ALPHA SYNUCLEIN MODULATES THE EXPRESSION OF NOTCH1 THROUGH A P53-DEPENDENT MECHANISM IN ADULT RAT HIPPOCAMPAL STEM CELLS: IMPLICATIONS FOR NEUROGENESIS IN PARKINSON'S DISEASE

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Parkinson’s disease (PD) is the second most common neurodegenerative disorder, affecting 1% of the population over 65. PD is manifested as a progressive movement disorder, with loss of dopaminergic neurons in the substantia nigra and presence of Lewy bodies containing aggregated alpha-synuclein (a-syn).

Neurogenesis in the mature CNS occurs in the olfactory bulb, the hippocampus, and the subventricular zone. Accumulation of a-syn in the CNS of tg mice was showed to reduced neurogenesis in the olfactory bulb and hippocampus. Moreover, overexpression of a-syn in human and mouse embryonic stem (ES) cells results in defective neurogenesis and cell death. We have recently shown that abnormal a-syn accumulation contributes to alterations in neurogenesis by reducing the survival of NPCs via downregulation of Notch-1 expression in mouse ES cells and in the DG of a-syn tg mice.

Here we investigated the effects of abnormal a-syn accumulation in Notch-1 transcriptional regulation in adult rat hippocampus neural stem cells (ARH-NS) as a model for mammalian adult neurogenesis. We present evidence showing that a-syn impairs neurogenesis by decreasing Notch signaling in ARH-NS cells, as evidenced by reduced levels of Notch1, Hes1 and Hes5 mRNAs. Furthermore, we identified p53 as a negative regulator of Notch1 transcription, who binds to a consensus site on Notch’s proximal promoter. Our results suggest that interaction between p53 and a-syn locks the repressor in its DNA binding site, which results in further inhibition of Notch1 transcription, providing a mechanistic explanation for the alterations in neurogenesis observed in PD.