Protein-misfolding in neurodegenerative disease

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Abstract

Many of the neurodegenerative diseases share common features and molecular patterns that suggest their pathology may be directly comparable. Diseases such as Parkinson's disease, Alzheimer's disease and Prion diseases are all characterised by abnormal accumulations of proteins and selective neuronal degeneration. This article reviews the known pathology and aetiology of these diseases in order to explore the links between them including defective free radical accumulation, mitochondrial dysfunction and impairment of protein degradation pathways.

INTRODUCTION

Proteins are the primary building blocks of cells. On average they compose over half of a cell's desiccated weight and vary greatly in their individual conformations. Their structures are determined by specific amino acid sequences being polymerised and folded into complex coiling patterns [1] . The physiological genesis of proteins seems constant across cells of the body including neuronal and glial cells [2] . The normal functions of cellular proteins are legion and include structure, storage, transport, receptor and enzymatic functions. However, in their defective and aggregated forms proteins may provide a commonality between neurodegenerative diseases. This is a rapidly expanding frontier of neuroscience research where a deeper understanding of pathophysiological protein interactions may lead to translational clinical benefits across a range of debilitating neurological diseases. This essay will examine the role of protein abnormalities in three diagnostically distinct diseases; Parkinson's disease, Alzheimer's disease and Prion diseases. Particular emphasis will be placed on the types and significance of abnormal proteins involved and the key similarities in pathology for each disease.

PARKINSON'S DISEASE

Parkinson's disease (PD) is a common akinetic/rigid movement disorder that is usually clinically diagnosed. Although there are many cause of 'parkinsonism'; a term that describes an akinetic state associated with extrapyramidal neurological disease, Parkinson's disease is usually assumed to refer to the idiopathic variety that constitutes the majority of cases. Idiopathic PD implies an unknown aetiology but it also tends to include a number of rare but diverse genetic varieties that have recently been identified. The unifying pathological confirmation of PD is based upon the findings of neuronal Lewy bodies; these are eosinophilic, intracytoplasmic inclusion bodies. While Lewy bodies are easily characterised by microscopy their actual composition can vary markedly. The key component is a protein aggregate that traditionally includes α-synuclein but can include ubiquitin proteosomal system (UPS) related components, proteosomal sub-units and a range of other abnormal proteins that have been shown to cause genetic PD (such as Parkin, DJ-1 and leucine-rich repeat kinase 2) [3] .

A s is well known, α-synuclein is an extremely common protein with large concentrations in synaptic regions. It is a normally unfolded protein that naturally displays a tendency to aggregate due to the individual properties of its domain components [4] . Its normal physiological role has not been clearly elucidated but it has been suggested that it may be important in the control of dopaminergic neurotransmission and also as a protective factor against neurodegeneration [5,6] . Other suggested functions include a role as an supplementary chaperone [6] . In idiopathic PD the amount of α-synuclein is increased throughout the brainstem and Braak et al showed a progression of Lewy body pathology that migrates with time through stereotyped regions of the brain from medulla up to cortex [7,8] . The significance of Lewy bodies and α-synuclein aggregation and why they occur in idiopathic PD is still not fully understood. One proposed theory suggests that toxic gain of function underlies damage associated with α-synuclein aggregation. The α-synuclein accumulation and its association into oligomeres and amyloid fibrils may result in an increased rate and concentration of protofibril formation, and it has been

suggested that these may lead directly to neuronal damage [9]. In some rare familial forms of PD there are duplications and triplications of the α-synuclein gene (PARK1 and PARK4 respectively) with subsequent overproduction of α-synuclein and early onset of PD, again lending weight to the theory of its central role in the disease pathogenesis.

Familial cases of PD have specific genetic aberrations that presumably lead to motor circuit dysfunction. The PARK2 mutation (Parkin) normally codes for ubiquitin E3 ligase. To understand the importance of this dysfunction we need to briefly review the UPS [10]. This system is the endogenous eukaryotic system for degrading cytosolic proteins. These proteins tend to be cellular debris that accumulate with age, a factor that may be relevant in explaining the strong correlation of advancing age with PD. The UPS acts by conjugating ubiquitin polypeptides to target substrate proteins in order to mark them for proteosomal proteolysis. In order to ubiquinate a substrate a 3-step process is required. This involves sequential activity of groups of enzymes termed E1, E2 and E3. The result is a polyubiquinated protein that is marked for ATP-dependent proteosomal degradation. It is likely that this system can be inhibited either directly or indirectly by mutant protein aggregation [11]. The loss or dysfunction of E3 ligase in the Parkin mutation will clearly impair the normal prevention of synuclein aggregation by proteosomal degradation. Specifically, this will occur due to a loss of catalytic function during the final-step of conjugation of the ubiquitin moiety and target protein. This is thought to lead to dysfunction by preventing the formation of substrates that the proteosomal system can breakdown. Other familial PD genes like PARK5 (UCH-L1) and PARK7 (DJ-1) are also implicated in UPS related dysfunction. The gene UCH-L1 (ubiquitin C-terminal hydrolase L1) in the non-mutated form codes a de-ubiquinating protein that may related to UPS dysfunction, however, this gene has been the target of controversy with questions mainly centred around its pathogenicity [12, 13]. PARK7 (DJ-1) in functionally intact dimerized form may also inhibit α-synuclein aggregation through chaperone activity relating to the UPS, a condition that is lost in mutations [14].

It seems that the pathogenesis of PD is more complicated than simply toxic protein accumulation. The UPS system and proteosomal dysfunction are intimately associated with mitochondrial function and dysfunction at the mitochondrial level and may contribute to downstream aggregation of toxic species and neurodegeneration [15].

It is notable that there are several examples of familial PD where mitochondrial dysfunction may be causative, and that many of these genes (though not all) also relate to the UPS. PARK 6 (PINK1 also known as PTEN induced kinase 1) is a mitochondrial protein kinase that when mutated leads to a loss of mitochondrial protection against free radical mediated oxidative stress conditions and subsequent alterations in protein phosphorylation [16]. Likewise, mutations in the PARK7 (DJ-1) gene affect mitochondrial function and survival. DJ-1 normally produces a predominantly astrocytic protein that has cytoplasmic and mitochondrial localization. It has a protective function with regards intracellular radical species in addition to the chaperone functions already mentioned [17]. Abnormalities of the PARK8 (leucine-rich repeat kinase 2, LRRK2) gene is the commonest autosomally inherited cause of PD. It codes for a cytoplasmic protein kinase (dardarin) that is closely associated to the outer mitochondrial membrane. There are numerous submutations including the most prevalent familial PD mutation; a G2019S variant, but how this triggers PD in relation to mitochondrial function is still unclear [18].

The importance of mitochondrial function in PD is probably not only linked to familial cases but may be important in sporadic cases too. The earliest links to mitochondrial dysfunction came from the demonstration of respiratory complex 1 deficiency in the substantia nigra and, at a later date, platelets of PD patients [19, 20]. A deficiency of the complex 1 respiratory molecule may impair ATP energy production and lead to excessive free radicals, this in turn lowers the apoptotic threshold and triggers cell death. Many exogenous toxins that cause an acquired parkinsonism state are known complex 1 respiratory molecule inhibitors. Only around one-third of cases of idiopathic PD demonstrate these deficiencies but in a complex disease this may still prove to be an important contributory pathway [20].

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a common and progressive neurodegenerative disease that particularly affects memory and cognition. Like PD the definitive diagnosis is a histopathological one. The diagnostic features include one intracellular and one extracellular feature, like PD these are based on proteinacious aggregates. Diagnosis requires the presence of neurofibrillary tangles and senile plaques. Neurofibrillary tangles are intraneuronal paired-helical filaments composed of subunits of multiphosphorylated tau protein. Senile plaques are extracellular lesions largely

composed of amyloid β-protein but will also contain other proteins in lesser degrees [21]. The relationship between the intraneuronal and extraneuronal lesions is still not well understood. Although not specific for AD, it is the neurofibrillary tangles that correlate most closely with the development of clinical AD [22]. Neurofibrillary tangles are spatially related to amyloid β-protein plaques and it seem likely that they are a consequence of the abnormal accumulation of amyloid β-proteins that triggers tau pathology. It may be this step that is key in neurodegeneration although at the time of writing how this might occur still remains unknown to researchers [23]. Proposed pathways include Aβ cleavage of tau and generation of pathogenic fragments [24]. This may be the rate limiting step in the induction of AD neurotoxicity [25]. We can see that like PD there is an accumulation of apparently toxic or responsive protein aggregations in AD. Although the forms of proteins differ it is important to consider if the probable disease mechanisms share any common themes.

If we consider the origins of amyloid β-protein we find that that it is the cleaved product of Amyloid Precursor Protein (APP) a normal cellular membrane protein commonly concentrated in synaptic regions. The normal role of APP is not fully understood but may be important in synapse formation and repair [26]. APP is cleaved by the protease 'β-secretase' into a peptide intermediate that is then terminally cleaved by another protease called 'γ-secretase'. The final product is amyloid β-protein of which there are two predominant isoforms, the commonest is the shorter $A\beta_{40}$ and a less common second form is $A\beta_{42}$ which is similar but with an extra 2 amino acid residues at the C-terminus. The key factors that seems to determine pathogenicity are either a net increase in Aβ products or a shift in production to favour the $A\beta_{42}$ form [21]. Aβ is a found in neural tissues of normal subjects and in its natural form (like α-synuclein) it does not show any signs of inducing neurotoxicity. It seems that the abnormal fibrillar organisation of Aβ is prone to amyloid assembly that then results in a directly neurotoxic product both in vitro and in vivo [27, 28]. However, it is controversial if this is the particular form of Aβ that actually produces neurotoxicity in idiopathic AD. There is a strong correlation between soluble forms of Aβ and severity of dementia, and studies have suggested that it may be the pre-fibrillar oligomeric form that is important in AD [29, 30]. The 'Aβ hypothesis' of AD is that multiple Aβ forms, both as oligomers and plaques, are neurotoxic to local synapses and trigger microglial activation with chemical mediator induction including cytokine activation. These factors lead to progressive synaptic and neuronal injury with disrupted homeostasis. This seems to occur concurrently across the cortex leading to neuronal cell loss and AD [21]. It is at the stage of altered homeostasis that there may be an alteration of kinase and phosphatase activities, these then lead to abnormal tau phosphorylation and subsequent tangle formation. Thus, the 'Aβ hypothesis' can be linked to the 'tau hypothesis', a theory that leans towards tau being the primary neurotoxic trigger. In this respect, as the abnormal tau deposition seems to occur as a result of Aβ deposition, ergo the AD can be considered a form of secondary tauopathy. Again, like PD there are some rarer inherited forms of AD called presenilin 1 and 2. These genes cause a severe early form of autosomal dominant AD. The presenilins code for subunits of γ-secretase that tend to shift the ratio of Aβ towards $A\beta_{42}$ throughout life [31].

Further evidence linking Aβ and AD (although not necessarily directly) comes from the strong correlation of Down syndrome with early onset AD. Down's syndrome is due to a trisomy of chromosome 21, the same chromosome coding for APP [32]. This is comparable to duplication or triplication of the α-synuclein gene in PD which has been shown to cause severe PD at an earlier age [33]. Likewise, ApoE3 (the gene coding for apolipoprotein E) of the e4 allele is a major risk factor for late onset AD, while e2 seems protective. These alleles are respectively linked to increased and decreased Aβ deposition [34].

We have discussed the importance of extra-neuronal senile plaques in AD and we will now consider the other key diagnostic marker that is intra-neuronal neurofibrillary tangles in more detail. As previously stated these are primarily composed of subunits of tau protein. In the healthy brain tau is an important microtubule assembly protein that also is necessary for stablilization [35]. There are 6 isoforms, half have a 3 tau repeat sequence and half are 4 tau repeat. These levels are normally fairly evenly balanced in the human cerebral cortex. The tau protein is natively unfolded and does not normally display much secondary conformation. Neurofibrillary tangles consist of paired helical filaments and straight filaments. In AD the deposition of neurofibrillary tangles follows a similar, though not identical, spread throughout the brain to that seen by Lewy bodies in PD. In this case the spread is from the entorhinal region to the limbic system and on to the cortex [22]. Although we can correlate the concentration and location of tau deposition well with AD it is evident that we still do not have a compelling explanation of how tau triggers this

specific neurodegeneration seen in AD.

Like PD we have seen that AD is a selective neurodegenerative disease that is associated with intracytoplasmic filamentous protein inclusions. In later stages of PD there is often an associated dementia and shared histological features with AD [36]. Although the protein inclusions in AD largely differ from PD, as do the preferred location of them, there is an underlying commonality of normally benign proteins that become dysfunctional and are associated w neurotoxic effects in both diseases. We hope that future research may identify new management strategies that can be applied similarly across the spectrum of protein folding diseases.

PRION DISEASES

There are 5 known human prion diseases; these are Creutzfeld Jakob disease, Gerstmann Straussler Scheinker disease, kuru, new variant Creutzfeld Jakob disease and fatal familial insomnia. All of these diseases are rare and universally fatal. The term 'prion' is an acronym for proteinaceous infectious particle and depending on the particular disease form they can be inherited in an autosomal dominant fashion, transmitted as infectious agents or arise de novo [37]. Regardless of aetiology prion diseases are classically neuropathologically identified by spongiosis (neuronal vacuolation), proliferation of astrocytes with activated microglia and deposition of amyloid plaques. The various prion diseases share different isoforms of a common pathogenic unit. The prion is an aggregation of glycoproteins; these are abnormal isoforms of host-encoded cellular prion proteins (PrP ^{c}) and are notable for the lack of nucleic acid residues. The only differences between the normal physiological PrP ^{c} and pathogenic varieties seem to be the monomer conformation and the resulting aggregation properties. There are many possibilities for the normal function of PrP ^{c} including synaptic function, anti-apoptotic signals or copper binding but importantly deletion of this protein does not cause seem to cause neurodegeneration [38]. In keeping with PD and AD implicated proteins its normal form it seems entirely benign. It has been proposed that prions are self-propagating fibrillar or amyloid forms of cellular prion protein that 'infect' and replicate by fibre fragmentation with bare polymer ends that can act as templates for monomer recruitment [39]. The original 'protein-only hypothesis' stated that an abnormal PrP isoform was the main transmissible agent and ultimate cause of disease [40].

The fact that prion diseases, PD and AD share the core commonality of abnormal protein accumulation allows them to be tenuously grouped as 'aggregopathies' or 'protein folding-diseases'. The normal form of prion protein PrP ^{c} is required for prion replication and knockout mice without this form seem to be effectively immune to prion disease [41]. Like $A\beta_{42}$ or tau in AD the true neurotoxic species is probably not PrP ^{c} but a protein intermediate, in the case of prion disease this is thought to be the oligomeric PrP ^{L} (lethal) species. This is a product of prion propagation and derived from PrP ^{sc} the initial abnormal isoform. Thus rapid propagation would increase PrP ^{L} production and as is seen account for rapid degeneration and death seen in some phenotypes of prion diseases [39]. The exact mechanism by which PrP ^{L} might cause neurodegeneration, cell death and a particular phenotype are unfortunately still unclear [42]. Both $A\beta$ and abnormal forms of PrP possess amphipathic properties that suggest a link to lipid membrane interactions where they may disrupt ionic transport and increased susceptibility to oxidative stress (cf. PD) have been implicated in neurotoxicity [43, 44]. Indeed, the clear association between advancing age and PD, AD and in many cases spontaneous prions diseases with prolonged latency may be in some way accounted for by aggregation of proteins with age-associated increases in oxidative stress. It seems possible that there is a final common pathway whereby protein aggregates, by whatever intermediate mechanisms, lead to inhibition of proteosomal machinery. The same proteosomal molecules have been shown to process both PrP and $A\beta$ and this may be the source of a shared irreversible protein accumulation [45]. Further evidence of commonality comes from evidence linking metal ions such as copper to polymerisation of abnormal proteins and oxidative species production in many neurodegenerative diseases including AD and prions [46].

It is perhaps notable that another similarity between AD and prions lies in the fact that the precursors of key pathogenic factors (APP and PrP) are both neuronal membrane proteins [47]. Recent research also suggests that prions, PD and AD also share a degree of transmissibility at least in experimental conditions. Certain forms of prion disease certainly have a clear history and experimental evidence of transmissibility. In the case of AD it is seen that injections of neural tissue from mice with APP mutations producing abnormal $A\beta$ to controls have demonstrated limited transmissibility [48]. In PD no direct transmission has been demonstrated, however, the apparent 'migration' of Lewy bodies is well known and there is now evidence that Lewy bodies can advance over time into previously normal brain

parenchyma with host-to-graft propagation [49].

One particularly unexpected direct link between prions and AD has recently been proposed by Lauren et al [50]. Their work suggests that PrP may mediate the pathogenic effects of A☐ in AD by acting as the anchoring receptor to which A☐-oligomers bind and mediate their effects. Further, they demonstrated that this binding can lead to impairment of long-term potentiation; the key mechanism for plasticity and learning, and a possible source of the cognitive decline found in AD [51].

CONCLUSION

There are numerous stark similarities between PD, AD and prion diseases. Despite varied clinical phenotypes all seem to have a pathogenic mechanism that involves the aggregation of abnormally folded proteins, either extracellularly or intraneuronally. We have seen that the pathogenic mechanisms are still poorly understood but that it is likely that toxic intermediates are actually the source of neurodegeneration. More recent research directly linking prion receptors and AD adds a layer of intimate complexity to the association. The similarities between these 3 groups of diseases give us hope that any lessons learned from each individual disease will help us understand the others. Likewise, it is hoped that any breakthrough in management for one of these conditions will rapidly lead to translational benefits for the other diseases

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