Aberrant Protein Deposition and Neurological Disease*

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The association of protein deposits with neurodegeneration has become a consistent finding in a large group of etiologically diverse diseases (1, 2) (Table I). The protein deposits are generally dense fibrillar structures containing a high percentage of β-pleated sheet secondary structure and can be located in various cellular compartments as well as extracellularly. Moreover, the deposits are generally ubiquitinated and may contain numerous cellular proteins.

Neurodegenerative Disorders Caused by Polyglutamine Expansion

Currently there are eight neurodegenerative disorders known to be caused by the expansion of a CAG trinucleotide repeat coding for polyglutamine. Protein aggregates have been observed in most of these disorders (1, 3). A mechanism of pathogenesis for these disorders has not been elucidated, although it is likely mediated through the polyglutamine tract because longer tracts lead to earlier ages of onset and more severe phenotypes.

Spinocerebellar Ataxia Type 1 (SCA1) — SCA1 is characterized clinically by gait and limb ataxia, dysarthria, dysmetria, and variable degrees of muscle wasting (4). SCA1 patients have CAG repeat tracts ranging in size from 39 to 83 glutamines. The SCA1 gene product, ataxin-1, is normally a nuclear protein except in Purkinje cells where it is also cytoplasmic. Ubiquitin-positive nuclear inclusions have been observed in SCA1 transgenic mice, transfected cells, and in affected brain regions of SCA1 patients (5) (Fig. 1).

In both cultured cells and cerebellar tissue of SCA1 transgenic mice, ataxin-1 associates with the nuclear matrix (5). An associated redistribution of the matrix-associated promyelocytic leukemia protein suggests that SCA1 pathogenesis may be due to morphologic changes within the nucleus. Transgenic mice expressing mutant ataxin-1 without a nuclear localization sequence fail to develop disease-related pathology and exhibit no signs of ataxin-1 aggregation (6). Interestingly, other transgenic mice lacking a self-association domain outside of the polyglutamine tract express mutant ataxin-1 in the nucleus and develop ataxia without evidence of ataxin-1 nuclear aggregates. Thus, nuclear localization of mutant ataxin-1 appears to be required for pathogenesis, whereas visible nuclear aggregation may not be required.

Spinocerebellar Ataxia Type 3/Machado-Joseph Disease (SCA3/MJD) — Clinically, SCA3 patients present with progressive ataxia, external ophthalmoplegia, muscle atrophy, and parkinsonian signs (4). These patients typically have repeat tract expansions ranging from 55 to 84 glutamines. Ataxin-3 is normally a cytoplasmic protein that accumulates in ubiquitinated aggregates in the nuclei of affected neurons (7). A necessary event in SCA3 pathogenesis is the entry of expanded ataxin-3 into the nucleus. Ubiquitinated intranuclear neuronal inclusions were only seen in neurons and not within glial cells, even though glial cells are immunoreactive with ataxin-3 antibodies. Cells expressing a truncated ataxin-3 fragment produce intranuclear inclusions, recruit full-length ataxin-3 into aggregates, and exhibit an induction of cell death (8). An ataxin-3 fragment may serve to catalyze the formation of intranuclear aggregates by translocating into the nucleus and recruiting endogenous ataxin-3 and other proteins into aggregates, in a dominant-negative manner.

Spinocerebellar Ataxia Type 6 (SCA6) — SCA6 is an autosomal dominant cerebellar ataxia caused by a CAG repeat expansion within the 3′-region of the α1A voltage-dependent calcium channel gene (CACNA1A) (9). Unlike the other CAG repeat expansion disorders, expansions within SCA6 patients are relatively small (21–30 glutamines) and fall within the normal range of other CAG tract lengths. In SCA6 brains numerous protein aggregates, appearing not to be ubiquitinated, were observed exclusively in the cytoplasm of Purkinje cells (3). Unlike this cytoplasmic localization, cells transfected with expanded SCA6 constructs exhibit perinuclear aggregates leading to apoptotic cell death.

Spinocerebellar Ataxia Type 7 (SCA7) — CAG repeat tract expansions in SCA7 patients have been shown to range from 34 to greater than 200 glutamines (1). In the brain of an early onset patient, intranuclear neuronal ubiquitinated inclusions occurred most frequently in the inferior olivary complex, a site of severe neuronal loss in SCA7 patients (10). However, inclusions were also observed in regions not affected by the disease, suggesting some cell specificity regarding the consequence of aggregation. Generally, inclusions in SCA7 brains were shown to be ubiquitinated to varying degrees. A critical observation is that the inclusions that are not ubiquitinated are found in regions that are not affected, suggesting ubiquitination is required for neurodegeneration. Similarly, ataxin-7 aggregates in Cos-1 cells that are localized to the nucleus are not ubiquitinated (11). Hence, some cell specificity with regard to ubiquitination also occurs.

Huntington Disease (HD) — The HD gene product, huntingtin, is predominantly a cytoplasmic protein (12). HD patients have CAG repeat tract lengths ranging from 38 to 180 glutamines. Nuclear inclusions in HD patients and transgenic mice have been found both in non-CNS tissue and neurons (13). Generally, the inclusions are immunoreactive with anti-N-terminal huntingtin and ubiquitin antibodies (Fig. 1). The striatum, which is predominantly affected in HD, actually contains far fewer aggregates compared with the cortex (14). This suggests that huntingtin aggregates may not be a good indicator of cells destined to die in HD (15). Interestingly, non-ubiquitinated aggregates have been found, suggesting that ubiquitination occurs late in formation.

Because there is no obvious nuclear localization sequence in huntingtin known nuclear import mechanisms are not responsible for translocating huntingtin to the nucleus. However, proteolytic processing may produce a smaller protein fragment that can enter the nucleus by diffusion (16). The activation of caspases appears to be involved in proteolytic cleavage, which leads to apoptotic cell death (17, 18). In addition, numerous reports have shown a correlation between the length of a truncated huntingtin protein and the size of the CAG tract with the frequency and localization of aggregates (19). Interestingly, transfection studies have shown that changing the subcellular localization of the huntingtin does not alter the frequency of aggregation or the level of toxicity (16). In contrast, HD constructs transfected into cultured striatal neurons produce intranuclear inclusions that do not correlate with apoptotic cell death (20).

Dentatorubral-Pallidoluysian Atrophy (DRPLA) — The clinical features of DRPLA are similar to HD (12). The DRPLA gene prod-
**Protein Aggregation in Other Neurodegenerative Disorders**

**Alzheimer’s Disease (AD)—**AD is characterized by the accumulation of extracellular plaques and cytoplasmic neurofibrillary tangles (NFTs) (2). The major component of the dense plaques is β-amyloid (Aβ), a 39–43-amino acid peptide derived from the larger amyloid precursor protein (APP). Accumulation of Aβ is an early event in development of AD that may preclude other brain lesions and symptoms by years. NFTs are bundles of paired helical filaments containing highly phosphorylated and ubiquitinated forms of the microtubule-associated factor tau (26).

Tissue-specific processing results in heterogeneity of the Aβ peptide at both its N and C termini (27). Both β- and γ-secretase have been shown to cleave APP, but this cleavage is not likely the first pathological alteration in AD because peptide resulting from this cleavage is found in deposits and in most other cells (28). The accumulation of Aβ is considered to be a central part of AD pathogenesis, which implies that over time preamyloid deposits are “transformed” into amyloid plaques (29). These lesions are thought to become compacted over a number of years while taking on the characteristics of amyloid and are associated with neuronal damage and tangles in the form of neuritic plaques.

**Parkinson’s Disease (PD)—**Clinically, Parkinson’s disease patients present with resting tremor, muscular rigidity, bradykinesia, and postural instability (30). The symptoms are suggested to result from abnormal dopamine levels or degeneration of dopaminergic neurons in affected regions of the CNS. In addition to neuronal degeneration ubiquitinated intracytoplasmic inclusion bodies (Lewy bodies) have been found in numerous brain regions (31). A major component of Lewy bodies is α-synuclein. Lewy bodies have been shown to be immunoreactive for ubiquitin, β-amyloid precursor protein, synaptophysin, neurofilaments, and ubiquitin C-terminal hydrolase (32, 33).

Two different α-synuclein missense mutations (A30P and A53T) have been found in dominant cases of PD. In vitro studies have shown that when compared with wild-type α-synuclein both of these PD-linked mutations accelerate aggregate formation (34). Because A30P and A53T accelerate aggregation the proteasome may have difficulty in clearing the aggregates. Furthermore, a mutation in the ubiquitin C-terminal hydrolase L1 gene (UCH-L1), a deubiquitinating protease that is thought to cleave polymeric ubiquitin to monomers, has been found in a family with PD (33). In vitro analysis has shown that a mutation in this gene results in reduced catalytic activity, supporting the hypothesis that the aggregates are inefficiently cleared by the proteasome.

**Prion Diseases—**Prion diseases comprise a group of disorders characterized by the accumulation of a conformationally modified form of the prion protein (PrP) (35). The infectious prion is an insoluble proteinaceous particle that lacks nucleic acid and to date has been shown to consist only of a modified isoform of PrP, designated PrPsc. The prion diseases are unique in that the proteinaceous prion particle is itself transmissible (36). Prion diseases include scrapie in sheep and bovine spongiform encephalopathy in cattle. In humans the prion diseases include Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, Kuru, and fatal familial insomnia.

Although mutations in PrP are found throughout the protein, some mutations in PrP have been shown to occur in regions adjacent to elements of putative secondary structure (35, 37). Structural changes may have dramatic effects on the cellular properties of the mutant protein. A form with decreased α-helical content and increased β-sheet content is insoluble and relatively resistant to proteases.

**Amyotrophic Lateral Sclerosis (ALS)—**Approximately 90% of ALS cases are sporadic in nature, and the remaining 10% represent

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**TABLE I**

**Neurological disorders with aberrant protein deposition**

| Disorder     | Protein        | Affected regions                          | Cellular location of aggregates |
|--------------|----------------|------------------------------------------|--------------------------------|
| AD           | Amyloid-β      | Hippocampus, cerebral cortex             | Extracellular                  |
| PD           | α-Synuclein    | Substantia nigra, hypothalamus           | Cytoplasmic                    |
| Prion diseases | PrP           | Various regions of CNS                   | Extraocular                    |
| ALS          | SOD1           | Motor cortex, brainstem                  | Cytoplasmic                    |
| SCA1         | ataxin-1       | Purkinje cells, brainstem                | Nuclear                        |
| SCA3         | ataxin-3       | Basal ganglia, brainstem                 | Nuclear, perinuclear           |
| SCA6         | Calcium channel| Purkinje cells                           | Cytoplasmic, Perinuclear       |
| SCA7         | ataxin-7       | Cerebellum, inferior olive               | Nuclear, nucleolar             |
| HD           | huntingtin     | Striatum, cerebral cortex               | Variable intracellular, variable intracellular |
| DRPLA        | atrophin-1     | Dentate nucleus, neocortex              | Nuclear                        |
| SBMA         | Androgen receptor | Spinal cord, cranial nerves           | Nuclear                        |

*ND, not determined.*
familial cases (38). Of the familial ALS cases, approximately 20% are due to mutations in the Cu,Zn-superoxide dismutase gene (SOD1). At least 50 mutations, the majority being missense mutations, have been found in the SOD1 gene in familial ALS families.

Transgenic mice have been made with transgenes harboring SOD1 mutations previously found in ALS patients. Initial indicators of disease in mice expressing a SOD1 G65R mutation include cytoplasmic ubiquitinated astrocytic inclusions reminiscent of Lewy bodies that stain intensely with SOD1 antibodies (39). The inclusions are 10 times more abundant in astrocytes than in neurons, and their frequency escalates markedly with disease progression. Like other SOD1 mutations this mutation occurs outside of the active site and may alter the stability of the protein backbone, resulting in conformational changes that ultimately lead to its abnormal deposition.

**Protein Aggregates and Pathogenesis**

*Formation of Inclusion Bodies—*The disorders discussed here present pathologically with inclusion bodies that are generally fibrillar in nature and contain a high percentage of β-sheet secondary structure. Conversion from a soluble form to an insoluble form may involve a change in the three-dimensional structure of the protein predominantly found in the aggregate. Protein interactions may occur by the formation of a stable β-sheet via a polar zipper (40). Alternatively, in the CAG triplet repeat disorders covalent bond formation between proteins has been suggested to occur via a transglutaminase-catalyzed reaction (23).

The formation of these aggregates may be a lengthy process, including numerous steps that culminate in targeting for degradation by ubiquitination. Perhaps the initiating event is proteolytic processing of the aggregate-forming protein. The major component of β-amyloid plaques in Alzheimer’s patients is a proteolytic fragment derived from the amyloid precursor protein (27). Four of the polyglutamine-containing proteins have been shown to be cleaved by caspases (41). Furthermore, in vitro cell toxicity in cultured neurons expressing an expanded polyglutamine fragment in vitro was observed with a PrP fragment (42). Together, these data indicate that proteolytic fragments may be toxic, leading to aggregate formation.

Other issues relevant to the formation of inclusions include the expression level of the protein and the amino acid sequence outside the polyglutamine tract. In HD transgenic mice expressing exon 1, inclusions appear earlier in homozygotes than in heterozygotes suggesting that the rate of inclusion formation is related to the level of transgene expression (43). Moreover, protein concentration and time are critical parameters for the formation of huntingtin aggregates in vitro (44). The protein context in which the expanded polyglutamine tract is located does not appear to be essential for aggregate formation. Ectopically expressed CAG repeats placed within the hypoxanthine phosphoribosyltransferase (HPRT) gene in transgenic mice produced a neurological phenotype and aggregates (45). However, ataxin-1 aggregates do not form in transgenic mice in which the ataxin-1 self-association domain has been deleted (6).

*Interacting Proteins—*One mechanism to impart a toxic gain of function by the mutant proteins is if they form stronger and/or more stable interactions with other proteins. Proteins that interact more strongly could be drawn into aggregates and prevented from carrying out their normal cellular function. Moreover, the remarkable cell specificity of the neurodegeneration in most of these disorders does not parallel the expression pattern of the primary protein and therefore may mimic the expression of such an interacting protein. Many proteins have been identified that interact with expanded polyglutamine-containing proteins (46, 47). For example, huntingtin interacts with HIP2, a ubiquitin-conjugating enzyme, suggesting a link between aggregate formation and protein disposal via the ubiquitin-dependent protein degradation pathway. Interestingly, in transfected striatal neurons coexpression of a dominant-negative ubiquitin-conjugating mutant prevented huntingtin aggregation but increased cell death (20).

Protein interactions have also been shown to be important for aggregate formation in AD. α2-Macroglobulin, a proteinase inhibitor released in response to inflammatory stimuli, strongly and specifically associates with the β-amyloid peptide and prevents fibril formation (48). These complexes are then cleared by the low density lipoprotein receptor-related protein (LRP), providing a mechanism of β amyloid clearance. This hypothesis suggests that the mechanism(s) for clearing aggregate complexes, possibly involving LRP, may be dysfunctional in AD patients.

*Abnormal Protein Processing and Disease Pathogenesis—*Molecular chaperones and proteasome components have been shown to co-localize to androgen receptor and ataxin-1 aggregates (49, 50). Overexpression of the chaperone HDJ-2/HSDJ in HeLa cells suppressed aggregate formation, suggesting that the affected neurons are unable to properly fold or degrade the expanded polyglutamine protein. The 26 S proteasome redistributes to ataxin-3 aggregates, and proteasome inhibition results in a repeat length-dependent increase in aggregate (51). This suggests that the proteasome may play a protective role by suppressing aggregate formation. The Aβ peptide binds to the proteasome and has been shown to inhibit its activity (52). The inhibition of proteasome activity therefore blocks ubiquitin-mediated degradation of the Aβ peptide and perhaps hampers the proteasome’s ability to degrade other ubiquitinated proteins. Furthermore, protein deposits in AD have been shown to contain ubiquitin-B with a +1 frameshift mutation, inhibiting the ability to polyubiquitinate proteins (53).

The persistence of ubiquitinated structures could be because of cellular inability to rescue misfolded proteins, failure to properly shuttle the complexes into degradation pathways, or exceeding the capacity of the proteasome (Fig. 2). Sequestering of ubiquitin and other protein degradation factors within the protein deposit or blocking of the proteasome lumen by the aggregate could alter the normal cellular role of the ubiquitin-mediated protein degradation pathway. Moreover, the function of cellular proteins in these disorders could be altered either by sequestration within the aggregate itself or by altered regulation due to sequestration of ubiquitin-proteasome components (Fig. 2). In support of this stably transfected PC12 cells expressing a huntingtin fragment with 150 glutamine repeats showed altered expression of numerous genes compared with a fragment expressing a normal repeat (54). Fur-
ther evidence for the direct involvement of the ubiquitin-proteasome pathway in neurodegenerative disorders comes from the discovery that an intragenic deletion in ubiquitin C-terminal hydrolase (Uch1) is responsible for gracial axonal dystrophy in mice (55). These mice exhibit neurodegeneration and accumulate amyloid B-protein and ubiquitin-positive deposits within the brain. Dysfunction of Uch1 inhibits the processing and reusage of free ubiquitin, and thus may allow the accumulation of abnormal proteins.

Additional disorders substantiate the idea that abnormal protein processing or degradation may play a key role in the pathogenesis of neurological disease. Early onset torsion dystonia is due to a 3-base pair deletion in the torsina gene (56). Torsina shows homology in several domains with a class of heat shock/chaperone proteins. Hence, mutation of torsina may lead to abnormal folding of proteins involved in early onset torsion dystonia. Autosomal recessive juvenile parkinsonism has been associated with mutations in the parkin gene (57). The N-terminal portion of parkin is fairly homologous to ubiquitin. Mutations in the ubiquitin protein ligase E6-AP are responsible for Angelman’s syndrome, an inherited form of mental retardation (58).

Whether protein aggregates directly cause neurodegeneration or are the result of a dying neuron is not yet known. In the CAG repeat disorders, aggregates precede the onset of neurological symptoms (19). Interestingly, small aggregates are not ubiquitinated, indicating that ubiquitination occurs late in the formation process. This suggests that the cell is attempting to clear the aggregated proteins but is unsuccessful. The inability to degrade the aggregate may impair the cell’s ability to carry out normal protein processing and degradation pathways, which could lead to altered half-lives of physiologically important proteins. Indeed, it may be that in the absence of cell division, the neuron is hypersensitive to changes in the balance of protein synthesis and degradation, which may ultimately lead to neurodegeneration.

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