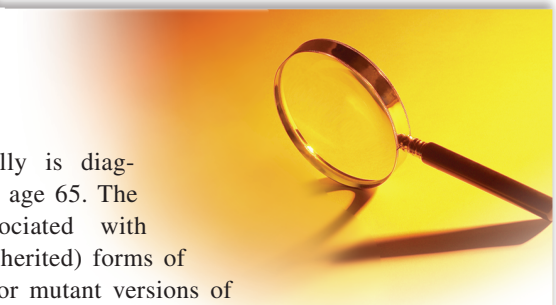
BIOCHEMISTRY IN PERSPECTIVE

Protein Folding and Human Disease



What are the effects of misfolded proteins on human health? The accumulation of insoluble, misfolded proteins is an important feature of several human neurodegenerative diseases. Alzheimer's and Huntington's diseases are prominent examples. Despite differences in their initiating events, specific brain areas affected, and symptoms, both diseases have in common cell-destroying dysfunctional processes set in motion by toxic proteins. A key feature of disease initiation is the conversion of normal protein structure, most commonly α-helices and random coils, into abnormal β-pleated sheet conformations. A brief overview of the molecular basis of each disease is provided.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive and ultimately fatal condition that is characterized by seriously impaired intellectual function. AD first manifests itself with short-term memory loss. Eventually, severe memory loss, disorientation, and agitation accompany a total loss of the patient's personality. Caused by neuronal death in brain regions related to memory and cognition, AD is a multifactorial disease. It is diagnosed at autopsy by the presence of insoluble aggregates of extracellular proteinaceous debris called **amyloid deposits** (or senile plaques) and intracellular accumulations of excessively phosphorylated versions of *tau*, an intrinsically unfolded microtubule-associated protein. Mutation of the tau gene, posttranslational modifications, and/or aberrant proteolysis of tau, all of which weaken its association with microtubules, increase the free concentration of tau in the cytoplasm. In its free form, tau aggregates into long filaments and/or becomes cleaved by the enzyme caspase-3, initiating apoptotic processes (p. 56) that lead to cell death. The link between this event and β-amyloid deposits is not clear, but *in vitro* studies show that β-amyloid fragments potentiate caspase-3/tau activity. The core of amyloid deposits is composed of Aβ40 and Aβ42 cleavage products of amyloid precursor protein (APP).

There are inherited and sporadic versions of AD. Most cases of inherited AD have an early onset (i.e., in middle age). Sporadic AD typically is diagnosed after age 65. The genes associated with familial (inherited) forms of AD code for mutant versions of APP, presenilin 1 (PS1), presenilin 2 (PS2), and apolipoprotein E4 (p. 392). APP is a transmembrane protein of unknown function with a large extracellular region that undergoes several proteolytic processing reactions. PS1 and PS2 are components of secretase γ, one of several proteases involved in APP processing. Mutations in the genes for APP, PS1, and PS2 have been associated with the release of the toxic Aβ40 and Aβ42 fragments. The mechanisms by which AD patients develop the sporadic form of the disease in the absence of known risk factors remain unresolved.

Huntington's Disease

Huntington's disease (HD) is one of a group of inherited neurodegenerative disorders called the polyglutamine diseases. The symptoms of HD (psychomotor skill loss, involuntary movements, and progressive dementia) are caused by neuron death in the frontal lobes and the basal ganglia of the brain. The HD gene codes for *huntingtin*, a large polypeptide of unknown function with a molecular mass of nearly 350 kD. A polyglutamine sequence containing between 6 and 34 glutamine residues occurs at the protein's N-terminal. In the mutant protein, the glutamine repeat sequence may contain as many as 150 glutamine residues, but as few as 37 residues can cause the disease. The age of symptom onset correlates with the length of the polyglutamine sequence. For example, early-onset (juvenile) HD occurs in individuals with over 55 repeats. It is believed that the initiating neurotoxic event is the association between polyglutamine sequences from nearby huntingtin molecules to form a β-sheet-like structure called a polar zipper. The subsequent formation of protein aggregates, which contain mutant huntingtin and other proteins, triggers a cascade of events that ends in apoptosis.

SUMMARY: The accumulation of misfolded proteins impedes cell function. Eventually protein aggregates cause cell death.