Title: STUDYING THE ROLE OF EXOSOMAL miRNA's IN INTERCELLULAR COMMUNICATION IN PARKINSON'S DISEASE

ABSTRACT:

Parkinson's disease (PD), the second most prevalent neurodegenerative disorder, is marked by the progressive demise of dopaminergic neurons. The central mystery lies in the intricate mechanisms triggering neuronal death. Exosomes, integral to intercellular communication, harbor signaling molecules that influence the functional outcomes of recipient cells. Notably, α-syn may propagate through exosomes, affecting neighboring neurons and inducing inflammation in glial cells. While mitochondrial dysfunction is established in PD, the interplay between mitochondria, lysosomes, and exosomes in PD stress conditions remains elusive. The study aims to elucidate this inter-organellar crosstalk, focusing on its role in exosome release and subsequent impact on neighboring cells. Moreover, Within the context of PD, the role of miRNAs remains elusive. MiRNAs, well-known regulators of post-transcriptional gene expression, have not been definitively identified in the pathogenesis of PD, nor has their potential transfer to neighboring cells via exosomes been explored. The study postulates that these elusive miRNAs, implicated in PD, might be transported via exosomes to bystander cells. This transfer could induce mitochondrial dysfunction in recipient cells, thereby influencing the observed neurodegeneration and cell death in PD. The proposed investigation aims to identify these miRNAs, study their transfer through exosomes to bystander cells, and the resultant mitochondrial dysfunction, ultimately contributing to the understanding and management of PD. The study reveals enhanced exosome release in PD-stressed neuroblastoma and glial cell lines, accompanied by complex-I inhibition, mitochondrial dysfunction, and lysosomal impairment. Autophagy flux inhibition exacerbates exosome release, while rapamycin intervention mitigates this effect. Neuronal exosomes, when internalized by recipient cells, localize to mitochondria, inducing dysfunction and cell death. Exosomal miRNA profiling reveals altered cargo in PD stress conditions, with downstream effects on crucial cellular processes and pathways. The dysregulation of specific miRNAs in exosomes during PD stress conditions emerges as a critical factor influencing cellular functions. Notably, two downregulated miRNAs,

hsa-miR-30a-5p and hsa-miR-181c-5p, when loaded into exosomes, mitigate mitochondrial dysfunction and cell death in recipient cells. In conclusion, this study unravels a complex interplay involving exosomes, microRNAs (miRNAs), mitochondria, and lysosomes in the intricate crosstalk of PD pathogenesis. The demonstrated enhancement in exosome release under PD stress conditions, coupled with the identified dysregulation of specific miRNAs, highlights the critical role of these extracellular vesicles in disease progression. Notably, hsa-miR-30a-5p and hsa-miR-181c-5p emerge as potential therapeutic candidates, indicated by their ability to ameliorate mitochondrial dysfunction and mitigate cell death in PD-stressed cells when delivered via exosomes. The unveiled inter-organellar crosstalk, particularly the delicate balance between mitochondrial and lysosomal functions, offers new insights into the mechanisms driving PD pathogenesis. The observed mutations in proteins regulating mitochondrial dysfunction not only impede lysosomal function but also amplify exosome release, laden with pathogenic cargo. By enhancing autophagy flux and inhibiting exosomal release, the spread of PD pathology might be reduced, presenting a potential avenue for disease modulation. Exosomal miRNAs, particularly miR-93-5p, miR-30a-5p, and miR-484, exhibit promise as early detection biomarkers in biofluids, offering a non-invasive method for identifying PD. The application of these findings in an acute model of rotenone-treated rats supports the potential of serum exosomes as indicators of disease progression, providing a valuable tool for monitoring PD onset and severity.