Pathophysiology of misfolded proteins leading to aggregation in parkinson's disease.

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Introduction

In cells, misfolded proteins coexist with unfolded, intermediately folded, and perfectly folded proteins. Chaperone proteins, which are involved in protein folding and trafficking as well as intermediate stabilisation, either destroy or refold misfolded proteins appropriately in healthy cells. Consequently, many, if not all, proteins are now thought to be capable of forming amyloid fibrils under the right biochemical conditions. Many disease-associated amyloidogenic proteins, on the other hand, include significant regions of intrinsic disorder in their free soluble forms, as well as specific, typically short internal amino acid sequences that are required and sufficient for aggregation. These motifs can also be found in non-disease proteins, and when these fragments are separated from the remainder of the protein, they form cytotoxic amyloid fibrils.

Misfolded proteins are routinely encountered by cells as a result of biogenesis errors, disease-causing mutations, and physiological stresses. They refold, degrade, or sequester misfolded proteins in specialised intracellular compartments, such as aggresomes or other forms of inclusion bodies. Chaperone proteins bind to nascent polypeptides as they emerge from ribosomes and aid in their folding, as well as supervise and participate in every step of misfolded protein handling. Chaperones also keep an eye on the folded chains' quality, and in some situations, they can unfold and refold misfolded proteins. Chaperones can also direct misfolded proteins to be degraded by the ubiquitin proteasome system or the autophagy process, or to be sequestered in other cellular compartments [1].

Aggregation of Alpha-Synuclein leads to Parkinson's Disease

The SNCA gene, which is found on the long arm of chromosome 4, encodes a 15-kDa protein called α-Syn (Chr 4q22.1). There are 140 amino acids in this protein, which are divided into three domains. The N-terminal region is made up of four sections with 11 "imperfect" repeats and a lysine-rich consensus sequence (KTKGEV). This region is important for the -syn protein's -helix shape, which allows it to bind to negatively charged lipids.

The centre region, known as the "Non-Amyloidogenic Component" (NAC), has hydrophobic qualities and is prone to aggregation under certain conditions. It is susceptible to conformational changes in α-syn, from random coiled-coils to β-sheet structures in an oligomeric state. The carboxyl-terminal region, which is characterised by acidic residues, confers an intrinsically formed structure to α-syn that mediates protein-protein interactions. This domain may show structural changes such as truncation, which involves the removal of acidic residues to promote the aggregation of α-syn into fibrils.

Physiological Reaction to Aggregation of α-Syn

α-syn, as well as other proteins and even cellular organelles, is degraded by the autophagy–lysosome (ALP) system. The ALP is made up of three pathways that transport intracellular components to lysosomes: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy. Proteins, plasma membrane constituents, and other extracellular substances are degraded or recycled by the latter. Indeed, data from human postmortem samples, transgenic mice, and cellular models of PD has linked changes in ALP to the buildup of α-syn [2]. Multiplications, mutations, and post-translational changes of the protein have also been shown to affect the operation of autophagy pathways, resulting in a vicious loop that leads to neuronal death. The two ALP mechanisms implicated in α-syn degradation are macroautophagy and CMA.

The development of autophagosomes leads to the destruction of α-syn in macroautophagy. Autolysosomes are formed when these fusion with lysosomes. In advanced stages of Parkinson's disease, α-syn aggregates hinder macroautophagy by lowering autophagosome clearance, which may contribute to increased dopaminergic neuron death. Indeed, in dopaminergic neurons, conditional deletion of the macroautophagy gene ATG-7 causes cell death and a reduction in striatal dopamine levels. As a result of this inhibition, ubiquitinated protein aggregates positive for p62 and ubiquitin develop. It also generates a buildup of α-syn in dopaminergic terminals in the striatum. The latter is in line with α-syn's physiological function at presynaptic terminals, as well as macroautophagy's role in axonal processes.

Macroautophagy is similarly hampered by α-syn mutations. Overexpression of α-syn WT and the A30P and A53T mutations, for example, inhibits macroautophagy in human cells and transgenic mice. This is because the RAB1A protein,

a GTPase implicated in early secretory pathways, is inhibited, producing a mislocalization of the early autophagy protein ATG-9 and limiting omegasome formation, an autophagic structure that is typically detected in connection with ER. Similarly, mutant α-syn expression causes morphological and functional defects in the autophagolysosomal system, inhibiting autophagosome lysosomal fusion and lowering mitophagy removal of both α-syn and defective mitochondria. Finally, phosphorylation and SUMOylation of α-syn speed up its turnover by macroautophagy [3].

The ubiquitin-proteasome system (UPS), also known as autophagy, is another important mechanism for the destruction of misfolded proteins in mammals, and is essential for maintaining cellular proteostasis. Misfolding of α-syn impairs UPS function, resulting in an increase in Lewy body development and neuronal death. This has been seen in both in vitro and in vivo PD models. Furthermore, when PD patients' brain tissue was compared to healthy control samples, there was a decrease in proteasome catalytic activity [4]. This evidence implies that misfolded α-syn has a direct effect on UPS function in advanced stages of PD. Inhibition of the UPS system in vivo, on the other hand, duplicates the neuropathological hallmarks of Parkinson's disease.

Protein misfolding causes protein aggregation, which is a recurrent motif in neurodegenerative disorders. Following the association of α-synuclein gene mutations with familial forms of the disease, and, more importantly, the identification of the protein as a major component of Lewy bodies, a pathological hallmark of PD, research on protein misfolding and aggregation has taken centre stage in Parkinson's disease (PD). Recent research has suggested that parkin may play a role in the clearance of insoluble protein aggregates via macroautophagy. Parkin, like α-synuclein, is susceptible to misfolding, especially when exposed to age-related stress. Protein misfolding can also influence the function of other important PD-related genes like DJ-1, PINK1, and possibly LRRK2 [5].

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