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The effect of increased levels of miR-132 on dopaminergic primary midbrain neurons

PD is the second most prevalent neurodegenerative disorder, affecting 7 to 10 million people worldwide. It is an age-related pathology, showing a prevalence of up to 2% in individuals aged over 60 years. PD is characterized by a marked cell loss in substantia nigra and consequent dopamine depletion in the striatum. Dopaminergic degeneration causes severe impairments to the nigrostriatal circuit, triggering serious deficits on motor control and initiation of voluntary movements. The late diagnosis together with the limited regenerative capability of nerve cells aggravate even more the possibilities for treatment and recovery of affected patients. For those reasons, therapeutic alternatives that focus on the rescue of dopaminergic neurons undergoing degeneration, provide neuroprotection or enable neuronal regeneration are of great relevance for the development of curative treatments for PD. The number of studies focusing on the role of miRNAs in physiological and pathophysiological mechanisms of the nervous system is rising. Defects in the miRNA network are known to be involved in a series of pathogenic processes. miRNAs comprise a class of post-transcriptional regulators of gene expression. They target messenger RNAs leading to cleavage or translational suppression of those. By manipulation of miRNA expression levels, neuroprotective and neuroregenerative strategies could be explored. Therefore, miRNAs figure as potential targets for the development of novel therapeutic alternatives for neurodegenerative diseases, as PD. The objective of this study was to investigate the effects of increased levels of miR-132 in dopaminergic PMNs. It was shown that high levels of miR-132 induce significant increase in neurite outgrowth and regeneration in dopaminergic primary midbrain neurons. We speculate that these effects are mediated by the repression of the miR-132 target protein P250GAP. This GTPase-activating protein regulates actin dynamics supressing the RAC1-PAK actin remodeling pathway, and directly influences neurite morphogenesis. Increasing miR-132 levels led to reduced levels of P250GAP in PMNs. On the other hand, higher levels of miR-132 mimic did not protect dopaminergic neurons in the MPP+-induced neurodegeneration model in PMNs. As dopaminergic neurons are especially sensitive to oxidative stress, further investigations have to be done in order to verify whether the employed model is appropriate for this kind of evaluation, and to evaluate the consistency of the presented data. The results presented here indicate that miR-132 plays an important role in dopaminergic morphogenesis and regeneration. This indicates that miR-132 might be a valuable tool for understanding PD pathophysiology, as well as for the development of novel curative treatments for this disease.