Thesis title: **Micro-RNA mediated regulation of neurodegeneration in Parkinson's disease models**

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Abstract

microRNAs (miRNAs/miRs) are non-coding small RNAs that are important for post-transcriptional gene regulation and maybe released from the parent cell packaged inside certain membrane-bound extracellular microvesicles called exosomes. For my Ph.D. thesis, I have focused on brain-enriched miRNAs- miR-128 (neuron-enriched) and miR-23a (astrocyte-enriched) and studied their role in Parkinson's disease (PD) pathogenesis. miR-128 is a neuron-enriched miRNA which was observed to be down-regulated in the cellular models of PD under 6-OHDA treatment. miR-128 prevented activation of the transcription factor FoXO3a and could regulate the expression of the downstream targets of FoXO3a- the pro-apoptotic proteins PUMA and FasL. By down-regulating these proteins, miR-128 could successfully shut-down both the intrinsic and extrinsic pathways of apoptosis. Additionally, miR-128 could prevent mitochondrial superoxide generation. Furthermore, miR-128 overexpression inhibited 6-OHDA induced neurite shortening and promoted neurite formation. Finally, miR-128 overexpression improved synaptic health by up-regulating the expressions of synaptic proteins synaptophysin and PSD-95. On the other hand, miR-23a is an astrocyte-enriched miRNA that was downregulated in astrocytes upon Rotenone treatment. Interestingly, Rotenone treatment led to Ca^{2+} surge in the astrocytes, followed by activation of the Ca^{2+}/CaM dependent protein phosphatase, Calcineurin. Calcineurin was also found to co-express in the reactive astrocytes of acute MPTP models of PD. Further downstream of Calcineurin pathway, miR-23a underwent release from the astrocytes via exosomes. This exosomal miR-23a proved to be neuroprotective in different neuronal models of PD. 3'UTR cloning revealed that miR-23a can directly bind to and down-regulate the expression of pro-apoptotic PUMA in the neuronal cells, thereby preventing induction of 6-OHDA mediated neuronal apoptosis. Finally, both miR-128 and miR-23a was found to be differentially expressed in the exosomes derived from the PD patient plasma. This data was further validated from human sRNA-Seq data obtained from miRNA expression and exosome repositories like DIANA-miTED and EVAtlas respectively. Thus, brain-enriched miRNAs- miR-128 (neuron-enriched) and miR-23a (astrocyte-enriched) proved to play significant roles in the pathogenesis of PD and showed potential to be important biomarkers and therapeutic targets for the detection, diagnosis and cure of PD.

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