Neurodegenerative disease pathogenesis

The pathogenesis of neurodegenerative diseases involves complex and interconnected mechanisms that lead to the progressive loss of neurons and their function. While each disease has distinct features, several common pathological processes underlie neurodegeneration:

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Protein Misfolding and Aggregation

1. **Pathological hallmark:** Misfolded proteins aggregate into toxic forms, disrupting cellular function.
2. **Examples:**
    1. **Alzheimer's disease (AD):** Accumulation of beta-amyloid plaques and hyperphosphorylated tau tangles.
    2. **Parkinson's disease (PD):** Aggregation of alpha-synuclein into Lewy bodies.
    3. **Huntington's disease (HD):** Polyglutamine expansions in the huntingtin protein.
3. **Mechanism:** Misfolded proteins evade the ubiquitin-proteasome system and autophagy, leading to toxic accumulation and neuronal death.

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2. Oxidative Stress

1. **Definition:** Imbalance between reactive oxygen species (ROS) production and antioxidant defenses.
2. **Impact:** ROS damage proteins, lipids, and DNA, contributing to cellular dysfunction and apoptosis.
3. **Link to diseases:**
    1. Mitochondrial dysfunction is a major source of ROS in PD and AD.
    2. Impaired oxidative stress responses exacerbate neuronal vulnerability.

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3. Mitochondrial Dysfunction

1. **Role of mitochondria:** Provide energy (ATP) and regulate cellular metabolism.
2. **Dysfunction mechanisms:**
    1. Impaired oxidative phosphorylation reduces energy supply.
    2. Release of cytochrome c triggers apoptotic pathways.
    3. Mitochondrial DNA mutations increase susceptibility.
3. **Implications:** Energy failure and increased oxidative stress contribute to neuronal death.

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4. Neuroinflammation

1. **Key players:**
    1. **Microglia:** Overactivated microglia release pro-inflammatory cytokines (e.g., IL-1β, TNF-

α) and ROS.
    2. **Astrocytes:** Reactive astrocytes exacerbate neurotoxic environments.
2. **Impact:**
    1. Chronic inflammation damages neurons and impairs repair mechanisms.
    2. Seen in multiple sclerosis, AD, PD, and amyotrophic lateral sclerosis (ALS).

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5. Excitotoxicity

1. **Definition:** Excessive activation of glutamate receptors (e.g., NMDA and AMPA receptors) causes neuronal injury.
2. **Mechanism:**
    1. Overactivation leads to calcium influx, triggering cascades of enzymatic reactions.
    2. Results in oxidative stress, mitochondrial dysfunction, and cell death.
3. **Diseases:**
    1. Prominent in ALS, AD, and ischemic brain injury.

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6. Impaired Autophagy and Lysosomal Function

1. **Autophagy:** Cellular process to degrade and recycle damaged organelles and proteins.
2. **Lysosomal dysfunction:** Impairs degradation of aggregated proteins.
3. **Disease links:**
    1. Lysosomal storage disorders contribute to neurodegenerative processes.
    2. In PD, mutations in lysosomal enzymes (e.g., GBA1) increase alpha-synuclein aggregation.

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7. Genetic and Epigenetic Contributions

1. **Inherited mutations:**
    1. AD: Mutations in **APP**, **PSEN1**, **PSEN2**.
    2. PD: Mutations in **LRRK2**, **PINK1**, **SNCA**.
    3. ALS: Mutations in **C9orf72**, **SOD1**.
2. **Epigenetics:** DNA methylation, histone modification, and non-coding RNAs influence gene expression and susceptibility.

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8. Synaptic Dysfunction

1. Early loss of synaptic function often precedes neuronal death.
2. Mechanisms:
    1. Toxic protein aggregates impair synaptic signaling.
    2. Disruption of neurotransmitter release and receptor activity.
3. Diseases:
    1. Synaptic dysfunction is a primary feature in AD and HD.

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9. Blood-Brain Barrier (BBB) Breakdown

1. **Role of BBB:** Maintains brain homeostasis and protects against toxins.
2. **Dysfunction:**
    1. BBB breakdown allows harmful molecules and immune cells to enter the brain.
    2. Exacerbates neuroinflammation and neuronal damage.
3. Seen in AD, MS, and other neurodegenerative diseases.

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10. Cellular Senescence

1. **Definition:** Age-related loss of cellular division and function.
2. **Role in neurodegeneration:**
    1. Senescent glial cells secrete pro-inflammatory factors.
    2. Accumulation of senescent neurons disrupts brain function.

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Interplay of Mechanisms These pathways are interconnected and amplify one another:

1. For example, mitochondrial dysfunction exacerbates oxidative stress, which in turn triggers protein aggregation and neuroinflammation.
2. The vicious cycle accelerates neuronal loss and disease progression.

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Implications for Therapy Understanding these mechanisms guides therapeutic approaches:

1. **Protein clearance:** Targeting aggregation (e.g., monoclonal antibodies in AD).
2. **Antioxidants:** Counteracting oxidative stress (e.g., edaravone in ALS).
3. **Neuroprotective strategies:** Modulating neuroinflammation and excitotoxicity.
4. **Gene therapy:** Correcting genetic defects.
5. **Mitochondrial support:** Enhancing energy production and reducing ROS.

Accumulation of oxidative stress is highly intertwined with the aging process and contributes to aging-related diseases, such as neurodegenerative diseases. Deciphering the molecular machinery that regulates oxidative stress is fundamental to further uncovering the pathogenesis of these diseases. chaperone-mediated autophagy (CMA), a highly selective lysosome-dependent degradation process, has been proven to be an important maintainer of cellular homeostasis through multiple mechanisms, one of which is the attenuation of oxidative stress. However, the specific mechanisms underlying this antioxidative action of CMA are not fully understood. In a study, Zhu et al. found that chaperone-mediated autophagy (CMA) directly degrades Kelch-like ECH-associated protein 1 (Keap1), an adaptor of the E3 ubiquitin ligase complex that promotes the degradation of nuclear factor erythroid 2-related factor 2 (Nrf2), which is a master transcriptional regulator in antioxidative response. Activated CMA induced by prolonged oxidative stress led to an increase in Nrf2 level by effectively degrading Keap1, contributing to Nrf2 nuclear translocation and the expression of multiple downstream antioxidative genes. Meanwhile, together with a previous study showing that Nrf2 can also transcriptionally regulate LAMP2A, the rate-limiting factor of the CMA process, we reveal a feed-forward loop between CMA and Nrf2. The study identifies CMA as a previously unrecognized regulator of the Keap1-Nrf2 pathway and reinforces the antioxidative role of chaperone-mediated autophagy (CMA) [1)].

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Zhu L, He S, Huang L, Ren D, Nie T, Tao K, Xia L, Lu F, Mao Z, Yang Q. Chaperone-mediated autophagy degrades Keap1 and promotes Nrf2-mediated antioxidative response. Aging Cell. 2022 May 10:e13616. doi: 10.1111/acel.13616. Epub ahead of print. PMID: 35535673.