3. AIM AND OBJECTIVES

The Recent experimental evidence clearly suggests that loss of dopaminergic neurons is one of the major causes of Parkinson's disease; however, its mechanisms still has not been studied in detail. The majority of the evidence supports the view that defect in cellular quality control of mechanisms like the ubiquitin-proteasome system (UPS) and autophagy plays a major role in the further pathogenesis of PD. It had been observed that accumulation of defective mitochondria, generation of ROS and cell death is primarily due to a decrease in the rate of autophagy or defect in the process of autophagy. Novel identified genes involved in PD pathogenesis have been shown to be associated with regulation of autophagy pathway. The Initially major efforts were undertaken to understand the mechanisms of cell death for modulating this process to increase the life span of the neurons. The emerging evidence suggests that enhancing the efficiency of the quality control mechanisms of neurons will help the neuronal health and survival.

Hence, it is essential to understand the endogenous modulators of the process of the autophagy in order to prevent the neuronal dysfunction either due to genetic or environmental causes. Recently it has been observed that miRNAs fine tunes the cellular processes by regulating the levels of protein at physiological concentrations. Many experimental evidence strongly suggest that miRNAs may play an important role in pathogenesis of PD. However, the systematic study has not been yet done in a case of PD stress conditions. We hypothesize that miRNAs may form characteristic expression signature pattern during inflammatory and toxin-mediated mitochondrial oxidative stress conditions and its combinatorial expression may modulate autophagy and mitochondrial function hence regulate neuronal cell death. Study of this crosstalk will lead to the discovery of new regulators of these pathways during onset of Parkinson's disease

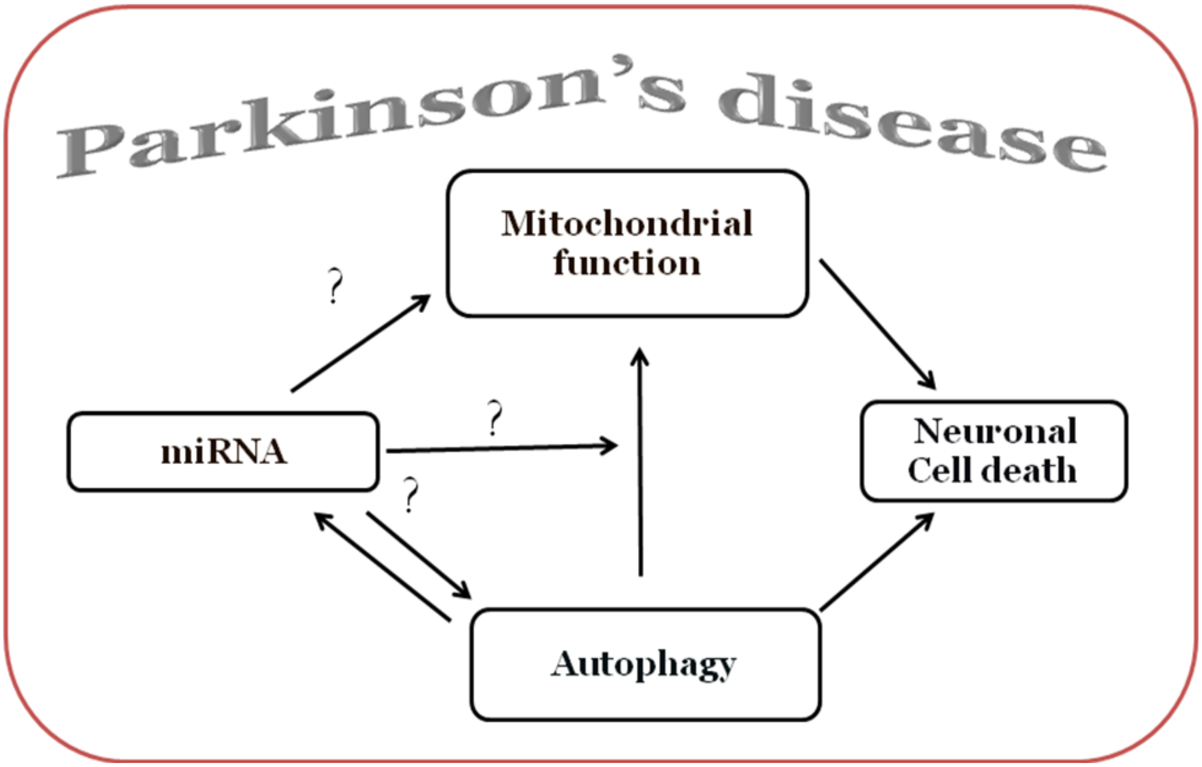

Figure-3.1: Diagrammatic representation of hypothesis of the study

Objectives:

- ✓ To study and establish cell based toxin and inflammatory mediated Parkinson's disease (PD) model in human SH-SY5Y cells.
- ✓ Analysis of differentially expressed miRNAs in PD stress conditions and role of identified miRNAs in regulation of autophagy.
- ✓ Study the role of differentially expressed miRNAs in mitochondrial function during PD stress conditions.
- ✓ Study the role of differentially expressed miRNAs in regulation of autophagy and cross talks with cell death.

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