Oral presentation abstract

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698.5. Inhibition of FK506-binding proteins reduces alpha-synuclein aggregation and Parkinson’s disease-like pathology Inhibition of FK506-binding proteins reduces alpha-synuclein aggregation and Parkinson’s disease-like pathology

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α-Synuclein is a key player in the pathogenesis of Parkinson’s Disease. It is found in disease conditions in a fibrillar, aggregated form inside cytoplasmic inclusions called Lewy Bodies. Members of the FK506 binding protein (FKBP) family are peptidyl-prolyl isomerases, which were recently shown by us to accelerate the aggregation of α-synuclein (α-SYN) in vitro. This enhanced aggregation was annihilated by FK506, a specific inhibitor of this family of proteins. To validate these findings in living cells, we established a high-content neuronal cell culture model for synucleinopathy which allows simultaneous recording of different parameters of aggregation and apoptotic cell death upon induction of oxidative stress in SHSY5Y cells. We demonstrate that FK506 inhibits α-synuclein aggregation and neuronal cell death in this model for synucleinopathy in a dose-dependent way. In addition, knock-down of FKBP12 or FKBP52 equally resulted in a decrease of the number of α-synuclein aggregates and protected against cell death, while viral vector-induced overexpression of FKBP12 or FKBP52 accelerated the aggregation of α-synuclein, suggesting that these FKBP members might be involved in the observed FK506 effect. To determine the specificity of the observed effects, we are currently evaluating the effect of other FKBPs with high expression levels in the brain (FKBP38, FKBP52 and FKBP65) and non FKBP PPIases (Cyclophilin A and Pin1) on the aggregation of α-SYN in vitro and in cell culture.

To corroborate the physiological relevance of our findings in vivo, we could show that oral administration of FK506 to mice after viral vector-mediated overexpression of α-SYN in adult brain reduced α-SYN aggregate formation and neuronal cell death. Our data might help to explain previously described neuroregenerative and neuroprotective effects of immunophilin ligands, allowing a more directed search for effective drugs against PD.