked pathologies. For example, inhibitors designed against heterogeneous protein aggregation (Dubey et al., 2017) may have higher efficacy in protecting the amyloid-induced cytotoxicity as compared to the effect of inhibitors found against homogenous protein aggregation. Though some compounds such as eugenol are known to possess the potential for inhibiting both coaggregation and individual aggregation of proteins (Dubey et al., 2017), further investigation is needed to clarify the protective effect of amyloid inhibitors against cytotoxic effect of both heterogeneous and homogenous aggregates. Similarly, knowledge on the protein components present in the amyloid hallmarks could inspire indirect strategies to prevent or to control the vital proteins/peptides from being recruited into the amyloid structures. Furthermore, strategies to promote disassembly of heterocomponent amyloids may possibly prove to be more beneficial than the strategies developed for disassembly of homogenous aggregates. Gaining greater insights from the research investigations on amyloid cross-seeding and protein coaggregation/co-recruitment certainly seems to raise new dimensions to our understanding of amyloidogenesis mechanism.

Declaration of Competing Interest

The authors declare no competing financial interest.

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