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The Pathology of Neurodegenerative Diseases: Understanding the Underlying Mechanisms

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Description

Neurodegenerative diseases are a diverse group of disorders characterized by the progressive degeneration of the structure and function of the nervous system. These conditions, which include Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS), are marked by a gradual decline in cognitive, motor, and sometimes sensory functions. Despite their differences, neurodegenerative diseases share common pathological features, including the accumulation of misfolded proteins, neuronal loss, and neuro-inflammation. Understanding these underlying mechanisms is crucial for developing effective treatments and interventions. The progressive loss of neurons is a common feature across neurodegenerative diseases. In Alzheimer's, neuronal loss occurs in the hippocampus and cortex, leading to memory deficits and cognitive decline. In Parkinson's, the loss of dopaminergic neurons in the substantia nigra results in motor symptoms. Huntington's disease involves the loss of neurons in the striatum, affecting movement and cognitive function. In ALS, the degeneration of upper and lower motor neurons leads to muscle weakness and atrophy. Chronic inflammation within the brain and spinal cord is a hallmark of neurodegenerative diseases. Microglia, the resident immune cells of the central nervous system, become activated in response to neuronal injury and protein aggregates. While initially protective, chronic microglial activation can exacerbate neuronal damage through the release of pro-inflammatory cytokines and reactive oxygen species. The pathogenesis of Alzheimer's disease is believed to be driven by the accumulation of amyloid-beta plaques and tau tangles. Amyloid-beta is produced from the cleavage of amyloid precursor protein (APP) and aggregates into plaques that disrupt cell function. Tau, a microtubule-associated protein, becomes hyperphosphorylated and forms tangles that impair neuronal transport and contribute to cell death. Additionally, genetic factors such as mutations in the APP, PSEN1, and PSEN2 genes, as well as the presence of the APOE ε4 allele, increase the risk of developing Alzheimer's. Parkinson's disease involves the selective loss of dopaminergic neurons in the substantia nigra. The accumulation of alpha-synuclein in Lewy bodies is thought to play a central role in this process. The exact mechanism by which alpha-synuclein aggregates cause cell death is not fully understood, but it is believed to involve mitochondrial dysfunction, impaired protein degradation pathways, and disruption of cellular homeostasis. Huntington's disease is caused by a CAG repeat expansion in the HTT gene, leading to the production of a mutant huntingtin protein with an abnormally long polyglutamine tract. This mutant protein forms aggregates that interfere with various cellular processes, including transcription, protein degradation, and mitochondrial function. The selective vulnerability of striatal neurons to mutant huntingtin is a key feature of the disease. ALS involves the degeneration of motor neurons, leading to muscle weakness and atrophy. Several genetic mutations have been linked to ALS, including those in the SOD1, C9orf72, TDP-43, and FUS genes. These mutations result in the production of misfolded proteins that aggregate and disrupt cellular function. The exact mechanisms of motor neuron degeneration in ALS are complex and involve oxidative stress, impaired RNA processing, and disrupted axonal transport. Research into the pathology of neurodegenerative diseases is ongoing, with the goal of developing effective treatments.

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Conflict of Interest

Authors declare that they have no conflict of interest.

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