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Review

Late-onset neurodegenerative diseases—the role of protein insolubility

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ABSTRACT

Recently, mutations of the alpha-synuclein gene were found to cause dominantly inherited Lewy-body Parkinson's disease (PD) and alpha-synuclein was identified as a major component of the Lewy body. However, the cause of the common form of PD, with a multifactorial rather than autosomal dominant inheritance pattern, remains unknown. Alpha-synuclein precipitates slowly and apparently spontaneously at high concentration in solution and the mutations that cause PD accelerate precipitation. Other dominantly inherited late-onset or adult-onset dominantly inherited neurodegenerative diseases are associated with precipitation of proteins. In Alzheimer disease, beta-amyloid and tau abnormalities are present and in prion disorders, prion proteins are found. In Huntington disease, a disorder with expanded CAG repeats, huntingtin precipitates occur. In dominantly inherited spinocerebellar ataxias, also expanded CAG repeat disorders, the corresponding ataxin protein precipitates are found. In multiple system atrophy, alpha-synuclein precipitates are encountered and in progressive supranuclear palsy, tau precipitates occur. In familial amyotrophic lateral sclerosis, a group of dominantly inherited disorders, SOD1 precipitates are found. Most of these disorders can involve the basal ganglia in some way.

Since similar processes seem to affect neurons of adults or older individuals and since a relatively limited group of proteins seems to be involved, each producing a form of neurodegeneration, it is possible that certain common features are present that affect this group of proteins. Candidates include a conformational shift, as in prions, an abnormality of the ubiquitin-proteosome pathway, as seen in PD, an abnormality of a pathway preventing precipitation (e.g. chaperonins), or potentiation of a pathway promoting precipitation (e.g. gamma-glutamyl-transpeptidase) or apoptosis. Elucidation of the pathways causing this protein insolubilisation is the first step towards approaching prevention and reversal in these late-onset neurodegenerative diseases.

Key words: Neurodegeneration; insoluble protein precipitation.

CLINICAL AND PATHOLOGICAL FEATURES OF LATE-ONSET NEURODEGENERATIVE DISEASES (Table)

Prion disorders

Over the past decade, an increasing number of neurodegenerative diseases of adults and older people has been associated with protein insolubility. Prion disorders are an example. In Creutzfeldt-Jakob disease (CJD), one form of prion disease, signs referable to the basal ganglia, such as dystonic posturing, may accompany the rapidly progressive dementia. In CJD, a form of prion protein is found in brain associated with spongiform degeneration. This protein is found in the most insoluble fraction of brain proteins and is associated with proteinase K resistance and amyloid formation. If injected or ingested, this abnormal form of prion protein appears to replicate the disease. This type of disease pathogenesis was regarded as highly aberrant and very rare.

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Alzheimer disease and Down syndrome: beta-amyloid, tau, and NAC proteins

Alzheimer disease (AD) has also been associated with an insoluble protein or peptide, the beta-amyloid fragment (A-beta) of the amyloid precursor protein. A-beta is found in amyloid plaques in the brain of AD patients, and a second insoluble protein, related to the tau protein, is seen in neurofibrillary tangles of affected Alzheimer neurons. Similar pathology is observed in Down syndrome, trisomy 21. Since A-beta does not precipitate spontaneously, other proteins in amyloid plaques were studied in search of a protein that could precipitate spontaneously and act as a nucleus for precipitation of other proteins such as beta-amyloid. Digestion of amyloid plaque with proteases and extraction yielded a peptide that was a component of the plaque but was not A-beta, i.e. the 'non-*A*-beta *c*omponent' of Alzheimer plaques or NAC. Cloning of the gene of which the NAC was a fragment yielded the NACP gene (NAC precursor protein gene) which was identical with the synuclein gene. Synuclein had previously been found in the electric eel, torpedo, and received its name, synuclein, because it was localised in the *syn*apse and the *nuc*leus of the neuron. Subsequently, it has been found in the synapse but not in the nucleus; however the name synuclein was retained. Related proteins were discovered named beta- and gamma-synuclein; the original synuclein protein became alpha-synuclein.

Alpha-synuclein has been found in other neurodegenerative diseases of ageing affecting the basal ganglia and their connections, especially those associated with Lewy bodies: familial Parkinson disease, apparently sporadic (multifactorial) PD, diffuse Lewy body disease, the Lewy body variant of AD, and incidental Lewy body disease, although not in Lewy bodies found incidentally and not associated with neuronal loss. Recently, alpha-synuclein has been detected in the glial cytoplasmic inclusions in oligodendroglia in multiple system atrophy (Arima et al. 1998; Gai et al. 1998; Spillantini et al. 1998; Tu et al. 1998; Wakabayashi et al. 1998*a*, *b*) and in the hippocampus following ischaemia (Ishimaru et al. 1998).

Parkinson disease: alpha-synuclein

Alpha-synuclein was implicated in PD because mutation of the alpha-synuclein gene on chromosome 4 (4q21-23) was found to be responsible in the large Contursi kindred in which PD was inherited as an autosomal dominant trait (Polymeropoulos et al. 1996, 1997). Affected members of this family have typical PD clinically, with Lewy bodies by neuropathology. The only atypical features were (1) the average of onset was age 46 y (although there was wide variation) compared with about 59 y in idiopathic PD, and (2) inheritance was autosomal dominant with high penetrance while idiopathic PD is sporadic or has a multifactorial inheritance pattern. Only a few PD families have alpha-synuclein mutations. The vast majority of patients with idiopathic PD have a normal alpha-synuclein DNA sequence, at least in the coding region.

After mutations of alpha-synuclein were found to cause PD, alpha-synuclein was identified as a major component of Lewy bodies by immunohistochemical staining. The Lewy body, an intraneuronal inclusion seen in surviving dopaminergic neurons in the substantia nigra, is the neuropathological hallmark of PD. This eosinophilic, cytoplasmic inclusion often has a dense centre surrounded by a clear area and a surrounding eosinophilic ring, although other morphologies can be seen. The ultrastructural appearance is that of matted fibrils. Over 50 proteins have been found in Lewy bodies of PD. These Lewy bodies are also seen in more widespread distribution in a related disorder, diffuse Lewy body disease, in which dementia prominently accompanies a movement disorder resembling PD. They also are seen with typical AD pathology in the so-called Lewy body variant of AD (Lippa et al. 1998; Takeda et al. 1998*a*, *b*).

Multiple system atrophy: alpha-synuclein

Alpha-synuclein was found by immunohistochemical staining in glial inclusions of multiple system atrophy (MSA) (Arima et al. 1998; Gai et al. 1998; Spillantini et al. 1998; Tu et al. 1998; Wakabayashi et al. 1998*a*, *b*), a group of 4 clinical disorders united by the neuropathological finding of microtubular tangles in oligodendroglia. In the first disorder, striatonigral degeneration, parkinsonism without tremor is associated with neuronal loss and gliosis in the substantia nigra and neostriatum. In a second variant, Shy-Drager syndrome, autonomic dysfunction is associated with loss of preganglionic sympathetic neurons in the intermediolateral horns of the spinal cord; the additional clinical features of parkinsonism, cerebellar ataxia, or amyotrophy may be associated with degeneration of nigral or striatal neurons, cerebellum, or anterior horn cells. In a third disorder, olivopontocerebellar atrophy, a mixture of clinical parkinsonism and cerebellar disorder is associated with neuronal

Table. *Late-onset neurodegenerative diseases with insoluble proteins*

Prion protein
Creutzfeldt-Jakob disease
Gerstmann-Sträussler-Scheinker disease
Kuru
Fatal familial insomnia
Beta-amyloid
Alzheimer disease
Alzheimer disease, Lewy body variant
Down syndrome
Alpha-synuclein
Parkinson disease, autosomal dominant
Parkinson disease, sporadic (multifactorial)
Alzheimer disease
Alzheimer disease, Lewy body variant
Multiple system atrophy
Diffuse Lewy body disease
Incidental Lewy body disease
Tau protein
Frontotemporal dementia-chromosome 17
Progressive supranuclear palsy
Pick disease
Corticobasal degeneration
Postencephalitic parkinsonism
Parkinsonism-dementia complex of Guam
Alzheimer disease
Superoxide dismutase 1
Amyotrophic lateral sclerosis
Diseases with expanded CAG repeats
Huntington disease
Spinocerebellar ataxia type 1 (SCA1)
Spinocerebellar ataxia type 3 (SCA3)
Spinocerebellar ataxia type 7 (SCA7)
Dentatorubropallidoluysian atrophy (DRPLA)
Spinal and bulbar muscular atrophy

loss in the substantia nigra and striatum as well as degeneration of the olives, pons, and cerebellum. Finally, in a fourth clinical syndrome, amyotrophy-parkinsonism, lower motor neuron disorder with parkinsonism is associated with anterior horn cell degeneration and degeneration of neurons in the striatum and substantia nigra.

Disorders in the MSA group are mostly sporadic although multiple affected individuals are sometimes seen in a single family. The coding sequence of alpha-synuclein was normal in a single studied case of MSA, but the alpha-synuclein gene has not been extensively studied in MSA.

Tauopathies

A number of disorders have extensive tau pathology (Feany et al. 1996*a*; Delacourte et al. 1997) documented by immunohistochemical staining. Tau is a microtubule-associated protein coded for by a gene on chromosome 17. Two tauopathies, AD and Down syndrome, were discussed earlier. Others are frontotemporal dementia (FTD-17), progressive supranuclear palsy, Pick disease, the parkinsonism-dementia complex of Guam, corticobasal degeneration, and postencephalitic parkinsonism.

Frontotemporal dementia is an autosomal dominant disorder with high penetrance that results from mutations (Hutton et al. 1998) affecting the tau gene on chromosome 17 (17q21-22). Besides dementia, these patients may have parkinsonism, amyotrophy, and abnormal behavioural features. The pathology is nonspecific involving spongiform degeneration in the basal ganglia, cerebrum and anterior horn cells.

Progressive supranuclear palsy (PSP), another tauopathy, is regarded as a sporadic disorder, but there are a few reports of multiple cases in a single family (de Yebenes et al. 1995; Tetrud et al. 1996) suggesting a genetic aetiology. The mode of inheritance in such families is not clear. The reports of occurrence in sibs along with an instance of parental consanguinity have suggested autosomal recessive inheritance, although the occurrence of PSP in 5 generations of a large family with 13 cases suggested autosomal dominant inheritance. The possibility of genetic heterogeneity thus arises. PSP has been associated first with a tau polymorphism allele and, more recently, a haplotype containing that allele.

The pathology of PSP is characterised by the presence of tau-reactive neurofibrillary tangles (NFTs) and neuropil threads, particularly in the brainstem and basal ganglia but also in the cortex. Tau-reactive neuronal and glial inclusions are widespread, while amyloid deposits and neuritic plaques are absent (Feany et al. 1996*b*).

Postencephalitic parkinsonism has a similar pathology to that of PSP. The disorder occurred chiefly after the epidemic of encephalitis lethargica, a mesencephalitis presumed to result from a viral infection, but the virus was never isolated. Affected individuals showed coma, eye movement disorders and pupillary abnormalities, and usually long after recovery developed parkinsonism similar to that of PD except that age of onset was earlier, progression was slower, and certain additional features, such as oculogyric crises, were seen.

Additional tauopathies include the parkinsonism-dementia complex of Guam, corticobasal degeneration and Pick disease.

Diseases caused by expanded CAG repeats

An increasingly large group of dominantly inherited neurodegenerative disorders is caused by expanded trinucleotide repeats of the CAG variety. The com-

mon biochemical feature seems to be the expanded polyglutamine tract in the abnormal protein resulting from the excess CAG repeats in the coding region of the gene. Disorders with other types of expanded trinucleotide repeats in noncoding regions, e.g. myotonic dystrophy, fragile X syndrome, and Friedreich ataxia may not result from the same mechanism.

Huntington disease and dentatorubropallidoluysian atrophy (DRPLA) are chiefly disorders of basal ganglia dysfunction with dementia, although occasionally a cerebellar syndrome may occur. Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease involves a cerebellar syndrome with basal ganglia features. Other types of SCA are characterised by cerebellar syndromes difficult to distinguish from SCA3 and each other as well as eye movement abnormalities, pyramidal dysfunction, or lower motor neuron involvement, but without dementia. All are of autosomal dominant inheritance.

X-linked spinal muscular atrophy is clinically distinct both because of its inheritance pattern and because it is accompanied by signs and symptoms of androgen deficiency. The CAG expansion occurs within the androgen receptor gene on the X chromosome.

SOD1 and amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a disorder in which progressive lower motor disease, progressive upper motor neuron disease, or more commonly both, occur in older individuals usually leading to death within 3–5 y. Usually the disorder is sporadic but affected relatives occur often enough to suggest multifactorial inheritance, and occasional autosomal dominant kindreds occur. Linkage studies in autosomal dominant families led to identification of the superoxide dismutase 1 (SOD1) gene on chromosome 21 as the cause in some of these families. A number of mutations in different portions of SOD1 have been identified in autosomal dominant ALS families but it is not clear how the mutations affect the activity of SOD1 to cause the disease. Recently, immunohistochemical studies have identified the SOD1 protein in the abnormal inclusions in anterior horn cells (Table).

PROTEIN INSOLUBILITY, A POSSIBLE MECHANISM OF LATE-ONSET NEURODEGENERATIVE DISEASE

Despite the great progress in identifying genes and proteins associated with and in at least some cases causing the late-onset neurodegenerative diseases, it is not clear how the mutations cause the diseases.

Loss-of-function and gain-of-function mutations

One possibility is that the mutations diminish the normal function of the protein. In most cases the function of the affected protein is unknown. In the cases where the function of the protein is known, e.g. tau, a microtubule-binding protein, and SOD1, an enzyme affecting oxidative stress pathways, knowing the protein's function has given little insight. In some cases, the protein may not have a normal function, at least not a major function: knocking out the prion protein, at least in mice, seems to have no effect on the health or function of the mice, except that it prevents prion disease from developing after parenteral seeding of prion protein. Thus prion protein may have no function at all or could have a function that is present in normal humans and not in normal mice.

A second possibility is that the mutations have nothing to do with the normal function of the protein. The mutation could cause a gain of function. The mutated protein would then have a new function, a harmful one unrelated to its normal action, for which the normal copies of the protein cannot compensate no matter how much normal protein is present. Thus the mutation has turned a protein with a normal function into a neurotoxin.

One possible type of abnormal function is suggested by the clinical and pathological similarities of these late-onset neurodegenerative diseases: the mutation produces a protein, which precipitates within the cell. First, it is interesting that all these disorders affect neurons, postmitotic cells that do not divide in the adult. Second, all these disorders occur late in life after decades during which neurons have survived without dividing. Third, these are diseases of humans, a long-lived species. Fourth, these diseases characteristically occur in neurons, a cell type with extended processes and dependent upon axonal transport. Thus, proteins in solution in neurons must remain soluble for decades. Long-lived postmitotic cells with extended processes in a long-lived species might be expected to be the cells most susceptible to a disease resulting from protein precipitation.

Two factors might lead to precipitation of proteins in this situation: (1) introduction into the cell of proteins with exceptionally low solubility and (2) damage to normal mechanisms designed to deal with protein insolubility.

Mechanisms of protein insolubilisation, amyloidogenesis and conformational change

A feature of a number of late-onset neurodegenerative diseases is the appearance of amyloid. Amyloid is characterised histologically by a green birefringence when viewed with polarisation optics after staining with certain dyes, e.g. Congo red or thioflavin S. Biochemically, amyloid is characterised by a beta structure, a form of secondary structure in which beta-pleated sheets occur. Amyloid fibrils are characterised by a cross-beta structure, in which the peptide chain is oriented perpendicular to the axis of the fibril and weaves back and forth across the diameter of the fibril gradually forming a helical structure as the fibril elongates (Jackson et al. 1999).

Amyloid is not a single protein; approximately 20 proteins are known that may form amyloid (Kelly, 1996, 1998*a*). These include the amyloid precursor protein, the immunoglobulin light chain, serum amyloid A, transthyretin, apolipoprotein A-1, prion protein, lysozyme, and even insulin (Kelly, 1996). Surprisingly, these proteins do not share sequence homology in the amyloidogenic region. Instead, they share a tendency to change conformation during denaturation from their native state to the molten globule form. The molten globule form is seen during protein synthesis when secondary structures have formed but tertiary structures have not yet formed.

During partial denaturation, these amyloidogenic proteins seem to be able to undergo a conformational change from an alpha to a beta structure, i.e. alpha-helix structure of the peptide chain disappears and reforms as beta-pleated sheet structure. When the protein renatures, this beta structure remains although in some cases, the beta and alpha structure may be in equilibrium. However, the proteins with beta structure may then aggregate, essentially locking in the beta structure and forming amyloid. It is not clear whether smaller modules of proteins in beta structure aggregate to form amyloid or whether individual protein molecules attach to the growing cross-beta amyloid fibril.

There appear to be at least 3 mechanisms for amyloidogenesis. In the first, the native protein is partially denatured by some environmental factor, e.g. heat, pH change or some as yet unknown factor. There is some evidence that the proper environmental factors could be present within the lysosome. During the transition toward the molten globule form, the protein reaches an amyloidogenic intermediate that can aggregate into a dimer or multimer with a key quaternary structure that goes on to form amyloid. There is some evidence for such a mechanism with prion proteins (Kelly, 1998*b*). Since there is a high energy barrier between the native protein form and the amyloidogenic form, such a transition will be rare or may require a great deal of time. This type of mechanism has been suggested for senile systemic amyloidosis in which amyloid is formed from the native transthyretin protein.

A second mechanism is seen in the presence of mutations. Interestingly, the mutations of amyloidogenic proteins that give rise to amyloid diseases do not usually cause a markedly abnormal structure or function of the protein. Instead, it has been suggested (Kelly, 1998*a*; Jackson et al. 1999) that these mutations reduce the energy barrier between the native protein and the partially denatured amyloidogenic intermediate. Thus amyloidogenesis occurs earlier in life and is more severe and rapidly progressive because the native protein is more likely to undergo the transition to amyloid.

A third mechanism is seeding of the amyloid protein directly into an individual either by injection or ingestion, e.g. as in Kuru or in CJD probably resulting from ingestion of beef from cattle affected with bovine spongiform encephalopathy. Production of amyloid disease by this method, e.g. prion disease, may involve a third and as yet unknown mechanism (Blake et al. 1996; Radford, 1999).

Mechanisms of protein insolubilisation: posttranslational modification

It is not yet clear whether posttranslational modification may be required for protein insolubilisation or whether this may occur incidentally or after insolubilisation. For example, the A-beta peptide, a 39–43 residue peptide of the amyloid precursor protein and the NAC fragment of alpha-synuclein occur as insoluble portions of the amyloid plaque in Alzheimer disease. Exon 1 of huntingtin, the portion containing the expanded polyglutamine repeat, is cleaved from huntingtin in the formation of insoluble precipitates.

In the same way, it has been suggested that a feature of posttranslational modification, glycosylation, may be required for the PrP^{c} to PrP^{sc} transition in prion diseases (Kelly, 1998*b*).

Another posttranslational modification implicated in protein insolubility is cross-linking of protein molecules. For example, gamma-glutamyltranspeptidase is such a cross linking enzyme and alpha-synuclein is a potential substrate for this enzyme.

Mechanisms of protein insolubilisation: gain or loss of a binding partner

Molecular chaperones, also known as heat-shock proteins, are required for the attainment of the correct tertiary structure of many proteins. These chaperones bind as the protein moves out from the ribosome and help the protein to fold properly. The chaperones play a more active role than was earlier thought. They bind to certain regions of the peptide chain, e.g. hydrophobic regions, and cleave ATP as they help the protein fold. Proteins that fail to fold properly after repeated attempts are degraded and recycled. Chaperones may bind to proteins that have become partially denatured and induce them to refold properly. Consequently, the chaperone mechanisms are points at which amyloidogenesis could be influenced. For example, if chaperones were defective in some way, then malfolded proteins could be produced that are more likely to undergo transition to amyloid. Alternatively, if a protein later becomes partially denatured and is not repaired soon enough because of a defective chaperone mechanism, the protein could undergo transition to amyloid (Radford, 1999).

Proteins may also have binding partners that help to stabilise them. Synphilin-1 is a newly recognised binding partner of alpha-synuclein (Engelender et al. 1999). It is possible that loss of synphilin-1 or damage to it by mutation could make it more likely that its binding partner, alpha-synuclein, could undergo a conformational change and become insolubilised (Davidson et al. 1998).

Mechanisms of protein insolubilisation: defect in the ubiquitin-proteasome system

Proteins that are targeted for degradation may be tagged with ubiquitin and thus be recognised by the proteasome system. The proteasome contains an ordered array of degradative enzymes. Proteins that enter the proteasome are degraded by proteases and the resulting amino acids or peptides are recycled by the cell. Proteins that have been partially denatured and would undergo the transition to amyloid will show markers that may be recognised by the ubiquitination complex and ubiquitinated, thus being tagged for destruction and protecting the cell from amyloid production. Thus, this system is also a point where damage could lead to protein insolubilisation.

Interestingly, a mutation in the ubiquitination system has recently been found to segregate with PD in an autosomal dominant kindred (Leroy et al. 1998).

HOW DOES PROTEIN INSOLUBILITY LEAD TO NEURONAL DEGENERATION?

A reasonable hypothesis is that protein insolubility leads to neuronal damage (Conway et al. 1998; Crowther et al. 1998; Hashimoto et al. 1998). Nonetheless, it remains possible that protein insolubility is merely an epiphenomenon and that the damage to neurons results from soluble factors. For example, it is possible that a soluble form of amyloid protein in beta structure, preceding the precipitation into the amyloid mass seen histologically, may be the actual toxin.

Two mechanisms have been suggested for damage to neurons by insoluble proteins: interference with axonal transport and apoptosis. Of course, these mechanisms are not mutually exclusive. Interference with axonal transport could itself trigger changes leading to apoptosis.

Interference with axonal transport

This mechanism is attractive because the various forms of axonal transport are critical for neuronal survival. Also, neurons are unique in having the extended processes known as axons and neurons also seem to be uniquely vulnerable to diseases of protein insolubility. However, is there evidence for interference with axonal transport by insoluble proteins?

Normally, alpha-synuclein appears to bind to vesicles involved with fast axonal transport. One of the mutations of alpha-synuclein responsible for autosomal dominant PD, the A30P mutation (Kruger et al. 1998) appears to interfere with fast vesicular axonal transport in the rat. A problem with this observation is that the more severe A53T mutation does not seem to interfere with fast vesicular axonal transport in this species. However, alpha-synuclein in the rat normally contains T not A at position 53 but there are differences at other positions between rat and human alpha-synuclein. Thus A53T is not a true mutation in the rat, but the amino acid differences at the other positions could allow alpha-synuclein to function normally in this species (Jensen et al. 1998).

Alpha-synuclein has been observed to precipitate within axons in at least 2 ways. First, insoluble alpha-synuclein coats the inner surface of dystrophic neurites to an extent that suggests this could interfere with axonal transport. Also, round aggregates of alpha-synuclein resembling Lewy bodies have been observed within the axon large enough to effectively block movement through the axon by acting as a plug (Braak et al. 1999; Narhi et al. 1999).

Thus is it plausible that insolubilisation of alpha-synuclein could interfere with axonal transport. Supporting this mechanism is the function of tau as a microtubule associated protein. It is reasonable that a protein that binds microtubules could also interfere directly with axonal transport.

Apoptosis

Apoptosis has been implicated in diseases associated with protein insolubilisation (Borden, 1998; El-Agnaf et al. 1998; Jackson et al. 1998; Liu et al. 1998; Ona et al. 1999). However, it is not clear whether the insoluble protein causes the apoptosis or could even in some cases be protecting the neuron from cell death (Saudou et al. 1998).

Activation of caspases, e.g. caspase 8, is seen in apoptosis. Caspases are activated from their pro-caspase form either by cleavage by other proteases or by bringing together 2 or more procaspase molecules such that the low proteolytic activity of each pro-caspase can cleave its neighbour thus activating it. This mechanism depends upon the binding of adaptor molecules to protein interaction regions that are located within the prodomains of some caspases. Two types of functional adaptor molecules are known. The first forms complexes with the intracellular domains of apoptosis-inducing members of the tumour necrosis factor receptor family known as 'death receptors'. The second type of adaptor molecule, Apaf-1, aggregates on binding to the cytochrome c that is released from mitochondria as part of the apoptosis mechanism. Recently, a third type of adaptor molecule mechanism has been proposed in which large polyglutamine repeats can trigger apoptosis. In this mechanism, polymerised polyglutamine repeat proteins bind adaptor molecules, such as FADD, which in turn bind procaspase-8, leading to trans-activation and generation of active caspase-8 (Green 1999; Sanchez et al. 1999).

CONCLUSIONS

Insoluble proteins have been associated with many human neurodegenerative diseases of ageing. At present there is rapid progress both in learning how some proteins become insoluble, e.g. amyloidogenesis, and how such protein changes may damage the cell. Approaches are being made in preventing amyloid formation and dissolving amyloid deposits. Thus it is possible that this work could lead to practical ways to prevent or reverse these diseases in humans.

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