IS THE ACCUMULATION OF ALPHA-SYNUCLEIN DETRIMENTAL AND A VALID TARGET FOR INTERVENTION IN PD? NO

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Parkinson's disease (PD) is considered as a synucleinopathy with α-synuclein (α-SYN) aggregation and inclusion body formation in selected brain regions. The inclusions formed by large and insoluble aggregates symbolize an end stage of a molecular cascade, while small intermediate 'soluble oligomers' in the aggregation process are toxic. Evidence suggests the role of misfolded proteins in the form of oligomers might lead to synaptic dysfunction, neuronal apoptosis and brain damage. Although the mechanism by which oligomers trigger neurodegeneration still remains mysterious, great efforts have been made to investigate potential therapeutics aimed to block α-SYN toxicity. They may include proteostasis agents to block alpha-synuclein filament assembly and toxicity, or promote the refolding of mutant proteins, modulators of alpha-synuclein transfer between cells, reagents to regulate cargo dynamics along axonal microtubule networks, stimulators of autophagy and/or modulators of cellular stress pathways. However, problems commonly associated with peptides in therapy are their high sensitivity to proteolytic degradation and lack of permeation into the cells. For RNAi-mediated suppression of a-synuclein potential caveats include the extent and duration of a-synuclein silencing. Partial suppression may not sufficient to achieve neuroprotection and a close-to complete reduction of a-synuclein may pose safety risks. Treatment of chronic a-synucleinopathies will likely involve long-term anti-a-synuclein intervention. Thus, the adverse side effects may become evident after prolonged silencing of a-synuclein expression. In addition, it is still unclear whether the bioactive molecules are truly effective at reversing aberrant cell phenotypes after the a-syn aggregation has caused cellular toxicity. Although rescue experiments were mostly performed in cell culture systems or simple animal models with positive results, it is necessary to perform these studies in other systems to show that the compounds are able to reverse the a-syn phenotype and not simply prevent it. Effective PD drugs need to be administered after the onset of disease, not before. Overall, there are still too many questions than answers before we are certain that whether a-syn aggregation is directly responsible for neurodegeneration and thus, blocking it may prevent the disease.