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Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer's and Parkinson's diseases.

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Abstract

Abnormal interactions and misfolding of synaptic proteins in the nervous system are being extensively explored as important pathogenic events resulting in neurodegeneration in various neurological disorders. These include Alzheimer's disease (AD), Parkinson's disease (PD), and dementia with Lewy bodies (DLB). In AD, misfolded amyloid beta peptide 1-42 (Abeta), a proteolytic product of amyloid precursor protein metabolism, accumulates in the neuronal endoplasmic reticulum and extracellularly as plaques. In contrast, in PD and DLB cases there is abnormal accumulation of alpha-synuclein in neuronal cell bodies, axons, and synapses. Furthermore, in DLB, Abeta 1-42 may promote alpha-synuclein accumulation and neurodegeneration. The central event leading to synaptic and neuronal loss in these diseases is not completely clear yet; however, recent advances in the field suggest that nerve damage might result from the conversion of nontoxic monomers to toxic oligomers and protofibrils. The mechanisms by which misfolded Abeta peptide and alpha-synuclein might lead to synapse loss are currently under investigation. Several lines of evidence support the possibility that Abeta peptide and alpha-synuclein might interact to cause mitochondrial and plasma membrane damage upon translocation of protofibrils to the membranes. Accumulation of Abeta and alpha-synuclein oligomers in the mitochondrial membrane might result in the release of cytochrome C with the subsequent activation of the apoptosis cascade. Conversely, the oxidative stress and mitochondrial dysfunction associated with AD and PD may also lead to increased membrane permeability and cytochrome C release, which promotes Abeta and alpha-synuclein oligomerization and neurodegeneration. Together, these studies suggest that the translocation of misfolded proteins to the mitochondrial membrane might play an important role in either triggering or perpetuating neurodegeneration. The insights obtained from the characterization of this process may be applied to the role of mitochondrial dysfunction in other neurodegenerative disorders, including AD. New evidence may also provide a rationale for the mitochondrial membrane as a target for therapy in a variety of neurodegenerative diseases.

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