MODIFYING ALPHA-SYNUCLEIN DIMERIZATION IN LIVING CELLS

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A common hallmark in several neurodegenerative disorders (ND) is the accumulation of misfolded proteins. These altered proteins enable aberrant protein-protein interactions, the formation of aggregates, and the disruption of several essential cellular functions.

The misfolding and aggregation of alpha-synuclein (α-syn) is the pathological hallmark of Parkinson's disease (PD), the second most common age related ND. Recently, it has been postulated that oligomeric species of α-syn represent the toxic genus, rather than the complex aggregated forms of the protein.

We have been investigating the molecular mechanisms underlying the initial steps involved in α-syn oligomerization through a novel system we established to monitor α-syn dimerization/oligomerization in living cells, using bimolecular fluorescence complementation (BiFC). Using this approach as a readout for α-syn dimerization/oligomerization, we started to identify and characterize genetic modifiers of α-syn oligomeric precursors, through an unbiased genome-wide lentiviral RNAi screen.

We identified 17 genetic modifiers of α-syn oligomerization, including genes involved in intracellular transport/trafficking, and in signal transduction pathways.

The identification of genetic modifiers of α-syn oligomerization, possible early events in the protein aggregation cascade, will represent a significant advance for the development of novel therapeutic strategies for PD and related diseases.