NUS National University of Singapore

Department of Anatomy
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PHD ORAL DEFENSE

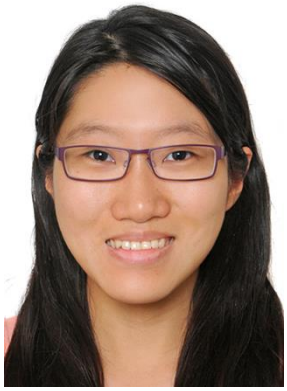
THE ROLES OF MIR-9 AND MIR-219 IN PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in the aging population. Owing to many gaps in knowledge about PD, current treatments only provide symptomatic relief and not neuroprotection. miRNAs are regulators of gene expressions and are found to be dysregulated in PD. In this study, the miRNA-mediated mechanisms involved in PD pathogenesis were investigated. Via qPCR, we verified the increase in miR-9 and miR-219 levels in in vitro PD models. The inhibition of miR-9 rescued MN9D neuronal cells from MPP+ neurotoxicity while miR-9 mimics treatment alone induced neuronal death. In contrast, miR-219 inhibitors aggravated MPP+-induced neurotoxicity. Using the Drosophila model, we observed that the overexpression of miR-9 or inhibition of miR-219 resulted in lower dopamine levels, loss of dopaminergic neurons and decreased climbing ability as compared to controls whereas the overexpression of miR-219 increased dopamine levels and improved climbing ability. For each miRNA, we identified a possible downstream target that could be responsible for mediating its actions, namely, SLC18A2/VMAT2 for miR-9 and REPS2 for miR-219. The binding between miRNAs and their respective target was validated via dual luciferase reporter assay. SLC18A2/VMAT2 knockdown promoted neuronal death while REPS2 knockdown partially rescued cells from MPP+ neurotoxicity. We also investigated if exosomal miRNAs mediate neuroinflammation, a key event in PD progression. By examining the exosomes released from MPP+-treated MN9D cells, we showed that they contained higher levels of miR-9 and miR-219 as compared to controls. The addition of these exosomes also promoted the activation of microglial BV2 cells (increased iNOS and TNF-a expressions). BV2 cells treated with miR-9 mimics showed increased TNF-a expression while BV2 cells treated with miR-219 mimics showed decreased iNOS expression. In addition, MN9D cells treated with conditioned media from miR-9-activated BV2 cells, but not miR-219-treated BV2 cells, showed decreased cell viability. Thus, we show that miR-9 and miR-219 are able to modulate the activation of microglia which can, in turn, affect the viability of neuronal cells. Therefore, our results support that miR-9 upregulation plays a neurotoxic role in PD and affect motor functions while miR-219 plays a neuroprotective compensatory function. Novel targets of miR-9 and miR-219 were also validated in this study that could be involved in PD pathogenesis.

Date :
Friday, 26 February 2021
Time:
2 PM to 3 PM

Zoom Meeting ID:
848 5700 9820
Password:
555666

Goh Suh Yee
Postgraduate Student



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