Abstract for Metabesity 2022:

Deregulated mTORC1 signaling and mRNA translation in Parkinson's disease pathogenesis

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The mechanistic Target of Rapamycin (mTOR) is a master regulator of cell growth and metabolism. Deregulated mTOR signaling underlie the progression of cancer, diabetes and age related neurodegenerative diseases. Here we report that pathologic α-synuclein (α-syn) deregulates mTORC1 signaling through binding of tuberous sclerosis protein (TSC) 2 and destabilizing the TSC1-TSC2 complex that leads to enhanced mTORC1 signaling and mRNA translation. Our novel proteomics and Single Molecule Pulldown (SiMPull) data strongly suggest that α-syn preformed fibril (PFF) directly interacts with TSC2 and destabilizes TSC1-TSC2 complex, which results in persistent mTORC1 activation and enhanced mRNA translation. Genetic and pharmacological inhibition of mTORC1 signaling and mRNA translation rescue the dopamine neuron loss, behavioral deficits and aberrant mTORC1 signaling in mouse α-syn PFF and *Drosophila* α-syn transgenic models of pathologic α-syn induced degeneration. Together, our findings establish a potential molecular mechanism by which pathologic α-syn activates mTORC1 leading to enhanced protein translation and concomitant neurodegeneration in PD.