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Exosomes Derived from Human Neural Stem Cells Mediate Cellular Stress Ability and Promote Neurological Function Recovery of Cerebral Ischemic Rats

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Introduction

The objective of this study is to determine the effects of human NSCs-derived exosomes on cellular stress and brain ischemic stroke, and to explore whether IFN-gamma stimulation can affect or alter the functions or contents of NSCs-derived exosomes.

Methods

IFN-gamma co-cultured with NSCs for 3 days, extracted exosomes from their cell medium (both NSCs and IFN-gamma stimulated-NSCs), which were identified by TEM, NTA and Western blot. In vitro cellular hydrogen peroxide (H2O2) model was built to induce cell apoptosis, then the therapeutic effects of exosomes were evaluated by CCK8 and live-dead assays etc. In vivo rat's ischemic stroke model was built by MCAO method, and then the exosomes were stereotaxically injected for treatment. Furthermore, exosomes were labeled with PKH67 to evaluate their endocytosis or migration capacities in vitro and in vivo. Finally, next generation sequencing (NGS) was used to compare the differential expressed miRNAs of hNSCs-Exo and IFN-gamma-hNSCs-Exo, and the significant differential expressed miRNAs were identified by qRT-PCR.

Results

Firstly, IFN-gamma stimulation affected the abilities of human NSCs-derived exosomes (hNSC-Exo), which played more roles in alleviating the level of oxidative stress of NSCs and augmenting the NSC survival after H2O2 stimulating, compared to hNSC-Exo, as well promoting hNSC differentiation. Secondly, in rat's ischemic stroke model, IFN-gamma-hNSC-Exo further facilitated the neurological function recovery (assessed by the modified Neurological Severity Score, Rotarod test, etc.) and decreased the infarct volume (assessed by MRI) compared to hNSC-Exo group, as well enhanced neural cell survival and promoted neovascularization (assessed by IF and IHC). Thirdly, exosomes can be internalized or endocytosed by cells in vitro and in vivo, after labeled with PKH67, it was showed that PKH67-Exo migrated into the cells of brain infarct regions, even entered into the nucleus. Finally, next generation sequencing (NGS) revealed a significant enrichment of hsa-miR-133a-3p and hsa-miR-3656 in IFN-gamma-hNSC-Exo compared with hNSC-Exo, and exosomes can deliver these specific exosomal miRNAs into hNSCs to increase cell survival and proliferation.

Conclusions

hNSCs-derived exosomes possess the ability of neural regeneration, modulate neurological function recovery, and play more positive roles by stimulating with IFN-gamma (IFN-gamma-hNSC-Exo).

Learning Objectives

hNSCs-derived exosomes may provide a novel and promising strategy in modulating neurological function recovery for ischemic stroke patients.

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