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EFFECT OF PRIONS ON NEURODEGENERATIVE DISEASES

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ABSTRACT

Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons. Many neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's occur as a result of neurodegenerative processes. Such diseases are incurable, resulting in progressive degeneration and/or death of neuron cells.As research progresses, many similarities appear that relate these diseases to one another on a sub-cellular level. Discovering these similarities offers hope for therapeutic advances that could ameliorate many diseases simultaneously. There are many parallels between different neurodegenerative disorders including atypical protein assemblies as well as induced cell death. Neurodegeneration can be found in many different levels of neuronal circuitry ranging from molecular to systemic.

Keywords : Neurodegeneration, neurons, Parkinson's, Alzheimer's, sub-cellular level

I. INTRODUCTION

Many neurodegenerative diseases are caused by genetic mutations, most of which are located in completely unrelated genes. In many of the different diseases, the mutated gene has a common feature: a repeat of the CAG nucleotide triplet. CAG encodes for the amino acid glutamine. A repeat of CAG results in a polyglutamine (polyQ) tract. Diseases showing this are known as polyglutamine diseases.

- **Polyglutamine:** A repeat in this causes dominant pathogenesis. Extra glutamine residues can acquire toxic properties through a variety of ways, including irregular protein folding and degradation pathways, altered subcellular localization, and abnormal interactions with other cellular proteins.[4] PolyQ studies often use a variety of animal models because there is such a clearly defined trigger – repeat expansion. Extensive research has been done using the models of nematode (*C. elegans*), and fruit fly (*Drosophila*), mice, and non-human primates. Mammalian data is often needed for FDA approval of drugs, which means that the bulk of the research is done using mice. Using data from the other animals (*C. elegans* and *Drosophila* primarily) is often a precursor to finding the equivalent mammalian gene.[5][6]
  - Nine inherited neurodegenerative diseases are caused by the expansion of the CAG trinucleotide and polyQ tract.[7] Two examples are Huntington's disease and the spinocerebellar ataxias. For a complete list, see the table under **Polyglutamine (PolyQ) Diseases** in the article Trinucleotide repeat disorder. While polyglutamine-repeat diseases encompass many different neurodegenerative disorders, there are many more it does not apply to. The genetics behind each disease are different and often unknown.

II.PROTEIN MISFOLDING

Several neurodegenerative diseases are classified as proteopathies as they are associated with the aggregation of misfolded proteins.

- **alpha-synuclein:** can aggregate to form insoluble fibrils in pathological conditions characterized by Lewy bodies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Alpha-synuclein is the primary structural component of Lewy body fibrils. In addition, an alpha-synuclein fragment, known as the non-Abeta component (NAC), is found in amyloid plaques in Alzheimer's disease.
- **tau:** hyperphosphorylated tau protein is the main component of neurofibrillary tangles in Alzheimer's disease.
- **beta amyloid:** the major component of senile plaques in Alzheimer's disease.
- **prion:** main component of prion diseases and transmissible spongiform encephalopathies.

III. INTRACELLULAR MECHANISMS

Protein degradation pathways

Parkinson's disease and Huntington's disease are both late-onset and associated with the accumulation of intracellular toxic proteins. Diseases caused by the aggregation of proteins are known as proteinopathies, and they are primarily caused by aggregates in the following structures:[2]

- cytosol, e.g. Parkinson's & Huntington's
- nucleus, e.g. Spinocerebellar ataxia type 1 (SCA1)
- endoplasmic reticulum (ER), (as seen with neuroserpin mutations that cause familial encephalopathy with neuroserpin inclusion bodies)
- extracellularly excreted proteins, amyloid-β in Alzheimer's disease

There are two main avenues eukaryotic cells use to remove troublesome proteins or organelles:

- **ubiquitin–proteasome:** protein ubiquitin along with enzymes is key for the degradation of many proteins that cause proteinopathies including polyQ expansions and alpha-synucleins. Research indicates proteasome enzymes may not be able to correctly cleave these irregular proteins, which could possibly result in a more toxic species. This is the primary route cells use to degrade proteins.
  - Decreased proteasome activity is consistent with models in which intracellular protein aggregates form. It is still unknown whether or not these aggregates are a cause or a result of neurodegeneration.
- **autophagy–lysosome pathways:** a form of programmed cell death (PCD), this becomes the favorable route when a protein is aggregate-prone meaning it is a poor proteasome substrate. This can be split into two forms of autophagy: **macroautophagy** and **chaperone-mediated autophagy (CMA)**
  - **macroautophagy** is involved with nutrient recycling of macromolecules under conditions of starvation, certain apoptotic pathways, and if absent, leads to the formation of ubiquinated inclusions. Experiments in mice with neuronally confined macroautophagy-gene knockouts develop intraneuronal aggregates leading to neurodegeneration. **chaperone-mediated autophagy** defects may also lead to neurodegeneration. Research has

shown that mutant proteins bind to the CMA-pathway receptors on lysosomal membrane and in doing so block their own degradation as well as the degradation of other substrates.

IV.MITOCHONDRIAL DYSFUNCTION

The most common form of cell death in neurodegeneration is through the intrinsic mitochondrial apoptotic pathway. This pathway controls the activation of caspase-9 by regulating the release of cytochrome c from the mitochondrial intermembrane space (IMS). Reactive oxygen species (ROS) are normal byproducts of mitochondrial respiratory chain activity. ROS concentration is mediated by mitochondrial antioxidants such as manganese superoxide dismutase (SOD2) and glutathione peroxidase. Over production of ROS (oxidative stress) is a central feature of all neurodegenerative disorders. In addition to the generation of ROS, mitochondria are also involved with life-sustaining functions including calcium homeostasis, PCD, mitochondrial fission and fusion, lipid concentration of the mitochondrial membranes, and the mitochondrial permeability transition. Mitochondrial disease leading to neurodegeneration is likely, at least on some level, to involve all of these functions.

There is strong evidence that mitochondrial dysfunction and oxidative stress play a causal role in neurodegenerative disease pathogenesis, including in four of the more well known diseases Alzheimer's,and Parkinson's,disease..

V.SPECIFIC DISORDERS

Alzheimer's disease

Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.[17]

Alzheimer's disease has been *hypothesized* to be a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain.[18] Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or Aβ). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair.[19][20] In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis.[21] One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques.[22][23]

Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder[24] and manifests as bradykinesia, rigidity, resting tremor and posture instability. The crude prevalence rate of PD has been reported to range from 15 per 100,000 to 12,500 per 100,000, and the incidence of PD from 15 per 100,000 to 328 per 100,000, with the disease being less common in Asian countries. Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopamine-generating cells in the substantia nigra, a region of the

midbrain; the cause of cell-death is unknown. The following paragraph is an excerpt from the Pathophysiology section of the article Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost *may* consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteasome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles — the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.[25]

Recent research suggests that impaired axonal transport of alpha-synuclein leads to its accumulation in the Lewy bodies. Experiments have revealed reduced transport rates of both wild-type and two familial Parkinson's disease-associated mutant alpha-synucleins through axons of cultured neurons.[11] Membrane damage by alpha-synuclein could be another Parkinson's disease mechanism.[8]

The main known risk factor is age. Susceptibility genes including α-synuclein, leucine-rich repeat kinase 2 (LRRK-2), and glucocerebrosidase (GBA) have shown that genetic predisposition is another important causal factor.

Aging

The greatest risk factor for neurodegenerative diseases is aging. Mitochondrial DNA mutations as well as oxidative stress both contribute to aging.[10] Many of these diseases are late-onset, meaning there is some factor that changes as a person ages for each disease.[2] One constant factor is that in each disease, neurons gradually lose function as the disease progresses with age.

Therapeutics

The process of neurodegeneration is not well understood, so the diseases that stem from it have, as yet, no cures. In the search for effective treatments (as opposed to palliative care), investigators employ animal models of disease to test potential therapeutic agents. Model organisms provide an inexpensive and relatively quick means to perform two main functions: target identification and target validation. Together, these help show the value of any specific therapeutic strategies and drugs when attempting to ameliorate disease severity. An example is the drug Dimebon (Medivation). This drug is in phase III clinical trials for use in Alzheimer's disease, and also recently finished phase II clinical trials for use in Huntington's disease.[5] In March 2010, the results of a clinical trial phase III were released; the investigational Alzheimer's disease drug Dimebon failed in the pivotal CONNECTION trial of patients with mild-to-moderate disease.[34] With CONCERT, the remaining Pfizer and Medivation Phase III trial for Dimebon (latrepirdine) in Alzheimer's disease failed in 2012, effectively ending the development in this indication.[35]

In another experiment using a rat model of Alzheimer's disease, it was demonstrated that systemic administration of hypothalamic proline-rich peptide (PRP)-1 offers neuroprotective effects and can prevent neurodegeneration in hippocampus amyloid-beta 25–35. This suggests that there could be therapeutic value to PRP-1.[36]

Protein degradation offers therapeutic options both in preventing the synthesis and degradation of irregular proteins. There is also interest in upregulating autophagy to help clear protein aggregates implicated in neurodegeneration. Both of these options involve very complex pathways that we are only beginning to understand.[2]

The goal of immunotherapy is to enhance aspects of the immune system. Both active and passive vaccinations have been proposed for Alzheimer's disease and other conditions, however more research must be done to prove safety and efficacy in humans.[37]

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