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Review

Unravelling protein aggregation as an ageing related process or a neuropathological response

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ABSTRACT

Protein aggregation is normally associated with amyloidosis, namely motor neurone, Alzheimer's, Parkinson's or prion diseases. However, recent results have unveiled a concept of gradual increase of protein aggregation associated with the ageing process, apparently not necessarily associated with pathological conditions. Given that protein aggregation is sufficient to activate stress-response and inflammation, impairing protein synthesis and quality control mechanisms, the former is assumed to negatively affect cellular metabolism and behaviour. In this review the state of the art in protein aggregation research is discussed, namely the relationship between pathology and proteostasis. The role of pathology and ageing in overriding protein quality-control mechanisms, and consequently, the effect of these faulty cellular processes on pathological and healthy ageing, are also addressed.

1. Introduction

Proteins are synthesized as linear chains, but, to be functional, most require a three-dimensional structure, termed the native fold. This fold is achieved through a series of weak interactions between different amino acids, in an error-prone process, due to all the possible conformations that any given amino acid sequence can have (Brockwell and Radford, 2007). Moreover, under some conditions, proteins risk unfolding, consequently exposing otherwise protected hydrophobic domains, which are prone to triggering their aggregation. This process of aggregation is characteristic of many disease states, including several neuropathologies, such as Alzheimer's (AD), Parkinson's (PD) diseases or systemic amyloidosis (Table 1).

Amyloidoses are characterised by the deposition of aggregates, either in intracellular inclusions or in extracellular plaques (amyloid), composed by a specific peptide or protein, varying with respect to the different diseases (Eisele et al., 2015; Knowles et al., 2014). Even though aggregating proteins and peptides have various properties and structures, amyloid fibrils are structurally conserved, with a characteristic increase of beta structure protein/peptide conformations that typically bind dyes like thioflavin T and Congo Red. As mentioned, several pathologies are associated with protein misfolding and aggregation (Gregersen et al., 2006; Valastyan and Lindquist, 2014); currently it is believed that most (possibly all) proteins have aggregating potential, in a pathway alternative to folding (Stefani, 2004).

Following an initial characterisation by x-ray diffraction (Sunde et al., 1997), aggregation and amyloid formation were traditionally assessed with thioflavin T staining, but alternative methodologies are now more frequent, such as filter trap assay (Nasir et al., 2015), differential detergent extraction and centrifugation (Shaw et al., 2008) and western blotting. Quantification of protein aggregates can be carried out by a plethora of techniques, like HPLC, western blotting, microscopy, capillary electrophoresis, analytical ultracentrifugion, or UV–vis spectroscopy, but characterisation of the aggregates normally requires a specific technique, such as circular dichroism, fluorescence, infrared, Raman spectroscopy, or nuclear magnetic resonance (Mahler et al., 2009). Recently, folding probes have started to be implemented as an alternative method (Matulis et al., 1999; Liu et al., 2014; Sagle et al., 2004).

In healthy organisms, aggregation is prevented by quality-control cellular processes present along the protein's lifetime (Meusser et al., 2005; Morimoto, 2008; Ron and Walter, 2007) (Fig. 1), with various chaperones supervising transcription, translation, and the folding of synthesised proteins (Hartl et al., 2011). When misfolding occurs, other chaperones, such as chaperonins, Heat shock protein (HSP) 70, and HSP90, recognise exposed hydrophobic residues and potentiate *de novo* folding through cycles of protein binding and release (Motojima, 2015).

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Table 1
List of main protein aggregation disorders, their characteristic pathology, proteins involved and most affected tissues. PrP: Prion protein; SOD1: Superoxide Dismutase 1; TTR: Transthyretin; ALS: Amyotrophic Lateral Sclerosis; SSA: Senile Systemic amyloidosis; FAP: Familial amyloid polyneuropathy; FAC: Familial amyloid cardiomyopathy.

	Disease	Characteristic Pathology	Protein/ Peptide	Most affected tissues
Neurodegenerative diseases	Alzheimer's disease (AD)	Senile Plaques	Aβ 1-40 or 1-42 peptide	Cortex, hippocampus, basal forebrain
		Neurofibrillary tangles	Tau	
	Parkinson's disease (PD)	Lewy Bodies	α-synuclein	Substantia nigra, cortex and stem brain
	Huntington's disease (HD)	Intranuclear inclusions and cytoplasmatic aggregates	Huntingtin with polyQ expansion	Cortex, hippocampus white matter, amygdala, thalamus
	Prion diseases (Creutzfeldt Jacob disease)	Spongiform degeneration, amyloid	Prp protein	Cortex, cerebellum, thalamus
	Frontotemporal Dementia	Pick Bodies, stress granules	Tau	Frontotemporal cortex
	Amyotrophic Lateral Sclerosis (ALS)	Bunina bodies, axonal spheroids, stress granules	Superoxide Dismutase (SOD1)	Spinal cord, cortical upper motor neurons
Nonneurophatic systemic amyloidoses	Senile Systemic amyloidosis (SSA)	TTR deposits	Wild-type transthyretin	Atria, cardiac ventricules, lungs and others
	Familial amyloid polyneuropathy (FAP)	TTR deposits	Mutants of transthyretin	Heart, eyes, kidney
	Familial amyloid cardiomyopathy (FAC)	TTR deposits	Mutants of transthyretin	Heart, atria

However, proteins can be irreversibly damaged if this mechanism is overwhelmed, in which case chaperones target proteins for degradation via the proteasomal and autophagy systems (Cuervo and Wong, 2014; Kettern et al., 2011; Magalhães et al., 2016). These cell-wide systems are complemented by organelle-specific ones, particularly in the nucleus, endoplasmic reticulum (ER), or mitochondria (Sidrauski and Walter, 1997; Haynes and Ron, 2010; Rosenbaum and Gardner, 2011). The ER, markedly, has a collection of stress-response signalling pathways in place to enforce correct protein-folding; the unfolded protein response (UPR). This system can be triggered by different conditions, such as hypoxia, hypoglycaemia, oxidative stress, infection, or mutations promoting unfolded protein accumulation (Ron and Walter, 2007). The most conserved UPR pathway is via the inositol-requiring enzyme-1 (IRE1), that increases the expression of ER chaperones (Cox et al., 1993) in response to unfolded protein presence (Shamu and Walter, 1996).

The UPR regulates proteostasis by inducing the expression of chaperones to ensure correct protein-folding, thus promoting unfolded protein clearance from the ER via the ER-associated protein degradation (ERAD) pathway, and inhibiting protein translation in the ER (Walter and Ron, 2011). In a mechanism associated with the pathogenesis of protein misfolding and aggregation-dependent diseases, the UPR can eventually trigger cell death, should it fail to restore proteostasis (Schröder and Kaufman, 2005).

All the above-mentioned regulatory processes of protein refolding and degradation can be disrupted or overcome (summarised in Fig. 1). This can result from mutations increasing a protein's tendency to unfold and aggregate, defects in proteogenesis (like translational errors), heat and oxidative stress conditions, or sustained protein aggregation during ageing. The net result is the accumulation and aggregation of unfolded and misfolded proteins. Aged cells, specifically, show a reduced capacity to deal with misfolded proteins, which is believed to contribute to late onset neurodegenerative disorders, notably Huntington's disease (HD) (Lipe and Bird, 2009), AD (Isik, 2010), or PD (Diederich et al., 2003), and ageing is indeed the main risk factor for the development of many neurodegenerative conditions (David, 2012; Rosa et al., 2017).

Ageing and lifespan are regulated by various mechanisms tightly-associated with metabolism, like diet caloric content (Mattison et al., 2000), the mitochondria electron transport chain (Sandhu and Kaur, 2003; Tatarková et al., 2011), and the insulin/IGF signalling pathway (Akintola and van Heemst, 2015; Baranowska-Bik and Bik, 2017). Concerning the latter mechanism, blocking the IGF-1 or the insulin receptors results in increased longevity (Dröge, 2005; Wolkow et al., 2000; Taguchi et al., 2007). On the other hand, mitochondrial dysfunction is also a consequence of ageing (Boveris and Navarro, 2008; Payne and Chinnery, 2015), taking a particularly high toll on the nervous system (Navarro and Boveris, 2010). Mechanistically, there is an age-related accumulation of oxidative damage (Floyd and Hensley, 2002; Wang and Michaelis, 2010), protein and nucleic acid damage (Lu et al., 2004; Goto and Radak, 2013; Floyd and Carney, 1992; Berlett and Stadtman, 1997; Grimm et al., 2011), and disrupted energy metabolism (Bratic and Trifunovic, 2010; Frisard and Ravussin, 2006). Metabolism disruption is likewise observed, evidenced by a reduction in brain glucose consumption, common to the lesion sites of AD, PD and HD patients (prior to clinical onset) (Minoshima et al., 1997; Dunn et al., 2014; Kuwert et al., 1990), and in reduced mitochondrial enzyme activities (Gibson et al., 1998) and mitochondria complex I activity in AD patients (Parker et al., 1994; Chandrasekaran et al., 1996).

1.1. The process of aggregation

When studying protein aggregation, a distinction must be made between non-native protein deposition (with no clear function, toxic or otherwise) and the formation of protein complexes related to the protein's biological role, such as the complement or IgG. A change in nomenclature distinguishing protein aggregates from protein complexes

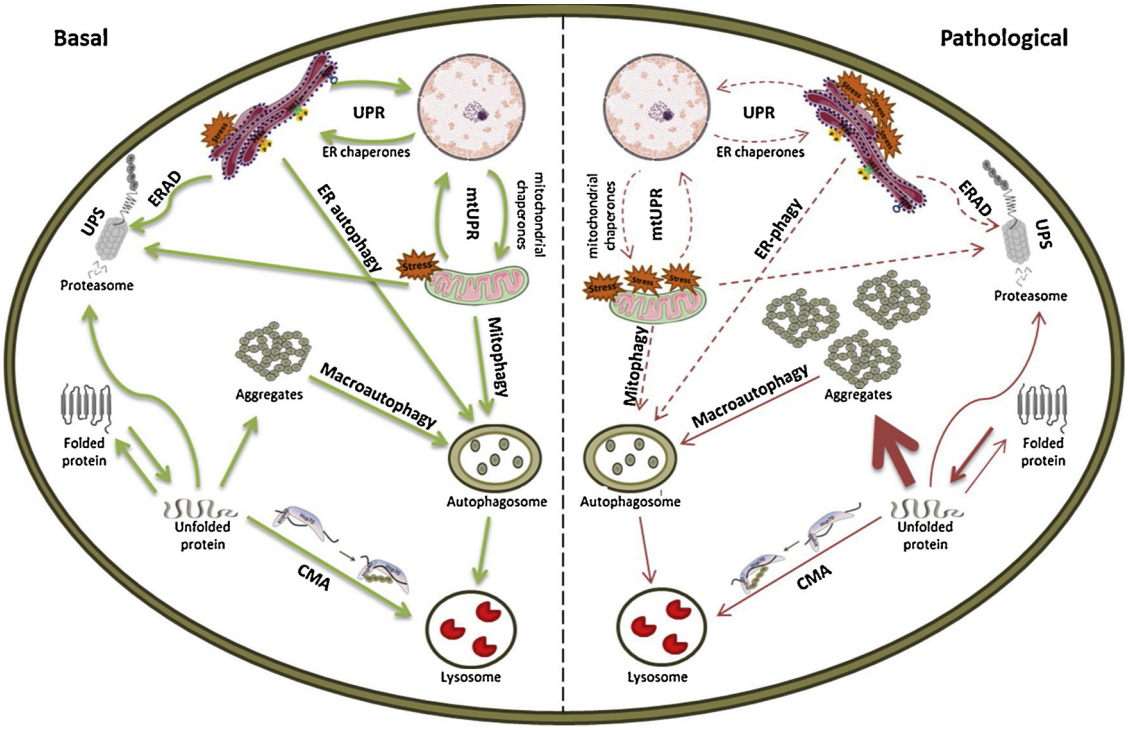

Fig. 1. Changes in the proteostasis system with pathology: Schematic representation of the mechanisms of proteostasis in the cytosol, ER, and mitochondria, in basal (left) and pathological (right) conditions. Accumulated unfolded proteins are targeted for degradation, in the proteasome (often after ubiquitination) or in lysosomes, by chaperone-mediated autophagy (CMA). Misfolded proteins can organise into insoluble aggregates and be eliminated via autophagosomes, and consequently degraded in lysosomes (macroautophagy). The ER and mitochondria can experience specialized forms of autophagy: ER-phagy and mitophagy, respectively. Under proteotoxic stress, ER or mitochondria activate signalling cascades leading to chaperone upregulation and attenuation of protein translation (UPR and mtUPR, respectively), and if this response is lacking, unfolded proteins are translocated for degradation in the proteasome. These processes might be disrupted if unfolded proteins overload the organelles, and in pathological conditions (right hand side) the aforementioned mechanisms are compromised, resulting in cellular accumulation of protein aggregates. Green arrows represent basal state mechanisms related to proteostasis; red arrows show the mechanisms affected by pathological state conditions, red dashed arrows indicate disrupted processes, thin red arrows represent impaired processes, and thick red arrows correspond to increased aggregation of misfolded proteins. Hsp70, Heat shock protein of 70 kDa; Ub, Ubiquitin; CMA, Chaperone-mediated autophagy; ERAD, Endoplasmatic Reticulum Associated Protein Degradation; UPS, Ubiquitin Proteasome System; UPR, Unfolded Protein Response; mtUPR, mitochondrial Unfolded Protein Response.

would help avoid misinterpretations.

The classical, pathological term ‘aggregate’ typically includes three types of protein aggregates: amorphous aggregates, oligomers, and amyloid fibrils. Most proteins, including amyloidogenic ones, have the capacity to form amorphous aggregates, a series of different types of aggregates characterised by the absence of any ordered intermolecular interactions. This type of aggregation is associated with protein denaturation, probably due to the greater aggregation propensity of unfolded conformations due to exposed hydrophobic surfaces (Michaels et al., 2015). In contrast to these aggregates, amyloid fibrils are quasi-crystalline structures with a characteristic ordered cross-β arrangement, formed when a supersaturated amyloidogenic protein self-assembles into a water-excluded structure (Michaels et al., 2015). Finally, oligomers are smaller (in some instances, soluble) aggregates of misfolded proteins, which can have, nonetheless, a pathological role (Kuo et al., 1996; Walsh et al., 2002).

The native fold of each specific protein is achieved through a series of interactions between substructural units that are eventually stabilised, notably by hydrophobic interactions (Fink, 1995). Protein aggregation occurs when such interactions exist between different molecules, normally between misfolded peptides or proteins, generating small, soluble aggregates. These can also self-assemble from monomeric proteins with self-complementary surfaces, from conformational alterations resulting from physical stress, mutations or post-translational modifications, that precipitate when the number of exposed hydrophobic surfaces increase, exceeding the solubility limit. Typically, this is an irreversible event in normal physiological conditions.

Given that aggregation competes kinetically with folding and degradation pathways, it is increased by conditions favouring the presence of partially folded intermediates, as longer-lived intermediates are more likely to interact with each other and to saturate aggregation-preventing chaperones. These conditions range from native state-destabilising mutations, the protein concentration, the presence of denaturants (such as urea, osmolytes, or ligands that interact with non-native conformations) or chaperones, to chemical conditions like pH, temperature or ionic strength (Fink, 1998).

As previously mentioned, these aggregates can take different forms, and can deposit intra or extra cellularly (Moreno and Soto, 2011). Even though most aggregates are amorphous, some take the form of extracellular insoluble deposits found in various types of tissues, the previously mentioned amyloid fibrils. These fibrils do not have a clear biological role and are associated with a series of pathological conditions, referred to as “amyloidosis” (Pepys, 2001). Highly ordered and stable, these structures are characterised by a β sheet arrangement along the protein’s chains. These sheets are hydrogen-bonded perpendicular to the fibril axis (Geddes et al., 1968), in an orientation theorised to minimise the energy of aggregated proteins (Dobson, 2001), thus resulting in a very stable structure hard to solubilize (Hirota-Nakaoka et al., 2003). Amyloid fibrils can self-assemble in vitro from various peptides and proteins associated with different pathologies, including AD (Kidd, 1963), spongiform encephalopathies (Piccardo et al., 2007), or Familial Amyloidotic Polyneuropathy (Saraiva et al., 2012). Currently, 36 human proteins are identified as human amyloid fibril proteins by the International Society of Amyloidosis (Sipe et al., 2016). These follow a specific nomenclature, in which the amyloid fibril protein is designated “protein A” (for Amyloid), followed by a suffix

derived from the precursor protein's name, such as "ATTR", derived from "Amyloid transthyretin".

A different specialized form of aggregation in the mammalian cytoplasm, the ubiquitin-rich aggresome, is found in some diseases (Johnston et al., 1998; Tyedmers et al., 2010), where misfolded proteins overlooked by the chaperone-refolding or UPS-degradation accumulate (Garcia-Mata et al., 2002; Kopito, 2000; Wójcik and DeMartino, 2003). When these systems are overwhelmed, for instance in the presence of inhibitors or protein overexpression (García-Mata et al., 1999, 2002), misfolded proteins are transported along the cytoskeleton to a single perinuclear location, which also accumulates other components like chaperones (HSP70, ubiquitin, ataxin 3 (AT3) and carboxy terminus of HSP70-interacting protein (CHIP)), proteasome components, and motor proteins (Garcia-Mata et al., 2002; Olzmann et al., 2008; Rodriguez-Gonzalez et al., 2008; Zhang and Qian, 2011). Believed to be a cellular response mechanism to toxic accumulation of aberrant proteins, the aggresome can, however, be toxic and play an apoptotic role, depending on the nature of its contents (Garcia-Mata et al., 2002; Kristiansen et al., 2005; Tanaka et al., 2004; Wójcik and DeMartino, 2003).

Inclusion bodies are another variation of protein aggregation in mammalian cells in a metabolically inactive structure. With a fibrillar or granular matrix unbound by a membrane (Martelli and Castellano, 1971), these structures normally accumulate different aggregated proteins, as well as chaperones, ubiquitin-pathway molecules, cytoskeletal and centrosomal material, and can also contain nucleic acids (Kopito, 2000). Organisms often have only one inclusion body per cell, believed to result from a self-polymerisation of misfolded monomers (Speed et al., 1996; Fink, 1998).

The autophagosome complex normally removes defective ribosomal products, but during stress situations these can accumulate in cytoplasmic aggresome-like induced structures (ALIS). These ubiquitinated-protein aggregates are not related to aggresomes. Although originally described in immune cells (Lelouard et al., 2002; Canadien et al., 2005), they have been found in several cell types outside the immune system, and are formed in response to stress, starvation, or oxidative stress (Vasconcellos et al., 2016). ALIS are hypothesised to accumulate for various reasons, namely to overcome the physiological degradative pathways, for preferential degradation of other cytosolic proteins, or for the favoured degradation defective ribosomal products themselves during stress (Szeto et al., 2006).

A different type of complexes is the protein and RNA rich Ribonucletoprotein (RNP) granules. These can be nuclear (as is the case of Cajal bodies, paraspeckles, or even the nucleolus) or cytoplasmic (Spector, 2006). Stress granules are of particular interest, due to a proposed role in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (Ash et al., 2014) and to an association with Tau aggregates in AD (Vanderweyde et al., 2012). These are conserved granules (Anderson and Kedersha, 2009; Buchan and Parker, 2009) formed in cellular stress conditions by translation of stalled mRNAs, containing RNA-binding and non-RNA-binding proteins (Jain et al., 2016).

In addition to protein deposits, other complexes constituted by proteins, carbohydrates or lipids commonly accumulate in the ageing brain, both extracellularly (such as corpora amylacea) and inside neurons or glial cells (such as lipofuscin). The role of these bodies is still unclear, even though they are posited to affect normal brain function (Mrak et al., 1997).

1.2. Molecular basis of aggregation

As previously mentioned, stabilisation of the native state prevents aggregation, as it is initiated by intermolecular interactions between partially unfolded intermediates (Fig. 1). Similar to what happens during folding, the unfolding process is driven by a series of interactions, such as geometric and steric constraints, electrostatic interactions, van der Waals interactions, hydrogen bonds, and hydrophobic attractions, resulting in chain entropy minimisation (Roberts, 2014). Partial unfolding (crucial for globular protein aggregation) (Chiti and Dobson, 2009) can result from a myriad of chemical factors, including pH (as it affects net charge and charge distribution on a protein), temperature, oxidative stress, or eventual mutations. This process exposes otherwise shielded hydrophobic regions (Knowles et al., 2014), which subsequently collapse (Rosa et al., 2017).

The surfaces of monomeric proteins are self-complementary, meaning that intermolecular interactions (such as electrostatic and van der Waals interactions) can occur, resulting in oligomerisation and potential amyloid aggregation (Fitzpatrick et al., 2011; Kumar et al., 2011). As stronger covalent bonds are established, notably disulphide ones, these oligomers can result in irreversible aggregates. Additionally, monomers can aggregate due to conformational alterations, resulting from stress, such as heat or shear (Chaturvedi et al., 2016).

Nucleation and seeding accelerate the aggregation process, in a manner similar to crystal formation (Jarrett and Lansbury, 1993; Come et al., 1993), with aggregates of critical size (referred to as 'critical nucleus') promoting an increase in size through monomer addition. This is the pathway normally taken for amyloid initiation, as monomer interactions are stronger with aggregates than with other monomers (Roberts, 2014).

Post-translational chemical modifications, like hyperphosphorylation, acetylation, glycation, nitration and truncation, have in later years been determined to play key roles in protein aggregation, particularly in relation to amyloid pathogenesis. Phosphorylation is an important regulator of alpha-synuclein aggregation in PD, a modification that influences its neurotoxicity (Chen et al., 2009; Fujiwara et al., 2002), with close to all alpha-synuclein (α-SYN) in Lewy bodies being phosphorylated on serine 219 (Chen and Feany, 2005). Even though the purpose of phosphorylation in pathophysiology remains unclear, this phosphorylation promotes α-SYN interaction with metal ions (Högen et al., 2012), a process essential for oligomer and fibril formation in PD (Kostka et al., 2008; Levin et al., 2011; Lu et al., 2011). Additionally, other post-translational modifications of α-SYN are associated with aggregation, including nitration at tyrosine residues (Giasson et al., 2000), and C-terminal truncation (Li et al., 2005).

Not exclusive to PD, but likewise found in AD and other tauopathies, such as frontotemporal dementia, aberrant modifications also play a role in pathogenesis by altering the structure of Tau, promoting fibrillation and cell toxicity (Kolarova et al., 2012; Šimić et al., 2016). Abnormal phosphorylation in monomeric Tau is hypothesised (von Bergen et al., 2000) to induce a conformational change in regulatory domains allowing homologous regions to interact, thus resulting in filament self-assembly (Alonso et al., 2001). Hyperphosphorylated Tau is indeed identified not only in filaments, but specifically in plaque-associated neurons in AD patients (Grundke-Iqbal et al., 1986; Iqbal et al., 2009).

1.3. Metal-binding proteins and protein aggregation

Metal-binding proteins (i.e. metalloproteins) constitute around one third of the proteome (Leal et al., 2012), playing important functions in catalysis, enzymatic function, structural stability, oxygen transport and cellular signalling (da Silva and Williams, 2019). The ion-protein association can be direct or indirect. The former results from electrostatic forces and interaction between specific residues (metal coordination motifs) within the binding site, and the latter can be established via a metal cluster or a larger chemical group (Gomes and Wittung-Stafshede, 2019; Wilson et al., 2006).

Due to their essential roles in the brain, solid evidence indicates that metal ions contribute to homeostatic dysfunction across different neurodegenerative diseases (Leal et al., 2012). Exposure to different metals can increase metal-induced toxicity (Caito and Aschner, 2015; da Cruze Silva, 2017), and sequestration can affect metal distribution, compromising homeostasis and contributing to neuronal dysfunction (Roberts

et al., 2014).

Exposure to different metals, such as aluminium, can lead to metal-induced neurotoxicity and protein aggregation, as is the case of the Aβ peptide (Leal et at., 2012), and senile plaques found in AD patients contain Al^{3+}, Cu^{2+}, Fe^{3+} and Zn^{2+}. In fact, several transition metals bind the Aβ peptide and consequently promote Aβ aggregation and the formation of toxic peptide aggregates (Bush and Tanzi, 2008), while some metals, like Al^{3+}, can additionally promote Tau hyperphosphorylation and, consequently, the formation of neurofibrillary tangles (Shin et al., 1994).

Exposure to aluminium is also associated with decreased expression and diminished activity of Protein phosphatase 1 (PP1) (Amador et al., 2004), and recent reports indicate that Fe^{2+} and Zn^{2+} are likely to bind to native PP1 (Heroes et al., 2015). Other ions, like Fe^{3+}, can bind to hyperphosphorylated Tau, inducing aggregation that can interestingly be reverted by reduction to Fe^{2+} (Yamamoto et al., 2002). Tau phosphorylation is also induced by Zn^{2+} through Protein Phosphatase 2 A inhibition (Sun et al., 2012).

As already discussed, protein aggregates are a histological hallmark of many other neuropathologies, and indeed exposure to environmental heavy metals is a risk factor for PD (Feldman et al., 2011). Disorders like AD or HD also feature copper dyshomeostasis (Gaggelli et al., 2006), and copper accumulation promotes not only protein aggregation but also the production of reactive oxygen species (Maynard et al., 2005; Fox et al., 2007). Finally, zinc dyshomeostasis is also described in AD, ALS and PD, concomitant with mitochondrial dysfunction and downstream oxidative damage (Higgins et al., 2003; Sasaki and Iwata, 2007; Schapira, 2008).

Many studies conclude that metals can bind to proteins, altering protein phosphorylation and mitochondria homeostasis, promoting protein aggregation, and consequently being involved in the pathogenesis of various neurodegenerative disorders, namely AD. Thus, understanding these mechanisms is essential for future, more accurate, pharmacological interventions, using metal targeted strategies. For example, instead of a metal overload, it is metal distribution and protein interaction that are perturbed in AD; thus, possible future therapeutic strategies for this disease could focus on remodelling metal redistribution and disrupting pathological metal-protein interactions (e.g. Curcumin and epigallocatechin), instead of using chelated agents that remove metals (e.g. Clioquinol and desferrioxamine) (Hegde et al., 2009).

1.4. Aggregation and healthy ageing

As mentioned in the introduction, in addition to its association with pathological conditions, protein aggregation is tightly correlated with ageing. Mammalian ageing is specifically associated with a dysregulation of proteostasis, namely the UPR (Brown and Naidoo, 2012), proteasome activity (Anselmi et al.,1998; Keller et al., 2000), and lysosomal chaperone-mediated autophagy activity (Cuervo and Dice, 2000), which can contribute to an increase in protein aggregation. In addition to an impairment in the regulation of correct protein folding, ageing is further characterised by increased and cumulative oxidative stress, contributing to the accumulation of transcriptional and translational errors (Gidalevitz et al., 2010) and to impaired protein degradation, due to oxidation and nitration (Squier, 2001). Taken together, the increased generation and the compromised clearing of misfolded proteins potentiate the accumulation of aggregated proteins with ageing (Nowotny et al., 2014). However, a current issue of debate is whether protein aggregation contributes to ageing-related pathological conditions or whether it is just a physiological consequence of ageing.

Proteins have a dynamic structure, where proteostasis requires constant surveillance. This mechanism, notably, together with the network of chaperones and protein degradation, deteriorates with ageing (Gaczynska et al., 2001). The oxidation of proteins during ageing has been hypothesised to prevent their lysosomal degradation (Brunk and Terman, 2002), and increased debris and damaged proteins associated with ageing could also overload the phagocytic machinery, which would result in material build up in the lysosome, as observed with the accumulation of myelin fragments in ageing glia (Safaiyan et al., 2016). As previously discussed, several neurodegenerative conditions feature protein unfolding and aggregation, with intra- or extracellular deposition (Taylor et al., 2002; Ross and Poirier, 2004). Notable examples are β-amyloid and Tau proteins in AD, α-SYN in PD, superoxide dismutase in ALS (Durham et al., 1997), huntingtin in HD, or prion protein (PrP) in prion diseases. However, even though the correlation between aggregation and disease has long been recognised (Davies et al., 1997; Scherzinger et al., 1999), causality is yet to be established. In fact, in some situations, the neurons with inclusions are not the ones that degenerate, and vice versa (Vonsattel et al., 1985; Kuemmerle et al., 1999).

However, ageing is consistently one of the major risk factors for these neuropathologies, and neurodegenerative diseases take a particular toll in ageing populations. In developed countries, prolonged life expectancy is accompanied by an increase in dementia, most commonly AD, for which ageing is constantly among the greatest risk factor (Kukull et al., 2002; Rosa et al., 2017). The underlying mechanism is believed to involve misfolding and aggregating proteins, even though oxidative stress accumulation and mitochondrial dysfunction in ageing could also be contributing (van Ham et al., 2009). Due to the brain's elevated energetic demands, it is particularly susceptible to mitochondria dysfunction, which is one of the hypotheses behind pyramidal neurodegeneration in AD (Moreira et al., 2010; Oliveira et al., 2017). Similarly, ageing is a risk factor for PD (Hinde, 2010), as already described, another prevalent pathology associated with protein misfolding and aggregation (van Ham et al., 2009).

Moreover, modulation and upregulation of protein aggregation, namely with a focus on the chaperone pathway, successfully increases lifespan and longevity. This has been observed with overexpression of heat-shock proteins (Vos et al., 2016), or by inducing the stress response pathway (Mark et al., 2016). On the other hand, aberrant endosomes, lysosomes, and autophagosomes are common in both ageing and neurodegeneration, especially accompanied by increased levels of lysosomal proteins and enzymes (Nixon et al., 2000, 2005; Menzies et al., 2015). Even though increasing lysosomal degradation and proteasome activity has a positive effect on disease-related protein aggregation (Tonoki et al., 2009; Yang et al., 2011), the latter is also present in asymptomatic ageing brains, in the form of amyloid plaques, neurofibrillary tangles, TAR DNA-binding protein 43 (TDP-43) inclusions and Lewy bodies (Elobeid et al., 2016). Hence, it is not yet clear whether these alterations are the cause or a consequence of ageing, but even though the cause and effect relationship has yet to be established, evidence nonetheless suggests that improved proteosasis could benefit the ageing organism (Wyss-Coray, 2016).

In addition to ageing, similar benefits are observed in other amyloidosis, such as the transthyretin deposition-associated senile systemic amyloidosis (SSA) (Westermark et al., 1990), familial amyloid polyneuropathy (FAP) (Andrade, 1952) and familial amyloid cardiomyopathy (FAC) (Jacobson et al., 1997), that are experimentally decreased with anti-oxidants (Macedo et al., 2010) or chaperones such as clusterin (Magalhães and Saraiva, 2012), αB-crystallin (HSPB5) (Magalhães et al., 2010), HSP27 and HSP70 (Santos et al., 2008).

Finally, prion disease, characterised by extensive neurodegeneration associated with the accumulation of misfolded PrP (Kovacs and Budka, 2008), is a classic model used to study the role of protein misfolding in neuronal loss (Moreno et al., 2012), namely in terms of ER stress response (Steele et al., 2007; Hetz et al., 2008). The ER stress response inhibits protein synthesis via phosphorylation of the translation factor eIF2α (Guan et al., 2014), which has been targeted by the eIF2α phosphatase inhibitor Sephin1 in Charcot-Marie-Tooth (Perez-Olle et al., 2002) and motor neuron diseases (Blokhuis et al., 2013),

successfully minimising the accumulation of misfolded proteins and promoting functional amelioration in models of both diseases (Das et al., 2015).

1.5. Stress, metabolism and protein misfolding

ER stress is particularly associated with protein aggregation; it occurs when the ERAD is compromised, allowing for the accumulation of misfolded proteins (Benyair et al., 2015; Leitman et al., 2013), and since in extreme, chronic cases of ER stress the UPR can turn into a toxic, pro-apoptotic signal, it can play a role in several pathologies, particularly in neurodegenerative diseases and ageing (Brown and Naidoo, 2012; Oakes and Papa, 2015; Roussel et al., 2013; Ogen-Shtern et al., 2016), namely when accompanied by chronic neuroinflammation (Zhang and Kaufman, 2008). It follows that ERAD inhibitors, such as eeyarestatin I (Wang et al., 2009, 2010) or kifunensine (Avezov et al., 2008; Wang et al., 2015a), have been used in some conditions to study the association between aggregation, proteostasis mechanisms (McKibbin et al., 2012), and cell death (Wang et al., 2009; Zemoura et al., 2013).

The hypoxia-driven accumulation of misfolded proteins contributes to ER stress (Pan et al., 2012), and hypoxia activates the UPR components PKR-like ER kinase (PERK) and IRE1 (Guo et al., 2017). ER stress also occurs in metabolic disorders such as obesity or diabetes as a result of adipotic hypoxia triggering the UPR via PERK and IRE1 (Turer and Scherer, 2012). Even though the number of studies using UPR-inhibitors is still limited, IRE1 (Tomasio et al., 2013) and PERK inhibitors (Axten et al., 2013) have recently started to be used to study ERAD and UPR as therapeutics approaches for conditions such as prion disease and neurodegeneration (Moreno et al., 2013) or even cancer (Mimura et al., 2012; Papandreou et al., 2011).

The PERK inhibitor GSK2606414 (Axten et al., 2013) and ISRIB, an inhibitor of the downstream targets of eIF2α (Sidrauski et al., 2015), successfully inhibits UPR mediated Tau phosphorylation (van der Harg, et al., 2014) and p-eIF2α activation, decreasing the levels of proinflammatory cytokines (Guthrie et al., 2016), and even though cognitive performance has not been assessed, GSK2606414 also shows neuroprotective properties in prion and tauopathy models (Radford et al., 2015; Koss and Platt, 2017). Although apparently contradicting the previously described ameliorating effects of eIF2α phosphatase inhibition (Perez-Olle et al., 2002; Blokhuis et al., 2013; Das et al., 2015), it has been hypothesised that intermediate levels of eIF2α phosphorylation result in low inflammatory responses not affecting cell survival, while severe stress, leading to maximal phosphorylation, triggers extreme immune response, activating phagocytic pathways (Guthrie et al., 2016).

Ischaemia and hypoxia result in increased oxidative stress and oxidants production, to which proteins are particularly sensitive. Hypoxia affects protein misfolding due to the oxygen-requirements of the folding process, namely the formation of disulphide bonds and post-translational folding, and oxidised proteins can aggregate due to chemical alterations, such as carbonylation, hydroxylation, or residue oxidation (Park et al., 1991; Grune et al., 2003), affecting protein secondary structure and surface hydrophobicity (Shringarpure et al., 2001). This process is proposed to contribute to huntingtin aggregation in HD (Perluigi et al., 2005), aggregation of enzymes and structural proteins preceding neurodegeneration in AD (Aksenov et al., 2001), sporadic ALS (Ferrante et al., 1997), and transthyretin amyloidosis (Zhao et al., 2013), and is hypothesised to contribute to neurodegeneration in ageing and PD (Floor and Wetzel, 1998).

Since, in addition to ATP production, mitochondria play crucial roles in calcium buffering and apoptosis signalling (Orth and Schapira, 2001), and considering that ageing mitochondria are particularly associated with oxidative stress (Brown et al., 2004), the accumulative damage through ageing can have serious consequences to the whole organism, namely in terms of oxidative stress, calcium homeostasis, and metabolism (Payne and Chinnery, 2015). Tightly apposed to the ER, mitochondria have shown susceptibility to stressing agents such as nitric oxide, abnormal calcium levels (Brown and Borutaite, 2001) or the ATP synthase inhibitor oligomycin (Brand and Nicholls, 2011). When triggered, mitochondria stress also acts through PERK (Silva et al., 2009; Lu et al., 2009), similarly inducing UPR activation (Xu et al., 2004). Moreover, mitochondria have a specific chaperone and protease system (Bender et al., 2011) and import misfolded proteins, helping to regulate proteostasis (Ruan et al., 2017). Besides the consequences of oxidative stress, direct disruption of mitochondria ATP production, affects cellular proteostasis by disturbing the ATP-dependent ubiquitin-proteasome system (Hershko, 1983; Solomon and Goldberg, 1996), potentiating the accumulation of misfolded proteins.

Aβ and α-SYN aggregate in vitro when oxidised by the Fenton reaction (Bush and Tanzi, 2002; Hashimoto et al., 1999), which is potentiated by mitochondria during oxidative stress (Thomas et al., 2009). Additionally, α-SYN aggregates following treatment with iron and hydrogen peroxide (Ostrerova-Golts et al., 2000) and also in response to other forms of oxidative stress, such as direct oxidation (Glaser et al., 2005) or nitration (Giasson et al., 2000). The increase in oxidative stress associated with mitochondria disruption by membrane uncouplers is further linked to protein oligomerisation and aggregation (notably of amyloidogenic proteins such as Aβ peptide or α-SYN) (Busciglio et al., 2002; Sherer et al., 2003), being actually associated with the PD pathogenesis (Jenner, 1998). Interestingly, protein aggregation itself can in turn disrupt mitochondria function (Hsu et al., 2000) and cause oxidative damage (Good et al., 1996; Smith et al., 1996). Amyloidogenic proteins, for example Aβ or α-SYN, cause mitochondrial damage upon translocation of protofibrils to the membranes, a process implicated in AD pathogenesis due to disruption of oxygen and glucose metabolism (Parker and Parks, 1995; Parker et al., 1990; Swerdlow et al., 1997). Aβ peptide can induce mitochondrial dysfunction in AD by disrupting the presequence mechanism, responsible for protein targeting and translocation to the mitochondria (Mossmann et al., 2014), and α-SYN disrupts the mitochondrial protein import machinery (Di Maio et al., 2016) causing mitochondria fragmentation and impairing complex I activity, promoting membrane depolarisation and deficient respiration, accompanied by increased ROS production (Nakamura, 2013). Deficits in mitochondrial function might also occur early in ALS, (Manfredi and Xu, 2005), with altered axon trafficking in mouse models (Wang et al., 2013) and patients (Sasaki et al., 2007), indicating that mitochondrial dysfunction plays a role in ALS pathogenesis.

1.6. Future perspectives

Even though a correlation between accumulation of protein aggregates with pathological and deleterious conditions is definitely established, and the formation of protein aggregates is widely considered a sign of dysfunction, the role of the aggregate in pathogenesis still warrants further investigation. Specifically, Tau, α-SYN, and Aβ, as well as their oligomeric forms, have been studied as potential biomarkers for neurodegenerative conditions, in the brain, and clinically more pertinent, peripheral fluids. Nonetheless, even though such biomarkers have had moderate success in differentiating control from diseased groups, diagnostics of early stage dementia in individual subjects has not yet been entirely achieved (Giacomelli et al., 2017). Current lines of work involve refining the association of aggregates with disease progression, including alternative biomarkers such as the ratio between red blood cells α-SYN oligomer and total protein ratio (Wang et al., 2015b).

In addition to diagnostic tools, therapeutic approaches are underway with clinical trials for PolyQ diseases (Takeuchi and Nagai, 2017), and although significant improvements have yet to be achieved (Aguzzi and O'Connor, 2010; Horrocks et al., 2016; Eisele et al., 2015; Wang et al., 2015b), new studies are optimising conditions taking into account the effect of confounding factors (Mohamed et al., 2016). In AD

research, the dynamics affecting the formation, interplay and cytotoxicity of Aβ-aggregates remain largely unknown, and a number of designed pharmacological tools targeting aggregates that can help, not only understand the Aβ-aggregation process but also have therapeutic value, are currently undergoing clinical trials (Schneider et al., 2014). However to date this approach has been unsuccessful (Cummings et al., 2014). This lack of success has been suggested to be, at least in part, due to a focus on disease stages that are too advanced (Pike et al., 2007), and current clinical trials are targeting healthy individuals with high risk of AD to address this concern (Sperling et al., 2014). It has additionally been proposed that a single-target approach could always be doomed to fail in such complex diseases (Stephenson et al., 2015), that the chosen targets were themselves misguided (De Strooper, 2014), or even that the amyloid hypothesis is altogether incorrect (Giacobini and Gold, 2013).

Effective therapies have to take into account not only the disease stage but also the nature of the target aggregate, but the current lack of diagnostic biomarkers further hinders the monitoring of therapeutic responses in clinical trials, strengthening the need for new biomarkers (Eisele et al., 2015). Thus, a general approach targeting aggregates in the pathogenesis of neurodegenerative diseases is a viable and promising avenue of research, and it is reasonable to predict that research in the near future will combine diagnostic and therapeutic approaches.

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